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Updates in ocular therapeutics and surgery

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Updates in ocular therapeutics and surgery

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Editorial: Updates in ocular therapeutics and surgery

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KEYWORDS

cornea, retina, strabismus, ocular surface, cataract surgery, intraocular lenses, glaucoma

Editorial on the Research Topic
Updates in ocular therapeutics and surgery

Ophthalmology is a field of medicine that has grown rapidly during the last few decades. Several new and promising treatments have become available for eye conditions, including age-related macular degeneration, glaucoma, retinal vein occlusions, diabetic macular oedema, genetic disorders, uveitis, and inflammations. On the other hand, recent technological developments and advanced surgical techniques have drastically changed the daily practice of eye surgeons, with new surgical options resulting in safer, faster, and more precise surgery.

This Research Topic summarized modern therapeutic and surgical approaches to ocular diseases, adding a valuable contribution to our existing knowledge, describing the current state-of-the-art, and providing directions for future research.

Cornea and ocular surface

A systematic review and meta-analysis conducted by Sun et al. demonstrated that in patients who have already undergone corneal refractive surgery, presbyopia-correcting intraocular lenses (IOLs) deliver satisfactory outcomes in terms of efficacy, safety, and predictability, but have a higher risk of photopic side effects such halos and glare. Wy et al. compared the clinical outcomes of maximum tolerated medical therapy in patients with penetrating keratoplasty with those of Ahmed glaucoma valve implantation and found no significant differences in the visual acuity, corneal thickness and in survival time. Zhang et al. compared visual outcomes and corneal optical quality after small incision lenticule extraction (SMILE), wavefront-optimized (WFO) FS-LASIK, and topography-guided customized ablation treatment (TCAT) FS-LASIK for myopia and found that all techniques provided similar visual results with the TCAT FS-LASIK to be superior in terms of corneal optical quality. The Management of Vernal Keratoconjunctivitis in Asia (MOVIA) Expert Working Group completed a consensus program to evaluate, review, and develop best-practice recommendations for the assessment, diagnosis, and management of Vernal Keratoconjunctivitis in Asia which was published in this Research Topic (Mehta et al.).

Glaucoma

A meta-analysis conducted by Chen X. et al. showed that XEN gel stent was effective and safe for primary and secondary open angle glaucoma with an overall complete success rate varying between 21.0 and 70.8% after 2 years and an incidence of sight-threatening complications below 1%. In a prospective case series, Chen M. et al. assessed the safety and efficiency of carbon dioxide (CO_2) laser-assisted sclerectomy surgery (CLASS) in Chinese patients with primary open-angle glaucoma and found that CLASS was a safe and effective approach, while Xiang et al. demonstrated that that pars plana Ahmed valve implantation can be safely performed for managing vitrectomised eyes with refractory glaucoma.

Oculoplastics and strabismus

In a prospective randomized control trial by Irawati et al., the modified tarsoraphy technique was found to be more efficient than the gold weight implant as a surgical treatment for paralytic lagophthalmos in patients with leprosy. Chi and Lai compared the endoscopic dacryocystorhinostomy with short-term, pushed-type bicanalicular intubation vs. the pulled-type monocanalicular intubation in patients with primary acquired nasolacrimal duct obstruction and found both techniques comparable in terms of surgical outcomes. Supramaximal horizontal rectus recession–resection surgery was found to be an effective treatment method for complete abduction deficiency in a retrospective study by Wang et al., while Lee et al. proposed a new simple marking system for accurate intraoperative monitoring and adjustment of cyclotorsion strabismus surgery.

Retina

Zhou et al. found that age, disease duration, baseline central macular thickness and visual acuity are predictive factors for the visual outcomes at 6-month of anti-VEGF treatment for macular oedema secondary to retinal vein occlusion and that a further metric that can be used to forecast improved long-term outcomes is the "2-week CMT decrease rate >37%" after the initial injection. Anti-VEGF agents as the primary treatment provide potential advantages over laser therapy for eyes with zone I type 1 ROP and A-ROP, according to a large retrospective study from China by Linghu et al.. Laser photocoagulation and anti-VEGF agent therapy were equally effective for treating eyes with zone II type 1 ROP, but the rate of reactivation with laser therapy was much lower than that with anti-VEGF agents. Finally, Lumi et al. described a new technique for macular pucker peeling without forceps by using a 25-gauge vitrectomy probe.

Cataract surgery and intraocular lenses implantation

Ye et al. described a modified technique for the scleral fixation of a secondary foldable three-piece intraocular lens, and reported successful outcomes in 10 eyes. The long-term endothelial cell count was better in low-energy femtosecond laser-assisted cataract surgery (FLACS) while the rest of the intraoperative and post-operative outcomes were comparable between these two procedures, according to Liu et al. randomized clinical trial. In a retrospective comparative study, Chen Z.-X. et al. demonstrated that supra-capsular and scleral-fixated intraocular lens (IOL) implantation was comparable to modified capsular tension ring and in-the-bag intraocular lens implantation in patients with microspherophakia. Finally, in an experimental study, Xie et al. identified primary calcification and vacuaoles as the main causes of US-860 UV and L-312 IOL opacification, respectively.

We hope that you will enjoy this Research Topic as much as we enjoyed editing it.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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SYSTEMATIC REVIEW
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Combined 5-Fluorouracil and Low Molecular Weight Heparin for the Prevention of Postoperative Proliferative Vitreoretinopathy in Patients With Retinal Detachment: A Meta-Analysis

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Background: Postoperative proliferative vitreoretinopathy (PVR) remains a dilemma for retinal surgeons. We performed a literature search and meta-analyses to figure out whether combined 5-fluorouracil (5-FU) and low molecular weight heparin (LMWH) treatment were effective in improving the primary success of vitrectomy and preventing postoperative PVR occurrence in patients with retinal detachment (RD).

Methods: Databases including PubMed, Embase, the Cochrane library, and China National Knowledge Infrastructure (CNKI) were searched from inception to May 2021. Comparative studies approaching the effects of combined 5-FU and LMWH on postoperative PVR were included. Quality assessment was performed using RoB 2 and ROBINS-I tool. Study data were pooled using Review manager 5.4.1. The main outcomes were: the primary success of vitrectomy at 6 months and the postoperative PVR occurrence. The additional outcomes were: number of patients who underwent vitreoretinal reoperations and the number of vitreoretinal reoperations due to postoperative PVR. Subgroup analyses and sensitivity analyses were also performed.

Results: Six clinical trials with a total of 1,208 participants were included. We found that combined 5-FU and LMWH infusion did not improve the primary success of vitrectomy at 6 months (RR = 1.00, 95% CI = 0.95, 1.07, $P = 0.89$, $I^2 = 50\%$). Also, the conjunct therapy had no effect on reducing the number of patients who underwent vitreoretinal reoperations (RR = 1.00, 95% CI = 0.78, 1.28, $P = 1.00$, $I^2 = 42\%$). The overall effect of the treatment on preventing postoperative PVR was negative. However, in patients with PVR grade C (PVRC) before intervention, the 5-FU and LMWH treatment significantly reduced PVR occurrence. Visual acuity was not different between the treatment and control groups. Nevertheless, in one RCT, a significant reduction of VA was observed in the treatment group in macular-sparing patients with RD. No complications were attributed to the conjunct therapy.

Conclusions: The combined 5-FU and LMWH treatment neither improved the primary success of vitrectomy at 6 months nor decreased number of patients who underwent vitreoretinal reoperations. Thus, the treatment should not be routinely used in vitrectomy for patients with RD. However, the treatment proved beneficial in reducing postoperative PVR in patients with PVRC before intervention. More high-quality clinical trials are needed to confirm the results.

Systematic Review Registration: https://inplasy.com/inplasy-2021-8-0117/, identifier: INPLASY202180117.

Keywords: proliferative vitreoretinopathy, retinal detachment, vitrectomy, 5-fluorouracil, low molecular weight heparin, meta-analysis

INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is a common sight-threatening disease that has an incidence of 5–26.2 cases per 100,000 person-years (1, 2). Pars plana vitrectomy (PPV) is one of the principal treatments for RRD. The primary and final success rates for retinal reattachment reported for PPV were around 72.0 and 96.4%, respectively (3, 4). Proliferative vitreoretinopathy (PVR) is a common pathological process following the detachment of the retina and is reported to develop in 5–10% of all RRD (5, 6). PVR also occurs in eyes that underwent retinal reattachment surgery and is widely considered as one of the most common causes of failure of vitrectomy (1). PVR is characterized by the abnormal growth of epiretinal and/or subretinal membranes, which tend to contract and pull off the retina. The inflammation process, as well as the proliferation and migration of retinal pigment epithelium (RPE) cells, glial cells, and macrophages, are involved in the onset and development of PVR (6). Based on the understanding of these pathogeneses, various anti-inflammatory, and anti-metabolic drugs have been used in clinical trials to prevent the formation of postoperative PVR (7–9).

The antimetabolite 5-fluorouracil (5-FU) inhibits DNA synthesis as well as messenger RNA (mRNA) translation, thus it has been used in chemotherapy against tumors (10). In ophthalmic practice, 5-FU is selectively employed in trabeculectomy for reducing conjunctiva scarring (11). Kon et al. reported that single, short-term exposure to 5-FU significantly inhibited the proliferation of cultured human RPE cells (12). In experimental PVR models, 5-FU was sufficient in reducing vitreoretinal scarring and tractional retinal detachment (13). On the other hand, low molecular weight heparin (LMWH) has been proved to inhibit the proliferation of human scleral fibroblasts and RPE cells, as well as the cell-mediated traction of collagen gel *in vitro* (14). Moreover, LMWH reduced postoperative fibrin formation and proved beneficial in retinal repair in a group of patients with RD (15).

In 2001, Asaria et al. reported the combined use of 5-FU and LMWH in vitrectomy for the first time. They found that in patients at high risk of PVR, adjuvant therapy was effective in the prevention of postoperative PVR (16). However, later studies utilizing these two drugs presented controversial results in patients with RD with different severity (17, 18). In 2013, a Cochrane systematic review discussing the effects and safety of conjunct therapy was published. The authors discussed the topic on the basis of two RCTs without pooling the data, because of the high heterogeneity between the two trials (19). In the current study, we integrated results from relevant RCTs and non-randomized comparative studies, to further understand the efficacy and safety of combined 5-FU and LMWH treatment on the primary success of vitrectomy for RD as well as on the prevention of postoperative PVR.

MATERIALS AND METHODS

Protocol and Registration

This meta-analysis was conducted and reported according to the guidelines of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (**Supplementary data sheet 1**) (20, 21). This study was registered at the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY) (registration number INPLASY202180117; https://inplasy.com/inplasy-2021-8-0117/).

Eligibility Criteria

The participants, intervention, comparisons, outcomes, and type of studies (PICOS) of the current meta-analysis were as follows:

Participants (P): Patients over 16 years of age, diagnosed with RD, and scheduled for pars plana vitrectomy were included. Patients with traumatic retinal detachment or diabetic retinopathy were excluded.

Intervention (I): Infusion of combined 5-FU and LMWH during vitrectomy.

Comparisons (C): Placebo (normal saline) added to the infusion, or just normal infusion during vitrectomy with no additional drugs added.

Outcomes (O): The main outcomes include primary success at 6 months (defined as retinal reattachment after a single vitreoretinal operation) and postoperative PVR formation. The additional outcomes include the number of patients who underwent vitreoretinal reoperations, as well as the number of vitreoretinal reoperations due to postoperative PVR.

Type of studies (S): Prospective, controlled clinical trials were included, either randomized or non-randomized. Only studies that reported at least one of the main or additional outcomes and that had a follow-up period of no <6 months were included. Only studies written in English or Chinese were included.

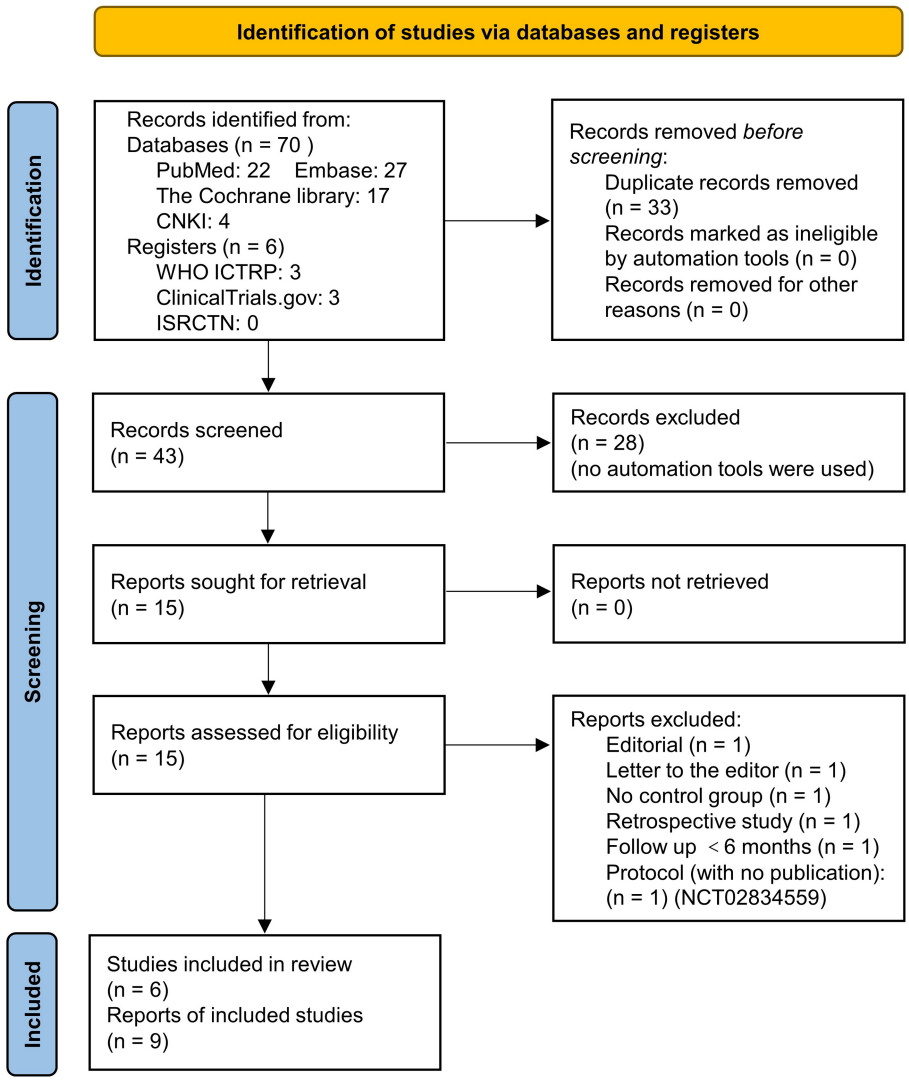

FIGURE 1 | Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram of literature search and screening.

Retrospective studies and single-arm studies were excluded. Studies that had either 5-FU or LMWH for intervention, but not a combination of the two, were also excluded.

Literature Search and Study Selection

We systematically searched the following electronic databases: PubMed, Embase, the Cochrane library, and China National Knowledge Infrastructure (CNKI), from inception to May 2021. We also searched the websites of ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), and International Standard Randomized Controlled Trial Number (ISRCTN). We used a combination of the keywords to search, including "proliferative vitreoretinopathy," "5-FU," "5-fluorouracil," "fluorouracil," "low molecular weight heparin," "dalteparin," "enoxaparin," "nadroparin," and "tinzaparin." Our search strategy was described in detail in **Supplementary data sheet 2**. Records were imported to the Endnote software (Clarivate Analytics, Philadelphia, USA), and duplicates were removed. Subsequently, the titles and abstracts of the records were screened, and irrelevant records were removed. The full texts of the remaining records were retrieved and judged according to our inclusion criteria. Two reviewers (CC and PC) independently performed the literature search and records screening, any disagreements were solved by discussion, or by consulting a third reviewer (HL).

Quality Assessment and Data Extraction

For the included RCTs, we assessed the study quality with the updated Cochrane risk-of-bias tool (RoB 2) (22). Bias was evaluated in five domains (the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) according to the instructions of the tool (22). For non-randomized studies of the effects of interventions (NRSI), the Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) tool was utilized to assess the bias (23). After quality

assessment, we extracted the following data from each included study: first author, year of publication, country where the study was carried out, language, study design, participants, mean age, treatment groups, number of eyes, 5-FU and LMWH infusion time, follow-up period, and intraocular tamponade. We also extracted the ratio of patients with preoperative PVR grade C (PVRC) or calculated the ratio from the original data. Two reviewers (CC and PC) independently assessed the study quality and extracted the data, consensus was reached by discussion or by consulting a third reviewer (HL).

Data Analysis and Synthesis

Review manager 5.4.1 (Revman, Cochrane Collaboration, Oxford, UK) was used to analyze and synthesize the study data. The number of patients with events and the total number of patients from the treatment and control group were input, and the risk ratio (RR) was calculated automatically, along with its 95% CI. We performed tests for heterogeneity before data synthesis. If $I^2 \leq 50\%$, heterogeneity was judged to be low or moderate, and fixed-effect model was used to pool the data. If $I^2 > 50\%$, heterogeneity was judged to be substantial, and a random effect model was used to synthesize the data. For the treatment effect, $P < 0.05$ was considered to be statistically significant.

For each outcome, we performed subgroup analyses to approach the origin of heterogeneity, as well as the possible differential effects of the 5-FU and LWMH treatment among the subgroups. The subgroups were divided according to the severity of the disease (different preoperative PVRC ratio), patient age, 5-FU and LMWH infusion time, and inclusion or exclusion of patients who underwent the previous vitrectomy.

Sensitivity analysis was performed by sequentially omitting individual studies, to assess the robustness of the current meta-analysis. If I^2 decreased substantially, the omitted study would be considered as the source of heterogeneity. If the final effect changed after a specific study was omitted, for example, *P*-value changed from >0.05 to <0.05, the meta-analysis for this outcome would be considered to be unstable.

RESULTS

Study Characteristics

In our comprehensive literature search, 76 records were identified. After duplicates and irrelevant records removal, 15 full-text publications were screened and six were excluded with reasons, as indicated in the PRISMA flow diagram (**Figure 1**). Finally, six studies (nine reports) (16–18, 24–29) with a total of 1,208 patients were included in the current meta-analysis. These studies were conducted in the UK (16–18), India (24), China (29), and Venezuela (25), and were published between 2001 and 2014 (**Table 1**). Among them, five studies were published in English and one in Chinese. There were four randomized controlled trials (RCTs) and two non-randomized studies of the effects of interventions (NRSI). Two were multicenter studies (17, 18) and four were conducted in a single center (16, 24, 25, 29). In all six studies, the infusion concentration of 5-FU and LMWH was 200 μg/ml and 5 IU/ml, respectively.

TABLE 1 | Characteristics of included studies.

References	Year	Location	Language	Design	Patients	Preoperative PVRC ratio (Treatment/Ctrl)	Group	5-FU+LMWH infusion time	Number of eyes (Treatment/Ctrl)	Mean age (years) (Treatment/Ctrl)	Follow-up period	Tamponade
Asaria et al. (16)	2001	UK	English	RCT	RRD patients at high risk of PVR	13.8/17.2%	5-FU+LMWH vs. Control	Infusion lasts until air exchange	87/87	62/64.3	6 m	SF_6, C_3F_8, Silicone oil
Charteris et al. (17)	2004	UK	English	RCT	RD patients with PVRC	100/100%	5-FU+LMWH vs. Control	≤60 min	73/84	65.8/66.2	12 m	Silicone oil
Wickham et al. (18)	2007	UK	English	RCT	RRD patients (unselected)	1.8/3.7%	5-FU+LMWH vs. Control	≤60 min	342/299	61.9/61.4	6 m	SF_6, C_3F_8, Silicone oil
Ganekal and Dorairaj (24)	2014	India	English	RCT	RRD patients at high risk of PVR	70/60%	5-FU+LMWH vs. Control	Infusion lasts until air exchange	20/20	28.5/38.5	6 m	Silicone oil, C_3F_8, Air
Zhu et al. (29)	2006	China	Chinese	NRSI	RD patients with PVRC	100/100%	5-FU+LMWH vs. Control	≤60min	66/66	46.2/45.4	6 m	C_3F_8, Silicone oil
Garcia et al. (25)	2007	Venezuela	English	NRSI	RD patients with PVRC	100%/100%	5-FU+LMWH vs. Control	Infusion lasts until air exchange	33/31	55/56.7	12 m	Silicone oil

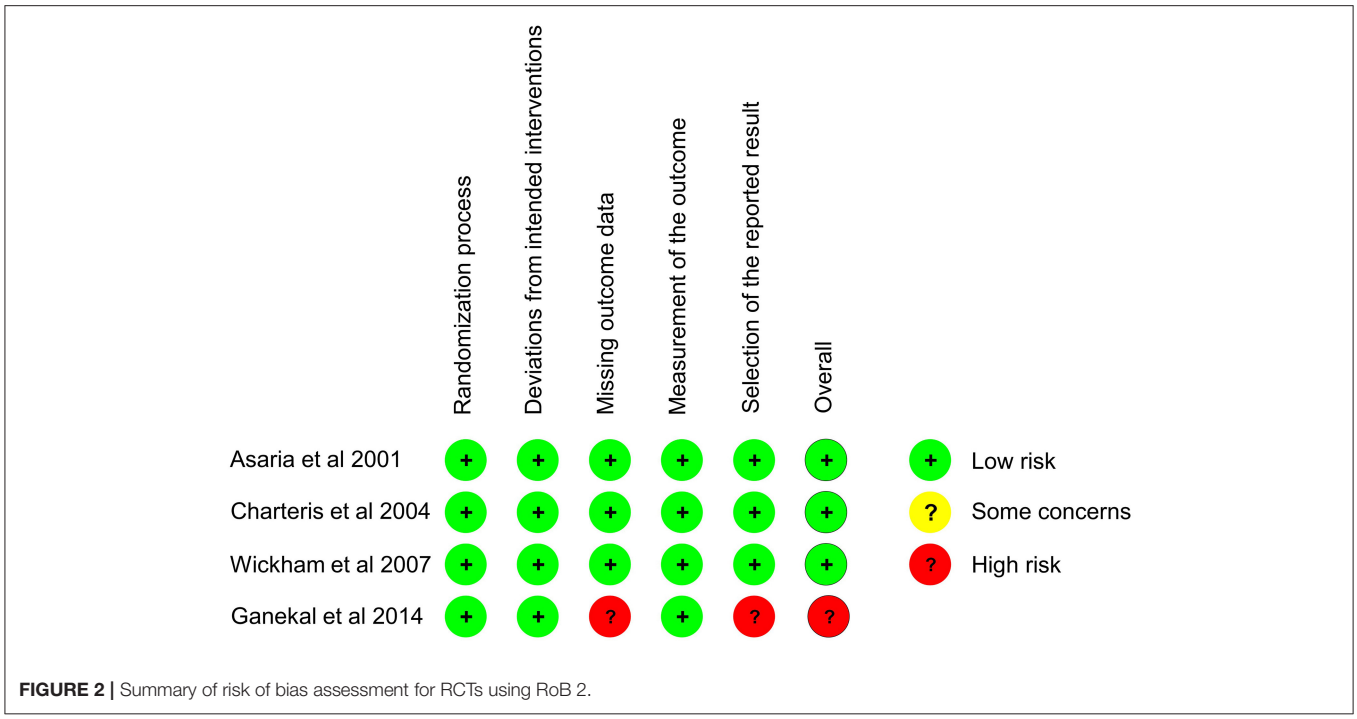

FIGURE 2 | Summary of risk of bias assessment for RCTs using RoB 2.

TABLE 2 | Quality assessment of non-randomized comparative studies using ROBINS-I tool.

	ROBINS-I domains							
Study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall ROBINS-I judgment**
Zhu et al. (29)	Moderate	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Garcia et al. (25)	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate

The control group received a placebo (normal saline) added to the infusion in three studies (16, 17, 24), and no drugs were added (just normal infusion) in the other three studies (18, 25, 29). Concerning the participants, one study enrolled unselected RRD patients with the preoperative PVRC rate of 1.8% in the treatment group and 3.7% in the control group (18), two studies enrolled RRD patients at high risk of postoperative PVR with the preoperative PVRC rate ranging from 13.8 to 70% (16, 24), three studies enrolled RD patients with 100% PVRC (17, 25, 29) (**Table 1**). Preoperative PVR was graded according to the updated classification by the Retina Society (1991) (30) in five studies (16–18, 24, 25), and was graded according to the 1983 classification (31) in one study (29). In the two editions of classifications, grades A and B were the same. The 1983 classification included grade C and D, and the 1991 updated classification included only grade C. We combined preoperative PVR grade C and grade D from Zhu (2006) (29) to be PVRC, in order to keep consistency. The infusion time of 5-FU and LMWH was no more than 60 min in three studies (17, 18, 29), while in the other three studies, the infusion lasted until air exchange (16, 24, 25). The average age of patients were <60 years in three studies (24, 25, 29), and more than 60 years in other three studies (16–18). In two studies, patients scheduled for primary vitrectomy were included (16, 18), while in the other four studies, a proportion of participants had undergone previous vitrectomy (17, 24, 25, 29).

Risk of Bias Assessment

The baseline characteristics of participants in the treatment and control groups were comparable in all six studies. All four RCTs (16–18, 24) performed concealment in allocation and during operation, three of them (16–18) mentioned the blinding of the outcome measurement personnel. Using the RoB 2 tool, three of the four RCTs were judged to be at low risk of bias across all five domains (16–18). However, one RCT was judged to be at high risk of bias because of obvious data missing and possible selection of the reported result (24) (**Figure 2**). For the two NRSI (25, 29), both studies were assessed to be at low or moderate risk of bias across all seven domains, thus, they were judged to be at an overall moderate risk of bias by the ROBINS-I tool (**Table 2**).

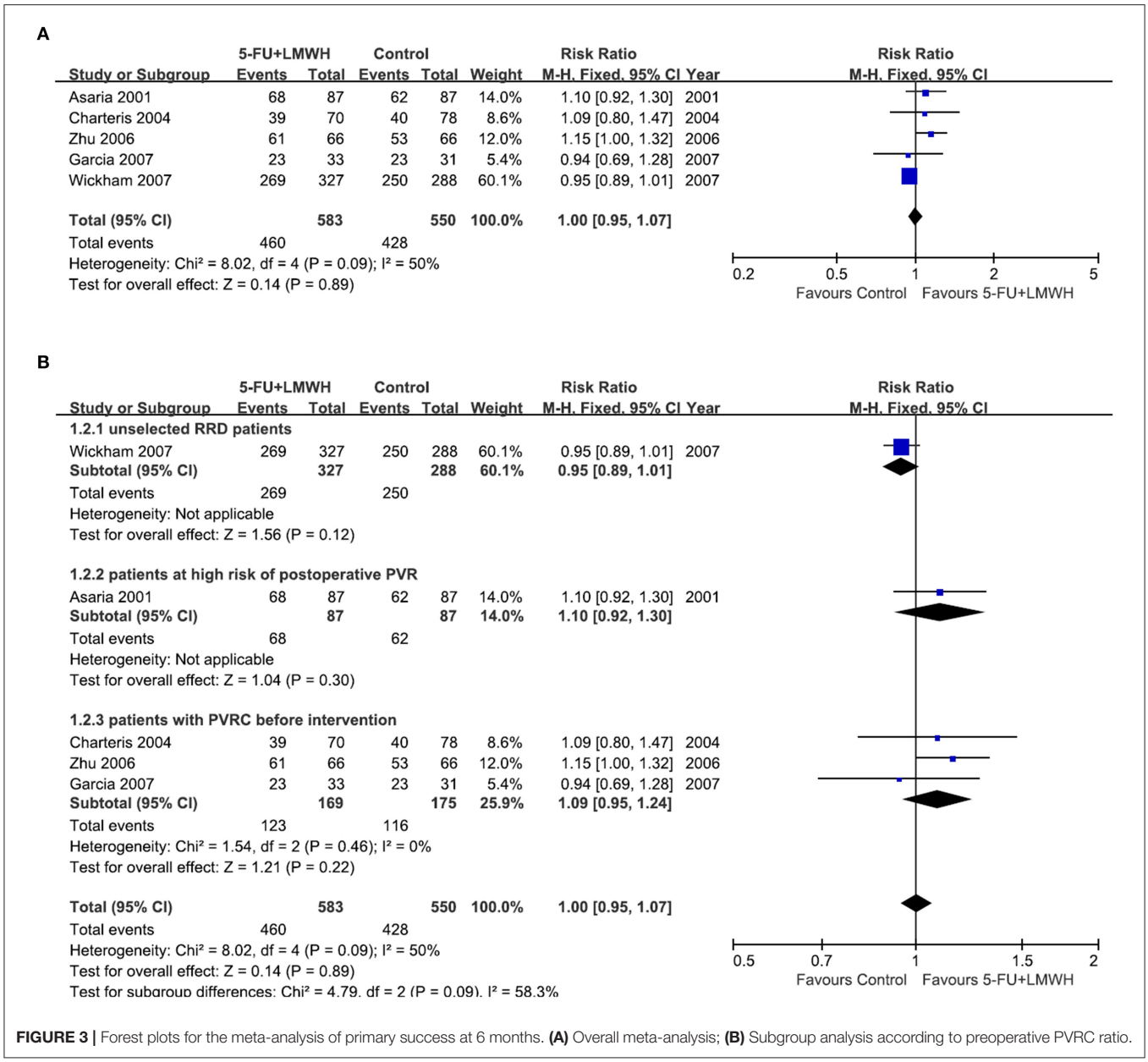

FIGURE 3 | Forest plots for the meta-analysis of primary success at 6 months. **(A)** Overall meta-analysis; **(B)** Subgroup analysis according to preoperative PVRC ratio.

Main Outcomes

Primary Success at 6 Months

Stable retinal reattachment is the standard for judging the success of vitrectomy for RRD. In our meta-analysis, data from five studies were pooled to analyze this outcome (16–18, 25, 29). The primary success number was either reported in the study (16–18), or calculated from the retinal redetachment ratio (29), or counted from the original data table (25). The pooled data demonstrated that 5-FU and LMWH infusion did not improve the primary success of vitrectomy at 6 months (RR = 1.00, 95% CI = 0.95, 1.07, $P = 0.89$, $I^2 = 50\%$) (**Figure 3A**).

Then we performed subgroup analyses to determine the origin of heterogeneity. When we defined subgroups according to different preoperative PVRC ratios, the heterogeneity decreased to 0%, indicating that the difference in preoperative PVRC ratio among the studies may be the primary source of heterogeneity. The *P*-values of the overall effect in all three subgroups were >0.05, indicating that the 5-FU and LMWH infusion improved the primary success in none of the subgroups (**Figure 3B**). We also defined the subgroups according to 5-FU and LMWH infusion time (≤60 min or lasted until air exchange), the average age of participants (≤60 years or >60 years), and inclusion or exclusion of patients who underwent the previous vitrectomy. We found that these factors were not the primary source of heterogeneity, as I^2 did not decrease substantially. Also, the overall effect of 5-FU and LMWH was not significant

TABLE 3 | Sensitivity analysis for main outcome: primary success at 6 months.

Omitted study	RR	95% CI		P of chi-square	I^2	Overall effect	Selected model
None	1	0.95	1.07	0.09	50%	$P = 0.89$	Fixed-effect model
None	1.04	0.93	1.15	0.09	50%	$P = 0.51$	Random-effect model
Asaria et al. (16)	1.02	0.9	1.16	0.08	55%	$P = 0.72$	Random-effect model
Charteris et al. (17)	1.03	0.92	1.16	0.05	61%	$P = 0.59$	Random-effect model
Zhu et al. (29)	0.98	0.92	1.05	0.36	7%*	$P = 0.63$	Fixed-effect model
Garcia et al. (25)	1.05	0.93	1.18	0.05	62%	$P = 0.42$	Random-effect model
Wickham et al. (18)	1.09	0.98	1.21	0.68	0%*	$P = 0.11$	Fixed-effect model

**Heterogeneity decreased after a particular study was omitted.*

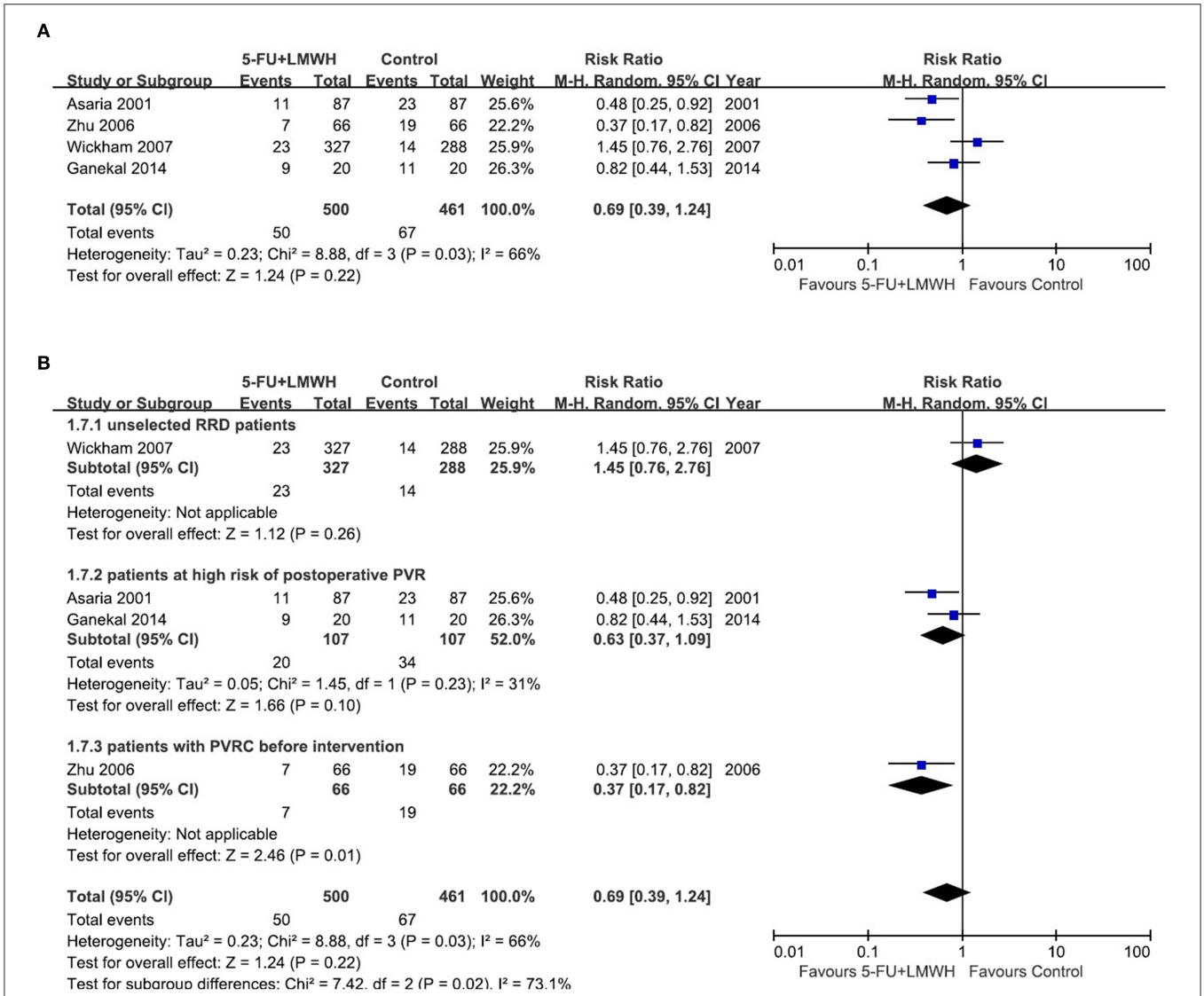

FIGURE 4 | Forest plots for the meta-analysis of postoperative proliferative vitreoretinopathy (PVR) occurrence. **(A)** Overall meta-analysis; **(B)** Subgroup analysis according to the preoperative PVRC ratio.

TABLE 4 | Sensitivity analysis for main outcome: postoperative PVR occurrence.

Omitted study	RR	95% CI		P of chi-square	I^2	Overall effect	Selected model
None	0.69	0.39	1.24	0.03	66%	$P = 0.22$	Random-effect model
Asaria et al. (16)	0.78	0.38	1.63	0.03	71%	$P = 0.51$	Random-effect model
Zhu et al. (29)	0.83	0.45	1.54	0.06	64%	$P = 0.55$	Random-effect model
Wickham et al. (18)	0.51	0.34	0.76	0.24	30%*	$P = 0.001$**	Fixed-effect model
Ganekal and Dorairaj (24)	0.65	0.28	1.49	0.01	77%	$P = 0.31$	Random-effect model

Heterogeneity decreased after a particular study was omitted.
***Overall effect changed when a particular study was omitted.*

FIGURE 5 | Forest plot for the meta-analysis of postoperative PVR occurrence when the study Wickham 2007 was omitted.

in any subgroup, as indicated by the P values of > 0.05 (**Supplementary Figure 1**).

To evaluate the robustness of the meta-analysis for this outcome, we performed sensitivity analysis by sequentially omitting individual studies. We found that Zhu (2006) (29) and Wickham (2007) (18) were the primary sources of heterogeneity since the I^2 decreased substantially after either of the two studies was omitted (**Table 3**). Nevertheless, the overall effect of 5-FU and LMWH was not changed (P-value remained > 0.05), indicating that our meta-analysis for this outcome was stable.

Postoperative PVR Occurrence

Postoperative PVR occurrence was reported in four studies (16, 18, 24, 29). The pooled data indicated the ineffectiveness of the combined 5-FU and LMWH in preventing postoperative PVR (RR = 0.69, 95% CI = 0.39, 1.24, $P = 0.22$, $I^2 = 66\%$) (**Figure 4A**). As $I^2 > 50\%$, we considered significant heterogeneity, and subgroup analyses were carried out. The effect of 5-FU and LMWH on preventing PVR was significant in the subgroup of patients with PVRC before intervention (**Figure 4B**). However, this subgroup contained only one study (29). Subgroup analyses defined by other factors did not show any significant change in the effect of 5-FU and LMWH or heterogeneity (**Supplementary Figure 2**). In the sensitivity analysis for this outcome, we found that when Wickham (2007) (18) was omitted, the heterogeneity decreased (I^2 changed from 66 to 30%), and the overall effect of the combined 5-FU and LMWH changed. A significant effect against postoperative PVR formation was shown, as indicated by the P-value of 0.001 (**Table 4**, **Figure 5**).

Additional Outcomes

Number of Patients Who Underwent Vitreoretinal Reoperations

Reoperation is a remedy for failed primary vitrectomy. However, surgery *per se*, will stimulate the tissue repairing and may contribute to PVR formation. Our meta-analysis for this outcome pooled the data from five studies (16–18, 25, 29). We found that the combined 5-FU and LMWH therapy was ineffective in reducing the number of patients who underwent vitreoretinal reoperations (RR = 1.00, 95% CI = 0.78, 1.28, $P = 1.00$, $I^2 = 42\%$) (**Figure 6A**). The subgroup analysis according to the preoperative PVRC level decreased the I^2 from 42 to 29%, however, the effect of 5-FU and LMWH was not significantly changed in any subgroup (**Figure 6B**). 5-FU and LMWH infusion time seemed to be the source of heterogeneity during the meta-analysis for this outcome since the I^2 decreased dramatically in subgroups divided by this factor, while age and inclusion/exclusion of patients who underwent the previous vitrectomy did not influence the heterogeneity (**Supplementary Figure 3**). Nevertheless, the effect of 5-FU and LMWH was not significantly changed in any subgroup analysis (**Supplementary Figure 3**).

By sensitivity analysis, we found Zhu (2006) (29) and Wickham (2007) (18) were the sources of heterogeneity since the omission of either study drastically decreased the heterogeneity (I^2 changed to 0%) (**Table 5**). However, the overall effect of 5-FU and LMWH in reducing the number of patients who underwent vitreoretinal reoperations was not changed, indicating that our meta-analysis for this outcome was quite stable.

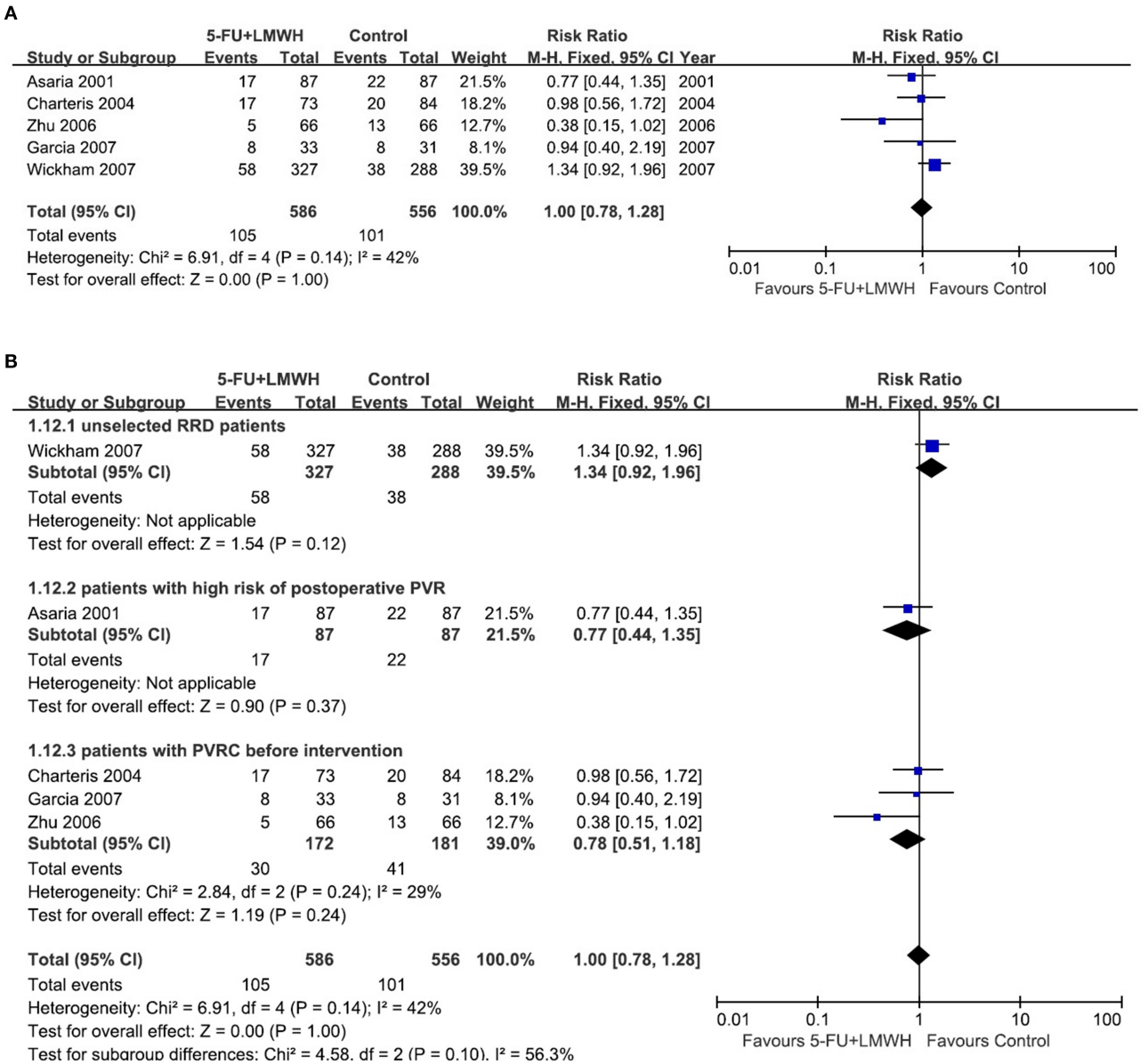

FIGURE 6 | Forest plots for the meta-analysis of the number of patients who underwent vitreoretinal reoperations. **(A)** Overall meta-analysis; **(B)** Subgroup analysis according to preoperative PVRC ratio.

TABLE 5 | Sensitivity analysis for additional outcome: number of patients underwent vitreoretinal reoperations.

Omitted study	RR	95% CI		P of chi-square	I^2	Overall effect	Selected model
None	1	0.78	1.28	0.14	42%	$P = 1.00$	Fixed-effect model
Asaria et al. (16)	1.06	0.8	1.4	0.12	49%	$P = 0.67$	Fixed-effect model
Charteris et al. (17)	0.88	0.54	1.42	0.08	57%	$P = 0.59$	Random-effect model
Zhu et al. (29)	1.09	0.84	1.41	0.41	0%*	$P = 0.52$	Fixed-effect model
Garcia et al. (25)	0.9	0.58	1.39	0.08	56%	$P = 0.64$	Random-effect model
Wickham et al. (18)	0.78	0.55	1.08	0.42	0%*	$P = 0.14$	Fixed-effect model

**Heterogeneity decreased after a particular study was omitted.*

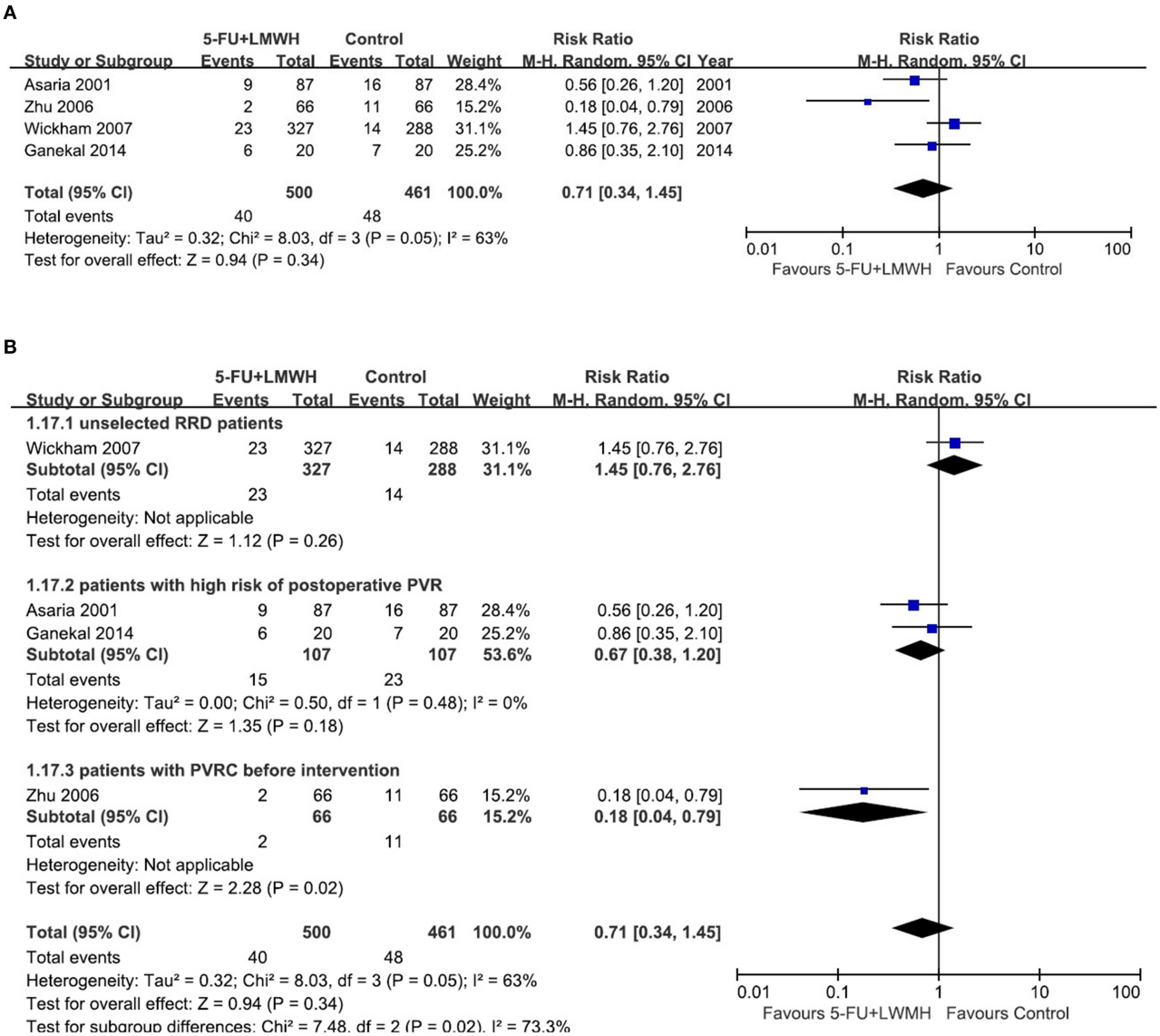

FIGURE 7 | Forest plots for the meta-analysis of the number of vitreoretinal reoperations due to postoperative PVR. **(A)** Overall meta-analysis; **(B)** Subgroup analysis according to preoperative PVRC ratio.

Number of Vitreoretinal Reoperations Due to Postoperative PVR

This outcome was reported in four studies (16, 18, 24, 29). Our meta-analysis demonstrated that 5-FU and LMWH had no effect on reducing the number of vitreoretinal reoperations due to postoperative PVR (pooled RR = 0.71, 95% CI = 0.34, 1.45, $P = 0.34$, $I^2 = 63\%$) (**Figure 7A**). However, in the subgroup analysis, the treatment efficacy was significant in the subgroup of patients with PVRC before intervention ($P = 0.02$, favors 5-FU and LMWH) (**Figure 7B**). Nevertheless, there was only one study included in this subgroup. Other subgroup analyses neither reduced heterogeneity nor changed the overall effect of 5-FU and LMWH (**Supplementary Figure 4**). In the sensitivity analysis, the omission of Zhu (2006) (29) or Wickham (2007) (18) decreased the heterogeneity. In addition, when Wickham (2007) (18) was omitted, the overall effect of the treatment changed ($P = 0.01$). A significant effect of combined 5-FU and LMWH on reducing the number of vitreoretinal reoperations due to postoperative PVR was observed in the remaining 3 studies (**Table 6**, **Figure 8**).

Visual Acuity

Methods of describing visual acuity (VA) varied among studies. Two studies classified the change of VA into "no change, better or worse" (16, 25), two sorted the VA before and after surgery into several extents (for example, CF to 0.02, 0.03–0.09, 0.1–0.2) (24, 29), and the other two presented the mean logMAR VA

TABLE 6 | Sensitivity analysis for additional outcome: number of vitreoretinal reoperations due to postoperative PVR.

Omitted study	RR	95% CI		P of chi-square	I^2	Overall effect	Selected model
None	0.71	0.34	1.45	0.05	63%	$P = 0.34$	random-effect model
Asaria et al. (16)	0.73	0.27	2	0.04	70%	$P = 0.54$	random-effect model
Zhu et al. (29)	0.96	0.63	1.48	0.17	43%*	$P = 0.87$	fixed-effect model
Wickham et al. (18)	0.5	0.29	0.85	0.19	39%*	$P = 0.01$**	fixed-effect model
Ganekal and Dorairaj (24)	0.62	0.22	1.74	0.02	75%	$P = 0.37$	random-effect model

Heterogeneity decreased after a particular study was omitted.
***Overall effect changed when a particular study was omitted.*

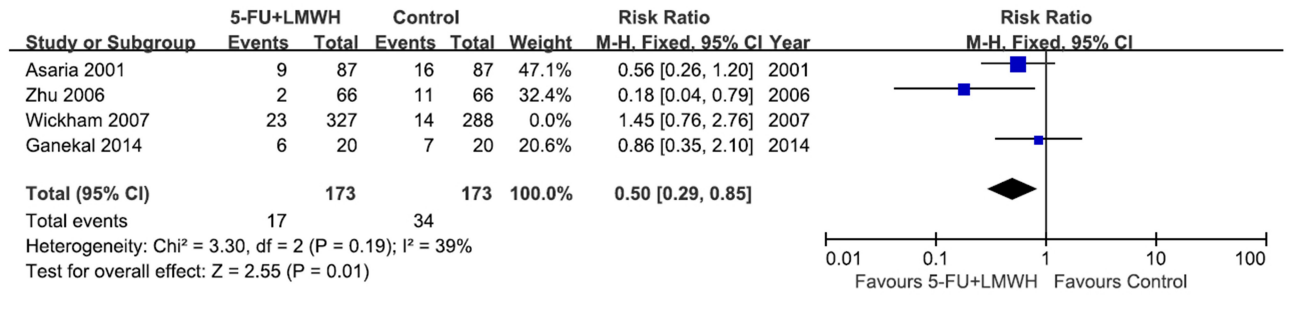

FIGURE 8 | Forest plot for the meta-analysis of the number of vitreoretinal reoperations due to postoperative PVR when the study Wickham 2007 was omitted.

with or without the interquartile range (17, 18). In general, no significant difference in VA change was reported between 5-FU and LWMH group and control group (**Supplementary Table 1**). It should be noted that one study reported a significant decrease in VA in the 5-FU and LMWH treatment groups in macular-sparing RD patients, and authors ascribed this result to the retinal toxicity of 5-FU (18).

Complications

Perioperative and postoperative complications were reported in four studies (16–18, 24). No specific complications were ascribed to the combined use of 5-FU and LMWH, as summarized in **Supplementary Table 2**, except one study (18) that had suspected the retinal toxicity of the treatment, as mentioned above.

Publication Bias

Funnel plots of the meta-analyses for all four outcomes were shown in **Figure 9**. The plots were symmetric on visual inspection, indicative of small publication bias.

DISCUSSION

The formation of PVR after retinal reattachment surgery is a frustrating event to retinal surgeons. In the past two decades, various drugs including steroids (32), methotrexate (8, 33), isotretinoin (7), and anti-VEGF reagents (9) have been tested in clinical trials to prevent postoperative PVR. However, none of them was routinely used in patients with RD due to the uncertainty of efficacy and possible retinal toxicity. In the current meta-analysis, we integrated data from four RCTs and two NRSI. We found that combined intraoperative infusion of 5-FU and LMWH neither increased primary success of vitrectomy at 6 months nor reduced the number of patients that underwent vitreoretinal reoperations. Subgroup analyses revealed the preoperative PVRC ratio to be the major source of heterogeneity. However, in none of these subgroups, the overall effect of the conjunct therapy was significant. Sensitivity analyses demonstrated Zhu (2006) (29) and Wickham (2007) (18) to be the potential source of heterogeneity. Nevertheless, the omission of either study did not change the overall conclusion, indicating that our meta-analyses for these two outcomes were quite reliable.

On the other hand, concerning whether the 5-FU and LMWH treatment reduced postoperative PVR, or decreased the number of vitreoretinal reoperations due to postoperative PVR, our meta-analyses were not stable. For both outcomes, in the subgroup of patients with PVRC before the intervention, the results significantly favored the conjunct therapy group. We have to take this result cautiously because there was only one study (Zhu 2006) in this subgroup. Moreover, in the sensitivity analyses for these two outcomes, the omission of Wickham (2007) (18) changed the overall conclusion and favored the conjunct therapy. Wickham (2007) (18) was a well-designed high-quality RCT. Nevertheless, it was the only study that included unselected RRD patients, with the preoperative PVRC ratio of 1.8% (treatment) and 3.7% (control), which was far lower than other included studies. This may account for the different effects of the conjunct therapy in this RCT compared with other studies. It is noteworthy that the determination of

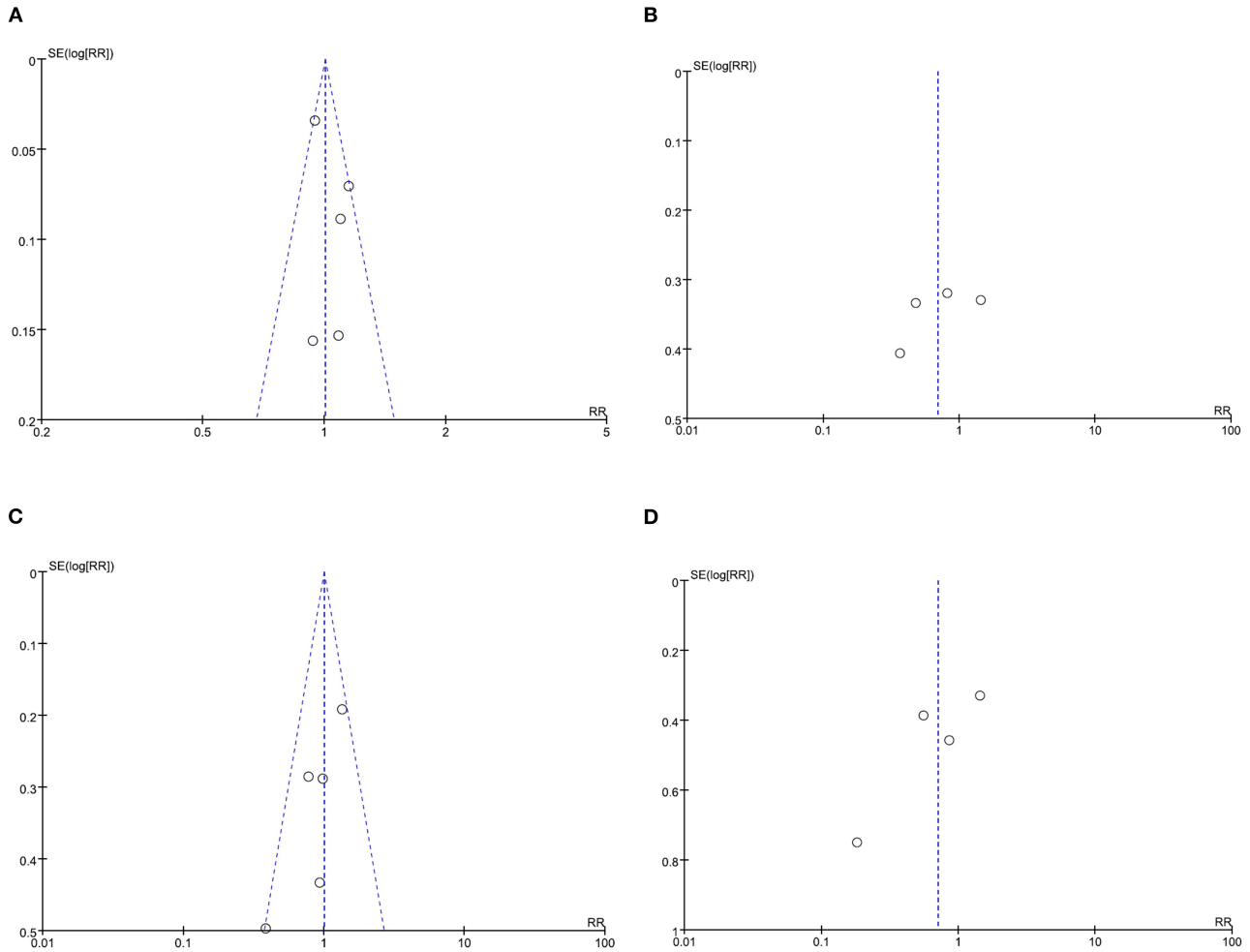

FIGURE 9 | Funnel plots demonstrate the publication bias. **(A)** Funnel plot for the outcome primary success at 6 months; **(B)** Funnel plot for the outcome postoperative PVR occurrence; **(C)** Funnel plot for the outcome number of patients who underwent vitreoretinal reoperations; **(D)** Funnel plot for the outcome number of vitreoretinal reoperations due to postoperative PVR.

PVR is subjective, and the judgment may vary among observers. In studies where concealment was not performed (24, 25, 29), the risk of bias in the measurement of postoperative PVR occurrence would be relatively high. In our meta-analyses, when Wickham (2007) (18) was omitted, pooled data from the three remaining studies (16, 24, 29) indicated that the 5-FU and LMWH treatment reduced the postoperative PVR and decreased the number of reoperations caused by postoperative PVR in patients with a high risk of PVR and patients with PVRC before intervention. However, more studies are needed in the future to verify these results. The preoperative risk factors associated with the failure of vitrectomy for RRD include choroidal detachment, hypotony, four detached quadrants, giant retinal breaks (34), previous lens extraction, and preoperative PVRC (26). On the other hand, the commonest cause of failure of vitrectomy for RRD includes missed retinal breaks and postoperative PVR (35). It is possible that although postoperative PVR was inhibited by 5-FU and LMWH treatment in certain participants, the overall primary success of vitrectomy for RRD was not improved, as PVR occurrence was not the only cause of failure of vitrectomy.

In the literature search process, we noticed a registered study at clinicaltrial.gov (NCT 02834559). The protocol of this study was published in 2018 (36). This was a multicenter RCT approaching the effect of 5-FU and LMWH treatment on the postoperative occurrence of PVRC in primary RRD patients at high risk of PVR. Instead of subjective judgment of the grade of preoperative PVR, this study assessed PVR risk by aqueous flare measurement using laser flare photometry (36). The study results have not been published yet. We contacted the principal investigator, Dr. Schaub, and were told that the study data were still under evaluation. However, in a recent publication, Dr. Schaub implied that 5-FU and LWMH therapy may not be beneficial in this registered trial (37). The details of this study in later publications will add up to our understanding in this field.

Eyes with retinal detachment may retain fair visual acuity after retinal reattachment surgery, especially when the macular is spared. One of our included studies (18) reported a significant reduction of VA in the 5-FU and LMWH treatment group in macular-sparing RD. This was not seen in the other five studies (16, 17, 24, 25, 29) probably because these studies included patients at high risk of PVR and patients with PVRC before intervention. The general poor VA before and after surgery in these patients might mask the possible harmful effect of the conjunct therapy on the retina. LMWH has not been reported to have toxicity to the retina. However, a high dose of 5-FU showed retinal toxicity in animal models. Stern et al. reported that injection of 1.25 mg fluorouracil every 12 h for 4 days and then every 24 h for 3 days had caused an irreversible decrease in electroretinographic b-wave in vitrectomized New Zealand albino rabbits, while injection of 0.5mg fluorouracil daily for 7 days was well-tolerated in the rabbit eye (38). In all our included studies, the 5-FU infusion concentration was 200 μg/ml, which was lower than the harmless dose in animal experiments (assume the eyeball volume of rabbits to be 2.2 ml, 0.5 mg in the eyeball would be 227 μg/ml). Also, the exposure time in all the included studies was far shorter compared with 7 days. Theoretically, 200 μg/ml of 5-FU infusion was a safe dose. However, animal studies may not be comparable to clinical trials. Moreover, in vitrectomy for RRD patients, the 5-FU and LMWH infusion not only works in the vitreous cavity as in animal studies but also goes into the subretinal space through the retina tear and acts directly on the RPE and photoreceptor outer segments, which may cause extra injury to the retina. Based on all these pieces of evidence, the 5-FU and LMWH intraoperative infusion should not be used in RD patients with potential good VA.

Our meta-analysis has limitations. First, the three high-quality RCTs were conducted fully or partially in the same center (Moorfields eye hospital, London), and this would bring about selection bias. Second, the limited number of studies and the difference in participants contributed to the unstableness of the meta-analyses for two outcomes (postoperative PVR occurrence, and a number of vitreoretinal reoperations due to PVR). The positive results ($P < 0.05$) from a one-study subgroup or after a particular study was omitted need to be taken with caution. More studies in patients at high risk of PVR and patients with PVRC before intervention are needed to confirm these results.

In conclusion, our study demonstrated that the intraoperative infusion of combined 5-FU and LMWH was not effective in improving the primary success of vitrectomy for RRD or in reducing the number of patients who underwent vitreoretinal reoperations. The treatment proved beneficial in reducing postoperative PVR in patients with PVRC before the intervention, however, more studies are needed to confirm this result. Based on current evidence, 5-FU and LMWH therapy should not be routinely used in vitrectomy for RRD patients, especially in patients with potential good VA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CC conceived the study, performed literature search, quality assessment, data extraction and meta-analysis, and participated in paper writing. PC performed the literature search, quality assessment, data extraction, and participated in meta-analysis and paper writing. XL participated in quality assessment and paper writing. HL conceived the study, interpreted the data, wrote the paper, and helped in quality assessment and data extraction. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.790460/full#supplementary-material

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Randomized Controlled Trial Comparing 1-Year Outcomes of Low-Energy Femtosecond Laser-Assisted Cataract Surgery versus Conventional Phacoemulsification

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Purpose: To compare 1-year clinical outcomes, phacoemulsification energy, aqueous profiles, and patient-reported outcomes of low-energy femtosecond laser-assisted cataract surgery (FLACS) vs. conventional phacoemulsification.

Methods: The study is a randomized controlled trial (RCT) with paired-eye design. Eighty-five patients were randomized to receive FLACS (Ziemer LDV Z8) in one eye and conventional phacoemulsification in the fellow eye. Clinical data including phacoemulsification energy parameters (cumulative dissipated energy, phacoemulsification power, and phacoemulsification time), uncorrected and corrected distance visual acuities (UCDVA and BCDVA), manifest refraction spherical equivalent (MRSE), central corneal thickness (CCT), endothelial cell count (ECC), anterior chamber flare, and post-operative complications were obtained for 1 year. Aqueous humor was collected for the analysis of prostaglandin $(PGE)_2$, cytokines and chemokines concentrations. Patients' reported-outcomes on surgical experiences were evaluated using an in-house questionnaire.

Results: Compared to conventional phacoemulsification, the low-energy assisted FLACS group had significantly less ECC reduction at 3 months (1.5 ± 0.3% vs. 7.0 ± 2.4%; $P < 0.01$) and 1 year (8.2 ± 2.8% vs. 11.2 ± 3.6%; $P = 0.03$). There were no significant differences in the phacoemulsification energy parameters, UCDVA, BCDVA, MRSE, CCT, occurrence of post-operative complications between the 2 groups throughout post-operative 1 year. Patients' subjective surgical experiences, including the surgical duration and perceived inconvenience, were comparable between the 2 groups. FLACS resulted in significantly higher aqueous PGE_2 ($P < 0.01$), interleukin (IL)-6 ($P = 0.03$), IL-8 ($P = 0.03$), and interferon (IFN)-γ ($P = 0.04$) concentrations and greater anterior chamber flare at 1 day ($P = 0.02$).

Conclusions: Our RCT presented 1-year longitudinal clinical and laboratory data. The long-term ECC result was more favorable in low-energy FLACS. The rest of the intraoperative and post-operative outcomes, as well as patient-reported outcomes, were comparable between these two procedures.

Keywords: low-energy femtosecond laser-assisted cataract surgery, conventional phacoemulsification, randomized controlled trial, aqueous profiles, patient-reported outcomes, clinical outcomes

INTRODUCTION

Femtosecond laser-assisted cataract surgery (FLACS) has been shown to be a safe and effective procedure (1), and increasingly being incorporated into surgical practice. Since its introduction in 2010 (2), numerous studies have been conducted to compare the clinical outcomes with those of conventional phacoemulsification. These results, however, were mainly from observational cohort studies and were not randomized controlled trials. Current published RCTs reported only limited post-operative outcomes, and the duration of follow-up was short (mostly 3 months) (3–8). Long-term RCTs with a paired-eye design, which is the most valid way of comparing FLACS and conventional phacoemulsification, are currently limited. Furthermore, literature on patient-reported outcomes mainly focus on the visual quality or quality of life following FLACS, but reports on surgical experiences in FLACS are lacking. As a concern of FLACS is the high cost, understanding patients' subjective surgical experiences, on top of visual quality, may provide another perspective for surgeons' consideration when deciding the choice of surgical procedure.

Among the five commercially available laser platforms, the Femto LDV Z8 (Ziemer Ophthalmic Systems AG, Port, Switzerland) delivers the laser spots in small spot size, and has a high numerical aperture as well as a low energy range [nanojoules (nJ) per pulse] with high frequency (9, 10). These characteristics may provide advantages of better precision of the laser cutting and reduction in the extent of collateral tissue damage (11). In addition, as the Femto LDV Z8 laser system is mobile and has the smallest footprint compared to the other femtosecond laser platforms, the procedure can be completed in the same operating table. This thus effectively overcomes the logistic difficulties in patient transfer, which is encountered with other laser systems and can slow down the patient flow. Studies on the clinical outcomes of low-energy FLACS are limited, and they have been limited to short-term reports or with limited clinical assessments (12). Three-months post-operative changes of central corneal thickness (CCT), endothelial cell count (ECC), and aqueous flare levels were reported when the low-energy system was introduced (12). However, a comparative conventional surgery arm was not included in that study. In another study, Pajic et al. presented that the 3-months visual and refractive outcomes in low-energy FLACS were comparable to those in conventional phacoemulsification (13). However, no other clinical parameters were further assessed.

It has been shown that the aqueous prostaglandin (PGE) level was significantly higher in FLACS than conventional phacoemulsification (1, 14, 15), and this PGE rise is a causative factor for intraoperative miosis (14, 16). Unlike the findings in many FLACS studies using high-energy systems in which significant intraoperative miosis was noted (17–20), two recent studies reported that there were no statistically significant changes between pre-operative and post-laser pupil areas following low-energy FLACS (21, 22). This may imply that the low-energy system offers the advantages of inducing less tissue reaction and less resultant PGE_2 release. Analysis of aqueous humor would allow us to understand more about how the low-energy system affects the breakdown of blood-aqueous barrier at a molecular level.

Phacoemulsification energy utilized during the surgery is another parameter that affects post-operative outcomes. Studies comparing phacoemulsification energy parameters in FLACS to conventional phacoemulsification have demonstrated inconsistent results, although the majority of the literature showed a significant difference in favor of FLACS, with respect to the cumulative dissipated energy (CDE) and phacoemulsification time (23). Whether the low-energy system provides greater benefits in the energy profile and whether this could be a beneficial option for patients with low endothelial cell density or dense cataract, has not been studied.

In the present study, we aimed to conduct a RCT with a paired-eye design to compare low-energy FLACS and conventional phacoemulsification in the same patient, with the main advantage of being that the outcomes were assessed with the elimination of inter-subject bias. The comprehensive data, covering 1-year clinical outcomes, aqueous humor profiles, phacoemulsification energy, and patient-reported outcomes on surgical experiences, were collected and compared.

METHODS

Study Designs and Patients

This study was a registered RCT (NCT03351894) in which we recruited 85 patients with bilateral cataracts from December 2017 to November 2019. The inclusion and exclusion criteria are listed in **Supplementary Table 1**. Approval for the study was granted by the institutional review board of SingHealth, Singapore (Number: 2015/2565), and the study was conducted in accordance to the Declaration of Helsinki. The randomization was performed using random allocation cards from computer-generated random numbers and allocated patients to each treatment group. Each patient underwent either conventional phacoemulsification or FLACS in the right eye, followed by

FLACS or conventional surgery in the left eye, which was operated 3–4 weeks apart from the surgery of the right eye.

FLACS and Phacoemulsification Procedure

All patients were prescribed 0.5% preservative-free cyclopentolate hydrochloride and 0.5% levofloxacin eye drops four times daily 1 day before surgery. Mydriasis was maintained with 0.5% tropicamide and 2.5% phenylepherine hydrochloride eye drops instilled three times within 1 h prior to surgery. All procedures were performed under local anesthesia with sedation.

The FLACS procedure was performed with the LDV Z8 system. The suction interface was filled up with balanced salt solution to create a fluid-patient interface. The hand-piece of the articulating arm was docked on the interface angled at -10° over (10). Laser pre-treatment started with an anterior capsulotomy with a pre-set diameter of 5.0 mm at 90% energy, followed by lens fragmentation with a 6-sector pie-cut pattern at 100% energy, and then a 2.6 mm corneal incision. Within 5 min of the completion of laser pre-treatment, ∼150 μL of aqueous humor was collected through a limbal paracentesis using a 30-gauge needle. Standard phacoemulsification and intraocular lens insertion were then performed. For the conventional phacoemulsification group, aqueous humor was collected in an identical way as that for the FLACS group. All aqueous samples were immediately transferred on dry ice to a laboratory, and the supernatants were stored at -80°C until analysis. The surgery, in both FLACS and conventional phacoemulsification groups, was performed with the same phacoemulsification machine (Infiniti Vision Ozil system, Alcon Laboratories, Inc., Fort, Worth, TX), with the same model of intraocular lens implantation (SA60AT, Alcon). The surgery was performed by 2 consultant-grade cataract surgeons (J.S.M and H.S.O). At the end of the surgery, the CDE, phacoemulsification power, and phacoemulsification time were recorded. All patients were given 0.5% levofloxacin and preservative-free dexamethasone eye drops 3 h for a week starting from the next day of surgery, and then tapered until 2 times daily over 4 weeks.

The pupil diameter and area were measured before and after laser treatment for the FLACS group, using the images with the same magnification captured from surgical videos and ImageJ software. The actual pupil area was calculated by using the following proportional formula: Actual pupil area (mm^2) = (Video pupil area)/(Video capsulotomy area) × π (Set capsulotomy diameter/2)^2.

Clinical Evaluation and Patient-Reported Outcomes on Surgical Experiences

Patient data collected included patient's age, gender, lens density assessed using the software Pentacam Nucleus Staging (PNS), uncorrected and best-corrected distance visual acuities (UCDVA and BCDVA) in logarithm of the minimum angle of resolution (logMAR) values, manifest refraction spherical equivalent (MRSE), CCT (Visante, Carl Zeiss, Dublin CA, USA), ECC (EB-10 specular microscopy, Konan Medical, Inc., Irvine, CA), and aqueous flare levels (flare meter, FM-600, Kowa, CA, USA). These assessments were performed at different study time points (**Supplementary Table 2**) over the study period of 1 year. For the ECC measurement, the central ECC was measured for 3 times using a fixed-frame method of cell counting, marking at least 100 cells per image by an experienced technician (24). The average was used for statistical analysis. Intraoperative and post-operative complications were also recorded. Patients' subjective pre-, peri-, and post-surgical experiences were evaluated 1 day after surgery by using an in-house 7-item questionnaire on a 10-point scale. The items included nervousness and confidence in the procedure, intraoperative discomfort, post-operative pain, visual satisfaction, and subjective feeling about the surgical duration and inconvenience.

Aqueous Analysis

The concentration of PGE_2 was analyzed using enzyme-linked immunosorbent assay (ELISA) kits (Cayman Chemical Co.). An immunoassay kit (Procartaplex Human Cytokine/Chemokine/Growth Factor Panel 1, Thermo Fisher Scientific, Inc.) was used to measure 45 cytokines, chemokines, and growth factors.

Statistical Analysis

The sample size was calculated using the results of the first six patients and CDE as the primary outcome, with a paired-eye design, power of 80%, significance level of 5%, and non-inferiority margin of 10%. The sample size of 77 patients was required to confirm the differences in the CDE between the FLACS and conventional phacoemulsification groups (CDE = 20.2 ± 5.8 and 22.8 ± 5.6 s, respectively, for the first 6 patients). Considering a 10% lost follow-up rate, we therefore recruited 85 patients. A paired-*t* test was used to compare the values between the FLACS and conventional phacoemulsification groups. Repeated–measures ANOVA and *post-hoc* tests were used to analyze the data of different follow-up visits. The correlation between the aqueous PGE_2 level and pupil area, as well as between the aqueous cytokines/chemokines/growth factors and post-operative aqueous flare level, was assessed with a Pearson correlation test. Each item of the patients' reported outcome scale was assessed individually. All data were expressed as mean ± standard deviation, and *P*-values < 0.05 were considered statistically significant (STATA; STATACrop, College Station, TX).

RESULTS

The mean patient age was 69.5 ± 6.8 years (female: male = 37:48). There were 4 patients who were lost the follow up during the 1-year study period due to COVID-19 pandemic (CONSORT diagram; **Supplementary Figure 1**).

Clinical Outcomes

The PNS grade was comparable between the FLACS (1.9 ± 1.0) and conventional phacoemulsification (2.0 ± 0.9) groups ($P = 0.88$), and there were no differences in the phacoemulsification energy parameters between 2 procedures. The mean CDE was 20.3 ± 6.7 and 21.2 ± 6.0 s ($P = 0.82$), phacoemulsification power was 30.1 ± 9.2% and 31.8 ± 10.5% ($P = 0.63$), and phacoemulsification time was 8.2 ± 3.0 and 9.3 ± 3.3 s

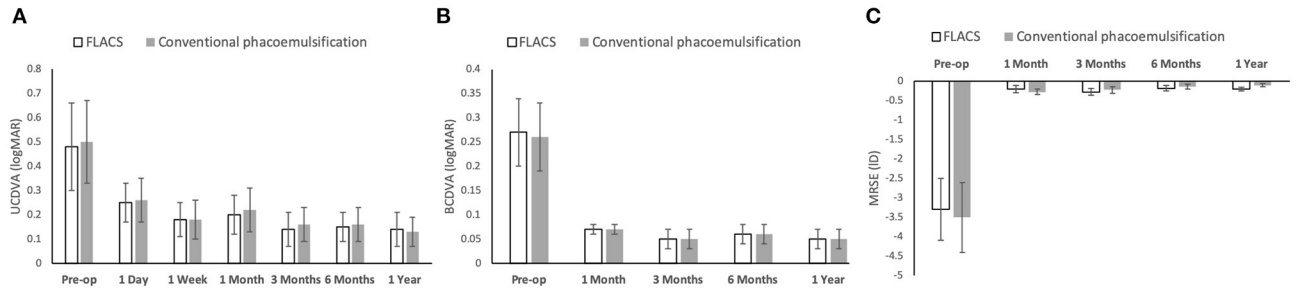

FIGURE 1 | Bar graph showing the visual and refractive outcomes following FLACS and conventional phacoemulsification over the study period of 1 year. There was no significant difference in the UCDVA **(A)**, BCDVA **(B)**, and MRSE **(C)** between the two groups at all the post-operative time points. Error bars indicate standard deviation.

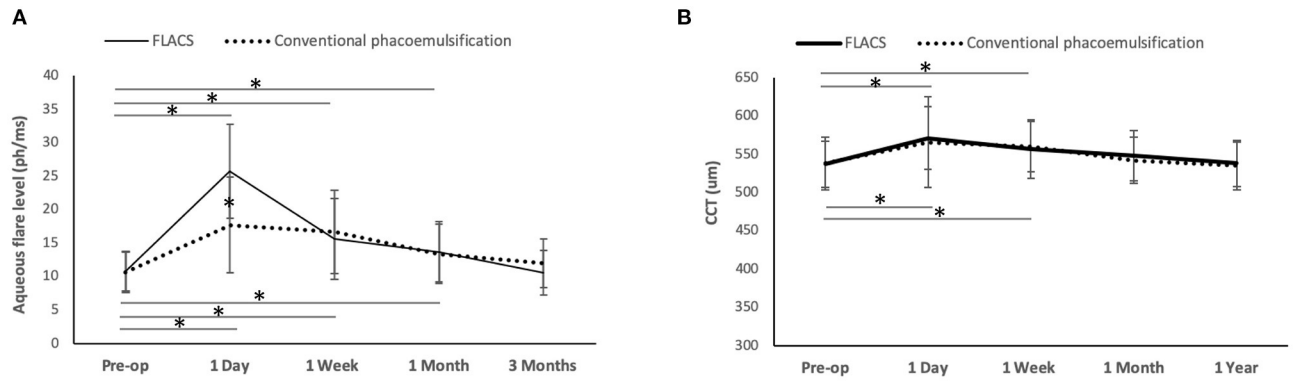

FIGURE 2 | Line graph showing the changes of aqueous flare levels and CCT after FLACS and conventional phacoemulsification. The flare levels significantly increased for one month post-operatively in both groups, and eyes underwent FLACS had significantly greater aqueous flare level than those underwent conventional phacoemulsification at day 1 **(A)**. The CCT increased significantly at 1 day and 1 week, regardless of the group. There was no significant difference between the two groups in the CCT at all the time points **(B)**. Error bars indicate standard deviation. *$P < 0.05$.

($P = 0.47$), for the FLACS and conventional procedures, respectively. For the FLACS group, the mean pupil area significantly reduced after laser pre-treatment, from 40.5 ± 8.9 to 32.5 ± 10.4 mm^2 ($P = 0.03$).

There were no intraoperative complications. Clinically cystoid macular edema (CME) was observed in 2 eyes in the conventional group (2.4%) and in 1 eye (1.2%) in the FLACS group ($P = 0.56$), occurring during 1–3 months post-operatively. As CME affected the BCDVA and UCDVA assessments, and the treatment with topical non-steroidal anti-inflammatory drug (NSAID) interfered with the aqueous flare level, these 3 subjects were excluded from the statistical analysis.

The pre-operative mean BCDVA and MRSE were comparable between the 2 groups ($P = 0.69$ and $P = 0.56$). We did not observe significant differences in the mean post-operative UCDVA, BCDVA and MRSE at all time points (**Figures 1A–C**; $P > 0.05$ for all time points). The BCDVA at 1 year was 0.05 ± 0.01 logMAR and 0.05 ± 0.01 logMAR, and the MRSE at 1 year was -0.20 ± 0.05 and -0.10 ± 0.04 diopters (D) for the FLACS and conventional groups ($P = 0.91$ and $P = 0.33$, respectively). Five and four eyes developed mild posterior capsule opacification (PCO) in the FLACS and conventional groups, respectively (6.4 and 5.1%; $P = 0.73$).

A significant increase of aqueous flare levels was observed after surgery for 1 month in both FLACS and conventional groups (day 1: $P < 0.001$ and $P < 0.001$; week 1: $P = 0.018$ and $P = 0.023$; month 1: $P = 0.039$ and $P = 0.028$ for the FLACS and conventional groups, respectively, when comparing to pre-operative levels). Eyes with FLACS treatment had significantly greater aqueous flare levels than eyes with conventional surgery at day 1 (25.7 ± 11.4 vs. 17.7 ± 9.2 ph/ms; $P = 0.02$), but no significant difference was noted thereafter (**Figure 2A**).

The CCT significantly increased for 1 week post-operatively regardless of groups (day 1: $P = 0.011$ and $P = 0.016$; week 1: $P = 0.029$ and $P = 0.026$ for the FLACS and conventional phacoemulsification groups, respectively, when comparing to pre-operative values). The difference in the CCT between the 2 groups was not significant throughout the study period of 1 year (**Figure 2B**). The absolute ECC value was comparable between the 2 groups at all time points. However, when evaluating the percentage of changes in ECC after surgery, the conventional group had significant ECC reduction at 1 year ($11.2 \pm 3.6\%$ decrease; $P = 0.012$ when comparing

TABLE 1 | Post-operative ECC changes in 2 groups over 1-year period.

ECC (% of decrease from pre-op level)	Pre-op	3 Months	6 Months	1 Year
FLACS	2,622 ± 315	2,583 ± 624 (1.5 ± 0.3%)	2,434 ± 448 (7.2 ± 1.9%)	2,406 ± 486 (8.2 ± 2.8%)
Conventional phacoemulsification	2,649 ± 419	2,462 ± 589 (7.0 ± 2.4%)	2,433 ± 532 (8.2 ± 2.6%)	2,353 ±4 16 (11.2 ± 3.6%)
P-value*		**<0.01**	0.26	**0.03**

**Comparison of the % of decrease between 2 groups.*
Bold values mean significant P values.

TABLE 2 | Scores of the patients' subjective pre-, peri-, and post-surgical experiences in the two groups.

Question	FLACS	Conventional phacoemulsification	*P*-value
How nervous were you for the surgery? (1: least; 10: most)	3.1 ± 1.8	2.5 ± 1.5	0.34
How much discomfort did you experience during the surgery? (1: least; 10: most)	2.1 ± 0.8	1.2 ± 0.7	0.05
How much confidence did you have in the surgery? (1: least; 10: most)	8.5 ± 1.4	8.6 ± 1.5	0.85
How long did you feel the surgery take? (1: quickest; 10: longest)	7.0 ± 2.2	6.7 ± 1.8	0.46
How much pain did you experience after the surgery? (1: least; 10: most)	1.9 ± 0.9	1.5 ± 0.7	0.37
How satisfied are you with the visual outcome after the surgery? (1: least; 10: most)	8.0 ± 1.4	8.4 ± 1.2	0.13
Please rate the convenience or inconvenience of the overall surgical procedure? (0: inconvenient; 10:convenient)	8.1 ± 1.8	8.5 ± 1.7	0.23

to the pre-operative level), while the ECC change was not statistically significant in the FLACS group (8.2 ± 2.8% decrease; $P = 0.08$ when comparing to the pre-operative level). At 3 months and 1 year, eyes that underwent FLACS presented with significantly less post-operative ECC changes than eyes that underwent conventional phacoemulsification ($P < 0.01$ and $P = 0.03$, respectively; **Table 1**).

For patient-reported outcomes on surgical experiences, no significant difference was shown between the 2 groups for the post-operative pain, confidence in the procedure, visual satisfaction, nervousness, and subjective feeling about the surgical duration and inconvenience, although the discomfort experienced during the surgery was borderline significantly greater in the FLACS than in the conventional group ($P = 0.05$; **Table 2**).

Aqueous Analysis

The FLACS group had a significantly higher aqueous PGE_2 level than conventional phacoemulsification (62.2 ± 22.4 vs. 23.8 ± 11.7 pg/mL; $P < 0.01$). FLACS also resulted in significantly higher aqueous interleukin (IL)-6 (13.6 ± 3.8 vs. 5.5 ± 2.8 pg/mL; $P = 0.03$), IL-8 (13.4 ± 4.8 vs. 5.5 ± 1.6 pg/mL; $P = 0.03$), and interferon (IFN)-γ (6.8 ± 1.9 vs. 0.3 ± 0.1 pg/mL; $P = 0.04$) concentrations. There was no significant difference between the 2 groups for the rest of the analytes (**Table 3**). The percentages of change in pupil area had moderate, significant and negative correlation with the aqueous PGE_2 levels ($r = -0.61$; $P = 0.02$). We did not observe significant correlation between the significantly increased analytes (PGE_2, IL-6, IL-8, and IFN-γ) and anterior chamber flare level at all time points (all $P > 0.05$).

DISCUSSION

Through a paired-eye RCT, we present comprehensive data on 1-year outcomes, including clinical results, phacoemulsification energy data, aqueous profiles, and patient-reported outcomes, in low-energy FLACS in comparison with conventional phacoemulsification. The strength of this study is the randomized trial design, as well as the use of data of paired eyes from the same patient, providing a more accurate assessment by minimizing inter-eye and inter-individual variations as well as selection bias. The visual, refractive and patient-reported outcomes on surgical experiences were comparable between these two procedures, although FLACS was associated with significantly higher degree of anterior chamber inflammation on the first day post-operatively. The ECC loss at 1 year was significantly less in low-energy FLACS. Similar to other FLACS laser platforms, there was significant release of PGE_2 and several pro-inflammatory cytokines such as IL-6, IL-8 and IFN-γ, in the aqueous.

The post-operative CCT significantly increased for 1 week regardless of the groups, with no significant differences between the 2 groups in the CCT and absolute ECC values throughout the 1-year study period. But it was observed that the FLACS group had significantly less ECC loss than conventional surgery at 1 year (8.2 vs. 11.2%). This finding is consistent with a retrospective observational study showing that the ECC loss was 12.4% and 18.1% for the low-energy FLACS vs. conventional bimanual microincision cataract surgery at 18 months post-operatively (25). The more favorable impact of FLACS on post-operative ECC change has been reported in the literature regardless of the femtosecond laser system used (1, 26), suggesting the protective effects of FLACS for those who are susceptible to intraoperative

TABLE 3 | Aqueous humor concentrations of cytokines, chemokines and growth factors.

	Conventional phacoemulsification	FLACS	*P*-value
Cytokines **(pg/mL)**			
IL-1 α	0.1 ± 0.06	1.1 ± 0.8	0.48
IL-1 β	0.8 ± 0.5	0.8 ± 0.4	0.82
IL-1RA	532.4 ± 299.8	988.3 ± 684.3	0.36
IL-4	0.2 ± 0.2	0.9 ± 0.7	0.33
IL-5	1.4 ± 0.8	1.8 ± 1.0	0.62
IL-6	5.5 ± 2.8	13.6 ± 3.8	**0.03**
IL-7	325.7 ± 112.1	333.6 ± 172.7	0.78
IL-8	5.5 ± 1.6	13.4 ± 4.8	**0.03**
IL-9	2.5 ± 1.9	12.5 ± 10.2	0.26
IL-10	0.04 ± 0.02	0.07 ± 0.04	0.60
IL-18	1.8 ± 0.8	2.0 ± 0.9	0.76
IL-21	3.4 ± 2.8	10.0 ± 8.2	0.27
IL-22	96.6 ± 55.8	109.6 ± 76.1	0.66
IL-23	0.8 ± 0.5	8.2 ± 5.5	0.10
IL-27	10.5 ± 6.4	12.8 ± 8.5	0.79
IL-31	11.9 ± 7.9	16.0 ± 10.5	0.31
IFN-α	0.3 ± 0.2	0.4 ± 0.2	0.87
IFN-γ	0.3 ± 0.1	6.8 ± 1.9	**0.04**
LIF	6.0 ± 3.8	6.9 ± 4.5	0.79
BDNF	0.9 ± 0.3	0.7 ± 0.3	0.88
TNF-α	0.2 ± 0.2	0.8 ± 0.5	0.79
Chemokines **(pg/mL)**			
Eotaxin	4.5 ± 2.5	4.2 ± 2.0	0.82
SCF	4.9 ± 3.0	5.5 ± 2.8	0.77
GRO-α	15.5 ± 9.9	18.6 ± 12.8	0.46
IP-10	234.6 ± 142.7	356.5 ± 246.6	0.32
MIP-α	35.2 ± 28.1	33.0 ± 25.0	0.83
MIP-1β	52.6 ± 30.1	55.3 ± 29.3	0.62
MCP-1	3,755.9 ± 1,265.3	4,131.6 ± 2,521.8	0.44
RANTES	36.9 ± 22.0	42.7 ± 25.8	0.50
SDF-α	1,622.8 ± 993.4	1,823.5 ± 1,043.2	0.39
Growth factors **(pg/mL)**			
EGF	1.1 ± 0.6	2.0 ± 1.4	0.39
VEGF-α	1,572.7 ± 692.4	1,625.3 ± 1,043.8	0.68
VEGF-D	0.4 ± 0.3	0.5 ± 0.3	0.90
FGF-2	1,896.9 ± 1,043.7	1,922.4 ± 943.7	0.45
HGF	432.8 ± 289.1	475.3 ± 175.9	0.22
PIGF-1	5.5 ± 1.8	7.9 ± 3.2	0.20
PDGF-BB	17.5 ± 7.0	25.8 ± 16.1	0.41

SCF, stem cell factor; GRO, growth-regulated oncogene; IP, interferon-inducible protein; MCP, monocyte chemoattractant protein; SDF, stromal cell-derived factor; HGF, hepatocyte growth factor; PIGF, placental growth factor.
Bold values mean significant P values.

and post-operative ECC loss. Future studies may include the comparisons of ECC changes between low-energy and high-energy systems to elucidate this further. With respect to visual and refractive outcomes, meta-analyses have demonstrated that these two procedures are equivalent (1, 27), and this was also seen in the present study.

Studies comparing phacoemulsification energy parameters in high-energy FLACS vs. conventional phacoemulsification have demonstrated inconsistent results. The heterogeneous results in the energy profiles (CDE and phacoemulsification time) in previously published studies may result from the disparity in the patient selection, laser platform used, surgical techniques, and the calculation formula used in different phacoemulsification machines (1, 28). However, a recent systematic review showed significant differences in favor of FLACS in terms of the CDE and effective phacoemulsification time (23). At present, there is only one study published on the comparison of phacoemulsification energy between the low-energy FLACS and conventional surgery, and the authors reported significantly lower effective phacoemulsification time in FLACS (13). We did not observe such differences in the CDE, phacoemulsification power and phacoemulsification time in our study, and it may be due to several reasons. Firstly, the above-mentioned study was not conducted in a contralateral eye design, and the variability in the cataract density in different individuals recruited in 2 groups might have introduced bias. Secondly, the cataract severity in our cohort was relatively mild (mean PNS grade = 1.9 and 2.0 for the FLACS and conventional groups). Ang et al. evaluated the differences in the CDE in FLACS vs. conventional phacoemulsification stratified by the Lens Opacities Classification System III grading, and significant differences in the CDE were only seen for patients with nuclear opalescence grade 4, but not for those with less than grade 4 opalescence (26). Thirdly, the majority of the surgery in the present study was performed by a senior consultant with 30-years of experience. With skillful phacoemulsification techniques, the advantages FLACS provides in ultrasound energy might be mitigated.

Unlike other studies that focused on the visual quality and quality of life in the patient-reported outcomes assessment, our study focuses on patient-reported surgical experiences. The questionnaire was conducted on the next day after surgery to avoid recall bias. Besides objective visual outcomes, the self-reported visual outcome was also comparable between these two types of surgery (**Table 2**). Of note, there was no difference in the subjective feelings with respect to post-operative pain, surgical time, inconvenience, and confidence in the surgical procedure. The perception of surgical duration is an important parameter affecting patient post-operative satisfaction. Unlike other FLACS procedures in which patients have to be transferred to another room following the laser procedure, the Ziemer LDV is a mobile system with a small footprint that allows the surgeon to push away the laser arm and complete the surgery on the same operating table. These might explain the high convenience score in the FLACS group, and the comparable score in the surgical time in the two groups. Patients reported borderline significantly greater intraoperative discomfort when receiving FLACS, and this might come from the docking, suction and laser pre-treatment steps, which lasted for ∼3.2 min. However, the discomfort score was low for both of the procedures (2.1 ± 0.8 vs. 1.2 ± 0.7 for the FLACS and conventional phacoemulsification groups, respectively).

Significant reduction in the pupil area was observed in the present study, while unchanged pupil size was reported in two

previous studies in which the low-energy system and no pre-operative NSAID were used (21, 22). However, those studies were conducted with fewer patient numbers and might be underpowered. Moreover, our FLACS procedure included the creation of a corneal incision, which might also result in a PGE_2 increase. The rise in PGE_2 in FLACS has been reported to cause intraoperative miosis (14, 16, 29), and the use of pre-operative NSAID therefore has been suggested to reduce the extent and occurrence of intraoperative miosis (14, 20). Pre-operative NSAID was not prescribed in this study, as the study was initiated in 2017 when the concept of the use of NSAID in FLACS was not fully recognized. Of note, when comparing the PGE_2 level of our FLACS group with those of published studies in which a high-energy (μJ) platform and no pre-operative NSAID were used, the aqueous PGE_2 concentration was much lower with the use of the nJ-system (62.2 pg/mL vs. 377.1 to 1,911.4 pg/mL) (16, 20, 30, 31). The PGE_2 concentration reported in the present study was also lower than those reported in the studies conducted with high-energy systems and with the use of pre-operative NSAID (65.3–743.6 pg/mL) (20, 30, 31). This highlights the potential advantage of the low-energy system as the result of fewer cavitation bubbles generated during lens fragmentation and minimal collateral tissue damage on the unpigmented epithelial cell layer of the ciliary body, triggering less PGE_2 release (14, 32, 33). In our study, the correlation between the aqueous PGE_2 level and the percentage of change in pupil area was only moderate, indicating that in addition to PGE_2, other factors, such as cholinergic or antisympathetic pathway, or anatomic dynamics of the pupil (34, 35), also play a role. The release of PGE_2 intraoperatively is also a proposed etiological factor for post-operative CME (36). Meta-analysis data have shown that there was no significant difference in the incidence of CME between FLACS and conventional phacoemulsification (23), which is in alignment with our study. Nuffel et al. further evaluated the changes in the central subfield macular thickness in low-energy FLACS vs. conventional surgery and reported no statistically significant difference (37).

Even with the low energy per spot, significantly greater release of pro-inflammatory and inflammatory cytokines, such as IL-6, IL-8 and IFN-γ, was still observed in the aqueous in the FLACS group. This might result from the breakdown of blood-aqueous barrier because of the shockwave, vibrations and temperature increase when laser spots passed through the aqueous humor (33). The increased cytokines could also account for the significantly greater anterior chamber flare values in the FLACS group at post-operative day 1, as IL-6, IL-8, and IFN-γ are known pro-inflammatory cytokines (38–40). IL-6 has been shown to play a role in the development of PCO after cataract surgery (41, 42). However, we did not observe a significant difference in the incidence of PCO between the two groups. Evaluation of PCO with a more detailed PCO grading system to quantify the opacification severity may help to distinguish more in future studies. Of note, the aqueous IL-6 level in the present study (13.6 pg/mL) was lower than those reported in the literature where high-energy FLACS platforms were used, with or without NSAID (24.6–57.6 pg/mL) (15, 43). The lack of significant correlation between significantly increased analytes (PGE_2, IL-6, IL-8, and IFN-γ) and anterior chamber flare level suggests that other cytokines, in conjunction with the cellular components of inflammatory cells, collectively account for the anterior chamber reaction.

In summary, the strength of our study is the RCT with paired-eye design and relatively low lost follow-up rate (4.7%), allowing us to achieve robust data collection and comparison over 1 year. We demonstrated for the first time the comparisons of low-energy FLACS vs. conventional phacoemulsification, with respect to clinical results, phacoemulsification energy, aqueous cytokine/chemokine profiles, and patient-reported outcomes. The visual, refractive and patient-reported outcomes on surgical experiences, phacoemulsification energy, post-operative CCT, and the occurrence of CME and PCO were comparable between these two procedures. The post-operative ECC loss was in favor of low-energy FLACS. Despite low energy per laser spot, patients receiving FLACS had significantly higher aqueous PGE_2, IL-6, IL-8, and IFN-γ levels, leading to greater anterior chamber inflammation on the 1st day after surgery. Nevertheless, the increased aqueous PGE_2 and IL-6 levels were lower than those in published studies with high-energy systems. Our study findings expand the knowledge on FLACS, with a comprehensive presentation ranging from objective clinical measures and subjective patient-reported outcomes, to laboratory analysis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of SingHealth, Singapore (Number: 2015/2565). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-CL collected the data, performed the analyses, and wrote the manuscript. MS, JC, and BW performed the laboratory analysis. HO collected the data and revised the manuscript. EL and JM supervised the manuscript writing. All authors contributed to the article and approved the submitted version.

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Structural Characteristics of the Lens in Presenile Cataract

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The purpose of this work is to examine the structure of the anterior lens epithelial cells (aLECs) of presenile idiopathic cortical cataract to investigate the possible structural reasons for its development. The anterior lens capsules (aLCs: basement membrane and associated lens epithelial cells) were obtained from routine uneventful cataract surgery of 5 presenile cataract patients (16 and 41 years old women and 29, 39, and 45 years old men). None of the patients had family history of cataract, medication, or trauma and they were otherwise healthy. In addition, the patients did not have any other abnormal features in the ocular status except cataract. The aLCs were prepared for scanning electron microscopy (SEM) and transmission electron microscopy (TEM). The most prominent abnormal features observed by SEM for all 5 studied presenile cataract patients were the changes of the aLECs structure with the dents, the selective concavity of some LECs, at their apical side centrally toward the nucleus. In addition, TEM showed the thinning of the lens epithelium with the segmentally concave cells and the compressed and elongated nuclei. Abnormal and distinguishable structural features were observed in the anterior lens epithelium aLECs in all 5 patients with presenile cataract. Disturbed structure of aLECs, regularly present in presenile cataract type is shown that might be associated with water accumulation in the presenile idiopathic cortical cataract lens.

Keywords: lens epithelial cells, presenile cataract, lens epithelium, cell morphology, scanning electron microscopy, transmission electron microscopy

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INTRODUCTION

Presenile cataracts, such as juvenile cataracts, are rare. A presenile cataract is considered as a cataract found in a person under 45 years of age (1). Juvenile cataracts have an onset within the first decade of life (2). Juvenile and presenile cataracts can range from mild and benign to advance and sight-threatening and usually have a distinct structure. Presenile cataracts may have a hereditary cause, or can result from trauma or chromosomal, endocrine, metabolic, or systemic disorders (3). Yet, a sizeable percentage of presenile cataracts is of unknown cause. Presenile cataracts can be sporadic or familial. The mode of its inheritance can be dominant—principally in isolated forms or recessive—typical in syndromic forms (4). Among inherited non-syndromic cataract phenotypes, cataracts affecting the lens nucleus are common while cataracts limited to the lens cortex are rare (5). The lens epithelium structure in idiopathic cortical presenile cataract to the best of our knowledge was not studied up to now.

The lens epithelium is the first physical and biological barrier of the lens. It is metabolically the most active part, thus maintaining the physiological health of the lens (6). The lens epithelium is located in the anterior of the lens between the basement membrane and the lens fiber cells and is

a cuboidal epithelium made from anterior lens epithelial cells (aLECs) (7). These cells have large-indented nuclei with two nucleoli and numerous pores (8). As the lens ages, aLECs become more flattened (8). In our previous studies, we have provided detailed evidence about the structural organization of the aLECs. With each of the three complementary techniques used, scanning electron microscopy (SEM), transmission electron microscopy (TEM), and confocal microscopy, we have shown that the apical surface of lens epithelial cells, oriented toward the fiber cells is smooth while at the basal surface, at the border with the lens capsule, the extensions and the entanglements of the cytoplasmic membrane of the lens epithelial cells are present (9). We have previously studied, by the complementary use of SEM and TEM, the structural features of the anterior lens epithelium in senile intumescent white cataract (10) and in retinitis pigmentosa (11). In senile intumescent cataracts' lens epithelium swollen cells, spherical formations and degraded cells were observed. In retinitis pigmentosa, holes and the degradation of the epithelium were observed with the dimensions from $<1\,\mu m$ to more than 50 μm.

In this work, the purpose was to study the structural features of the anterior lens epithelium in 1 case of juvenile and 4 cases of idiopathic presenile cortical cataract to investigate the possible structural reasons for its development.

MATERIALS AND METHODS

Ethics Statement

The research followed the tenets of the Declaration of Helsinki. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia and all patients signed informed consent before the operation.

Patients

The aLCs were obtained by capsulorhexis from routine uneventful cataract surgery of 5 patients with presenile cataract (16 and 41 years old women and 29, 39, and 45 years old men) performed at the Eye Hospital, University Medical Centre (UMC), Ljubljana, Slovenia by the same surgeon (M.H.). None of the patients had a family history of cataract, medication, or trauma and they were otherwise healthy. None had any other abnormal features in the ocular status except cataract. In all five patients, the cataract was of cortical subcapsular type while in one, the cataract was of cortical intumescent type. All the patients were uneventfully operated in topical anesthesia. In three patients, preoperative examination included imaging with anterior segment optical coherence tomography (OCT) (Heidelberg Engineering Spectralis), for the other two, this was unavailable. The first patient was 16 years old female with juvenile cataract that caused gradual loss of vision with corrected visual acuity of 0.3 on the right and 0.6 on the left eye. The second patient was 41 years old female. On presentation, her corrected visual acuity was 0.5 on the right eye and 0.1 on the left eye. Left eye was operated and the posterior capsule was found to be partly fibrosed as well but did not significantly affect postoperative vision. The third patient was 29 years old male with corrected visual acuity on the right eye of 0.1 and 0.7 on the left eye. Right eye was operated and postoperative visual acuity was 0.7 due to fibrosis of the posterior capsule, which was later opened by YAG laser to gain distance visual acuity of 1.0. The fourth patient was 39 years old male with corrected preoperative visual acuity on the right eye of hand movement and 1.0 on the left eye. Right eye was operated and postoperative visual acuity was 1.0. The fifth patient was 45 years old male with corrected visual acuity on the right eye of 0.05 and 1.0 on the left eye. Right eye was operated and postoperative visual acuity was normal. In general, none of the patients had amblyopia or reduced visual acuity due to other ocular pathology.

Tissue Preparation

The anterior capsules of one eye operated in five patients were studied. The 5–5.5 mm circles of the central aLC were carefully removed by continuous curvilinear capsulorhexis with forceps and cut in half. Each specimen was examined in detail both by SEM and TEM. One-half was immediately prepared for SEM performed at Biotechnical Faculty. A washing step was applied to the specimens with sodium cacodylate buffer 0.1 M, pH 7.2. Then, the specimens were double fixed: first, by 1% glutaraldehyde and 0.5% formaldehyde in 0.1 M cacodylate buffer, pH 7.2 for 2 h (25% glutaraldehyde EM grade; SPI and formalin were obtained from paraformaldehyde, Sigma); second, by 1% OsO_4 in cacodylate buffer for 45 min. Dehydration of the aLC tissue was performed in an ethanol cascade. For drying of specimens, critical point drying (CPD, Balzers CPD 030 Critical Point Dryer) procedure with CO_2 was applied. Dried specimens were glued by carbon adhesive discs to specimen stubs, then, Pt sputtered (Bal-Tec SCD 050 Sputter Coater) and examined in a field emission scanning electron microscope (FESEM, 7500 F, JEOL, Tokyo, Japan). The other half of the aLC was prepared for TEM at the Institute of Pathology. For TEM, specimens were immediately fixed in a solution of neutral buffered 10% formaldehyde and postfixated in 2% OsO_4. All capsules were then dehydrated in increasing concentrations of ethanol and embedded in Epon 812. Semi-thin sections (1 μm) were made in the central part perpendicular to the capsule plane, stained with Azur II, in selected cases, they were also stained with Jones methenamine silver (JMS) and analyzed by using light microscopy. Ultrathin sections (30–50 nm) were stained with uranyl-acetate and lead-citrate and examined by a JEOL 1200 Ex II transmission electron microscope. Each specimen was examined in detail both by the SEM and the TEM.

RESULTS

Detailed photograph and OCT imaging of the lens were available for four patients: images of the 16-year-old female patient are shown in **Figure 1**, while in the supporting information **Supplementary Figures S1, S2** images are available for the 39 and 45 years old male patients. In all three patients, subcapsular opacities and vacuoles between the lens capsule and cortex can be seen (**Figure 1**; **Supplementary Figures S1, S2**). The subcapsular changes in the opacity are visible on the anterior part of the lens as shown by the slit lamp (**Figures 1B,C**; **Supplementary Figures S1B,C, S2B,C**) and

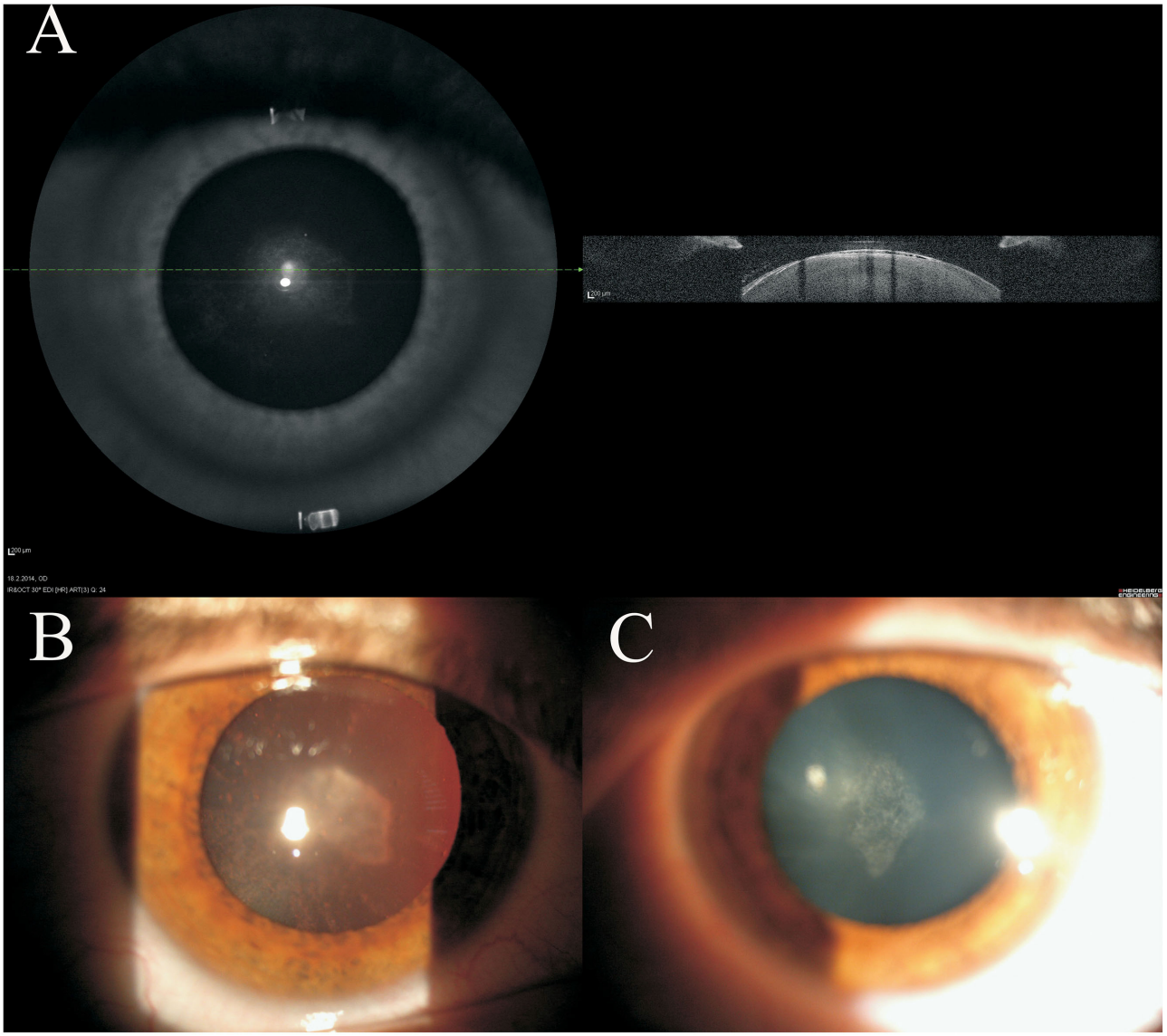

FIGURE 1 | Clinical imaging of 16 years old female juvenile cataract patient's lens before cataract surgery. Spectralis optical coherence tomography (OCT) **(A)** and the slit lamp **(B,C)** images are shown. On the anterior part of the lens subcapsular opacities are visible.

by the high-resolution Spectralis OCT images (**Figure 1A**; **Supplementary Figures S1A, S2A**). As shown on high-resolution Spectralis OCT images, vacuolation can be seen between the lens capsule and cortex (**Figure 1A**; **Supplementary Figures S1A, S2A**).

The following figures represent the results of the SEM and TEM study of the anterior lens epithelium of each patient. The most prominent abnormal features observed by SEM of all patients were the changes of the aLECs structure with the dents on their apical side centrally toward the nucleus.

Patient 1 (16 Years Old Female)

Figure 2 shows that the individual aLECs (**Figures 2A,C**) or smaller regions of the lens epithelium (**Figures 2B,D**) are damaged. There are several smaller lesions of this type that are present diffusely (**Figures 2A,B**). The damaged aLECs can be surrounded by normal aLECs (**Figure 2C**) or can be next to each other (**Figure 2D**). Single healthy and damaged aLECs are presented to clearly show the differences with the dents on the apical side centrally toward the nucleus on the damaged aLEC (**Figure 2E**) and not on the healthy aLEC (**Figure 2F**). Pathological aLECs do not only have an apical indent, but their surface is not smooth compared with the normal aLEC.

Transmission electron microscopy composite of the same 16 years old female patient (**Figure 3**) is made from the four images of higher magnifications, and the same area at the lower magnification. The four images show the characteristic regions (**Figures 3B–E**), in which locations are visible on the low

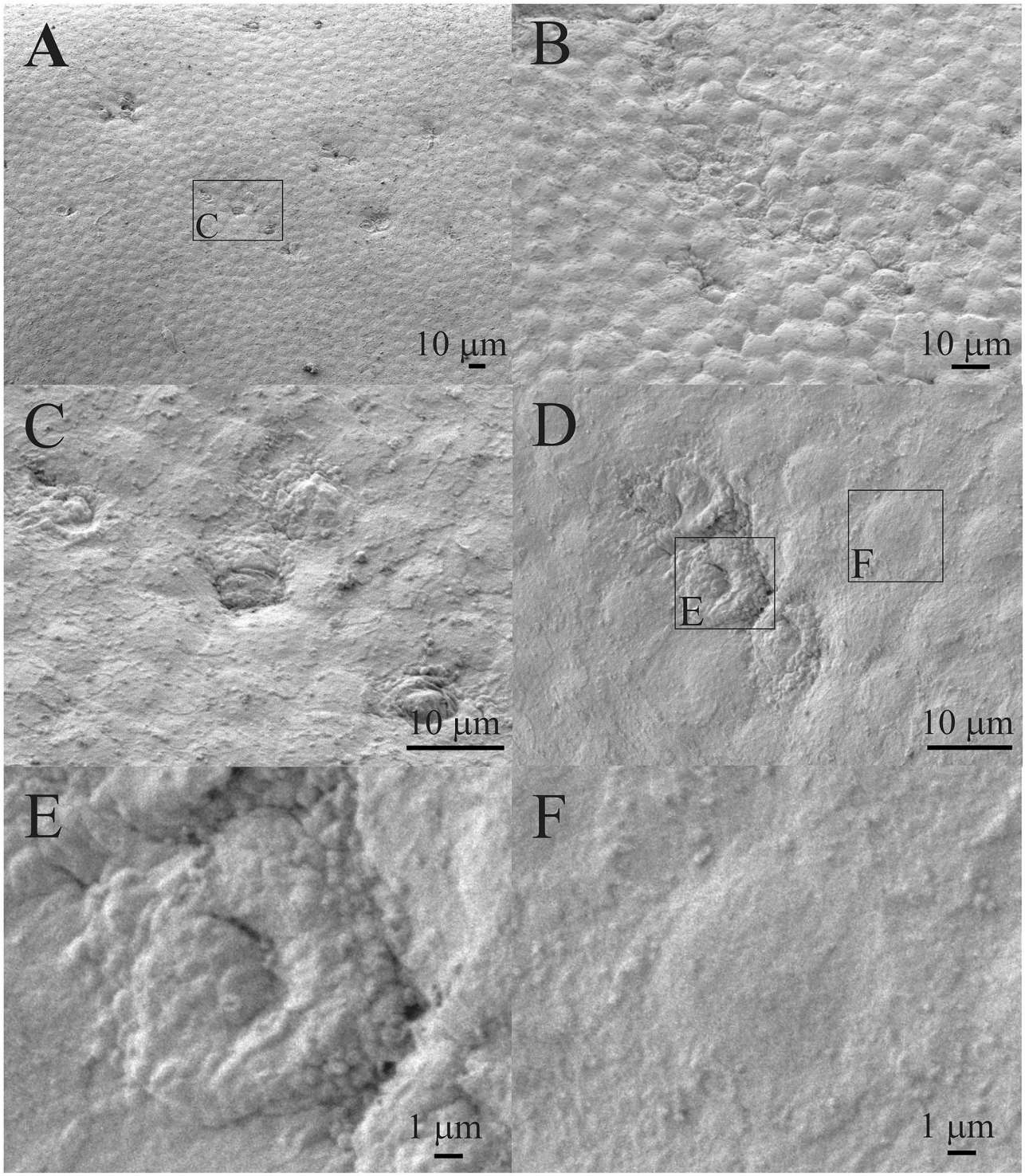

FIGURE 2 | Scanning electron microscopy (SEM) of the 16 years old female juvenile cataract patient's anterior lens capsule (aLC). SEM is showing damaged individual anterior lens epithelial cells (aLECs) **(A,C)** or regions of lens epithelium **(B,D)**, with the dents on the apical side centrally toward the nucleus in the damaged aLECs **(D,E)**, and not the healthy aLECs **(D,F)**. The squares represent the regions that are enlarged and are labeled by letters.

magnified image (**Figure 3A**). The changes in the lens epithelium are unevenly distributed: the thinning of the lens epithelium (**Figures 3A,B**), the degradation of the aLECs where the nucleus of the aLECs has degenerated with the spacing between the adjacent aLECs laterally due to the absent cells (**Figures 3A,C**), and the non-thinned lens epithelium (**Figures 3A,D,E**). The

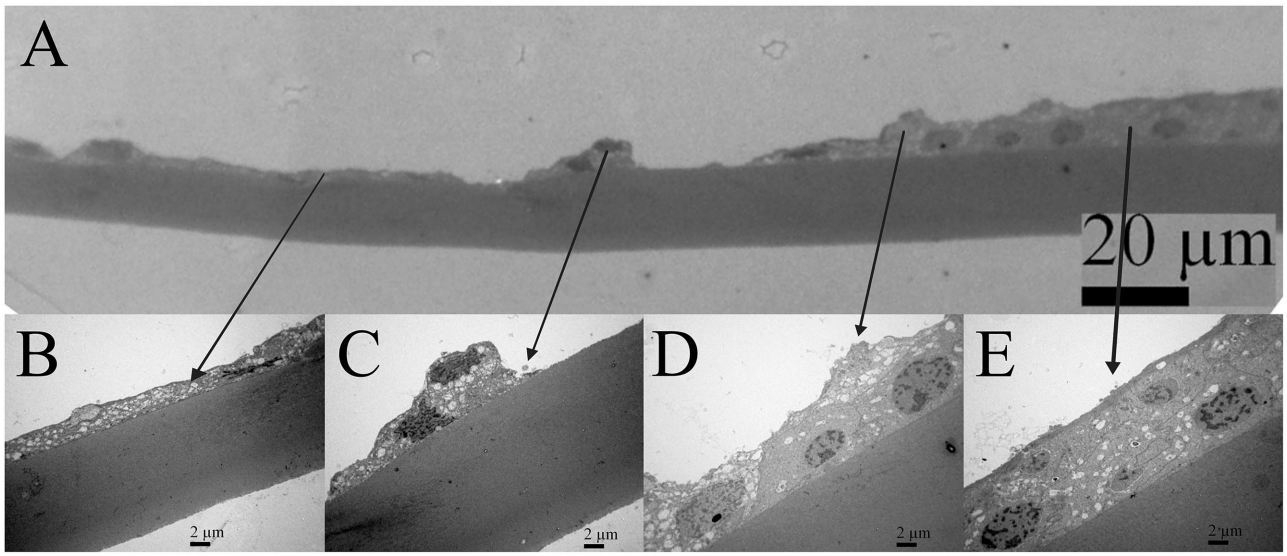

FIGURE 3 | Transmission electron microscopy (TEM) of the 16 years old female juvenile cataract patient's aLC. TEM is showing thinning of the lens epithelium and degradation of the aLECs where the nucleus is degenerated **(A–C)** with the spacing between the adjacent aLECs laterally, in comparison with the non-thinned lens epithelium where aLECs nucleus is intact **(A,D,E)**.

aLECs with the surface that is not smooth could be considered to have an apical indent (**Figure 3D**, left). The aLECs exhibit a great variety in "heights", and create an irregular margin of the apical lens epithelium. In addition, multilayering of cells is visible (**Figures 3A,E**).

Patient 2 (41 Years Old Female)

Figure 4A shows the lens epithelium region in which a bigger part of the aLECs is damaged, while **Figure 4B** shows the lens epithelium region in which only individual aLECs are damaged and the aLECs surrounding them are healthy. Several lesions of both types are present diffusely and are pronounced. **Figure 4C** shows two enlarged regions, left with the normal aLECs and right with the damaged aLECs. **Figure 4D** shows enlarged individual damaged aLECs surrounded by the normal aLECs. Different degrees of damage can be observed for different aLECs, as on some, the dents on the apical side centrally toward the nucleus are less pronounced (**Figure 4E**) and on the others are more pronounced (**Figure 4F**).

In **Figure 5**, the cross-section of the part of the lens capsule preparation of the same patient is considered which shows unevenness in thinning of the lens epithelium. The changes on the lens capsule are diffuse, but they do not look as pronounced as on SEM. While **Figure 5A** shows relatively normal cell, **Figures 5B,C** show the lens epithelial regions in which the cytoplasm of aLECs is vacuolated and thinned; the cells are segmentally concave and the nuclei are compressed and elongated. Transparent vacuoles of various sizes are visible. While nuclei look different, their shape can also reflect the thinner and flatter shape of cells; the concavity is subtle compared with that shown in the SEM. **Figure 5D** shows the shelling of the cells with the loose connection between the cell and the basement membrane, leading to complete detachment of the cell from the basement membrane.

Patient 3 (29 Years Old Male)

Figure 6A shows the region of damaged aLECs surrounded by the region of normal/healthy aLECs. **Figure 6B** shows the region of normal/healthy aLECs on the left and the smaller region of damaged aLECs on the right. Several lesions are present diffusely and are pronounced. **Figure 6C** shows the bigger region with damaged aLECs, which is enlarged (**Figure 6D**), so that the changes on individual aLECs can be shown better. Small holes (around 1 μm^2 or less) can be seen on damaged aLECs (**Figures 6E,F**).

Figure 7 shows the TEM of the same patient. The cytoplasm of aLECs is thinned, the cells are segmentally concave. The degradation of the aLECs with the signs of necrosis is visible, invading the underlying lens capsule that has lost its smooth surface. The nuclei are compressed, elongated, and condensed.

Patient 4 (39 Years Old Male)

Figure 8 shows that the individual aLECs are damaged. **Figure 8B** shows an enlarged region in the center of which is the damaged aLECs with the dents on the apical side centrally toward the nucleus. **Figures 8C,D** show enlarged individual damaged aLECs with different degrees of dents on the apical side centrally toward the nucleus. Small holes (around 1 μm^2 or less) can be seen on the damaged region of the lens epithelium (**Figures 8E,F**).

Figure 9 shows the TEM of the same patient. While **Figure 9A** shows a normal lens epithelial region where the aLECs nucleus is intact, **Figures 9B–D** shows the lens epithelial regions in which the thinning of the lens epithelium (**Figure 9B**) and degradation of the aLECs with the degenerated nuclei (**Figures 9B–D**) and

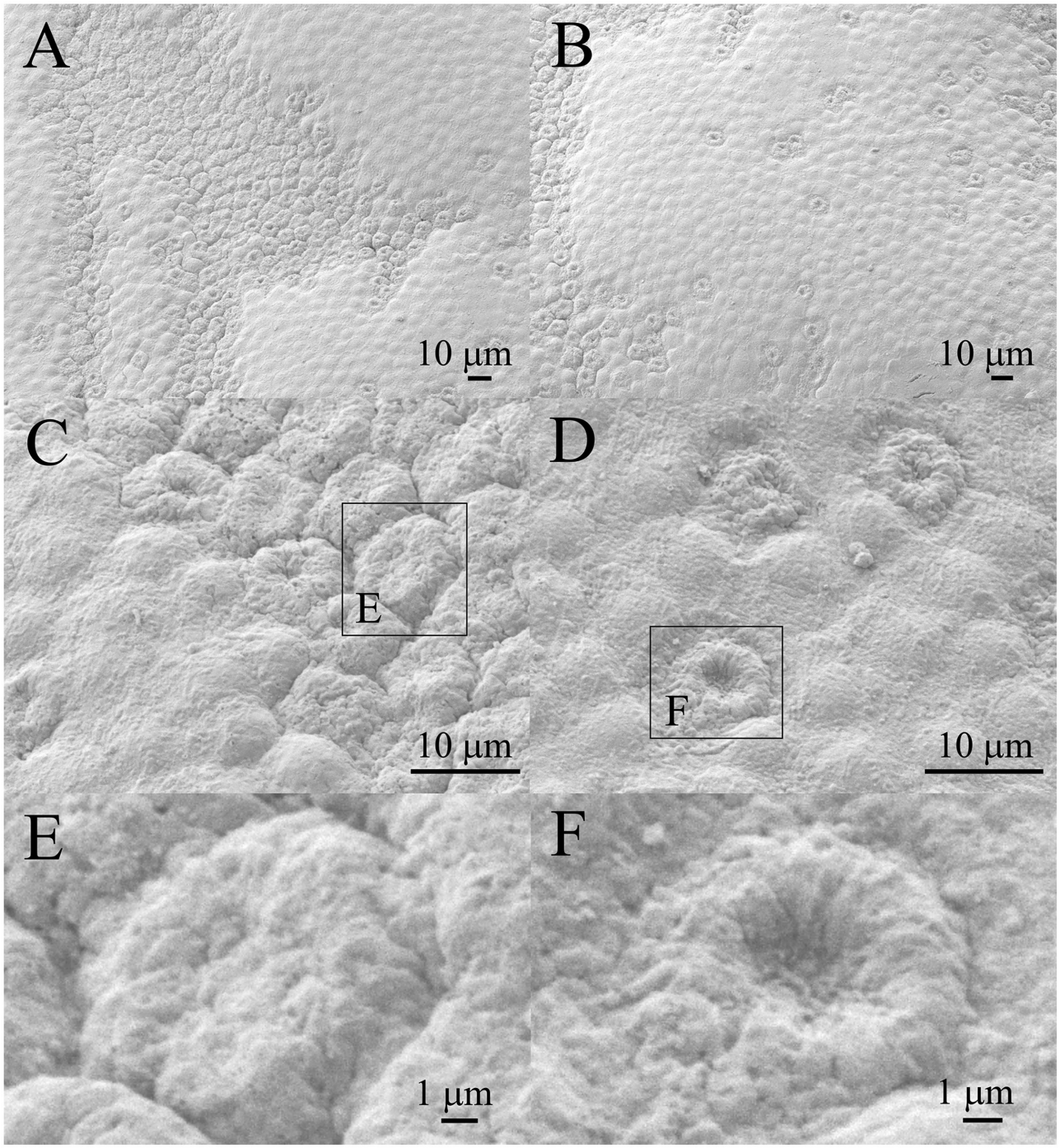

FIGURE 4 | Scanning electron microscopy of the 41 years old female presenile cataract patient's with aLC. SEM is showing that both the larger regions of the lens epithelium **(A)** and the individual aLECs are damaged **(B)**, with the different degree of dents on the apical side centrally toward the nucleus on different damaged aLECs **(C–F)**. The squares represent the regions that are enlarged and are labeled by letters.

the vacuolated cytoplasm of aLECs (**Figures 9B,C**) are visible. The loss of the regular shape of LECs and their nuclei is visible. Features of intracellular edema can be seen. A transparent vacuole can be observed between two cells making the loose connection of cells (**Figure 9D**).

Patient 5 (45 Years Old Male)

Figures 10A,B show that the smaller regions of the lens epithelium (**Figures 10A,B**) have the damaged aLECs with the dents on the apical side centrally toward the nucleus. The damaged aLECs can be next to each other (**Figure 10B**).

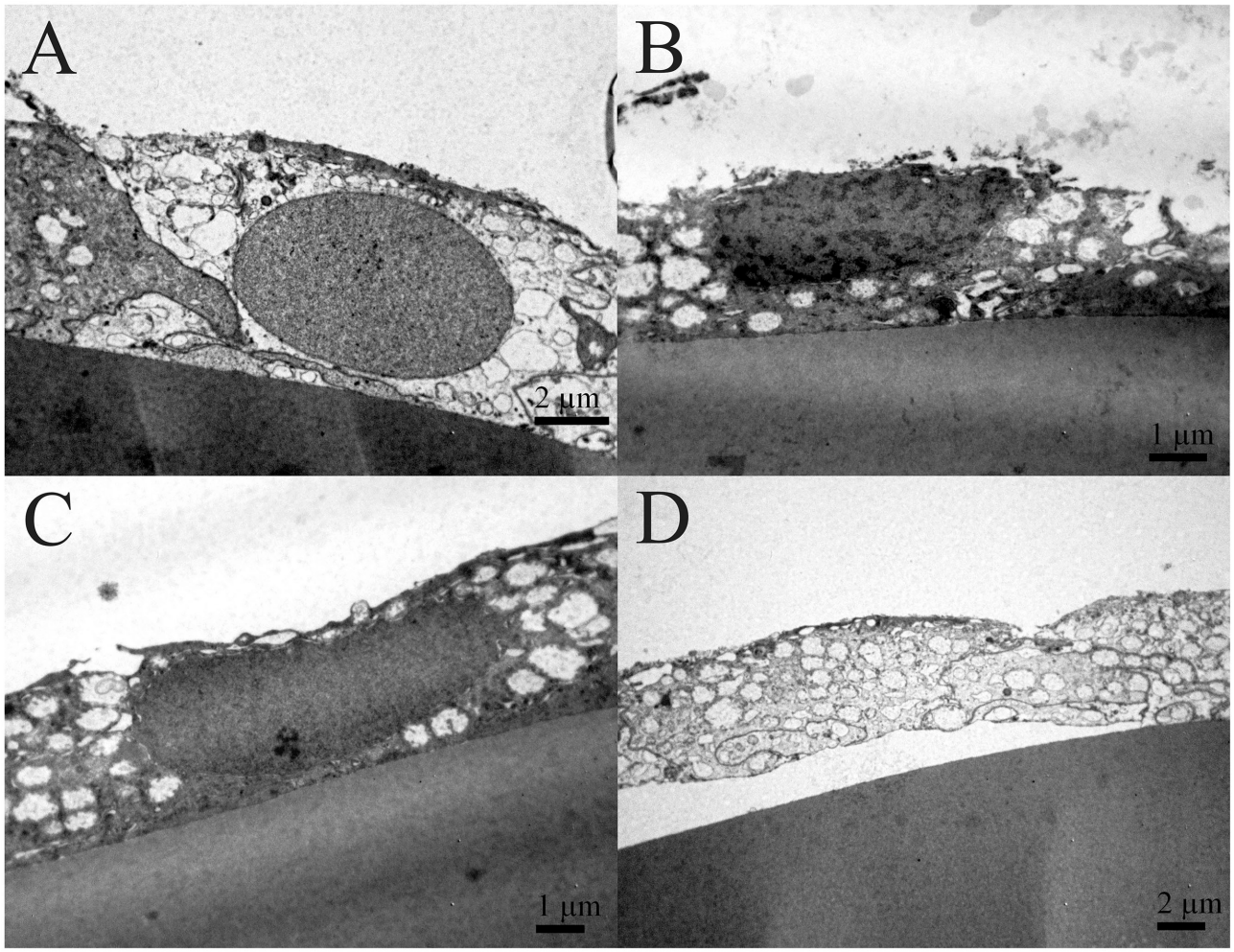

FIGURE 5 | Transmission electron microscopy of the 41 years old female presenile cataract patient's aLC. TEM is showing the lens epithelial regions in which the cytoplasm of aLECs is vacuolated and thinned, the cells are segmentally concave, and the nuclei are compressed and elongated **(B,C)**. The shelling of the cells **(D)** in comparison with the normal aLEC **(A)** is also shown.

Figures 10C,D show enlarged individual damaged aLECs with different degrees of dents on the apical side centrally toward the nucleus. Bigger holes (more than 5 μm^2) can be seen on the damaged region of the lens epithelium (**Figures 10E,F**).

Figure 11 shows the TEM of the same patient. While the non-thinned lens epithelium where the aLECs nucleus is intact is shown in **Figure 11A**. **Figures 11B–D** show the lens epithelial regions in which large intercellular space is present (**Figure 11B**), the cytoplasm of aLECs is vacuolated and thinned, and the nuclei are compressed and elongated (**Figures 11C,D**). More importantly, the cell is segmentally concave (**Figure 11D**), so the loss of the regular shape of aLECs and their nuclei is visible. Transparent vacuoles of various sizes can be observed between the cells and between the cells and the basic membrane making loose connection with the basement membrane (**Figures 11B–D**).

DISCUSSION

We have shown by using SEM and TEM that the aLECs of anterior lens capsule in idiopathic presenile cortical cataract have pronounced abnormal structural features reflected in the form of thinning of the lens epithelium, with segmentally concave aLECs, the dents on the aLECs apical side centrally toward the nucleus, and compressed and elongated nuclei. In some regions, the single aLECs in lens epithelium are damaged, while in the others, larger zones of the lens epithelium are damaged. So, there are the regions with mild lens epithelial impairment, and the regions with larger epithelial impairment. To the best of our knowledge, this is the first time that the structural features as the dents, the selective concavity of some LECs, at their apical side centrally toward the nucleus, are shown on the lens epithelium of patients with presenile cataract when studied simultaneously by SEM and TEM in the same preparation.

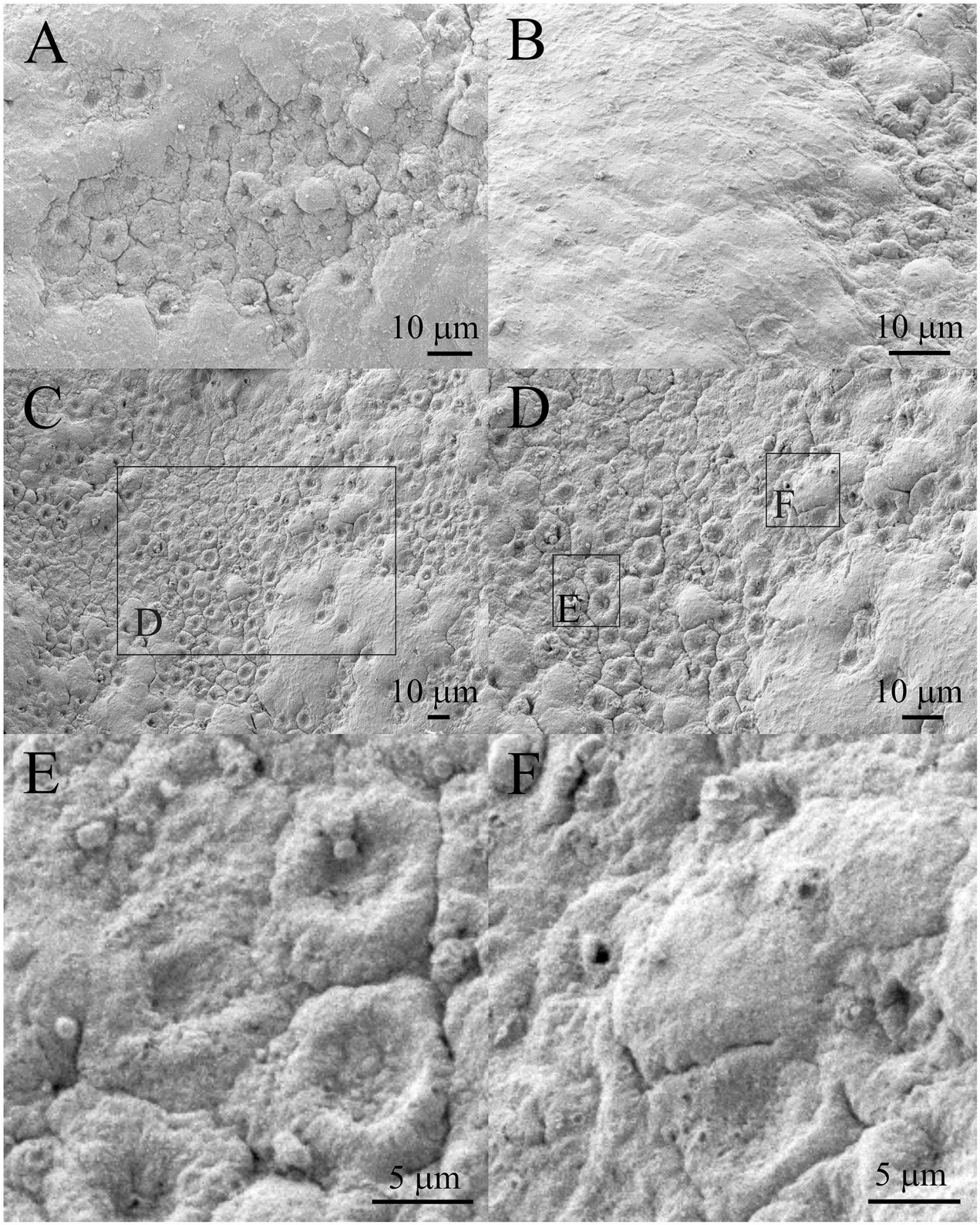

FIGURE 6 | Scanning electron microscopy of the 29 years old male presenile cataract patient's aLC. SEM is showing the larger regions of lens epithelium that are damaged **(A–D)**. The small holes can be observed **(E,F)**. The squares represent the regions that are enlarged and are labeled by letters.

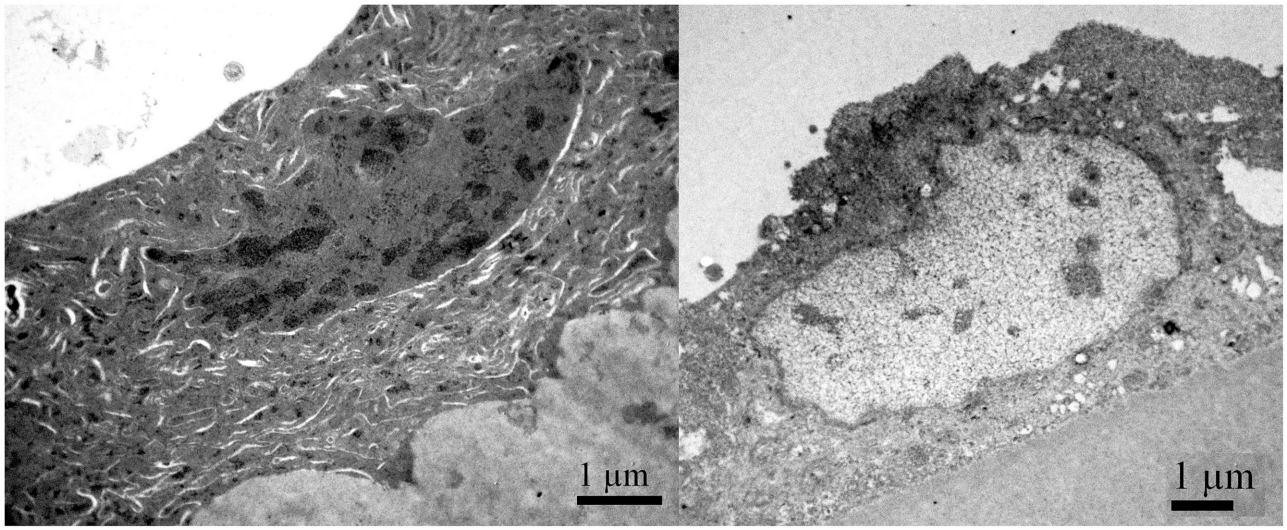

FIGURE 7 | Transmission electron microscopy of the 29 years old male presenile cataract patient's aLC. TEM is showing that the cytoplasm of aLECs is thinned, the cells are segmentally concave, the nuclei are compressed and elongated, and the chromatin is condensed.

Interestingly, when compared with the lens epithelia from 49 patients with different senile cataract types (nuclear (N), cortical (C), N+C, intumescent white cataract, and retinitis pigmentosa) that we studied by SEM and TEM, we found similar changes of the aLECs structure in the form of the dents only in 2 patients (4%), while in other 47 patients (96%) no such changes were observed (10, 11). This suggests that the damaged epithelial regions are due to the presenile cataract and are not an artifact of the surgical extraction and separation from the normal contact with fiber cells or tissue processing.

Already with clinical examination before the cataract surgery, the subcapsular changes in the opacity are visible both on the anterior part of the lens and in the posterior subcapsular part. As shown in high resolution OCT images, vacuolation can be seen between the lens capsule and cortex, probably representing water accumulation under the capsule (**Figure 1**), which may leak further along the lens fibers to the posterior pole causing posterior subcapsular cataract. Generally, in any damage of the lens epithelium and its transport function, water passively enters the lens. Lens epithelium plays a key role in maintaining the levels of electrolytes and water in the lens, which are necessary for lens transparency (6, 12, 13). Therefore, an influx of the water through the impaired lens epithelium may represent the mechanism of development of the presenile cataract and may be indicative of a common mechanism of cataract development, involving the water mechanism. Laursen and Fledelius in 1979 (14) have already suggested that the opacities of the anterior capsular/subcapsular layers and, in particular, a posterior subcapsular cataract, may be associated with an increase in permeability of the lens "membrane" consisting of the basement membrane + the epithelium anteriorly and the lens basement membrane posteriorly.

In all five patients, regions of degenerated aLECs were found. The death of aLECs leads to rearrangement of aLECs, which may further lead to uncoupling of cells, which is vital for the maintenance of the transparency of lens (15). It was shown that such uncoupling of cells and the breakdown of aLECs intercellular connectivity causes dysfunction of active transport of electrolytes, causing passive inward movement of water and the progression of cortical cataract development (16).

Lens epithelial cell apoptosis was suggested to be a common cellular basis for non-congenital cataract development in humans and animals (17). Depletion of patches of aLECs eliminates homeostatic epithelial cell control of the underlying fiber cells, leading to the impairment of the integrity and transparency of these underlying fiber cells (18). By SEM and TEM, we found the regions with the impaired lens epithelium, where the aLECs are damaged, often with the concave nuclear region.

Anterior lens epithelium in presenile cataract was observed by SEM and TEM only in one study (19) in which the abnormal structural features of aLECs were observed in the presenile compared with age-related cataract patients. While TEM and SEM showed some common changes as also observed in our presenile cataract samples, such as vacuolated cytoplasm, and elongated nuclei, holes formed by the aLECs stretching were only seen in the patients with presenile cataract. In addition to these, we show features not described previously, in particular, the dents at aLECs apical side centrally toward the nucleus which were very well distinguished by SEM. The swollen cells and spheres were observed in intumescent cataract lens epithelia (10).

In comparing the cellular features in presenile cataracts to those already described in senile cataracts, it is important to depict specific morphological features that would only be inherent to presenile cataracts. However, there are very few recent research that studied SEM and TEM features of the lens epithelium in senile cataracts and they do not distinguish cortical from nuclear senile cataracts, whereas cortical cataracts would be more relevant to compare. These document irregular

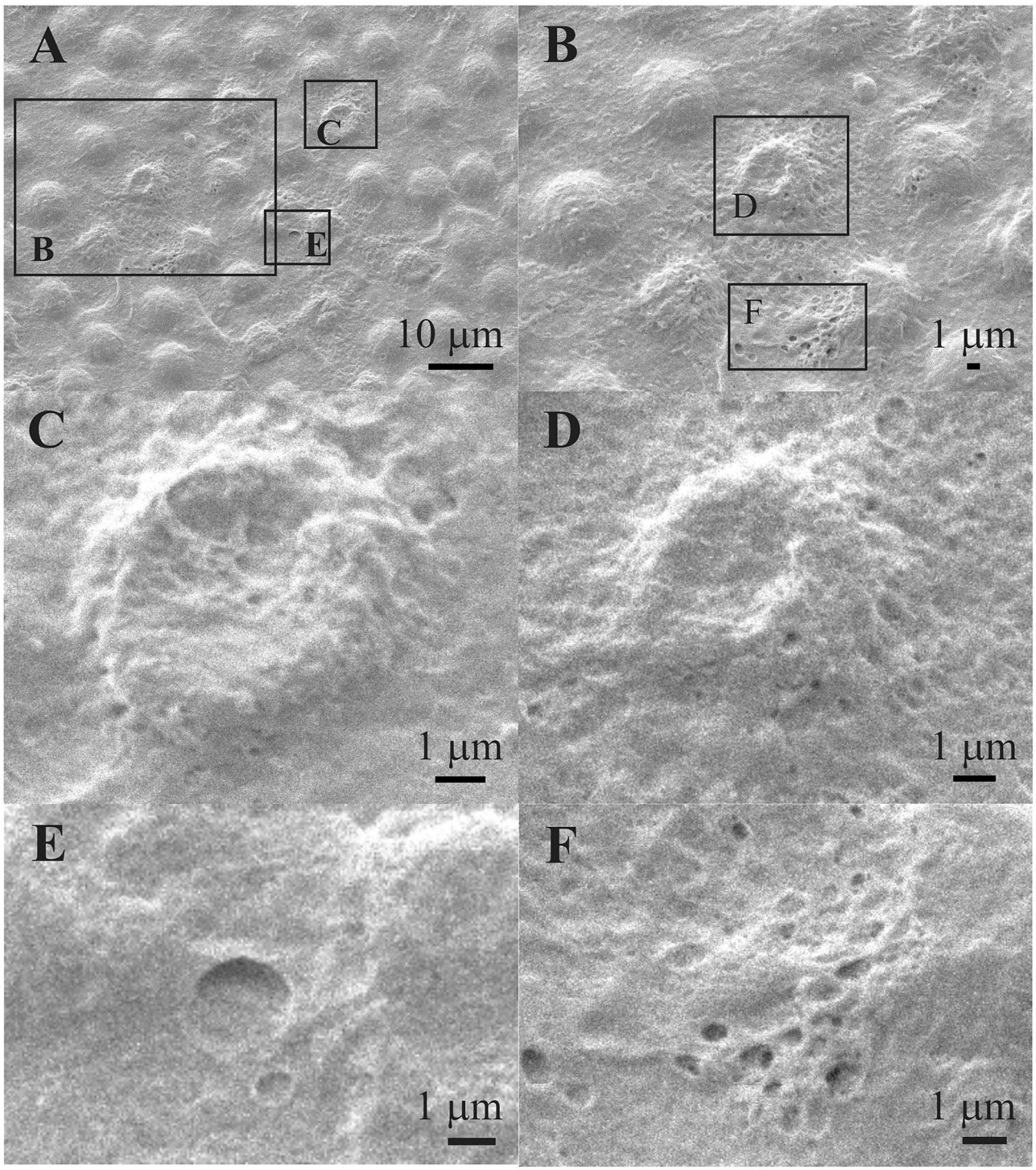

FIGURE 8 | Scanning electron microscopy of the 39 years old male presenile cataract patient's aLC. SEM is showing damaged individual aLECs **(A,B)** with the different degree of dents on the apical side centrally toward the nucleus **(C,D)**. The small holes can be observed on the damaged lens epithelium **(E,F)**. The squares represent the regions that are enlarged and are labeled by letters.

apical surfaces of the lens epithelium (20–22). TEM examination revealed ultrastructural abnormalities, such as transparent vacuoles of various sizes that were detected between the cells and between cells and the basal membrane, influencing the appearance of both the nucleus and the whole cell, and were detected in all patients with age-related cataracts. Additionally,

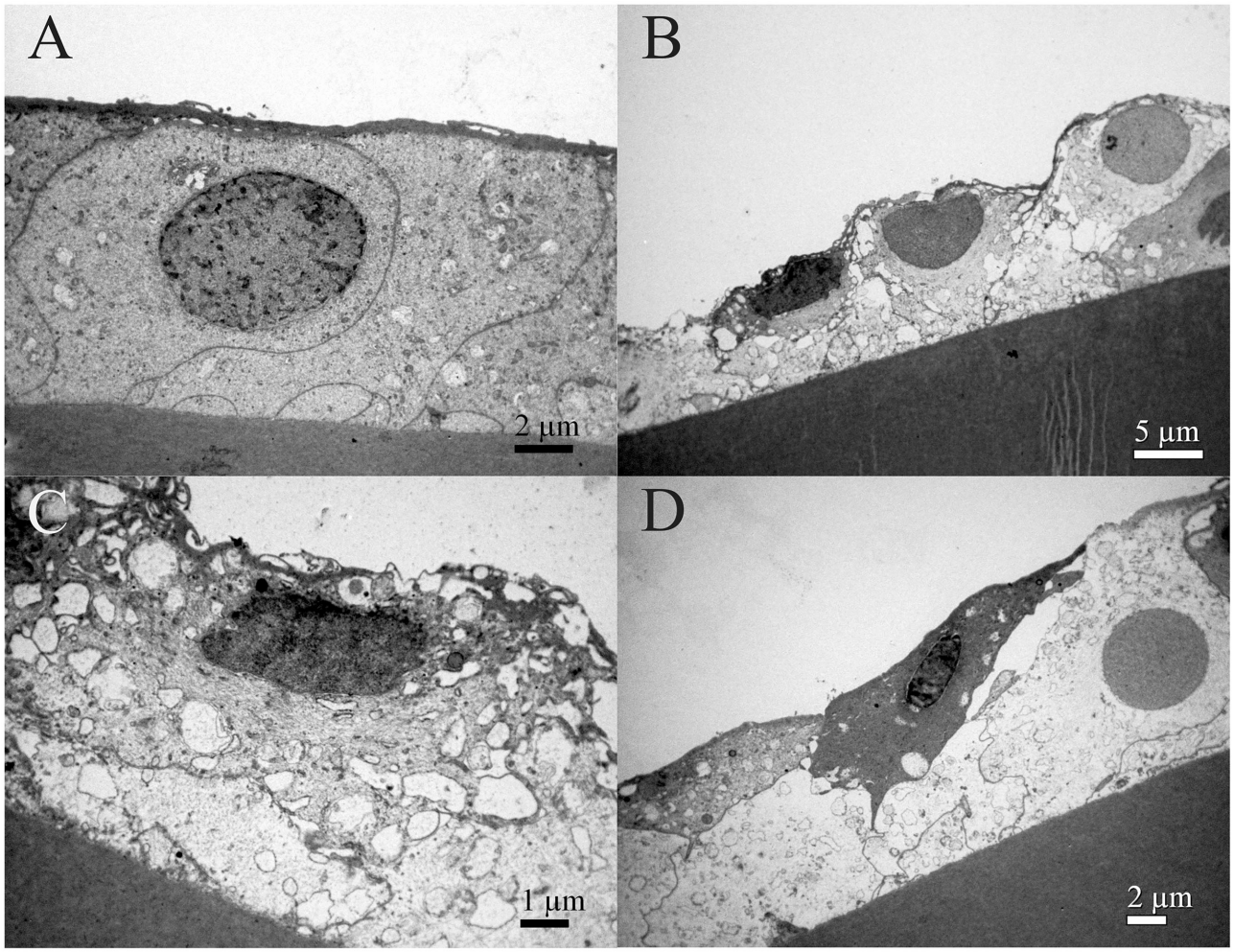

FIGURE 9 | Transmission electron microscopy of the 39 years old male presenile cataract patient's aLC. TEM is showing thinning of the lens epithelium **(B)** and degradation of the aLECs where the nuclei are degenerated **(B–D)** and the cytoplasm of aLECs is vacuolated **(B, C)**, in comparison with the non-thinned lens epithelium where aLECs nucleus is intact **(A)**.

diffuse intracellular edema was observed, and was more extended and more frequently observed in the exfoliation syndrome group. Many other ultrastructural features were shown in all patients with age-related cataracts. The irregularly shaped nuclei and aLECs were also observed. Cells exhibited a great variety in "heights". The cells were loosely connected among them and with the basement membrane or were in some cases absent. Sometimes the epithelium was completely detached from the basement membrane. Very often there was more than one layer of cells (21). However, in exfoliation syndrome, SEM did not show the dents on the aLECs as described in our studies (20). Large intercellular and a few intracellular vacuoles were also seen in the anterior part of the epithelium, both light- and electron-microscopically in senile cataract lenses (23). Similar degenerative changes in aLECs were shown in different types of cataracts, such as multilayered cells, nuclei of abnormal diameters and shapes, vacuolation of nuclei, and cytoplasm (24). These studies report many similar alterations to the ones observed in our study by TEM, even though none of the patients had presenile cataracts. There are certainly many common features, however, we report others, previously not described, especially by SEM, as the dents, the selective concavity of some LECs, at their apical side centrally toward the nucleus. Although it shares similarities to senile cataracts, the occurrence of such changes in such young people is unusual, so it is worth studying.

A limitation of this study is the unavailability of the normal lens capsules for comparison, as we obtain lens epithelium after cataract surgery and the changes were compared with common nuclear cataract, in which lens epithelia were largely normal (10). Another limitation of the study was the small sample size as such cataracts are relatively rare. For this reason, these findings may not be regarded as the general principle but as a report of changes documented by both, SEM and TEM, along with the

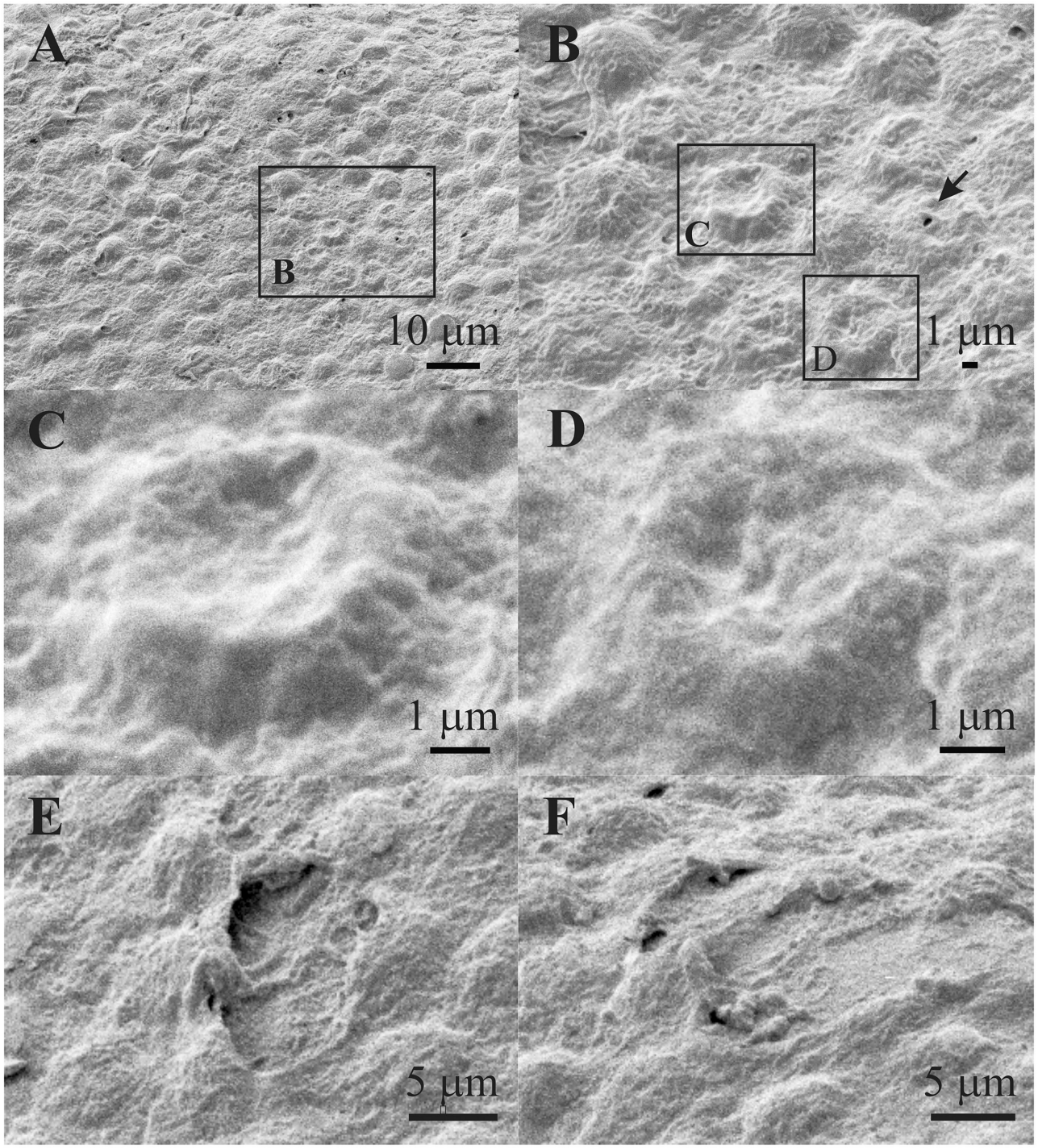

FIGURE 10 | Scanning electron microscopy of the 45 years old male presenile cataract patient's aLC. SEM is showing that the smaller regions of the lens epithelium **(A,B)** are with the damaged aLECs having different degree of dents on the apical side centrally toward the nucleus **(C,D)**. Bigger holes can be seen on damaged region of the lens epithelium **(E,F)**. The squares represent the regions that are enlarged and are labeled by letters.

high-resolution preoperative OCT in the same preparation not previously shown in this type of cataract, as a contribution toward finding the specific origins of dysfunction of the lens epithelium in this type of cataract.

In conclusion, structural studies of the presenile cataract lens epithelia by SEM and TEM show abnormal distinguishable features present in presenile idiopathic cortical cataract that may play a role in water accumulation and cataract formation.

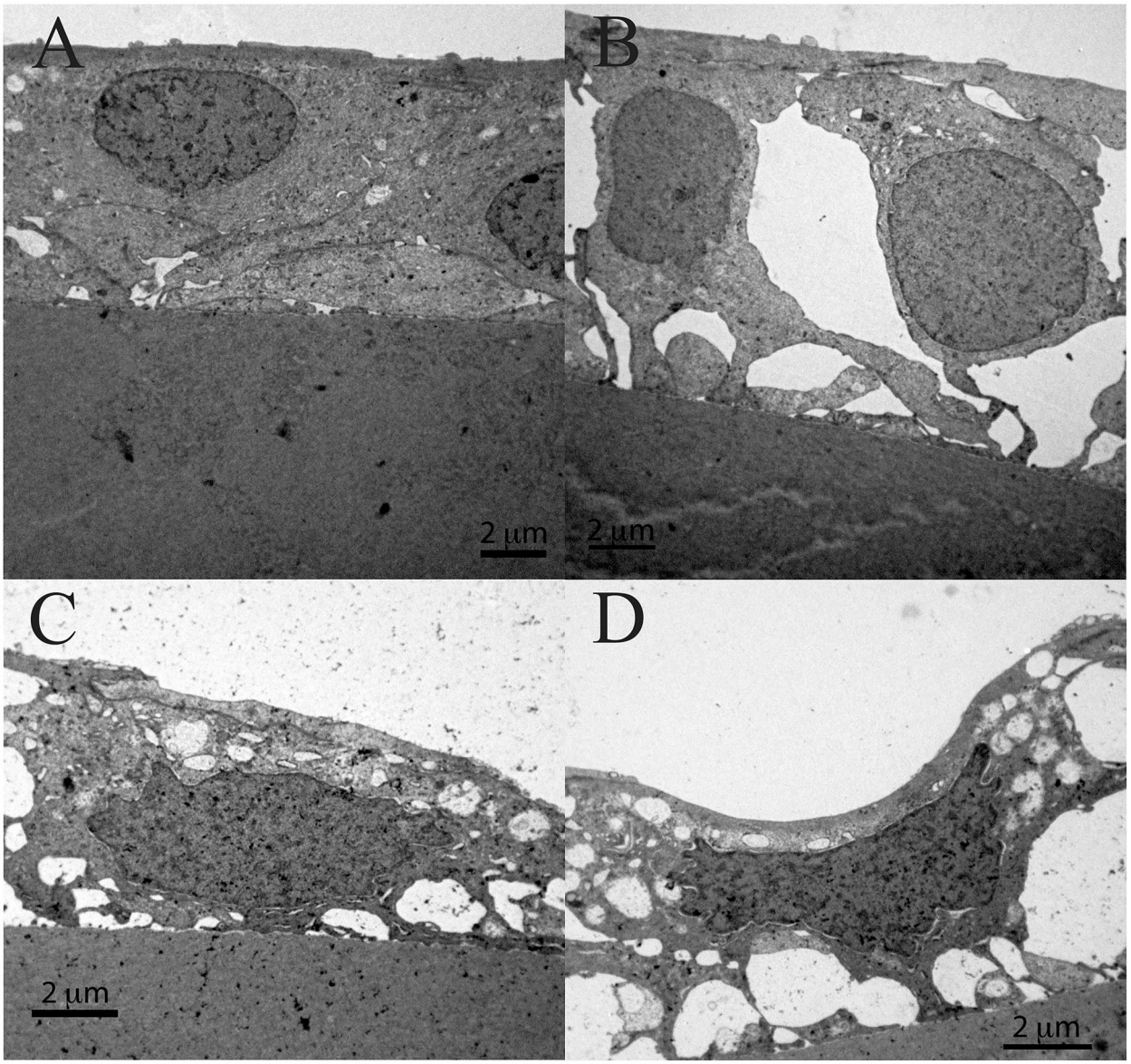

FIGURE 11 | Transmission electron microscopy of the 45 years old male presenile cataract patient's aLC. TEM is showing the lens epithelial regions in which the large intercellular space is present **(B)**, the cytoplasm of aLECs is vacuolated and thinned, and the nuclei are compressed and elongated **(C,D)** and importantly, the cell is segmentally concave **(D)**, in comparison with the non-thinned lens epithelium where aLECs nucleus is intact **(A)**.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the National Medical Ethics Committee of the Republic of Slovenia and all patients signed informed consent before the operation. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MH: conceptualization, funding acquisition, resources, and supervision. SA, KD, and AH: data curation, investigation,

and validation. SA: formal analysis, visualization, and writing—original draft. KD and AH: methodology. SA and MH: project administration and writing—reviewing and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.802275/full#supplementary-material

Figure S1 | Clinical imaging of 39 years old male presenile cataract patient's lens before cataract surgery. Spectralis OCT **(A)** and the slit lamp **(B,C)** images are shown. Subcapsular opacities and vacuoles between the lens capsule and cortex can be seen.

Figure S2 | Clinical imaging of 45 years old male presenile cataract patient's lens before cataract surgery. Spectralis OCT **(A)** and the slit lamp **(B,C)** images are shown. Vacuoles and subcapsular opacities between the lens capsule and cortex are visible.

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Management of Intraocular Pressure Elevation After CO_2 Laser-Assisted Sclerectomy Surgery in Patients With Primary Open-Angle Glaucoma

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Purpose: To report the safety and efficiency of carbon dioxide (CO_2) laser-assisted sclerectomy surgery (CLASS) in Chinese patients with primary open-angle glaucoma (POAG) and the management of unexpected postoperative intraocular pressure (IOP) elevation.

Methods: This was a prospective case series study. A total of 23 eyes from 23 patients with POAG who underwent CLASS were involved and followed-up for 12 months. The primary outcomes included the changes in best corrected visual acuity (BCVA), IOP, and medications before and after CLASS. The secondary outcomes were success rate and postoperative laser interventions.

Results: The mean age of the patient was 42.6 ± 16.0 years. There was no significant change in BCVA and visual field at baseline and 12 months after CLASS. The number of medications was significantly reduced after CLASS. The IOP was also significantly decreased and remained well controlled during the follow-up period, except for a transient elevation at 1 month postoperatively, due to the occurrence of peripheral anterior synechiae (PAS). Generally, 17 patients (73.9%) were treated with neodymium-doped yttrium aluminum garnet (Nd:YAG) laser synechiolysis to remove iris obstruction in the filtration site and seven patients (30.4%) underwent Nd:YAG laser goniopuncture to deal with scleral reservoir reduction. Only one patient (4.3%) received surgical repositioning due to iris incarceration. The complete success rate and total success rate at 12 months were 69.6 and 95.7%, respectively.

Conclusion: CLASS was a safe and effective approach for Chinese patients with POAG. Peripheral anterior synechiae (PAS), iris incarceration, and scleral reservoir reduction were common causes of unexpected postoperative IOP elevation. Individualized Nd:YAG laser intervention helps to improve the long-term outcomes after CLASS.

Keywords: CO_2 laser, deep sclerectomy, Nd:YAG laser, intraocular pressure, primary open-angle glaucoma

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness worldwide. Elevated intraocular pressure (IOP) is the major factor leading to visual field loss and optic atrophy (1). At present, the treatment of glaucoma is focused on reducing IOP through medications, laser, or surgery (2).

Conventional trabeculectomy (Trab) remains to be the gold standard for filtering glaucoma surgery (3). However, there are various potential complications, including hypotony, shadow anterior chamber, infection, cataract development, malignant glaucoma, fistula failure, and suprachoroidal hemorrhage, which have direct influence on the success of the surgery (4).

Nonpenetrating deep sclerectomy (NPDS) is an alternative filtering surgery. Compared with Trab, NPDS has a higher safety, but is more technically demanding (5). It was designed to reduce the resistance of aqueous humor outflow by removing the outer wall of Schlemm's canal and the external part of the adjacent trabecular meshwork tissue, while avoiding penetrating the anterior chamber (6). The tissue must be dissected deep enough to achieve effective percolation, which is difficult to manipulate by manual procedure. Perforation of the trabeculo-Descemet membrane (TDM) is the most common intraoperative complication (7).

Carbon dioxide (CO_2) laser-assisted sclerectomy surgery (CLASS) is an optimized approach of NPDS. CLASS uses a CO_2 laser to ablate the scleral tissue instead of manual procedure, leaving a thin and intact TDM just sufficient for aqueous percolation without penetrating to the anterior chamber. During the process, the energy can be accurately controlled and the depth and size of the ablating area can be adjusted (8). It has been successfully used to treat primary open-angle glaucoma (POAG) during the recent years, both in the Caucasian and in Chinese patients (9–11). Compared with other filtering surgeries, CLASS requires a shorter learning curve and less technical challenge and also achieves higher safety (12).

Despite these unique advantages, CLASS also has some complications, including peripheral anterior synechiae (PAS), iris incarceration, shallow anterior chamber, choroidal detachment, etc. (13). It was reported that the incidence of PAS and iris incarceration was relatively high after CLASS, which resulted in a temporary increase of IOP (13). However, the difference between PAS and iris incarceration was vaguely described among previous studies. Insufficient penetration of the aqueous humor due to the decrease in the scleral reservoir is another reason leading to IOP elevation (14). So far, there is a lack of consensus on postoperative management of CLASS and laser intervention before and after CLASS remains controversial. Antiglaucoma medication was still the common treatment to deal with postoperative IOP elevation for most of Chinese patients. If we failed to identify the specific causes of IOP elevation and give proper interventions in time, it might lead to failure of the surgery.

In this study, we described a series of patients with POAG who underwent CLASS. For the first time, we analyzed possible causes of postoperative IOP elevation and proposed an ultrasound biomicroscopy (UBM)-guided individualized interventions according to different situations. We attempt to give some enlightenment to postoperative management of CLASS, in order to improve the long-term outcomes for Chinese patients with POAG.

MATERIALS AND METHODS

Study Population

This was a prospective case series study, involving 23 eyes of 23 patients with POAG, who underwent CLASS and completed 1 year follow-up. All the subjects were recruited from our eye center between August 2020 and October 2021. The inclusion criteria were: patients aged $\geq$ 18 years, diagnosed with POAG, and with uncontrolled IOP under maximum hypotensive medications. The exclusion criteria were: patients with other systemic or ocular disorders, trauma or secondary glaucoma, or history of any ocular surgery or laser treatment. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Zhejiang University. A written informed consent was obtained from all the subjects before all the procedures.

Surgical Procedure and Postoperative Management

All the CLASS procedures were performed by a single surgeon (KJ Wang). In details, a fornix-based conjunctival flap was created to expose the sclera, then a one-third thickness limbus-based 5 mm × 5 mm scleral flap was made, and extended by 1 mm into the clear cornea. Mitomycin C (MMC) (0.4 mg/ml) was applied under the conjunctival and scleral flaps for 3 min and the area was washed with 20 ml balanced salt solution (BSS). A 4 mm × 2 mm scleral lake was created at the posterior scleral bed using a commercially available OT-135P2 CO_2 laser system (IOPtiMate, IOPtima Ltd., Ramat Gan, Israel), with the depth of approximately 90% scleral thickness. MMC was applied again on the scleral lake for 1 min and washed out by BSS. Then, the CO_2 laser beam was applied to ablate the outer wall of the Schlemm's canal and the trabecular meshwork, about 4 mm × 1.4 mm, until a continuous fluid percolation was observed. Finally, the two corners of the scleral flap and the conjunctival flap were sutured with 10/0 nylon sutures.

For all the patients, tobramycin and dexamethasone were prescribed postoperatively four times a day (QID) for 1 month and pilocarpine eyedrop was used QID for 3 months to prevent PAS. IOP was measured by the same experienced technician at each visit with Goldmann applanation tonometry. UBM and gonioscopy examination were performed at 1 month (M), 3, 6, 9, 12 M, and other situations of IOP elevation.

Management of PAS

Peripheral anterior synechiae appeared as a physical contact at the filtrating area by UBM examination. A neodymium-doped yttrium aluminum garnet (Nd:YAG) laser synechiolysis was performed in clinic to remove iris obstruction and reopen the filtration site. After miosis with 2% pilocarpine (Furuida Corporation Ltd., Shandong, China) and instillation of topical alcaine (S.A. Alcon-Couvreur N.V., Belgium, UK), the superior

angle was visualized under the Hwang-Latina 5.0 SLT Lens (Ocular Instruments, Bellevue, Washington, USA). Nd:YAG laser (Visulas YAG III Combi, Carl Zeiss Meditec AG, Jena, Germany, UK) spots were applied on the area of PAS with a power of 3–5 mJ, until the iris retreated from the trabeculodescemetic window (TDW). We do not puncture the TDW at the same time.

Management of Iris Incarceration

Patients with iris incarceration can be identified by UBM examination as a prolapsed iris or have a pear-shaped pupil. Surgical repositioning was performed under the microscope. After topical anesthesia with alcaine, a 23-G needle was inserted from the clear corneal limbus into the superior anterior chamber angle to pull the incarcerated iris centrally, until the pupil returns to circular.

Management of Scleral Reservoir Reduction

Once the postoperative IOP raised above the desired target IOP or the evidence of scleral reservoir reduction was observed by UBM examination, a Nd:YAG laser goniopuncture was performed to enhance the IOP-lowing effect. The energy was set at 3–5 mJ to create very small tears in the TDW and allows aqueous humor to flow from the anterior chamber into the sclera reservoir.

Therapeutic Outcomes and Success Criteria

The primary outcomes included the changes in best corrected visual acuity (BCVA), IOP, and antiglaucoma medications before and after CLASS. Fixed combination medications were recorded as two types of agents. The secondary outcomes were success rate and postoperative laser interventions.

"Complete success" was defined as IOP values ranging between 5 and 18 mm Hg and IOP reduction of $\geq$ 20% from the baseline, without antiglaucoma medications or any interventions (including laser treatment, surgical repositioning, or needling). "Qualified success" referred to IOP values within the above criteria after postoperative interventions (including laser treatment, surgical repositioning, or needling) or under the application of antiglaucoma medications. "Failure" was defined as IOP $<$ 5 mm Hg or $>$ 18 mm Hg despite postoperative intervention or medications, or IOP reduction of $<$ 20% from the baseline, or underwent additional glaucoma surgery within 1 year.

Statistical Analysis

Statistical analyses were performed with the GraphPad Prism version 8.0 software (GraphPad Software Incorporation, San Diego, California, USA). The sample size was calculated based on a power calculation (power = 0.80; $p = 0.05$) using standard deviations (SDs) obtained in a previous study (11) and 17 eyes per group were considered well suited for the purpose of this study. Quantitative data were expressed as mean values including the SD. Descriptive statistics were performed to calculate the demographic characteristics of the study cohort. Normality was tested by means of D'Agostino and Pearson normality test. The Kruskal–Wallis test followed by the Dunn's *post-hoc* analysis was used to compare IOP values and medications before and after CLASS. The Wilcoxon matched-pairs signed rank test was applied to compare BCVA and mean defect (MD) at baseline and 12 M after CLASS. The Mann–Whitney *U* test was used to compare parameters between the two groups. The chi-squared test was used to compare incidence of complications between the two groups. A *p*-value of $<$ 0.05 was considered to be statistically significant.

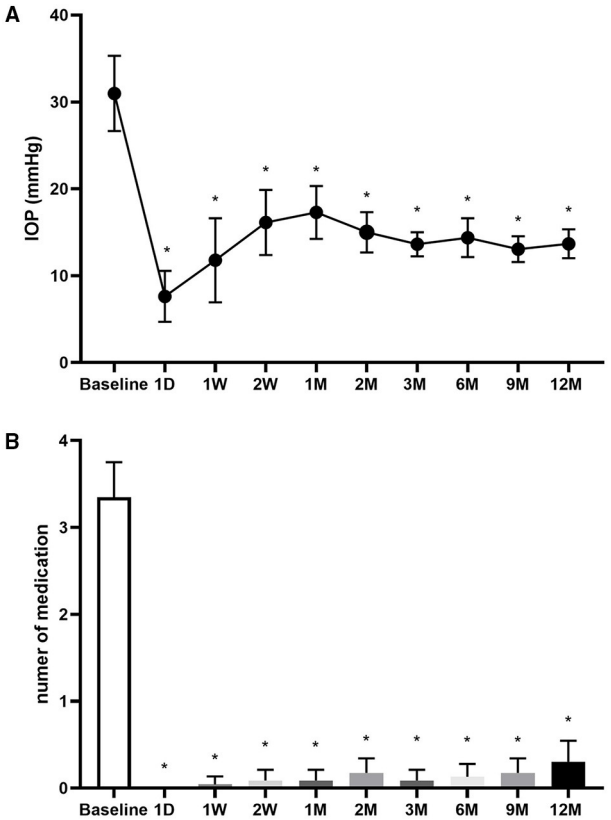

FIGURE 1 | Changes in intraocular pressure (IOP) and number of medications. **(A)** Changes in IOP at baseline and 1 day (D), 1 week (W), 2 W, 1 month (M), 2, 3, 6 9, and 12 M after carbon dioxide (CO_2) laser-assisted sclerectomy surgery (CLASS). **(B)** Changes in number of medications at baseline and 1 D, 1 W, 2 W, 1, 2, 3, 6, 9, and 12 M after CLASS. *Compared with baseline, $p < 0.001$, Kruskal–Wallis test followed by the Dunn's *post-hoc* analysis.

RESULTS

Baseline Characteristics and Changes in Visual Acuity

A total of 23 eyes with POAG that underwent CLASS were recruited in this study including 14 males (60.9%) and 9 females (39.1%). The mean age was 42.6 $\pm$ 16.0 years (range 20–68 years). There was no significant difference between the BCVA at baseline [0.4 $\pm$ 0.6 logarithm of the minimum angle of resolution (logMAR)] and 12 M (0.3 $\pm$ 0.4 logMAR) postoperation ($p =$ 0.125, Wilcoxon matched-pairs signed rank test). Besides, these

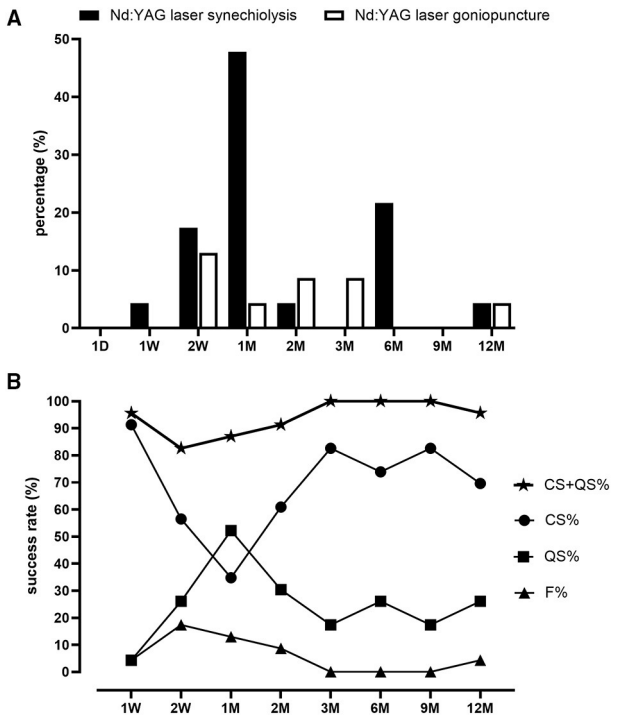

FIGURE 2 | Proportions of postoperative laser interventions and success rate after CLASS. **(A)** Proportions of patients underwent neodymium-doped yttrium aluminum garnet (Nd:YAG) laser synechiolysis and Nd:YAG laser goniopuncture at different timepoints within 1 year follow-up. **(B)** Changes of complete success (CS) rate, qualified success (QS) rate, total success rate (QS + CS), and failure rate (F) at different timepoints within 1 year follow-up.

TABLE 1 | Comparisons of patients treated with Nd:YAG laser after CO_2 laser-assisted sclerectomy surgery (CLASS).

	Nd:YAG laser synechiolysis	Nd:YAG laser goniopuncture	*P*-value$^{\Delta}$
N	17	7	
Female/Male	6/11	3/4	>0.999
Age	43.2 ± 17.4	36.9 ± 12.6	0.426
Number of medications	3.5 ± 0.8	2.9 ± 1.2	0.228
Weeks after CLASS	6.1 ± 6.9	12.1 ± 16.2	0.299
Baseline IOP[a]	39.7 ± 11.8	26.4 ± 10.2	0.565
Pre IOP[b]	25.4 ± 11.2	20.8 ± 6.4	0.390
Post IOP[c]	12.9 ± 4.2**	11.8 ± 2.2[#]	0.458
1 M IOP[d]	13.0 ± 3.7*	9.3 ± 2.8[#]	0.108
3 M IOP[e]	13.1 ± 3.1*	10.5 ± 1.9[#]	0.164
Post IOP reduction%	43.6 ± 16.9	40.9 ± 13.8	0.939
1 M IOP reduction%	46.4 ± 21.1	47.8 ± 12.6	0.975
3 M IOP reduction%	42.3 ± 22.3	40.4 ± 7.2	0.832

Nd:YAG, neodymium-doped yttrium aluminum garnet; IOP, intraocular pressure.
[a]Baseline IOP means IOP values before CLASS.
[b]Pre-IOP means IOP values before Nd:YAG laser treatment.
[c]Post-IOP means IOP values immediately after Nd:YAG laser treatment.
[d]1 M IOP means IOP values at 1 month after Nd:YAG laser treatment.
[e]3 M IOP means IOP values at 3 months after Nd:YAG laser treatment.
[**]Compared with pre-IOP, $p < 0.0001$, [*]Compared with pre-IOP, $p < 0.001$, [#]Compared with pre-IOP, $p < 0.05$, Kruskal–Wallis test followed by the Dunn's post-hoc analysis; [Δ]Compared with the Mann–Whitney U test.

patients had no significant progress in visual field at 1-year follow-up. The MD was 17.2 ± 7.0 dB at baseline and 18.5 ± 8.4 dB at 12 M ($p = 0.210$, Wilcoxon matched-pairs signed rank test), respectively.

Changes in IOP and Medications

The baseline IOP was 31.0 ± 10.0 mm Hg, which significantly decreased to 11.8 ± 11.2 mm Hg at 1 week (W) after CLASS and gradually increased to 17.3 ± 7.0 mm Hg at 1 M, due to the occurrence of PAS. Through prompt intervention by Nd:YAG laser synechiolysis, the IOP decreased and remained well controlled during the subsequent follow-ups (**Figure 1A**).

The number of medications was 3.4 ± 0.9 before operation. After CLASS, most of the patients did not need to use antiglaucoma medications (**Figure 1B**). At 12 M postoperatively, the mean medication was only 0.3 ± 0.6 ($p < 0.0001$, compared with baseline, the Kruskal–Wallis test followed by Dunn's *post-hoc* analysis).

Intraocular Pressure Elevation and Postoperative Interventions

Postoperative interventions of the patients are given in **Supplemental Table 1**. PAS most often occurred at 1 M after CLASS (11 in 23 eyes, 47.8%, **Figure 2A**), which was the main cause of postoperative IOP elevation. Among the 23 patients, six patients developed PAS twice and two patients were treated with Nd:YAG laser goniopuncture twice. Data of the first treatment were included for analysis. Generally, 17 patients (73.9%) were treated with Nd:YAG laser synechiolysis due to PAS and seven patients (30.4%) underwent Nd:YAG laser goniopuncture to deal with scleral reservoir reduction during the 1-year follow-up. The IOP was significantly reduced after laser interventions immediately and the effect lasted for at least 3 months (**Table 1**).

Figure 3 shows the images of a 61-year-old male patient (patient six in **Supplemental Table 1**), with a baseline IOP of 45.3 mm Hg under three antiglaucoma agents. He developed PAS at 3 weeks after CLASS and the IOP elevated to 20.5 mm Hg. After Nd:YAG laser synechiolysis treatment, the iris was retreated from the TDW and the IOP reduced to 10 mm Hg immediately. At 6 M postoperatively, there was no evidence of PAS from the UBM examination and the IOP was 15 mm Hg, without any medication. However, PAS occurred again at 12 M after CLASS and the IOP raised to 20.5 mm Hg. He underwent a second Nd:YAG laser synechiolysis treatment and the IOP dropped to 15 mm Hg immediately.

Figure 4 displays the examinations of a 46-year-old female patient (patient 23 in **Supplemental Table 1**), who underwent an uneventful CLASS. The IOP decreased from 39.5 mm Hg at baseline to 6.0 mm Hg at 1 W postoperatively. At 1 M after CLASS, the IOP remained 6.0 mm Hg; however, UBM examination indicated reduction of the scleral reservoir. At 2 M after CLASS, the IOP raised to 25.7 mm Hg and

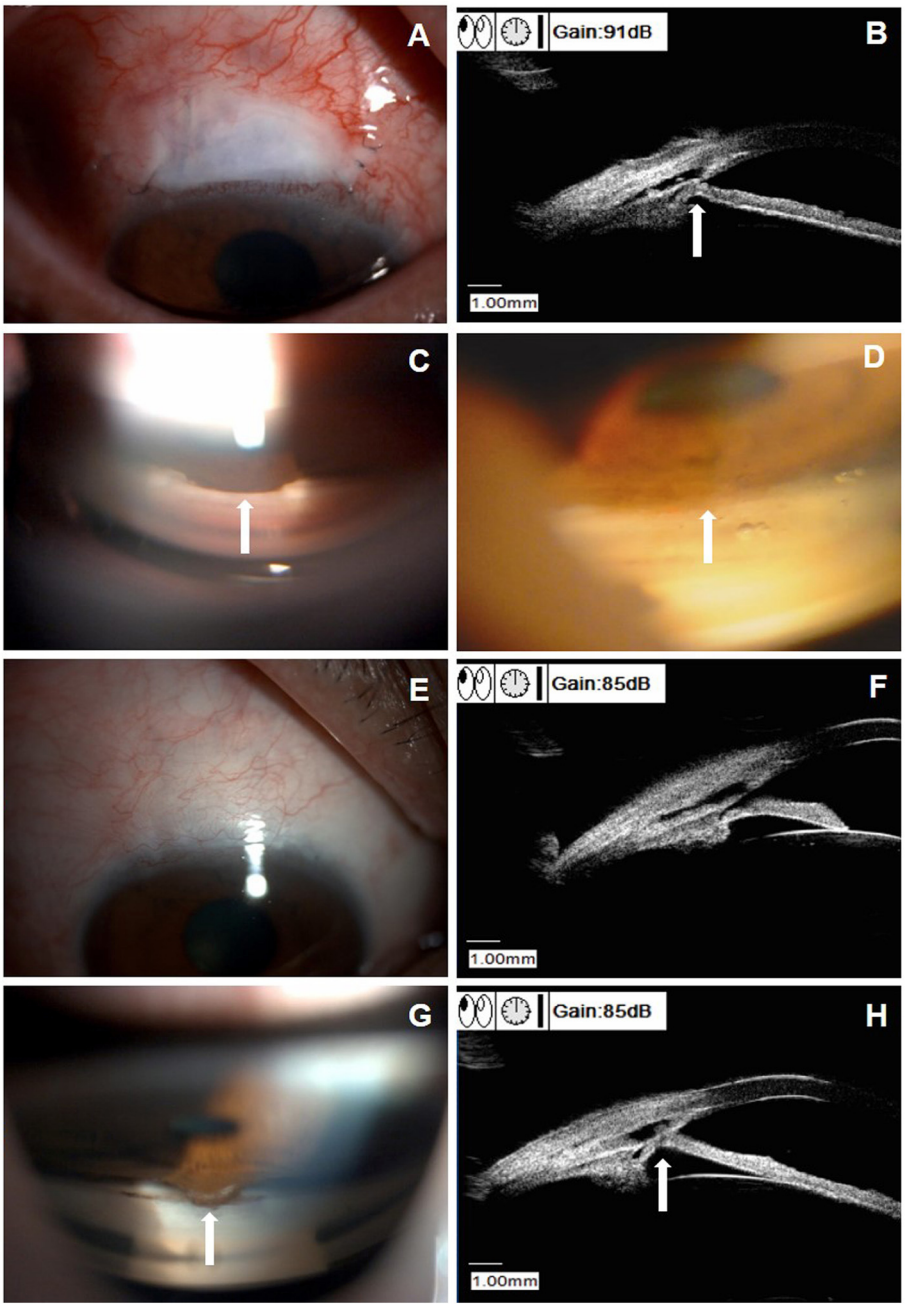

FIGURE 3 | Clinical presentations of a patient (patient six in **Supplemental Table 1**) with peripheral anterior synechiae (PAS) after CLASS. **(A)** Slit-lamp examination (DC-4, Topcon Corporation, magnification 16X) of a 61-year-old male patient at 3 weeks after CLASS. **(B)** Ultrasound biomicroscopy (UBM) examination indicated PAS (white arrow). **(C)** Gonioscopy examination confirmed PAS around the treating area (white arrow). **(D)** After Nd:YAG laser synechiolysis treatment, the iris retreated from the trabeculodescemetic window (TDW) (white arrow). **(E)** Slit-lamp examination of the patient at 6 months after CLASS showed no obvious filtering bleb. **(F)** UBM examination at 6 months after CLASS showed no PAS. **(G)** Gonioscopy examination at 12 months after CLASS showed a second PAS (white arrow). **(H)** UBM examination confirmed a second PAS (white arrow) at 12 months after CLASS.

gonioscopy examination indicated no PAS around the treating area. Then, a ND:YAG laser goniopuncture was performed and the IOP reduced to 13 mm Hg immediately. During the follow-up period, the patient developed a flat and diffuse bleb and the IOP was maintained 11–12 mm Hg without any medication.

Therapeutic Outcomes

As shown in **Figure 2B**, the complete success (CS) rate was 91.3% at 1 W after CLASS and decreased to 56.5% at 2 W and only 34.8% at 1 M. Through prompt laser intervention, CS was gradually increased to 60.9% at 2 M, 82.6% at 3 M, 73.9% at 6 M, 82.6% at 9 M, and 69.6% at 12 M, respectively. Meanwhile,

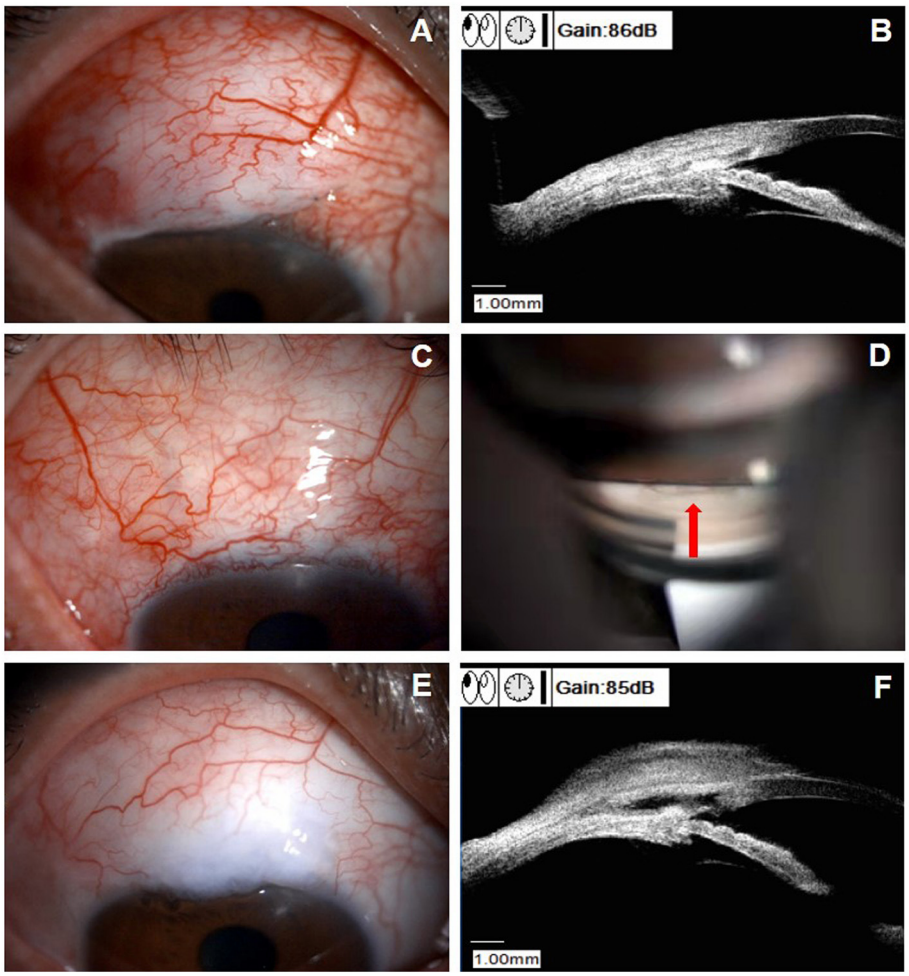

FIGURE 4 | Clinical presentations of a patient (patient 23 in **Supplemental Table 1**) with scleral reservoir reduction. **(A)** Slit-lamp examination of a 46-year-old female patient at 1 month after CLASS, with a flat congested bleb at the filtering area. **(B)** UBM examination indicated a decrease in the scleral reservoir, although the IOP was 6.0 mm Hg. **(C)** Slit-lamp examination at 2 months after CLASS showed no obvious bleb with conjunctival congestion around the filtering area and the IOP raised to 25.7 mm Hg. **(D)** Gonioscopy examination indicated no PAS and Nd:YAG laser goniopuncture was performed at the TDW (red arrow) to enhance aqueous humor outflow. **(E)** Slit-lamp examination of the patient at 9 months after CLASS showed a flat and diffuse bleb. **(F)** UBM examination at 9 months after CLASS showed an enlarged scleral reservoir with a small hole in the TDW after Nd:YAG laser goniopuncture treatment.

the qualified success (QS) rate increased from 4.3% at 1 W after CLASS to 52.2% at 1 M, which was gradually decreased during the subsequent follow-up. Total success rate (CS + QS) was over 80% at each timepoint (ranged from 82.6 to 100%). At 12 M after CLASS, the total success rate was 95.7%.

Possible Factors Associated With PAS

We compared PAS incidence between young (< 45 years) and middle-aged to elderly patients (≥ 45 years). The results showed that the PAS incidence at 1 M was significantly higher in patients younger than 45 years (83.3%) than patients older than 45 years (18.2%, $p = 0.003$, chi-squared test, **Table 2**).

Then, PAS incidence was compared according to IOP. Our results showed that PAS incidence at the early stage (within 3 months) and within 12 months follow-up was higher, although not significantly, in patients with baseline IOP ≥ 30 mm Hg than patients with baseline IOP < 30 mm Hg (**Table 2**). Within 3 months after CLASS, 14 patients developed different degrees of PAS, while the other nine patients did not show any sign of PAS. Comparisons between the two groups showed no significant difference in mean age, baseline IOP, or IOP value at the first day after CLASS, but the degree of IOP reduction was significantly higher in patients with PAS (**Table 3**, $p = 0.015$, Mann–Whitney *U* test).

Surgical Complications

Uneventful CLASS was performed in all the patients, expect for one patient who had intraoperative microperforation (4.3%). The patient developed iris incarceration and received surgical repositioning at 2 M after CLASS (**Figure 5**). During follow-ups,

TABLE 2 | Comparison of peripheral anterior synechiae (PAS) incidence after CLASS stratified by age and baseline IOP.

	Age < 45 years	Age ≥ 45 years	*P*-value	Baseline IOP < 30 mm Hg	Baseline IOP ≥ 30 mm Hg	*P*-value
N	12	11		12	11	
Age (years)	29.1 ± 6.4	57.3 ± 8.1	< 0.001*	44.8 ± 16.1	40.2 ± 16.4	0.66
Number of medications (mean ± SD)	3.3 ± 1.1	3.5 ± 0.8	0.76	3.3 ± 1.0	3.4 ± 0.9	0.89
Baseline IOP (mean ± SD)	30.1 ± 6.9	31.9 ± 12.9	1.00	23.6 ± 3.6	39.1 ± 8.3	< 0.0001*
PAS incidence at 1 month (%)	83.3%	18.2%	0.003#	33.3%	63.6%	0.22
PAS incidence within 1 month (%)	83.3%	45.5%	0.09	41.7%	81.8%	0.09
PAS incidence within 12 months (%)	83.3%	63.6%	0.37	66.7%	81.8%	0.64

**Compared by the Mann–Whitney U test; #Compared by the chi-squared (Fisher's exact) test.*

subconjunctival injection of 5-fluorouracil (5-FU) was performed in one patient (4.3%) and one patient (4.3%) developed shallow anterior chamber. No other complications were observed during the follow-up period.

TABLE 3 | Comparisons of patients with PAS within 3 months after CLASS.

	With PAS	Without PAS	*P*-value
N	14	9	
Female/Male	9/5	5/4	
Age	42.2 ± 17.2	43.1 ± 15.1	0.988
Baseline IOP	33.9 ± 10.6	26.4 ± 7.5	0.074
1 D IOP	6.7 ± 4.4	9.0 ± 9.6	0.699
IOP reduction	27.2 ± 11.0	17.4 ± 8.5	0.015*
IOP reduction%	79.3 ± 12.0	67.7 ± 26.1	0.993

IOP, intraocular pressure, D, day.
**Mann–Whitney U test, $p < 0.05$.*

DISCUSSION

Conventional trabeculectomy has been acknowledged to be the gold standard for glaucoma surgery (3). Considering the limited success rate and potential complications of Trab, efforts have been made to develop new surgical approaches. In the recent years, laser-assisted techniques have gained increasing attention and CO_2 laser is most commonly used in glaucoma surgery (15). CO_2 laser irradiation can achieve effective photoablation on dry tissue, but has a high absorption affinity for water such as aqueous humor (16). Due to its unique advantage, CO_2 laser was first applied by Assia et al. as a simplified NPDS in 2007, named as CLASS (16).

Clinical studies have demonstrated its efficacy and safety in patients with POAG (12). **Table 4** summarizes long-term outcomes of CLASS among published studies. The CS rate ranged from 45.5 to 67.9% at 12 M and ranged from 34.1 to 73.0% at 24 M. Meanwhile, the QS rate ranged from 69.2 to 93.1% at 12 M and ranged from 76.9 to 96.0% at 24 M. Compared between different populations, the mean CS at 12 M after CLASS was higher in Chinese patients (64.6%) than in Caucasian patients (44.9%). Zhang et al. conducted a study in a group of Chinese patients with POAG and reported a CS of 58.6% and QS of 93.1% at 12 M after CLASS (11). In this study, the CS was 69.8% at 1-year follow-up, which was better than their results. As shown in **Supplemental Table 2**, the definition of QS in this study was different from previous studies. Therefore, the value of (CS + QS) in this study (95.7%) was consistent with QS value in published literatures, which was also higher than previous studies (**Table 4**). In case of unexpected IOP elevation after CLASS, we preferred to reduce IOP by timely interventions (including laser treatment, surgical repositioning, or needling) according to different causes, rather than by antiglaucoma medications, which might contribute to the better long-term outcomes in this study.

Compared with Trab, CLASS had fewer complications, quicker visual recovery, and similar IOP lowering efficacy (11). As an optimized NPDS, CLASS was found to be a relatively easy procedure (13). Theoretically, CLASS offers the advantage of enhanced safety and accuracy under controllable laser ablation. However, the main drawback of laser-assisted surgery was potential collateral damage and tissue coagulation induced by the scattered energy (15). The most advanced system (OT-135P2, IOPtiMate) with a higher laser power and less beam dwell time was applied in this study to achieve effective ablation during the CLASS procedure and minimize residual momentary heating and tissue coagulation. Despite such improvement, postoperative complications such as PAS seemed to be inevitable after CLASS. As shown in **Table 4**, the incidence of PAS after CLASS ranged from 0.0 to 30.7% among previous studies. Compared with Caucasian patients, relatively higher rates of PAS were found in Chinese patients. Jankowska-Szmul et al. (9) reported only 3.0% PAS incidence and Cutolo et al. (17) reported 9.5% PAS incidence, while Zhang et al. showed a 30.0% PAS incidence after CLASS (11). In this study, the incidence of PAS was significantly higher than the abovementioned studies. Totally, 17 patients (73.9%) experienced different degrees of PAS during the follow-up period and almost half of the patient (47.8%) occurred PAS at 1 M postoperatively, which was the main cause of IOP elevation at the early stage after CLASS. We also found that the variation of PAS incidence was consistent with the fluctuation of CS and QS, which indicated that 1 M after CLASS was a critical timepoint for postoperative management.

The following factors might be associated with PAS after CLASS: (1) The TDM was a narrow and thin membrane near

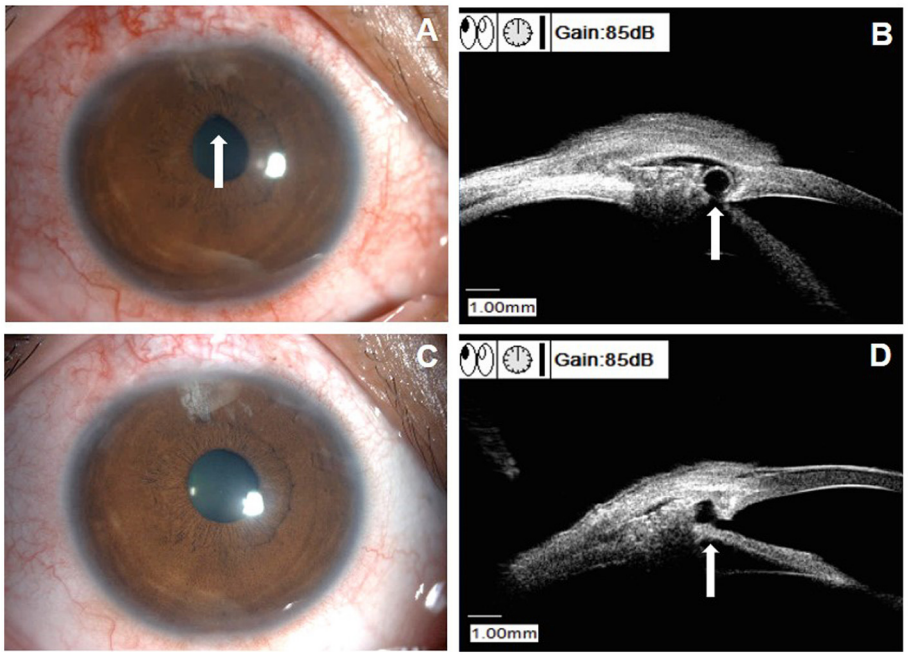

FIGURE 5 | Clinical characteristics of a patient with iris incarceration (patient 10 in **Supplemental Table 1**). **(A)** Slit-lamp examination showed a pear-shaped pupil (white arrow). **(B)** UBM examination identified iris incarceration (white arrow). **(C)** Slit-lamp examination showed the pupil shape returned to circular after surgical repositioning. **(D)** UBM examination showed the iris root returned to normal site after surgical repositioning (white arrow).

the iris root, which increased the risk of PAS (11). Recently, a modified CLASS was reported by Zhang et al., who created the TDW forward to the Schlemm's canal and relatively far from the iris root, in order to reduce the PAS incidence (18); (2) The intraoperative outflow and postoperative overfiltering promoted occurrence of PAS (11). Our results indicated a higher baseline IOP and a greater IOP reduction at the first day that might be potential risk factors of PAS. Therefore, we suggested that the IOP of the patient should be controlled lower than 30 mm Hg before operation to avoid rapid outflow of the aqueous humor during the surgery. Besides, the scleral flap should be sutured with appropriate tightness to prevent overfiltering at the early stage after CLASS; (3) Collateral thermal damage around the ablated area might lead to local inflammation and synechiae formation (11). Topical anti-inflammatory treatment was necessary during the early postoperative period; (4) A crowded anterior segment in Chinese patients with POAG (19), especially for those aged > 50 years (20), might be another reason for high PAS incidence. In this study, young patients (< 45 years) seemed to have a higher PAS incidence at the early stage after CLASS. Limited sample size and higher baseline IOP might be possible reasons for this inconsistency, which needed to be further confirmed in future studies.

Whether prophylactic laser treatment was needed before CLASS, it remains controversial so far. Zhang et al. conducted preventive laser peripheral iridotomy (LPI) and argon laser peripheral iridoplasty (ALPI) in 29 patients with POAG before a modified CLASS and reported only 6.9% of PAS incidence (18). Zhang et al. also performed LPI + ALPI in seven eyes with narrow angle before CLASS and six of them did not develop PAS postoperatively (11). In this study, none of the patient received prophylactic laser treatment before CLASS, which might be one of the reasons for the higher PAS incidence than previous studies. Based on our experience, PAS did not occur in all the patients after CLASS. Even if happened, it could be easily resolved by Nd:YAG laser intervention as long as it could be identified in time. Therefore, it is not necessary to add two invasive treatments to all the patients in order to prevent a potential complication. Also, it was difficult to ensure that the position of preoperative laser treatment was consistent with the laser ablation area. Besides, we found that PAS may occur at any time after CLASS and some patients experienced PAS more than once during the follow-up period. Regular follow-ups and individualized postoperative management were more important than prevention for these patients to achieve satisfactory long-term outcomes.

Iris incarceration was another cause of IOP elevation after CLASS. As shown in Table 5, the rate of iris incarceration ranged from 3.0 to 48.0% and only 4.3% (1/23) incidence of iris incarceration was found in this study. There was no clear definition of iris incarceration in published literatures. Sometimes, the incidence of PAS and iris incarceration were reported together. In this study, only one patient (patient 10 in **Supplemental Table 1**) developed iris incarceration after CLASS. She experienced PAS at 2 W and 1 M postoperatively and underwent Nd:YAG laser synechiolysis treatment twice. However, the IOP rose again with a pear-shaped pupil. Iris

TABLE 4 | Comparison of long-term outcomes of CLASS among published studies.

No.	First author	Year	Population	Surgery	N (eye)	PAS incidence (%)	Iris incarceration (%)	Complete success rate (%)				Qualified success rate (%)			
								6 M	12 M	24 M	36 M	6 M	12 M	24 M	36 M
1	Geffen et al.	2010	Mixed	CLASS	37	0.0%	0.0%	76.7%	60.0%	—	—	83.3%	86.6%	—	—
2	Greifner et al.	2014	Caucasian	CLASS	27	0.0%	48.0%	—	—	73.0%	—	—	—	96.0%	—
				NPDS	31	0.0%	0.0%	—	—	71.0%	—	—	—	89.0%	—
3	Skaat et al.	2014	Caucasian	CLASS	15	0.0%	6.7%	—	45.5%	—	—	—	90.9%	—	—
4	Geffen et al.	2016	Mixed	CLASS	97	5.6%	8.3%	—	60.2%	57.9%	47.8%	—	79.6%	91.2%	84.8%
5	Yick et al.	2016	Chinese	CLASS	23	0.0%	0.0%	—	—	—	—	81.8%	—	—	—
6	Cutolo et al.	2017	Caucasian	CLASS	21	9.5%	14.3%	—	—	—	—	—	—	—	—
7	Yu et al.	2018	Chinese	CLASS + Phaco	17	0.0%	0.0%	—	65.0%	—	—	—	88.0%	—	—
8	Jankowska-Szmul et al.	2018	Caucasian	CLASS	66	0.0%	4.5%	—	35.0%	—	—	—	74.0%	—	—
				Trab	65	0.0%	3.1%	—	60.0%	—	—	—	75.0%	—	—
9	Villavicencio et al.	2018	Caucasian	CLASS + Phaco	33	0.0%	33.3%	—	—	—	—	—	97.2%	—	—
				Trab + Phaco	37	0.0%	0.0%	—	—	—	—	—	86.4%	—	—
10	Jankowska-Szmul et al.	2018	Caucasian	CLASS	66	3.0%	3.0%	—	35.0%	—	—	—	74.0%	—	—
11	Zhang et al.	2020	Chinese	Modified CLASS	25	6.9%	0.0%	—	62.1%	48.3%	—	—	89.7%	89.7%	—
12	Sohajda et al.	2020	Caucasian	CLASS	22	0.0%	0.0%	72.7%	64.0%	—	—	77.0%	72.7%	—	—
13	Yan et al.	2020	Chinese	CLASS	28	10.7%	0.0%	71.4%	67.9%	64.3%	—	92.9%	85.7%	85.7%	—
14	Zhang et al.	2021	Chinese	CLASS	30	30.0%	6.7%	82.8%	58.6%	51.7%	—	100.0%	93.1%	86.2%	—
				Trab	47	0.0%	0.0%	82.6%	60.0%	47.7%	—	95.7%	93.3%	84.1%	—
15	Ho et al.	2021	Asian	CLASS	13	0.0%	0.0%	41.5%	41.5%	34.1%	24.4%	48.8%	69.2%	76.9%	53.8%
				CLASS + Phaco	28	0.0%	0.0%	—	—	—	—	—	46.4%	53.6%	50.0%
16	Current study	2021	Chinese	CLASS	23	73.9%	4.3%	—	69.8%	—	—	—	95.7%	—	—

PAS, peripheral anterior synechiae; Phaco, phacoemulsification; Trab, trabeculectomy; NPDS, nonpenetrating deep sclerectomy; IOP, intraocular pressure; M, months.

incarceration was identified by UBM examination and surgical repositioning was performed (**Figure 5**). We speculated that this patient developed microperforation during the surgery and previous laser intervention might cause small tears in the TDW, which aggravated iris incarceration. Therefore, carefully ablation and energy adjustment were critical to avoid perforation during the surgery. Also, laser spots should be applied on the attached iris when dealing with PAS without excessive puncture on the TDW. Besides, compression, massage of the eyeball, or severe cough should be avoid after CLASS, which might cause rupture of the thin TDW and the internal Schlemm's canal wall (11).

Reduction of the scleral reservoir was the third cause of postoperative IOP elevation after CLASS. Compared with Caucasian populations, fibrotic responses were more common in Chinese patients after glaucoma surgery (21, 22). Excessive coagulation around the ablating area might cause synechiae formation (23). For these reasons, either the "window" or the "lake" could scar down over time, which could be easily identified by UBM. Nd:YAG laser goniopuncture was an adjunctive procedure to achieve further reduction of IOP, by turning a nonpenetrative surgery into a micropenetrating surgery (24). It was reported that Nd:YAG laser goniopuncture could reduce the IOP by 42% after NPDS (25) and over 50% patients achieved IOP $<$ 15 mm Hg without any hypotonic medication for at least 2 years (24). About 41 to 63% proportion of Nd:YAG laser goniopuncture treatment was reported in published studies (26, 27). In this study, 30.4% patients underwent Nd:YAG laser goniopuncture at 12.1 $\pm$ 16.2 weeks after CLASS and the IOP reduced by 40.4% at 3 months after the laser treatment. Despite the beneficial effect, Nd:YAG laser goniopuncture was associated with some potential complications. The most common one was iris incarceration, which occurred in 17.6% eyes underwent Nd:YAG laser goniopuncture (24). High IOP before the treatment and laser intervention within 3 months after NPDS were two predicting factors of iris incarceration (24). In this study, we did not observe any remarkable iris incarceration after Nd:YAG laser goniopuncture. Although both the laser interventions in this study were carried out with Nd:YAG laser shot, the sites were totally different. We do not recommend performing Nd:YAG laser synechiolysis and Nd:YAG laser goniopuncture at the same time when dealing with PAS because it may increase the risk of iris incarceration.

This study had several limitations. First, the sample size was relatively small and the follow-up period was limited. It is necessary to conduct a randomized prospective study with larger sample size and longer follow-up period to further evaluate the long-term safety and efficacy of CLASS. Second, control group was not included in this study, which made the results less impactful. Moreover, there was a lack of morphological classification of the bleb and quantitative comparison of the scleral reservoir, which could provide useful information to evaluate the mechanisms after CLASS. Besides, degree of PAS was not evaluated, which might be helpful to investigate the possible reasons behind the high incidence of PAS. Despite these limitations, we distinguished PAS from iris incarceration through UBM examination and proposed a UBM-guided individualized intervention. The effect and duration of Nd:YAG laser treatment were analyzed and the risk factors associated with PAS were also evaluated in this study. These have never been addressed in detail among previous studies. We hope that our preliminary results can fill up the study gap in this field and also provide a valuable reference for clinical treatment.

In conclusion, CLASS was a safe and effective approach for Chinese patients with POAG. PAS, iris incarceration, and reduction of scleral reservoir were common causes of unexpected postoperative IOP elevation. A UBM-guided individualized Nd:YAG laser intervention can not only resolve PAS at the early stage after CLASS, but also achieve further IOP reduction whenever necessary, which helps to improve the long-term outcomes after CLASS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Second Affiliated Hospital of Zhejiang University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

MC and YG contributed to the design and concept of study, data collection and analysis, and drafting and revision of manuscript. KW contributed to the design and concept of study and performing operation. YY, XL, and QZ contributed to the data collection and analysis and interpreting results. All the authors listed have made a substantial contribution to the work and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.806734/full#supplementary-material

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SYSTEMATIC REVIEW
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The Outcomes of XEN Gel Stent Implantation: A Systematic Review and Meta-Analysis

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Purpose: XEN gel stents are used for the treatment of open-angle glaucoma (OAG), including primary and secondary glaucoma that are uncontrolled by previous medical therapy and cases with previous failed surgery. Our aim was to systematically review of the clinical data of currently published ab-interno XEN gel stents with an emphasis on intraocular pressure (IOP), antiglaucoma medication outcomes, and safety profiles.

Methods: We analyzed all of the publications (MEDLINE, EMBASE, Cochrane Library) on the ab-interno XEN gel stent to evaluate the reduction in IOP and antiglaucoma medications following the procedure. The primary outcomes measured for the meta-analysis were reduction in IOP and anti-glaucoma medications. The secondary outcome were adverse events. For each study, we used a random effects analysis model to calculate the mean difference and 95% confidence intervals for the continuous results (reduction in IOP and antiglaucoma medications) using the inverse variance statistical method.

Results: Five hundred twenty-seven articles were checked and 56 studies were found to be relevant with a total of 4,410 eyes. There was a significant reduction in IOP as well as in the number of medications required in patients treated with ab-interno XEN implant either alone or combined with cataract surgery. This new treatment for various types of glaucoma reduced the IOP by 35% to a final average close to 15 mmHg. This reduction was accompanied by a decrease in the number of antiglaucoma medications in all the studies, approximately 2 classes of medication at the price of more needlings. The overall complete success rate was 21.0–70.8% after 2 years using strict criteria originally designed to record success rate in filtration surgery. The incidence of complications vision-threatening was low at $<1\%$.

Conclusions: XEN gel stent was effective and safe for primary and secondary OAG. Further studies should be performed to investigate the impact of ethnicity on the success and failure rate after XEN implantation.

Keywords: XEN gel stent, meta-analysis, minimally invasive glaucoma surgeries, trabeculectomy, complications

INTRODUCTION

Minimally invasive glaucoma surgeries (MIGSs) are surgical interventions for mild or moderate glaucoma via the ab-interno or ab-externo approach for lowering intraocular pressure (IOP) with minimal or no scleral dissection, aiming to provide a safe profile and rapid recovery compared with traditional surgery (1, 2). MIGSs always target Schlemm's canal and the suprachoroidal space to lower IOP, which is the main complement of outflow resistance in the pathophysiology of glaucoma, whereas the XEN gel stent is the first MIGS procedure to drain aqueous to subconjunctival space. It is a 6-mm hydrophilic tube of a collagen-derived gelatin cross-linked with glutaraldehyde to prevent degradation in the tissue given the lack of a foreign-body reaction (3). XEN gel stents are preloaded in a specifically designed handheld inserter, and there are three models with different inner diameters of 140, 63, and 45 μm, which were chosen to reduce the occurrence of postoperative hypotony by the flow resistance of the tube itself according to the Hagen–Poiseuille equation (4). The outflow resistance was 0–1, 2–3, and 6–8 mmHg for devices with inner diameters of 140, 63, and 45 μm, respectively (5–7). To exclude the difference in outcomes caused by different inner diameters, the meta-analysis only included the studies focused on the devices with inner diameter of 45 μm.

XEN gel stents are used for the treatment of open-angle glaucoma, including primary and secondary glaucoma that are uncontrolled by previous medical therapy and cases with previous failed surgery (8–10). Lewczuk et al. (8) demonstrated that repeat XEN implantation might be beneficial for patients previously undergone multiple glaucoma surgeries. However, the surgical success rate after XEN implantation did not differ from that in patients with previous anti-glaucoma surgeries. Meanwhile, Lewczuk et al. (11) have demonstrated that the applied of XEN surgery appears to show promising results in patients with uncontrolled glaucoma. Patients with Shaffer 3 or 4 angles were considered as a contraindication because the iris may cause occlusion of the anterior chamber (AC) portion of the XEN implant; patients with Shaffer 2 or less could be selected provided combined with the lens extraction. Of all published studies that reported glaucoma subtypes, primary open-angle glaucoma (POAG) accounts for greater than three-fourths (75.8%). The second largest subgroup was pseudoexfoliation glaucoma in total (13.6%). Other types of glaucoma include pigmentary glaucoma, uveitic secondary glaucoma, juvenile open-angle glaucoma, and steroid-induced glaucoma, etc. Some studies enrolled patients with ocular hypertension to reduce IOP (12–16). Other studies introduced XEN to patients with primary angle-closure glaucoma (PACG), although it was originally a contraindication (9, 13, 16–21). Details on the degree of narrow angles were not reported in all studies. Sng et al. (20) reported no significant difference in the IOP reduction ($p = 0.503$) or in the decrease in the number of antiglaucoma medications ($p = 0.332$) between eyes with POAG and PACG at 12 months after XEN implantation.

XEN gel stents obtained the CE mark in December 2015 and were approved by the Food and Drug Administration (FDA) in November 2016. Since then, many studies have been published. However, no randomized control trials (RCTs) have not been performed to date. Our aim was to systematically review of the clinical data of currently published ab-interno XEN gel stents with an emphasis on IOP, antiglaucoma medication outcomes, and safety profiles.

Abbreviations: IOP, intraocular pressure; OAG, open-angle glaucoma; MIGSs, Minimally invasive glaucoma surgeries; AC, anterior chamber; POAG, primary open-angle glaucoma; PACG, primary angle-closure glaucoma; FDA, Food and Drug Administration; RCTs, randomized control trials; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MD, mean difference; CIs, confidence intervals; MMC, mitomycin C; TVT, Tube vs. Trabeculectomy; OCT, optical coherence tomography; GSS, Glaucoma Symptom Scale; GATT, gonioscopy-assisted transluminal trabeculotomy; NPDS, non-penetrating deep sclerectomy; AVB, Ahmed vs. baerveldt.

MATERIALS AND METHODS

Search Strategy

This meta-analysis is reported on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (22). Two researchers independently selected relevant studies by searching the PubMed database, the Cochrane Library, and EMBASE using the MeSH terms, including "glaucoma," "open-angle," "XEN," "micro stent," and "gel implant." We also conducted a manual search using references of major articles published in English. The studies were published between September 14, 2015 and December 15, 2021.

Study Selection and Data Extraction

The inclusion criteria were as follows: (1) prospective or retrospective case series or cohort; (2) glaucoma patients without restriction for age, sex, ethnicity, use of antiglaucoma medications; (3) XEN implantation combined with phacoemulsification or not; and (4) IOP, antiglaucoma medications, success rate, failure rate, reoperation rate, and complications. Only the studies with the longest follow-up were included for studies with overlapping populations. Case reports and reviews with <12 months of follow-up and articles lacking essential information for meta-analysis were excluded.

The following data were independently extracted from published studies by two researchers (X-zC and Z-qL) using standardized protocols: first author's last name, year of publication, study design, number of eyes enrolled, the number of different glaucoma subtypes, differences in surgical technique between studies, success, failure and reoperation rate, and complications during follow-up.

Outcome Measures

The primary outcomes measured for the meta-analysis were reduction in IOP and anti-glaucoma medications. The secondary outcome were adverse events.

Statistical Analysis

Data were processed using REVMAN (Version 5.0; The Cochrane Collaboration, Copenhagen, Denmark). For each study, we used a random effects analysis model to calculate the mean difference (MD) and 95% confidence intervals (CIs)

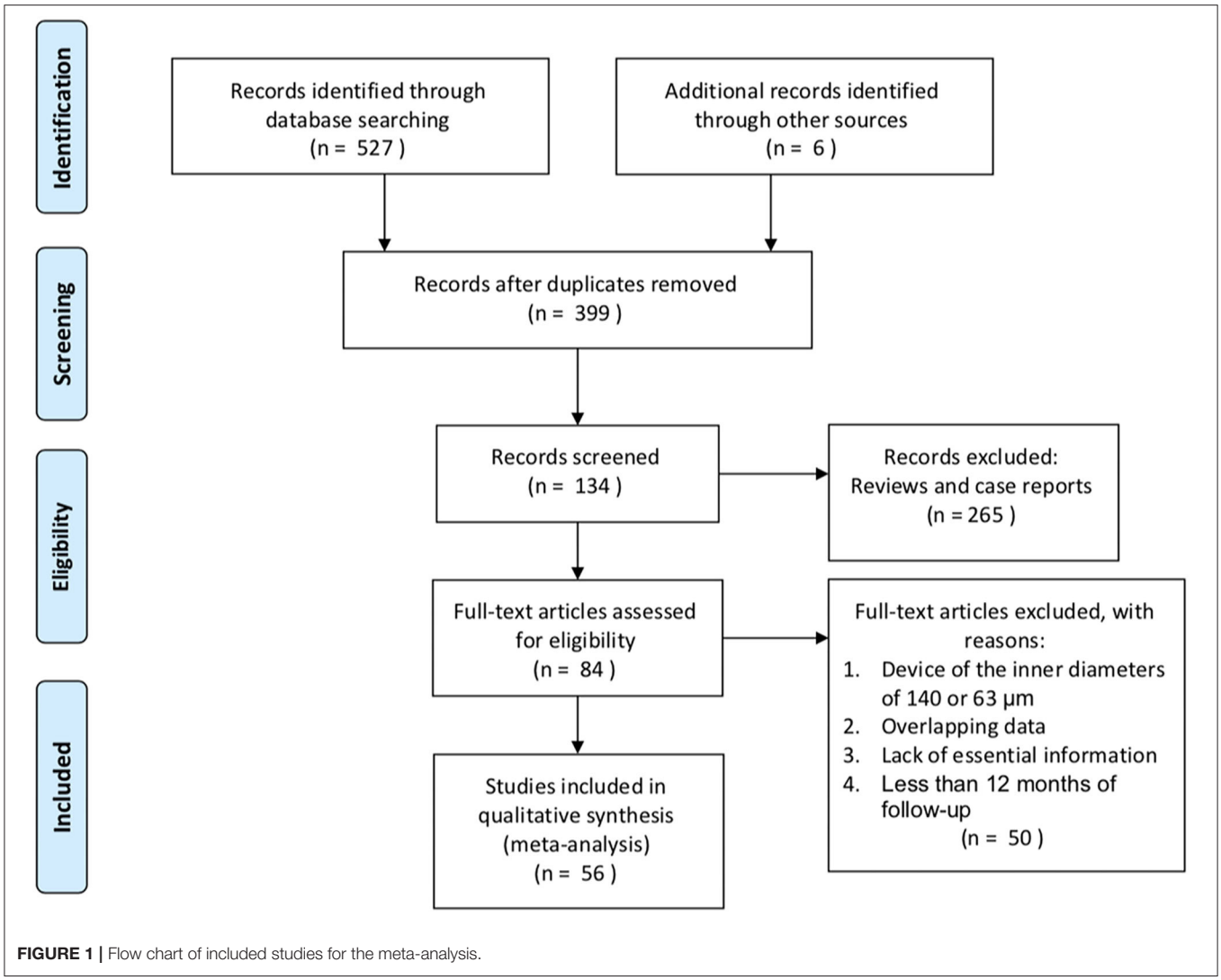

FIGURE 1 | Flow chart of included studies for the meta-analysis.

for the continuous results (change in IOP and antiglaucoma medications) using the inverse variance statistical method.

The between-study heterogeneity was tested by the chi-square-based Cochran's statistics and the inconsistency index (I-squared value) (23). I^2 testing with values >50% indicated moderate-to-high heterogeneity. $P < 0.05$ was considered statistically significant. Given the limited number of trials involved in the final analysis, we did not perform subgroup analysis and asymmetry assessment of the funnel plot for evaluating publication bias.

Surgical Technique

The surgical techniques of most studies followed similar key steps. Briefly, the preloaded injector was inserted into viscoelastic gel-filled AC through a corneal paracentesis incision. The implant entered into the subconjunctival space to a distance of 3 mm from the limbus without a conjunctival peritomy. For patients with indications for cataract surgery, the standard phacoemulsification technique was used. After the operation, as mentioned above, XEN was implanted.

The possible sources of variation in technique include the inner diameter of the gel stent and whether using mitomycin C (MMC) was used before implantation. Most studies used gel stents with an inner diameter of 45 μm, and a few studies used gel stents with lumen diameters of 140 μm (7) and 63 μm (24–26). To exclude the difference in outcomes caused by different inner diameters, the meta-analysis only included the studies focused on the devices with inner diameter of 45 μm. MMC was introduced as an adjunctive agent in the area where the XEN gel stent was to be implanted in most studies. In the studies (7, 26) that did not use intraoperative MMC, no additional bleb-related complications were reported.

In most studies, all antiglaucoma medications were stopped on the day of surgery. In addition, 1% prednisolone acetate drops were placed in the operative eye followed by a slow taper over. Prophylactic antibiotic drops were continued according to the patients' condition. When the target IOP was not reached during follow-up postoperatively, or when the progression of glaucoma was found, further treatment was performed, including reintroduction of IOP-lowering medications, needling revision,

TABLE 1 | Intraocular pressure (IOP) and medication outcomes following XEN implantation.

References	Year	Type of study	Total	Length of study (months)	(Baseline IOP (mmHg) mean ± SD)	(Final IOP (mmHg) an ± SD)	IOP decrease (%)	Mean decrease in medication
Standalone XEN outcomes								
Lenzhofer et al. (26)	2019	Prospective	69	24	22.5 ± 6.5	13.0 ± 5.2	42.2	2.2
Gillmann et al. (17)	2020	Prospective	26	36	21.0 ± 7.4	12.9 ± 2.9	38.6	2.1
Ozal et al. (32)	2017	Retrospective	9	12	36.7 ± 4.1	17.0 ± 4.2	53.7	3.1
Reitsamer et al. (33)	2019	Prospective	106	24	21.7 ± 3.8	15.4 ± 4.2	29.0	1.5
Qureshi et al. (34)	2019	Retrospective	37	12	36.1 ± 9.6	12.6 ± 4.1	65.1	3.1
Post et al. (35)	2020	Not reported	20	12	21.6 ± 2.3	17.7 ± 2.1	18.1	1.6
Bravetti et al. (27)	2020	Retrospective	60	12	29.9 ± 13.3	15.2 ± 6.6	49.2	1.7
Kalina et al. (36)	2019	Prospective	20	12	24.2 ± 8.2	13.0 ± 4.5	46.3	Not reported
Scheres et al. (37)	2020	Retrospective	41	24	19.2 ± 4.4	13.8 ± 3.8	28.1	1.6
Chao et al. (28)	2020	Retrospective	37	12	21.7 ± 7.7	15.0 ± 2.0	30.9	2.1
Olgun et al. (38)	2020	Retrospective	51	24	24.4 ± 4.3	14.2 ± 2.2	33.6	1.4
Marcos Parra et al. (39)	2019	Retrospective	17	12	22.2 ± 6.8	15.5*	30.2	2.3
Schargus et al. (14)	2020	Retrospective	153	12	23.9 ± 7.4	15.4 ± 5.1	35.6	1.8
Theilig et al. (40)	2020	Retrospective	48	12	24.4 ± 6.6	16.6 ± 5.9	32.0	1.7
Stoner et al. (15)	2021	Retrospective	52	12	21.4 ± 8.3	13.0 ± 0.6	39.3	1.3
Gillmann (17)	2021	Prospective	26	36	21.0 ± 7.4	12.9 ± 2.9	38.6	2.1
Düzgün et al. (10)	2021	Retrospective	14	12	24.1 ± 2.7	12.2 ± 2.9	49.4	2.4
Schargus (41)	2021	Retrospective	38	24	24.1 ± 4.7	15.7 ± 3.0	34.9	2.5
Nuzzi et al. (42)	2021	Retrospective	23	36	24.9 ± 6.1	19.6 ± 2.1	21.3	Not reported
Eraslan et al. (43)	2021	Retrospective	26	12	23.7 ± 6.0	16.3 ± 3.0	31.2	1.9
Bormann (44)	2021	Retrospective	31	12	23.5 ± 6.5	18.0 ± 5.3	23.4	1.7
Lewczuk et al. (8)	2021	Retrospective	43	24	25.0 ± 7.5	16.8 ± 5.1	32.8	Not reported
Wanichwecharungruang and Ratprasatporn (9)	2021	Retrospective	57	24	21.6 ± 4.0	14.6 ± 3.5	32.4	1.7
Lewczuk et al. (11)	2021	Retrospective	72	24	24.8 ± 8.0	17.5 ± 5.8	29.4	Not reported
Combined phacoemulsification with XEN outcomes								
Pérez-Torregrosa et al. (45)	2016	Prospective	30	12	21.2 ± 3.4	15.0 ± 2.5	29.2	2.9
Galal et al. (30)	2017	Prospective	10	12	16.0 ± 4.0	14.0 ± 3.0	12.5	1.5
Ozal et al. (32)	2017	Retrospective	6	12	35.2 ± 3.2	15.5 ± 2.3	56.0	3.5
De Gregorio et al. (46)	2018	Prospective	41	12	22.5 ± 3.7	13.1 ± 2.4	41.8	2.2
Kalina et al. (36)	2019	Prospective	27	12	21.0 ± 6.5	13.6 ± 2.9	35.2	Not reported
Lenzhofer et al. (47)	2019	Prospective	68	24	23.4 ± 6.3	12.7 ± 6.9	45.7	1.5
Reitsamer et al. (33)	2019	Prospective	79	24	21.0 ± 3.4	14.9 ± 4.5	29.0	1.5

(Continued)

TABLE 1 | Continued

References	Year	Type of study	Total	Length of study (months)	(Baseline IOP (mmHg) mean ± SD)	(Final IOP (mmHg) an ± SD)	IOP decrease (%)	Mean decrease in medication
Sng et al. (20)	2019	Prospective	31	12	22.1 ± 3.6	12.1 ± 2.6	45.2	1.3
Gillmann et al. (17)	2020	Prospective	66	36	20.0 ± 6.9	12.9 ± 3.4	35.5	1.4
Olgun et al. (38)	2020	Retrospective	45	24	24.8 ± 3.5	13.4 ± 1.4	46.0	1.6
Marcos Parra et al. (39)	2019	Retrospective	48	12	18.0 ± 4.5	14.3*	20.6	2
Theillac et al. (48)	2020	Retrospective	47	12	20.8 ± 6.8	16.2 ± 2.8	22.1	1.7
Theilig et al. (40)	2020	Retrospective	52	12	24.8 ± 6.9	16.4 ± 4.2	33.9	1.7
Subaşı (49)	2020	Retrospective	30	24	20.4 ± 4.8	14.8 ± 1.9	19.7	2.0
Gillmann (17)	2021	Prospective	76	36	20.0 ± 6.9	12.9 ± 3.4	35.5	1.4
Schargus (41)	2021	Retrospective	32	24	25.4 ± 5.6	14.7 ± 3.2	42.1	2.3
Eraslan et al. (43)	2021	Retrospective	32	12	24.4 ± 7.2	16.4 ± 2.3	32.8	2.1
Both outcomes								
Fea et al. (12)	2020	Prospective	171	12	23.9 ± 7.0	15.5 ± 3.9	35.1	2.5
Fernández-García et al. (24)	2020	Retrospective	40	12	18.0 ± 5.2	14.6 ± 1.9	18.9	0.6
Gabbay et al. (50)	2019	Retrospective	151	24	22.1 ± 6.5	14.5 ± 3.3	34.4	2.27
Grover et al. (51)	2017	Prospective	65	12	25.1 ± 3.7	15.9 ± 5.2	36.7	1.8
Heidinger et al. (18)	2019	Retrospective	199	12	22.8 ± 6.9	17.1 ± 5.9	25.0	1.1
Hengerer et al. (19)	2017	Retrospective	242	12	32.2 ± 9.1	14.2 ± 4.0	55.9	2.8
Ibáñez-Muñoz et al. (52)	2019	Retrospective	21	12	21.1 ± 3.8	15.2 ± 3.9	28.0	1.7
Karimi et al. (53)	2019	Retrospective	258	18	19.3 ± 6.0	13.5 ± 3.3	30.1	1.4
Laroche et al. (31)	2019	Retrospective	12	12	15.3 ± 6.2	12.9 ± 4.5	15.7	1.8
Mansouri et al. (29)	2018	Prospective	149	12	20.0 ± 7.1	13.9 ± 4.3	30.5	1.4
Rauchegger et al. (54)	2020	Retrospective	79	24	23.4 ± 7.9	14.8 ± 4.4	34.2	1.7
Smithet al. (13)	2019	Retrospective	68	12	22.1 ± 6.4	14.8 ± 5.1	33.0	1.8
Tan et al. (55)	2018	Retrospective	39	12	24.9 ± 7.8	14.5 ± 3.4	41.8	Not reported
Widder (56)	2018	Retrospective	233	18	24.3 ± 6.6	16.8 ± 7.6	30.9	2.4
Wagner et al. (57)	2020	Retrospective	82	12	Not reported	Not reported	28.9	Not reported
Teus et al. (58)	2019	Cross-Sectional	10	Not reported	19.5 ± 6.4	Not reported	43.6	Not reported
Tan et al. (59)	2021	Retrospective	50	12	23.5 ± 8.5	14.7 ± 0.8	22.9	Not reported
Busch et al. (60)	2020	Retrospective	113	12	23.8 ± 6.2	16.1 ± 4.7	32.4	2.1
Barão (61)	2020	Cross-Sectional	25	18	22.8 ± 8.4	18.2 ± 9.6	20.2	1.8

(Continued)

TABLE 1 | Continued

References	Year	Type of study	Total	Length of study (months)	(Baseline IOP (mmHg) mean ± SD)	(Final IOP (mmHg) an ± SD)	IOP decrease (%)	Mean decrease in medication
Ucar and Cetinkaya (62)	2020	Retrospective	44	12	27.4 ± 8.6	11.3 ± 1.7	58.8	2.4
Reitsamer et al. (63)	2021	Retrospective	76	36	20.7 ± 5.1	13.9 ± 4.3	32.9	1.4
Gabbay et al. (64)	2021	Retrospective	205	36	22.6 ± 7.0	14.0 ± 2.9	38.1	2.0
Baser (2020)	2020	Retrospective	29	36	24.5 ± 8.7	15.6 ± 3.6	36.3	2.0
José et al. (21)	2021	Retrospective	94	24	24.0 ± 5.2	13.5 ± 5.9	43.8	0.4
Nicolaou et al. (16)	2021	Retrospective	186	24	18.1 ± 5.8	12.6 ± 3.1	30.4	0.8
Olsen (65)	2021	Retrospective	27	12	17.8 ± 7.4	11.5 ± 3.3	35.4	2.2
Navero-Rodríguez et al. (66)	2020	Retrospective	39	12	Not reported	Not reported	19.7	2.2

The trials that only reported one set of results for both standalone and combined cases defined as both outcomes.
**Standard deviation was not reported.*

XEN replacement, and alternative filtering surgery or glaucoma drainage device surgery in refractory cases.

RESULTS

Literature Search

We identified 527 potentially eligible literature citations, of which 56 were included in this meta-analysis with a total of 4,410 eyes. The aim of most studies was to determine the postoperative course after XEN implantation in Caucasian patients with glaucoma. However, a few studies focused on Asian patients (9, 20, 27–29) and black or Afro-Latino patients (30, 31) with glaucoma. The flow chart of the search results is shown in **Figure 1**.

Overall Results

Table 1 provides the detailed characteristics of the participants from the 56 studies. There were no RCTs involving XEN. These studies were published between September 14, 2015 and December 15, 2021. The main participants in most studies were patients with POAG. However, some studies focused on the efficacy of XEN implantation in the treatment of secondary open-angle glaucoma, including pseudoexfoliative glaucoma (52, 60, 67–70) and glaucoma secondary to uveitis (34). Furthermore, a few studies introduced this gel stent to narrow- or close-angle glaucoma (13, 15, 16, 18–21, 50). All patients were treated and followed as routine clinical practice between May 2013 and February 2020. The mean sample size was 79 ± 67. The average follow-up time was 17.0 ± 8.1 months, and the follow-up loss rate of most studies was reported as <20%.

The Tube vs. Trabeculectomy (TVT) Study (71) defined success as IOP ≤ 21 mmHg or 20% lower than baseline without reoperation. Eyes meeting the above criteria and not receiving supplemental medical therapy were considered complete successes. Eyes requiring complementary medications were defined as qualified successes. This definition was used in seven studies (13, 14, 16, 34, 50, 53, 55). The complete success rate was 74.0–89.2% after 1 year (based on $n = 4$ studies) and 21.0–70.8% after 2 years ($n = 3$). The qualified success rate was 60.0–90.2% after 1 year ($n = 4$) and 34.0–86.0% after 2 years ($n = 3$). If the absolute IOP threshold was decreased to 18 mmHg (13, 18, 19, 28, 29, 36, 43, 50, 54), the qualified success rate was 25.0–90.6% and the complete success rate was 15.4–76.7% at the last follow-up. In a 4-year follow-up study (26), which was the longest follow-up period, XEN with an inner diameter of 63 μm was applied in patients with open-angle glaucoma. Fifty-three percent of patients achieved qualified surgical success, and 25% of patients achieved complete success after 4 years.

Decreasing IOP and Reducing Antiglaucoma Medications

A pooled analysis with a random-effects model showed that the IOP of the final follow-up was significantly lower than that of the baseline: XEN standalone MD = −7.80 mmHg (95% CI −7.38 to −8.21, $p < 0.001$) and Phaco + XEN MD = −8.35 mmHg (95% CI −6.88 to −9.82, $p < 0.001$; **Figure 2**). For XEN standalone studies, patients with glaucoma secondary to uveitis had the greatest reduction in IOP [MD = −23.47 in Qureshi's study (34)] followed by studies on XEN introduced in refractory glaucoma subgroups [MD = −19.70 (32), −14.70, and −11.70 (27, 36)]. Overall, XEN lowers IOP by approximately 35% to a final average close to 15 mmHg. In most studies, the proportion of IOP decreases was >30%. Only 6 studies reported that IOP decreased by <20% (24, 30, 31, 35, 49, 66). A common feature was found among these studies, which was that the baseline IOP was at a relatively low level of <22 mmHg. Patients in 4 studies attained a >50% of decrease in IOP after XEN implantation (19, 32, 34, 62). We found that the baseline IOP in these studies was in a relatively high level and most of them were >32 mmHg.

The number of antiglaucoma medications also showed a significant reduction: XEN standalone MD =-1.97 (95% CI −1.75 to −2.19, $p < 0.001$) and Phaco + XEN MD = −1.86

(95% CI −1.60 to −2.11, $p < 0.001$; **Figure 3**). Despite high heterogeneity in all analysis ($I^2 > 75\%$), a limited meta-analysis showed that the IOP and medications for both XEN standalone and Phaco + XEN were significantly decreased. Given that this review combined studies of different sample sizes, glaucoma subtypes, follow-up durations, and races, heterogeneity can be predicted. Due to the variable research design, limited number of clinical trials, and lack of specific data of subjects, it is difficult to explore the source of heterogeneity.

Risk Factors for Failure

Five studies analyzed the risk factors for failure from different points of view (12, 17, 20, 26, 29).

Many potential predictive factors for failure were taken into consideration, including age, ethnicity, systemic diseases, sex, glaucoma subtype, number of pre-operative antiglaucoma medications, pre-operative medicated and unmedicated IOP, a diagnosis of POAG, baseline MD and combined cataract surgery.

Three studies (12, 20, 29) demonstrated that none of the analyzed factors were statistically significantly ($P > 0.05$) associated with failure. One of the predictor of surgical failure is being male. The other two studies showed similar results: males had more failures than females [95% CI for effect: 4.3–56%, $p = 0.023$ (26); OR: 3.57, $p = 0.030$ (17)]. However, Gabbay et al. (64) reported that female was found to be 2.3 times (95% CI 1.1–4.9, $p = 0.02$) more likely to fail. Conflicting results have also been reported by Mansouri et al. (29) and Sng et al. (20). Gillmann et al. (17) postulated that a diagnosis of POAG (OR: 4.52; $p = 0.005$) and requiring needling revisions (OR: 4.56; $p = 0.002$) are other risk factors for failure. By analyzing the interactions between the type of surgery and the diagnosis, we found that the failure rate of POAG patients receiving combined surgery was significantly increased (univariate OR: 7.29; $p = 0.023$). The severity of glaucoma defined by MD was a suspicious risk factor (Cox hazard ratio = 1.04), but it was not statistically significant ($p = 0.14$) (29). Schlenker et al. (72) and Gabbay et al. (64) demonstrated that white ethnicity was associated with a lower risk of failure (adjusted HR, 0.49; 95% CI, 0.25–0.96; 95% CI 1.9–12.4, $p = 0.001$), whereas diabetes was associated with an increased risk of failure (adjusted HR, 4.21; 95% CI, 2.10–8.45).

Two studies reported potential factors for the requirement for bleb needling (12, 20). Fea et al. (12) demonstrated a significant correlation between the number of needling procedures and 1-day ($r = 0.24$, $p = 0.006$), 1-week ($r = 0.27$, $p < 0.001$), and 1-month ($r = 0.32$, $p < 0.0001$) postoperative IOP. However, Sng et al. (20) indicated univariate logistic regression analysis showed that age ($p = 0.43$), sex ($p = 0.32$), glaucoma subtype ($p = 0.66$), number of preoperative glaucoma medications ($p = 0.34$), preoperative medicated IOP ($p = 0.88$), and preoperative unmedicated IOP ($p = 0.76$) were not correlated with the requirement for bleb needling.

Post-operative Interventions and Reoperations

The largest part of postoperative interventions and reoperations is needling of the XEN conjunctival bleb, the rate of which was 38.7% (5–62%). In a two-year follow-up study (54), 62% of patients required a needling procedure. In most cases, a needling was required within the first month postoperatively (25%). Less than half of the needled eyes (42%) required one procedure. One study reported that after bleb needling, IOP decreased from 25.4 to 13.3 mmHg (47.6%) (6). José et al. (21) hold the idea that a small, flat, non-diffuse or large persistent fibrosis are indicators that needling was needed. Intervention in the early stages of the wound healing process may be considered more effective in improving long-term outcomes. Repeated XEN implantation has been reported in a small number of studies (8, 19, 20, 29, 53, 59, 60, 73). Filtering surgery, including trabeculectomy, Bearveldt glaucoma implant and Ahmed glaucoma valve, was another IOP-lowering method following failed XEN implantation surgery. In one study, 40% of patients required secondary glaucoma filtration surgery within 12 months in the Blacks and Afro-Latino population (31), suggesting that the increased reoperation rate may be multifactorial, including but not limited to intraluminal scarring and pigment occlusion. Following failed XEN implantation surgery, other types of laser and surgery have been subsequently reported, including selective laser trabeculoplasty (26), iSTENT (55), Cypass (53), and cyclodestructive procedures (19, 26, 53).

Complications

The published complications of XEN implantation with an inner diameter of 45 μm were shown in **Table 2**. The most common complication was transient hypotony (9.59%). Hypotony was defined as IOP <6 mmHg regardless of outcome in most studies (16, 19, 27, 29, 33, 34, 36, 50, 51, 74), and only 3 studies defined IOP as <5 mmHg (20, 37, 45). Most patients who experienced hypotony do not require additional surgical intervention and will be relieved within 1 month. The rate of chronic hypotony was low due to an intrinsic flow-limiting design based on the tube length and internal lumen diameter. In a study that introduced XEN in glaucoma secondary to medically uncontrolled uveitis, the rate of early hypotony was much higher than average, given that half of eyes (51.3%) experienced transient hypotony. However, all IOPs had stabilized by 1 month, and 18.9% of eyes required further intervention. Notably, in two studies focused on the diameters of 63 or 140 μm (7, 26), the incidence of transient hypotony was surprisingly not greater than that of XEN with the diameters of 45 μm (8.16 and 4.69%). Hypotony-related complications consisted of choroidal effusion and maculopathy, which occurred in 1.31 and 0.86% of patients post-XEN implantation respectively.

The second most common complication was hyphema, which was noted in 5.53% of patients. Most of these patients had blood occupying less than one-third of the AC (grade I hyphema), which resolved spontaneously by the first week after surgery (20). One study reported that the eye developed hyphema requiring AC washout due to vision loss caused by blood blockage (55). Transient IOP spikes ≥30 mmHg occurred in 0.67% (29)−21.54% (51) (2.11% on average) following hyphema.

Common device-related adverse events included implant occlusion (0.93%), implant malposition (0.88%), and implant exposure (0.57%). XEN implants were found to be occluded by iris tissue or blood in some studies and these were successfully

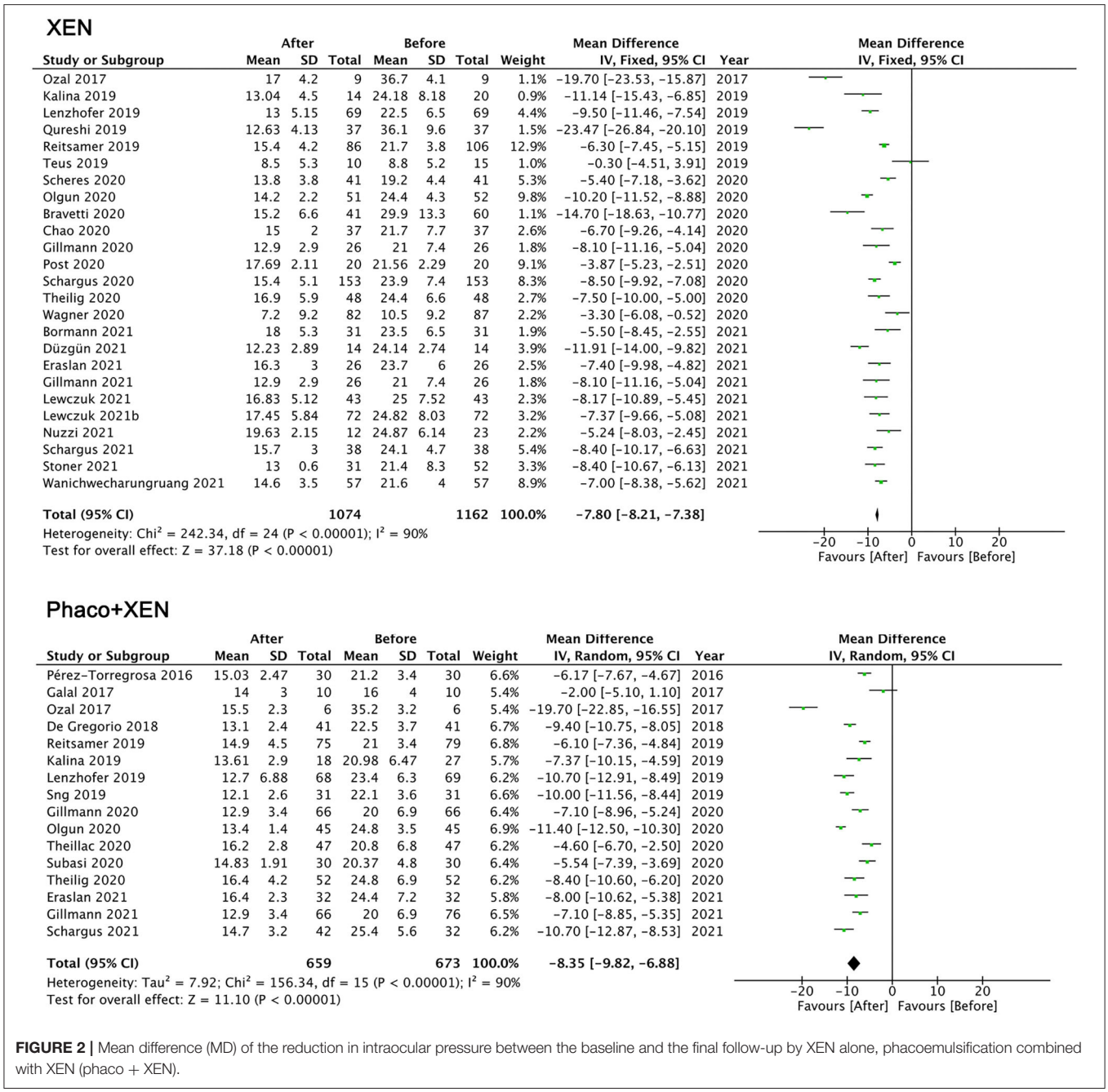

FIGURE 2 | Mean difference (MD) of the reduction in intraocular pressure between the baseline and the final follow-up by XEN alone, phacoemulsification combined with XEN (phaco + XEN).

treated with argon laser iridoplasty (55) or a second XEN device (29). Cases of stent malposition needed to remove or reimplant of the stent (12). Bleb-related complications comprised bleb leakage (0.68%) and dysesthetic blebs (0.01%) that required sutures (34, 53) or revisions (15, 35, 75).

Late-onset endophthalmitis was one of the serious complications following XEN implantation in 0.15% of patients. A case of endophthalmitis was observed 9 months after XEN implantation and a secondary surgical intervention (deep sclerectomy) (17). Another case of late-onset postoperative endophthalmitis in the fourth month postoperatively was treated with intravitreal injection of antibiotics, although microbial cultures remained negative (18). Filtering bleb leakage is a potential cause of endophthalmitis (53). Aqueous misdirection or malignant glaucoma developed in 2 patients 4–5 days after XEN implantation and vitrectomy was necessary in both cases (12, 18). Although the IOP was stable after intervention, visual acuity was reduced to a poor level (1/10) (12). Most of the studies directly specified that no patient lost >2 lines of vision. Only 13 patients (0.34%) reported permanent best-corrected visual acuity loss of ≥2 Snellen lines (26, 29, 51). Macular changes were the most possible etiology, including macular puckering, significant drusen, macular edema, and hypotony maculopathy. Other causes consisted of retinal detachment (29)

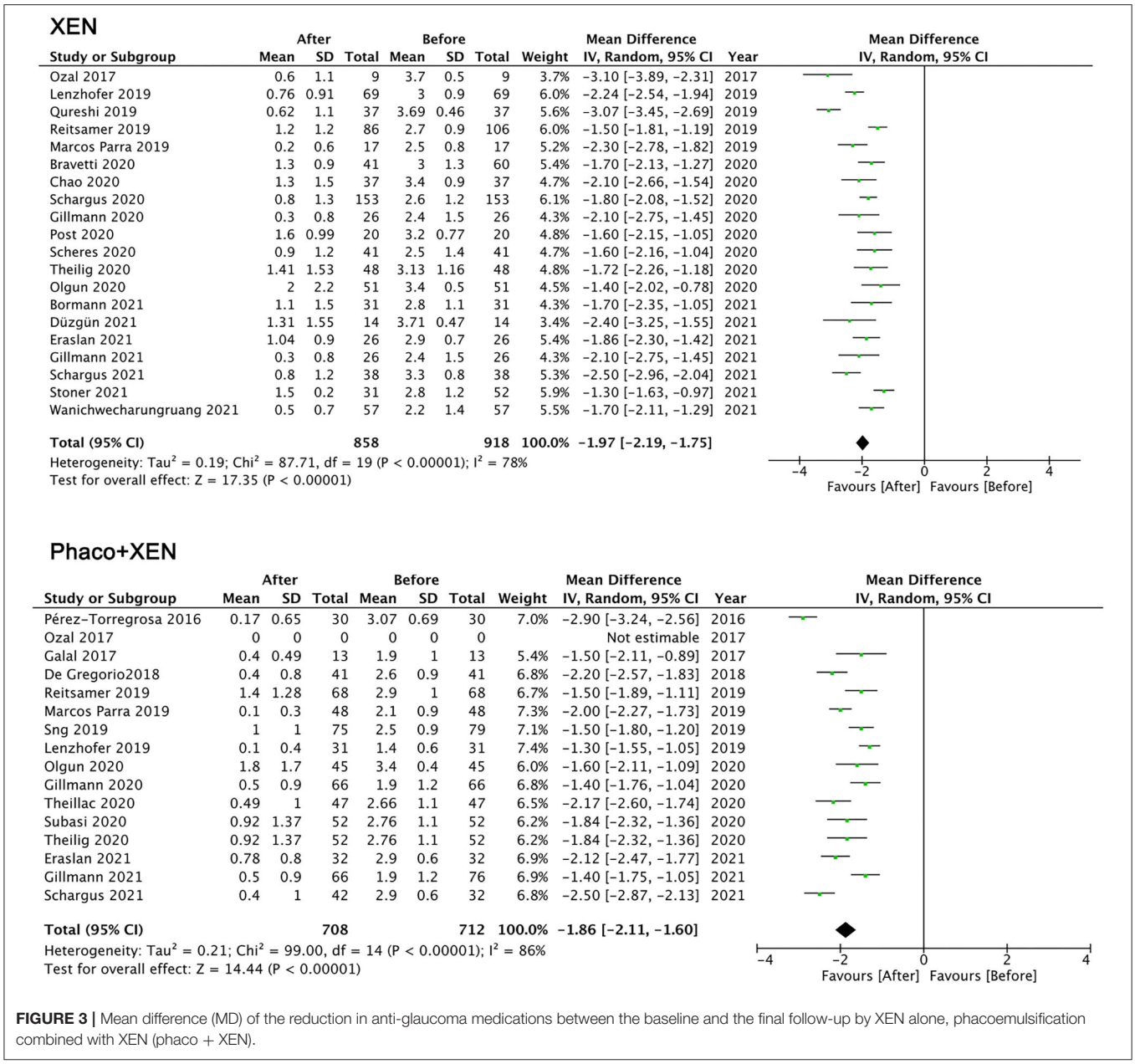

FIGURE 3 | Mean difference (MD) of the reduction in anti-glaucoma medications between the baseline and the final follow-up by XEN alone, phacoemulsification combined with XEN (phaco + XEN).

and cataracts (26, 51). None of the patients suffered from loss of light perception in any of the published studies.

Other rare complications included macular edema (0.91%), corneal edema (0.29%), retinal detachment (0.01%), and retinal vein occlusion (0.01%). There is no detailed explanation of the possible causes, whether these were of clinical significance and whether further treatment is needed.

Comparison With Other Surgeries

Eight studies compared XEN surgery with trabeculectomy. Wagner et al. (57) demonstrated that the success rate of trabeculectomy group was similar to the XEN group in the first 6 months. However, the success rate of trabeculectomy was greater than that of the XEN group after 6 months ($p < 0.05$). The reduction in IOP was greater for trabeculectomy compared with XEN ($p = 0.003$). The rate of reoperation for IOP reduction was similar between the two groups (XEN 56.5% vs. trabeculectomy 58.3%), whereas hypotony after surgery occurred more often in the trabeculectomy group (XEN 8.7% vs. trabeculectomy 25.0%). Teus et al. (58) used anterior segment optical coherence tomography (OCT) to compare the morphology of blebs formed when eyes are treated with XEN implants and trabeculectomy. The study showed that the filtering bleb formed after XEN implantation is flatter and smaller with fewer intrableb cystic cavities. Compared with filtering trabeculectomy, the degree of fibrosis of the filtering bleb after XEN implantation is lower.

The main reason for a failed trabeculectomy is episcleral or subconjunctival fibrosis (76, 77). The bleb wall was thicker after XEN implantation, which represented more functional blebs. Olgun et al. (78) reported during short-term follow-up, trabeculectomy caused more endothelial cell damage than XEN gel stent implantation. A pooled analysis with a random-effects model showed that IOP decreased more in trabeculectomy group with no significant difference; MD = −3.04 mmHg (95% CI −0.70 to −5.38, $p = 0.01$; **Figure 4**). Marcos Parra et al. (39) observed that the decrease in IOP in the trabeculectomy group was significantly greater than that in the XEN group ($p = 0.001$), and the reduction in topical glaucoma medications was similar. In terms of success rates, the proportion of patients with IOP ≥6 and ≤16 mmHg was slightly lower at 66.2% in the XEN group than 78.6% in the trabeculectomy groups ($p = 0.1317$). The incidence of hyphema and AC flattening was significantly increased compared with that in the trabeculectomy group, whereas the requirement of needlings was much higher in the XEN group. Schlenker et al. (72) demonstrated that the rates of complete success and qualified success for both interventions were similar for the threshold of 6–17 mmHg. Trabeculectomy leads to more transient complications, which are mostly driven by leaks or dehiscences, such as shallow AC. In terms of the reoperation rate, two studies (40, 79) proved that the frequency of necessary postoperative needling procedures was higher in XEN group than in the trabeculectomy group. Basílio et al. (80) evaluated and compared the quality of life of patients after XEN implantation and trabeculectomy through the Glaucoma Symptom Scale (GSS) questionnaire. The results showed that there was no significant difference in quality of life between the two groups.

In three other studies, XEN was compared with other procedures. Compared with gonioscopy-assisted transluminal trabeculotomy (GATT), XEN implantation could achieve more improvement in best-corrected visual acuity and a greater reduction in IOP and the number of antiglaucoma medications ($p < 0.05$) (38). This study revealed that the reduction in IOP was greater in the XEN group with higher medication dependence than in the GATT group, which may be due to the wound healing response in the subconjunctival area. The most common adverse event in both groups was hyphema, and endophthalmitis occurred in the XEN group. Similar to trabeculectomy, both the XEN gel stent and the PRESERFLOTM MicroShunt drain aqueous humor into the subconjunctival space. However, the MicroShunt is typically implanted through the ab-externo approach. Scheres et al. (37) demonstrated that XEN and PRESERFLOTM MicroShunt implantations achieved comparable results in IOP reduction and success rates in POAG eyes. Lower IOP values were found in the MicroShunt group at all time points, but this difference was not statistically significant at the last follow-up. The requirements for bleb needling and additional glaucoma surgery procedures were similar in both groups. In another study comparing XEN implantation and EX-PRESS drainage device implantation (15), EX-PRESS showed superiority in terms of success rate although XEN implantation could reduce the risk of hypotony and choroidal effusion with fewer postoperative clinical visits. In another 9-month follow-up study, non-penetrating deep sclerectomy (NPDS) with MMC was compared with XEN gel stent implantation with MMC (48). The mean reduction in IOP between baseline and the last follow-up was −18.9 ± 5.2% and −25.6 ± 4.3% in the XEN and NPDS groups, respectively ($p = 0.39$). The number of early complications and the number of needling procedures were similar between the two groups. A significant difference of 14.82 min in operation time (XEN 39.09 ± 12.75 min vs. NPDS 52.97 ± 14.37 min, $p < 0.001$) was noted, which made it possible to perform more procedures when XEN was used. In a 3 year follow-up study, Nuzzi et al. (42) evaluate the efficacy of XEN implantation, Cypass, trabeculectomy, and Baerveldt glaucoma

TABLE 2 | Complications reported after XEN implantation ($n = 4,410$).

Complication	Number (%)
Transient hypotony	423 (9.59)
Hyphema	244 (5.53)
IOP spikes	93 (2.11)
Choroidal effusions	58 (1.31)
Implant occlusion	41 (0.93)
Macular edema	40 (0.91)
Implant malposition	39 (0.88)
Shallow anterior chamber	39 (0.88)
Hypotonous maculopathy	38 (0.86)
Bleb leakage	30 (0.68)
Implant exposure	25 (0.57)
≥2 Snellen lines vison loss lasting >1 month	15 (0.34)
Corneal edema	13 (0.29)
Endophthalmitis	6 (0.15)

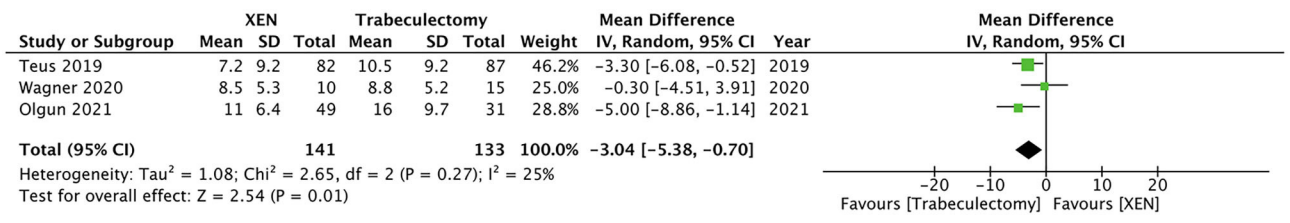

FIGURE 4 | Mean difference (MD) of the reduction in intraocular pressure between the patients after XEN implantation and trabeculectomy.

implantation. The IOP reduction >20% compared to baseline was 39.1, 55.6, 84.6, and 86.7% respectively. The rate of needling after XEN implantation was the highest, as high as 94.4%.

Eight non-randomized studies compared the outcomes between XEN standalone and XEN combined with cataract surgery. Six studies directly noted that there was no significant difference between the two groups (9, 19, 43, 53, 63, 81). Fea et al. (12) demonstrated that compared with the combined group, more patients in the standalone group achieved complete success with IOP ≤14 mmHg and no antiglaucoma medications (41.6 vs. 22.9%, respectively; $p = 0.03$). At 1 week, IOP in the standalone group was significantly reduced compared with that in the combined group ($p = 0.04$), but no significant difference was found in the follow-up. Another study (47) showed that the number of antiglaucoma medications in the standalone group was considerably reduced compared with that in the phaco + XEN group (0.76 vs. 1.4; $p = 0.06$).

DISCUSSION

This article provides the latest results on the efficacy and safety of ab-interno XEN gel stents. Previous studies have found that this new treatment for various types of glaucoma can reduce IOP by approximately 35%, and the final average value is close to 15 mmHg. In all studies, this reduction was accompanied by a decrease in the number of antiglaucoma medications, approximately 2 classes of medication. The 2-year complete success rate was 21.0–70.8% using the strict criteria originally designed to record the success rate in filtration surgery. The qualified success rate was 34.0–86.0% after 2 years. The largest proportion of reoperation and postoperative interventions was needling of the XEN conjunctival bleb, the rate of which was 38.7% with an excellent IOP-lowering effect (48.7%). Needling should be considered as a part of routine postoperative treatment. Approximately half of the needled eyes required only one procedure. A diagnosis of POAG and requiring needling revisions was postulated as a risk factor for failure. White ethnicity was associated with a lower risk of failure, whereas diabetes was associated with an increased risk of failure. For complications, the most common complication was transient hypotony (9.59%) followed by hyphema (5.53%) and IOP spikes (2.11%). The incidence of vision-threatening complications was very low at <1%.

XEN gel stent is widely implanted through ab-interno approach, however it can be successfully implanted ab-externo as well (59, 62, 75, 82, 83). Vera et al. (84) have verified that both ab-interno and ab-externo approaches for XEN implantation allowed surgeons to better optimize surgery according to the patient's personal conditions, and allows customized surgery to better adapt to the surgeon's preferences. Tan et al. (59), Ucar and Cetinkaya (62) and Do et al. (75) reported that there were no differences in outcomes between ab-interno and ab-externo approaches of the XEN implantation in terms of the IOP reduction and the success rate. Great interest has been expressed in the rate of needling in eyes undergoing XEN implantation. Nuzzi et al. (42) reported the rate of needling after ab-interno XEN implantation was as high as 94.4%. However, many studies (62, 75, 82, 83) have demonstrated that the ab-externo XEN implantation could reduce the rate of needling to as low as 11.8%. They hold a similar view that through ab-external implantation, blunt and broad dissection between Tenon's tissue and scleral could form a better separation between the tissue and the distal end of the gel stent, which helped to reduce the requirement to perform needling postoperatively.

At present, the most frequently performed procedure to combat glaucoma is trabeculectomy (85), relieving the intraocular pressure by draining aqueous to the subconjunctival space and representing the gold standard for surgical treatment of glaucoma. Although it effectively reduces IOP and is cost-effective, it requires close follow-up because of potential complications, such as shallow AC and bleb-related adverse events, which may lead to severe vision loss (86). Similar to trabeculectomy, XEN implantation allows subconjunctival filtration to form a permanent outflow channel to reduce IOP from the AC to the subconjunctival space. The primary advantage of XEN compared with trabeculectomy is that it is a less time-consuming procedure with less surgical trauma, which causes lower rates of intra- and postoperative complications (46). Although the lack of randomization may be unfortunate, there were several interesting studies comparing the safety and efficacy of XEN implantation to trabeculectomy in patients with POAG. The decrease in IOP was greater in patients after trabeculectomy compared with those after XEN implantation. These authors demonstrate that there is no significant difference in the relative risk of failure between XEN implantation and traditional trabeculectomy. Transient hypotony after surgery occurred more frequently in the trabeculectomy group. The rate of hyphema and AC flattening was significantly greater in the trabeculectomy group, whereas the requirement of needling was greater in the XEN group.

The multicentre studies by Kirwan et al. (85) of 428 eyes and the TVT study (87) of 117 eyes confirmed a higher rate of IOP reduction with trabeculectomy of 46.1 and 46.0% over 2 and 3 years of follow-up, respectively, when comparing the IOP reduction of XEN to trabeculectomy. which was much higher than we reported in our review on XEN implantation (35%). With less trauma intraoperatively and the specific designed tube to prevent excessive drainage, the rate of shallow AC after XEN implantation was much lower than that after trabeculectomy (0.88 vs. 0.90–3%). Loss of 2 or more Snellen lines from baseline visual acuity had occurred in 15% of patients and was lower in the stent group than in the trabeculectomy group at 3 years. Regarding bleb needling to lower IOP, the rate after XEN implantation was much higher than that after trabeculectomy (38.7 vs. 16 and 20%). Subconjunctival fibrosis has been considered a key factor leading to surgical failure and postoperative intervention such as needling. Although the degree of conjunctival manipulation in XEN implantation is lower than that in trabeculectomy, postoperative loss of IOP control due to subconjunctival fibrosis is more common. Marcos Parra et al. (39) found the incidence of needling and bleb fibrosis was greater in the XEN implant group. However, in a study using OCT to evaluate the morphology of blebs, Teus

et al. (58) found high reflectivity regions in 40% of patients who received trabeculectomy, which was considered a sign of subconjunctival fibrosis, but not as high as in the blebs formed after XEN implantation. Therefore, further studies are required to investigate the incidence and difference in mechanisms between these two procedures.

Both the Ahmed and Baerveldt implants are 2 frequently used aqueous shunts for glaucoma. The Ahmed Versus Baerveldt (AVB) study (88) showed that the reduction in IOP was 47% in the Ahmed group and 57% in the Baerveldt group after 5 years, and these values were considerably greater compared with that found for the stent (35%) in this review. The AVB study reported that the most common complications were shallow AC (15% Ahmed, 17% Baerveldt), choroidal effusions (13% Ahmed, 16% Baerveldt), and persistent corneal edema (11% Ahmed, 12% Baerveldt), all of which were lower with the XEN stent. Bleb needling was necessary in 3% of patients in both aqueous shunt groups and in 38.7% of patients after XEN implantation. Therefore, the efficacy of the XEN gel stent have less reduction in IOP to that of trabeculectomy and other aqueous shunt procedures with fewer complications, but at the price of more needlings.

To date, cost-effectiveness evidence for the XEN gel stent is not available (89), which will be the main consideration that will definitely affect the acceptance of new surgical procedures. Theillac et al. (48) suggested that compared with the traditional filtration surgery, XEN implantation could reduce operation time, which could be used to perform other surgical procedures, and offset the additional cost. Marques et al. (90) and Busch et al. (60) intended to evaluate the learning curve of XEN gel stents with several surgeons from different professional fields. It has been demonstrated that for experienced surgeons and novice residents, XEN implantation showed a fast learning curve. By the time of the sixth implantation, the average operation time and the incidence of complications were reduced in both groups, which was not related to the surgical background or expertise. A shorter learning curve and shorter operation time than other procedures will influence surgeons' choice of diverse microinvasive surgeries.

Different opinions have been raised on whether ethnicity is an influencing factor of the surgical failure rate. Laroche et al. (31) found that among the Black and Afro-Latino patients who received XEN implantation, 40% required additional surgery within 12 months. The success rate was lower than that of studies conducted in a predominantly Caucasian population because the amount of pigment in the iris was significantly higher in the Black and Afro-Latino populations (91), resulting in pigment obstruction of the XEN gel stent. Subconjunctival scarring and fibrosis may be other possible causes of the increased surgical failure rate in Blacks and Afro-Latino patients. Gabbay et al. (50) hold a similar opinion that more postoperative interventions were conducted for the non-Caucasian group. Chao et al. (28) demonstrated that a reoperation rate as high as 45.9% may be related to patients of Chinese ethnicity. Previous studies (92–94) have reported that Asian and Black/African ethnicities exhibit an increased risk of failure with trabeculectomy. Broadway et al. (95) found that the number of fibroblasts and macrophages in the superficial and deep layers of the conjunctival propria in African descent patients was higher than that in European descent patients. This finding partly explains the high tendency of scar formation and failure after filtration surgery in African descent patients. However, the other two studies (27, 51) showed that ethnicity had no statistically significant impact on outcomes. The difference of this may be due to the fact that Asian or Black patients in these two studies accounted for <25%. Therefore, further studies should be performed to investigate the impact of ethnicity on the success and failure rate after XEN implantation.

Although XEN gel implantation is a novel procedure, it has long-term potential in the treatment of glaucoma. Future large-scale, randomized clinical data will help surgeons develop personalized management strategies for each patient. First, it is urgent to study mixed ethnicity or African/Asian populations because most published studies were on Caucasian patients. Second, more studies are required to compare the characteristics of blebs formed when eyes are treated with XEN implants and trabeculetomy or aqueous shunts, which is one of the major factors influencing the outcomes. Third, needling rates and effects should also be studied because minimal conjunctival tissue dissection was required during implantation of the device; however, excessive manipulation of conjunctiva was introduced by the needling procedure. Finally, although the XEN device used in angle-closure glaucoma has been studied, more research and large-scale, standardized, randomized studies are needed to evaluate the outcomes for patients with angle-closure glaucoma. If XEN gel stents are effective in treating such cases, they may become a choice for surgeons in the face of various types of glaucoma.

CONCLUSIONS

The XEN gel stent is the first ab-interno MIGS method used to drain aqueous to subconjunctival space. This implant obtained the CE mark in December 2015 and was approved by the FDA in November 2016. XEN can be expected to reduce IOP by approximately 35%, and the final average value is close to 15 mmHg, which is accompanied by a decrease in the number of antiglaucoma medications, approximately 2 classes of medication. Further studies should be performed to investigate the impact of ethnicity on the success and failure rate after XEN implantation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

X-zC and Z-qL searched literatures, analyzed and interpreted the patient data, and drafted the manuscript regarding the XEN gel stent used for OAG. M-yL, KL, YM, and K-yY helped to search literatures. H-jW designed the work and substantively revised it. All authors have read and approved the final manuscript.

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Mycophenolate Mofetil (CellCept®) in Combination With Low Dose Prednisolone in Moderate to Severe Graves' Orbitopathy

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Although corticosteroids are currently the first-choice drug for thyroid eye disease (TED), in 20–30% of cases, patients show poor or non-existent responses, and when the drug is withdrawn, 10–20% of patients relapse. Thus, in this study, we aimed to investigate the efficacy of the combined use of mycophenolate mofetil (CellCept®) and low dose oral prednisolone in patients with moderate to severe Graves' orbitopathy (GO). For the first time, we investigated the relationship between TED-related parameters and proptosis reduction. In a prospective, non-randomized, interventional case series, 242 patients with moderate-to-severe GO were, assigned to receive oral prednisolone (5 mg/ d) and mycophenolate mofetil (CellCept®) (one 500 mg tablet twice per day according to the therapeutic response). The patients were monitored regularly during the 3rd, 6th, 12th, and 18th month of treatment. The main outcome measures were the clinical activity score (CAS), intraocular pressure (IOP), diplopia, proptosis and visual acuity. We also assessed the relationship between the main outcomes with proptosis changes and time to improvement (months). Adverse effects were recorded during each visit. The clinical response rate increased from 67.7% on the third month to 89.2% on the sixth month, and 94.2% on the 12th month. This therapeutic response continued until the 18th month of follow-up. The CAS responses [disease inactivation (CAS < 3)] improved during our study: 70.6% on the third month, 90.0% on the sixth month, and 92.5% at 12th month. These conditions continued until the 18th month of follow-up. Proptosis improvement was 52% on the third month, 71% on the sixth month, 83% on the 12th month, and 87.1% on the 18th month. Changes in IOP and visual acuity were not significant ($P = 0.568$ and 0.668, respectively). The patient showed significant improvement in the Gorman score. A Shorter duration of treatment was seen in patients with earlier onset of intervention, younger age, and lack of all extraocular muscle (EOM) enlargement on computed tomography (CT) scan ($p < 0.05$). In addition, a better response (more reduction) in proptosis was related to: younger age at disease, earlier treatment intervention (less interval from the time the diagnosis of moderate-to-severe

GO was made until medication initiation), shorter treatment time (less time to improvement), less IOP, lack of EOM enlargement on CT scan, and lack of diplopia ($P < 0.05$). Adverse events occurred in six patients. Findings show that mycophenolate mofetil (CellCept®) plus low-dose prednisolone can be introduced as a new optimal dosing regimen in GO due to its better effect on chronic complications such as proptosis and diplopia.

Keywords: Graves' orbitopathy, prednisolone, CellCept®, mycophenolate mofetil (MMF), thyroid eye disease (TED)

INTRODUCTION

Graves' orbitopathy (GO) is an inflammatory disorder of the orbit that occurs more frequently in females than in males and in the middle age than in other age groups. Moreover, GO is associated with autoimmune thyroid disease (1). Although the etiology of GO is unknown, the role of B and T lymphocytes has been established, and histological examination has shown infiltration of activated B cells, T cells, and macrophages, and expansion of orbital fat tissues and extraocular muscle (EOM) (2). Unfortunately, the medical treatment of GO remains a big problem and challenge in some patients.

In a much as 20–60% of patients with active GO, medical treatment with oral and/or intravenous steroids may fail and mainly depend on the form of administration and dosage, and these patients suffer recurrence and experience significant adverse effects (3–5). Due to these limitations, new treatments that directly target pathogenic mechanisms of GO have long been sought (6).

Numerous new treatments using novel immunomodulatory drugs, such as rituximab have been introduced to modulate inflammatory disorders but in (GO), immunosuppressive drugs such as methotrexate, tumor necrosis factor (TNF)-alpha inhibitors, or azathioprine have limited effects on the long-term sequelae of thyroid eye disease, such as disability from proptosis and diplopia, which impair quality of life (7–9).

Mycophenolate mofetil (MMF) is a selective, reversible and competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH) that is used in combination with cyclosporine and corticosteroids to prevent graft rejection subsequent after stem cell or solid organ transplantation. Metabolite mycophenolic acid (MPA) is the prodrug of MMF that is hydrolyzed by esterases. Metabolite mycophenolic acid inhibits inosine monophosphate dehydrogenase (IMPD), leading to the inhibition of the *de novo* pathway for guanosine monophosphate (GMP) synthesis, which suppresses the *de novo* synthesis of purines, primarily blocking proliferation and inducing the apoptosis of activated B and T lymphocytes. In addition, MPA by guanosine-tri-phosphate (GTP) depletion leads to decreased expression of adhesion molecules and modulation of the chemotaxis of activated lymphocytes in inflammatory tissues (10, 11).

Due to immune modulatory effect, MMF has been evaluated and used in various autoimmune diseases; however, the results of using MMF in GO have been very variable and performed in patient with moderate to severe GO and on a low sample size. Thus, in this study, we aimed to assess the efficacy and tolerability of combined therapy with MMF (CellCept®) and low doses oral prednisolone in GO and provide the basis for further studies to introduce a new regimen for moderate to severe thyroid eye disease (TED).

PATIENTS AND METHODS

In a prospective, non-randomized, interventional case series, 261 patients who were diagnosed with GO, between September 29, 2014 and July 31, 2018 in the Farabi Eye Hospital were enrolled in this study. Approval for the study was obtained from the ethical committee of the Tehran University of Medical Sciences which is in compliance with the Helsinki Declaration. All patients received a thorough explanation of the study design and aims, and were provided with written informed consent.

The patients enrolled in this study were: (1) 18–60 years old; (2) diagnosed with hyperthyroidism and were on antithyroid therapy or diagnosed with euthyroidism who previously used antithyroid therapy; and (3) diagnosed with active TED [clinical activity score $\geq$ 3: gaze-provoked orbital pain, orbital pain at rest, lid swelling, lid redness, conjunctiva redness, chemosis, or swelling of the caruncle (12)] that was moderate to severe [according to the European Group on Graves' Orbitopathy (EUGOGO) color atlas evaluation (13)]. The patients should not have previously received corticosteroid or immunosuppressive treatment for GO or any reason within the past 3 months. Patients with impaired heart, kidney, and liver function, intraocular pressure (IOP) above 40 mm/Hg, other inflammatory diseases of the orbit, sinusitis, optic neuropathy, exposure keratopathy (EK), orbital radiotherapy and any relevant malignancy were excluded from this study.

Oral prednisolone combined with mycophenolate mofetil (CellCept®) was administrated to all patients. Oral prednisolone was started at dose of 20 mg and was gradually tapered, with a reduction of 5 mg per week for 3 weeks and then continued at a dose of 5 mg (orally once a day). Patients also received 500 mg of mycophenolate mofetil (CellCept®) orally twice per day which is a commonly used dose in patients with autoimmune diseases and continued depending on the clinical response. This regimen was continued for 3 months after clinical response, and then discontinued in such a way that, prednisolone was abruptly discontinued and CellCept® was gradually tapered, with a reduction of 500 mg for 1 month (orally one per day), and then discontinued.

All patients underwent complete ophthalmic at baseline and at 3, 6, 12, and 18 months after starting the treatment, and monthly

endocrine assessments. Ophthalmic assessment was performed by a single ophthalmologist, using a researcher-made form, including soft tissue involvement (inflammatory eyelid swelling), clinical activity score (seven items) (12), proptosis in mm (measured using a Hertel exophthalmometer), diplopia [assessed using the Gorman diplopia score: no diplopia (absent), diplopia when the patient was tired or awakening (intermittent), diplopia at extremes of gaze (inconstant) and continuous diplopia in the primary and reading position (constant)], visual acuity using the Snellen chart in decimals, and IOP using the Goldmann applanation tonometer. At the beginning of the study, all patients underwent spiral orbital computed tomography (CT) scans to assess the size and enlargement of extraocular muscles.

The primary outcome was the overall response at the 3rd, 6th, 12th, and 18th month. Response was defined as the reduction of at least two measures in the composite index in at least one eye, without deterioration in any of the same measures in either eye; that is, improvement in soft tissue involvement by one grade in any of the following: eyelid swelling, eyelid erythema, conjunctival redness, or conjunctival edema; improvement in clinical activity score by at least 2 points or more points or disease inactivation, improvement in proptosis of at least 2 mm, improvement in vertical palpebral fissure of at least 2 mm, improvement in diplopia (disappearance or change in the degree), increase in visual acuity $\geq$ 2/10 and IOP changes.

The tolerability and safety of this regimen were assessed by recording the adverse events, physical examinations and laboratory parameters. At each visit, all patients were questioned about any adverse events. Adverse events were defined as any undesirable symptoms or sign that occurred after the initiation of treatment, regardless of its relation to the study drug. A serious adverse event was defined as any untoward medical occurrence that, at any dose, was life-threatening, required hospitalization, required medical intervention, or resulted in persistent or significant disability, incapacity, or a congenital malformation. Adverse events were usually monitored by the endocrinologist and did not influence the ophthalmological examination. Laboratory tests including glucose, electrolytes, transaminases, serum lipid and uric acid, kidney function, and body weight were assessed every month.

All statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). The mean, median, standard deviation, median, frequency and percentage were used to express the data. A linear mixed model was used to investigate changes in the parameters during the study and changes in proptosis. Kaplan–Meier survival graphs were used to determine the intensity of the treatment. $P < 0.05$ indicated a statistically significant difference.

RESULTS

A total of 261 patients received MMF in combination with prednisolone. Thirteen patients due to lack of documentation and six patients due to adverse events were excluded from this study. A total of 61.2% (148) of our study were female, and the mean age was 39 ± 12 years old. Of the patients, 20.2% were under 30 years old, 55.4% were between 31 and 45 years old, and 24.4% were over 45 years old. The demographic and clinical data of the patients at baseline are summarized in **Table 1**. The mean start time of medication (from the time diagnosis of moderate to severe GO was made) was 7 ± 4 months. In 122 patients (50.4%), the start time of medication was <6 months from the time of the GO diagnosis, and in 120 patients, more than 6 months had passed since the onset of the GO before treatment was initiated.

The clinical response rate increased from 67.7% on the third month to 89.2% on the sixth month and 94.2% on the 12th month. This therapeutic response continued until the 18th month of follow-up (**Table 2**; **Figure 1**).

TABLE 1 | Baseline demographic and clinical data.

Parameter		Value
Age	Mean ± standard deviation (SD)	39 ± 12
	≤30	49 (20.2%)
	31–45	134 (55.4%)
	46+	59 (24.4%)
Sex	F	148 (61.2%)
	M	94 (38.8%)
Start time of medication [from the time the diagnosis of moderate to severe Graves' orbitopathy (GO) was made]	Mean ± SD	7 ± 4
	≤6	122 (50.4%)
	7+	120 (49.6%)
Time to improvement (months)	Mean ± SD	10 ± 6
	Median (range)	9 (2 to 26)
Clinical activity score (CAS)	Mean ± SD	5.4 ± 0.2
Intraocular pressure (IOP)	Mean ± SD	20 ± 4
	Median (range)	18 (10 to 34)
Proptosis	Mean ± SD	21.5 ± 1.8
	Median (range)	22 (17 to 26)
Visual acuity (mean, most affected eye)	Mean ± SD	0.93 ± 0.13
All extraocular muscle (EOM) enlargement	No	196 (81.0%)
	Yes	46 (19.0%)
Conjunctival injection	No	83 (34.3%)
	Yes	159 (65.7%)
Caruncular/plica injection	No	120 (49.6%)
	Yes	122 (50.4%)
Chemosis	No	85 (35.1%)
	Yes	157 (64.9%)
Lid swelling	No	135 (55.8%)
	Yes	107 (44.2%)
Pain	No	158 (65.3%)
	Yes	84 (34.7%)
Retraction	No	87 (36.0%)
	Yes	155 (64.0%)
Diplopia (Gorman)		
Absent	96 (39.6%)	
Intermittent	84 (34.7%)	
Inconstant	44 (18.1%)	
Constant	18 (7.4%)	

TABLE 2 | Ophthalmological evaluation during the study.

Parameter	Time									
	Baseline	Month 3		Month 6		Month 12		Month 18		*P*-value
			P		*P*		*P*		*P*	
Clinical activity score (CAS; [mean ± standard deviation (SD)]	5.4 ± 0.2	2.8 ± 1.1	<0.001	2.3 ± 1.2	<0.001	1.5 ± 1.2	<0.001	1.2 ± 1.1	<0.001	<0.001
Improved	–	171 (70.6%)		218 (90.0%)		224 (92.5%)		224 (92.5%)		
Unchanged	–	71 (29.4%)		24 (10.0%)		8 (7.5%)		18 (7.5%)		
Worsened	–	0		0		0		0		
Intraocular pressure (IOP, mmHg; mean ± SD)	19.7 ± 4.3	19.5 ± 4.1	0.98	20.0 ± 32.9	0.999	19.5 ± 4.2	0.996	19.6 ± 4.4	>0.99	0.568
Proptosis (Mean ± SD)										
Right eye	21.5 ± 1.8	20.3 ± 1.7	< 0.001	19.3± 1.9	<0.001	18.4 ± 2	<0.001	18.06 ± 1.8	<0.001	<0.001
Left eye	21.31 ± 1.25	20.19 ± 1.57	< 0.001	18.97 ± 1.7	<0.001	18.28 ± 2	<0.001	17.85 ± 1.8	<0.001	
Improved	–	126 (52%)		172 (71%)		201 (83%)		211 (87.1%)		
Unchanged	–	116 (48%)		71 (29%)		41 (17%)		31 (12.9%)		
Worsened	–	0		0		0		0		
Diplopia (Gorman)										
Absent	96 (39.6%)	130 (53.7%)	<0.001	182 (75.2%)	<0.001	208 (85%)	<0.001	214 (88.4%)	<0.001	<0.001
Intermittent	84 (34.7%)	70 (28.9%)	0.012	39 (16.1%)	<0.001	16 (6.6%)	<0.001	11 (4.5%)		
Inconstant	44 (18.1%)	32(13.2%)		17 (7%)		14 (5.7%)		13 (5.3%)		
Constant	18 (7.4%)	10 (4.1%)		4 (1.6%)		4 (1.6%)		4 (1.6%)		
Improved	–	179 (73.9%)		212 (87.6%)		228 (94.21%)		231 (95.4%)		
Unchanged	–	63 (26.03%)		27 (11.15%)		14 (5.78%)		11 (4.6%)		
Worsened	–	0		3 (1.2%)		0				
Visual Acuity (mean ± SD)	0.93 ± 0.13	0.92 ± 0.14	0.999	0.92 ± 0.12	0.985	0.94 ± 0.13	0.898	0.95 ± 0.11	0.777	0.668
Response	–	164 (67.7%)		216 (89.2%)		228 (94.2%)		228 (94.2%)		

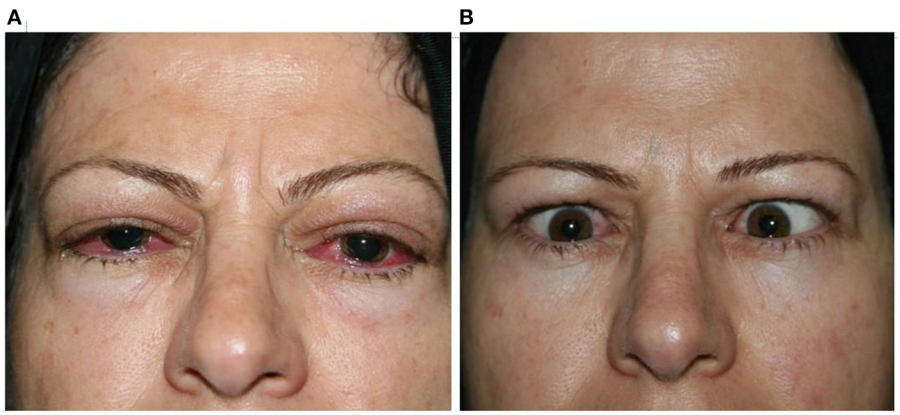

FIGURE 1 | Clinical response 2 months [**(A)** before; **(B)** after] after receiving MMF combined with low-dose prednisolone.

The mean clinical activity score (CAS) decreased significantly from a baseline of 5.4 ± 0.2 to 2.8 ± 1.1 on the third month, to 2.3 ± 1.2 on the sixth month, to 1.5 ± 1.2 on the 12th month, and 1.2 ± 1.1 on the 18th month ($P < 0.001$). Furthermore, the CAS responses [disease inactivation (CAS < 3)] improved during our study: 70.6% on the third month, 90.0% on the sixth month, and 92.5% on the 12th month. These conditions continued until the 18th month of follow-up (**Table 2**).

Similarly, the proptosis response improved: by 52% on the third month, by 71% on the sixth month, by 83% on the 12th month, and by 87.1% at 18th month. The mean proptosis values decreased significantly at 3 and 6 months (**Table 2**).

During the treatment, there was no evidence of an increase in IOP, so that, IOP was 19.7 ± 4.3 at baseline, 19.5 ± 4.1 on the third month, 20.0 ± 32.9 on the six month, 19.5 ± 4.2 on the

TABLE 3 | Relationship between time to improvement (as the time it takes for patients to recover) with other study parameters.

Parameter	Level	Univariate				Multivariable			
		HR	95% confidence interval (CI)		P	AHR	95% CI		P
			Lower	Upper			Lower	Upper	
Medical intervention time (from the time the diagnosis was made)	≤6	1.00				1.00			
	7+	11.80	8.07	17.24	0.001	9.97	6.76	14.70	0.001
All extraocular muscles (EOM) enlargement	No	1.00				1.00			
	Yes	3.75	2.58	5.46	0.001	2.89	1.88	4.45	0.001
Age	≤30	1.00				1.00			
	31–45	2.47	1.66	3.68	0.001	1.14	0.74	1.75	0.559
	46+	1.71	1.24	2.35	0.001	1.02	0.71	1.46	0.930
Caruncular/plica injection	No	1.00				1.00			
	Yes	0.97	0.75	1.25	0.824	1.03	0.78	1.35	0.858
Chemosis	No	1.00				1.00			
	Yes	0.84	0.64	1.09	0.189	0.97	0.74	1.29	0.849
Lid swelling	No					1.00			
	Yes	0.90	0.70	1.16	0.412	0.94	0.71	1.25	0.692
Pain	No					1.00			
	Yes	1.07	0.82	1.40	0.596	1.05	0.77	1.41	0.776
Retraction	No					1.00			
	Yes	1.04	0.80	1.36	0.753	1.04	0.79	1.37	0.796

12th month and 19.6 ± 4.4 on the 18th month, and these changes were not statistically significant (*P*: 0.568; **Table 2**).

The visual acuity changes were 0.93 ± 0.13 at baseline, 0.92 ± 0.14 on the third month, 0.92 ± 0.12 on the sixth month, 0.94 ± 0.13 on the 12th month, and 0.95 ± 0.11 on the 18th month, and the differences were not significant (*P*: 0.668; **Table 2**).

Diplopia was significantly improved in 179 patients (73.9%) at 3 months, 212 patients (87.6%) at 6 months, 228 patients (94.21%) at 12th months, and 231 patients (95.4%) at 18th months ($P < 0.001$). At baseline, absent, intermittent, inconstant and constant diplopia was present in 96 (39.6%), 84 (34.7%), 44 (18.1%) and 18 (7.4%) patients, respectively. Following treatment, diplopia not observed in 214 (88.4%) patients, while 11 (4.5%), 13 (5.3%), and 4 (1.6%) patients had intermittent, inconstant, and constant diplopia, respectively ($P < 0.01$ vs. before treatment; **Table 2**).

Table 3 shows the relationship between time to improvement and other study parameters. Patients who started medication earlier (<6 months compared to over 6 months); in other words, those who had a medical intervention time < 6 months, had a younger age at diagnosis of the disease, and had a lack of all EOM enlargement responded faster to treatment ($P < 0.05$); however, age was not a significant factor in the multivariate analysis (**Table 3**). Furthermore, the median time to improvement in the case of medical intervention time < 6 months was 6 months, while if the medical intervention time was more than 6 months, the time to improvement reached to 12 months ($P < 0.05$; **Figure 2**). Moreover, if all EOMs on the CT scan were not large, the median time to improvement was 8 months, whereas if all the muscles on the CT scan were large, the time to improvement was 12 months ($P < 0.05$; **Figure 3**; **Table 4**).

In this study, we evaluated proptosis changes and examined their relationship with other parameters. The results showed that better response (more reduction) in proptosis was associated with: younger age at the start of treatment, earlier treatment intervention (ever since the diagnosis of moderate to severe was made), shorter treatment time (less time to improvement), less IOP, lack of all EOM enlargement on CT scan and lack of diplopia ($P < 0.05$; **Table 5**).

No severe adverse events, exacerbation, or recurrence of symptoms were recorded in the patients treated with MMF and prednisolone. Adverse events occurred in six of 261 patients (excluded from this study). Four patients showed impaired liver function (liver enzymes values slightly more than the upper limit), which recovered after internal medicine consult and hepatoprotective drug treatment. Two patients had gastrointestinal (GI) complications and did not want to continue the study due to old age and were therefore excluded from the study.

DISCUSSION

To the best of our knowledge, only a few studies have described and evaluated the use of MMF in a real clinical setting for GO treatment. Moreover, this is study to reaffirmation the efficacy and safety of MMF and examine "MMF (CellCept®) + oral prednisolone" as a routine treatment for GO patients

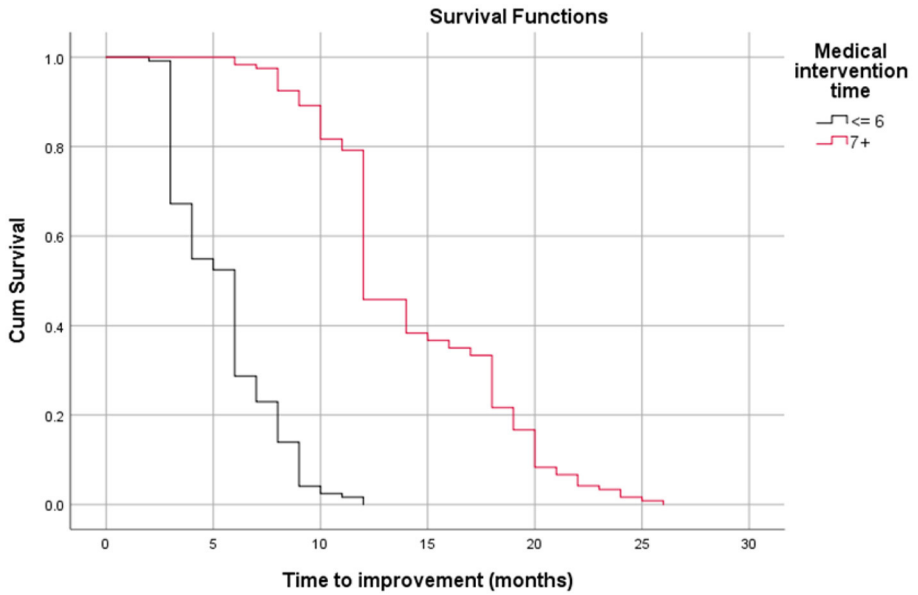

FIGURE 2 | Relationship between time to improvement and medical intervention time (start time) (log-rank test, $p < 0.05$).

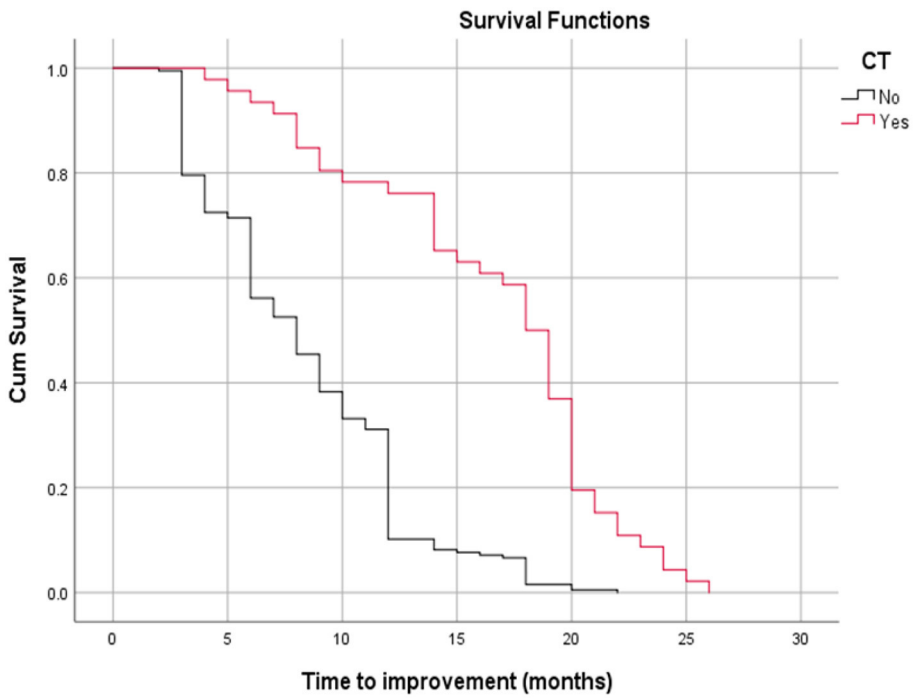

FIGURE 3 | Relationship between time to improvement with all extra ocular muscle's enlargement on a CT scan (log-rank test, $p < 0.05$).

and evaluate the factors associated with a better response to this regimen; that is, a reduction in proptosis and time to improvement.

Various studies have evaluated the effect of steroids on GO, and currently, these drugs are the most used in the clinic as a first-line treatment (14, 15). However, due to the high adverse effects of steroids, it is necessary to introduce alternative therapies for these patients. Various studies have shown the effect of immunomodulatory therapies in the treatment of GO, and indicated a new approach in the treatment of this

TABLE 4 | The relationship between all extraocular muscle (EOM) enlargement in the computed tomography (CT) scan and medical intervention time (start time) with the length of the treatment period until the disappearance of all symptoms.

Parameter		Median	95% confidence interval (CI)		*P*-value
			Lower	Upper	
Medical intervention time (from the time the diagnosis was made)	≤6	6.000	5.375	6.625	<0.001
	7+	12.000	11.345	12.655	
CT scan of all EOM enlargement	No	8.000	6.829	9.171	<0.001
	Yes	18.000	16.671	19.329	

TABLE 5 | Relationship between proptosis changes and the other study parameters.

Parameter		Beta	95% confidence interval (CI)		*P*-value
			Lower	Upper	
Sex	M	−0.02	−0.11	0.07	0.701
	F	ref			
Age		0.01	0.00	0.01	0.001
Start time of medication		0.03	0.02	0.04	0.001
Time to improvement		0.02	0.017913	0.032048	0.001
Conjunctival injection		−0.06	−0.14915	0.031844	0.204
Caruncular/plica Injection		0	−0.082	0.090152	0.926
Chemosis		0	−0.09203	0.088293	0.968
Lid swelling		0.02	−0.06885	0.104465	0.687
Pain		0.02	−0.07174	0.109128	0.685
Retraction		0.01	−0.0781	0.101282	0.8
CT scan of all EOM enlargement		−0.42	−0.51395	−0.33087	0.001
Intraocular pressure (IOP) baseline		0.02	0.008447	0.027924	0.001
Diplopia any gaze		−0.21	−0.29606	−0.12159	0.001
Diplopia primary position		−0.13	−0.23021	−0.03528	0.008
Proptosis baseline		0.02	−0.00627	0.040567	0.151

disease, so that immunomodulatory drugs cover most of the treatment (7–9). For example, Kahaly et al. compared the use of mycophenolate combined with methylprednisolone vs. methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy and, showed that the addition of a moderate daily oral dose of mycophenolate (one 360 mg tablet twice per day for 24 weeks) to an established moderate dose of intravenous methylprednisolone (500 mg once per week for 6 weeks, followed by 250 mg per week for 6 weeks) did not significantly affect the rate of response at 12 weeks or rate of relapse at 24 and 36 weeks, but the addition of mycophenolate did lead to significant improvements in the patients' quality of life and ophthalmic symptoms and signs (16). Despite these studies and according to Jiskra, the effects of biologic drugs such as MMF and cyclosporine in TED patients have not been adequately studied, and there is a controversy about their use in the treatment (17).

This prospective interventional case series showed that MMF plus low-dose oral prednisolone as a new treatment regimen was significantly effective in 94.2% of patients, consistent with data previously reported on the effect of MMF on moderate to severe GO (16, 18–21). Similar to the results of teprotumumab (novel insulin-like growth factor I receptor antibody) in active TED (22, 23), as expected, MMF plus low-dose oral prednisolone showed the greatest effectiveness on CAS, proptosis and diplopia, and this factor significantly decreased during the study, and this decrease occurred earlier in CAS than proptosis and diplopia, suggesting that; MMF like teprotumumab was more efficient than corticosteroids in controlling local inflammation. The overall clinical response rate of the patients who received MMF + oral low-dose prednisolone significantly increased with increasing time, confirming that a fixed dosage in a longer duration of oral MMF + oral-low dosage prednisolone might lead to a better response. Our results showed that visual acuity and IOP did not change significantly during the study period. In this regard, Xiaozhen et al. showed that after 24 months of treatment, the response in the group treated with MMF was significantly better than that in the group treated with corticosteroids (91.3 vs. 67.9%, $P = 0.000$), and this study also found that adverse events were more common in the corticosteroid-treated group than in the other groups, and the results showed that the rate of diplopia and proptosis in the group treated with MMF significantly improved compared to that in the group treated with corticosteroids (90.4 and 68.8% improved) (18).

The MMF dosage that was initially used in combination with low-dose prednisolone, according to the study design, was based on a previous work in autoimmunity (24–26). A previous study showed that even low doses of MMF (1,000 mg/d) were effective in suppressing orbital inflammation (16–21). However, in our study, to better respond to MMF, we added the lowest dose of corticosteroids (oral prednisolone, 5 mg/d) to the treatment regimen. With a lower MMF and prednisolone dose, patients would be exposed to lower risks of side effects, such as menstrual disorders, weight gain, and reactivation of infections. In this study, we found significant response rate and fewer adverse events with this treatment regimen. For active GO, a course of low-dose oral MMF (1,000 mg/d) plus low-dose oral prednisolone (5 mg/d) within 12 months can therefore be recommended. However, to prove the effectiveness of this regimen, a clinical trial study and the presence of a control group are required.

Another important finding of our study is, the understanding of the relationship between time to improvement and other study parameters. Our results showed that early onset of drug intervention (under 6 months compared to over 6 months), younger age at disease onset, and lack of all EOM enlargement on CT scan respond faster to treatment; they have less time to improve. Therefore, it seems that the EOM enlargement is one of the reasons for the late response to the treatment regimen. In this regard, Wang et al. showed that patient with fibrotic changes, which cause chronic complications, are difficult to respond to treatment; therefore, early intervention with a proper regimen, especially immune system modulators (primary pathophysiology), can provide a better and faster response (22).

Our study first examined the factors associated with decreased proptosis during GO treatment. Our study showed that a better response (more reduction) in proptosis was related to younger age at disease onset, earlier treatment intervention, shorter treatment duration (less time to improvement), less IOP, lack of EOM enlargement on CT scan, and lack of diplopia. Regarding the better reduction of proptosis with MMF, Ye et al. and Kahaly et al. showed a significant improvement in diplopia and proptosis in the group treated with MMF compared with those in the corticosteroid-treated group (16, 18).

Mycophenolate mofetil is safe and tolerable and the main adverse events of MMF are hematological and GI disorders (26–28). Adverse events associated with steroids include GI effects, glucose intolerance, weight gain, osteoporosis, and skin thinning. Steroids and MMF are potent immunosuppressive and anti-inflammatory drugs; therefore, infections are common and are potentially dangerous adverse effects (28–30). In our study, side effects occurred in six of 261 patients, which was statistically negligible.

The current study had a high number of samples, that is, 242 patients, emphasizing the significance of our findings. In addition, unlike previous studies, we performed a long follow-up observation period of up to 6 months after the therapeutic response (18th month follow-up). However, due to the lack of a control group, the results of our study could not be confirmed nor rejected; thus, it is necessary to conduct trial studies in the future.

In conclusion, MMF combined with low-dose prednisolone may be considered for GO treatment due to its better therapeutic effect and fewer adverse reactions compared with those of other treatment strategies. This regimen may be introduced as a novel, comprehensive, safer, and more effective regimen for chronic complications such as proptosis and diplopia. Further high-quality clinical trials with large sample sizes, are needed to confirm these results and to evaluate the efficacy and safety of MMF (CellCept®) plus low-dose prednisolone for the treatment of active GO.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Tehran University of Medical Sciences, Ethics Code: IR.TUMS.FARABIH.REC.1397.053. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MTR, SR, and BE contributed to conception and design of the study. NM, SH, and MBR organized the database. MK and MS performed the statistical analysis. AM wrote the first draft of the manuscript. MTR, SP, and MP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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CASE REPORT
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Case Report: Microincision Vitreous Surgery Induces Bleb Failure in Eyes With Functional Filtering Bleb

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Purpose: To investigate the effect of microincision vitreous surgery (MIVS) on intraocular pressure (IOP) control in glaucomatous eyes with functional filtering bleb.

Methods: We enrolled 18 patients (15 males; median age, 73 years) who previously had filtering surgery and underwent MIVS with functional filtering bleb. Kaplan–Meier method was used to calculate the survival rate with defined the failure as when more number of preoperative antiglaucoma medication was started or additional glaucoma surgery including bleb revisions were performed, and IOP increase of 20% (criteria 1) and 30% (criteria 2) from preoperative levels after 2 weeks of MIVS.

Results: The median follow-up duration was 970 days. Preoperative IOP was 13.3 ± 3.8 mmHg (mean ± SD). Postoperative IOP were 14.7 ± 4.9 (P=0.365), 15.2 ± 3.5 (P=0.137), 16.4 ± 5.6 (P = 0.073), 17.6 ± 6.1(P = 0.020), and 14.5 ± 4.0 (P = 0.402) mmHg at 3, 6, 12, and 15 months and final visit, respectively (compared to preoperative IOP). The number of antiglaucoma medications was a median of 1.0 (range 0–4) preoperatively and 0 (0–4) at the final visit (P = 0.238). The survival rates were 55%/61% at 3 months, 50%/61% at 6 months, and 38%/55% at 12 months with criteria 1 and 2, respectively. Four eyes (22%) received additional glaucoma surgery during follow-up.

Conclusion: After several months of MIVS, IOP was likely to increase. We should focus on IOP control by conducting long-term follow-ups.

Keywords: glaucoma, trabeculectomy, Ex-PRESS, microincision vitreous surgery, IOP (intraocular pressure)

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INTRODUCTION

Microincision vitreous surgery (MIVS) using 23-G, 25-G, and 27-G systems is much less invasive compared with vitreous surgery using a 20-G system and currently performed worldwide. Therefore, MIVS may be beneficial for patients with glaucoma, especially for those who have undergone filtering surgery. Meanwhile, it has been suggested that the removal of the vitreous itself, regardless of the mode of surgery (MIVS or 20-G system), may result in the increase in intraocular pressure (IOP) (1, 2) and glaucoma prevalence (3–5). The entire mechanism underlying chronic

IOP increase after vitrectomy is unknown; however, it may be attributed to the increase in the partial pressure of oxygen (pO_2) (3, 4, 6). pO_2 is the highest near the retinal surface, low in the anterior vitreous chamber, and lowest at the center of the lens (3). However, after cataract surgery and vitrectomy, pO_2 level increased in the vitreous cavity and anterior chamber angle, leading to oxidative damage of the trabecular meshwork cells, thus decreasing outflow facility (6). This implies that in a patient with filtering bleb after vitrectomy, careful considerations regarding IOP must be made even when performing MIVS. To date, there are only two reports that have examined postoperative IOP control in patients with bleb who had undergone MIVS (7, 8). Both studies showed that there were some patients who needed more antiglaucoma medications and additional glaucoma surgeries after MIVS, although mean IOP during follow-up had not significantly changed (7, 8). However, they added the effect of additional glaucoma surgery in their analysis and the follow-up duration was relatively short (11.5 and 16.0 months). Therefore, the actual effect of MIVS on IOP control in patients with functional filtering bleb remains to be fully elucidated. This study aims to evaluate the effect of MIVS on IOP control in patients that have functional filtering bleb.

MATERIALS AND METHODS

This retrospective study received approval from the Institutional Review Board of Saneikai Tsukazaki Hospital, Himeji, Japan (No: 211031) and was conducted according to the tenets of the Declaration of Helsinki. We reviewed the medical records of Saneikai Tsukazaki Hospital to enroll patients who had undergone MIVS after filtering surgery [trabeculectomy or EX-PRESS shunt (Alcon Laboratories, Fort Worth, TX, USA)] between January 2014 and December 2020.

The inclusion criteria were as follows: (1) patients with glaucoma and functional filtering bleb (functional bleb was defined as an IOP of ≤21 mmHg before MIVS and >20% reduction compared to that before filtering surgery), (2) a minimum follow-up duration of at least 6 months after MIVS, and (3) patients without additional MIVS or those with endophthalmitis caused by bleb infections. Among the 30 patients enrolled during the specified period, 18 patients who met the selection criteria were included. Furthermore, we subcategorized patients who underwent MIVS into full vitrectomy and core vitrectomy only groups.

Most vitreous surgeons once quite the glaucoma medications after MIVS because of increase in the use of postoperative medications (such as antibiotics, nonsteroidal anti-inflammatory drugs, and steroids) or the presence of small leakages from wounds caused by the use of trocars during vitrectomy. IOP increases after MIVS were dealt according to each surgeon's choice (e.g., reinitiating antiglaucoma medication or performing bleb revision or bleb needling). Therefore, we defined failure as the condition in which a high number of preoperative antiglaucoma medications or additional glaucoma surgery including bleb revisions was required and when IOP increases of 20% (criteria 1) or 30% (criteria 2) from preoperative levels were observed at two consecutive follow-ups performed after 2 weeks of MIVS.

Statistical analyses were performed using BellCurve for Excel (Social Survey Research Information Co., Tokyo, Japan) and the statistical program R software (version 3.6.1, http://www.rproject.org/). The Shapiro–Wilk test was used to verify data distribution normality. IOPs were presented as mean ± standard deviation and compared using the paired *t*-test. The number of glaucoma medications was presented as median (min–max) and compared using the Mann–Whitney *U*-test. $P < 0.05\%$ was considered statistically significant. Multivariate Cox proportional hazards regression analysis was conducted for MIVS type (full vitrectomy/core vitrectomy), glaucoma type, previous filtering surgery type (trabeculectomy/EX-PRESS shunt), preoperative IOP, and preoperative antiglaucoma medication number to identify risk factors for surgical failure. All IOPs were measured using IcareTA01i (Icare Finland Oy, Helsinki, Finland) to prevent discrepancies in the tonometery performed during follow-ups. Central corneal thickness before MIVS was measured using a specular microscope (Konan Noncon ROBO SP-6000, Konan Medical Inc., Hyogo, Japan).

RESULTS

Among the 18 included patients, 15 were males (83%) accounting for 12 (66%) right eyes. The median age of the patients was 73 (quantile; 68–78). The types of glaucoma were primary open-angle glaucoma ($N = 8$, 44%), neovascular glaucoma ($N = 4$, 22%), exfoliation glaucoma ($N = 4$, 22%), and secondary glaucoma ($N = 2$, 11%). The median follow-up duration after MIVS was 970 days (506–1,474) and that after filtering surgery (performed before MIVS) was 419 days (165–900). Eleven and 7 eyes underwent previous filtering surgery by trabeculectomy and EX-PRESS shunt, respectively. The reason for performing MIVS was transconjunctival intrascleral fixation of an intraocular lens in seven eyes, vitreous hemorrhage in five eyes, macular hole in two eyes, macular edema in two eyes, and proliferative tissue removal in two eyes. Central corneal thickness was 517 ± 47 (range: 448–615) μm.

Change in IOP with additional glaucoma medication and interventions, number of glaucoma medications are summarized in **Table 1**. IOPs tended to gradually increase post-MIVS. IOP at 15 months post-MIVS was significantly higher than that of pre-MIVS (17.6 mmHg vs. 13.3 mmHg, $P = 0.020$). However, no significant difference was found between IOPs pre-MIVS and those at 1, 2, 3, 6, 9, and 12 months post-MIVS. The number of medications was lesser at 3 months post-MIVS compared to that of pre-MIVS. However, compared with pre-MIVS, the number of medications at 6 months post-MIVS was not significantly different from that observed between 6 months post-MIVS and final visit. Before the final visit, two eyes underwent additional revision surgery and bleb needling (67 and 336 days post-MIVS, respectively), one eye underwent Ahmed glaucoma valve implantation (838 days post-MIVS), and one eye underwent EX-PRESS shunt operation (1,234 days post-MIVS). None of the eyes satisfied

TABLE 1 | Changes in IOPs including additional intervention and the number of antiglaucoma medications.

	Number	IOP	*P*-value	Number of glaucoma medications	*P*-value
Pre-MIVS	18	13.3 ± 3.8 (3–19)		1.0 (0–4)	
1 month	18	15.0 ± 4.6 (3–26)	0.262	0 (0–2)	0.001
2 months	16	15.1 ± 5.3 (3–23)	0.262	0 (0–2)	0.003
3 months	17	14.7 ± 4.9 (6–25)	0.365	0 (0–3)	0.027
6 months	18	15.2 ± 3.5 (7–21)	0.137	0 (0–3)	0.161
9 months	17	14.7 ± 5.3 (4–25)	0.407	0 (0–3)	0.147
12 months	15	16.4 ± 5.6 (6–32)	0.073	0 (0–3)	0.266
15 months	15	17.6 ± 6.1 (12–30)	0.020	0 (0–3)	0.266
18 months	11	15.2 ± 4.4 (9–25)	0.203	0 (0–3)	0.356
21 months	11	15.3 ± 4.1 (9–25)	0.230	0 (0–3)	0.474
24 months	11	17.7 ± 4.1 (7–30)	0.041	0 (0–3)	0.542
Final visit	18	14.5 ± 4.0 (8–22)	0.402	0 (0–4)	0.238

Each P value was compared pre-MIVS, and IOPs at each time point were calculated using paired t-test and Mann–Whitney U-test. The number of glaucoma medications was expressed as median with range.

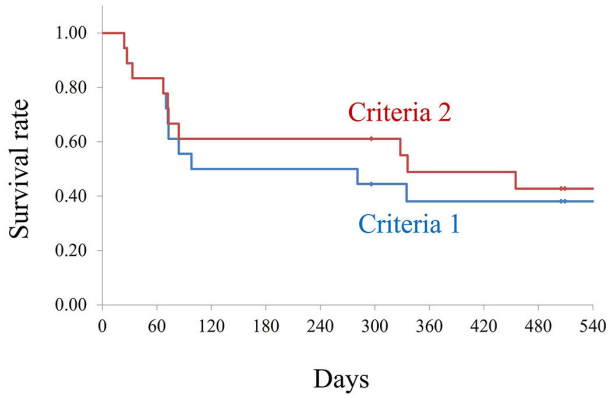

FIGURE 1 | Kaplan–Meier survival analysis for both the criteria. Criteria 1: Number of antiglaucoma medications similar or less than the preoperative number, no additional glaucoma surgery, and introcular pressure (IOP) increase of less than 20% compared with pre-microincision vitreous surgery (pre-MIVS) IOP. Criteria 2: Number of antiglaucoma medications similar or less than the preoperative number, no additional glaucoma surgery, and IOP increase of <30% compared with pre-MIVS IOP. The log-rank test did not show any statistically significant differences between the two criteria ($P = 0.386$).

the criteria of failure when defined as more number of preoperative anti-glaucoma medication after 2 weeks of MIVS, with both criteria.

To exclude the effect of glaucoma medications and IOP after additional glaucoma surgery, we used Kaplan–Meier plots, as shown in **Figure 1**. The survival rates for criteria 1 were 88, 83, 55, 50, 50, 38, 38, 38, and 38% at 1, 2, 3, 6, 9, 12, 15, 18, and 24 months, respectively. The survival rates for criteria 2 were 88, 83, 61, 61, 61, 55, 42, 42, and 42% at 1, 2, 3, 6, 9, 12, 15, 18, and 24 months, respectively.

Multivariate Cox proportional hazards regression analysis revealed no significant predictive factor (**Supplementary Table 1**).

DISCUSSION

Our results revealed that the risk of IOP increases after MIVS in patients with functional blebs. The survival rate decreased to 50% and 61% at 6 months. Two previous studies concluded that MIVS does not adversely affect bleb function (7, 8). To elaborate, Kunikakta et al. reported 15 cases of MIVS performed after filtering surgery; preoperative IOP was 11.9 mmHg with the use of 1.2 glaucoma medications, which changed to 15.7 mmHg with the use of 1.9 glaucoma medication at the final visit (mean follow-up duration was 11.5 months), and 3 eyes needed additional trabeculectomy (7). Kim et al. also reported 11 cases in which preoperative IOP was 13.8 mmHg, which increased to 15.8 mmHg at the final visit (mean follow-up duration was 16.0 months), and 1 eye needed additional glaucoma surgery (8).

IOPs were not statistically significant during the follow-up period ($P = 0.20$, 0.758, respectively) (7, 8). However, they added the effect of additional glaucoma surgery in their analysis and their follow-up duration was shorter than that in our study; they also did not perform life survival analysis. Therefore, our results shed light on the actual IOP control after MIVS.

Toyokawa et al. showed no significant differences in the incidence of IOP increase (>4 mmHg) after MIVS among the patients with different types of vitreoretinal diseases (mean follow-up duration of 47.8 months) (1). However, Yamamoto et al. reported that IOP increases (≥ 4 mmHg) were observed only in the eyes undergoing rhegmatogenous retinal detachment surgery (full vitrectomy) and not in those undergoing epiretinal membrane and macular hole surgeries (core vitrectomy) (mean follow-up of 23.9 months) (2). Thus, we investigated the effect of MIVS type (full vitrectomy/core vitrectomy) using multivariate Cox proportional hazards regression analysis, but it was not identified as a signficant factor. Studies investigating the effect of removing the vitreous cavity on IOP increases are needed. A previous review by Rossi reported that the causes of chronic IOP increases after vitrectomy are angle synechia (chronic inflammation in the anterior chamber, intermittent closure), neovascularization (secondary to anterior segment ischemia), silicon oil glaucoma, and open-angle glaucoma (oxidative stress increases trabecular resistance) (4). We speculate that the reason for IOP increases in our cases may be a combination of both chronic inflammation and oxidative stress as described above. Therefore, we should pay attention to patients with glaucoma who have undergone MIVS and need longer follow-ups.

The first limitation of our study was the inclusion of a small number of cases because of the single-center design and the lack of a control group. Nonetheless, our sample size is larger than that of previous studies (7, 8). The second limitation is the study's retrospective nature. Furthermore, the fact that the medications were added or their use was reinitiated as per the vitreous

surgeon did not lead to uniform analysis. Third, IcareTA01i has the tendency to show lower IOPs compared to Goldmann applanation tonometer (9).

In conclusion, after MIVS, we should pay attention to IOP control by conducting long-term follow-ups. Studies with larger sample sizes are needed to confirm the effect of MIVS on IOP control in patients with bleb.

PRECIS

After MIVS, we should pay attention to IOP increase during long-term follow-up since MIVS may induce early bleb failure in patients with functional bleb.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by IRB at Saneikai Tsukazaki Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SN and RA: writing and statics. All authors confirmed the submitting this article and data collected. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

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ORIGINAL RESEARCH
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Supramaximal Horizontal Rectus Recession–Resection Surgery for Complete Unilateral Abducens Nerve Palsy

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Purpose: To review the surgical procedures and outcomes of supramaximal horizontal rectus recession–resection surgery for abduction deficiency and esotropia resulting from complete unilateral abducens nerve palsy.

Methods: A total of 36 consecutive cases diagnosed as complete abducens nerve palsy, receiving supramaximal medial rectus recession (8.5 ± 1.4 mm, range: 6–10) combined with a supramaximal lateral rectus resection (11.1 ± 1.7 mm, range: 8–14) as performed over the period from 2017 to 2020, were reviewed retrospectively. All surgeries were performed by a single surgeon. Pre- and post-operative ocular motility, ocular alignment, forced duction test, binocular vision, abnormal head posture, and surgical complications were assessed.

Results: Of these 36 cases, 23 (63.8%) were followed up for greater than 2 months (Mean ± SD = 8.4 ± 6.0, range: 2–24) after surgery and the collected data was presented**.** Mean ± SD age of these patients was 41.7 ± 14.4 (range: 12–67) years with 73.9% being female. Trauma (52.2%, 12/23) and cerebral lesions (21.7%, 5/23) were the primary etiologies for this condition. Esodeviation in primary position improved from 55.5 ± 27.2 prism diopters (PD) (range: +25 to +123) to 0.04 ± 7.3 PD (range: −18 to +12) as assessed on their last visit. Pre-operative abduction deficits of −5.6 ± 1.0 (range: −8 to −4) reduced to −2.4 ± 1.4 (range: −4 to 0) post-operatively. The mean dose-effect coefficient of 2.80 ± 1.20 PD/mm (range: 1.07–6.05) was positively correlated with pre-operative esodeviation. Rates of overcorrection and ortho were 69.6 and 26.1%, respectively, on the first day after surgery, while on their last visit the respective levels were 4.3 and 82.6%.

Conclusion: Supramaximal horizontal rectus recession–resection surgery is an effective treatment method for complete abduction deficiency. The dose-effect was positively correlated with pre-operative esodeviation. Overcorrection on the first day post-operatively is required for a long-term satisfactory surgical outcome.

Keywords: paralytic strabismus, rectus recession-resection, complete abducens palsy, surgical dosage-effect, surgical outcome

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INTRODUCTION

The abducens nerve represents the most vulnerable ocular motor nerve, with abducens nerve palsy resulting in esodeviation and horizontal diplopia. Such a condition often involves a compensatory head turn to minimize or eliminate the diplopia. If the esodeviation is permanent and remains stable for more than six months, strabismus surgery will be required to decrease or eliminate head turn, center and expand the single binocular visual fields, and increase abduction while preserving adduction (1).

Horizontal rectus recession–resection without transposition of the vertical rectus can correct this deviation and improve the abduction in cases with partial paralysis (2, 3). However, this recession–resection surgery is not recommended for patients with complete lateral rectus paralysis, due to the lack of a successful outcome resulting from regression of ocular alignment and failure to restore abduction function (4).

A complete abduction deficiency always involves treatment with various surgical techniques consisting of vertical rectus transposition (VRT), including the Hummelsheim or Jensen procedure (4–8) and isolated superior rectus transposition (SRT) (9). However, many disadvantages are associated with VRT, such as the risk of anterior segment ischemia syndrome and new vertical/torsional deviations, which are often difficult to manage even with reoperation (10, 11). In addition, the effects of transposition depend on the tension of the transposed muscle and may not effectively increase the abduction function of the affected eye. In this way, the velocity of rotation into the paretic field is fairly slow and may not be useful when rapid pursuit or saccadic movements are required (12).

Lee (13) reported that maximal medial rectus muscle recession and lateral rectus muscle resection, i.e., the Hummelsheim procedure and the Jensen procedure, may be equally effective in the surgical treatment of complete and partial lateral rectus muscle paralysis. Bagheri (14) suggested that the horizontal rectus resection/recession procedure may also be effective in the treatment of complete abducens palsy. Since 2017, we have employed a supramaximal horizontal rectus recession–resection procedure for the treatment of complete lateral rectus muscle paralysis in our center. We found that this surgical approach proved effective, not only in correcting the horizontal deviation in the primary position but also in improving the abduction function. The purpose of this report is to review the outcomes of supramaximal horizontal rectus recession–resection surgery for complete unilateral abduction deficiency and esodeviation as resulting from an acquired complete sixth nerve palsy.

PATIENTS AND METHODS

Patients

Institutional approval (Approval No: 2021KYPJ050) for this study was obtained from the Research Ethics Board of the Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University, China. All procedures were performed in accordance with the 1964 Declaration of Helsinki. A retrospective analysis was conducted on all consecutive patients with complete abduction deficiency resulting from acquired sixth nerve palsy, who underwent supramaximal horizontal rectus recession–resection surgery in the ZOC during the period from January 2017 to December 2020. All patients were surgically treated by the corresponding author (JH Yan). Written informed consent to participate in this study was obtained before surgery from all patients or from the parents of those younger than 18 years of age.

Complete unilateral abducens palsy was defined as an acquired paralytic esotropia with abduction failing to cross the middle line during monocular gaze (abduction $<$-4). A force generate test was conducted to confirm the absence of active contracture of the lateral rectus, while forced duction tests (FDTs) were employed to rule out any restrictive elements. The exclusion criteria included previous strabismus surgery or botulinum toxin injections, orbital fracture related to mechanical limitations as confirmed by imaging and/or FDT results, and any other combination of cranial nerve palsies. Surgery was planned when the angle of esotropia was stable and $>$15 PD after a minimal period of 6 months of conservative treatment.

Data Collection

All patients underwent a complete ophthalmic evaluation. Data collected included sex, age, etiology, pre- and post-operative deviations in the primary and six diagnostic positions of gaze, FDT, ocular motility, abnormal head posture, binocular vision, and recordings of vertical deviation or any other complications. Deviations in the primary position at a distance (6 m) were measured using the simultaneous prism and cover test, with the prism over the paretic eye. Patients with poor visual acuity were tested using the Krimsky test. Prisms were split between the two eyes in patients with $>$50 PD esodeviation. Duction was recorded on a scale of 0 to −8, with 0 indicating full duction, −4 indicating eye rotation only to the midline, and −8 indicating that the eye was fixed in an extreme adducted position (9). Duction range of the paretic eye was quantitatively evaluated by the sum of abduction and adduction scales with 8 as the full duction range. Fusion and stereopsis were determined with the use of the worth-4-dot, synoptophore, and random dot stereo tests. Patients were followed up on day 1, after 2 months, and then every 3 to 6 months after surgery. Alignment success was defined as a deviation within 10 PD in primary position, as determined on their last visit.

Surgical Technique

All surgeries were performed through fornix conjunctival incisions while patients were under general anesthesia. The forced duction test was routinely performed during surgery. Supramaximal recession–resection dosage of the horizontal rectus was performed according to the horizontal deviation (**Table 1**). The medial rectus was recessed 6–10 mm using the "hang-back" technique with 6–0 polyglactin suture, while lateral rectus was resected 8–14 mm.

Statistical Analysis

Statistical analysis was performed using the SPSS version 23.0 program (SPSS Inc., Chicago, IL, USA). Quantitative data were analyzed using independent sample and paired *t*-tests.

TABLE 1 | Surgical dosage form of supramaximal R-R operation.

Deviation (PD)	MR Rec (mm)	LR Res (mm)
25	6	7
35	7	8
45	8	10
50	9	11
55	10	12
>55	10	13–14

PD, Prism diopter; MR, Medial rectus; LR, Lateral rectus; Rec, Recession; Res, Resection.

Qualitative classification data were analyzed using the chi-square test. Normality of the data was tested using Kolmogorv–Smirnov (K-S) test and Q-Q plots, and homogeneity of variance was assessed with the use of Levene's test. paired T-test or independent-sample T-test were performed for variables data which conforming to normal distribution. Non-parametric statistical tests were used for the data which did not conform to the normal distribution, i.e., paired samples were based on Wilcoxon test, and independent samples were based on Mann–Whitney *U*-test. Multiple linear regression was used to analyze the independent factors of surgical dosage effect. A P value <0.05 was required for results to be considered as statistically significant.

RESULTS

A total of 36 consecutive patients, who were diagnosed with complete abducens palsy resulting from acquired sixth nerve paresis and underwent supramaximal horizontal rectus recession–resection surgery, were reviewed. Of these 36 cases, 23 (63.9%) were followed up for >2 months post-operatively. Data presented represents that from the 23 cases with the >2 months follow-up periods**.** Ages ranged from 12 to 67 years (Mean ± SD = 41.7 ± 14.4), with 73.9.0% (17/23) being females. The median course of the sixth nerve palsy was 18 months (range: 8–720). Trauma was considered as the main cause of this condition in 52.2% (12/23) of the cases, while 21.7% (5/23) had cranial lesions, 8.7% (2/23) had vascular lesions, and 17.4% (4/23) were of unknown etiology. Surgery dosages were 8.5 ± 1.4 mm (range: 6–10) for medial rectus recession and 11.1 ± 1.7 mm (range: 8–11) for lateral rectus resection. There were no statistically significant differences in demographics, clinical characteristics, or surgical dosage among the 23 patients with the >2 months follow-up periods and the 13 lost cases, except that this latter group was younger in age (**Table 2**). The mean follow-up time was 8.4 ± 6.0 months (range: 2–24).

Ocular Alignment

The mean pre-operative horizontal esodeviation of 55.5 ± 27.2 PD (range: +25 to +123) significantly improved to −11.5 ± 11.0 PD (range: −35 to +12) on the first day after surgery, and further improved to 0.04 ± 7.3 PD (range: −18 to +12) as determined on their last visit (**Figure 1A**). On the first day after surgery, overcorrection rates and ortho rates were 69.6% and 26.1%, respectively, while they were 4.3% and 82.6%, respectively, on their last visit (**Table 3**). Vertical deviation was present in 26.1% of pre-operative cases and in 34.7% cases as determined on their last visit, while the mean deviations were 5.0 ± 3.2 PD pre-operatively and 9.6 ± 4.7 PD on their last visit. These differences in mean deviations were not statistically significant.

Ocular Motility

The mean pre-operative abduction function of −5.6 ± 1.0 (range: −8 to −4) increased to −1.9 ± 1.4 (range: −4 to 0) on the first day after surgery, and the abduction function significantly improved to a mean abduction deficit of −2.4 ± 1.4 (range: −4 to 0) on their last visit (**Figure 1B**). Mean adductions of the paretic eye were −3.1 ± 0.9 (range: −4 to −1) on the first day after surgery and presented as a mean deficiency of −1.8 ± 0.7 (range: −3 to 0) on their last visit (**Figure 1C**). Mean duction ranges in the paretic eye increased from 2.4 ± 1.0 pre-operatively to 3.0 ± 1.5 on the first day after surgery and to 3.8 ± 1.4 on their last visit. No statistically significant difference was found ($P = 0.10$) (**Figure 1D**; **Table 3**).

When assessed on their last visit, 15 cases could abduct over the middle line (ABD improved group), while the remaining 8 cases could not abduct over the middle line (ABD unimproved group). Pre-operative abduction deficits were milder in the ABD improved (−5.2 ± 1.0) when compared to the ABD unimproved (−6.30 ± 0.7) group, with pre-operative deviations showing no statistically significant differences between the two groups. In the ABD improved group, 14/15 patients demonstrated a positive FDT test with slight to little resistance, while only 2/8 patients in the ABD unimproved group showed this result (**Table 4**).

Sensory Assessments

Prior to surgery, 56.6% (13/23) of the patients had fusion and stereopsis, 73.9% (17/23) had diplopia in the primary position, and 34.8% (8/23) had abnormal head posture (**Table 3**). On their last visit, fusion and stereopsis were restored in 78.3% (18/23) of the cases and abnormal head posture and diplopia in the primary position were eliminated in all cases.

Surgical Dose-Effect of the Supramaximal R-R Surgery

The mean surgical dosage of the recession–resection surgery was 19.7 ± 2.9 mm (range: 14 to 24) and the mean dose-effect coefficient was 2.80 ± 1.20 PD/mm (range: 1.07 to 6.05). The dose-effect coefficients were not constant and increased as a function of surgical dosage, with PD/mm values being 1.79 (range: 1.07 to 2.5) for 10–15 mm, 2.56 (range: 1.94 to 6.05) for 16–20 mm, and 2.93 (range: 1.39 to 5.23) for 21–25 mm (**Table 5**). The dose-effect coefficient was linearly related to the pre-operative esodeviation (**Table 6**; **Figure 2**).

Typical Case Presentation

Case1

The left eye of a 24-year-old male deviated inward for 10 months after an injury resulting from a fall (**Figures 3A–C**). He was diagnosed with a complete traumatic abducens nerve palsy, and

TABLE 2 | General demographic and clincial features of patients with sixth nerve palsy.

	Total cases ($n = 36$)	Included cases ($n = 23$)	Failure to visit cases ($n = 13$)	*P*
Age (range), year	37.8 ± 14.9 (12–67)	41.7 ± 14.4 (12–67)	31.0 ± 13.7 (14–62)	0.035a*
Sex, male/female	9/27	6/17	3/10	0.84b
Laterality, right/left	17/19	11/12	6/7	0.92b
Course (median, range), months	24 (8–720)	18 (8–720)	36 (12–444)	0.24c
Etiology				0.81b
Trauma, *n* (%)	17 (47.2)	12 (52.2)	5 (38.5)	
Cerebral lesions, *n* (%)	9 (25)	5 (21.7)	4 (30.8)	
Microvascular lesions, *n* (%)	4 (11.1)	2 (8.7)	2 (15.4)	
Unknwon, *n* (%)	6 (6.7)	4 (17.4)	2 (15.4)	
Deviation (range), PD	59.9 ± 27.9	55.5 ± 27.2 (25–123)	67.7 ± 28.6 (30–113)	0.15c
Abduction (range)	5.44 ± 1.1	−5.6 ± 1.0 (−4–−8)	−5.2 ± 1.2 (−4–−8)	0.34c
Adduction (range)	1.0 ± 0.7 (0–3)	1.0 ± 0.7 (0–2)	1.2 ± 0.9 (0–3)	0.60c
Amount of surgery MR recession (range), mm	8.4 ± 1.4 (5–10)	8.5 ± 1.4 (6–10)	8.1 ± 1.5 (5–10)	0.38c
LR resection (range), mm	11.1 ± 1.8 (7–15)	11.1 ± 1.7 (8–14)	11.2 ± 2.0 (7–15)	0.92c

*PD, Prism diopter; MR, Medial rectus; LR, Lateral rectus; n, Number; a, Based on T test; b, Based on chi-square test; c, Based on Mann-Whiteney U-test; P, P-value; *, P-value < 0.05.*

received a medial rectus recession of 10 mm and lateral rectus resection of 13 mm in his left eye while under general anesthesia. The FDT performed during surgery was negative. **Figure 3A**: The patient's 9-gaze eye position photo is shown preoperatively with left eye esotropia 50PD (LET = 50PD), abduction-6, adduction +1; **Figure 3B**: 1 days postoperatively with left eye exotropia 30PD (LXT = 30PD), abduction-2, adduction-4; **Figure 3C**: 2 months postoperatively with esotropia 3PD (ET = 3PD), abduction-4, adduction-2.

Case 2

The right eye of a 55-year-old male deviated inward for 1 year after resection of a trigeminal neuroma (**Figures 4A–C**). He was diagnosed with complete traumatic abducens nerve palsy, and received a medial rectus recession of 8 mm and lateral resection of 11 mm in his right eye while under general anesthesia. The FDT performed during surgery was positive. **Figure 4A**: The patient's 9-gaze eye position photo is shown preoperatively with right eye esotropia 40PD (RET = 40PD), abduction-4, adduction normal; **Figure 4B**: 1 days postoperatively with right eye exotropia 20PD (RXT = 20 PD), abduction-1, adduction-4; **Figure 4C**: 2 months postoperatively with right eye exotropia 8PD (RXT = 8 PD), abduction-2, adduction-2.

CASE 3

The right eye of a 47-year-old male deviated inward for 6 years. He was diagnosed with complete traumatic abducens nerve palsy (**Figures 5A-C**), and received a medial rectus recession of 10 mm and lateral rectus resection of 12 mm in his right eye while under general anesthesia. The FDT performed during surgery was (+ + +). **Figure 5A**: The patient's 9-gaze eye position photo is shown preoperatively with right eye esotropia 60PD (RET = 60PD), abduction+5, adduction+1.5; **Figure 5B**: 1 days postoperatively with right eye exotropia 20PD (RXT = 20PD), abduction 0, adduction-4; **Figure 5C**: 2 months post-opeatively with right eye exotropia 7PD (RXT = 7PD), abduction 0, adduction-2.

DISCUSSION

Clinically, more than half of the patients with unilateral abducens nerve palsy can recover spontaneously, while an inability to abduct past midline at presentation and bilaterality were associated with a failure to recover (1). Relatively few of these patients require surgical treatment (15). Results from previous studies in patients receiving surgery with sample sizes greater than 30 (range: $n = 33$ to 71) (3, 13, 14, 16) have indicated that the average age of patients with abducens nerve palsy ranged from 20.4 to 43 years. In these patients, trauma was the leading cause of this condition, accounting for 54.5–63% of the patients, followed by 6.1–16.4% patients showing craniocerebral lesions. Ratios of males to females ranged from (0.97 :1) to (1.3 :1), while ratios of right to left eye ranged from (0.43 :1) to (1.35 :1). Similar to that reported in these studies, our current results indicate that the average age of patients with this condition was 37.8 ± 14.9 years, with women (27/36, 75%) being more susceptible. Trauma (47.2%, 17/36), followed by cerebral lesions (25%, 9/36) were the primary causes for this condition in these mostly middle-aged patients. There were no obvious differences between right and left eyes, but a significant gender difference was present.

In the present study, supramaximal recession–resection surgery without transposition procedure was sufficient for the treatment of complete sixth nerve palsy. In these patients, 82.6% achieved orthotropia, which was greater than that reported previously in patients receiving VRT or SRT surgery (**Table 7**). Excessive esotropia deviations resulting from complete sixth

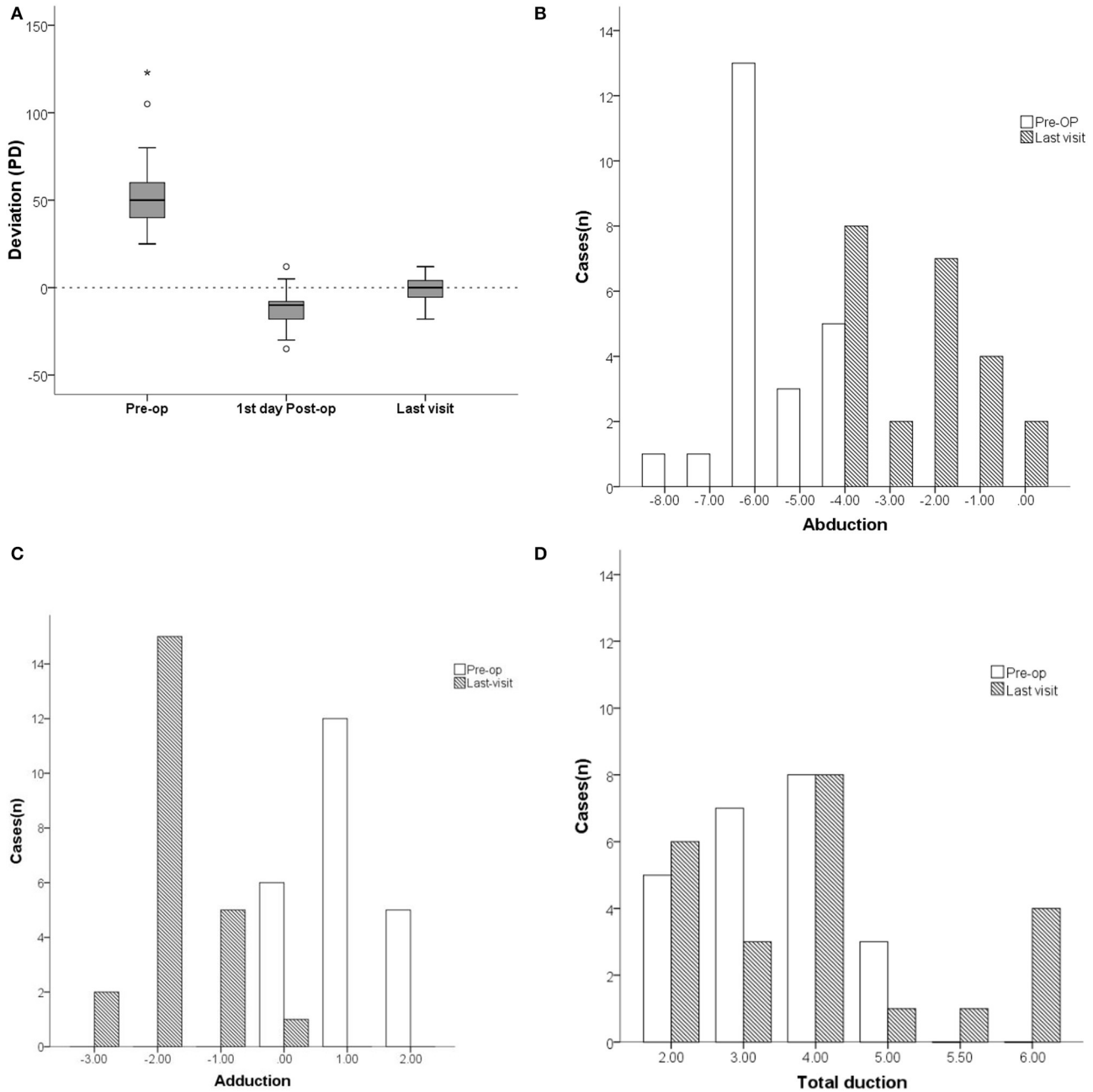

FIGURE 1 | Comparison of deviation (PD) and ocular motility between pre- and postoperation of patients with unilateral complete abducens nerve plasy. **(A)** The mean pre-operative horizontal esodeviation of 55.5 ± 27.2 PD (range: +25 to +123) significantly improved to −11.5 ± 11.0 PD (range: −35 to +12) on the first day after surgery, and further improved to 0.04 ± 7.3 PD (range: −18 to +12) as determined on their last visit. **(B)** The mean abduction function increased form −5.6 ± 1.0 (range: −8 to −4) preoperatively to −2.4 ± 1.4 (range: −4 to 0) on their last visit. **(C)** The mean adductions of the paretic eye decreased from 0.0 ± 0.0 (range: 0 to +2) pre-operatively to a mean deficiency of −1.8 ± 0.7 (range: −3 to 0) on their last visit. **(D)** The mean duction ranges in the paretic eye increased from 2.4 ± 1.0 pre-operatively to 3.8 ± 1.4 on their last visit. In the box plot **(A)**, the value that is more than 1.5 times the distance from the quartile value is the outlier and is represented by "o", while the value that is more than 2 times is the extreme value and is marked by "*". Pre-op, pre-operatively.

nerve dysfunction could be corrected with a simple recession–resection procedure, an effect which could be attributable to the following reasons. First, this procedure involved a 6–10 mm medial rectus "hang-back" recession, which could then result in a complete relaxation in the tonic contracture of the antagonist. The degree of ipsilateral medial rectus contracture is related to the efficacy of the tendon transposition procedure in sixth nerve palsy. A combination of medial rectus recession and partial transposition was reported to achieve a greater surgical corrective effect of 39 to 52 PD (22, 24). Second, lateral rectus

TABLE 3 | Pre- and Postoperative motor/sensory features of patients with unilateral complete abducens nerve palsy.

Motor and sensory assessment	Pre-op ($n = 23$)	1st day post-op ($n = 23$)	Last visit ($n = 23$)	P1	P2
Duction					
Abduction	−5.6 ± 1.0 (−8–−4)	−1.9 ± 1.4 (−4–0)	−2.4 ± 1.4 (−4–0)	0.00d*	0.057d
Adduction	0	−3.1 ± 0.9 (−4–−1)	−1.8 ± 0.7 (−3–0)	0.00d*	0.00d*
Duction range	2.4 ± 1.0	3.0 ± 1.5	3.8 ± 1.4	0.10d	0.10d
Deviation					
Horizontal esodeviation (range), PD	55.5 ± 27.2 (25–123)	−11.5 ± 11.0 (−35–12)	0.04 ± 7.3 (−18–12)	0.00d*	0.00d*
Vertical hyperdeviaion (range), PD	5.0 ± 3.2	6.7 ± 2.9	9.6 ± 4.7		
Vertical deviaion, *n* (%)	6 (26.1)	3 (13.0)	8 (34.8)		
Ortho, *n* (%)	–	6 (26.1)	19 (82.6)		
Undercorrection, *n* (%)	–	1 (4.3)	3 (13.1)		
Overcorrection, *n* (%)	–	16 (69.6)	1 (4.3)		
Sensory					
Binocular single vision, *n* (%)	13 (56.5)	14 (60.9)	18 (78.3)		0.18b
Diplopia in the primary position, *n* (%)	17 (73.9)	10 (43.5)	0 (0.0)		0.00b*
Abnormal head posture, *n* (%)	8 (34.8)	3 (13.0)	0 (0.0)		0.00b*

*Pre-op, Pre-operation; post-op, Post-operation; n, Number; PD, Prism diopter; Ortho, orthotropic; P1, Last visit vs. pre; P2, Last visit vs. 1st day post-op, b, Based on chi-square test; d, Based on Wilcoxon test; *, P-value < 0.05.*

TABLE 4 | Comparison of clinical characteristics between patients with improved and unimproved abduction.

Clinical features	ABD improved ($n = 15$)	No ABD improved ($n = 8$)	*P*
Sex (M/F)	10/5	1/7	0.28b
Age (years)	43.9 ± 13.9	37.6 ± 15.2	0.33a
Etiology(trauma/cerebral lesions/others /no)	6/5/1/3	6/0/1/1	0.23b
Deviation	57.2 ± 26.9	52.3 ± 29.2	0.39c
Course (moths)	80.4 ± 180.7	41.4 ± 38.9	0.88c
Abduction	−5.2 ± 1.0	−6.3 ± 0.7	0.04c*
Adduction	0.9 ± 0.6	1.1 ± 0.8	0.47c
FDT positive	14/15	2/8	0.01c*
MR Rec (mm)	8.2 ± 1.5	9.1 ± 1.0	0.17c
LR Res (mm)	10.9 ± 1.8	11.5 ± 1.5	0.51c
Rec+Res (mm)	19.1 ± 3.0	20.6 ± 2.4	0.36a

*ABD improved, ABD>-4 (over the midline); M, male; F, female; FDT, Forced duction tests; MR, Medial rectus; LR, Lateral rectus; Rec, Recession; Res, Resection; R-R, Recession-Resection, a, Based on T test; b, Based on chi-square test; c, Based on Mann-Whiteney U-test; *, P-value < 0.05.*

TABLE 5 | The dose-effect of maximal R-R surgery.

Rec+Res (mm)	*n*	Corrected Deviation (PD) Median (range)	PD/mm Median (range)
10–15	2	28 (25–30)	1.79 (1.07–2.5)
16–20	9	40 (35–123)	2.56 (1.94–6.05)
21–25	12	50 (35–123)	2.93 (1.39–5.23)

R-R, Rec-Res = Recession-Resection; PD, Prism diopter.

resections of 8–14 mm generate pure mechanical tonic forces upon the paralyzed lateral rectus, although such procedures fail to regenerate the innervation needed to move the eyeball across the middle line with a slight over-correction in this cohort. "Muscle length adaption," according to eye position and muscle stretch as described by Guyton, could play an important role in eye alignment (25). The medial rectus could be lengthened with the addition of sarcomeres to the medial and the lateral rectus could be shortened with the removal of sarcomeres from the shortened lateral rectus in this slightly exotropic eye position (26, 27). Finally, with the anatomical orientation of horizontal rectus muscles being in line with the visual axis, a maximal rotation force to maintain the eyeball straight in the primary position could be achieved than vertical muscle transposition procedure. Moreover, most adult patients with acquired abducens palsy have well-developed binocular vision. Retinal image disparity elicits fast fusional vergence which, in the short term, leads

to vergence adaptation, producing a change in vergence tonus. As a result, these events stimulate muscle length adaptation over the long term, all of which reduce retinal image disparity. This three-level feedback process, as described by Guyton (25), completes the dynamic feedback system for maintenance of long-term binocular alignment after supramaximal horizontal rectus recession–resection surgery.

In addition, abduction deficiencies also significantly improved, enabling a middle line cross in 65% (15/23) of the cases, with a few cases showing complete recovery. Patients with complete abducens palsy can also achieve a complete spontaneous recovery (1, 15). An inability to actively abduct across the midline was not taken to indicate an unrecovered palsy (3). The failure to recover within 6 months after palsy onset does not necessarily indicate that compensatory mechanisms of the nerve and muscles do not exist, it just means that they have yet to fully compensated or work. Supramaximal horizontal rectus recession–resection surgery may improve and/or partially restore abduction function by increasing the compensatory capacity of muscles and/or innervation through the following potential mechanisms. First, in the early post-operative period, a mechanical correction of eye position (mild overcorrection) produces muscle length adaptation, which regulates the number of muscle sarcomeres and muscle extensibility (26, 27). Second, a subset of patients developing clinical lateral rectus palsy may be due to lateral rectus superior compartment palsy, despite an intact lateral rectus inferior compartment (28). Residual lateral rectus function of contraction could not be detected until a supramaximal R-R procedure restored the ocular alignment. Supramaximal medial rectus recession has the effect of releasing tonic contraction and decreasing innervation impulses of the medial rectus, resulting in a reduced afterload of the lateral rectus during abduction. Furthermore, the enhanced mechanical tonic force resulting from supramaximal lateral resection increases the initial length of the muscle fiber sarcomeres, and muscle contraction forces are increased through the Frank–Starling law (29, 30). Finally, extraocular muscles may affect the functioning of extraocular muscle (EOM) stem cells, as activated by the

TABLE 6 | Factors associated with the dose-effect relationship of ultra R-R surgery.

	Multi-factor analysis			
	R	***p***	***B***	***p***
Sex	0.12	0.59	–	–
Age	0.13	0.55	–	–
Etiology	0.38	0.07	0.62	0.26e
Course	0.57	0.005	0.29	0.49e
Deviation	0.92	0.00	11.07	0.001e**
Adduction	0.46	0.03	1.74	0.06e
Abductution	0.223	0.31	–	–
FDT	0.32	0.13	–	–
Binocular vision	0.24	0.27	–	–

*FDT, Forced duction tests; **, P-Value<0.001; e, Based on one-way ANOVA.*

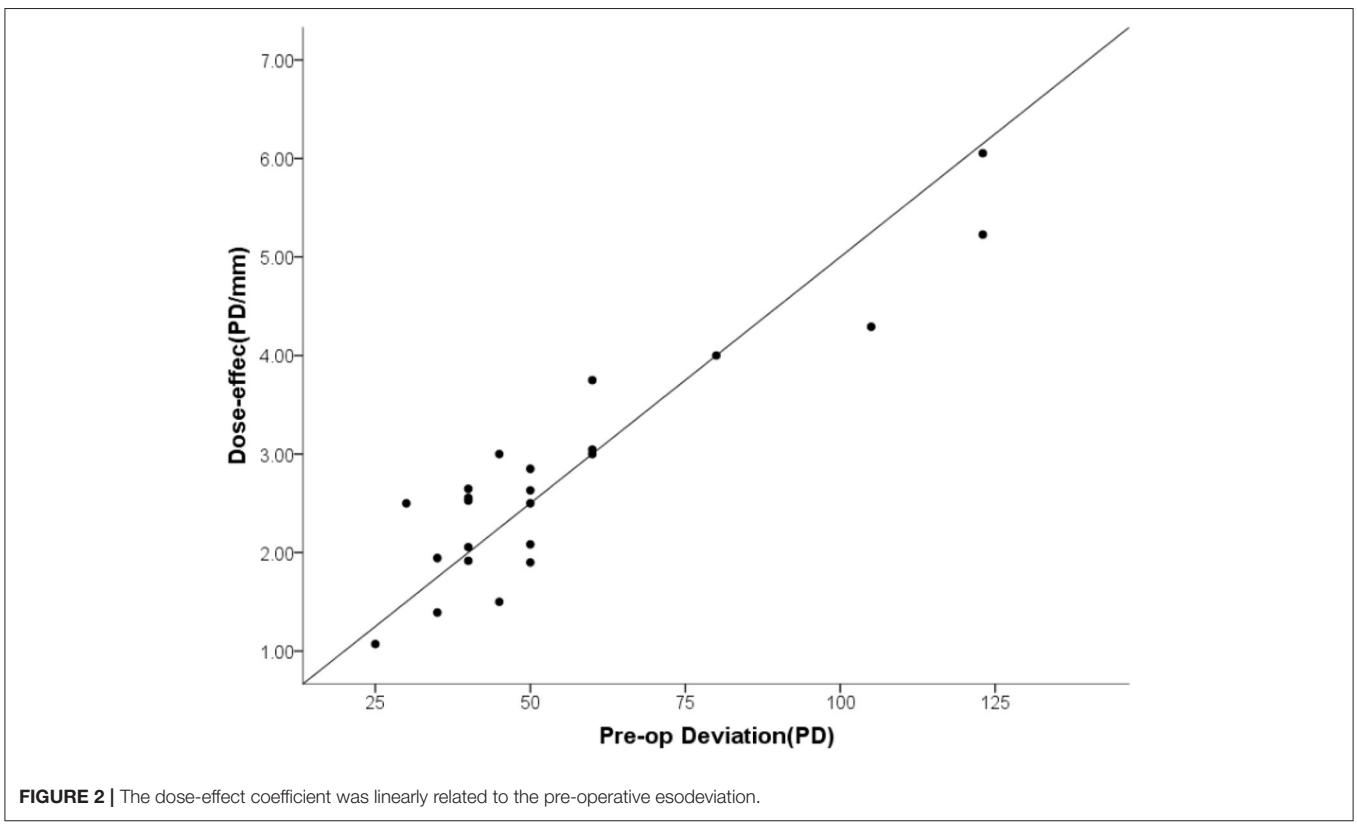

FIGURE 2 | The dose-effect coefficient was linearly related to the pre-operative esodeviation.

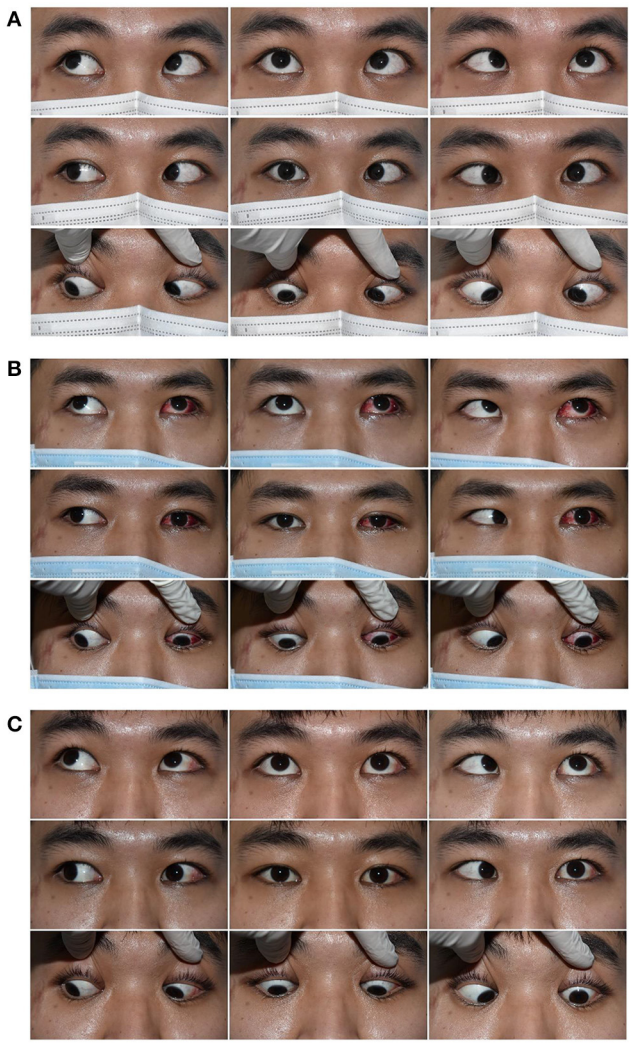

FIGURE 3 | Typical case 1 showed the patient with abduction = −4 on the last visit. A 24-year-old male whose left eye deviated inward for 10 months after an injury resulting from a fall. He was diagnosed as a complete traumatic abducens nerve palsy and received a medial rectus recession of 10 mm and lateral rectus resection of 13 mm in his left eye while under general anesthesia. The FDT performed during surgery was negative. **(A)** The patient's 9-gaze eye position photo is shown preoperatively with left eye esotropia 50PD (LET = 50PD), abduction-6, adduction +1. **(B)** 1 day postoperatively with left eye exotropia 30PD (LXT = 30PD), abduction-2, adduction-4. **(C)** 2 months postoperatively with esotropia 3PD (ET = 3PD), abduction-4, adduction-2.

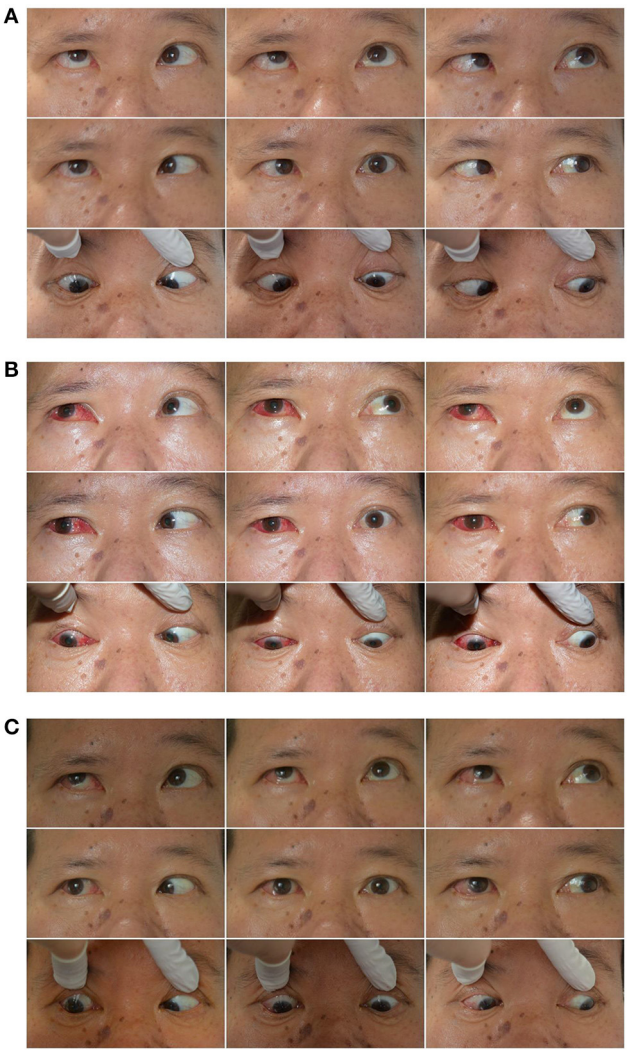

FIGURE 4 | Typical case 2 showed the patient with abduction = −2 on the last visit. A 55-year-old male whose right eye deviated inward for one year after resection of a trigeminal neuroma. He was diagnosed as complete traumatic abducens nerve palsy and received a medial rectus recession of 8 mm and lateral resection of 11 mm in his right eye while under general anesthesia. The FDT performed during surgery was positive. **(A)** The patient's 9-gaze eye position photo is shown preoperatively with right eye esotropia 40PD (RET = 40PD), abduction-4, adduction normal. **(B)** 1 day postoperatively with right eye exotropia 20PD (RXT = 20 PD), abduction-1, adduction-4. **(C)** 2 months postoperatively with right eye exotropia 8PD (RXT = 8 PD), abduction-2, adduction-2.

maximal R-R procedure. Gene expression profiles of resected lateral recti in patients with complete lateral rectus paralysis were examined using microarray analysis and quantitative reversetranscription polymerase chain reaction (qRT-PCR) in our previous study (31). In that study, we found a decreased expression of Myogenic differentiation (MYOD) suggesting that differentiation processes of extraocular muscle satellite cells (EOMSCs) were inhibited. On the other hand, the high expression levels of the transcription factor Paired box 7 (PAX7), SIX homeobox 1/4 (SIX1/4), and Myogenin (MYOG), suggest that these EOMSCs were showing an effective potential for differentiation. The stimulation resulting from muscle surgery may induce EOMSCs to differentiate and thus produce a compensatory restoration of abduction.

When comparing the clinical characteristics of patients who were able to cross the midline with those who were not, we found

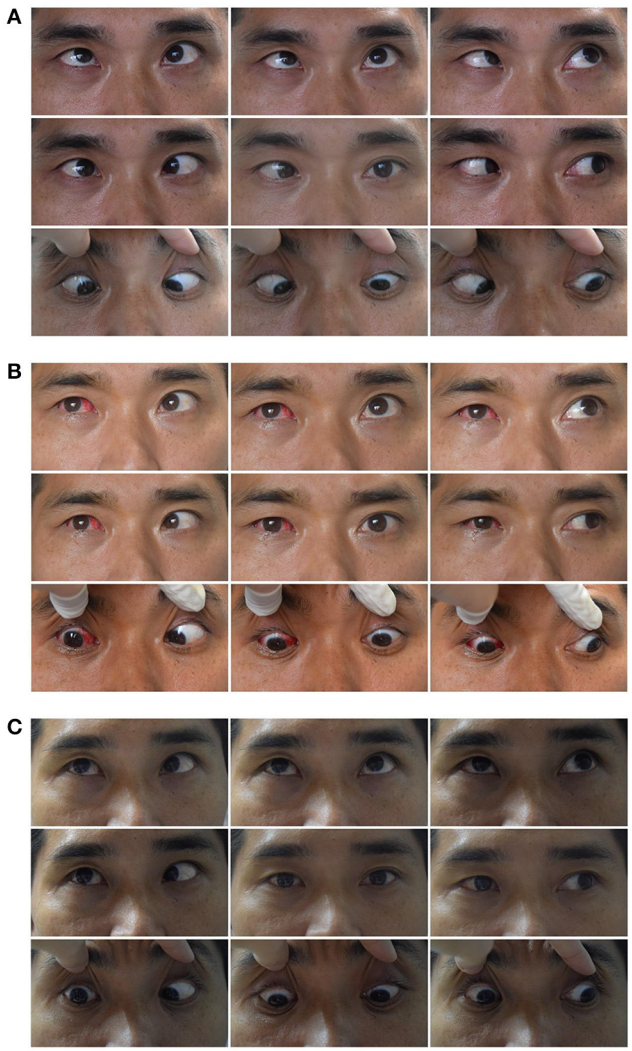

FIGURE 5 | Typical case 3 showed the patient with abduction = 0 on the last visit. A 47-year-old male whose right eye deviated inward for 6 years. He was diagnosed as complete traumatic abducens nerve palsy and received a medial rectus recession of 10 mm and lateral rectus resection of 12 mm in his right eye while under general anesthesia. The FDT performed during surgery was (+ + +). **(A)** The patient's 9-gaze eye position photo is shown preoperatively with right eye esotropia 60PD (RET = 60PD), abduction-5, adduction + 1.5. **(B)** 1 day postoperatively with right eye exotropia 20PD (RXT = 20PD), abduction 0, adduction-4. **(C)** 2 months post-opeatively with right eye exotropia 7PD (RXT = 7PD), abduction 0, adduction-2.

that 93.3% (14/15) of the patients who were able to abduct and cross the midline post-operatively showed a mild resistance in their pre-operative FDTs, while only 25% (2/8) of patients who were unable to cross the midline post-operatively had resistance in their pre-operative FDTs. Moreover, this latter group also demonstrated greater insufficiencies of external rotation before surgery. Interestingly, no differences were present between these two groups with regard to pre-operative esodeviation, which indicated that the degree of esodeviation may not serve as a good index for evaluating the degree of lateral rectus function.

Based on our observations, all supramaximal recession–resection procedures resulted in overcorrection and adduction deficiencies as assessed on the first day after surgery. However, this overcorrection regressed, and adduction efficiency gradually improved and stabilized when evaluated 2 months after surgery. Mean overcorrections on the first day post-operatively was -11.5 ± 11.0 PD, while inward back deviations of 12 PD were observed from the first day post-operatively to their last visit. Despite a decrease in adduction function after surgery, mean horizontal duction range changed from 3.4 ± 1.0 units pre-operatively to 3.8 ± 1.4 units on their last visit, but the difference was not statistically significant. These findings demonstrate that improvements in alignment and duction did not decrease the duction range of the affected eye. Therefore, in supramaximal recession–resection procedures with an adjusted suture technique as performed under local anesthesia, the intraoperative eye position should be directed to an exodeviation of 12 PD, which could improve the long-term orthotopic probability.

Surgical dose-effect coefficients, the deviation corrected per mm in the R-R procedure, were much smaller in complete abducens palsy than in concomitant esotropia. Such an effect results in the failure of conventional dosage designed for recession–resection procedures in complete abducens palsy. The small dose-effect coefficients were determined by low or absent tonic forces of paralyzed lateral rectus, which necessitate more recession to reduce medial rectus contracture and/or antagonistic tonic forces. Although etiology, disease duration, pre-operative deviation, and adduction function were all associated with dose-effect coefficients in the univariate analysis, only pre-operative deviation was an independent factor of surgical dose-effects as based on multifactorial analysis. These findings imply that the supramaximal R-R surgery is a self-adjusting surgery and the same surgical dosage can correct esodeviations in patients with larger esotropia, as were evident in cases with esotropia >50 PD.

Bagheri (14) assessed the correlation between baseline eye deviations and post-operative improvement. They found that the greater the primary deviation, the better the response to primary surgery procedures, including not only horizontal rectus surgery without transposition but also vertical rectus transposition procedures and botulinum toxin injection, with the recession–resection procedure producing the steepest slope. This self-adjusting feature could likely be due to the excessive horizontal rectus recession and resection, which exceeds the range of the muscle's elastic modulus. In addition, when contraction of the medial rectus muscle is sufficiently diminished by a large recession along with a diminished or lost paralytic lateral rectus muscle force, orbital anatomic structures including the tapered structures of the bony orbit, the extraocular muscular cone, the orbital fat, and the fascial pulley system could exert a natural role in maintaining the eye in the primary position.

Recession–resection procedures avoid the potential complications of vertical rectus transpositions, including new vertical deviations in the primary position, new torsion and anterior segment ischemia, as reported in the literature (5, 32, 33). In the current study, vertical deviations were

TABLE 7 | Comparison of supramaximal–RR surgery with previous SRT and VRT procedures for abducens nerve palsy treatment.

References	Year/Journal	Cases	Operation	Augmentation	Pre/post deviation (PD)	deviation corrected (PD)	Pre/post abduction deficition	Mean follow up (month)	Successful rate	Vertical deviation
Rosenbaum et al. (17)	1989 Arch Ophthalmol	10	VRT	MRc/BT	55/5.4	49.6	-/20°	17.4	80%	–
Flanders et al. (5)	2001Can J ophthalmol	5	VRT	MRc/BT	52/1	66	−6/−1.7	21	100%	–
del Pilar González and Kraft (18)	2015J AAPOS	9	VRT	–	38.2/2.2	36	−4.1/−3.2	7.2	60%	–
		7	VRT	Resec 4 mm	48.9/2.5	46.4	−4.4/−2.7	6.7		
		9	VRT	Foster suture	60.3/19	41.3	−4.7/−3.3	9.5		
Lee and Lambert (9)	2017AMJ	8	VRT	Foster suture/BT/MRc	55.6/10.3	45.4	−4.5/−3.8	17.3	1.8additional surgery	–
		8	SRT	MRc/Foster suture	41.9/7.1	36.4	−4.6/−3.0	6.2	0 additional surgery	
Akar et al. (16)	2013Eye	47	VRT	Foster suture 64%BT	42.2/0.9	41.3	−3.9/−1.6	37	79%	–
Leiba et al. (19)	2010J AAPOS	22	VRT	BT 5u	38.1/7.8	30	−6/−2	44.2	59%	7
Yurdakul et al. (20)	2011opthalmic surgrey lasers imaging	17	VRT	MRc/FDT (+) Traction suture>65PD	64.1/9.6	54.5	−3.8/−2.5	18.7	76.5%	–
Kinori et al. (21)	2015J AAPOS	9	1/2VRT +Fostersuture	Plication augmentation BT/MRc, FDT (+)	70/1.5	83	−6.4/−2.7	28	67%	1
Couser et al. (22)	2012J AAPOS	9	1/2VRT+4 mm Resec	9cases MRc	43/6	39	−4/−3	7	80%	–
Patil-Chhab et al. (23)	2016 J AAPOS	13 (15 eyes)	SRT/Foster suture	MRc	55.4/9.9	46.7	−5/−3.1	5.2	69%	1
Mehendale et al. (8)	2012Arch ophthalmol	7	SRT/Foster suture	Adjusted MRc	53.5/16.8	36.5	−4.8/−3	10	71.4%	2
Current study		23	Ultra R-R	–	55.5/0.04	48	−6/−2	8.4	82.6%	9.6 (34.7%)

VRT, Vertical rectus transposition; SRT, Superior rectus transposition; MRc, Medial rectus recession; BT, Botulinum; FDT, Forced duction tests; Ultra R-R, Supramaximal R-R operation; PD, Prism dioptre.

comparable and slightly increased from 26.1 to 34.7% after maximal recession–resection surgery. Four cases of vertical deviation were eliminated and 6 cases occurred after surgery. Hypertropia is commonly associated with isolated, unilateral abducens nerve palsy. The reported incidence ranged from 19 to 61%, with deviations ranging from 4 to 16 PD, depending on the measurement method employed (28, 34, 35). Etiology of this hypertropia has been controversial, but has been hypothesized to involve a physiological hyperphoria unmasked by a horizontal, compartmental paralysis of the superior or inferior zones of the affected lateral rectus muscle (36). As the recession–resection procedure did not change the direction of the horizontal muscle force, there were no significant pre- vs. post-surgery differences in the proportion and degree of vertical deviation.

There are some inherent limitations in our study. It was a retrospective clinical study with no controls. All clinical data were from a single center and all surgeries were performed by one surgeon. Complete abducens palsies were diagnosed only based on abductions that failed to cross the middle line, although this method is simpler to assess and commonly used in clinical settings. Follow-up periods were relatively short. It will be necessary to prospectively evaluate and compare the supramaximal horizontal rectus recession–resection procedure with vertical rectus transposition in complete abducens palsy as assessed in randomized clinical trial studies.

Despite these limitations this study represents the first investigation directed at evaluating the clinical effects of supramaximal horizontal rectus recession–resection procedures as applied for the treatment of complete abducens palsy. The findings of this study offer important, new perspectives as related to complete abducens palsy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Board of the Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University, China; Institutional approval (Approval No: 2021KYPJ050). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual (s), and minor (s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZW, LF, and JY were involved in the methodology. JY was involved in the validation. ZW, LF, TS, and XQ performed the formal analysis. ZW and JY were in charge of the resources. ZW and LF were responsible for data curation. ZW, LF, and TS wrote the original draft. TS, XQ, XY, and JY were involved in reviewing and editing the draft. HS and JY supervised the study and took care of project administration. JY was involved in funding acquisition. All authors contributed to the article and approved the submitted version.

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Clinical Outcomes in Maximum Tolerated Medical Therapy in Penetrating Keratoplasty for Bullous Keratopathy

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Purpose: To compare the clinical outcomes of maximum tolerated medical therapy (MTMT) in patients with penetrating keratoplasty (PKP) with those of Ahmed glaucoma valve (AGV) implantation.

Methods: The medical records were retrospectively reviewed in patients who had undergone PKP for bullous keratopathy and were treated with MTMT or AGV implantation for the management of glaucoma. A total of 18 bullous keratopathic patients were investigated between January 2010 and February 2017: 9 patients treated with MTMT and 9 patients treated with AGV implantation. Non-corrected visual acuity (NCVA), intraocular pressure (IOP), endothelial cell density (ECD), hexagonality, coefficient of variation (CV), central corneal thickness (CCT), median survival time of the graft, and the presence of epithelial keratopathy were compared between the groups at each time point or between baseline and after treatment of glaucoma in each group.

Results: There were no significant differences in the visual acuity and corneal thickness between the two groups or within each group over time. Both groups showed a significant reduction in IOP compared with the baseline IOP, and IOP reductions were greater in the AGV group than in the MTMT group ($p = 0.040$). Significant ECD reductions were found in each group between the baseline and 6 months ($p = 0.008$ in the MTMT group, $p = 0.015$ in the AGV group); however, no differences were found between the two groups until 12 months. The significant hexagonality reduction was found in the AGV group between the baseline and 12 months ($p = 0.018$). The median survival time showed no significant difference in the survival analysis.

Conclusions: Maximum tolerated medical therapy in penetrating keratoplasty for bullous keratopathy seems to similarly affect the endothelial cell density or graft survival when compared with at least 12 month-followed Ahmed glaucoma valve implantation.

Keywords: Ahmed glaucoma valve, cornea, endothelial cell, maximum tolerated medical therapy, penetrating keratoplasty

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INTRODUCTION

Glaucoma is a well-known risk factor for corneal endothelial decompensation after penetrating keratoplasty (1–4). Both uncontrolled intraocular pressure (IOP) and Ahmed glaucoma valve (AGV) implantation may affect the endothelial cell decompensation of the graft (1, 5). To avoid endothelial damage associated with AGV implantation, maximum tolerated medical therapy (MTMT) can be maintained in patients with glaucoma after penetrating keratoplasty (PKP). Although the graft survival with anti-glaucoma medication was reported to be lower in PKP than that without glaucoma (6), the long-term effect of MTMT on the graft survival or endothelial cell density (ECD) has not been clearly established.

Evidence suggests that the topical anti-glaucoma medication is not directly involved in the reduction of ECD in patients with glaucoma patients (7) or corneal donor grafts (8). However, the long-term use of topical anti-glaucoma medication induces significant ocular surface changes in patients who underwent PKP, such as dry eye, superficial punctate keratitis, conjunctival scarring, and ocular surface inflammation (9–13), which may affect not only the success of subsequent glaucoma surgery but also graft survival. These toxic effects on the ocular surface may be attributed to multiple factors, such as preservatives, low pH, or active ingredients *per se* (11). Ocular surface damage with topical anti-glaucoma medication may lead to poor compliance, resulting in either less-controlled or fluctuated IOP. Given recent confocal microscopic findings showing a significant increase in the density of dendritic cells with topical anti-glaucoma medication (9), the long-term MTMT may also affect the graft rejection in the early period. Considering that the rapid reduction of ECD in PKP (7.5%/year) compared with that in normal cornea (0.6%/year) over time (14, 15), MTMT may also affect the overall graft survival in the compromised cornea due to PKP. Therefore, this study aimed to compare the effect of MTMT with that of AGV implantation on the changes in endothelial cell density (ECD), hexagonality, CV, or the survival of grafts in patients who underwent PKP for a bullous keratopathy.

MATERIALS AND METHODS

Patient Selection

This retrospective study was approved by the Institutional Review Board of Seoul National University College of Medicine (IRB No. 1905-038-1031, Seoul, South Korea) and adhered to the tenets of the Declaration of Helsinki. We retrospectively reviewed medical records of patients who were treated with PKP, such as re-PKP, for bullous keratopathy and MTMT or AGV implantation for the management of glaucoma following PKP. The study included patients who were followed-up for at least 12 months after MTMT or AGV implantation at the cornea clinic in Seoul National University Hospital between January 2010 and February 2017. The choice of AGV implantation was determined by the clinical judgment of two glaucoma specialists (Y. K. Kim and J. W. Jeoung), when the IOP was unacceptably high even with MTMT based on the visual field defect status and the severity/or progression of the optic nerve damage in each patient. The exclusion criteria were as follows: the patients who had diagnosed with other corneal disease with glaucoma, who had undergone any other intraocular surgeries within 6 months before PKP, who had undergone any other intraocular surgeries between PKP and AGV implantation, who had undergone any other intraocular surgeries during MTMT in PKP, and who had not regular examination.

TABLE 1 | Demographics of the patients in the MTMT and AGV groups.

	MTMT	AGV	*P*-value*
Number of patients	9	9	
Age (years)	66.1 ± 12.4 (47–79)	60.9 ± 12.8 (35–73)	0.489
Sex (male: female)	8: 1	7: 2	0.527
Laterality (right: left)	4: 5	5: 4	0.637
No. of re-PKP	3 (33.3%)	1 (11%)	0.576
Time interval between PKP and onset of anti-glaucoma treatment (months)	12.4 ± 9.9 (3–23)	23.8 ± 21.7 (1–58)	0.340
Follow-up duration (months)	34.2 ± 17.8 (4–67)	50.4 ± 40.0 (4–113)	0.546

**Using the Mann–Whitney test or the Fisher's exact test or the Chi-square test where appropriate.*

Data was presented as Mean ± SD (ranges).

MTMT, maximum tolerated medical therapy; AGV, Ahmed glaucoma valve; PKP, penetrating keratoplasty.

The study included a total of 18 patients: 9 patients who had MTMT and 9 patients who underwent AGV implantation. The demographics of the patients in each group were shown in **Table 1**. The patients who had undergone re-PKP before AGV were also included in both groups (3 patients in the MTMT group and 1 patient in the AGV group). The proportions of re-PKPs did not show a statistically significant difference between the groups. The mean age of patients in the MTMT and AGV groups was 66.1 years (47–79 years) and 60.9 years (35–75 years), respectively. The mean time intervals between PKP and the onset of anti-glaucoma treatment were 12.4 months (3–23 months) and 23.8 months (1–58 months) in the MTMT and the AGV groups ($p > 0.05$), respectively. The mean follow-up durations were 36.6 months (4–67 months) and 36.9 months (4–113 months) in the MTMT and the AGV groups, respectively. There were no statistically significant differences in all demographic characteristics.

Surgical Procedures and MTMT

Penetrating keratoplasty was conducted by a single corneal surgeon (M. K. Kim) with 10-0 interrupted sutures, and the lens extraction combined with intraocular lens insertion was performed in 1 eye in the AGV group.

Ahmed glaucoma valve implantation was performed on the superotemporal aspect of each eye. A traction suture through the clear cornea was used in the upper peripheral cornea to enhance the exposure to the surgical field. A 5-mm circumferential and vertical incision was made in the conjunctiva and Tenon's capsule, 1 mm posterior to the corneal limbus, followed by a

TABLE 2 | The types of combinations of anti-glaucoma medications used in the MTMT and AGV groups.

Anti-glaucoma medications	MTMT	AGV	*P*-value*
The types of combinations	2% dorzolamide/0.5% timolol + 0.15% brimonidine + 0.005% latanoprost + oral acetazolamide	2% dorzolamide/0.5% timolol + 0.15% brimonidine + 0.005% latanoprost + oral acetazolamide	
	2% dorzolamide/0.5% timolol + 0.15% brimonidine + 0.004% travoprost + oral acetazolamide	1% brinzolamide/0.5% timolol + 0.15% brimonidine + 0.005% latanoprost + oral acetazolamide	
	2% dorzolamide/0.5% timolol + 0.5% apraclonidine + 0.004% travoprost + oral acetazolamide	2% dorzolamide + 0.2% brimonidine/0.5% timolol + 0.004% travoprost + oral acetazolamide	
Mean number	3.5 ± 1.3 (2–5)	4.1 ± 0.9 (3–5)	0.387

**Using the Mann–Whitney test.*
MTMT, maximum tolerated medical therapy; AGV, Ahmed glaucoma valve.

dissection between the Tenon's capsule and the sclera. The body of the AGV (model S2 with a surface area of 184 mm^2; New World Medical, Rancho Cucamonga, CA, USA) was inserted under the Tenon's capsule between the superior rectus muscle and the lateral rectus muscle. The body of the AGV was fixed to the sclera by two 8-0 prolene (Ethicon, Inc.) anchoring sutures at the front edge of the plate bilaterally, 8–9 mm from the corneal limbus. An anterior chamber puncture, parallel with the iris surface, was made 1 mm posterior to the corneal limbus, using a 23-gauge needle. A silicone tube was cut and ∼2 mm was inserted into the anterior chamber, in a bevel-up position. The silicon tube near the corneal limbus was covered using a 4 mm × 3 mm half-thickness sclera flap. The surgery was completed using continuous running sutures of the Tenon's capsule and the conjunctiva.

Maximum tolerated medical therapy was defined as the use of two or more of the following medications for lowering IOP; topical carbonic anhydrase inhibitor (CAI) (2% dorzolamide or 1% brinzolamide), topical beta-blocker (0.5% timolol), topical alpha-agonist (0.15% brimonidine, or 0.2% brimonidine, or 0.5% apraclonidine), topical prostaglandin analog (0.005% latanoprost or 0.004% travoprost), and oral administration of acetazolamide. **Table 2** summarizes the representative types of combinations of anti-glaucoma medications used in each group. The number of anti-glaucoma medications was not statistically different between those two groups.

Clinical Evaluation

Data, such as demographics, type of glaucoma treatment, non-corrected visual acuity (NCVA), IOP, ECD, central corneal thickness (CCT), number of anti-glaucoma medications, presence of epithelial keratopathy, and graft survival, were collected. ECD was measured *via* a non-contact specular microscopy (SP-8800, Konan, Hyogo, Japan). CCT was measured using a pachymeter (Pocket II, Quantel Medical, Paris, France), and IOP was measured using a rebound tonometer (Icare® PRO, Icare Finland Oy, Helsinki, Finland). Graft failure was assessed through slit-lamp examination by the cornea specialist who performed PKP. We defined "graft failure" as the persistent corneal edema when the corneal edema did not disappear within 2 months of immunosuppressive treatment.

Data Analysis

Each parameter was evaluated before anti-glaucoma treatment (AGV implantation vs. MTMT) and at intervals of 6 and 12 months after the anti-glaucoma treatment. NCVA, IOP, ECD, CCT, and number of anti-glaucoma medications were compared between the AGV and MTMT groups at each time point (inter-group analysis), and compared between the baseline and 6 or 12 months after the anti-glaucoma treatment in each group (intra-group analysis). Graft survival was analyzed and compared between the two groups.

Statistical Analysis

A statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The Mann–Whitney test was used to compare each of the parameters at the baseline and after treatment between AGV and MTMT groups and categorical variables were compared using Fisher's exact test or chi-square test (inter-group analysis). The Wilcoxon signed-rank test was used to compare parameters between the baseline and after treatment in each group (intra-group analysis). Graft survival was analyzed using the Kaplan–Meier method to estimate the median survival time (MST). The log-rank test was used to assess the significant differences in MST between the groups. A value of $p < 0.05$ was considered statistically significant for all tests.

RESULTS

Table 3 summarizes baseline parameters in each group before AGV implantation. The mean baseline IOPs were 24.0 (range, 15–42) and 32.6 (range, 21–56) mmHg in the MTMT and the AGV groups ($p > 0.05$), respectively. The mean size of the donor graft was 7.88 ± 0.18 (range, 7.25–8.25) mm in the MTMT group, and 7.72 ± 0.29 (range, 7.75–8.25) mm in the AGV group, which showed no statistical significance. There were no statistically significant differences in ECD, CV, and hexagonality between those two groups.

TABLE 3 | Clinical characteristics in the MTMT and AGV groups before AGV implantation.

	MTMT	AGV	*P*-value*
Baseline ocular parameters			
Visual acuity (logMAR)	1.6 ± 1.1 (0.7–3.7)	1.6 ± 1.0 (0.7–3.7)	0.931
Intraocular pressure (mmHg)	24.0 ± 8.6 (15–42)	32.6 ± 10.3 (21–56)	0.063
Endothelial cell density (/mm^2)	1683.4 ± 531.3 (1,259–2,564)	1879.8 ± 1096.9 (343–3,663)	0.605
Central corneal thickness (μm)	538.1 ± 42.8 (465–595)	556.7 ± 59.6 (466–908)	0.931
Coefficient of variation	36.8 ± 5.4 (25–43)	34.0 ± 8.2 (23–46)	0.409
Hexagonality (%)	57.7 ± 10.2 (42–74)	55.0 ± 13.5 (33–67)	0.644
Lens status (phakia: pseudophakia: aphakia)	0: 7: 2	1: 8: 0	0.471
Factors associated with PKP			
Combined cataract extraction	0 (0%)	1 (11%)$^+$	0.303
Donor graft size (mm)	7.88 ± 0.18 (7.75–8.25)	7.72 ± 0.29 (7.25–8.25)	0.190

**Using the Mann–Whitney test or the Fisher's exact test or the chi-square test where appropriate.*

+PKP combined with simultaneous cataract surgery was undergone 3 years prior to AGV implantation.

Data were presented as mean ± SD (ranges).

MTMT, maximum tolerated medical therapy; AGV, Ahmed glaucoma valve; PKP, penetrating keratoplasty.

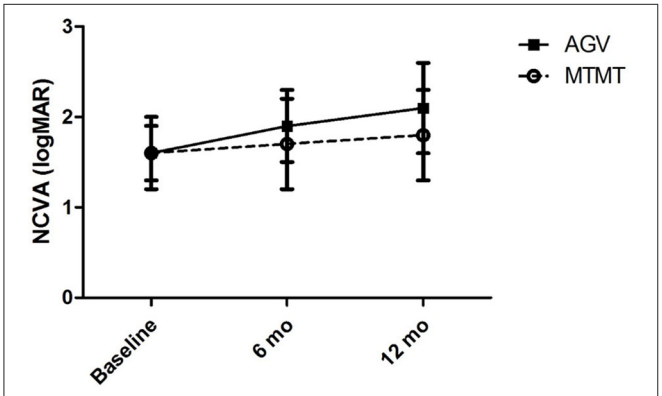

FIGURE 1 | Changes in the non-corrected visual acuity (NCVA) after glaucoma treatment. No significant difference was found between the two groups, and between before and after the treatment in each group.

The visual acuities before the anti-glaucoma treatment, and at 6 and 12 months after the treatment are presented in **Figure 1**. The mean visual acuities before the treatment, and at 6 and 12 months after the treatment were 1.6 ± 1.1 (range, 0.7–3.7), 1.7 ± 1.4 (range, 0.4–4.7), and 1.8 ± 1.5 (range, 0.4–4.7) logMAR units in the MTMT group, and 1.6 ± 1.0 (range, 0.7–3.7), 1.9 ± 1.3 (range, 0.5–4.7), and 2.1 ± 1.4 (range, 0.5–4.7) logMAR units in the AGV group. Although, the average VA was worsened by 0.2 logMAR units after MTMT and by 0.5 logMAR units after AGV, there was no statistically significant difference in each group over the treatment or between two groups at each time point.

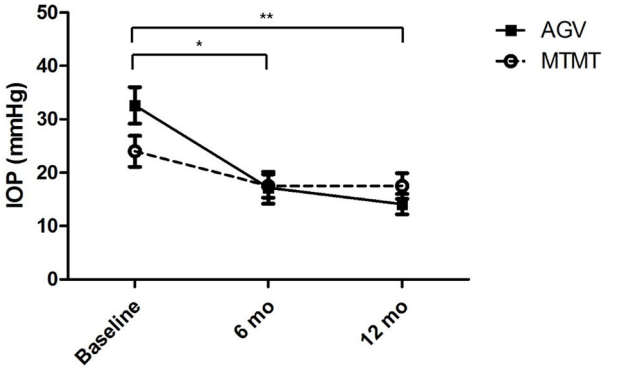

FIGURE 2 | Changes in intraocular pressure (IOP) after anti-glaucoma treatment. No significant difference was found between the two groups. There were significant IOP reductions in the AGV group between baseline and 6 or 12 months after the treatment (*$p = 0.020$, **$p = 0.008$; Wilcoxon signed-rank test for intra-group analysis).

The changes in IOP are presented in **Figure 2**. The mean IOP before, and at 6 and 12 months after the treatment were 24.0 ± 8.6 (range, 15–42), 17.5 ± 6.6 (range, 10–32), and 17.5 ± 7.3 (range, 10–33) mmHg in the MTMT group and 32.6 ± 10.3 (range, 21–56), 17.2 ± 5.8 (range, 10–39), and 14.1 ± 5.6 (range, 7–26) mmHg in the AGV group, respectively. After AGV implantation, there were significant IOP reductions between the baseline and post-operative 6 months ($p = 0.020$) and between the baseline and post-operative 12 months ($p = 0.008$). IOP reductions were greater in the AGV group than in the MTMT group ($p = 0.040$).

The changes in ECD, hexagonality, CV, and central corneal thickness between the two groups are presented in **Figures 3**, **4**. The mean ECD before, and at 6 and 12 months after the treatment were 1,638.4 ± 531.3 (range, 1,259–2,564), 777.5 ± 321.7 (range 372–1,404), and 588.8 ± 324.5 (range 331–1,262) cells/mm^2 in the MTMT group, and 1,879.8 ± 1,096.9 (range, 343–3,663), 1,509.3 ± 1,291.6 (range, 504–3,703), and 1,226.0 ± 1,227.7 (range, 606–3,333) cells/mm^2 in the AGV group, respectively. There were significant ECD reductions between the baseline and 6 months after the treatment in both groups (MTMT, $p = 0.008$; AGV, $p = 0.015$), and between the baseline and 12 months after the treatment in the MTMT group ($p = 0.008$). Notably, there were no statistically significant differences between two groups over time. The mean hexagonality before, and at 6 and 12 months after the treatment were 57.7 ± 10.2 (range, 42–74), 53.0 ± 15.0 (range, 30–70), and 55.8 ± 11.3 (40–71)% in the MTMT group, and 55.0 ± 13.5 (range, 33–67), 54.8 ± 13.2 (range, 33–66), and 49.9 ± 15.2 (range, 35–75)% in the AGV group. There was a significant hexagonality reduction between the baseline and 12 months after the treatment in the AGV group ($p = 0.018$), but there were no statistically significant differences in hexagonality between the two groups. The mean CV before,

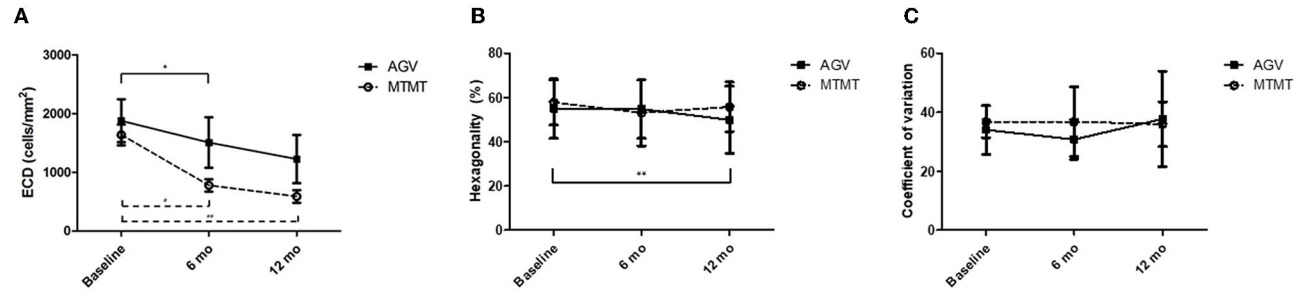

FIGURE 3 | Changes in corneal endothelial cell measurements after anti-glaucoma treatment. **(A)** Changes in the endothelial cell density (ECD). No significant difference was found between the two groups. There was a significant ECD reduction in the AGV group between baseline and 6 months. There were significant ECD reductions in the AGV group between baseline and 6 and 12 months after the treatment (*$p = 0.015$, $^{\#}p = 0.008$, $^{\#\#}p = 0.008$; Wilcoxon signed-rank test for intra-group analysis). **(B)** Changes in hexagonality. No significant difference was found between the two groups. There was a significant hexagonality reduction in the AGV group between baseline and 12 months after the treatment in the AGV group (**$p = 0.018$; Wilcoxon signed-rank test). **(C)** Changes in coefficient of variation. No significant difference was found between the two groups, and between before and after the treatment in each group.

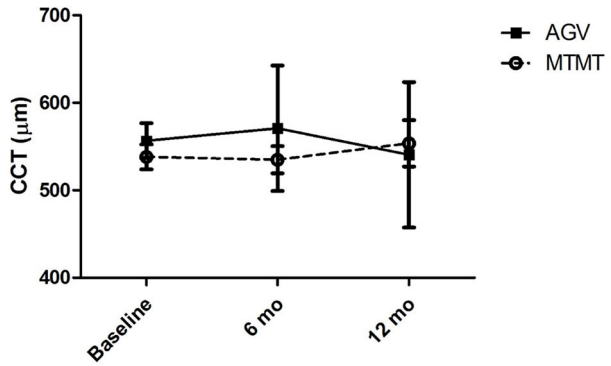

FIGURE 4 | Changes in central corneal thickness (CCT) after anti-glaucoma treatment. No significant difference was found between the two groups, and between before and after the treatment in each group.

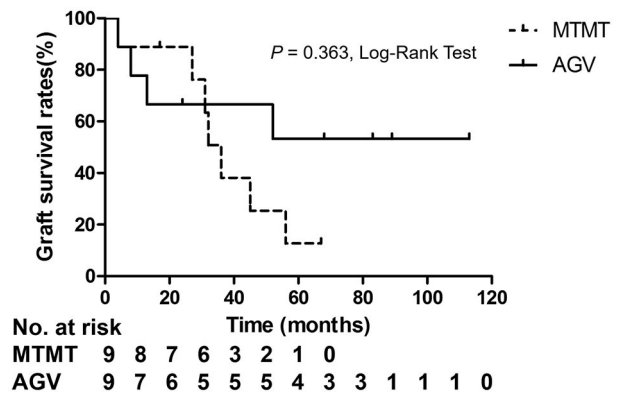

FIGURE 5 | Kaplan–Meier analysis showed no significant differences in graft survival between the two groups.

and at 6 and 12 months after the treatment were 36.8 ± 5.4 (range, 25–43), 36.8 ± 11.9 (range 26–64), and 35.9 ± 7.6 (range, 40–71) in the MTMT group, and 34.0 ± 8.2 (range, 23–46), 30.8 ± 6.7 (range, 22–46), and 37.7 ± 16.2 (range, 26–72) in the AGV group. There were no statistically significant differences in CV before treatment, and at 6 and 12 months after the treatment in each group and between two groups. The mean corneal thickness before, and at 6 and 12 months after the treatment were 538.1 ± 42.8 (range, 465–595, 534.8 ± 46.4 (range, 470–623), and 553.6 ± 79.5 (range, 460–642) μm in the MTMT group, and 556.7 ± 59.6 (range, 493–697), 570.8 ± 108.2 (range, 449–807), and 540.6 ± 83.9 (range, 412–908) μm in the AGV group, respectively. There were no statistically significant differences in corneal thickness before the treatment, and at 6 and 12 months after the treatment in each group and between two groups.

Corneal graft failure occurred in 7 patients (77.7%) in the MTMT group and 3 patients (33.3%) in the AGV group eventually. There were no statistically significant differences between the two groups. The median survival time (MST) was 1,050.0 ± 575.1 (range, 120–2,010) days in the MTMT group, and 1,513.3 ± 1201.4 (range, 120–3,390) days in the AGV group, which showed no significant difference in the survival analysis ($p = 0.363$, log-rank test) (**Figure 5**). Superficial punctate epithelial keratopathy of the corneal grafts occurred in 10 patients (77.7%) in the MTMT group and 3 patients (33.3%) in the AGV group, and there was no statistically significant difference between the two groups (**Table 4**).

TABLE 4 | Superficial punctate epithelial keratopathy of the corneal grafts in the MTMT and AGV groups.

		MTMT	AGV	*P*-value*
Superficial punctate epithelial keratopathy (No. of patients)	Yes	7	3	
	No	2	6	
Percentages (%)		77.7	33.3	0.153

**Using the Fisher's exact test.*
MTMT, maximum tolerated medical therapy; AGV, Ahmed glaucoma valve.

TABLE 5 | Number of topical medications in the MTMT and AGV groups.

	MTMT	AGV	*P*-value*
Pre-treatment	3.5 ± 1.3 (2–5)	4.1 ± 0.9 (3–5)	0.387
At 12 months	3.0 ± 1.2 (2–5)	1.3 ± 1.7 (0–5)	0.024

**Using the Mann–Whitney test.*
MTMT, maximum tolerated medical therapy; AGV, Ahmed glaucoma valve.

The mean number of anti-glaucoma medications before the treatment and at 12 months after the treatment were 3.5 (range, 2–5) and 3.0 (range, 2–5) in the MTMT group and 4.1 (range, 3–5) and 1.3 (range, 0–5) in the AGV group (**Table 5**). There were no differences in the mean number of medications between two groups before the treatment ($p = 0.387$), while the number of medications was significantly lower in the AGV group than in the MTMT group at 12 months ($p = 0.024$).

DISCUSSION

In this study, effects of AGV implantation were comparable to effects of MTMT on ECD changes and graft survival in patients with penetrating keratoplasty for at least 12 months. However, surprisingly, the reduction in ECD with MTMT of PKP eyes for bullous keratopathy was greater than those eyes with normal ECD in previous studies (5, 7, 16). This is the first report to evaluate ECD changes with MTMT in corneal transplanted eyes so far. In previous reports, they described the effect of each anti-glaucoma drug on ECD, neither the combined anti-glaucoma drugs nor MTMT. Therefore, it is still noteworthy to report that the effect on ECD can be influenced by both multiple combined topical anti-glaucoma drugs and compromised endothelial cells in the host owing to the transplantation and previous history of bullous keratopathy. In the AGV group, a patient who had undergone PKP combined with simultaneous cataract surgery 3 years prior to AGV implantation was included. Since previous studies have reported that the decrease in ECD after 6 months after cataract surgery was not significant (17–19), the fact that PKP with simultaneous cataract surgery was included in the AGV group would not have affected the outcome of ECD.

Based on previous reports that suggested a graft failure of 8∼26% with AGV implantation at 12 months in patients with penetrating keratoplasty (2, 20–22), our data showed a graft failure of 33% with AGV implantation, which were comparable with previous reports. The mean loss of ECD was 653/mm^2/year in the AGV, which was comparable with previous reports (−315 cells/mm^2/year) (21) and a recent study has suggested ECD loss of −519.97 cells/mm^2 for 2 years (23). Given that the patients who showed unacceptably high IOP based on their severity or progression of the optic nerve damages or visual field defects had undergone AGV implantation, high pre-operative IOP in AGV, although it was insignificant, may also affect changes of ECD. In this study, hexagonality of corneal endothelial cells significantly decreased after 1 year of AGV implantation, whereas a previous study showed no significant difference in hexagonality after AGV implantation or compared with the control group (24).

Notably, the MTMT group showed a remarkable reduction in ECD (−1,050 cells/mm^2/year), which was insignificant compared with the AGV group, but was significant compared with the baseline. The ECD changes with MTMT in glaucoma patients who underwent PKP have yet to be reported probably due to the failure to consider reduction in ECD following MTMT. The effect of topical CAIs on ECD remains controversial. Some clinical studies showed no significant reduction in ECD following the application of topical CAIs in patients with glaucoma who did not undergo intraocular surgery although corneal thickness was increased occasionally (25, 26). The other studies show that CAI effect on ECD is primarily related to attenuation of the bicarbonate efflux (3, 4). Eye bank data showed no significant correlation of ECD loss with anti-glaucoma medication in the absence of ocular surgery (8). However, the ECD of the donor graft in recipients after PKP may be affected differently by anti-glaucoma medications. The annual rate of endothelial cell loss is 0.6% in the normal adult human cornea (15). By contrast, the compromised cornea after PKP loses endothelial cells at a rate of 7.8–7.9% per year over 10 years (14, 27, 28). The endothelial cells can be significantly affected by topical CAIs in compromised corneas with guttata (29, 30). Therefore, the long-term MTMT using topical CAIs may affect ECD in compromised corneas as in PKP. In line with this, our study suggested that ECD may be significantly reduced by the long-term MTMT in patients who underwent PKP. Another possibility is that the long-term exposure to higher IOP in MTMT compared with AGV implantation may cause a reduction of ECD. Meanwhile, MTMT did not show any differences in hexagonality and CV. It indicates that the functional attenuation may be less in MTMT when compared with AGV implantation despite the reduction of ECD. Besides, the prevalence of superficial punctate epithelial keratopathy in patients with MTMT was also higher than in patients with AGV. Therefore, we hypothesized how to lose endothelial cells with either MTMT or glaucoma drainage device (**Figure 6**). With long-term anti-glaucoma medication, endothelial toxicity related to low pH, preservatives of anti-glaucoma eyedrops, ocular inflammation related to an ingredient, such as prostaglandin analogs, or CAIs' effects on corneal endothelial transports may contribute to the reduction of endothelial cell density in corneal grafts (**Figure 6**, upper chart) (30–34). Whereas, turbulent aqueous flow or mechanical stress near the tube seems to contribute directly in the reduction of endothelial cell density in corneal grafts (**Figure 6**, lower chart) (35). Long-term graft survival with the shunt surgery was known to be lower than that with anti-glaucoma medication (6), whereas damaged ocular surface may end up with poor compliances, and it can induce less-controlled IOP along with the reduced graft survival in MTMT. Given that the prevalence of SPK was more than double in MTMT, although it was not significant, increased SPK may contribute to further ocular surface inflammation or may affect drug compliance. Therefore, AGV implantation can be still considered as an alternative option for patients who require long-term MTMT in the compromised cornea with PKP.

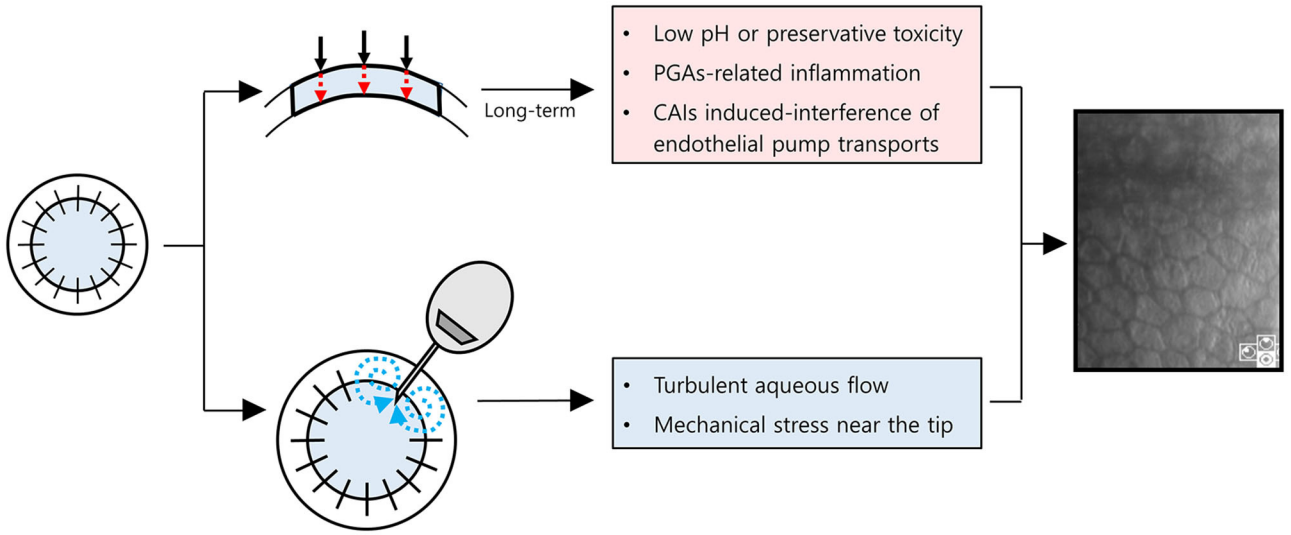

FIGURE 6 | Schematic diagram for a hypothesis on how to damage corneal endothelial cells with maximum tolerated medical therapy or glaucoma drainage device. Red dot arrows indicate anti-glaucoma eyedrops are permeable to endothelial cells with (1) low pH or preservative toxicity, (2) PGAs-related inflammation, or (3) CAIs induced-interference of endothelial pump transports. Blue dot arrows indicate turbulent aqueous flow near the tube. PGAs, prostaglandin analogs; CAIs, Carbonic anhydrase inhibitors.

Besides, current studies investigated the effect of minimally invasive glaucoma surgery (MIGS) on corneal endothelial cells. The CyPass supraciliary microshunt (Alcon Laboratories, Fort Worth, TX) has been withdrawn from the global marketplace because of its adverse effect on ECD (36, 37). It has been reported that endothelial cell loss at 24 months after the XEN gel stent (Allergan, Belfast, Ireland) implantation was 14.5% (38). As for the Ex-Press mini-shunt (Alcon Laboratories), endothelial cell loss at 12 months was 10.0% and at 24 months was 18.0% in long-term studies (39, 40). There are only several case reports describing the effects of MIGS on corneal endothelial cells in post-keratoplasty glaucoma so far, and the results are controversial (41, 42).

The study was limited by the small number of cases, the retrospective study design, and the short-term outcome based on 1-year data analysis. Due to the retrospective nature, the study design was failed to show direct head-to-head comparison and randomization of MTMT or AGV implantation was unavailable due to an ethical issue. Although not statistically significant, the mean age of patients in the MTMT group was almost 5 years older than that of the AGV group, pre-operative IOP was high in the AGV group, and the time between PKP and onset of anti-glaucoma treatment was almost double that of the MTMT group. These differences may have affected the corneal endothelial cells loss. For the survival analysis, limited follow-up and different follow-up duration may have increased the risk of bias in the comparative survival analysis. Finally, re-PKP in both groups, which was insignificant, may also have affected the survival of the corneal grafts. Therefore, further long-term prospective study is pending.

Although this study is preliminary, it is still worthwhile to reveal the possible endothelial toxicity with long-term MTMT in transplanted corneal graft for previous bullous keratopathy. It indicates that an alternative option with an AGV implantation or MIGS may be required in patients with PKP when the long-term MTMT is mandatory. In summary, MTMT seems to affect the endothelial cell density in patients who underwent PKP for bullous keratopathy, and it appears to be similar to the initial effect of AGV implantation. Therefore, careful monitoring of ECD should be considered in corneal transplanted patients with MTMT for glaucoma.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets contains patient information and is not publicly available. Requests to access these datasets should be directed to Mee Kum Kim, kmk9@snu.ac.kr.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Seoul National University College of Medicine. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MK is the principal investigator of the study and made substantial contributions to the design for this study and participated in the interpretation of data and the critical

revision of the manuscript for important intellectual content. SW made substantial contributions to the acquisition of data and analysis of data for this study and drafted the article. YK and JJ participated in the interpretation of data and the revision of the manuscript. All authors read and approved the final manuscript.

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Two-Week Central Macular Thickness Reduction Rate >37% Predicts the Long-Term Efficacy of Anti-vascular Endothelial Growth Factor Treatment for Macular Edema Secondary to Retinal Vein Occlusion

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Objective: To determine if the early response assessments can predict the long-term efficacy of anti-vascular endothelial growth factor (VEGF) treatment for macular edema secondary to retinal vein occlusion (RVO-ME).

Methods: A retrospective study of patients with diagnosis of RVO-ME and intravitreal anti-VEGF treatment was conducted. Clinical characteristics including age, gender, disease subtype and disease duration were recorded at baseline. The best corrected visual acuity (BCVA and logMAR), intraocular pressure (IOP), and central macular thickness (CMT) were recorded at baseline, 2 weeks, and every month (months 1–6) after injection. Further, we compared the early response assessments between the cured group (6-month CMT $\leq$ 250 μm) and the uncured group (6-month CMT $>$ 250 μm).

Results: A total of 164 eyes in 164 patients (77 male and 87 female) were included. At each post-injection time point, both BCVA and CMT are significantly decreased from baseline (all $P < 0.001$). Spearman's test showed that 2-week CMT reduction rate after the first injection was negatively correlated with BCVA at 6 months ($r = -0.359$, $P < 0.001$). Compared with the uncured group (47 cases), the cured group (117 cases) was younger (59.53 $\pm$ 11.68 vs. 65.19 $\pm$ 13.10 years old, $P < 0.01$), had more BRVO patients (76.1% vs. 44.7%, $P < 0.01$), a shorter disease duration (1.92 $\pm$ 2.43 vs. 5.05 $\pm$ 4.32 months, $P < 0.01$), lower baseline CMT (527.09 $\pm$ 154.95 vs. 768.96 $\pm$ 287.75 μm, $P < 0.01$), and lower baseline BCVA (0.86 $\pm$ 0.44 vs. 1.31 $\pm$ 0.51, $P < 0.01$). At each post-injection time point, the cured group had lower CMT and BCVA values when compared to the uncured group (all $P < 0.01$), and the 2-week CMT reduction rate was identified as the earliest response time to predict the long-term treatment efficacy. Moreover, ROC curve analysis indicated that a 2-week CMT reduction rate >37% yielded the best cut-off point for predicting the long-term cure of

anti-VEGF treatment at 6 months ($P < 0.001$). Multivariable logistic regression confirmed that the 2-week CMT reduction rate >37% was independently associated with the 6-month cured rate (OR = 9.639, 95% CI = 1.030–90.227, $P = 0.047$).

Conclusion: Age, disease duration, baseline CMT, and baseline BCVA are associated with visual outcomes at 6-month of anti-VEGF treatment for RVO-ME. The "2-week CMT reduction rate >37%" after the first injection is an independent factor to predict better long-term outcomes.

Keywords: retinal vein occlusion (RVO), macular edema (ME), anti-vascular endothelial growth factor (anti-VEGF), early response assessments, central macular thickness (CMT)

INTRODUCTION

Retinal vein occlusion (RVO) is the second most blinded retinal vascular disease in the world (1), which is characterized with the blockage of small veins that carries blood away from the retina. This blockage is often associated with the hardening of arteries (such as atherosclerosis) and the formation of a blood clot (2). Risk factors for RVO include older age, active smoking, hypertension, diabetes mellitus type II, hyperhomocysteinemia, dyslipidemia, carotid artery disease, glaucoma, and obstructive sleep apnea syndrome (3–5). The two most common types of RVO are central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO) according to where the occlusion is located. Though the pathogenesis is different, they both may cause retinal ischemia which gives rise to up-regulation of some cytokines such as vascular endothelial growth factor (VEGF), placental growth factor (PlGF), etc., and further lead to macular edema (ME) (6). Notably, ME, the most common complication of RVO, often results in decreased vision and even blindness, which seriously influences the prognosis of patients (7). Recent RVO guidelines have recommend intravitreal injection of anti-VEGF drugs as the first-line treatment for RVO-ME, due to its ability to inhibit angiogenesis, reduce vascular permeability, relieve inflammation, thus reducing central macular thickness (CMT) and ME (6–8). In clinics, the anti-VEGF drugs are mainly divided into the monoclonal antibody (mAb, such as ranibizumab) and the Fc-fusion protein (Fc, such as aflibercept, conbercept, etc.). However, some patients continue to have ME or relapse after repeated injection in clinic practice, namely refractory ME, which requires long-term, repeated, and combined treatment (9, 10).

Optical coherence tomography (OCT) is one of the commonly used detection techniques in ophthalmology. It can accurately measure CMT which is a key index for evaluating the efficacy of ME treatment and determining if repeated injection is necessary. Previous studies have found that visual function increases the most at 7 days after anti-VEGF treatment (11–13). While recent studies on BRVO state that CMT decreases most 24 h after the first anti-VEGF treatment, and it can be utilized as a prognostic factor for long-term efficacy (14). Similar investigation is limited and current studies have variable standards to determine the treatment efficacy of patients (15, 16).

Therefore, this study aimed to investigate if the early response assessments such as the best corrected visual acuity (BCVA), intraocular pressure (IOP), CMT value, and CMT reduction rate, can predict the long-term efficacy of anti-VEGF treatment for RVO-ME. We are also interested in the comparison of the long-term efficacy between the monoclonal antibody (mAb) and Fc-fusion protein (Fc)-based anti-VEGF drugs. The receiver operating characteristic (ROC) curve plot is utilized to illustrate the best classifier of early CMT reduction rate to predict the long-term efficacy of anti-VEGF treatment. In this way, refractory ME can be found early in the clinic and provide evidence for individualized therapy.

MATERIALS AND METHODS

Study Design and Participants

This retrospective study was conducted at Ophthalmology Department of the Second Affiliated Hospital of Chongqing Medical University from July 2017 to January 2021 in accordance with the Declaration of Helsinki. The local institutional ethics review boards approved the study's protocol (number 2018-56) and written informed consent was obtained from all patients. The inclusion criteria were as follows (13): (1) Patients were $\geq$ 18 years old and had disease duration (the time from the onset of RVO-related symptoms to the first anti-VEGF treatment) $\leq$ 1year. (2) Patients were diagnosed with macular edema secondary to CRVO or BRVO with the central macular thickness (CMT) > 250 μm per OCT examination. (3) The baseline of the best corrected visual acuity (BCVA, logMAR) fell into the range of 0.3–1.0 (6–8). (4) Patients underwent multiple intravitreal injections of anti-VEGF drugs (mAb or Fc-binds) alone by the same surgeon. The exclusion criteria (13) were patients who had other ocular diseases such as severe cataracts, glaucoma, uveitis, high myopia (over −6.00D), and macular diseases, or had ocular surgeries within 3 months before the first anti-VEGF injection such as retinal photocoagulation, vitrectomy and vitreous injection. Patients who experienced a change in anti-VEGF agent or underwent retinal photocoagulation after baseline were excluded. Patients who were unable to obtain OCT and

Abbreviations: BCVA, best corrected visual acuity; BRVO, branch retinal vein occlusion; CMT, central macular thickness; CRVO, central retinal vein occlusion; DRIL, disorganization of retinal inner layer; ELM, external limiting membrane; EZ, ellipsoid zone; Fc, Fc-fusion protein; HF, hyperreflective foci; IOP, intraocular pressure; IZ, interdigitation zone; mAb, monoclonal antibody; ME, macular edema; OCT, optical coherence tomography; PIGF, placental growth factor; ROC, receiver operating characteristic; RVO, retinal vein occlusion; SRF, subretinal fluid; VEGF, vascular endothelial growth factor.

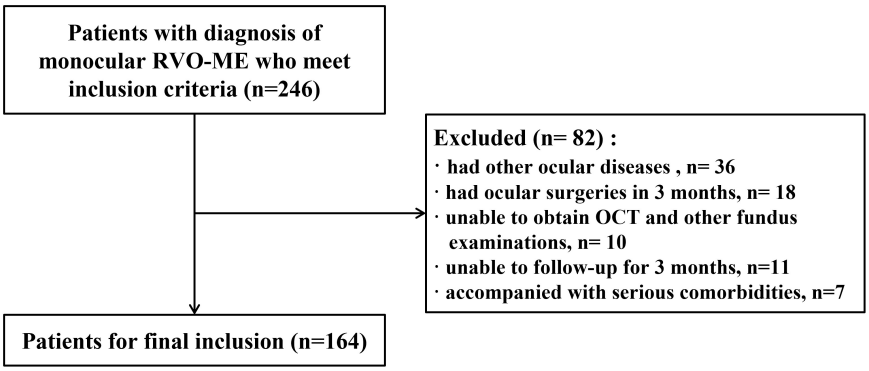

FIGURE 1 | The flow chart of enrolled patients.

TABLE 1 | Demographic characteristics of patients.

Characteristics	Mean ± SD
Age (years)	61.15 ± 12.33
Disease duration (month)	2.82 ± 3.39
Baseline of best corrected visual acuity (logMAR)	0.99 ± 0.51
Baseline of central macular thickness (μm)	596.41 ± 229.10
Preoperative intraocular pressure (mmHg)	15.12 ± 5.76

other fundus examinations due to refractive stroma turbidity, unable to follow-up for 3 months, and accompanied with serious comorbidities such as stroke and myocardial infarction were excluded. The flow chart of enrolled patients was showed in **Figure 1**.

Materials and Instruments

Anti-vascular endothelial growth factor drugs used in our hospital include ranibizumab (Swiss Novartis), conbercept (Chengdu Kanghong Biotechnology Co., Ltd.), and aflibercept (Germany Bayer). IOP was measured by Full Auto Tonometer (Canon, Japan) and central macular thickness (CMT) was measured in a 512*128 mode by Cirrus HD-OCT 5000 (Zeiss, Germany).

Data Collection, Treatment, and Follow-Up

The patients' characteristics including gender, age, disease subtype, disease duration, BCVA (logMAR), CMT, IOP, and other baseline indexes were retrospectively reviewed and retrieved. LogMAR is a notation of vision loss. Zero logMAR indicates standard vision, positive values indicate poor vision, and negative values indicate good visions. The patients were qualified for repeated anti-VEGF injection only when they met such criteria: persisted macular edema or recurrent worse macular edema (CMT > 250 μm), or intraretinal fluids/subretinal fluids was visible in OCT (12, 17). All patients' monocular eyes were treated with anti-VEGF drugs intravitreally in accord with the principle of first-time and on-demand treatment (1+PRN). The first follow-up time was 2-weeks after the first injection, followed by 1 to 6 months after injection (once a month). At each follow-up time point, BCVA, IOP, CMT, and the adverse reactions were recorded. Macular edema was defined as CMT > 250 μm, the cure of macular edema was defined as CMT ≤ 250 μm, and the CMT reduction rate was defined below (14). There should be at least a 4-week gap between the adjacent two injections.

$$\text{CMT reduction rate} = \frac{\text{CMT}_{\text{before treatment}} - \text{CMT}_{\text{after treatment}}}{\text{CMT}_{\text{before treatment}}}$$

Comparison of the Efficacy of Different Anti-vascular Endothelial Growth Factor Drugs

The anti-VEGF agents used in the study were classified into two groups based on their different mechanisms of action. They were the monoclonal antibody (mAb) group (injection of ranibizumab, 95 eyes) and Fc-fusion protein (Fc) group (injection of conbercept or aflibercept, 69 eyes). The two groups were compared at baselines such as age, disease subtype, disease duration, BCVA (logMAR), IOP, and CMT, and changes of CMT and BCVA (logMAR) against baselines at each observation time point after treatment. The number of injections was also compared between the two groups.

The Relationship Between Early Response Assessments and Long-Term Efficacy After Anti-vascular Endothelial Growth Factor Treatment

To find the earliest time possible with the most change of BCVA (logMAR) and CMT, the alternation of BCVA (logMAR) and CMT relative to the baseline among 2-weeks after treatment, 1–6 months after treatment were compared. Spearman correlation analysis was used to evaluate the correlation between the baseline indexes, the early response assessments, and the prognosis of BCVA (logMAR) after 6 months. The strength of the correlation was defined by the absolute value of the correlation coefficient: 0.8–1.0 as very strong correlation, 0.6–0.8 as strong correlation, 0.4–0.6 as moderate correlation, 0.2–0.4 as weak correlation, and 0.0–0.2 as extremely weak or no correlation. The patients were then divided into the cured group (CMT ≤ 250 μm)

TABLE 2 | Comparison the baseline between the monoclonal antibody group and the Fc-fusion protein group.

Characteristics	Monoclonal antibody group (*n* = 95)	Fc-fusion protein group (*n* = 69)	χ^2/t	*P* value
Age (years old)	61.48 ± 11.70	60.70 ± 13.23	0.403	0.687
Gender, *n* (%)				
Male	43 (45.3%)	34 (49.3%)	0.258	0.611
Female	52 (54.7%)	35 (50.7%)		
Disease subtype, *n* (%)				
BRVO	63 (66.3%)	47 (68.1%)	0.059	0.809
CRVO	32 (33.7%)	22 (31.9%)		
Disease duration (month)	2.79 ± 3.41	2.85 ± 3.38	−0.105	0.917
Baseline BCVA (logMAR)	0.93 ± 0.43	1.07 ± 0.59	−1.673	0.097
Baseline CMT	588.19 ± 231.71	607.72 ± 226.66	−0.538	0.591
Baseline IOP (mmHg)	15.69 ± 7.24	14.34 ± 2.44	1.482	0.140
Number of injections	2.21 ± 1.12	2.23 ± 1.30	−0.113	0.910

BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; BCVA, best corrected visual acuity; CMT, central macular thickness; IOP, intraocular pressure. There are no significant differences in terms of gender, age, disease subtype, disease duration, BCVA (logMAR), IOP, CMT, and the number of injections between the mAb group and the Fc group (P > 0.05).

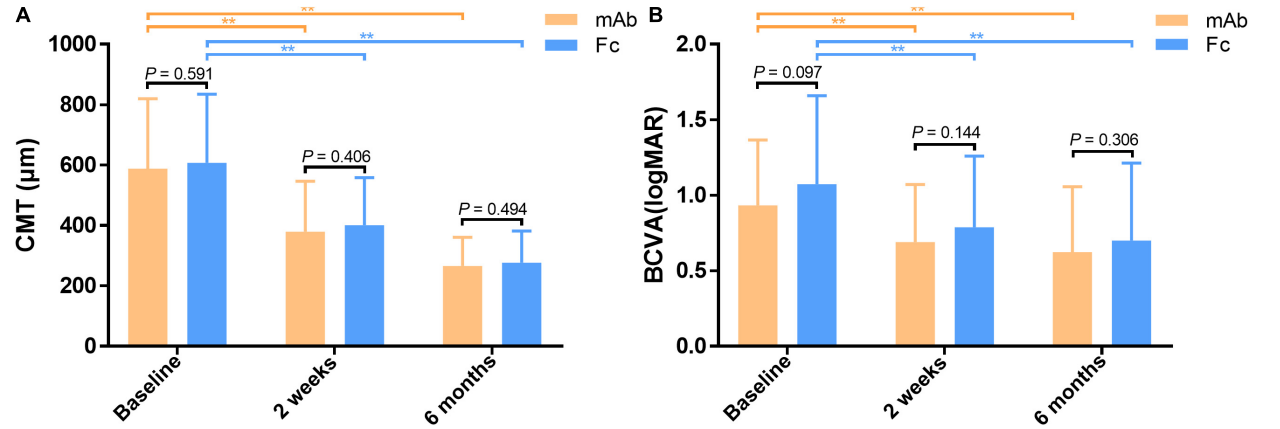

FIGURE 2 | (A) Comparison of CMT between the monoclonal antibody-treated group and the Fc-fusion protein-treated group. **(B)** Comparison of BCVA between the monoclonal antibody-treated group and the Fc-fusion protein-treated group. CMT and BCVA (logMAR) are significantly decreased from the baseline in both groups at half-month and 6 months after treatment. **Significant difference compared to the baseline ($P < 0.01$). However, there is no significant difference in mean CMT and BCVA (logMAR) between the two groups at half-month and 6 months post-treatment ($P > 0.05$). BCVA, best corrected visual acuity (logMAR). CMT, central macular thickness (μm).

and the uncured group (CMT > 250 μm) based on their CMT measurement at the 6-month follow-up time. Then the baseline indexes, the early response assessments, and the long-term efficacy via the ROC curve were compared between the two groups. Finally, the early CMT reduction rate threshold that can predict the long-term cure in 6-month were determined and its predictive value in 6-month was further verified by using the multivariable logistic regression analysis.

Statistical Analysis

The statistical analysis was performed by the SPSS 26.0 software (IBM/SPSS, Chicago, IL, United States). The continuous variables are described as mean ± SD. An independent-sample t-test was used for comparison between the two groups. A paired-sample t-test was used for comparison before and after treatment. The enumeration variables were described as *n* (%) and were compared by a Chi-square test. Spearman's test and multivariable logistic regression analysis were used to analyze the correlation between the early response assessments of the affected eye and long-term efficacy following anti-VEGF treatment for RVO-ME. The receiver operating characteristic (ROC) curve was used to determine the early CMT deduction rate threshold for predicting long-term efficacy at 6 months. All tests were two-side and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics

This study included 164 eyes in 164 RVO patients, of whom 77 were male and 87 were female. The age was 61.15 ± 12.33 years old. A total of 110 patients were diagnosed with BRVO, and 54 patients were diagnosed with CRVO. The disease duration were2.82 ± 3.39 months, the baseline BCVA (logMAR) was

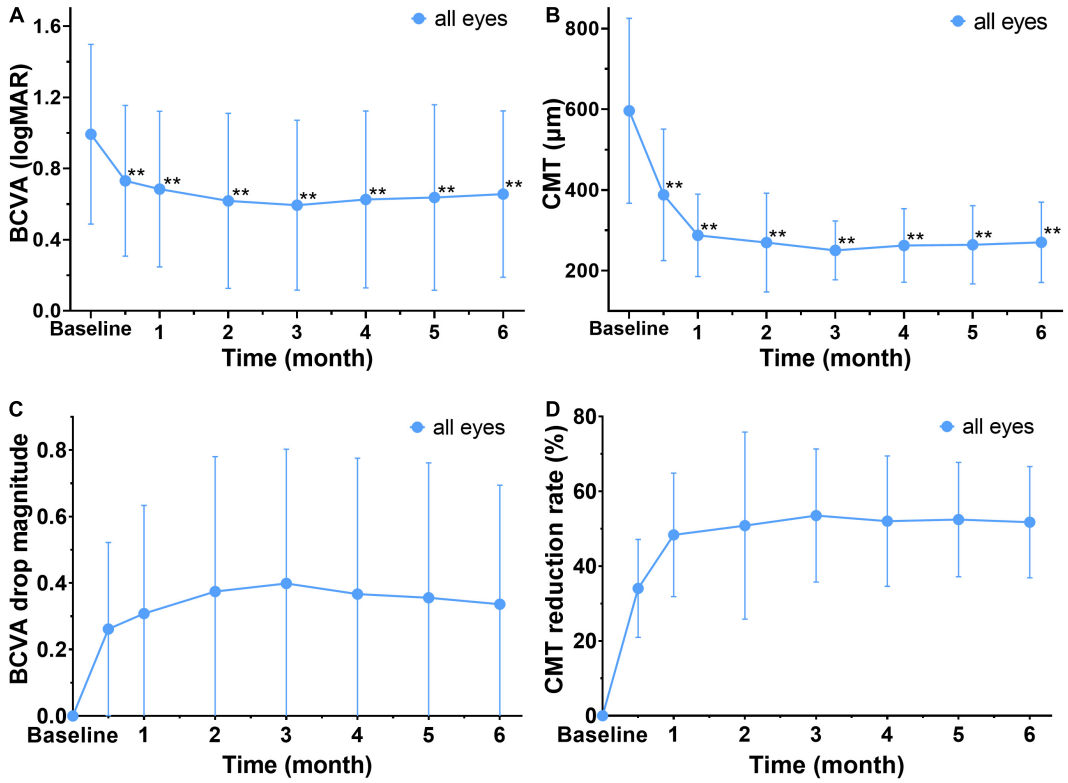

FIGURE 3 | Changes in mean BCVA and CMT before and after treatment in all affected eyes. **(A,B)** The mean BCVA (logMAR) and CMT are decreased significantly after treatment when compared to baseline. **Significant different compared to baseline ($P < 0.01$). **(C)** The drop magnitude of mean BCVA (logMAR) is compared to baseline at each observation time point after treatment, and it shows a notable decrease at 2 weeks after the first treatment with a change of 0.34 ± 0.36. **(D)** The drop rate of CMT at each observation time after treatment. It shows a notable reduction of CMT at 2 weeks after the first treatment, with a drop rate 34 ± 13 %. BCVA, best corrected visual acuity (logMAR). CMT, central macular thickness (μm).

0.99 ± 0.51, and the baseline CMT was 596.41 ± 229.10 μm (**Table 1**). No intraocular adverse events such as increased IOP, vitreous hemorrhage, and endophthalmitis are observed in all patients. During the study period, there were no patients who experienced a change in anti-VEGF agent or underwent retinal photocoagulation.

Comparison of the Efficacy of Different Anti-vascular Endothelial Growth Factor Drugs

There were no significant differences in terms of gender, age, disease subtype, disease duration, BCVA (logMAR), IOP, CMT, and the number of injections between the mAb group and the Fc group ($P > 0.05$) (**Table 2**). The CMT and BCVA (logMAR) within the two groups are significantly reduced than the baseline at each observation time after anti-VEGF treatment, indicating a statistically significant difference ($P < 0.01$); while the comparison between the two groups showed no statistical difference ($P > 0.05$) (**Figure 2**). According to the criteria of repeated injection, 65.26% (62/95 eyes) of patients in the mAb group had repeated injections, and 23.16% (22/95 eyes) had no recurrence followed up for 6 months after the first injection. The average injection was 2.21 ± 1.12 times. In comparison, 57.97% (40/69 eyes) of patients in the Fc group had repeated injections, and 24.64% (17/69 eyes) had no recurrence followed up for 6 months after the first injection. The average injection had 2.23 ± 1.30 times. The injection times between the two groups were not statistically significant ($t = -0.113$, $P = 0.910$). All patients had significantly decreased CMT and improved vision following anti-VEGF treatment in both mAb and Fc group. There was no significant difference in terms of the efficacy and the number of injections between the two different drugs.

The Relationship Between Early Response Assessments and Long-Term Efficacy After Anti-vascular Endothelial Growth Factor Treatment

Determination of the Early Response Time

The patients were analyzed to investigate the relationship between early response assessments and the long-term efficacy of anti-VEGF treatment. The results showed that the BCVA (logMAR) of the patients was significantly lower than that in the baseline (0.99 ± 0.51) after 2 weeks, 1, 2, 3, 4, 5, and 6 months of treatment ($P < 0.01$) (**Figures 3A,C**). The CMT of the observed eyes was significantly lower than the baseline after 2 weeks, 1, 2, 3, 4, 5, and 6 months of treatment, and the difference

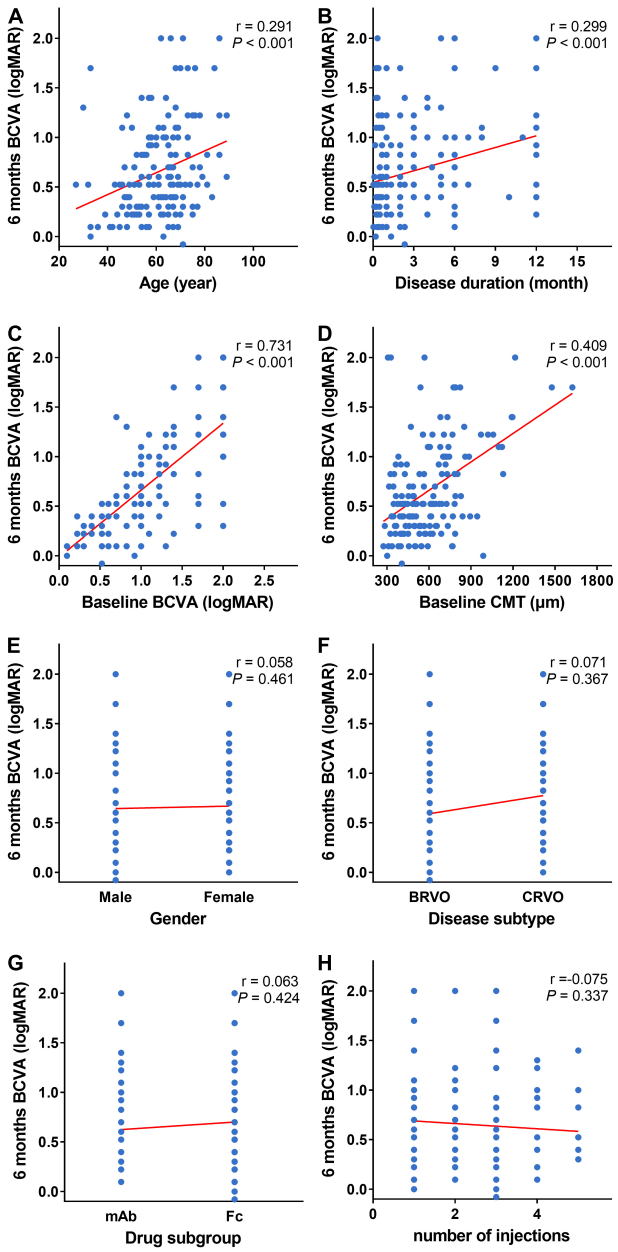

FIGURE 4 | Scatter plots of baseline and 6-month BCVA. **(A–H)** Scatter plots of 6-month BCVA (logMAR) and baseline indexes (age, disease duration, BCVA (logMAR), CMT, gender, disease subtype, and anti-VEGF drug subgroup). Six-month BCVA (logMAR) is strongly correlated with baseline BCVA (logMAR) **(C)**, moderately correlated with baseline CMT **(D),** and weekly correlated with age **(A)** and duration of disease **(B)**. Six-month BCVA (logMAR) is not correlated with gender **(E)**, disease subtype **(F)**, anti-VEGF drug subgroup **(G)**, and the number of injections **(H)**. BCVA: Best corrected visual acuity (logMAR). CMT, central macular thickness (μm); VEGF, vascular endothelial growth factor.

was statistically significant ($P < 0.01$) (**Figures 3B,D**). Thus, the macular edema was resolved significantly, and vision was improved remarkably after anti-VEGF treatment. Furthermore, the mean CMT and BCVA (logMAR) had decreased the most in 2 weeks post the first injection (**Figures 3C,D**). Therefore, 2 weeks was the earliest response time for follow-up investigation.

Analysis of Indexes That May Affect Long-Term Efficacy

The Spearman correlation analysis was used to analyze the correlation between the baseline, the early follow-up indexes, and the prognosis of BCVA (logMAR) after 6 months. The 6-month BCVA (logMAR) post the first treatment was considered as the outcome to measure prognosis of BCVA.

It showed the 6-month BCVA (logMAR) was strongly correlated with the baseline BCVA (logMAR), moderately correlated with the baseline CMT and weakly correlated with the age and disease duration. Moreover, the 6-month BCVA (logMAR) is not correlated with gender, disease subtype, anti-VEGF drug subgroup and the number of injections (**Figures 4A–H**).

It also showed the 6-month BCVA (logMAR) was strongly correlated with the 2-week BCVA (logMAR) post the first injection, moderately correlated with the 2-week CMT post the first treatment, and weakly correlated with the 2-week CMT reduction rate (**Figures 5A–C**).

Relationship Between Early Response Assessments and Long-Term Efficacy

The patients were divided into the cured group (CMT $\leq$ 250 μm, 117 eyes) and the uncured group (CMT > 250 μm, 47 eyes) based on their CMT measurement in OCT at the 6-month follow-up time. There was no significant difference in gender, anti-VEGF drug subgroup, IOP, and the number of injections between the cured and uncured groups. Comparison of the baseline age reveals the age in the cured group was significantly younger than that of the uncured group ($t = -2.709$, $P = 0.007$). The cured group had 76.1% of BRVO, while the uncured group had 44.7 % of BRVO, and the difference was statistically significant ($\chi^2 = 14.957$, $P < 0.001$). The duration of disease in the cured group was notably shorter than that of the uncured group ($t = 4.678$, $P < 0.001$). Both baseline CMT and baseline BCVA (logMAR) in the uncured group were significantly higher than that of the cured group ($t = 5.454$, 5.588, respectively, both $P < 0.001$) (**Figure 6**). In summary, the cured group was younger, had a shorter disease duration, a greater proportion of BRVO, lower values of baseline CMT and baseline BCVA (logMAR) when compared to the uncured group.

After the first injection of anti-VEGF drugs, the 2-week CMT reduction rate in the cured group was greater than that in the uncured group ($P < 0.001$) (**Figure 7F**). The CMT and BCVA (logMAR) values in the cured groups were significantly lower than those in the uncured group at each observation time point from 2 weeks to 6 months ($P < 0.01$) (**Figures 7A–D**). In addition, there was no significant difference in the number of injections between the two groups ($P > 0.05$) (**Figure 7E**). Taken together, it suggested that the cured group had a higher 2-week CMT reduction rate and vision improvement than the uncured group after the same number of anti-VEGF injections, and the effect was maintained to 6 months after treatment (**Figure 8**).

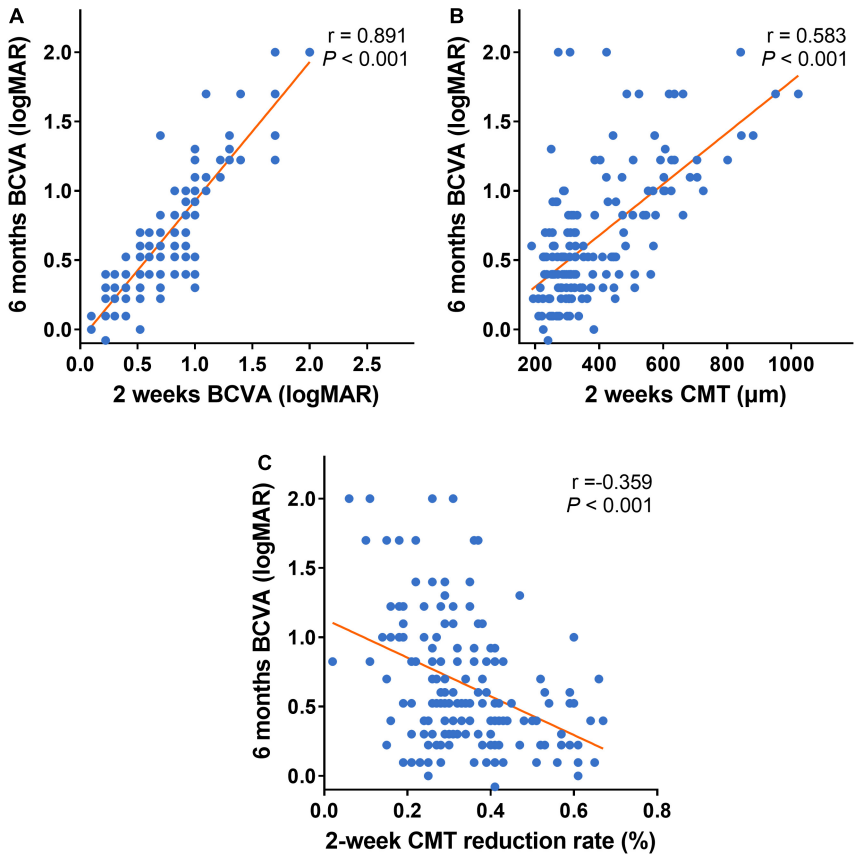

FIGURE 5 | Scatter plots of the early follow-up indexes and 6-month BCVA. **(A–C)** Scatter plots of 6-month BCVA (logMAR) and early follow-up indexes (2-week BCVA (logMAR), 2-week CMT, and 2-week CMT reduction rate). Six-month BCVA (logMAR) is strongly correlated with 2-week BCVA (logMAR) after the first treatment **(A)**. Six-month BCVA (logMAR) is moderately correlated with 2-week CMT after the first treatment **(B)**. Six-month BCVA (logMAR) is weekly correlated with 2-week CMT reduction rate after the first treatment **(C)**. BCVA: Best corrected visual acuity (logMAR). CMT, central macular thickness (μm).

Receiver Operating Characteristic Curve Plot to Illustrate the Predicting Ability of Early Response Assessments

Two-week CMT reduction rate after the first treatment was used as the binary classifier to define RVO patients as cured or uncured in 6 months. Then the 2-week CMT reduction rate after the first treatment and the cure of RVO patients after 6 months follow up were utilized to plot the receiver operating characteristic (ROC) curve (**Figure 9**). The result showed that a 2-week CMT reduction rate >37% after the first treatment was the best classifier to determine the efficacy of anti-VEGF treatment after 6 months (AUC = 0.816, sensitivity = 95.74%, specificity = 48.72%, Youden index = 0.4446, $P < 0.001$).

Logistic Regression Analysis

To further verify the predicting ability of 2-week CMT reduction rate for a long-term cure, a multivariable logistic regression analysis was used to predict the relationship between predictors (the independent variables such as age, disease subtype, disease duration, 2-week CMT, 2-week CMT reduction rate, and 2-week BCVA (logMAR)) and a predicted variable (the dependent variable: cure of RVO patients at 6 months). The results revealed that the 2-week CMT reduction rate >37% after the first injection was the best predictor for the cure at 6 months (OR = 9.639, 95% Cl = 1.030–90.227, $P = 0.047$). In addition, a longer disease duration (OR = 0.675, 95% Cl = 0.546–0.835, $P < 0.001$), a higher 2-week CMT value (OR = 0.982, 95% Cl = 0.974–0.990, $P < 0.001$), and a higher 2-week BCVA (logMAR) (OR = 0.087, 95% Cl = 0.012–0.609, $P = 0.014$), were negative predictors for the cure of RVO at 6 months (**Table 3**).

DISCUSSION

Previously most studies focus on utilizing the loss of baseline indexes such as CMT, disorganization of the retinal inner layer (DRIL), subretinal fluid (SRF), hyperreflective foci (HF), external limiting membrane (ELM), ellipsoid zone (EZ), and interdigitation zone (IZ) to predict the long-term efficacy in RVO-ME (10, 17–21). However, due to blockade of retinal hemorrhage before treatment, large CMT, and poor ocular fixation due to poor visual function, the quality of the retinal interlayer structure obtained from OCT images is far from satisfactory. Therefore, using these baseline retinal interlayer

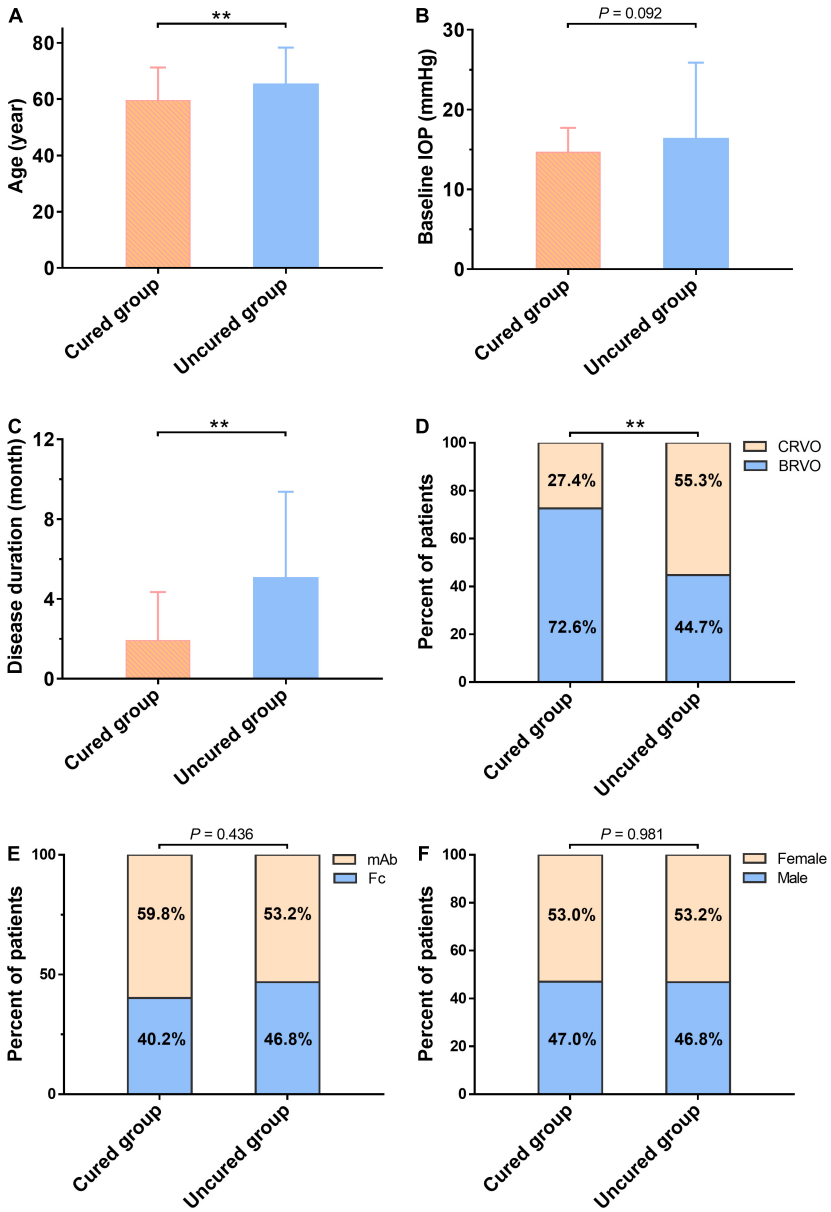

FIGURE 6 | Comparison of baseline characteristics between the cured group and the uncured group at the 6-month follow-up. There is no significant difference in Gender **(F)**, anti-VEGF drug subgroup **(E)**, and IOP **(B)** between the two groups. Comparison of the baseline age reveals the age in the cured group is significantly younger than that of the uncured group ($t = -2.709$, $P = 0.007$) **(A)**. The cured group has 76.1% of BRVO, while the uncured group has 44.7% of BRVO, and the difference is statistically significant ($\chi^2 = 14.957$, $P < 0.001$) **(D)**. The duration of disease in the cured group is notably shorter than that of the uncured group ($t = 4.678$, $P < 0.001$) **(C)**. **The difference is statistically significant ($P < 0.01$). mAb, the monoclonal antibody-based anti-VEGF drugs; Fc, Fc-fusion protein-based anti-VEGF drugs; BCVA, best corrected visual acuity (logMAR); BRVO, branch retinal vein occlusion; CMT, central macular thickness (μm); IOP, intraocular pressure; VEGF, vascular endothelial growth factor.

structure parameters to predict the long-term efficacy is limited (22). Recent studies have reported that the RVO patients who respond well to anti-VEGF therapy in the early stage are expected to have a better visual function recovery and less burden of long-term treatment. Hoeh et al. (23) have treated 27 CRVO-ME patients with anti-VEGF treatment, and have found 78% of patients who have no recurrence of ME at 6 months have completely resolved ME in 6 weeks after the first injection. Wang et al. (16) have found that early responders (CMT $<$ 320 μm at 3 months after the first injection of anti-VEGF drugs) can achieve better visual improvement than those late or incomplete responders (CMT $\geq$ 320 μm at 3 months after injection). Bhisitkul et al. (15) did a post-mortem analysis of the BRAVO and CRUISE trials and have found about three-quarters of CRVO patients had CMT dropped to 250 μm or less at 3 months after the first anti-VEGF treatment and they had a better vision at 6–12

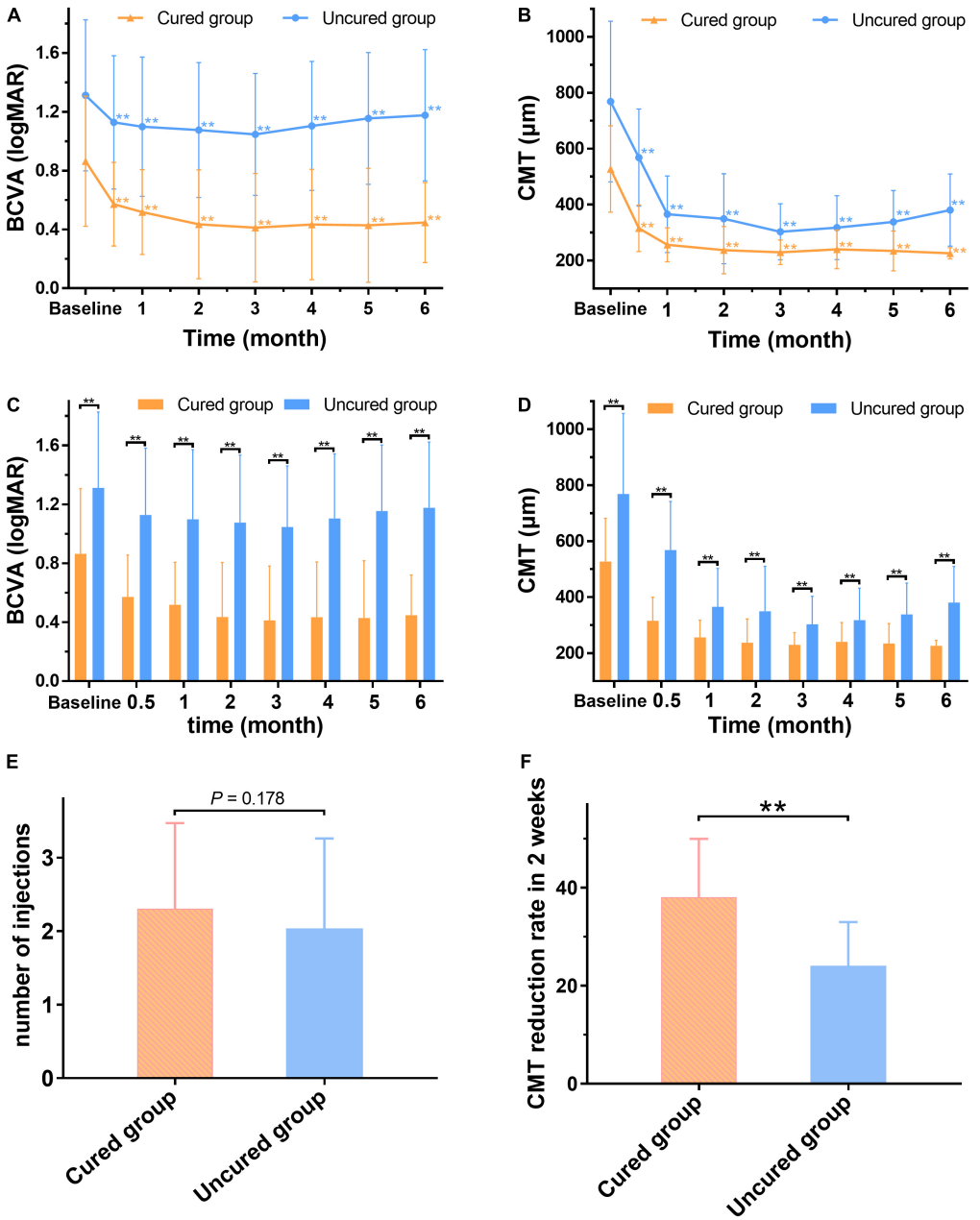

FIGURE 7 | The changes of BCVA and CMT between the cured and uncured eyes before and after treatment. After treatment, the mean BCVA (logMAR) and CMT of the two groups are significantly lower than the baseline ($p < 0.01$). **(A,B)** Both mean BCVA (logMAR) and CMT of the cured group and uncured group are significantly lower than those of baseline ($P < 0.01$). **(C,D)** The cured group has significantly lower BCVA (logMAR) and CMT values compared with the uncured group at any time point after treatment ($P < 0.01$). **(E)** There is no significant difference in the number of injections between the cured group and the uncured group ($P > 0.05$). **(F)** The CMT reduction rate in the cured group is significantly higher than that of the uncured group 2 weeks after the first injection ($P < 0.01$). **The difference is statistically significant ($P < 0.01$). BCVA: Best corrected visual acuity (logMAR). CMT: Central macular thickness (μm).

months follow-up. Jiang et al. (14) have advanced the detection time to 24 h after injection and have found that BRVO patients whose CMT reduction rate is greater than 18% at 24 h after the first injection will have a better visual prognosis at the 1-year follow-up. However, this study does not include CRVO patients.

Our study is the first one, to the best of our knowledge, to explore the correlation between the early changes of CMT and the long-term prognosis of all types of RVO-ME following anti-VEGF treatment. The results reveal that after 6 months of anti-VEGF therapy (1+PRN principle) in RVO-ME patients, BCVA is significantly improved and CMT is significantly reduced. The 2-week CMT reduction rate after the first injection can be used as an early response assessment to predict the long-term efficacy of anti-VEGF treatment. At 2-week, the CMT and

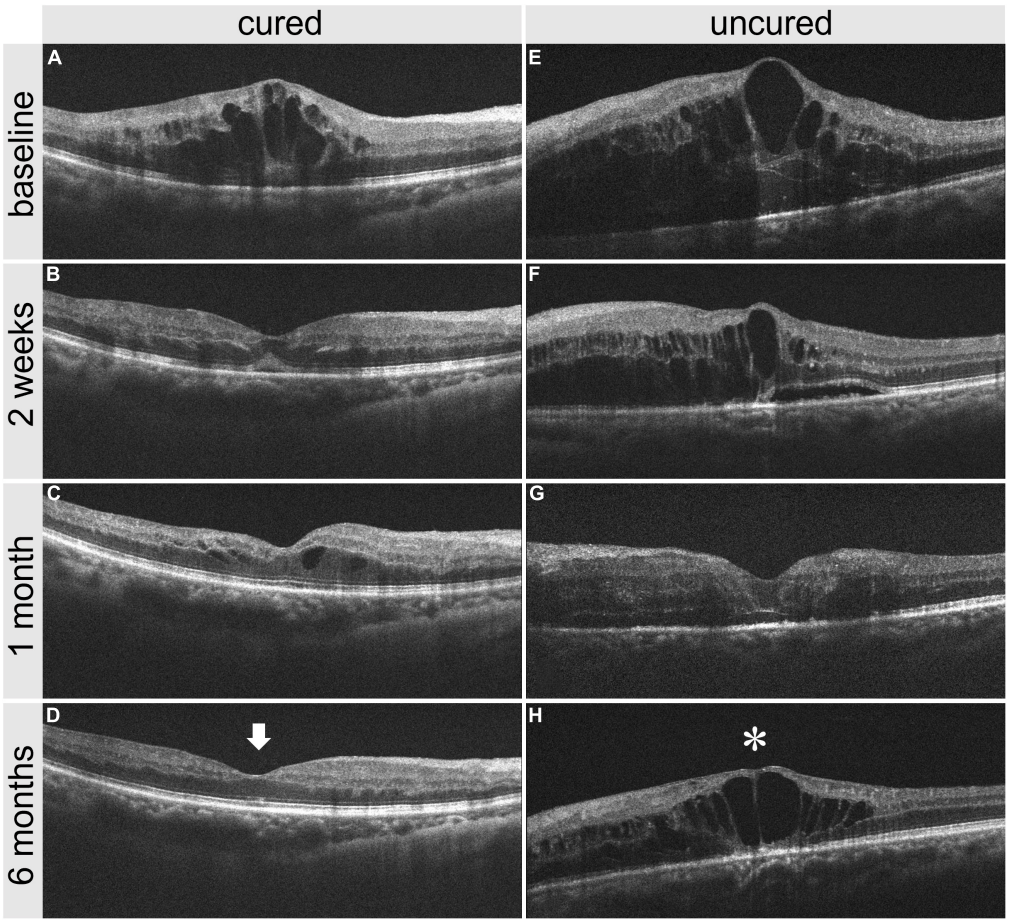

FIGURE 8 | Comparison of OCT images between one cured patient and one uncured patient before and after treatment. **(A–D)** panel shows the OCT images of a cured patient before treatment, 2 weeks, 1 month, and 6 months after treatment. **(E–H)** panel shows the OCT images of an uncured patient before treatment, 2 weeks, 1 month, and 6 months after treatment. It is noted that the CMT reduction in the cured patient is greater than that in the uncured patient 2 weeks after treatment. The CMT in the cured patient is 216 μm (arrow) at 6 months after treatment, versus 541 μm (star) in the uncured patient. CMT, central macular thickness; OCT, optical coherence tomography.

BCVA have the largest magnitudes of reduction and the degree of improvement gradually gets stabilized. No significant difference is found between the mAb and Fc-based anti-VEGF treatment in terms of the efficacy of RVO-ME. Further correlation analysis reveals the CMT reduction rate at 2 weeks after the first injection is significantly correlated with better BCVA at 6 months. Moreover, the CMT reduction rate at 2 weeks in the cured group is significantly higher than that in the uncured group. These findings provide evidence that early response assessments can predict the long-term efficacy of anti-VEGF treatment. In addition, the ROC curve analysis suggests when the 2-week CMT drop rate is greater than 37%, the patient is more likely to achieve a long-term cure, with an AUC of 0.816 (the closer the AUC is to 1, the higher the accuracy rate). This suggests that a 2-week CMT reduction rate >37% after the first treatment is the best classifier to determine the cure of anti-VEGF treatment after 6 months. To further verify the predicting ability of 2-week CMT reduction rate for a long-term cure, the binary logistic regression analysis is used to predict the relationship between the independent variables such as age, disease subtype, disease duration, 2-week CMT, 2-week CMT reduction rate, and 2-week BCVA, and a predicted variable which is the cure of RVO patients at 6 months. We find that the 2-week CMT reduction rate >37% after the first injection is the best predictor for a cure at 6 months. Therefore, the early CMT reduction rate after anti-VEGF treatment can serve as one of the simple and reliable methods to predict the long-term efficacy of RVO-ME. In conclusion, the 2-week CMT reduction rate >37% is a predictor for long-term cure following anti-VEGF treatment. The "2-week CMT reduction rate >37%" will serve as the quantitative evaluation standard to predict the outcome of anti-VEGF therapy and help to guide the individualized treatment for RVO-ME.

Why early CMT reduction rate could predict the low-term efficacy of anti-VEGF treatment? The aquaporin water channels in the retinal Müller glial cells and retinal pigment epithelium (RPE) cells contribute greatly to eliminating ME (24). A high level of VEGF caused by ischemia increases vascular permeability, promotes the release of inflammatory factors and

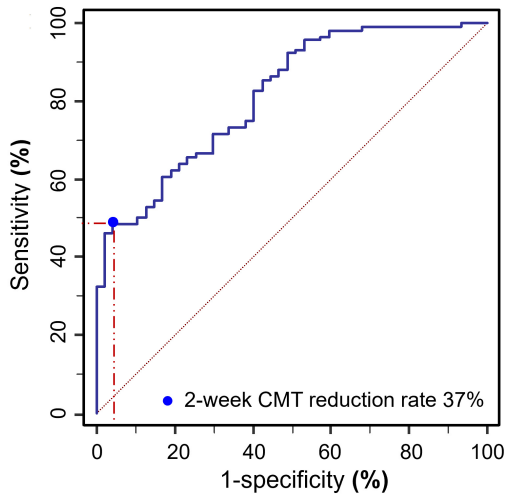

FIGURE 9 | ROC curve plot of the 2-week CMT reduction rate after the first treatment and the cure of RVO patients after 6 months follow up (AUC = 0.816, sensitivity = 95.74%, specificity = 48.72%, Youden index = 0.4446, $P < 0.001$).

white blood cell adhesion, and slows the blood flow. This in return causes a positive feedback loop that continues to worsen ischemia and bring forth dysfunction and apoptosis of Müller cell and RPE cells (25). The anti-VEGF drugs can block this loop, thereby boosting the aquaporin water channels of residual Müller cells and RPE cells to eliminate ME (25). We are speculating that the difference in early CMT reduction rate may reflect the different degrees of damage to the aquaporin water channels in different patients. In this study, patients whose 2-week CMT reduction rate >37% may have less damage and greater recovery potential of the aquaporin water channels. Therefore, these patients will have a higher rate of long-term cure.

In addition, our study has found other baseline indexes that are correlated with long-term efficacy following anti-VEGF treatment. Spearman's analysis shows that baseline indexes such as age, disease duration, baseline BCVA, and baseline CMT are significantly positively correlated with the endpoint BCVA. The included patients are divided into a cured group (6 months CMT $\leq$ 250 μm) and an uncured group (6 months CMT > 250 μm) based on their 6 months CMT values. The comparison between the two groups shows that the cured group is younger, has a shorter disease duration, has a greater proportion of BRVO, and has lower values of baseline CMT and baseline BCVA when compared with the uncured group. This is consistent with previous studies investigating the baseline indexes to predict the long-term efficacy in RVO-ME (26–30). Scott et al. (31) have treated RVO-ME patients with anti-VEGF treatments for six consecutive (once a month) months, and the univariate regression analysis shows that the baseline BCVA and the baseline CMT are significantly correlated with 6-month BCVA. Those patients who have a poor end-point visual acuity usually have a poor baseline BCVA and a high CMT value. In the multivariate model of this study, age and baseline BCVA can independently predict the treatment efficacy. In other studies, age and disease duration are baseline factors that can affect visual function following anti-VEGF treatment (16, 31). The eyes of ME secondary to BRVO are showing a better visual prognosis compared with CRVO (32, 33). In this study, younger patients with a shorter disease duration are associated with better visual outcomes. This may be due to the elderly patients being more likely to have ischemic RVO than younger patients, and younger patients have intact and healthy photoreceptors which hold greater potential for recovery after acute injury (34). Further, some studies have demonstrated that in patients with a long duration of disease, the damage to the photoreceptor and other retinal structures is irreversible. Even when ME is completely dissolved, the long-term visual outcome may be poor (17, 33, 35). This is consistent with our research results. More importantly, the eyes with ME secondary to BRVO have better long-term vision compared with eyes in CRVO at each follow-up time in our study. This confirms the finding of a previous study that the more extensive damage of retinal venous circulation the more severe retinal damage (36).

Our research results also reveal that there is no significant difference between the mAb and Fc-based anti-VEGF treatment in terms of the efficacy of RVO-ME. The anti-VEGF drugs have been widely used in ocular diseases such as exudative age-related macular degeneration, diabetic macular edema, choroidal neovascularization, and RVO-ME, and have shown good safety and efficacy. Previous retrospective and prospective studies have shown that the anti-VEGF treatment for RVO-ME in real-word

TABLE 3 | Logistic regression analysis of indexes that may affect the cure of RVO at 6 months.

Risk index	β	OR	95% confidence interval (CI)		*P* value
			Lower limit	Upper limit	
Age	−0.060	0.942	0.880	1.007	0.080
Disease subtype	−0.488	0.614	0.145	2.609	0.509
Disease duration	−0.393	0.675	0.546	0.835	<0.001
2-week CMT	−0.018	0.982	0.974	0.990	<0.001
2-week CMT reduction rate >37%	2.266	9.639	1.030	90.227	0.047
2-week BCVA (logMAR)	−2.443	0.087	0.012	0.609	0.014

During the effect risk index ($P < 0.05$), 2-week CMT reduction rate >37% is the best predictor for the cure at 6 months (OR = 9.639, 95% CI = 1.030–90.227, P = 0.047). In addition, disease duration, 2-week CMT and 2-week BCVA (logMAR) are negative predictors for the cure of RVO at 6 months.

has achieved significant retinal structure improvement and visual function recovery (5, 17, 29, 33, 37, 38). The patients included in this study are divided into the mAb group (ranibizumab injection) and the Fc group (injection of conbercept or aflibercept) according to their mechanism of action. At the end of the 6-month follow-up, the mean CMT is significantly decreased ($P < 0.001$), and the mean BCVA is significantly improved ($P < 0.001$) in both groups. There is no statistical difference in the mean CMT, BCVA, and the number of injections at any follow-up time between the two groups. It is known that mAb mainly binds to VEGF-A and Fc binds to multiple sites such as VEGF-A, VEGF-B, PlGF, etc (25). The binding affinity of Fc-fusion proteins to VEGF-A is higher than that of mAb, as a result, it is generally considered Fc is more effective to treat RVO-ME than mAb. However, mAbs have a smaller molecular weight compared with Fc-fusion proteins, hence it will enhance their permeability and offset the defect of lower affinity to some extent. Previous clinical trials and the meta-analysis have shown that mAb and Fc-based anti-VEGF treatment have equivalent effects to RVO-ME (37–39), which is consistent with our results.

There are limitations of this study. Our study has a relatively short-term follow-up time and a small sample size. Thereby largescale, high-quality multi-center randomized controlled trials are warranted for stronger evidence based on the conclusion we made here.

CONCLUSION

Intravitreal injection of anti-VEGF drugs is a safe and effective avenue for RVO-ME, and mAb and Fc-based anti-VEGF drugs have equivalent effects. Younger patients, a shorter disease duration, lower baseline CMT, and better baseline BCVA are associated with better visual outcomes at 6-month. BRVO-ME has a better visual outcome than CRVO-ME. The early assessment of CMT can predict the long-term efficacy of anti-VEGF drugs. The 2-week CMT reduction rate >37% predicts the long-term cure of anti-VEGF treatment for RVO-ME.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DL, XZ, and HM contributed to the conception and design of the study. JZ, CC, WL, SL, and QW organized the database. JZ and ZL performed the statistical analysis. JZ wrote the first draft of the manuscript. JZ, DL, and ZL wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Comparison of Anterior Capsule Polishing on the Rate of Neodymium: YAG Laser Capsulotomy After Two Multifocal Intraocular Lens Implantation

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Purpose: To compare the impact of anterior capsule polishing (ACP) during cataract surgery on the rate of neodymium: YAG (Nd: YAG) laser capsulotomy in pseudophakic eyes with two multifocal intraocular lenses (MIOLs).

Methods: Data were collected on patients who underwent cataract surgery and implanted segmental refractive MIOLs (SBL-3, Lenstec) or diffracted MIOLs (AT LISA tri 839MP, Carl Zeiss Meditec). The participants were divided into ACP and non-ACP groups based on whether the anterior capsule was polished. The primary outcome measure was whether Nd: YAG capsulotomy was performed during the 3 years follow-up. We used Kaplan–Meier survival curves to determine the time from IOL implantation to Nd: YAG laser capsulotomy.

Results: ACP and non-ACP groups comprised 70 and 60 eyes, respectively. One year postoperatively, 7.14% of ACP group eyes and 8.33% of non-ACP group required Nd: YAG laser capsulotomy ($P > 0.99$). After 2 years, it was 24.29 and 18.33%, respectively ($P = 0.52$), while after 3 years, it reached 30.0 and 28.33% ($P = 0.85$). No distinct difference existed in the probability of using Nd: YAG laser in both groups evaluated using Kaplan-Meier survival curves ($P = 0.81$). Patients with diffractive MIOLs (AT LISA tri 839MP) implantation were more likely to require Nd: YAG laser capsulotomy ($P < 0.01$).

Conclusion: Polishing the anterior capsule had no remarkable effect on reducing the rate of Nd: YAG laser capsulotomy following phacoemulsification in MIOLs. Patients with diffractive MIOLs implantation had a high probability of requiring Nd: YAG laser capsulotomy.

Keywords: anterior capsule polishing, Nd: YAG laser capsulotomy, multifocal intraocular lens, cataract, posterior capsule opacification

INTRODUCTION

Posterior capsule opacification (PCO) is the most frequent long-term adverse event following cataract surgery, resulting in visual impairment and requiring additional surgery (1). While PCO can be treated by cutting a hole in the dorsal capsule using Nd: YAG laser, this process might cause other unintended consequences, such as raised intraocular pressure (IOP), corneal haze, uveitis, intraocular lens (IOL) pits, cystoid macular edema, and retinal detachment (2).

Numerous studies have assessed the pathogenicity of PCO to establish potential prevention methods (3–5). Capsular opacification is caused by the proliferation, migration, and transdifferentiation of lens epithelial cells (LECs) that are usually located on the interior of the frontal capsule and remain there following cataract operation (3, 4). These LECs attempt to differentiate or undergo epithelial-mesenchymal transformation, creating different kinds of cell groups in the posterior capsule and resulting in lens capsule contraction and fibrosis (4, 5). Therefore, removing residual LECs could reduce the likelihood of PCO development.

The IOL evolved and developed from a traditional monofocal IOL to a multifocal intraocular lens (MIOLs) for improved near vision. Patients receiving MIOLs have high expectations for their postoperative vision and may require IOL exchange due to various causes (6). Patients with MIOLs appear to be more susceptible to PCO than those with monofocal IOLs (7). No conclusive evidence previously existed regarding the influence of anterior capsule polishing (ACP) on the PCO of monofocal IOLs, and studies on the impact of MIOLs are scarce. We aimed to explore the impact of ACPon MIOLs and whether this impact differed for different effects for different MIOL design types. In this study, we retrospectively evaluated ACP's impact on PCO and the requisites for Nd: YAG laser capsulotomy after the implantation of two different designs of MIOLs.

PATIENTS AND METHODS

This 3-year retrospective consecutive case-series study was conducted at Shandong Eye Institute, Qingdao Eye Hospital. We mined and collected medical data from the hospital's patient files. A clinical research assistant supervised the anonymous completion of a form. The study's protocol and measurements were in line with the tenets of the Declaration of Helsinki. The study followed appropriate guidelines and was approved by the Qingdao Eye Hospital committee (ChiCTR1800015251). The inclusion criteria for patients were as follows: being of an age greater than 18 years; having pre-operative and post-operative corneal astigmatism within?1.00 D and axial length between 22.0 and 24.5 mm; and giving written informed consent for participation in this study. Exclusion criteria were as follows: having intra- and postoperative complications; having previous ocular trauma; and having ocular pathologies such as glaucoma, diabetes mellitus, complicated cataracts, progressive retinopathy, uveitis, and previous ocular surgery.

Using electronic medical records, a list of patients who underwent cataract surgery and the implantation of segmental refractive MIOL (SBL-3, Lenstec, Inc., Christ Church, Barbados) or diffracted MIOL (AT LISA tri 839MP, Carl Zeiss Meditec, Jena, Germany) from May 2016 to April 2017 was collected. **Table 1** summarizes the specific features of the two MIOLs designs. We reviewed all corresponding medical records and included patients who met the criteria. All relevant pre- and post-data before and after surgery were checked and extracted by the end of April 2020.

Patients were categorized into two groups, ACP and non-ACP, based on their operation mode. The decision to perform ACP was based on the amount of visible residual LECs. The surgeon was unaware that relevant data could be used later in this comparative study. An experienced ophthalmologist (WXM) conducted all operations under topical anesthesia. The ophthalmologist made a precise 2.2 mm corneal incision, followed by a 5–5.5 mm continuous circular capsulorhexis (CCC), phacoemulsification, and irrigation and aspiration of the cortex. A segmental refractive MIOL or a diffractive MIOL was then put into a capsular bag. In the ACP group, undersurface polishing of the anterior capsule was done in all quadrants and at all clock hours within the visible range using a polisher (MR-I117-2, Suzhou Mingren Medical Apparatus and Instruments Co., Ltd., Suzhou, China).

All patients received topical prednisolone (1.0% eye drops, four times daily, in a tapering dose for 4 weeks), topical levofloxacin (0.5% eye drops four times daily for 2 weeks), and sodium bromfenate (0.1% eye drops, two times daily for 4 weeks). Both postoperative uncorrected distance visual acuity (UDVA) and best-corrected visual acuity (BCVA) were recorded in logMAR units during the follow-up period. Our primary endpoint was the incidence of Nd: YAG laser capsulotomy. The secondary endpoint was the time at which Nd: YAG laser capsulotomy was performed after cataract surgery. We defined PCO as any central opacity or wrinkling of the posterior capsule on slit lamp examination. Indications for Nd: YAG laser capsulotomy were similar for the two groups, based on the following visual acuity and clinical signs: proximal or distal visual acuity decreased by two lines and confirmed by PCO during a clinical examination.

The data were statistically analyzed using IBM SPSS Statistics version 22.0 (IBM Corp., New York, NY, United States).

TABLE 1 | Characteristics of the two multifocal intraocular lens.

Parameters	AT LISA tri 839MP	SBL-3
Optical diameter, mm	6.00	5.75
Length, mm	11.0	11.0
Diopter range, D	0 to +32.0	+10.0 to +36.0
Add power, D	3.33	3.00
Material	Hydrophilic acrylic with hydrophobic surface (25%)	Hydrophilic acrylic
Construcion	1 piece	1 piece
Haptic style	Plate-haptic	Closed-loop
Optic type	A central trifocal zone over a diameter of 4.34 mm, and a peripheral bifocal zone from 4.34 to 6 mm	Bi-aspheric, neutral aberration
A-constant	118.6	118.4

Group comparisons at the time of intervention were assessed using the chi-square or Fisher exact test for qualitative data and an independent *t*-test for quantitative data. We utilized Kaplan–Meier probability curves to determine the risk of Nd: YAG laser capsulotomy in a certain period following surgery. A logarithmic rank test was employed to compare two groups of probability curves. Differences with a *P*-value of 0.05 or less were considered statistically significant.

RESULTS

This study enrolled 121 patients (130 eyes). Among them, 66 were male, and 55 were female. The ACP and non-ACP groups comprised 70 and 60 eyes, respectively. **Table 2** summarizes the characteristics of the patients and their corresponding ocular parameters. There were no remarkable differences in preoperative patient characteristics between the ACP and non-ACP groups, such as age, grade of lens nuclearity, lens thickness, anterior chamber depth, and axial length.

Refraction, UDVA, and BCVA measurements were assessed postoperatively at 1, 2, and 3 years after surgery (**Table 3**). If patients had undergone the Nd: YAG capsulotomy at the time of the follow-up examination, they were not included in the analysis. **Table 4** displays the characteristics of patients who underwent Nd: YAG capsulotomy during the follow-up period.

TABLE 2 | Preoperative patient characteristics.

Parameter	Group		*P*-value
	ACP	Non-ACP	
Patients/Eyes (n)	65/70	56/60	–
Male/Female (n)	34/31	32/24	0.71^{+}
Age (years)	50.20 ± 11.03	53.13 ± 13.14	0.17*
Eye laterality (right/left)	41/29	32/28	–
Grade of lens nuclear	3.01 ± 0.66	3.24 ± 0.97	0.77*
Lens thickness (mm)	2.93 ± 0.18	2.89 ± 0.25	0.91*
Corneal power (D)	43.11 ± 1.76	42.48 ± 1.91	0.87*
ACD (mm)	3.12 ± 0.26	3.14 ± 0.19	0.92*
AL (mm)	23.49 ± 0.90	23.52 ± 0.91	0.85*

*ACP, anterior capsule polishing; ACD, anterior chamber depth; AL, axial length; $^{+}$chi-square test; * independent t-test.*

TABLE 3 | Visual acuity and refractive outcomes of all patients.

		Postoperative		
Parameter	Preoperative	1 Year	2 Year	3 Year
SE (D)	−1.32 ± 1.64	−0.05 ± 0.83	−0.06 ± 0.95	0.06 ± 0.80
Visual acuity (log MAR)				
UDVA	0.59 ± 0.38	0.16 ± 0.10	0.14 ± 0.10	0.13 ± 0.14
BCVA	0.41 ± 0.27	0.09 ± 0.08	0.09 ± 0.11	0.10 ± 0.09

SE, spherical equivalent; UDVA, uncorrected distance visual acuity; BCVA, best corrected visual acuity.

The ACP and non-ACP groups consisted of 21 and 17 eyes operated on using the Nd: YAG capsulotomy approach. Before Nd: YAG capsulotomy, no significant difference was found in the UDVA (0.42 ± 0.22 log MAR vs. 0.49 ± 0.42 log MAR, $P > 0.05$) and BCVA (0.31 ± 0.38 log MAR vs. 0.35 ± 0.40 log MAR, $P > 0.05$) between the ACP group and non-ACP group (**Table 4**). Both UDVA and BCVA significantly improved after Nd: YAG capsulotomy, however, there was still no statistical between-group difference in UDVA (0.13 ± 0.41 log MAR vs. 0.15 ± 0.20 log MAR, $P > 0.05$) and BCVA (0.07 ± 0.19 log MAR vs. 0.08 ± 0.27 log MAR, $P > 0.05$). One year postoperatively, 7.14% of eyes in the ACP group and 8.33% in the non-ACP group required Nd: YAG laser capsulotomy ($P > 0.99$). After 2 years, these numbers were 24.29% and 18.33%, respectively ($P = 0.52$), and after 3 years, they were 30.0 and 28.33% ($P = 0.85$).

Table 5 illustrates the distribution of patients implanted with segmental refractive and diffractive MIOLs who underwent Nd: YAG laser capsulotomy during the 3-year follow-up period. All segmental refractive MIOL implantation procedures that required Nd: YAG laser capsulotomy occurred within the first 2 years after cataract surgery.

Figure 1 depicts the survival curves for the percentage of patients who did not require Nd: YAG laser therapy as a function of time. The survival curves demonstrated no remarkable difference in the probability of receiving

TABLE 4 | Characteristics of patients who underwent of Nd: YAG capsulotomy during the follow-up period.

Parameter	Group		*P*-value
	ACP	Non-ACP	
Eyes (n)	21	17	–
Mean time (months)*	18.05 ± 6.50	19.06 ± 11.45	0.74#
UDVA (log MAR)	0.42 ± 0.22	0.49 ± 0.42	0.50#
BCVA (log MAR)	0.31 ± 0.38	0.35 ± 0.40	0.81#
Nd:YAG rate (%)			
1 year	7.14	8.33	> 0.99^{+}
2 years	24.29	18.33	0.52^{+}
3 years	30.0	28.33	0.85^{+}

*ACP, anterior capsule polishing; UDVA, uncorrected distance visual acuity; BCVA, best-corrected visual acuity; # independent t-test; *days from surgery to Nd:YAG; + chi-square test.*

TABLE 5 | Neodymium: YAG laser capsulotomies performed in the 3-year follow-up examination.

IOL	Group	Years		
		1	2	3
Segmental refractive MIOL (*n* = 41)	ACP	1	4	0
Diffractive MIOL (*n* = 29)	ACP	4	8	4
Segmental refractive MIOL (*n* = 27)	Non-ACP	3	1	0
Diffractive MIOL (*n* = 33)	Non-ACP	2	5	6

IOL, intraocular lens; MIOL, multifocal intraocular lens; ACP, anterior capsule polishing.

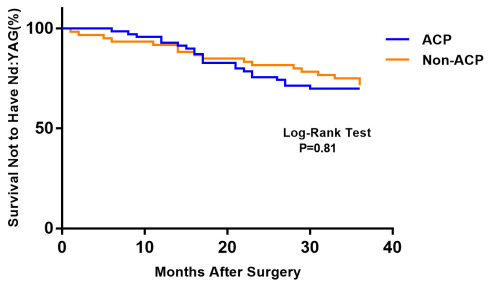

FIGURE 1 | Kaplan–Meier survival plots for eyes by surgical treatment (Nd:YAG, neodymium:YAG laser capsulotomy; ACP, anterior capsule polishing).

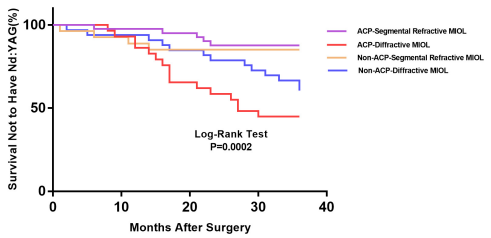

FIGURE 2 | Kaplan–Meier survival plots for eyes by different IOL types in different surgical treatments (Nd:YAG, neodymium:YAG laser capsulotomy; ACP, anterior capsule polishing).

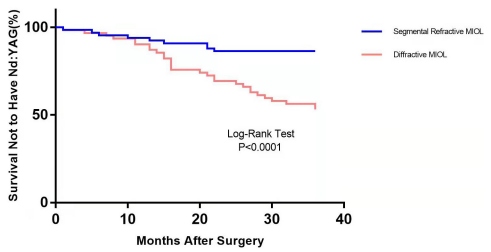

FIGURE 3 | Kaplan–Meier survival plots for eyes by different IOL types (Nd:YAG, neodymium:YAG laser capsulotomy).

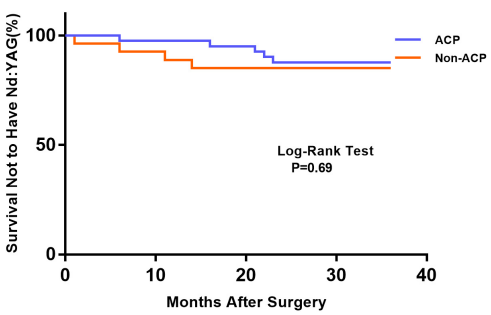

FIGURE 4 | Kaplan–Meier survival plots for eyes by different surgical treatments about segmental refractive MIOL (SBL-3) (Nd:YAG, neodymium: YAG laser capsulotomy; ACP, anterior capsule polishing).

Nd: YAG laser treatment between the ACP and non-ACP groups (P = 0.81). Based on the kind of IOL implanted, we conducted an analysis of the survival curves by mode of operation using Kaplan-Meier. Consequently, statistical differences were observed (P = 0.0002, **Figure 2**). Patients with implantation of diffractive MIOLs (AT LISA tri 839MP) were more likely to require Nd: YAG laser capsulotomy (P < 0.0001, **Figure 3**). There was no statistically significant difference between patients with segmental refractive MIOL implantation, with or without ACP (P = 0.69, **Figure 4**). Moreover, no marked difference was observed between patients with diffractive MIOL implantation, as shown in **Figure 5** (P = 0.13).

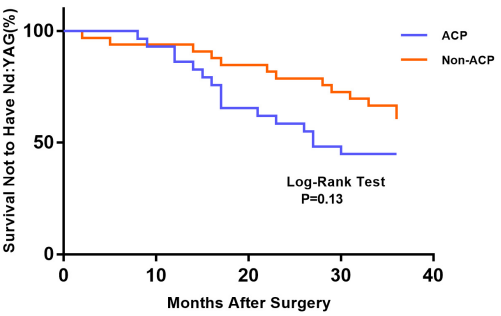

FIGURE 5 | Kaplan–Meier survival plots for eyes by different surgical treatments about diffractive MIOL (AT LISA tri 839MP) (Nd:YAG, neodymium:YAG laser capsulotomy; ACP, anterior capsule polishing).

DISCUSSION

In the past two decades, the use of ACP to prevent PCO after uneventful phacoemulsification has been a frequent topic of discussion and research among cataract surgeons worldwide (8–12). Nevertheless, no consensus has been reached on the efficacy of polishing. To our knowledge, this is the first study to investigate the effect of ACP on the rate of Nd: YAG laser capsulotomy for different designs of MIOL. According to this retrospective analysis, polishing the anterior capsule had no remarkable effect on reducing the need for Nd: YAG laser capsulotomy; however, patients with diffractive MIOL (AT LISA tri 839MP) implantation had a high probability of requiring Nd: YAG laser capsulotomy.

No significant difference in the rate of Nd: YAG capsulotomy was found between non-polishing and polishing groups 3 years postoperatively. The current research findings indicate that the effect of ACP on the rates of PCO and Nd: YAG capsulotomy remains inconclusive. A meta-analysis of studies revealed that the rate of PCO was reduced in the ACP group based on the summary odds ratio of the PCO rate (OR: 0.42; 95% CI: 0.24–0.73) and that ACP improved visual function (12). Sacu et al. (13) hypothesized that lower anterior capsule opacification (ACO) and fibrotic PCO with both round-edged silicone IOLs 2 years postoeratively in eyes with extensively polished anterior capsules. Other articles about ACP found that it did not affect PCO (14–18). A 3-year randomized trial revealed that ACP did not prevent PCO

formation but enabled the formation of more regeneratory cataracts (14). Sachdev et al. (15) demonstrated that PCO incidence in a 360-degree polishing study group was lower but not markedly different at a 1-year follow-up. Consistent with this finding, a different study revealed no apparent advantages of scraping on ACO development in a cohort of 120 eyes at a 6 month follow-up (16). Liu et al. (18) explained why polishing the anterior capsule did not reduce PCO rates: surgical techniques, including ACP, had a crucial effect on residual cell growth. Notably, although the cells under the anterior capsule were almost entirely removed by polishing before culturing, ACP significantly promoted the growth of pouch cells cultured during phacoemulsification. Capsule polishing did not eliminate all LECs but stimulated the strong proliferation of remaining cells, whereas numerous living cells tended to die in unpolished eyes, leading to decreased proliferation. When Menapace et al. (14) prospectively analyzed YAG rates after 3 years, they discovered that 54% of eyes that received ACP required Nd: YAG capsulotomy compared to only 36% of eyes without ACP. The exact mechanism by which PCO is initiated is still unknown. Additional research is required to elucidate the physiology of PCO and the mechanism of barrier formation at the IOL optic barrier.

In the present study, we employed Kaplan–Meier survival curves primarily to analyze the rate of Nd: YAG capsulotomies between the two groups. We found statistical differences between the two groups based on the type of IOL implanted. In the ACP and non-ACP groups, we found that diffractive MIOLs (AT LISA tri 839MP) produced a higher incidence of PCO than segmental refractive MIOLs (SBL-3). It has previously been found that hydrophobic IOLs could reduce the incidence of PCO compared with hydrophilic IOLs (19). Both optics are hydrophilic materials, but the surface of AT LISA tri MIOL is coated with hydrophobic materials, which should theoretically result in better PCO inhibition performance. However, our study did not support this conclusion. Optic edge profile and haptic design could also affect PCO occurrence. Nováček et al. (20) compared two diffractive IOLs of the same material and discovered that the percentage of eyes undergoing Nd: YAG capsulotomy for PCO was significantly higher in the AT LISA tri group than in the Liberty (Medicontur Medical Engineering Ltd., Zsámbék, Hungary) group. They speculated that differences in haptic design might result in remarkable differences in PCO severity between groups (20). Sacu et al. (13) suggested that residual LECs left in the capsular bag may invade the retro-optical capsule through the optic-edge barrier. The oversized haptics stretch the capsular bag into an oval shape, inducing stress folds and fusion along the IOL axis, as well as incomplete capsule closure, resulting in barrier failure and invasion by LECs (21). Compared to solid haptic, closed-loop haptics are more flexible and thus easier to deform under the compressive force of the capsular bag, causing the bag to fit better. The difference in haptic design could account for the differences observed in Nd: YAG capsulotomy rates between the two types of MIOLs.

With the continuous improvement of IOL design technology, new MIOLs are designed to enable patients to achieve independence from glasses. Modern MIOLs use a non-physiological optic method of refracting light to create multiple focal points and facilitate a solution to presbyopia, which is more susceptible to PCO occurrence (22). Previous studies have focused more on ACP's impact on the rate of PCO or Nd: YAG capsulotomy in patients with monofocal IOLs (13–18). In this study, we demonstrated that ACP had no impact on PCO formation in patients with MIOLs. A recent study recommended ACP for eyes only with a higher risk of anterior capsule contraction, such as those with myotonic dystrophy and high myopia, and those requiring a peripheral retinal examination following surgery (23). As a result, ophthalmologists may not routinely use intraoperative ACP to reduce PCO incidence. However, the role of ACP in maintaining the stability of IOLs cannot be ignored, particularly for MIOLs, as some studies have demonstrated that ACP reduces the occurrence of ACO and anterior capsule contraction (12, 24, 25).

Some limitations of our study should be considered. First, study was not randomized because implanted MIOLs were selected according to patients' requirements for intermediate vision and according to the cost of MIOLs. Second, the grade of the PCO would be a more objective and quantitative index than the incidence of Nd: YAG laser capsulotomy. The retrospective design of our study is considered another limitation, so prospective studies should be performed to avoid potential bias.

CONCLUSION

Our study indicates no significant advantage of polishing on the anterior capsule to decrease the rate of Nd: YAG laser capsulotomy after phacoemulsification in different MIOLs. ACP might not be a routine choice for ophthalmologists when attempting to reduce PCO. However, eyes with diffractive MIOLs (AT LISA tri 839MP) had a higher incidence of Nd: YAG capsulotomies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Qingdao Eye Hospital of Shandong First Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the

individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LL and XW were the major contributors to the experimental design and drafting of the manuscript. HL and HB analyzed and interpreted the collected data. DL and YH contributed to the study concept and design. All authors reviewed and approved the final manuscript.

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Comparison of Corneal Optical Quality After SMILE, Wavefront-Optimized LASIK and Topography-Guided LASIK for Myopia and Myopic Astigmatism

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Purpose: To compare visual outcomes and corneal optical quality after small incision lenticule extraction (SMILE), wavefront-optimized (WFO) FS-LASIK, and topography-guided customized ablation treatment (TCAT) FS-LASIK for myopia.

Methods: This prospective case-series study included 283 eyes of 283 myopic patients who underwent SMILE or FS-LASIK. There were 102, 100, and 81 eyes in the SMILE group, WFO group and TCAT group, respectively. The tomography system (Sirius) was used to measure corneal aberrations and optical quality.

Results: At postoperative 1 and 6 months, there were no significant differences in uncorrected distance visual acuity and corrected distance visual acuity among the three groups ($P > 0.05$). Postoperative manifest refractive spherical equivalent was similar among the groups ($P > 0.05$). There was statistically significant difference in cylinder at 1 month among the three groups, with the highest mean value in TCAT group ($P < 0.05$). The corneal optical path difference, root mean square of corneal astigmatism and strehl ratio were the most superior in the TCAT group at postoperative 1 and 6 months ($P < 0.05$).

Conclusion: SMILE, WFO FS-LASIK, and TCAT FS-LASIK provided similar visual results. The corneal visual quality after TCAT FS-LASIK was the best.

Keywords: SMILE, FS-LASIK, optical quality, topography-guided, wavefront-optimized, optical path difference, strehl ratio

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INTRODUCTION

Small incision lenticule extraction (SMILE) and femtosecond laser-assisted LASIK (FS-LASIK) are two main stream laser surgical procedures of myopia and myopic astigmatism correction (1, 2). SMILE has been shown its potential advantages of reduced denervation, faster resolution of postoperative dry eye, and no flap-related risks (3–5). SMILE, however, relies on subjective fixation on a target light and has only one symmetric spherical ablation profile without eye tracking, iris registration and customized ablation profile. Several customized ablation algorithms of FS-LASIK have been developed. Wavefront-optimized (WFO) ablation attempts to reduce the induction of spherical aberration by adding peripheral pulses, blending it with the central ablation profile and

maintaining the prolate shape of the cornea (6). Topography-guided customized ablation treatment (TCAT) attempts to maintain the aspheric shape of the cornea and neutralize corneal irregularities (7). There are some discussions on which of the two surgical methods is better for vision and visual quality. Some studies have found no significant difference between the two procedures (2, 8–12), whereas other studies have indicated that either SMILE or FS-LASIK should be preferred in terms of refractive results or higher-order aberrations (13–19).

Because the comparing results are still controversial, we conducted this prospective study comparing SMILE, WFO LASIK, and TCAT LASIK simultaneously regarding vision, refraction, corneal aberrations, and optical quality.

METHODS

Patients

The present study was a prospective, non-randomized, comparative clinical study enrolling patients with myopia or myopic astigmatism. Two hundred and eighty-three eyes of 283 patients who underwent bilateral myopia and myopic astigmatism correction with FS-LASIK or SMILE from 2017 to 2019 were included in this prospective study. SMILE was performed in 102 patients (SMILE group). WFO FS-LASIK was performed in 100 patients (WFO group). TCAT FS-LASIK was performed in 81 patients (TCAT group). One eye of each patient was randomly chosen for analysis.

Inclusion criteria were age $\geq$18 years, myopic sphere up to 8.00 D, cylinder up to 1.50 D, with a documented refractive stability for a minimum period of 1 year and discontinuation of soft contact lenses for at least 2 weeks. Exclusion criteria included a residual stromal bed less than 280 μm, topographic evidence of corneal ectasia, previous ocular surgery, history of herpetic eye disease, collagen vascular disease, pregnancy, and lactation.

The study received approval from the Ethics Committee of Peking University Third Hospital and was conducted in accordance with the tenets of the Declaration of Helsinki. A written informed consent was obtained from each patient prior to the surgical procedure.

Preoperative Examinations

Preoperative evaluation included uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), manifest refraction, slit lamp bio-microscopy, dilated fundus evaluation, corneal thickness (A scan, Tomey Japan), corneal tomography (Sirius, CSO, Italy) and corneal topography (Vario Topolyzer, WaveLight, Alcon Laboratories, Inc., Fort Worth, TX, United States). The total corneal aberrations and optical quality in a 6-mm zone were obtained from corneal tomography. Parameters of corneal aberrations and optical quality included optical path difference (OPD), root mean square of higher order aberration (RMSh), RMS of corneal astigmatism, RMS of spherical aberration (SA), RMS of coma, and strehl ratio (SR). Corneal topography data of kappa angle, static cyclotorsion compensation for excimer laser ablation and anterior corneal map for topography guided procedure were obtained from the Vario Topolyzer placido-based topography.

Surgical Procedures

All surgeries were performed under topical anesthesia by an experienced refractive surgeon. For FS-LASIK, all flaps were created by the WaveLight FS200 femtosecond laser. The flap/canal/hinge parameters were as followed: flap thickness, 110 μm; flap diameter, 8.5–9.0 mm; side-cut angle, 90°; hinge angle, 50°; canal width, 1.5 mm. Following blunt dissection and flap lift, the stromal bed was ablated with excimer laser (EX500 WaveLight) using an optic zone of 6.5 mm with a 1.25 mm transition zone. The refraction data (sphere, cylinder, and axis) used for the eyes in the WFO group was the subjective manifest refraction. The refraction data used for the eyes in the TCAT group partially followed topography-modified refraction (TMR) scheme introduced by AJ Kanellopoulos (7).

SMILE was performed with the VisuMax femtosecond laser system (Zeiss, Germany, Nomogram version 3.0). The energy setting was 140 nJ, and the laser spot spacing was 4.5μm for the lenticule and cap interface, 2.0 μm for the lenticule side cut and cap side cut. The spherical refraction data was 10% more on the basis of manifest refraction. The lenticule base thickness was 10–15 μm. The cap thickness was 120μm, and the cap diameter was 7.6 mm with 2 mm small incision width. The lenticule optical zone (OZ) was 6.5 mm with 0.1 mm transition zone for astigmatism.

Postoperative Care and Follow-Up

Postoperatively, all the eyes received treatment with 0.1% fluorometholone (FML, Allergan, Inc., Irvine, CA, United States) in tapering dose for 4 weeks, 0.5% levofloxacin (Cravit, Santen, Inc., Japan) four times a day for 2 weeks and lubricating drops four times a day for 4 weeks. Follow-up visits included postoperative day 1 and 7, month 1, 3, and 6. The follow-up examinations involved measurements of UDVA, slit-lamp examination, manifest refraction, CDVA and corneal tomography (Sirius, CSO, Italy). Corneal tomography was measured by the same technician who didn't know the grouping of patients.

Statistical Analysis

Data were analyzed using SPSS software (version 21.0; SPSS, Inc., Chicago, IL, United States). The Kolmogorov-Smirnov test was used for confirming normality of data. The normally distributed data were represented as mean ± standard deviation. Data not following normal distribution were presented as median (min, max). The normally distributed data were compared among the three groups using One-way ANOVA. *Post-hoc* multiple comparisons were performed between groups using Dunnett's T3. Kruskal-Wallis H test was used to compare the non-normally distributed data among the three groups. If the Kruskal-Wallis test showed statistical significance, *post-hoc* pairwise comparisons were performed using Dunn-Bonferroni test. Comparisons of the distribution of visual acuity and refraction among the three groups were analyzed by Pearson chi-square test. A *P*-value of less than 0.05 was considered statistically significant.

TABLE 1 | Baseline clinical data and demographics in the three groups.

	SMILE (n = 102)	WFO (n = 100)	TCAT (n = 81)	F/χ^2	P
Sex (male/female)	22/80	24/76	15/66	0.795	0.672
Age (year)	28.2 ± 6.1	29.9 ± 7.2	29.5 ± 6.7	1.929	0.147
Sphere (D)	−5.09 ± 1.26	−4.95 ± 1.57	−5.22 ± 1.49	0.754	0.471
Cylinder (D)	−0.63 ± 0.31	−0.63 ± 0.38	−0.65 ± 0.37	0.110	0.896
ThkMin (μm)	548 ± 24	544 ± 31	545 ± 26	0.623	0.538
OPD (μm)	0.88 ± 0.35	0.93 ± 0.41	0.98 ± 0.39	1.550	0.214
RMSh (μm)	0.41 ± 0.13	0.42 ± 0.13	0.44 ± 0.15	0.763	0.467
RMS-AST (μm)	0.75 ± 0.40	0.80 ± 0.45	0.86 ± 0.42	1.527	0.219
RMS-coma (μm)	0.22 ± 0.13	0.22 ± 0.13	0.25 ± 0.15	1.417	0.244
RMS-SA (μm)	0.22 ± 0.07	0.22 ± 0.07	0.23 ± 0.08	0.683	0.506
Strehl ratio	0.14 (0.06, 0.72)	0.15 (0.05, 0.32)	0.15 (0.06, 0.27)	0.844	0.656

SMILE, small incision lenticule extraction; WFO, Wavefront-optimized laser in situ keratomileusis; TCAT, Topography-guided custom laser in situ keratomileusis; ThkMin, thinnest corneal thickness; OPD, optical path difference; RMSh, root mean square of higher order aberrations; AST, corneal astigmatism; SA, spherical aberration.

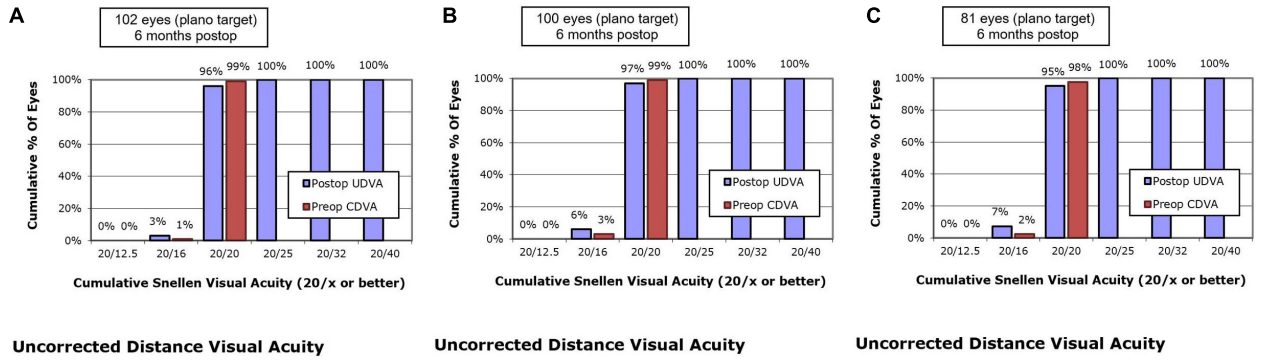

FIGURE 1 | Postoperative 6-month uncorrected distance visual acuity vs. preoperative corrected distance visual acuity. **(A)** SMILE group, **(B)** wavefront optimized group, **(C)** topography-guided custom ablation treatment group.

RESULTS

This study included 283 eyes of 283 patients. There were 102 eyes, 100 eyes and 81 eyes in the SMILE group, WFO group and TCAT group, respectively. There was no statistically significant difference in the baseline data among the three groups regarding age, sex, preoperative refraction, corneal thickness, corneal aberrations, and Strehl ratio ($P > 0.05$) (**Table 1**). The mean maximal lenticule thickness or ablation depth were 109 ± 17 μm, 81 ± 19 μm and 90 ± 19 μm in the SMILE group, WFO group and TCAT group, respectively ($P < 0.001$). Thus, the mean thinnest corneal thickness were 442 ± 30 μm, 465 ± 33 μm, and 458 ± 29 μm at 6 months, respectively ($P < 0.001$). All patients completed 6-month follow-ups.

Uncorrected Distance Visual Acuity Outcomes

At postoperative 1 month, UDVA of 20/20 or better was measured in 95.1% of eyes in the SMILE group, 97.0% of eyes in the WFO group and 93.8% of eyes in the TCAT group ($P = 0.393$).

At postoperative 6 months, UDVA of 20/20 or better was measured in 96.1% of eyes in the SMILE group, 97.0% of eyes in the WFO group and 95.1% of eyes in the TCAT group ($P = 0.658$) (**Figure 1**).

Corrected Distance Visual Acuity Outcomes

At postoperative 1 month, 10.8% of the eyes in the SMILE group, 17.0% in the WFO group and 9.9% in the TCAT group gained one line of CDVA. A loss of one line was noted in 5.9, 7.0, and 9.9% of the eyes in the SMILE, WFO and TCAT groups, respectively. No change in line was noted in 78.4, 61.0, and 71.6% of the eyes in the SMILE, WFO, and TCAT groups, respectively ($P = 0.083$).

At postoperative 6 months, 9.8% of the eyes in the SMILE group, 16.0% in the WFO group and 13.6% in the TCAT group gained one line of CDVA. A loss of one line was noted in 6.9, 5.0, and 3.7% of the eyes in the SMILE, WFO, and TCAT groups, respectively. No change in line was noted in 71.6, 60.0, and 65.4% of the eyes in the SMILE, WFO, and TCAT groups, respectively ($P = 0.501$) (**Figure 2**).

Refractive Outcomes

Postoperative MRSE and cylinder at 1 and 6 months are shown in **Table 2**. There was statistically significant difference in cylinder

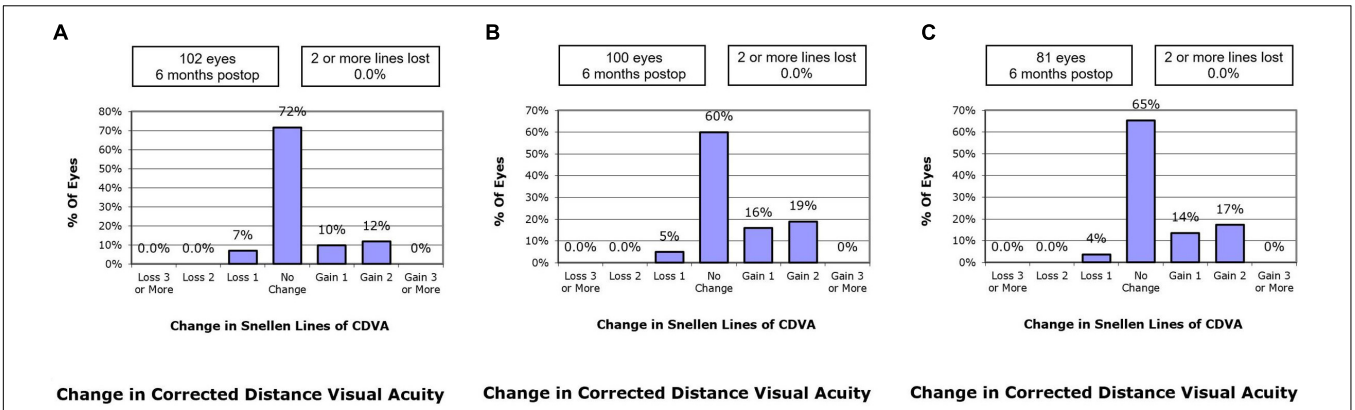

FIGURE 2 | Change in Snellen lines of corrected distance visual acuity at postoperative 6-month. **(A)** SMILE group, **(B)** wavefront optimized group, **(C)** topography-guided custom ablation treatment group.

TABLE 2 | Comparison of postoperative manifest refraction among the three groups.

	SMILE (n = 102)	WFO (n = 100)	TCAT (n = 81)	χ^2	P
MRSE 1M (D)	0 (−0.75, 0.75)	0 (−1.00, 1.00)	0 (−1.25, 1.13)	5.293	0.071
MRSE 6M (D)	0 (−0.75, 0.63)	0 (−0.63, 0.88)	0 (−0.63, 1.00)	3.445	0.179
Cylinder 1M (D)	−0.25 (−1.25, 0)	0 (−1.00, 0)*	−0.25 (−1.00, 0)*	6.655	0.036
Cylinder 6M (D)	0 (−1.00, 0)	0 (−1.00, 0)	−0.25 (−1.00, 0)	1.959	0.375

**The value was significantly different between the two groups.*
SMILE, small incision lenticule extraction; WFO, Wavefront-optimized laser in situ keratomileusis; TCAT, Topography-guided custom laser in situ keratomileusis; MRSE, manifest refractive spherical equivalent.

at 1 month among the three groups ($P < 0.05$). Meanwhile, the cylinder at 1 month in the WFO group was significant less than that in the TCAT group ($P < 0.05$).

At postoperative 1 month, the residual MRSE within ± 0.13 D was achieved by 55.9% of eyes in the SMILE group, 55.0% of eyes in the WFO group and 48.1% of eyes in the TCAT group (P = 0.543). At postoperative 6 months, the residual MRSE within ± 0.13 D was achieved by 54.9% of eyes in the SMILE group, 64.0% of eyes in the WFO group and 54.3% of eyes in the TCAT group (P = 0.127) (**Figure 3**).

At 1 month, 76.5% of eyes in the SMILE group, 76.0% of eyes in the WFO group and 65.4% of eyes in the TCAT group showed refractive astigmatism of 0.25 D or less. There was no statistically significant difference in refractive astigmatism among the three groups (P = 0.095). At 6 months, 76.5% of eyes in the SMILE group, 82.0% of eyes in the WFO group and 69.2% of eyes in the TCAT group showed refractive astigmatism of 0.25 D or less (P = 0.055) (**Figure 4**).

Corneal Aberrations and Optical Quality

At both 1 and 6 months, OPD and RMS of corneal astigmatism in the TCAT group were significantly lower than the other two groups ($P < 0.05$). However, there were no statistically significant differences in RMSh, RMS of coma or SA among the three groups ($P > 0.05$). At postoperative 1 month, SR in the TCAT group was significantly higher than that in the other two groups ($P < 0.05$). At 6 months, SR was significantly different among the three groups ($P < 0.05$), and SR in the SMILE group was significantly less than the other two groups ($P < 0.05$) (**Tables 3**, **4**).

Complications

All surgeries were successfully completed and no serious intraoperative and postoperative complications occurred. Two eyes in the WFO group and one eye in the TCAT group had mild DLK in the first week after operation. Slight corneal interface edema occurred in two eyes in the SMILE group because of difficult separation of the lenticule. No patients needed re-treatment because of unsatisfactory vision or complications.

DISCUSSION

The current study found no significant differences in postoperative UDVA or CDVA among SMILE, WFO, and TCAT groups, indicating that the three procedures were comparably effective and safe. The majority of previous studies demonstrated the similar results (2, 8–15, 17–19). A randomized, paired-eye study found that SMILE achieved similar results to WFO LASIK in terms of efficacy index (0.97 ± 0.20 vs. 0.99 ± 0.20; P = 0.56), UDVA of 20/40 or better (100 vs. 100%; P = 1.0), and UDVA of 20/20 or better (84 vs. 87%; P = 0.63) (9). However, a prospective, randomized contralateral eye study found that 86.4% of the topography-guided LASIK

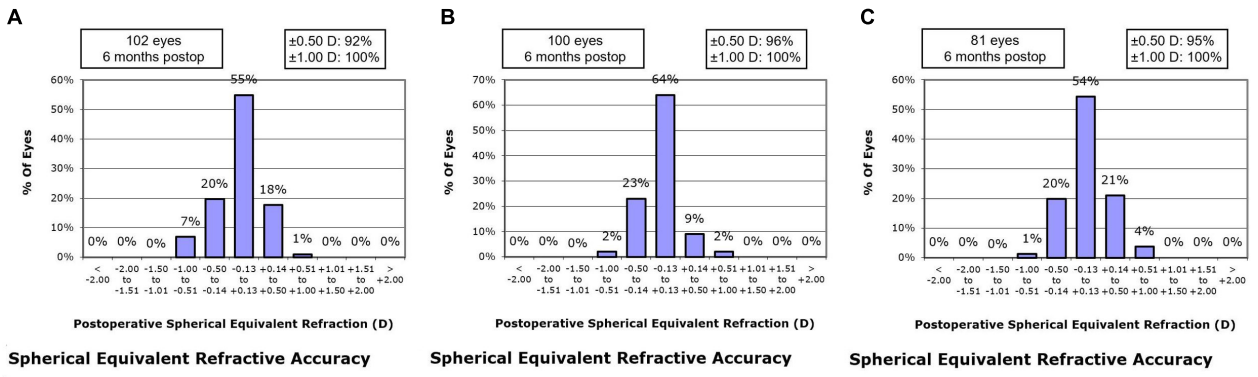

FIGURE 3 | Spherical equivalent refractive accuracy at postoperative 6-month. **(A)** SMILE group, **(B)** wavefront optimized group, **(C)** topography-guided custom ablation treatment group.

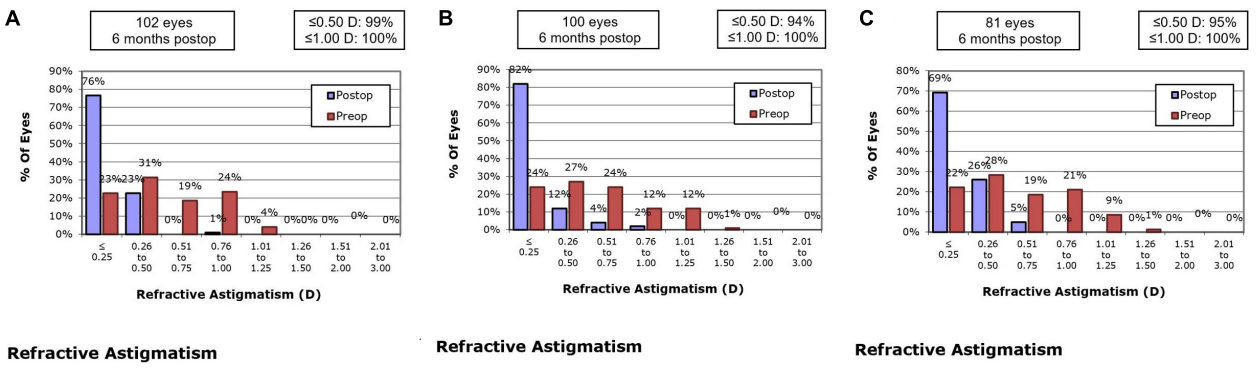

FIGURE 4 | Refractive astigmatism accuracy at postoperative 6-month. **(A)** SMILE group, **(B)** wavefront optimized group, **(C)** topography-guided custom ablation treatment group.

group and 68.2% of the SMILE group had UDVA of 20/20 ($P < 0.002$) and 59.1 and 31.8%, respectively, had UDVA of 20/16 ($P < 0.002$) at 3 months (16). The inferior results of SMILE may be due to a steeper surgeon learning curve of SMILE, which may cause inferior visual outcomes during the early stage of operations (20). The surgeon of the present study had more than 1 year experience of performing SMILE, so SMILE group showed good visual results similar to WFO group and TCAT group.

The present study found that postoperative refractive results at 1 and 6 months were similar among the three groups, except that the 1-month postoperative cylinder was significantly different among the three groups, and more residual cylinder was noted in the TCAT group than WFO group ($P < 0.05$). Most previous studies showed comparable refractive results between SMILE and FS-LASIK (2, 8–15, 18, 19, 21). The high residual cylinder in the TCAT group of the present study was similar to our previous study

TABLE 3 | Comparison of corneal aberrations and optical quality among the three groups at 1 month postoperatively.

	SMILE (n = 102)	WFO (n = 100)	TCAT (n = 81)	F	P
OPD (μm)	0.92 ± 0.40	0.90 ± 0.31	0.77 ± 0.28*	5.028	0.007
RMSh (μm)	0.67 ± 0.26	0.69 ± 0.25	0.67 ± 0.27	0.305	0.738
RMS-AST (μm)	0.57 ± 0.41	0.52 ± 0.30	0.33 ± 0.19*	13.450	0.000
RMS-coma (μm)	0.38 ± 0.22	0.38 ± 0.21	0.34 ± 0.21	1.178	0.309
RMS-SA (μm)	0.42 ± 0.16	0.45 ± 0.21	0.44 ± 0.20	0.681	0.507
Strehl ratio	0.16 ± 0.04	0.16 ± 0.04	0.19 ± 0.05*	12.938	0.000

**The value was significantly different from that in the other two groups.*
SMILE, small incision lenticule extraction; WFO, Wavefront-optimized laser in situ keratomileusis; TCAT, Topography-guided custom laser in situ keratomileusis; OPD, optical path difference; RMSh, root mean square of higher order aberrations; AST, corneal astigmatism; SA, spherical aberration.

TABLE 4 | Comparison of corneal aberrations and optical quality among the three groups at 6 months postoperatively.

	SMILE (*n* = 102)	WFO (*n* = 100)	TCAT (*n* = 81)	F	P
OPD (μm)	0.91 ± 0.26	0.93 ± 0.29	0.81 ± 0.27*	5.078	0.007
RMSh (μm)	0.70 ± 0.20	0.73 ± 0.23	0.71 ± 0.27	0.462	0.631
RMS-AST (μm)	0.53 ± 0.30	0.52 ± 0.30	0.34 ± 0.19*	13.547	0.000
RMS-coma (μm)	0.40 ± 0.20	0.40 ± 0.22	0.38 ± 0.22	0.330	0.719
RMS-SA (μm)	0.45 ± 0.16	0.47 ± 0.19	0.47 ± 0.20	0.414	0.662
Strehl ratio	0.16 ± 0.04*	0.17 ± 0.06	0.19 ± 0.05	9.450	0.000

**The value was significantly different from that in the other two groups.*
SMILE, small incision lenticule extraction; WFO, Wavefront-optimized laser in situ keratomileusis; TCAT, Topography-guided custom laser in situ keratomileusis; OPD, optical path difference; RMSh, root mean square of higher order aberrations; AST, corneal astigmatism; SA, spherical aberration.

(22), which might be caused by the compensation method for TCAT design. In the present study, partial TMR was applied to the TCAT design of cylinder and axis. However, Kanellopoulos AJ (16) compared SMILE and Topo-LASIK with TMR method and found that Topo LASIK was superior in postoperative MRSE and cylinder to SMILE. The higher residual refraction in SMILE might be caused by inappropriate nomogram of parameter design, high preoperative cylinder, lack of eye tracking and cyclotorsion compensation. Better design methods for TCAT are needed to obtain more accurate refractive results. The Phorcides Analytic Engine for topography-guided surgery planning was preliminarily proved to have good refractive results, with 83% of eyes showing a refractive cylinder of less than 0.25 D postoperatively (23). Interestingly, 6-month postoperative cylinder in TCAT group decreased and was similar to the other groups. We speculate that the astigmatism change was due to the compensative morphological change of the lens, which need further verification in the future.

Most aberrations come from the cornea. Good corneal optical quality is the premise of the visual quality. The present study also found that corneal OPD, RMS of corneal astigmatism and SR in the TCAT group were the most superior, showing that corneal optical quality after TCAT LASIK was the best. To the best of our knowledge, no previous study compared the corneal aberrations and optical qualities among the three procedures. The lowest OPD in the TCAT group mainly derived from the lowest corneal astigmatism, but not from the higher-order aberrations. Several studies showed lower corneal coma after wavefront-guided LASIK compared to SMILE, which might be due to automatic eye tracking with active centration control and cyclotorsion compensation in LASIK (14, 19). In the present study, however, RMS of coma was comparably low in the TCAT group, but the difference wasn't statistically significant. On the contrary, Yin Y et al. found lower coma aberration at 1 month after SMILE than FS-LASIK, which may be due to high myopic correction and iTrace analyzer measurement (24). Some studies also found lower corneal SA after SMILE compared to FS-LASIK (13–15). As we known, SMILE procedure could achieve a larger functional optical zone than do FS-LASIK procedures because of less biomechanical alterations in the peripheral area of the cornea after SMILE (25, 26). Postoperative spherical aberration was associated with the area of functional optical zone (27, 28). Yet, in the present study, postoperative SA in the SMILE group was comparably low, but compared with the other two groups, there was no significant difference. Similar to the present study, El-Mayah et al. also found a similar comparative trend of postoperative coma and SA between SMILE and FS-LASIK ($P > 0.05$) (12). In the future, larger sample, randomized controlled studies are needed to further compare corneal aberrations and optical quality among the three surgical procedures.

In our previous study, we found similar visual and refractive results between WFO and TCAT groups, and higher corneal optical quality in the TCAT group (22). The purpose of the present study is to compare SMILE and FS-LASIK. WFO and TCAT are two common customized ablation profiles of FS-LASIK, so SMILE was compared with WFO and TCAT at the same time in the present study. We found SMILE was almost similar to WFO LASIK in terms of visual result, refractive outcomes and corneal optical quality. However, SMILE provided inferior outcomes in corneal optical quality to TCAT LASIK. Thus, the comparison of corneal optical quality between SMILE and FS-LASIK depends on the different ablation profiles, which can't be generalized.

The limitations of the present study are as follows. First, we only compared visual acuity, refraction, corneal aberrations and optical qualities among the three groups, and other examinations related with visual quality, such as contrast-sensitivity function, objective scatter index, and questionnaires regarding glare and halo weren't studied. Second, the study had not a randomized sample and was subject to selection bias that might result in an unbalanced selection of patients. Third, we only included myopic subjects with low astigmatism (<1.50 D). Future randomized studies with more parameters of optical quality and greater astigmatism range are needed.

In conclusion, SMILE, WFO FS-LASIK and TCAT FS-LASIK provided similar visual and refractive results. TCAT FS-LASIK could induce fewer corneal optical path difference and astigmatism, and higher strehl ratio than the others. However, TCAT FS-LASIK could induce more manifest residual cylinder and a more accurate algorithm for compensating the irregular ablation, corneal posterior surface and internal eye astigmatism is needed to further improve postoperative visual acuity and refractive outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Peking University Third Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ conducted the statistical analysis and wrote the manuscript. XS collected the data. YC designed the study and supervised the project. All authors contributed to the article and approved the submitted version.

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BRIEF RESEARCH REPORT
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Comparison Between L-312 Hydrophobic-Hydrophilic Acrylate and US-860 UV Hydrophilic Acrylate IOL Opacification Characteristic

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Objective: To compare opacity characteristics of US-860 UV and L-312 IOL, and report the phenomenon of glistenings in hydrophobic-hydrophilic acrylic IOLs.

Setting: Qingdao Eye Hospital.

Design: Experimental study.

Methods: Four medical records (4 eyes) of patients with L-312 or US-860 UV IOL opacification reporting decreased or lost vision who underwent IOL explanation between 2019 and 2021 were reviewed. Explanted IOLs were analyzed by slit-lamp examination, confocal microscopy, scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS) at Qingdao Eye Hospital and Qingdao university of science and technology.

Results: The 4 explanted IOLs were represented by 2 hydrophilic acrylic designs. The preoperative mean corrected distance visual acuity changed from 1.84 ± 1.09 logarithm of the minimum angle of resolution (log MAR) to 0.20 ± 0.03 log MAR postoperatively except case 3. The mean interval of the L-312 IOL was 56.67 ± 14.19 months (range 44 to 72 months), and the interval of the US-860 UV IOL was 27 months. Morphological findings were surface, subsurface calcifications of the US-860 UV IOL material, and the optical region of L-312 IOLs are teeming with a great number of vacuoles by light microscope, scanning electron microscope and Energy Dispersive X-ray Spectral.

Conclusion: The cause of US-860 UV opacification was primary calcification, and vacuoles resulted in L-312 IOL opacification.

Keywords: hydrophobic-hydrophilic acrylate IOL, calcium, glistenings, opacification, hydrophilic acrylate IOL

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INTRODUCTION

With the development of cataract phacoemulsification technology, intraocular lens (IOL) opacification, as one of its complications, had gradually attracted the attention of researchers and clinicians. Cataract is one of the diseases with the highest morbidity, disability, and blindness in the world, which has been a serious threat to the health and quality of life of the middle-aged and elderly people (1). Cataract ultrasonic phacoemulsification and IOL implantation is the most effective method for cataract treatment (2). However, but there are chances of serious complications

(such as infective endophthalmitis after cataract surgery, capsular block syndrome, toxic anterior segment syndrome, posterior capsular opacification, IOL opacification, et al.) and irreversible loss of vision associated with the surgery (3). While the occurrence of IOL opacification has declined with the use of modern surgical techniques, recently developed surgical materials and IOL design, IOL opacification can still occur even following uneventful cataract surgery.

With the development of materials science and Chemical Technology, biosynthetic materials are widely used in biology, medical treatment, chemical detection (4). Nanoparticles can retain the biocompatibility of materials and play a role in drug delivery systems (5). Frohn (6) found that premature aging of the ultraviolet blocking agent is one of the reasons for IOL opacification, and some nanocomposites can be used as photocatalysts to affect the stability of compounds (7). Microstructures such as nanoparticles need to be observed and detected by scanning electron microscope (SEM) (8–10), and Energy Dispersive X-ray Spectral (EDS) can analyze the composition of chemical elements (11). In previous studies, SEM and EDS were used to analyze IOL opacification. By comparison with hydrophobic acrylic IOLs, Hydrophilic acrylic IOLs have higher tissue compatibility due to a higher water-content and higher uveal biocompatibility. Since the 1990s, an increasing number of studies report opacification of hydrophilic acrylic IOLs. According to the related research reported that hydrophilic acrylic IOL is more likely to become opacification (12, 13).

In the current study, we describe late postoperative opacification after cataract surgery with implantation of 1 case hydrophilic acrylic and 3 cases hydrophilic-hydrophobic acrylic IOL, and compare the characteristics of two different types of late IOL opacifications. In addition, IOL exchange can improve final visual acuity.

METHODS

This retrospective case series study was performed at the Qingdao Eye Hospital of Shandong First Medical University. This study was approved by the ethics committee of the Qingdao Eye Hospital of Shandong First Medical University (Qingdao, China), and all procedures adhered to the tenets of the Declaration of Helsinki. All patients signed the informed consent of operation and anesthesia before cataract surgery. After the operation, they allowed to use their clinical data and signed written informed consent.

Collecting retrospective data regarding general and ophthalmologic conditions of several patients with postoperative opacification of IOL and a significant visual acuity impairment were referred for IOL replacement to the eye hospital from August 2019 to March 2021, including the patient's condition, date of IOL implantation, IOL serial number, IOL type, intraoperative and postoperative complications, and additional intraocular surgical procedures. All patients had cataract surgery in Qingdao Eye Hospital by two different cataract surgeons. Phacoemulsification was performed under topical anesthesia through a 2.8 mm incision with the Visalis 100 (Alcon Laboratories, Inc.). A balanced salt solution (BSS, Alcon) and healon LG were used in the surgery. The diagnosis of IOL opacification was based on a careful slit lamp examination.

Ophthalmologic evaluation including visual acuity, corrected distance visual acuity (CDVA, Snellen) assessment, ultrasound biomicroscopy (UBM), tonometry, and fundus examination including macular optical coherence tomography, retinoscopy and anterior segment tomography was performed preoperatively and 1 week postoperatively.

All patients accepted povidone iodine rinsed the conjunctival sac before surgery, Intraocular irrigation solution, prepared by 0.75 g Cefuroxime sodium, 5 mg dexamethasone, and 500 ml balance salt solutions, was used during surgery. After operation, the operated eyes received dexamethasone/tobramycin eye ointment. Besides, a combination of tobramycin dexamethasone eyedrops, prednisolone acetate 1.0% and levofloxacin 0.5% eyedrops administered four times a day for 2 weeks and then nonsteroidal antiinflammatory eyedrops were administered four times per day for 4 weeks postoperatively.

The IOL replacement surgery need to save the capsule during mobilization and remove the opacified IOL through a 3.0 mm corneal tunnel, sometimes by cutting the IOL optic into two halves with Vannas/micro scissors, and then, implant a new IOL. The opacified IOLs were sent in the dry state to the Shandong Key Laboratory of Ophthalmology, Shandong Eye Institute, Qingdao, China, where gross and microscopic analyses were performed, and then sent to test in Qingdao University of Science and Technology by SEM coupled with EDS.

In our study, CDVA was measured with the Snellen chart at 5 meters and was then converted to logarithm of the correct minimum angle of resolution (log MAR) values for statistical calculations. Patients who could only perceive hand motion at 2 feet (or less) were considered to have Snellen equivalent 20/20 000 (3.0 log MAR) vision.

The statistical analysis was done with the help of SPSS software version 23.0 (Armonk, NY: IBM Corp.).

RESULTS

Table 1 shows the general characteristics of each of the 4 cases analyzed so far. The mean patient age at the time of IOL opacification was 71.25 years ± 16.41 (SD) (range 47–83 years). There were three women and one man, and three left eyes and one right eye. All patients with an opacified IOL had cataract surgery in both eyes except case 1 between 2015 and 2017.

Case 1 has a history of coronary insufficiency and underwent meningioma and thyroidectomy before 10 and 20 years ago, and case 4, diagnosed with high blood pressure, underwent gonioplasty in left eye because of angle closure glaucoma (PACG) during the cataract surgery. Patient two and patient three were diagnosed a diabetic. In addition, patient two had nonproliferative diabetic retinopathy (DR) and hypertension.

Intraocular pressure before and after the procedure was <21 in all affected eyes, and all the results of UBM, and fundus examination were normal (**Table 1**). The results of UBM showed that the anterior chamber angles were open, the position of IOLs

TABLE 1 | Characteristics of the 4 cases opacity IOLs.

PT	PT 1	PT 2	PT 3	PT 4
Sex	Female	Female	Male	Female
Age (year)	83	76	47	79
Associated disease	Meningioma, thyroidectomy	Diabetes, hypertension,NPDR	Diabetes	Hypertension, angle closure gla-ucoma
UBM	Normal	Normal	Normal	Normal
Fundus	Normal	Normal	Normal	Normal
IOL	L-312	L-312	L-312	US-860UV
IOP-1 (mmHg)	11	11.1	14	11
IOP-2 (mmHg)	15	9	16	11
HbA1c (%)	-	-	8.6	5.8
Eye-1	OD	OU	OU	OU
Eye-2	OD	OS	OS	OS
IT (month)	72	55	44	27
SN	91308761001	91307941002	91310521013	O-04817001-005
IOL model	AR40e	AR40e	iSert 251	SoftecHD
Visual acuity-1	0.15	0.001	1.0	0.02
CDVA-1	0.15	0.001	1.0	0.02
Visual acuity-2	0.15	0.6	1.0	0.7
CDVA-2	0.6	0.6	1.0	0.7

PT, patient; HbA1c, hemoglobin A1c; IT, interval time; SN, serial number; UBM, ultrasound biomicroscopy; IOP1, IOP before IOL replacement; IOP2, IOP after IOL replacement; Eye-1, eyes of cataract surgery; Eye-2, eyes of IOL opacification; Visual acuity-1, Visual acuity before IOL replacement; Visual acuity-2, Visual acuity after IOL replacement; CDVA-1, CDVA before IOL replacement; CDVA-2, CDVA after IOL replacement; NPDR, nonproliferative diabetic retinopathy; "-", express no accurate information.

was acceptable, the retina attached and the lens zonule remained intact, and no problems of macular edema macular scar, and fundus hemorrhage by fundus examination.

Four opacity IOLs contain two different designs, including 3 cases L-312 hydrophilic-hydrophobic acrylic IOL, and 1 case US-860 UV hydrophilic acrylic IOL. All the IOLs showed a grayish white or brownish opacification with a diffuse ground glass appearance in Slit lamp (**Figure 1**), and IOL opacification mainly concentrated in the central area of IOL optical part.

In our study, the mean interval of the L-312 IOL between the initial cataract surgery and the IOL exchange because of opacification was 56.67 ± 14.19 months (range 44–72 months), and the time interval of the US-860 UV IOL was 27 months. There were no serious intraoperative complications during IOL replacement surgery, and all IOL implanted into capsular.

The serial numbers of the L-312 hydrophilic-hydrophobic acrylic IOL were 9130871001(IOL#1), 9130791002(IOL#2), and 91310521013(IOL#3), The serial numbers of the US-860UV IOL was O-04817001-005(IOL#4). All replacement IOLs were hydrophobic IOLs, including 2 AR40e IOLs (Abbott Medical Optics, Inc., US), 1 iSert 251 IOL (Hoya Corporation, Japan), and 1 SoftecHD IOL (Lenstec, Inc., US).

The CDVA was equal to visual acuity, therefore, the CDVA was used for comparison in subsequent studies. The CDVA of Case 1, 2, 4 was a significant improvement after IOL exchange (mean CDVA 1.84 ± 1.09 log MAR to mean CDVA 0.20 ± 0.03 log MAR) compared with case 3. Regarding this patient, 47 years old, although the degree of opacification of the L-312 IOL relatively light, and had no obvious influence upon the vision, but a large number of glistenings caused a significant straylight increase and glare-related problems, and had a significant impact on patients' life (especially night driving). All patients recovered well postoperatively, with no complications. Therefore, IOL replacement can safely and effectively improve the visual acuity and visual quality of patients.

Light microscope images of the explanted IOLs from Case 1,2,3 show a characteristic vacuole-like structure and surface lesions extending into the body of the L-312 IOL, but the analysis of the explanted IOL from Case 4 showed cerebriform and granular appearance of the surface of the cloudy US-860 UV IOL (**Figure 1**). The characteristic of L-312 IOL opacification were markedly different to those in Case 4.

For case 4, the surface changes that appeared cerebriform by light microscopy appeared as a large number of particles settle on the surface of the crystal to form a gully by electron microscopy. However, the surface of L-312 IOL (IOL#1) showed smooth and clean under SEM, and vacuole-like structure cannot be detected by SEM (**Figure 1**). Elemental analysis used with EDS (**Figure 2**) confirmed that the deposits on the US-860 UV IOL surface were composed of calcification and phosphorus, both of which are characteristically absent in normal IOLs of this type. The weight ratio of calcium to phosphorus in opacity area of IOL was about 2:1, and the atomic ratio was about 3:2. Besides, trace amounts of magnesium (0.24%) and fluorine (0.74%) were also found. Nevertheless, there were no other elements except carbon and oxygen in opacity L-312 IOL (IOL#1). The results showed that the turbidity types of the two different intraocular lenses were different.

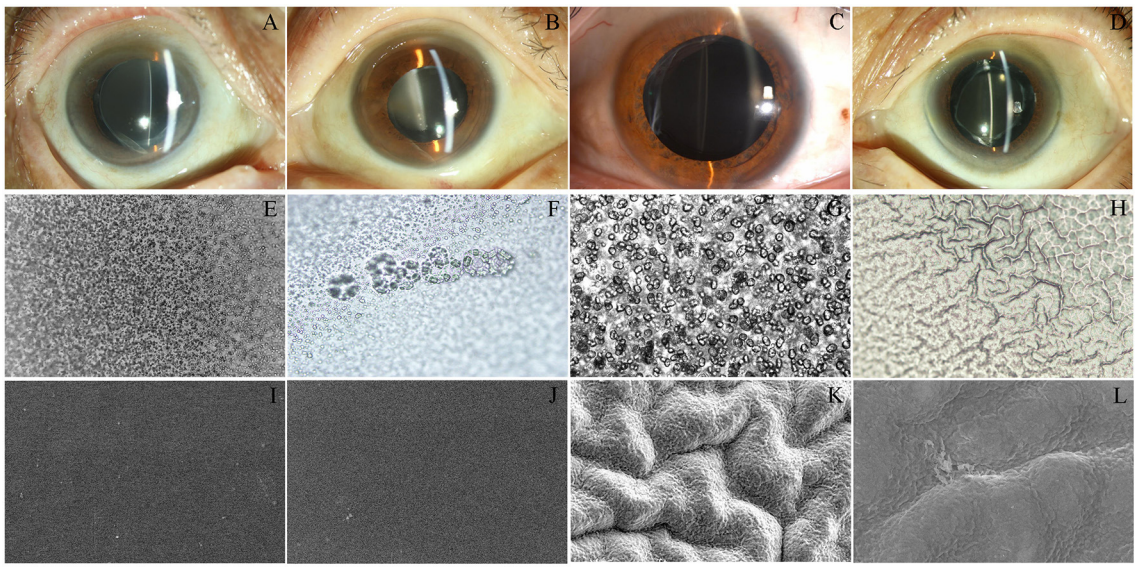
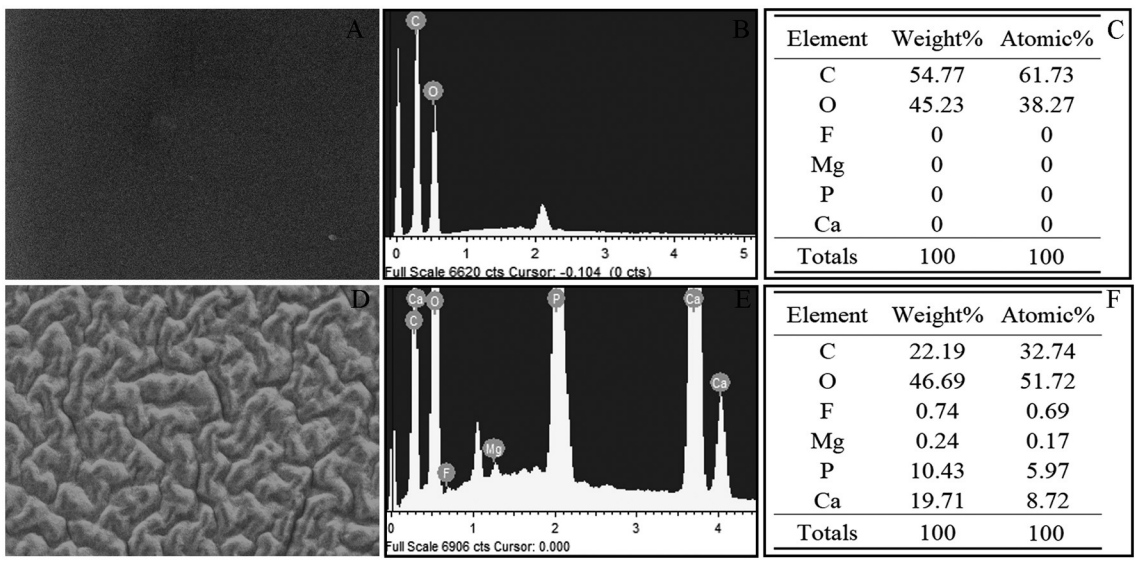


FIGURE 1 | Characteristics of the implanted IOL. Slit-lamp photographs **(A–D)** from the four patients, showing grayish white with a diffuse ground glass appearance on the anterior surface of the lens. **(A–D)** Obtained from case 1, 2, 3, 4. L-312 IOLs **(E–G)** showed a great quantity of vacuoles and US-860 UV **(H)** presented cerebriform under light microscopy (original magnification ×40). **(E–H)** Obtained from case 1, 2, 3, 4. Scanning electron micrographs obtained from case 1 **(I,J)** and case 4 **(K,L)** showed that the surface of L-312 IOL was smooth and US-860 UV IOL appeared as rough mountain. **(I,K)** Original magnification 500, **(J,L)** Original magnification 1,000.



Element	Weight%	Atomic%
C	54.77	61.73
O	45.23	38.27
F	0	0
Mg	0	0
P	0	0
Ca	0	0
Totals	100	100

Element	Weight%	Atomic%
C	22.19	32.74
O	46.69	51.72
F	0.74	0.69
Mg	0.24	0.17
P	10.43	5.97
Ca	19.71	8.72
Totals	100	100

FIGURE 2 | Energy Dispersive X-ray Spectral from case 4 revealed the presence of calcium and phosphorous in the turbid area of US-860 UV, but L-312 IOL (case 1) contains only carbon and oxygen. **(A–C)** Obtained from case 1, **(D–F)** obtained from case 4. C, carbon; O, oxygen; P, phosphorus; Ca, calcium; F, fluorine; and Mg, magnesium.

DISCUSSION

In recent years, with the increasing reports of long-term postoperative IOL opacity, it has attracted the attention of ophthalmologists. The types of IOL mainly includes silicone IOL, Poly Methyl Methacrylate (PMMA) IOL, hydrophobic acrylic IOL and hydrophilic acrylic IOL. IOL opacifications has been reported in all types of IOL, mainly including calcification, glistening, subsurface nanoglistenings and snowflake degeneration (14, 15). The risk of IOL opacification including severe reduction of visual function, straylight, glare, interfere fundus examination and treatment.

In previous research reports, Calcium and phosphorus deposition was the important common reason for the turbidity of hydrophilic IOL and hydrophobic-hydrophilic acrylate IOL (16–20). Neuhann et al. described three forms of hydrophobic acrylate IOL calcification (21, 22). The first form was called primary calcification, which refers to calcification that is inherent in the IOL, and may be caused by fabrication of the IOL, issues with its packaging process, or inadequate formulation of the polymer. The calcification presumably occurs in otherwise normal eyes and generally is not associated with comorbidities. The second form was secondary calcification that refers to secondary superficial calcium deposits on the IOL, most likely because of environmental circumstances with changes in the intraocular aqueous milieu. These patients generally have systemic and (or) ophthalmic disease, including diabetes, uveitis, or had vitreoretinal surgery, which can result in fluid–gas exchange and disrupt the blood–aqueous barrier. Therefore, the secondary calcification is not related to any problem with the IOL itself. The third form called false-positive calcification. By definition, the type represents the phenomena when another pathology is mistaken for calcification or false positive staining for calcium occurs.

In this study, we used light microscopy, electron microscopic, as well as elemental or molecular surface analytical techniques by SEM have demonstrated that the opacification was related to calcium and phosphate precipitation on the surface and subsurface of the US-860 UV IOL, and confirmed the previous experimental results. Even if there was no definite evidence that US-860UV IOL opacification was related to its production, package or transportation, but we still considered that US-860UV IOL belong to primary calcification, because we've ensured that the patient (#4) did not experience disease or surgery that resulted in impaired blood–aqueous barrier. It's reported that the most frequently primary calcification IOL designs contained the SC60B-OUV IOL (Medical Development Research, Inc.), and the LS-502-1 IOL (Lentis, Oculentis GmbH) (17, 20, 23). The turbidity characteristics of these two types of IOLs are similar to those of US-860UV IOL.

Hydrophobic-hydrophilic acrylate IOL with a layer of hydrophobic material on the framework of hydrophilic material, so it has the common advantages of the two materials. Paula et al. (10) described a significant number of cases of severe opacification of hydrophobic-hydrophilic acrylic IOLs (LS-502-1 IOL), and all IOLs had a similar pattern of opacification, with yellowish diffuse opacification uniformly distributed and calcium deposits on the surface and/or subsurface of the optic and haptics and within the IOL material. Nicolas (20) considered Lentis LS-502-1 IOL opacification attributed to primary calcification, and might be caused by the interaction of patients' individual factors (altering intraocular ion concentrations), IOL material traits, and manufacturing associated contamination. In 2018 (18), studies of cases involving L-312 IOLs with uneven distributed part calcification were published, and the researchers confirmed a manufacture issue might be the reason for the opacification.

Interestingly, in our study, the L-312 IOL opacification do not seem to be bound up with calcium and phosphate depositions, but more similar to the characteristic of hydrophobic acrylic IOL. Several test results of L-312 IOL suggest that the cause of opacification may be related to glistening.

Glistening has been reported in almost all IOL materials and designs; Nonetheless, it is most common and has the greatest severity in hydrophobic acrylic IOLs (24). It was reported that the risk factors for development of glistening IOL including material properties (water content), time from IOL implantation, temperature changes, breakdown of the blood-retinal barrier (e.g., postoperative inflammation, diabetes, uveitis), glaucoma, and issues related with the IOL packaging process (25, 26).

In 1996, Dhaliwal first reported glistenings of Acrysof (Alcon, Inc., Fort Worth, Texas) hydrophobic acrylic IOLs, and considered the glistenings are likely caused by water vacuoles that form within the lens after hydration within the eyes (27). Wang et al. reported that the change in the temperature of the surrounding environment might be the cause for this vacuolation of IOL by vitro studies (13). Grzegorz et al. immersed the IOLs in a balanced salt solution at temperatures ranging from 37°C to 60°C and cooled to room temperature, and the IOLs created different numbers of glistenings (28). Kang described optic opacification of the IOL (Acrysof® MA60BM Alcon, Fort Worth, Texas, USA) extracted from a 55-year-old male who underwent binocular cataract 11 years ago, and the extracted IOL optics at 4°C, room temperature, and 37°C were transparent at dry conditions. On the contrary, when the dried IOL was immersed in normal saline at room temperature and 37°C, opacification appeared. However, when the dried IOL was immersed in normal saline at 4°C, opacification of the IOL did not appear. They believed that the IOL opacification can occur depending on temperature and hydration conditions (29). In addition, the changes in water content of the IOLs can significantly affect the formation of glistenings, recent studies have indicated that a low water content of hydrophobic acrylic materials (typically $<$0.5% water) might be partially responsible for glistenings (30). In our present study, because IOL opacification occurred mean 56.67 months after surgery, we therefore believe that hydration resulted in L-312 IOL opacification rather than temperature.

Generally speaking, the US-860 UV hydrophilic acrylic IOL opacification caused by calcification can result in visual impairment so obvious that the patient needs to exchange the opacity IOL; however, the glistenings of hydrophobic acrylic lenses are actually refractile micro vacuoles in the IOL optic formed in aqueous environment, but rarely resulting in blurred vision (31). Meanwhile, the impact of glistenings on postoperative visual function and the evolution of glistenings years after surgery remain controversial, and IOL replacement induced by glistenings has rarely been reported in the current researches (25). Nevertheless, in this study, three patients underwent IOL replacement surgery because of visual impairment caused by calcium and phosphorus deposition or glistenings of IOL, and one patient changed IOL due to the effect of straight light on visual quality.

Combined with previous report (13), the visually significant late postoperative opacification of US-860 UV hydrophilic acrylic IOLs occurred about 12–48 months (mean 24.57 $\pm$ 11.40) after the IOL implantation, and all the L-312 IOLs explanted at our

center opacified in a various range of time, from 44 to 72 months (mean 57.40 ± 10.09) postoperatively. Paula (17) reported that the mean interval between implantation of the Lentis LS-502-1 hydrophilic–hydrophobic acrylic IOLs and the diagnosis of calcified opacification was 29.15 ± 9.57 months. This interval of glistenings of L-312 IOL is much longer than the interval of US-860 UV IOLs. What's more, although the L-312 IOL (IOL#3) looked obvious turbidity, but the visual acuity was not affected. Therefore, the hydrophobic coatings, attached to the hydrophilic acrylic IOL surface had the function of delaying or preventing IOL opacity and maintaining IOL performance.

According to the time of postoperative IOL opacification, some researchers divided it into early and late postoperative opacification, both L-312 IOL and US-860 UV IOL opacity were late postoperative opacification (32).

The main limitation of this study is the small sample size. More cases, research and long-term follow-ups are necessary to investigate the true influence of individual factors and to confirm whether IOL calcification can be definitely linked to certain circumstances of patient or whether IOL calcification is the unique result of slight differences between every single IOL due to production. Besides, the cause of the glistenings of L-312 hydrophobic-hydrophilic acrylic IOLs is also worth studying further.

In summary, we compared opacity characteristics of US-860 UV and L-312 IOL, and found that the causes and mechanisms of opacification were different. This study expanded the IOL type of IOL opacification, and the study is the first, to our knowledge, reported that L-312 IOL opacification is characterized glistenings. Besides, IOL replacement can safely and effectively improve the visual acuity of patients. US-860 UV IOL opacification was related to calcium and phosphorus deposited on the surface of the IOL optical region because of hydrophilic acrylate material or production, package and transportation of those IOL, but L-312 IOL opacification, called glistenings, caused by a large number of vacuoles, which may be depend on temperature and hydration conditions. In addition, the interval of L-312 hydrophobic-hydrophilic acrylic IOLs was longer than that of US-860UV hydrophilic acrylic IOL in this study, the hydrophobic coating may play a protective role against IOL opacification. We hope with this study, we reveal the detailed features of this phenomenon for future studies to reference and compare, and help assist clinicians in selecting appropriate IOL.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JX, JS, and SM collected and analyzed the data. JX and JS wrote the manuscript. YD, TL, and JX designed the research. All authors contributed to the article and approved the submitted version.

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Presbyopia-Correcting Intraocular Lenses Implantation in Eyes After Corneal Refractive Laser Surgery: A Meta-Analysis and Systematic Review

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Purpose: To assess the efficacy, safety, and predictability of presbyopia-correcting intraocular lenses (IOLs) in cataract patients with previous corneal refractive surgery.

Methods: A systematic literature search was performed to identify studies evaluating the clinical outcomes of presbyopia-correcting IOLs implantation in cataract surgery after laser refractive surgery. Outcomes were efficacy, safety and predictability parameters.

Results: The authors identified 13 studies, involving a total of 128 patients and 445 eyes. Presbyopia-correcting IOLs were effective at improving distance, intermediate and near visual acuity aftercataract surgery. The proportion of post-laser surgery eyes with uncorrected distance visual acuity (UDVA) $\geq$ 20/25 was 0.82 [95% confidence interval (CI), 0.74-0.90] and the pooled rates of spectacle independence at near, intermediate, and far distances were 0.98 (95% CI, 0.94-1.00), 0.99 (95% CI, 0.95-1.00) and 0.78 (95% CI, 0.65-0.94) respectively. The percentage of participants who suffered from halos and glare was 0.40 (95% CI, 0.25-0.64) and 0.31 (95% CI, 0.16-0.60), respectively. The predictability had a percentage of 0.66 (95% CI, 0.57-0.75) and 0.90 (95% CI, 0.85-0.96) of eyes within ±0.5 diopters (D) and ±1.0 D from the targeted spherical equivalent.

Conclusions: Presbyopia-correcting IOLs provide satisfactory results in terms of efficacy, safety and predictability in patients with previous corneal refractive surgery, but have a higher risk of photopic side effects such as halos and glare.

Keywords: corneal refractive surgery, presbyopia-correcting intraocular lenses, meta-analysis, systematic review, efficacy and safety

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INTRODUCTION

Laser refractive surgery, considered as the mainstay of refractive surgery, has been well established as a safe and effective treatment for refractive error (1, 2). The corneal refractive surgery procedures that are most commonly performed include photorefractive keratectomy (PRK), laser *in-situ* keratomileusis (LASIK) and small incision lenticule extraction (SMILE). Currently, LASIK is widely accepted all over the world with high quality of life and patient satisfaction (3). With time,

post-refractive surgery patients develop symptomatic cataract, possibly presenting earlier than those without history of previous corneal refractive surgery (4). Accustomed to being spectacle independent after corneal refractive surgery, they might seek to remain spectacle-free after cataract surgery (5). One option would be the use of presbyopia-correcting intraocular lenses (IOLs). Presbyopia-correcting IOLs are generally classified into three main categories: multifocal IOLs (MIOLs) including diffractive or refractive designs, extended depth-of-focus (EDOF) IOLs, and accommodative IOLs (6). It has been shown that presbyopia-correcting IOLs can successfully restore both near and intermediate vision together with high spectacle independence compared to monofocal IOLs. However, presbyopia-correcting IOLs are frequently associated with side effects, such as photic disturbances, a decrease in contrast sensitivity, and a high incidence of residual refractive errors, which have an impact on patient satisfaction (6).

Currently, there are only a few studies investigating the visual outcomes of presbyopia-correcting IOLs implantation in cataract surgery after corneal refractive surgery. Thus, we conducted a systematic review of the existing studies on presbyopia-correcting IOLs implantation in post corneal refractive surgery, in respect of the uncorrected and corrected monocular visual acuity at near and distance, the refractive outcomes, the rate of spectacle independence as well as the photic phenomena such as halos and glare.

The purpose of the current study is to summarize and evaluate the evidence regarding the efficacy, safety and predictability of various options of presbyopia-correcting IOLs in cataract patients with previous corneal refractive surgery and to make recommendations on the management based on current clinical knowledge.

METHODS

Study Inclusion and Exclusion Criteria

Eligible for inclusion were clinical studies published in full text or abstract, evaluating the clinical outcomes of presbyopia-correcting IOLs implantation in cataract surgery after laser refractive surgery.

Studies were included in this study if they were confirmed to meet the following inclusion criteria: (1) population: patients who had corneal refractive laser surgery and subsequent cataract surgery or refractive lenses exchange, (2) intervention: presbyopia-correcting IOL implantation, (3) study design: observational studies, prospective or retrospective, randomized controlled trial (RCT), controlled, or case series, (4) studies reported data on at least one of the following outcome measurement: efficacy, safety and predictability. Exclusion criteria included (1) studies on analysis of IOL power calculation methods, (2) eyes that have not in-the-bag fixed IOL implantation.

Method of Literature Search

A literature search was performed in Pubmed MEDLINE, Ovid MEDLINE, Web of science, EBM Reviews (all Cochrane Library), Scopus—Health Sciences, ISI Web of Knowledge, EBSCO (Academic Search Complete, CINAHL and ERIC). A manual search of the reference lists of included articles and relevant systematic reviews was conducted to locate additional studies. We used Boolean logic operator through a combination of MeSHs, Entry Terms and Keywords to identify studies. Complete search strategies for each database were described in **Supplementary Table S1**. There was no restriction on publication year, study design, or language.

All titles and abstracts of papers identified by the search strategies were screened independently by two researchers (Y.S. and Y.H.), and disagreements were resolved through discussions and consultations with a third investigator (X.R.). The reference software EndNote (version X9, Philadelphia, PA, USA) was used to manage the retrieved records and remove the duplicate records. Full texts of all potentially eligible articles were retrieved for detailed assessment according to predetermined criteria.

Outcomes Measures

The following visual outcomes were documented at the last follow-up time: uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), uncorrected intermediate visual acuity (UIVA) and uncorrected near visual acuity (UNVA). We only extracted logMAR visual acuity for meta-analysis. Efficacy was interpreted as the proportion of post-laser surgery eyes with a postoperative UDVA $\geq$ 20/25 and the reported rates of spectacle independence at near, intermediate, and far distances. The safety factors analyzed consisted of the photopic side effects such as halos and glare. The refractive results were evaluated in terms of the postoperative spherical equivalent and the predictability (percentage of eyes within $\pm$0.5D and $\pm$1.0D from the targeted spherical equivalent).

Data Extraction

Data were extracted by two of the authors (Y.S. and Y.H.) independently and combined by a third reviewer (X.R.). If the data and the methods for obtaining it were considered relatively homogeneous, a meta-analysis was conducted. For continuous data like visual acuity, the mean values and standard deviations were extracted. For categorical data, the number of events were extracted.

Quality Assessment

Each included study was assigned a level of evidence based on the Oxford Centre for Evidence-based Medicine (CEBM) and adopted by the American Academy of Ophthalmology (7). Methodological Index for Non-randomized studies (MINORS) have been used to assess the quality of non-randomized studies (8). The checklist for included studies uses eight criteria for non-comparative studies and four additional criteria in the case of comparative studies. Each component was scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The ideal score for non-comparative studies is 16 and for comparative studies is 24. With a score of 0-8 or 0-12, the risk of bias classification was low, 9-12 or 13-18 was considered fair quality, and 13-16 or 19-24 was high risk of bias for non-comparative and comparative studies, respectively. Two investigators (Y.S. and Y.H.) evaluated the quality of each study

independently, with disagreements resolved through discussion and consensus.

Statistical Analysis

The statistical analysis was carried out using the meta-package in *R* language (version 3.6.0). Statistical heterogeneity between studies was tested by means of a chi-square statistics with an I^2 value exceeding 50% and a *P*-value of <0.05 of statistical significance. In the absence of statistical heterogeneity, a fixed-effects model was used, otherwise a random-effects model was applied as the expected heterogeneity.

RESULTS

The initial searches yielded a total of 1,580 articles: 387 from PubMed Medline, 715 from Scopus, 63 from EBSCO, 121 from Ovid MEDLINE, 289 from Web of Science and 5 from Cochrane Library (Cochrane Reviews). After the removal of 587 duplicates, 993 studies remained. After reading the titles and abstracts, 15 remaining articles were evaluated by full text and one study were excluded because the full article could not be obtained (9). In the case of two different publications of the same studies, the most recent one was included. (10, 11) The flow diagram of the selection process was present in **Figure 1**.

Study Characteristics

The characteristics of the 13 studies included in the final analysis were presented in **Supplementary Table S2** (11–23). Among them, nine were retrospective case series, and four were prospective studies with only three involving a control group. A total of 128 patients and 445 eyes were identified. For geographical location, seven studies were conducted in Europe, three in America, and three in Asia.

Quality Assessment

Overall, 2 studies (11, 21) were assigned a level III rating and 12 were assigned a level IV rating. Analysis on risk of bias of included studies were recorded in **Supplementary Table S3**. The mean MINORS score for non-comparative and comparative studies was 12.00 ± 0.85 and 19.67 ± 0.47, respectively, indicating fair quality of evidence for non-randomized studies and high quality for non-randomized studies. However, only one study (16) (7.14%) reported prospective calculation of the study size and none had an unbiased assessment of the endpoints.

Visual Outcomes

Seven studies reported uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) as outcomes (**Supplementary Table S4**). The pooled proportion of eyes with postoperative UDVA ≥ 20/25 was 0.82 [95% confidence interval (CI), 0.74-0.90] and the I^2 was 73% (**Figure 2**). We performed a subgroup analysis by the IOLs types; presbyopia-correcting IOLs were split into diffractive MIOLs and EDOF IOLs (**Figure 2**). In diffractive MIOLs group, the I^2 dropped to 0%, with a proportion of 0.79 (95% CI, 0.75-0.84). In EDOF IOLs group, the pooled proportion was 0.94 (95% CI, 0.88-1.00), which was higher than of the MIOLs group. Next, we conducted further subgroup analyses and divided the diffractive MIOLs into bifocal and trifocal IOLs (**Supplementary Figure S1**). The proportion in trifocal IOLs group was higher than that in bifocal IOLs group.

The mean CDVA was 0.01 logMAR (95% CI, −0.02-0.04) (**Figure 3**). The I^2 was 91%, indicating a large heterogeneity across included studies, thus sensitivity analyses were conducted by omitting one study at a time. Then we performed a subgroup analysis by different types of IOL implanted in cataract surgery. Respectively, 4 and 3 studies reported on diffractive MIOLs and EDOF IOL. The mean CDVA was 0.01 logMAR (95% CI, −0.01-0.03) and −0.00 logMAR (95% CI, −0.10-0.10), respectively. However, although the final results were stable, there was significant heterogeneity which we were unable to eliminate.

Only three studies provided data on uncorrected intermediate visual acuity (UIVA) (**Supplementary Table S4**). The mean UIVA in the studies by Li et al. (13) and Chow et al. (15) were 0.10 ± 0.10 logMAR and 0.22 ± 0.15 logMAR.

Five studies reported the data on mean postoperative uncorrected near visual acuity (UNVA) (**Figure 4**). The mean UNVA was 0.09 logMAR (95% CI, 0.04-0.14) and the I^2 was 93%. Although different subgroup and sensitivity analyses were performed, the source of heterogeneity remained unidentifiable.

Spectacle Independence

Four studies reported spectacle independence of far, intermediate and near distance. At far and intermediate distances, no heterogeneity was detected in spectacle independence (**Figure 5**). The pooled proportion of spectacle independence were 0.98 (95% CI, 0.94-1.00) and 0.99 (95% CI, 0.95-1.00) for far and intermediate distance. However, less patients achieved spectacle independence at near distance, with a proportion of 0.78 (95% CI, 0.65-0.94). We conducted sensitivity analyses and found that after excluding study of Ferreira et al. (21), the heterogeneity decreased (from 57 to 0%), with a proportion of 0.84 (95% CI, 0.75-0.94) (**Supplementary Figure S2**).

Visual Quality

We identified five studies that evaluated visual quality such as halos and glare (**Figure 6**). The pooled proportion of patients who suffered from halos was 0.31 (95% CI, 0.16-0.60) and the percentage of participants who were troubled with glare was 0.25 (95% CI, 0.09-0.69). High heterogeneity was found in the halos and glare effects ($I^2 = 66\%$, $P = 0.30$ and $I^2 = 83\%$, $P < 0.01$, respectively). Thus, we performed a sensitivity analysis to analyze the sources of heterogeneity. After removing the study by Chang et al. (20), the heterogeneity decreased ($I^2 = 17\%$, $P = 0.30$ and $I^2 = 0\%$, $P = 0.69$) in each group **Supplementary Figure S3**).

Refractive Outcomes

The postoperative spherical equivalent (SE) was recorded in 11 studies. Eight studies reported postoperative SE within ±0.5D from the targeted refraction and seven within ± 1.0D (**Figure 7**). The proportion of treated eyes with a postoperative refraction of ±0.5D and ±1.0D within the target refraction was 0.66 (95% CI, 0.57-0.75) and 0.90 (95% CI, 0.85-0.96), respectively. We did a sensitivity analysis, and it turned out that, after removing the study by Brenner et al. (14) the I^2 dropped to 8 and

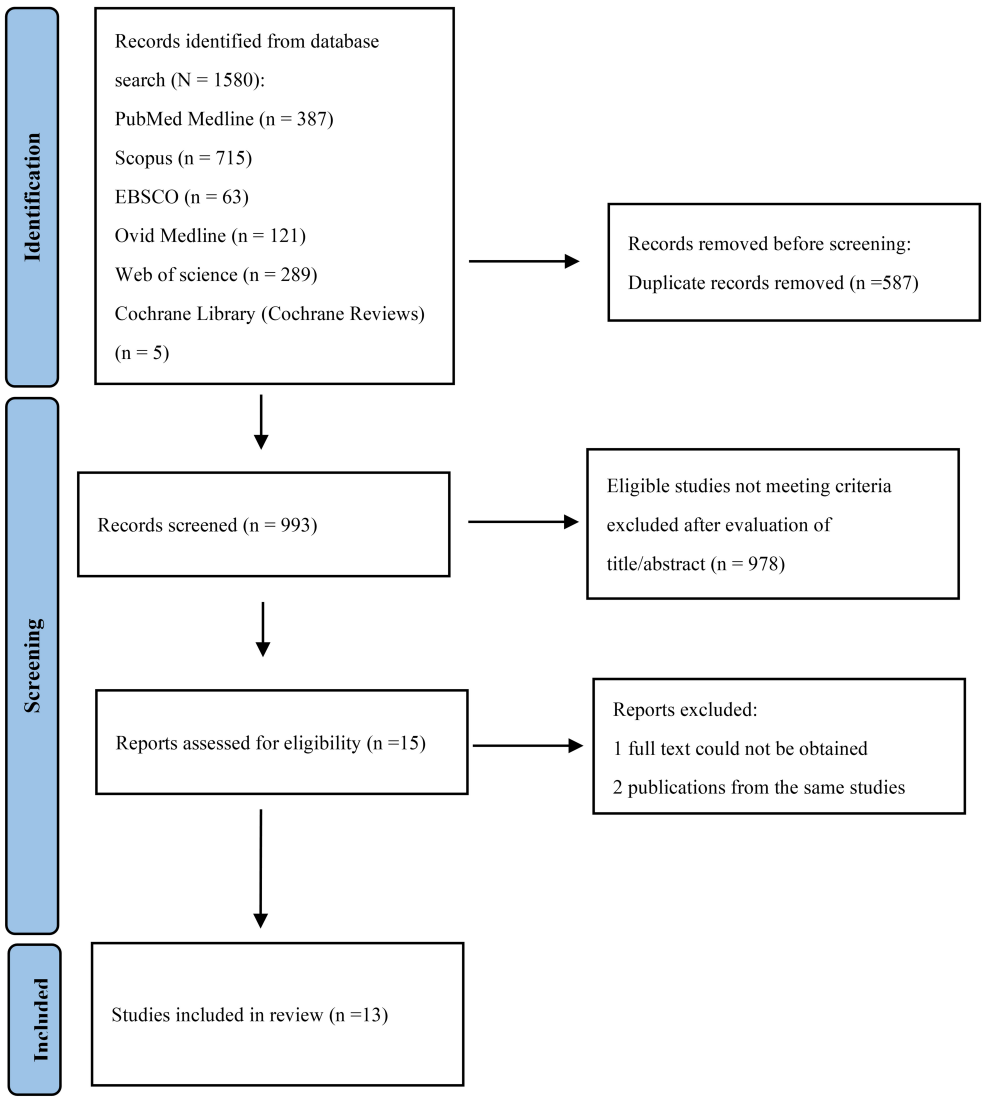

FIGURE 1 | Flow chart depicting the selection of included studies.

40%, with a proportion of 0.64 (95% CI: 0.58, 0.70) and 0.90 (95% CI: 0.86, 0.94) (**Supplementary Figure S4**). Then, we did a subgroup analysis, splitting the studies into two subgroups according to the follow-up time (<6 months vs. ≥6 months) (**Supplementary Figure S4**). Two studies that did not provide the follow-up time were excluded in this subgroup analysis. No heterogeneity was detected in 2 subgroups ($I^2 = 0$). In the studies with 6-month or more follow-up time, the proportion of postoperative spherical equivalent within ± 0.5D from the targeted refraction was higher (0.66, 95% CI, 0.57-0.76) than that in the studies with follow-up time <6 months (0.58, 95% CI, 0.50-0.67), while the incidence of postoperative spherical equivalent within ±1.0D was similar in both groups.

We also did a subgroup analysis by mean axial length (<26 vs. ≥26 mm) and identified no heterogeneity ($I^2 = 0$) between each group (**Supplementary Figure S5**). The pooled proportion of eyes within ±0.5D from the target refraction in the group with mean axial length <26 mm (0.52, 95% CI, 0.38-0.69) was lower than that in the other group (0.65, 95% CI, 0.58-0.73).

DISCUSSION

Cataract patients with previous corneal refractive surgery are eager for spectacle independence and a high visual quality after cataract surgery. One of the major defects of monofocal intraocular lenses (IOLs) as replacements for human crystalline lenses is the fixed focus of the IOLs. Compared to monofocal IOLs, presbyopia-correcting IOLs provide wider range of vision and continuation of spectacle independence for distance, intermediate and near vision in post-myopic or post-hyperopic refractive surgery eyes. Many types of presbyopia-correcting

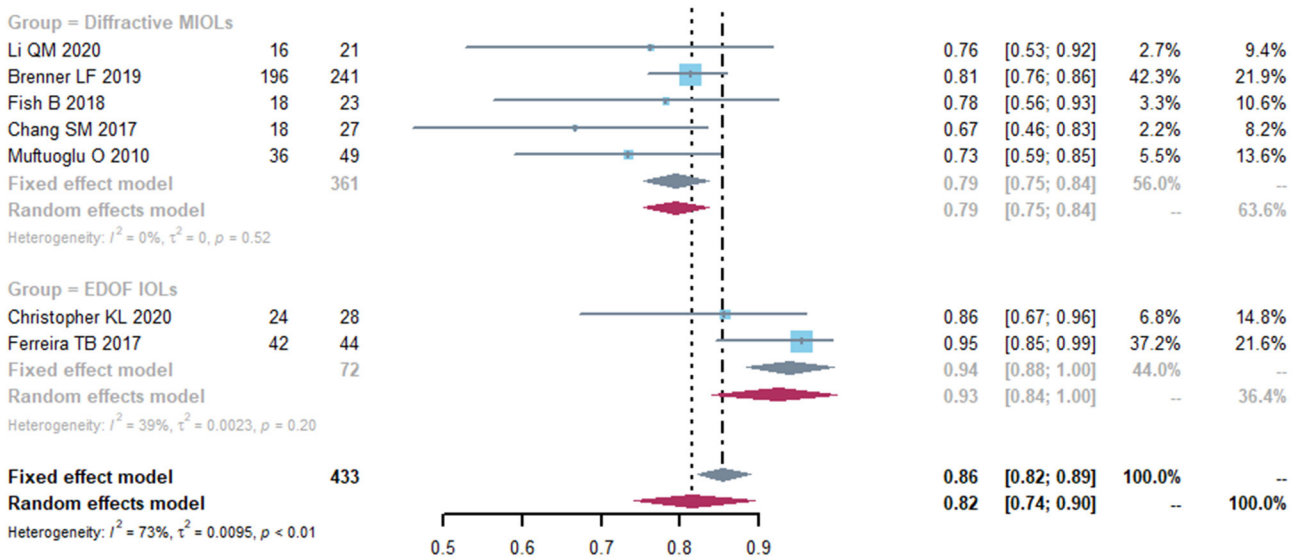

FIGURE 2 | Forest plot of uncorrected distance visual acuity (UDVA). The proportion of the eyes with a postoperative visual acuity ≥ 20/25 was represented in this graph. Events, number of treated eyes with a postoperative visual acuity ≥ 20/25. Total, total number of treated eyes. Proportion, proportion of eyes ≥ 20/25. CI, confidence interval; IOL, intraocular lense; MIOLs, multifocal intraocular lenses; EDOF, extended depth-of-focus.

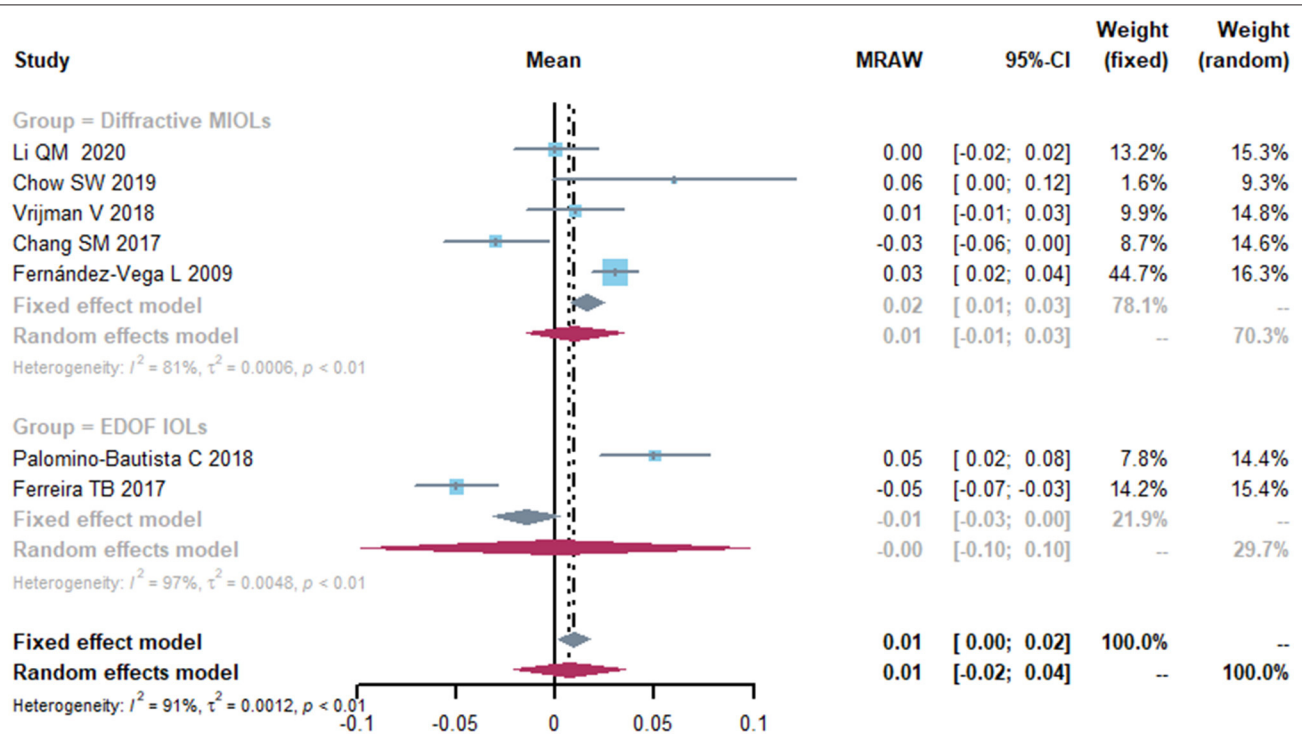

FIGURE 3 | Forest plot of corrected distance visual acuity (CDVA) in logMAR. IOL, intraocular lense; MIOLs, multifocal intraocular lenses; EDOF, extended depth-of-focus; MRAW, the row mean from the study.

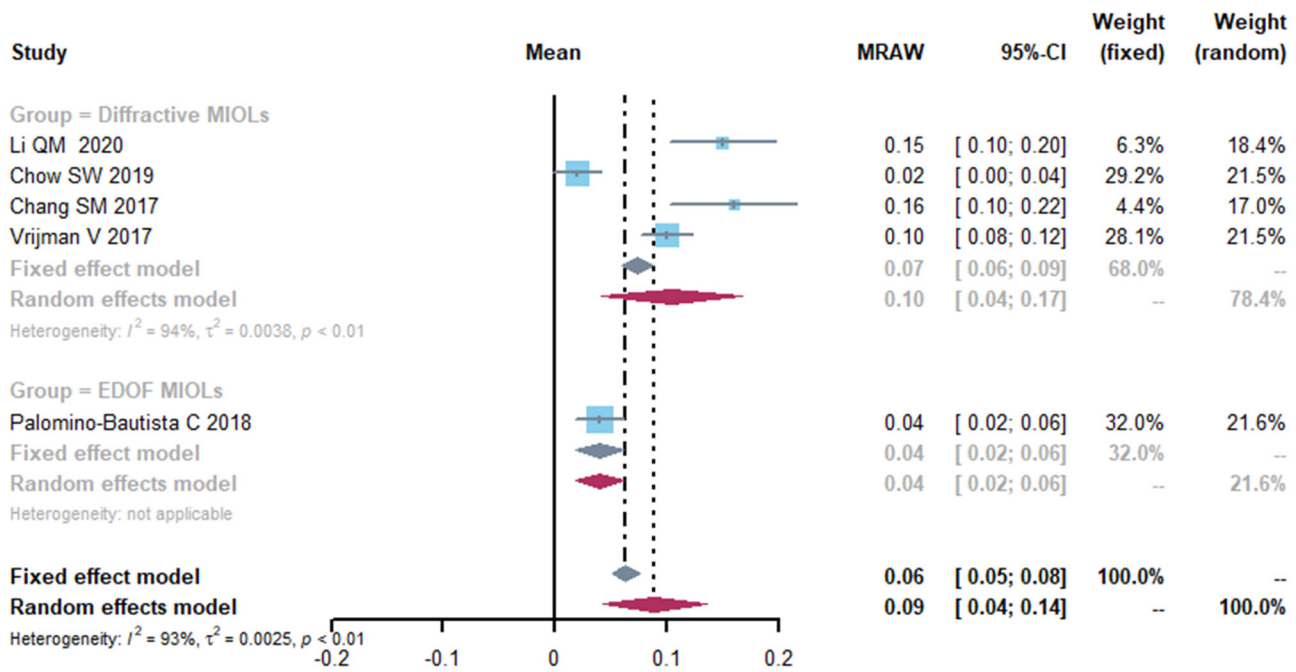

FIGURE 4 | Forest plot of uncorrected near visual acuity (UNVA) in logMAR. IOL, intraocular lense; MIOLs, multifocal intraocular lenses; EDOF, extended depth-of-focus; MRAW, the row mean from the study.

IOLs are now available, including multifocal IOLs (MIOLs), extended depth-of-focus (EDOF) IOLs and accommodating IOLs. To date, there has been no systematic review and meta-analysis conducted on this topic.

Efficacy Analysis

The distance, intermediate and near visual acuity and spectacle independence are the most important endpoints for satisfaction in patients with previous corneal refractive surgery. For distance vision, we performed a meta-analysis on the proportion for UDVA of 20/25 or better in post refractive surgery eyes and found better results in EDOF IOLs group than diffractive MIOLs group. After splitting the diffractive MIOLs into bifocal and trifocal IOLs, the trifocal IOLs showed an improvement in UDVA when compared to bifocal IOLs. However, no significant differences were identified between trifocal and bifocal IOLs for distant VA in patients without previous corneal refractive surgery (24). Thus, further studies are required to demonstrated this clearly. In terms of CDVA, Fernández-Vega et al. (11) and Chow et al. (15) reported an improvement in CDVA after MIOLs implantation in post-myopic LASIK patients. In the present study, although diffractive MIOLs yield better CDVA than EDOF IOL, the result would not be credible to conclude that MIOLs provided better distance vision than EDOF IOL in such cases due to the high heterogeneity and limited number of available studies.

With regards to intermediate and near vision, Ferreira et al. (21) found that the uncorrected near and intermediate visual acuities were better after implantation of EDOF IOL than monofocal IOL, which was in accordance with those results in eyes without previous corneal refractive surgery (25, 26). They reported binocular UIVA and UNVA of 0.1 logMAR or better in 100% and 59.09% of eyes in EDOF IOLs group, and 59.09% and 0% in monofocal group, indicating that EDOF IOLs implanted in eyes that had previous LASIK was able to restore the intermediate and near visual function. In a study by Chang et al. (20), binocular post-operative UIVA and UNVA values of 0.1 logMAR or better were 60.87 and 34.78% of eyes, respectively, in eyes implanted with the diffractive bifocal Tecnis ZMA00 and ZMB00 MIOLs. In eyes without previous corneal refractive surgery, multifocal IOLs presented better near visual acuity while EDOF IOLs showed better results in intermediate vision. However, the present study's results showed better mean UNVA in eyes with EDOF IOLs than diffractive multifocal IOLs. Considering the limited number of studies available and the high between-study heterogeneity, our evidence of intermediate and near VA was insufficient to reach a definitive conclusion. Further research comparing MIOLs and EDOF IOLs in patients with previous corneal refractive surgery is warranted.

In present study, MIOLs and EDOF IOLs performed a good result of spectacle independence for far and intermediate distances. At near distance, the proportion of spectacle dependence increased (from 0.78 to 0.84) and heterogeneity decreased after omitting the study by Ferreira et al. (21), who investigated the clinical outcomes of EDOF IOLs in eyes with previous myopic LASIK. Therefore, it is indicated the postoperative level in dependence for near vision was possibly higher in the EDOF IOLs than the diffractive MIOLs. It is also consistent with the fact that EDOF IOLs, with an extended far focus area which reaches to the intermediate distance, restore distance and intermediate visual function but with restraint of near vision (27–29). In Ferreira et al.'s study (21), more patients implanted with EDOF IOLs were free from glasses than

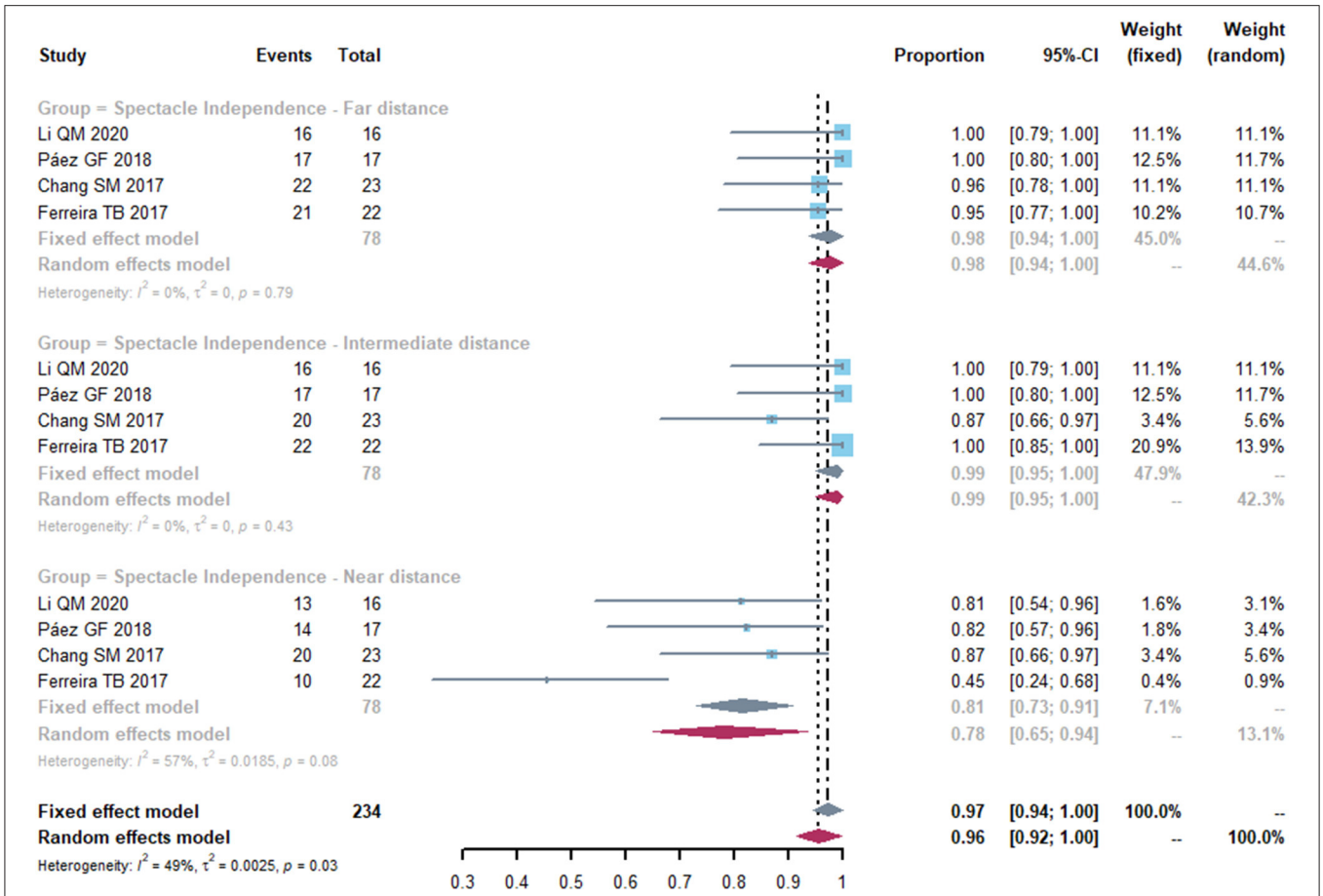

FIGURE 5 | Forest plot of spectacle independence of far, intermediate and near distance. Total, total number of treated eyes. Proportion, proportion of eyes achieved spectacle independence at far, intermediate and near distance.

those receiving monofocal IOLs. Although there were no studies comparing MIOLs and monofocal IOLs in eyes with previous corneal surgery, it is proved that MIOLs performed far better than monofocal IOLs on spectacle independence in eyes without previous corneal surgery (30).

Safety Analysis

It has been reported that the frequency of phenomena including halo, glare, and difficulty in night vision in patients who underwent successful corneal refractive surgery is increased, which are related to excessive postoperative higher order aberration values (19). Studies show that myopic and hyperopic ablation significantly increased corneal higher-order aberration (HOAs), inducing positive and negative spherical aberration (SA) respectively (31). Presbyopia-correcting IOLs with enhanced asphericity may be more appropriate for post-myopic surgery eyes (11, 32, 33). The spherical aberration–correcting Tecnis MIOLs (Johnson & Johnson Vision, Inc.) has −0.27 μm SA and aims to correct the total amount of corneal SA (34). ReSTOR (Alcon Laboratories Inc.) SN6AD1 MIOLs corrects for 0.1 μm of spherical aberration while the SN60D3 does not correct for any (35). The AT LISA MIOLs (Carl Zeiss Meditec AG) and FineVision IOL (PhysIOL) has −0.18 and −0.11 μm SA, respectively. Conversely, eyes that underwent hyperopic LASIK should be implanted with a spherical IOL (36).

In addition to the introduction of HOAs after laser refractive surgery, the position and functional deviation of intraocular lenses might also contribute to photic phenomena such as halos and glare. The capsule in high myopic patients who underwent refractive laser surgery was larger compared to normal patients and the stability of IOLs is slightly worse, which are more likely to lead to photopic side effects (13).

To understand the visual quality obtained with different types of IOLs, we analyzed the incidence of halos and glare in five studies. Ferreira et al. (21) found no significantly difference in the incidence of halos and glare between EDOF IOLs and monofocal IOLs implanted in eyes with previous LASIK. Further decrease in heterogeneity was obtained in the sensitivity analyses, which suggested that the heterogeneity might come from the study by Chang et al. (20). One possible explanation is that the study reported patients who had at least a very mild severity of visual symptoms, increasing the proportion of patients with halos and glare. Spherical aberration is a consideration when choosing the presbyopia-correcting IOLs in eyes that have undergone

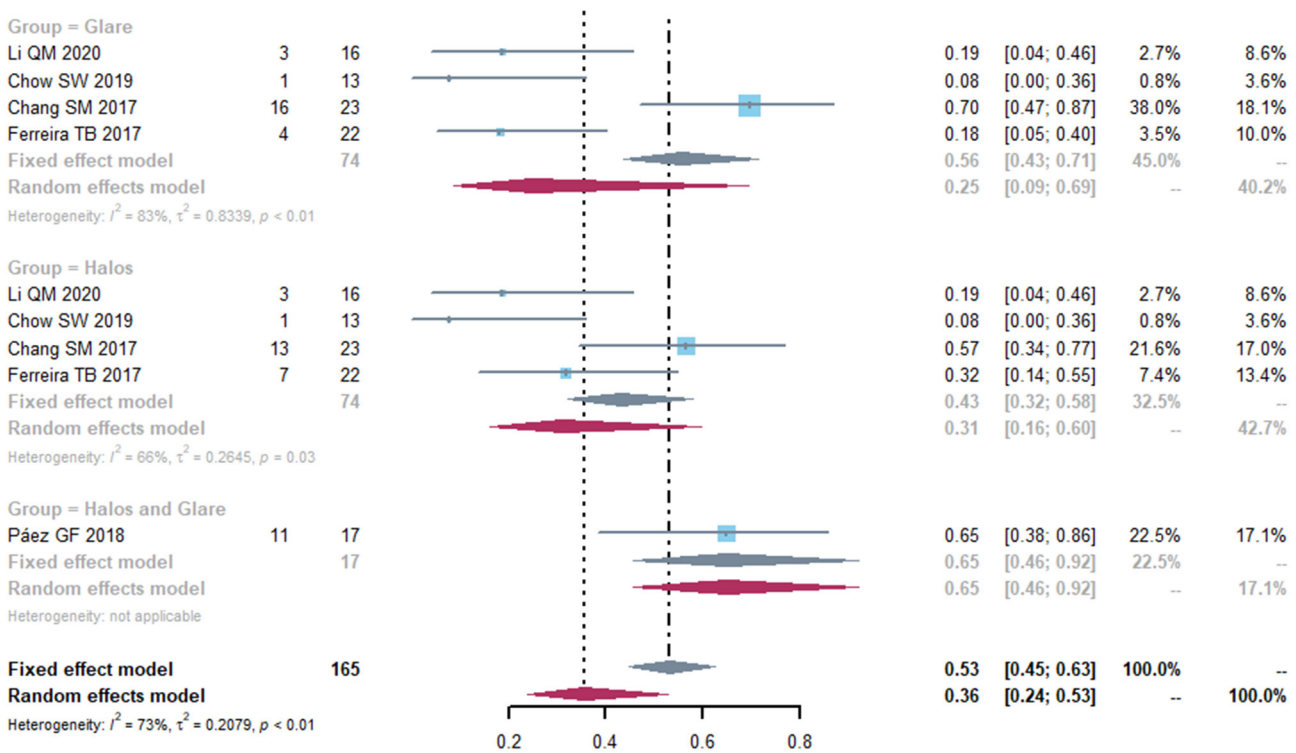

FIGURE 6 | Forest plot of photic disturbance of halos and glare. Total, total number of the patients. Proportion, proportion of patients who suffered from halos and glare.

myopic and hyperopic refractive surgery (37). To date, no explicit guidance exists to preclude the use of presbyopia-correcting IOLs regarding the amount of spherical aberrations or other HOAs. It is suggested that potential MIOLs contraindication thresholds for total HOAs was >2.0 SD (38).

Previous studies showed patients with corneal refractive surgery are more prone to have degradation in contrast sensitivity (9). Among 13 included studies, only two studies provided the result of CS. Chang et al. (20) found no significant difference in CS of the operated eyes with Tecnis MIOLs from that of the unoperated eyes]. However, CS at spatial frequency of 3 cpd in the operated eyes was worse in comparison of their previous study of the Tecnis MIOLs in eyes with virgin cornea, suggesting that visual quality after MIOLs implantation could be affected by LASIK attributed to the increased SA (20). In the study by Ferreira et al. (21), no significant difference between EDOF IOLs and monofocal IOLs implanted in eyes with previous LASIK were found for any spatial frequency evaluated, similarly to the results of Pedrotti et al. (26), in eyes without previous LASIK. The authors concluded that there are no significant differences in terms of distance visual degradation between the monofocal IOLs and EDOF IOLs, confirming the good optical performance of this EDOF IOLs implanted in post- LASIK eyes.

Alternative optical quality parameters are used to quantify visual quality after presbyopia-correcting IOLs implantation in eyes that have had refractive surgery, including the modulation transfer function (MTF) cutoff frequency, the objective scatter index (OSI) and the strehl ratio (SR). MTF is obtained by Fourier transform from the point spread function (PSF) and MTF cutoff is used to express visual quality, referring to the frequency at which the MTF reaches 1% contrast (39). OSI is defined as the amount of the light outside the double-pass retinal intensity PSF image in the peripheral zone vs. that on the central zone (40). SR is calculated as the ratio of the peak focal intensities in aberrated PSF and ideal PSF, reflecting the retinal imaging quality with a value between 0 and 1 (41). The higher MTF cut-off values and the lower OSI values indicate better optical quality. The closer SR is to 1, the smaller the aberration of the eye. Camps et al. stimulated optical performance of three presbyopia-correcting IOLs through MTF and reported the worsening of the ocular optical quality at near and intermediate distances as the pupil increased (42). They demonstrated that the Mini Well and Symfony IOLs worked better than the Mplus IOL in eyes with previous myopic LASIK, and the Mini Well IOL provided acceptable results in eyes with previous myopic LASIK. However, none of the included studies in our paper presented the results of MTF, OSI or SR. Thus, further clinical studies performing the measurement of these parameters are needed in the future.

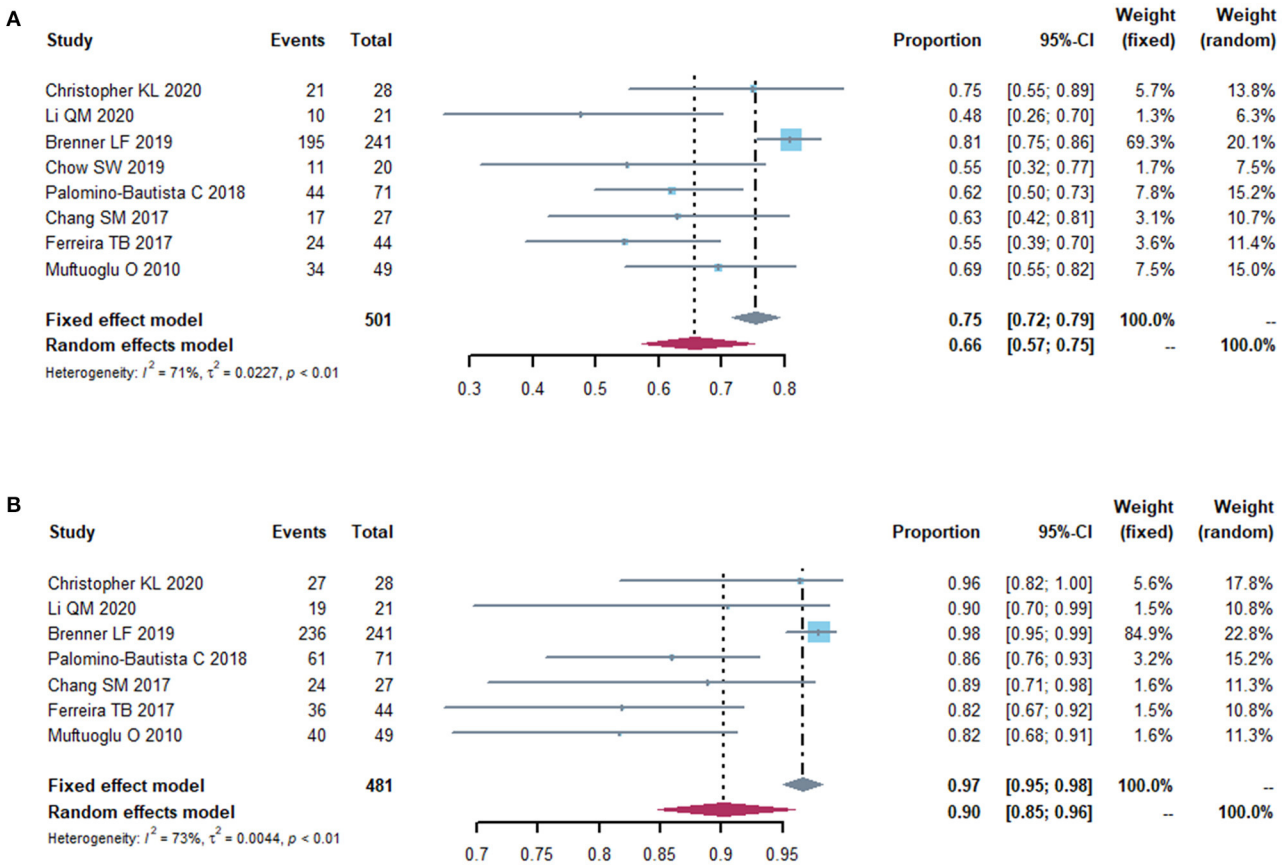

FIGURE 7 | Forest plot of postoperative refraction. The proportion of eyes with a postoperative refraction of 0.5 diopters **(A)** and 1.0 diopters **(B)** from the target refraction.

Predictability Analysis

Presbyopia-correcting IOLs implantation in cases with previous corneal refractive surgery could be challenging for the IOL power calculations attributed primarily to two factors: (1) inaccurate measurement of the true total corneal refractive power given by keratometers and corneal topography systems (43), (2) incorrect calculation of the effective lens position (ELP) by third- or fourth-generation formulas through an estimation based on the postoperative corneal powers (44, 45). Over the past two decades, investigators have made great effort to present different formulas and keratometry measurements to overcome this problem and provide more predictable outcomes (46). There are mainly two categories of methods for IOL power calculations after corneal refractive surgery. Formulas that required perioperative data and information about the refractive change, which have been proved inaccurate and not helpful in improving the predictability of outcomes (47). The other is the formula independent on the historical information. Currently, there are three major methods in IOL power calculations for eyes without clinical data, including the American Society of Cataract and Refractive Surgery (ASCRS) online calculator, the Barrett True-K formula and the OCT-based IOL calculation formula. Wang et al. suggested that the OCT and True-K No History (TKNH) were promising formulas for post-corneal refractive surgery eyes, which were included in the latest update of the ASCRS IOL calculator (48). For cataract eyes with previous LASIK or PRK, Barrett True-K formula provided more stable predictions than alternative methods (18, 49). Similar results were obtained in a prospective study on the IOL calculations in patients undergoing cataract surgery after SMILE (50). In eyes with previous RK lacking historical data, TKNH and Haigis formulae were recommended for IOL calculation (51).

In this meta-analysis, the postoperative percentages of eyes with expected spherical equivalent within ±0.5 D and ±1.0 D of plano in the study by Brenner et al. (14) was higher and comparable to results in untreated cornea (5). They concluded that the possible reasons for the higher accuracy in their study than others were the exclusion of corneas with abnormal optics and the ablation profiles with better transitions zones, which made the *K*-values for IOL power calculations more reliable. It is demonstrated that the myopia status before laser refractive surgery had an effect on the treatment outcomes (52). In treatments with higher amounts of myopia correction, efficacy measures including accuracy and predictability tended to be lower, which in turn impacted postoperative outcomes of IOL implantation (53, 54).

Total keratometry (TK) from IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany) offer an advantage in measuring anterior and posterior corneal curvatures together with corneal thickness in patients whose anterior to posterior corneal relationships are altered, such as post laser surgery (55). It has been proved that the accuracy of formulas combined with TK was comparable to the existing no-history post-myopic laser refractive surgery formulas (56). Although there has been progress in IOL power calculation for presbyopia-correcting IOLs over the past few years, the difficulties still remain. Considering the tolerance to residual refractive error among different types of IOLs, EDOF IOLs may be preferable in post-laser surgery eyes.

In eyes with previous corneal refractive laser surgery for high axial myopia, the IOL calculation have become even more difficult. AL measurement is one of the most influential parameters contributing to the deviation between actual diopter and prediction of diopter after cataract surgery (57, 58). In this study, the predictability percentage of eyes with residual refractive error within 0.5D from the target refraction had a lower value in studies with longer axial length, which was in consistent with the study by Zhou et al. evaluating the accuracy of the refractive prediction in highly myopic eyes without previous refractive surgery (59). Therefore, in patients who have underwent previous corneal refractive laser surgery for high myopia, the axial length of the eyes should be measured by appropriate prediction formula to reduce the refractive error absolute value. A recent study demonstrated that both Barrett True-K No History and SToP (SRK/T) were performed well in calculating EDOF IOLs power in eyes with a history of myopic LASIK/PRK surgery when AL $\geq$ 28.0 mm (60).

According to previous studies and clinical experience, the refractive status could be stabilized at 3 months postoperatively (61). Therefore, we pooled the data reported at the end of follow-up for subgroup analysis. After splitting the studies into two subgroups, the results suggested that the differences among the various studies may be related to follow-up time. In general, the refractive outcomes should be interpreted in the context of different follow-up durations and it is possible that refractive predictability may become better with longer follow-up.

The limitations of this meta-analysis stem from the quality of evidence available due to the scarcity of prospective or randomized controlled studies on this topic. The majority of included studies were Level IV evidence (84.62%) and only 2 (15.38%) studies were Level III. Additionally, the number of included studies was relatively small, and few studies measured and reported the same outcomes consistently, leading to the difficulties for the credibility of some results. Finally, we attempted to diminish the impact of heterogeneity (e.g., types of IOLs, follow-up time, etc.) by performing sensitivity analysis, but the effect of heterogeneity still could not be eliminated completely.

CONCLUSIONS

Overall, the presbyopia-correcting IOLs were effective at providing satisfactory visual outcomes at near, intermediate and far distance and wider range of spectacle independence in eyes with previous corneal refractive surgery. Although presbyopia-correcting IOLs in eyes with previous corneal laser correction was safe, they inevitably generated more photic effects in the form of halos and glare and decreased in contrast sensitivity. Considering the induction of spherical aberration by corneal laser surgery, eyes that underwent myopic ablation should be implanted with aspheric IOLs and spherical IOLs for hyperopic ablation. The progress in IOL power calculations for presbyopia-correcting IOLs and formulas combined with total keratometry (TK) provide accurate predictability for achieving a better refractive result within $\pm$0.5D and $\pm$1.0D of target refraction. More evidence-based publications and RCTs, making a comparison between presbyopia-correcting IOLs and monofocal IOLs or among different types of the presbyopia-correcting IOLs, are warranted to provide guidelines for IOLs selection in patients who have had corneal refractive surgery in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YJ was responsible for conception and design. YS and YH collected the literatures, extracted and analyzed the data. YS prepared the final manuscript. XR was involved in reviewing of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Phacoemulsification Combined With Supra-Capsular and Scleral-Fixated Intraocular Lens Implantation in Microspherophakia: A Retrospective Comparative Study

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Background: Microspherophakia (MSP) is a rare ocular condition, the lens surgery of which is complicated by both insufficient zonules and undersized capsule.

Methods: This study included MSP eyes managed with phacoemulsification combined with supra-capsular and scleral-fixated intraocular lens implantation (SCSF-IOL) and made the comparison with those treated by transscleral-fixated modified capsular tension ring and in-the-bag intraocular lens implantation (MCTR-IOL).

Results: A total of 20 MSP patients underwent SCSF-IOL, and 17 patients received MCTR-IOL. The postoperative best corrected visual acuity was significantly improved in both groups ($P < 0.001$), but no difference was found between the groups ($P = 0.326$). The IOL tilt was also comparable ($P = 0.216$). Prophylactic Nd:YAG laser posterior capsulotomy was performed 1 week to 1 month after the SCSF-IOL procedure. In the SCSF-IOL group, two eyes (10.00%) needed repeated laser treatment and one eye (5.00%) had a decentered capsule opening. Posterior capsule opacification was the most common complication (6, 35.29%) in the MCTR group. No IOL dislocation, secondary glaucoma, or retinal detachment was observed during follow-up.

Conclusions: SCSF-IOL is a viable option for managing MSP and is comparable with the MCTR-IOL. Nd:YAG laser posterior capsulotomy was necessary to prevent residual capsule complications after the SCSF-IOL procedure.

Keywords: microspherophakia, capsular bag, phacoemulsification, modified capsular tension ring, Nd:YAG laser capsulotomy

INTRODUCTION

Lens zonules are not only involved in accommodation by transferring the tensive force exerted by the ciliary body, but they also modulate the proliferation of lens epithelial cells (1). Microspherophakia (MSP) is a rare congenital abnormality in which lens growth is arrested by the lack of tension from rudimentary zonules. Without sufficient

stretching, the lens fails to develop a biconvex shape and remains spherical at the fifth to the 6 month of embryonic life (2), in that the entire lenticular equator is visible under complete pupil dilation. As their lens is smaller and more spherically shaped, patients with MSP are often complicated by lens subluxation (44%) and high lenticular myopia (84.6%) and have a high propensity for secondary glaucoma (44.4–51%) (3), also known as reverse angle-closure glaucoma (4). The etiology of MSP is postulated to be the maldevelopment of the mesoderm (5). The condition may occur in an isolated form or as an ocular manifestation of systematic disorders, including Marfan syndrome (6), Weill-Marchesani syndrome (7), Alport's syndrome (8), cri-du-chat syndrome (9), homocystinuria (10), and chondrodysplasia punctata (11).

The unique morphology and potential complications of MSP challenge the management of the condition. Various surgical approaches have been attempted in sporadic MSP cases, including angle-supported IOL (12), iris-claw IOL (13), retropupillary iris-claw IOL (14), and sutured (15) or sutureless (16, 17) sclera-fixated IOL. However, most of the procedures adapt lensectomy or capsulotomy to remove the capsular bag, and anterior vitrectomy is often requisite. The risk of retinal detachment is expected to increase, especially in those with connective tissue disorders (18). The tilt, decentration, and dislocation of the IOLs are also of great concern (19).

Although the capsular bag of the eyes of MSP patients is relatively small, the preservation of the posterior capsule and residual zonules is still valuable, as they maintain the continuity of the physical barrier between the anterior and posterior segments. Here, we report a novel and feasible surgical procedure, supra-capsular and scleral-fixated intraocular lens implantation (SCSF-IOL), that can overcome some of the challenges in MSP surgery. This study aimed to ascertain the surgical outcomes in a series of consecutive patients with MSP who underwent the SCSF-IOL procedure and compare them with those that received transscleral-fixated modified capsular tension ring and in-the-bag intraocular lens implantation (MCTR-IOL). The visual outcomes and postoperative complications were evaluated to compare the efficacy and safety of these two procedures.

METHODS

Patient Eligibility and Ethics Statement

Patients with MSP were recruited, all of whom received lens surgery at the Eye and ENT Hospital of Fudan University, Shanghai, China, from Jan 2019 onwards. The MCTR-IOL procedures were performed before June 2020 when the registration certificate of MCTR expired in mainland China. From then on, all MSP eyes underwent the SCSF-IOL procedures. MSP was diagnosed in accordance with a previous study (3). Briefly, MSP was diagnosed if the entire lens equator was observed under complete pupil dilation and, for eyes with limited pupil diameter, anterior segment optical coherence tomography (AS-OCT) was supplemented. The surgical indications were as follows: (1) a best corrected distance visual acuity (BCVA) (LogMAR) worse than 0.5; (2) uncorrectable lenticular astigmatism; (3) pupillary block due to lens dislocation; and (4) a high risk of amblyopia progression. Patients with the following features were not enrolled: (1) lens dislocated into the anterior chamber or posterior pole; (2) a history of eye trauma or intraocular surgery; and (3) the coexistence of retinal detachment, retinal pigmentosa, end-stage glaucoma, or cornea endothelium decompensation. The surgical eyes were registered for patients who undergone unilateral surgery. One of the eyes was randomly selected if the patient was operated bilaterally. All procedures performed on human participants followed the 1964 Declaration of Helsinki and its later amendments after receiving proper approval from the Human Research Ethics Committee of the Eye & ENT Hospital of Fudan University (no. 2020126-1). Informed consent was obtained from all candidates and the guardians of those under 18.

Ophthalmic Examinations

All enrolled patients underwent slit-lamp examination under complete pupillary dilation by the same experienced ophthalmologist. Their BCVA was measured by an experienced optometrist. The ocular biometry was obtained using partial coherence interferometry (IOLMaster 500 & 700, Carl Zeiss Meditec AG, Jena, Germany). The intraocular pressure (IOP) was measured with a non-contact tonometer (CT-80, Topcon Medical Systems, Oakland, US), and the retro illumination images and ocular aberrations were recorded with a wave front aberrometer (OPD-Scan III, Nidek Co, Ltd., Gamagori, Japan). The tilt of the IOL was obtained indirectly from the wave front aberrations, including tilt, coma, and trefoil, as was previously described (20). The anterior segment was visualized by swept-source AS-OCT (CASIA2; Tomey Corp, Nagoya, Japan).

Surgical Management

All procedures were performed by the same experienced surgeon (YX.J.) and in the same setting. The step-by-step procedure was shown in **Figure 1**. The phacoemulsification procedure and MCTR implantation were performed as described in detail in our previous study (21), but four capsular hooks (CapsuleCare, Med Devices Lifesciences, Vaishali, India) were applied to stabilize the bag in cases of MSP. In the SCSF-IOL group, a single-piece IOL (Superflex Aspheric 920H or C-flex Aspheric 970C, Rayner Surgical Group Ltd., West Sussex, UK) was injected into the anterior chamber through a 2.6-mm clear corneal tunnel incision. The loop of the pre-loaded IOL was sutured to the sclera by double-strand 9–0 polypropylene (MANI Inc., Tokyo, Japan) through the sulcus, and the capsular bag was left intact. Z-suturing was applied to fixate the suture in the sclera with no need to generate a scleral flap (22). An 8–0 vicryl polyglactin suture (Ethicon, NJ, USA) was applied to close the conjunctival flap. In the SCSF-IOL group, prophylactic Nd:YAG laser posterior capsulotomy was performed 1 week to 1-month postoperatively. Limited posterior capsulotomy and anterior vitrectomy (23G, Alcon Laboratories Inc., Geneva, Switzerland) were performed intraoperatively using a limbal approach in children who were expected not to cooperate with laser treatment. For patients in the MCTR-IOL group, laser capsulotomy was performed only when

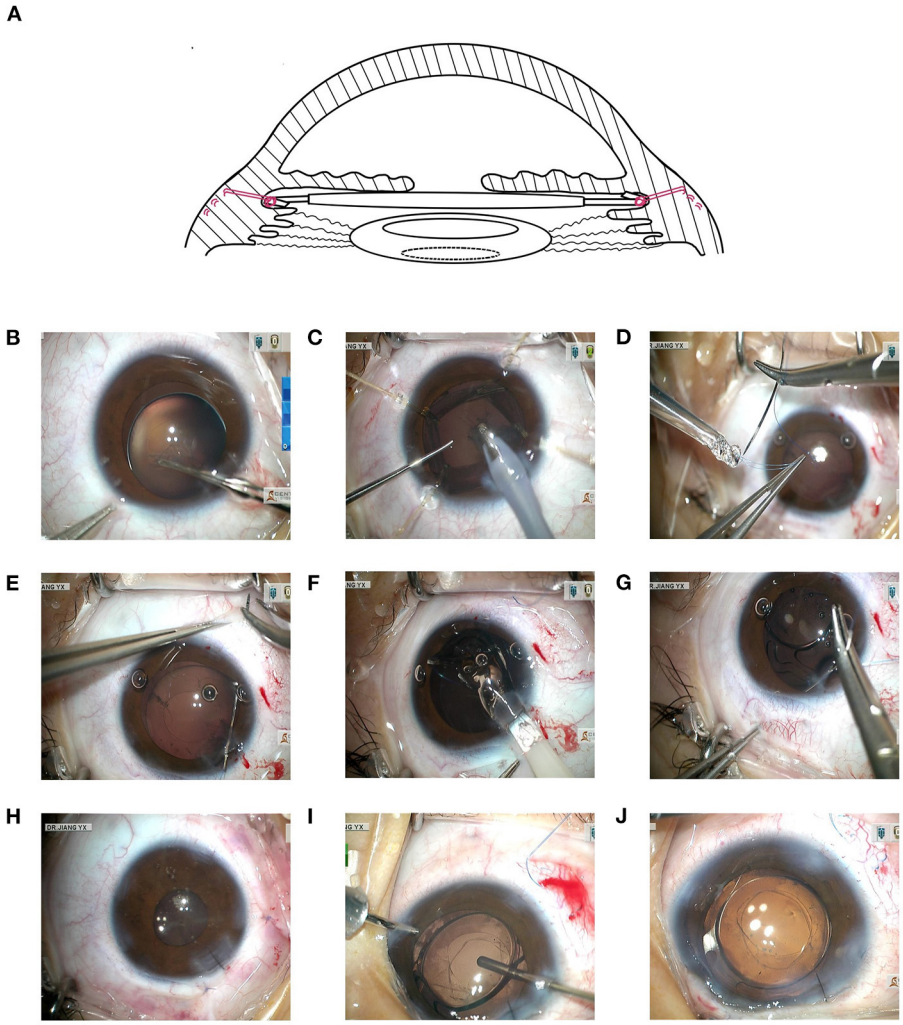

FIGURE 1 | Detailed processes of SCSF-IOL in MSP. **(A)** A demonstration of the principles of the SCSF-IOL procedure. The intraocular lens was sutured with 9–0 polypropylene (in red) through the sulcus and placed above the preserved capsule. Prophylactic posterior capsulotomy is shown within the dashed circle. **(B)** Continuous circular capsulorhexis was carefully performed. **(C)** The lens was removed using irrigation/aspiration (I/A) mode at reduced vacuum, slow aspiration flow rate, and low bottle height, with the aid of four capsular hooks. **(D)** Double-strand 9–0 polypropylene was used to suture one loop of the pre-loaded IOL. **(E)** A puncture point was made using the ab interno approach at 1.5–2.0 mm posterior to the corneal limbus. **(F)** The pre-loaded IOL with the pre-sutured loop was injected into the anterior chamber through a 2.6-mm clear corneal tunnel incision. **(G)** The other loop was sutured opposite to the previous one. **(H)** The main incision and conjunctival flap were closed. **(I)** For young patients who were expected to be uncooperative during laser capsulotomy, the posterior capsule of the visual axis was excised and limited anterior vitrectomy was performed via the limbus with the cutter in cut I/A mode. **(J)** At the center of the IOL, the anterior and posterior capsulorhexis openings were checked at the end of the surgery. This is shown in the same eye as in **(I)**. SCSF-IOL, supra-capsular and scleral-fixated intraocular lens implantation; I/A, irrigation/aspiration; MSP, microspherophakia.

posterior capsule opacification or anterior capsule contraction was visually significant.

Statistical Analysis

Data normality was confirmed using the Shapiro–Wilk test. Student's *t*-test and Mann–Whitney *U* test were applied as appropriate for comparisons between the two independent groups. Descriptive statistics included the mean ± standard deviation and median (interquartile, IQ) where appropriate. The paired Student's *t*-test or paired Wilcoxon test was used to compare preoperative with postoperative measurements within the same group. The results of the two-sided tests were considered significant at $P < 0.05$. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Preoperative Characteristics

A total of 37 patients (37 eyes) with MSP were recruited. Twenty eyes underwent the SCSF-IOL procedure and 17 eyes received MCTR-IOL. The representative clinical features are shown in

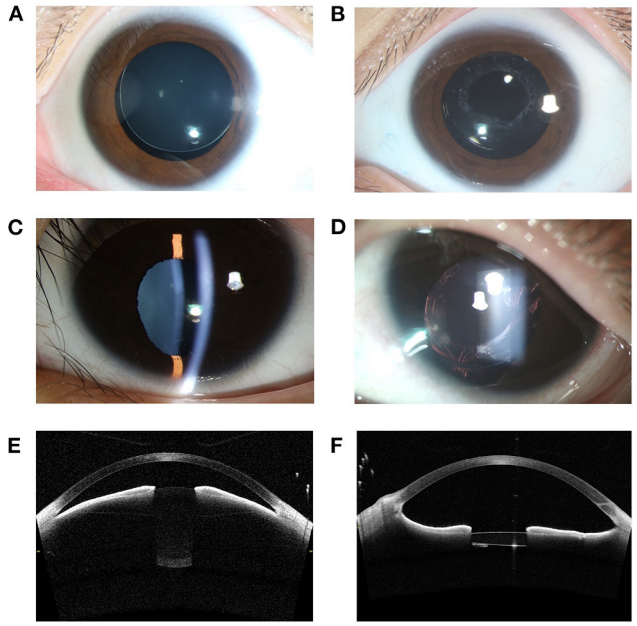

FIGURE 2 | Representative photographic images and AS-OCT images of MSP eyes. **(A)** A slit-lamp photograph of a MSP eye with Marfan syndrome before surgery revealed a small lens with superior dislocation. **(B)** The preserved capsule on 1-year follow-up after Nd:YAG laser treatment. This is the same eye as in **(A)**. **(C)** One eye of MSP was complicated with ectopia pupillae. **(D)** The visual axis was clear on 1-year follow-up after the SCSF-IOL procedure and Nd:YAG laser capsulotomy. This is the same eye as in **(C)**. **(E)** AS-OCT showed the spherically shaped lens and forward migration of the iris-lens diaphragm in one MSP eye with Marfan syndrome. **(F)** The narrowing of the anterior chamber angle was significantly relieved 3-month postoperatively. This is the same eye as in **(E)**. AS-OCT, anterior segment optical coherence tomography; SCSF-IOL, supra-capsular and scleral-fixated intraocular lens implantation; MSP, microspherophakia.

TABLE 1 | Preoperative characteristics of patients with MSP.

Characteristics	Group[a]		*P*-value
	SCSF-IOL	MCTR-IOL	
No. patients	20	17	
Male/female	12/8	10/7	1.000
Clinical diagnosis	8	9	0.517
Isolated			
Syndromic (MFS/HCY)	11/1	7/1	
No. eyes	20	17	
Right/left	10/10	10/7	0.743
Age at the surgery (years)	12.00 (5.00, 21.00)	6.50 (5.50, 27.50)	0.562
BCVA (LogMAR)	0.70 (0.40, 0.80)	0.70 (0.40, 1.00)	0.405
IOP (mmHg)	14.57 ± 3.22	15.20 ± 5.28	0.669
Cataract (%)	15.0%	11.8%	1.000
Glaucoma (%)	10.0%	23.5%	0.383
Follow up (month)	4.50 (2.25, 6.50)	4.00 (2.00, 7.00)	0.988

BCVA, best-corrected visual acuity; HCY, homocystinuria; LogMAR, logarithm of the minimal angle of resolution; IOP, intraocular pressure; MCTR-IOL, transscleral-fixated modified capsular tension ring and in-the-bag intraocular lens implantation. MFS, Marfan syndrome; MSP, microspherophakia. SCSF-IOL, supra-capsular and scleral-fixated intraocular lens implantation.

[a]Normally distributed data are shown in the mean ± standard deviation, while skewed data are shown in median (interquartile).

Figure 2, and the characteristics of the patients in the two groups are shown in **Table 1**. The demographic parameters, including sex, clinical diagnosis, age at surgery, preoperative BCVA, and prevalence of cataract and glaucoma, were not significantly different between the two groups.

Postoperative Surgical Outcomes

The patients were followed up for a similar duration in the two groups (**Table 1**). The patient's BCVA was evaluated at the last follow-up. Most of the eyes showed improved BCVA, and the difference was significant in both the SCSF-IOL group (paired t test, $P < 0.001$) and the MCTR-IOL group (paired t test, $P < 0.001$) (**Figure 3A**). The BCVA (LogMAR) at last follow-up was 0.13 (IQ: 0.02, 0.28) in the SCSF-IOL group and 0.15 (IQ: 0.10, 0.46) in the MCTR-IOL group, and the difference between the two groups was insignificant (Mann–Whitney test, $P = 0.326$) (**Figure 3B**). Both of the procedures didn't lower the IOP (SCSF group, paired Wilcoxon test, $P = 0.196$; MCTR group, paired Student's t-test, $P = 0.824$) and the postoperative IOP is similar between the two groups (Mann–Whitney test, $P = 0.755$) (**Figure 3C**). No secondary glaucoma was observed after the surgery. The Ocular aberrations were evaluated to indirectly compare the severity of IOL tilt between the two groups. The tilt (Mann–Whitney test, $P = 0.216$), coma (Mann–Whitney test, $P = 0.151$), and trefoil (Mann–Whitney test, $P = 0.264$) were not significantly different between the two groups (**Figure 3D** and **Supplementary Table 1**).

Postoperative Capsule Changes and Complications

In the SCSF-IOL group, the preserved capsule was clear and flat 1 week postoperatively (**Figure 4A**) and began shrinking 1 month after surgery (**Figure 4B**), and prophylactic laser capsulotomy was applied to clear the visual axis (**Figure 4C**). The position of the posterior capsulorhexis opening can be seen to be steady in some patients on a 1-year follow-up (**Figures 4D–F**). Two eyes (10.00%) were laser-treated twice to achieve a satisfying posterior capsulorhexis opening, all of whom were under 8 years old. For two young patients who had undergone regional posterior capsulotomy and limited anterior vitrectomy during the operation, the capsule opening remained centered with minimal contraction, and no further laser treatment was required (**Figures 4G–I**). One eye (5.00%) had an unexpectedly decentered capsule opening after laser treatment (**Figures 4J–L**). In the MCTR-IOL group, significant visual posterior capsular opacification (PCO) developed postoperatively in six eyes (35.29%), which were treated by Nd:YAG laser capsulotomy. Excepting transient visual complaints of floating material from several patients, no other complications were recorded after laser treatment in both groups. Two eyes (10.00%) in the SCSF-IOL group and 4 eyes (23.53%) in the MCTR group were

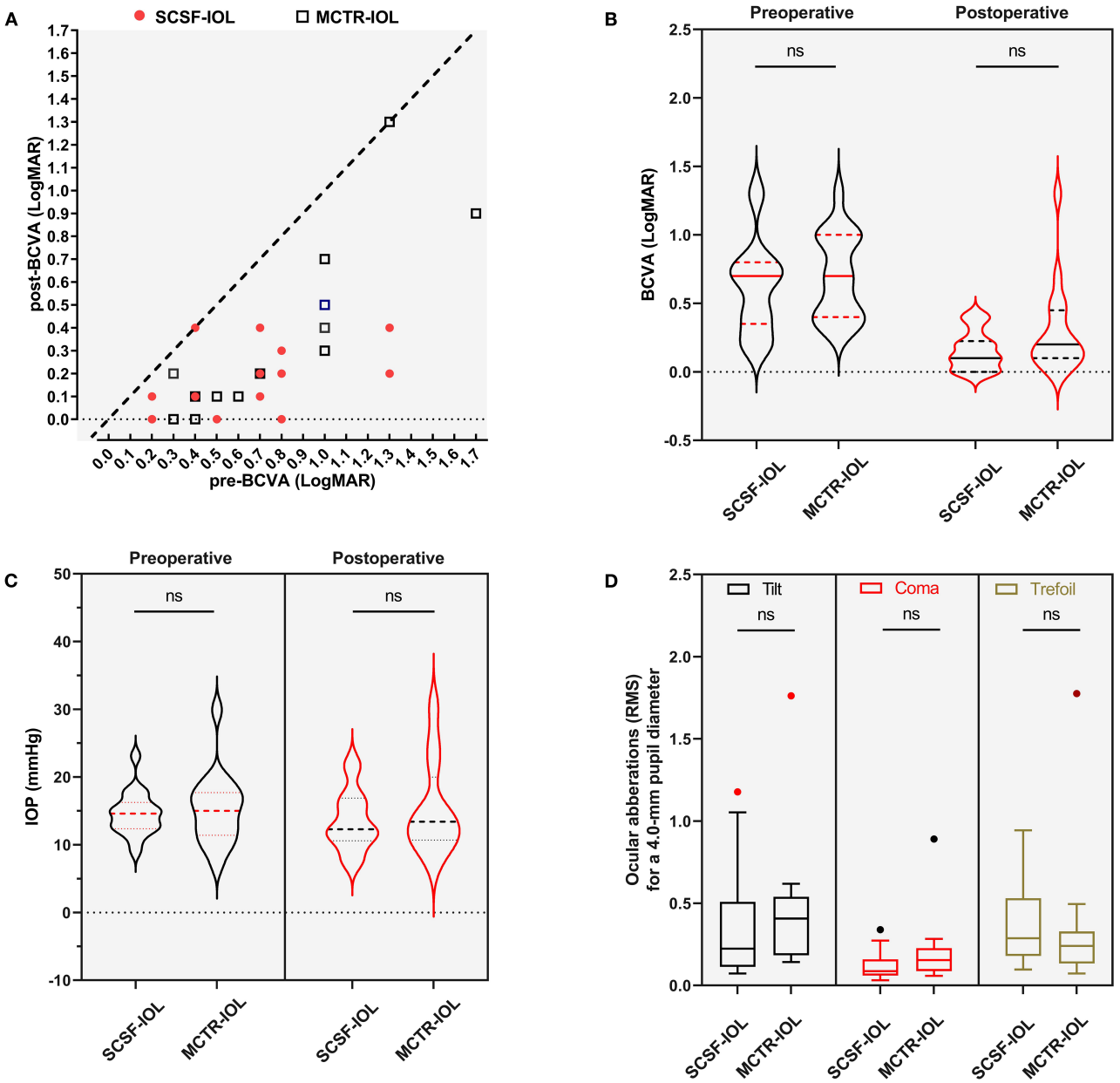

FIGURE 3 | Comparison of surgical outcomes of SCSF-IOL and MCTR-IOL in eyes with MSP. **(A)** Scatterplot of preoperative and postoperative BCVA on final follow-up in the SCSF-IOL (red dots) and MCTR-IOL (black square) groups. **(B)** Nested violin graph of preoperative and postoperative BCVA on final follow-up in the SCSF-IOL and MCTR-IOL groups. The medians are shown in solid lines, and the interquartiles are presented as dashed lines. **(C)** Nested violin graph of preoperative and postoperative IOP on final follow-up in the SCSF-IOL and MCTR-IOL groups. The medians are shown in solid lines, and the interquartiles are presented as dashed lines. **(D)** Comparison of postoperative ocular aberration (tilt, coma, and trefoil) between SCSF-IOL and MCTR-IOL groups. BCVA, best-corrected visual acuity; IOP, intraocular pressure; SCSF-IOL, supra-capsular and scleral-fixated intraocular lens implantation; LogMAR, logarithm of the minimal angle of resolution; MCTR-IOL, transscleral-fixated modified capsular tension ring and in-the-bag intraocular lens implantation. RMS, root mean square.

diagnosed with glaucoma before surgery. All cases demanded anti-glaucoma eye drops postoperatively but in a less intensive manner. No secondary glaucoma was observed in either group. No incidences of suture exposure, IOL dislocation, cystoid macular edema, or retinal detachment were recorded in either group.

DISCUSSION

The high risk of lenticular ametropia and complications secondary to lens dislocation threaten the long-term visual prognosis of patients with MSP. Early surgical intervention is recommended, but lens extraction plus IOL implantation

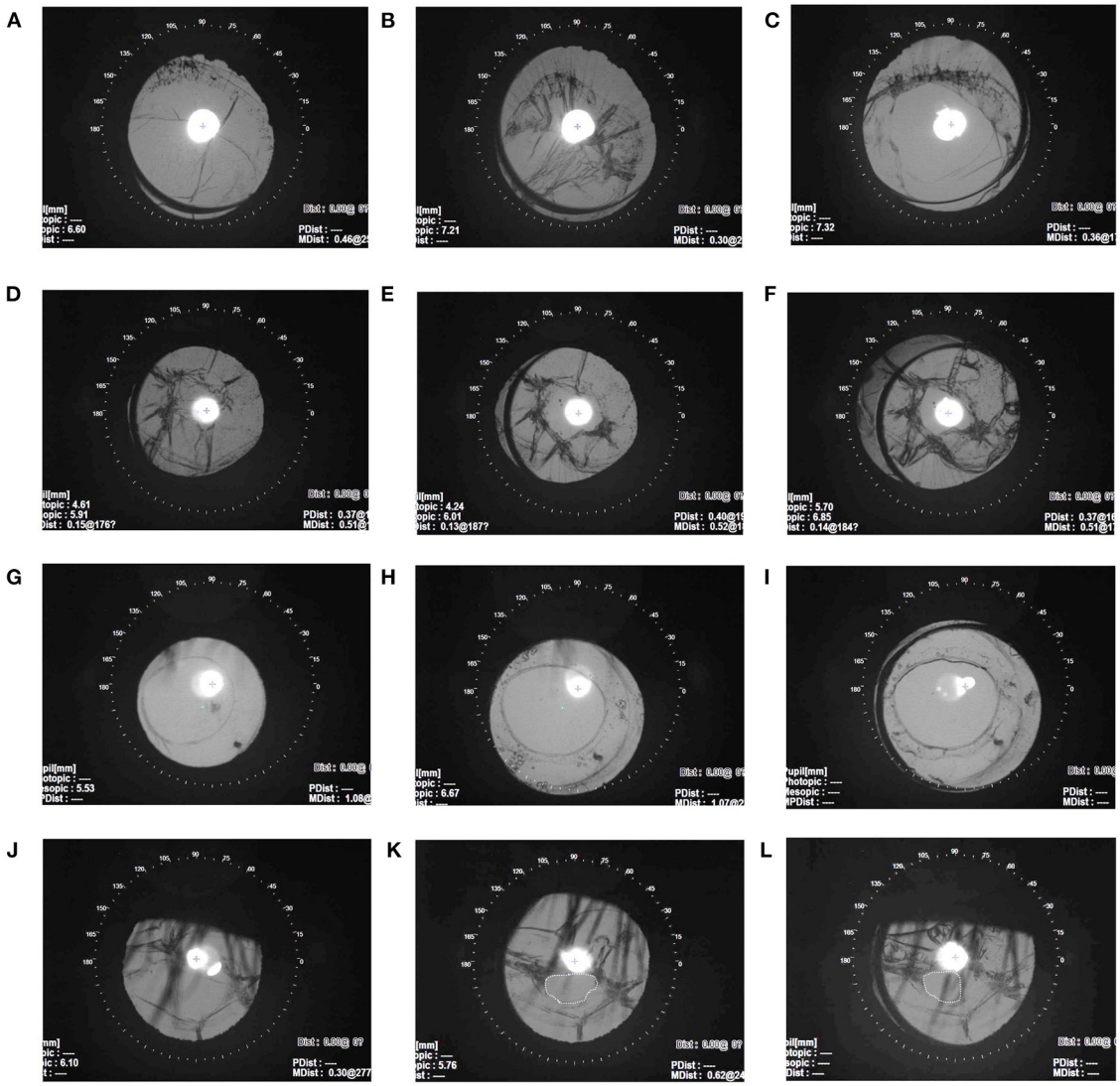

FIGURE 4 | Postoperative capsule change in the SCSF-IOL group. **(A–C)** The retro illumination images show residual capsule postoperative changes in the same MSP eye. The capsule was clear and flat 1 week after surgery **(A)** and contracted 1-month postoperatively **(B)**. After laser treatment for 1 month, the contraction was ameliorated, and the visual axis was clear **(C)**. **(D–F)** Capsule changes in the same MSP eye 1 day before Nd:YAG laser capsulotomy **(D)** and 1 month after laser treatment **(E)**. The opening remained centered, and the BCVA achieved 0.0 LogMAR at 1-year follow-up **(F)**. **(G–I)** A 5-year-old boy with MSP underwent regional posterior capsulotomy and limited anterior vitrectomy during the surgery. The capsule remained stable at the 1-week **(G)**, 6-month **(H)**, and 9-month **(I)** follow-up visits. **(J–L)** A 12-year-old girl with MSP had an unexpected decentered posterior capsulorhexis opening (dashed circle). The retro illumination images show the capsule before laser treatment **(J)**. The posterior capsule opening was decentered 5 months after laser capsulotomy **(K)** and 1 year after surgery **(L)**. The BCVA was 0.4 LogMAR at 1-year follow-up. BCVA, best-corrected visual acuity; SCSF-IOL, supra-capsular and scleral-fixated intraocular lens implantation; LogMAR, logarithm of the minimal angle of resolution; MSP, microspherophakia.

is challenged by the combined effects of insufficient zonules and undersized capsules. Currently, we are lacking a gold standard treatment for MSP patients. In this study, we demonstrated a novel and minimally invasive procedure, SCSF-IOL, which involves suturing the IOL through the sulcus without complete capsulotomy or vitrectomy. The SCSF-IOL procedure resulted in significant visual improvements, fine IOL stability, and a tolerant range of complications. Though the results show insignificant difference when compared to that of the MCTR-IOL group, we proposed that the SCSF-IOL procedure is simple and practicable for the surgeons familiar with anterior approaches.

Various approaches are available for the surgical removal of a dislocated lens. In the 1970s, intracapsular or extracapsular removal had a high incidence of vitreous loss and retinal detachment in eyes with ectopia lentis (23, 24). With the development of medical instruments, phacoemulsification has gained popularity as a technique for removing a dislocated lens, but it was considered difficult to use in the eyes of MSP, probably because of the severe loss of capsular support

(25). Thus, surgeons have tended to not save the capsular bag and perform capsulotomy and vitrectomy. However, the preservation of the capsular bag and residual zonules is worthy, as this leaves the posterior segments intact, which minimizes the risk of vitreoretinal complications, such as retinal detachment, vitreous prolapse, suprachoroidal, and vitreous hemorrhage. The incidence of retinal detachment of scleral fixated IOL after capsulotomy and anterior vitrectomy was relatively high (4.1–17.2%) (18, 26–29), but it was less common in capsule-reserved procedures such as capsular tension ring (CTR), capsular tension segment (CTS), and MCTR (0.00–2.40%) (30–32). Meanwhile, the preserved capsular bag and intact anterior vitreous body were likely to provide additional support to secure the position of IOL and thus reduce the possibility of the IOL falling into the vitreous body (33, 34). Thus, it is reasonable that no retinal detachment nor IOL dislocation was observed in this study and the tilt of IOLs was comparable in both groups. One published study reported the application of a similar capsule-reserved approach in MSP (35). The surgeon persevered the anterior capsule leaves and incarcerated them with the optic region of the sulcus-implanted IOL without suturing. However, we postulated that suturing of the IOL is essential in eyes with MSP, considering the limited support provided by the residual capsule, especially when the bag has not undergone fibrosis or zonule weakness becomes progressive.

In addition to lens removal, the other issue is how to fix the IOL properly in the setting of insufficient capsular support. The success of in-the-bag IOL implantation stabilized by a CTR has been reported for cases of MSP (36). With the aid of capsular hooks, the CTR can be delivered uneventfully in the small and unset capsular bag and is well-tolerated. However, a sutureless CTR might not be stable in MSP, in which the zonular weakness covers 360-degrees and is very likely to be progressive. Thus, in several cases, CTS together with CTR was implemented and sutured to the scleral (37, 38), which exerted almost the same effect as MCTR. Although MCTR has been widely used in eyes of ectopia lentis patients, the application of MCTR in MSP has been reported in a limited number of studies. One case study reported using single-eyelet MCTR together with CTS to achieve two-point scleral suturing in one eye of MSP (39). The authors did not employ two-eyelet MCTR, as they thought this technique was difficult and less repeatable (39). We agreed with the perspective that it is technically demanding to implant the standard size MCTR in the already small and lax bag. The tearing of capsulorhexis may happen during the MCTR or IOL implantation and the surgeon has to perform the capsulotomy and deal with the prolapsed vitreous. Our study showed similar visual outcomes in MSP patients in both the SCSF-IOL and MCTR-IOL groups. However, the SCSF-IOL procedure is relatively simple. Another relatively large case series also reported the use of MCTR in three eyes of MSP with good postoperative stability; however, the author still favored the anterior chamber IOL due to its easy availability and affordability (12). In our opinion, the most common complication is bullous keratopathy when it comes to the anterior chamber IOLs, and some less common but potentially devastating complications should be considered, such as macular edema, secondary glaucoma, and IOL dislocation (40). A larger corneal incision was also required for the anterior chamber IOL implantation compared to that of this study (41). Hence, we recommended the use of posterior chamber IOL and the pre-loaded system. Scleral fixated IOLs were associated with conjunctival erosion (42). However, using the knotless Z-suture technique, the complications related to a scleral flap and exposed knots are becoming less common. Furthermore, the knotless and double-strand 9-0 polypropylene may also contribute to the stability of the fixation.

Capsule opacification and contraction are almost inevitable with the SCSF-IOL procedure due to the preservation of the capsular bag without contact with the optic region of the IOL. Therefore, Nd: YAG laser capsulotomy is routinely prescribed to prevent the contraction or clouding of the capsule in the visual axis 1-month after the SCSF-IOL procedure, and as early as 1-week for young patients. Though some children underwent repeated laser capsulotomy, satisfying laser capsulorhexis was achieved in most eyes. The Nd: YAG laser capsulotomy was proved to be both effective and safe in young patients (43), however, considering the risk of poor cooperation of some young patients, regional capsulotomy and limited vitrectomy were applied in the primary surgery. One eye, unfortunately, had a small and decentered opening, probably due to the asymmetric weakness of the zonules or contraction of the fibrotic capsule. Therefore, we propose that the eyes of ectopia lentis without MSP or MSP complicated by severe lateral dislocation may not benefit from the SCSF-IOL procedure. The asymmetric force from the residual zonules is likely to make the position of the capsular bag unpredictable, and visual acuity could be compromised once the equatorial capsule blocks the visual axis, which can be refractory to the laser capsulotomy.

Glaucoma is another concern in eyes of MSP, but the incidence of glaucoma before the surgery was lower than that in the existing literature (4, 44). This is probably because the enrolled patients were relatively young and their peripheral anterior synechiae had not yet developed. Although lens extraction plus IOL implantation could ameliorate the crowding of the anterior chamber, some patients still need adjunctive medication to control the IOP. This finding is consistent with previous studies that found anti-glaucoma medicine is necessary for some patients with MSP despite lens surgery (36, 44). In addition, we did not exclude the possibility that angle dysplasia coexisted with MSP in some individuals (4).

The drawbacks of the study included its retrospective design, limited duration of follow-up, and relatively small cohort size. However, considering the rarity of this disease, this is one of the largest studies that has focused on the surgical management of MSP. The long-term curative effects and late-onset complications of the two capsule-reserved approaches remain to be recorded during further follow-up. Despite the above limitations, we feel that our investigation may contribute to the development of appropriate surgical options in the setting of MSP.

In conclusion, the current study, involving a relatively large number of consecutive patients with MSP, reported the efficacy of a novel technique, SCSF-IOL, which removes lens material by phacoemulsification and preserves the residual capsule in

a relatively simple way. This procedure resulted in a good prognosis and limited complications, comparable to those achieved by MCTR-IOL. We consider the SCSF-IOL procedure to be a feasible option for the treatment of MSP, especially for anterior surgeons.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

All procedures performed on human participants followed the 1964 Declaration of Helsinki and its later amendments after receiving proper approval from the Human Research Ethics Committee of the Eye & ENT Hospital of Fudan University (no. 2020126-1). Informed consent was obtained from all candidates and the guardians of those under 18. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Z-XC and Z-NZ conceived and designed the study. YS, W-NJ, J-LZ, J-HC, T-HC, and L-NL collected the clinical samples. Y-XJ performed clinical examinations of patients and clinical interpretation. Z-XC and Z-NZ drafted and revised the manuscript. Y-XJ supervised the whole project and provided critical reviews. All authors read and approved the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.869539/full#supplementary-material

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Pars Plana Ahmed Valve Implantation for Vitrectomized Eyes With Refractory Glaucoma

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This study aimed to analyze the surgical outcomes of pars plana Ahmed valve implantation in vitrectomized eyes with refractory glaucoma. We performed a retrospective case review of consecutive patients with refractory glaucoma after undergoing pars plana vitrectomy who underwent pars plana Ahmed valve implantation between July 2019 and December 2020 at the glaucoma unit of the Affiliated Changshu Hospital of Xuzhou Medical University (Changshu, China). All the patients were followed up for ≥12 months postoperatively. We recorded pre- to postoperative changes in best-corrected visual acuity (BCVA), intraocular pressure (IOP), number of anti-glaucoma medication, corneal endothelial count, and surgical complications, if any. There was a significant improvement in the median BCVA from 2.30 (0.87, 2.30) logMAR preoperatively to 1.70 (0.70, 2.30) logMAR at discharge and 1.0 (0.52, 1.85) at final examination ($p = 0.011$, $p = 0.001$). Compared with the preoperative IOP level, there was a significant decrease in the postoperative IOP at each postoperative time point ($p < 0.001$). There was a significant reduction in the median number of anti-glaucoma drugs (including postoperative ocular massage), from 3.00 (2.00, 3.00) preoperatively to 0.00 (0.00, 1.00) at the last follow-up postoperative examination ($p < 0.001$). A 29-year-old woman with proliferative diabetic retinopathy who underwent surgical treatment at 5 months postoperatively for fibrous wrapping formed around the plate of the Ahmed valve showed an IOP of 14 mmHg at the last follow-up. Our findings indicated that pars plana Ahmed valve implantation can be safely performed for managing vitrectomized eyes with refractory glaucoma.

Keywords: Ahmed valve implantation, refractory glaucoma, surgery, ophthalmology, vitrectomy

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INTRODUCTION

Refractory glaucoma, including neovascular glaucoma (NVG), aphakic or intraocular lens eye glaucoma, failed filtering surgery-induced glaucoma, congenital juvenile glaucoma, glaucoma combined with uveitis, traumatic glaucoma, and glaucoma after vitrectomy, remains an issue in the field of glaucoma treatment (1). The glaucoma drainage implant (GDI) is an external filtering

Abbreviations: AGV, Ahmed glaucoma valve; BCVA, best-corrected visual acuity; GDI, glaucoma drainage implant; IOP, intraocular pressure; NVG, neovascular glaucoma; PPV, pars plana vitrectomy; SD, standard deviation.

anti-glaucoma surgical device that is especially suitable for refractory glaucoma (2). However, implanting this device may involve several complications (3). GDIs can be implanted in the anterior chamber, ciliary sulcus, or vitreous cavity. In some cases of corneal disease, iris abnormalities, or peripheral anterior synechia, the tube cannot be placed in the anterior chamber (4); tube implantation into the vitreous cavity is a viable option for resolving refractory tube-related anterior complications (5).

The Ahmed glaucoma valve (AGV) was introduced in 1993 as the first GDI with a one-way valve mechanism that allows immediate postoperative flow and prevents ocular hypotension (6). Therefore, an AGV may be preferred for patients at risk of low intraocular pressure (IOP), including those who have undergone vitrectomy, and may be effective for treating vitrectomized eyes with refractory glaucoma (7). The AGV implantation technique takes advantage of the relatively wide and easily separated posterior superior scleral space. Specifically, a large AGV drainage tray is implanted into the posterior superior scleral space (mostly between the external rectus and superior rectus sheath) to reduce fascial interference and form a permanent functional filtering area around the drainage tray to allow sufficient IOP control (8).

Moreover, AGV implantation is the only restricted GDI approved by the National Medical Products Administration for listing in China (8). This study aimed to analyze the surgical outcomes of pars plana Ahmed valve implantation in vitrectomized eyes with refractory glaucoma in patients from the Changshu city of Jiangsu province, China.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of Changshu Hospital of Xuzhou Medical University (Changshu, China; approval number: 2016034). It was conducted in accordance with the Declaration of Helsinki. Informed consent for surgery and study participation obtained from all the patients before treatment was part of their medical records.

Patients

This retrospective observational case series included consecutive patients with refractory glaucoma after pars plana vitrectomy (PPV) who underwent pars plana Ahmed valve implantation between July 2019 and December 2020 at the glaucoma unit of the Affiliated Changshu Hospital of Xuzhou Medical University (Changshu, China). The inclusion criteria were as follows: (1) a diagnosis of glaucoma, with IOP not controlled by confirmed medical treatment (IOP $\geq$ 30 mmHg despite maximal tolerable medication use); (2) having undergone total vitrectomy, with the vitreous cavity being filled with water or gas; and (3) the AGV tube was inserted into the vitreous cavity through the pars plana. Bilateral eye surgery was performed, in which case we recorded the eye in which the AGV was initially implanted. The exclusion criteria were loss to follow-up or a follow-up period <12 months.

Assessments

We obtained ophthalmic examination results from inpatient and outpatient medical records and additionally recorded the history of glaucoma.

All the patients underwent the following preoperative procedures: (1) slit-lamp microscopy; (2) fundus examination; (3) B ultrasound (Quantel Medical Aviso); (4) ultrasonic biological microscopy (Aviso, Quantel Medical, France); (5) Humphrey field of vision assessment (Carl Zeiss, Germany); (6) retinal nerve fiber layer thickness (Cirrus HD-OCT5000, Carl Zeiss, Germany); and (7) corneal endothelioscopy (SP-3000P, Topcon, Japan).

Additionally, we recorded (1) the best-corrected visual acuity (BCVA); (2) IOP; (3) corneal endothelial count; (4) intraoperative complications; (5) postoperative complications; (6) time of occurrence; and (7) the type and quantity of anti-glaucoma medication used pre- and postoperatively. Furthermore, eye massage was included as an anti-glaucoma medication.

Best-corrected visual acuity was recorded in decimal form and converted to logMAR for statistical analysis (logMAR = log [1/VA]) (9). IOP was measured using Goldmann applanation tonometry. All patients with increased IOP after AGV implantation underwent treatment, including eye massage and anti-glaucoma medication, and anti-glaucoma surgery would be performed as required.

Surgical Procedures

All surgeries were performed by an experienced ophthalmologist (ZH) using AGV Model FP7 (New World Medical Inc., Rancho Cucamonga, CA, United States). All patients underwent surgery under peribulbar anesthesia. The conjunctival flap was made based on the conjunctival fornix. We created a rectangular limbal-based half-thickness scleral flap. After the AGV was primed, it was placed 10 mm behind the corneal limbus in the superotemporal quadrant between the superior and lateral rectus muscles. The AGV plate was secured to the sclera using a 5–0 braided polyester suture. The vitreous cavity was accessed with a 22-gauge needle at 3.5–4 mm behind the corneal limbus under the scleral flap. The tube length was trimmed, and the tube was placed in the vitreous cavity 3–4 mm through the needle track. The tube bevel was directed toward the vitreous cavity. The tube and its entry site were covered using an autologous scleral flap. The scleral flap was reset, and both ends were sutured using 8–0 Vicryl sutures without tension. The drainage tube after the scleral tunnel was fixed on the scleral surface using 8–0 Vicryl sutures. The conjunctiva was sutured using 8–0 Vicryl sutures (**Figure 1**).

Statistical Analysis

Data are expressed as mean $\pm$ standard deviation (SD), median (P25, P75), or number (percentage;%). For quantitative variables, we used histograms, box plots, and Shapiro–Wilk tests to evaluate the distribution normality. Changes in variables between time points were analyzed using paired sample *t*-test for normally distributed variables or the related samples Wilcoxon signed-rank test and Friedman's two-way analysis of variance for non-normally distributed variables. The relationship between

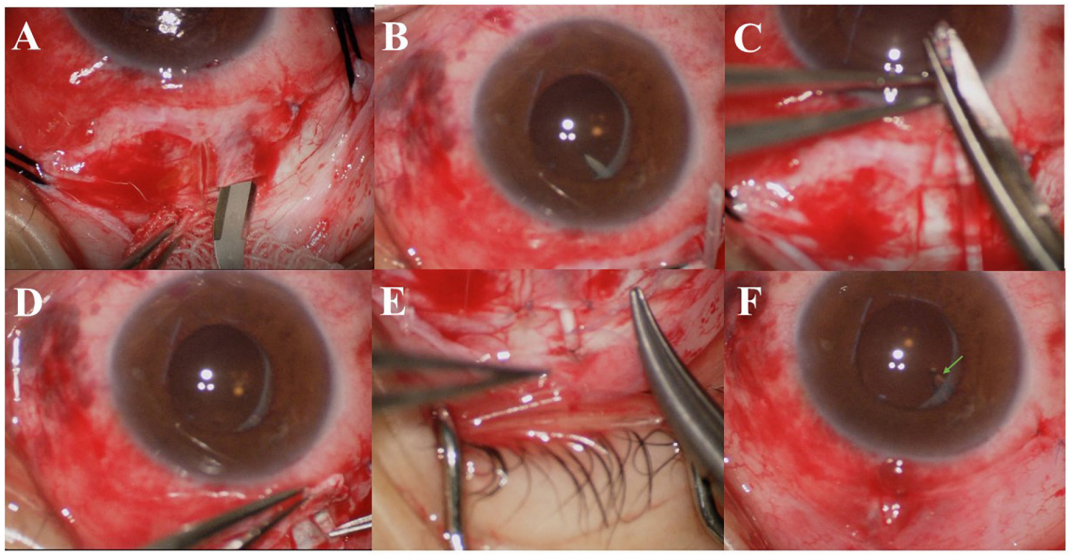

FIGURE 1 | (A) A rectangular, limbal-based half-thickness scleral flap was created. **(B)** The vitreous cavity was accessed using a 22-gauge needle at 3.5–4 mm behind the corneal limbus under the scleral flap. **(C)** The tube length was trimmed. **(D)** The tube was placed into the vitreous cavity at 3–4 mm through the needle track, and the tube inside the vitreous chamber can be seen under the dilated pupil. **(E)** The drainage tube after the scleral tunnel was fixed on the scleral surface using 8–0 Vicryl sutures. **(F)** The conjunctiva was sutured using 8–0 Vicryl sutures, and the tube (arrow) inside the vitreous chamber can be seen under the dilated pupil.

categorical variables was analyzed using the chi-squared test. We performed a Kaplan–Meier survival analysis of the operation success rate (criteria for success: 8 mm Hg $\leq$ postoperative IOP $\leq$ 21 mm Hg, without drug treatment). Log-rank test was used to compare the differences among groups in the distribution of survival time. All statistical analyses were performed using SPSS (version 19.0; SPSS Inc., Chicago, IL, United States) and GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, United States). Statistical analyses were performed with a 5% significance level; moreover, statistical significance was set at a two-sided p-value < 0.05.

RESULTS

Baseline Characteristics

We included 21 eyes from 21 patients with vitrectomized refractory glaucoma. Among them, there were 11 cases (11 eyes) of NVG. The mean age was 61.95 $\pm$ 16.42 years, and 11 (52.4%) patients were female. There were 10 right eyes. Furthermore, there were 6.98 $\pm$ 11.20 months from the last surgery until the pars plana Ahmed valve implantation surgery (**Table 1**).

Best-Corrected Visual Acuity

There was a significant improvement in the BCVA from a median of 2.30 (0.87, 2.30) logMAR preoperatively to 1.70 (0.70, 2.30) logMAR at discharge and 1.0 (0.52, 1.85) at the final examination (p = 0.011 and p = 0.001, respectively, **Table 2**). Overall, there was a correlation between BCVA at last follow-up and at baseline (Spearman correlation; $r = 0.729$, $p < 0.001$). Preoperative BCVA, BCVA at discharge, and BCVA at last follow-up of patients without NVG were better than those of patients with NVG, and the differences were statistically significant (p = 0.007, p = 0.005, and p = 0.018, respectively, **Table 3**). However, stratum analysis showed no correlation between visual acuity at last follow-up and at baseline in patients with NVG (r = 0.235, p = 0.487); furthermore, there was a correlation between visual acuity at last follow-up and at baseline in patients without NVG (r = 0.708, p = 0.022).

Intraocular Pressure

The median IOP was 45.00 (32.00, 60.00) mmHg preoperatively and 15.00 (13.50, 17.50) mmHg at 1 day postoperatively. The IOP at 1 day postoperatively was lower than the preoperative IOP in all eyes. The IOP was 15.00 (13.00, 20.00) mmHg at 7 days postoperatively. The IOP at 7 days postoperatively was higher than the preoperative IOP in one eye. The median IOP at 1 month postoperatively was 15.00 (13.50, 18.00) mmHg, which was higher than the preoperative IOP in one eye (aforementioned patient). The IOP was 16.00 (14.00, 20.00) mmHg at 3 months postoperatively, 16.00 (13.00, 19.00) mmHg at 6 months postoperatively, and 16.00 (14.00, 19.00) mmHg at the final examination. Compared with the preoperative IOP, the postoperative IOP significantly decreased at each postoperative time point ($p < 0.001$; **Figure 2** and **Table 2**). However, there were no significant differences in the IOP values among the postoperative time points (p = 0.616). There was no significant difference in the IOP between patients with and without NVG at each time point (**Table 3**).

Figure 3 shows the Kaplan–Meier survival curve. The total success rates were 85.71% at 3 months, 76.19% at 6 months, and 71.43% at 1 year postoperatively. There were no significant

TABLE 1 | Baseline characteristics of patients before pars plana Ahmed valve implantation surgery.

Parameters	Total	NVG	Non-NVG	*p*-value
Number of eyes	21	11	10	
Right-side N (%)	10(47.6)	5(45.5)	5(50)	
Female, eyes N (%)	11(52.4)	7(63.6)	4(40)	
Age (years) Mean ± SD	61.95 ± 16.42	56.55 ± 20.16	67.90 ± 8.53	0.168
Glaucoma type N (%)				
Neovascular (in the angle-closure stage)	11(52.4)	11(100)		
Open angle	3(14.3)		3(30)	
Traumatic	3(14.3)		3(30)	
Malignant	2(9.5)		2(20)	
Steroid response	2(9.5)		2(20)	
Indication of vitrectomy N (%)				
RVO	4(19)	4(36.4)		
PDR	7(33.3)	7(63.6)		
Macular disease	5(23.8)		5(50)	
Trauma	3(14.3)		3(30)	
Malignant glaucoma	2(9.5)		2(20)	
Interval between PPV and AGV (months) Mean ± SD	6.98 ± 11.20	4.10 ± 3.84	10.15 ± 15.54	0.437
Follow-up period (months) Mean ± SD	17.67 ± 5.33	18.83 ± 5.64	16.50 ± 4.99	0.321
Pre-AGV IOP (mmHg) Mean ± SD	44.76 ± 12.63	44.64 ± 12.53	44.90 ± 13.43	0.858
Pre-AGV BCVA (logMAR) Mean ± SD	1.75 ± 0.79	2.15 ± 0.56	1.31 ± 0.78	0.007
Pre-AGV number of medication Mean ± SD	2.71 ± 0.46	2.73 ± 0.47	2.70 ± 0.48	0.893

NVG, neovascular glaucoma; AGV, Ahmed glaucoma valve; BCVA, best-corrected visual acuity; IOP, intraocular pressure; PPV, pars plana vitrectomy; SD, standard deviation; RVO, retinal vein occlusion; PDR, proliferative diabetic retinopathy.

TABLE 2 | Intraocular pressure (IOP), best-corrected visual acuity (BCVA), and number of anti-glaucoma drugs at different time points for patients who underwent pars plana Ahmed valve implantation surgery.

	Mean ± SD	Median (P25, P75)	Median difference (95% CI)	*P*-value
IOP (mmHg) (*n* = 21)				
Pre-AGV	44.76 ± 12.64	45.00 (32.00, 60.00)		
1 day	16.81 ± 5.97	15.00 (13.50, 17.50)	28.50 (22.00, 34.00)	<0.001
1 week	17.10 ± 6.39	15.00 (13.00, 20.00)	29.00 (23.00, 34.50)	<0.001
1 month	15.81 ± 4.30	15.00 (13.50, 18.00)	29.50 (23.00, 35.00)	<0.001
3 months	17.09 ± 4.48	16.00 (14.00, 20.00)	28.00 (22.00, 34.50)	<0.001
6 months	16.38 ± 3.97	16.00 (13.00, 19.00)	28.00 (22.50, 34.50)	<0.001
Last follow-up	17.06 ± 3.43	16.00 (14.00, 19.00)	27.50 (22.50, 33.50)	<0.001
BCVA (logMAR) (*n* = 21)				
Pre-AGV	1.75 ± 0.79	2.30 (0.87, 2.30)		
At discharge	1.55 ± 0.82	1.70 (0.70, 2.30)	0.11(0.00, 0.30)	0.011
Last follow-up	1.29 ± 0.80	1.00 (0.52, 1.85)	0.41 (0.15, 0.73)	0.001
Number of anti-glaucoma drugs (*n* = 21)				
Pre-AGV	2.71 ± 0.46	3.00 (2.00, 3.00)		
Last follow-up	0.48 ± 0.60	0.00 (0.00, 1.00)	2.50 (2.00, 2.50)	<0.001
Corneal endothelial count (cells/mm^2) (*n* = 19)				
1 week	1668.35 ± 376.32	1760.70 (1394.00,1885.60)		
6 months	1632.75 ± 369.67	1691.50 (1379.80,1895.20)	24.48 (0.15, 65.85)	0.053

AGV, Ahmed glaucoma valve; BCVA, best-corrected visual acuity; IOP, intraocular pressure; SD, standard deviation; CI, confidence interval.

differences in the survival time distributions between patients with and without NVG ($p = 0.691$).

Number of Anti-glaucoma Drugs

At 1 year postoperatively, the IOP was maintained below 20 and 15 mmHg in 18 and 10 patients, respectively, without any anti-glaucoma drugs. There was a significant reduction in the use of anti-glaucoma drugs (including postoperative ocular massage) from a median of 3.00 (2.00, 3.00) preoperatively to 0.00 (0.00, 1.00) at the last follow-up ($p < 0.001$, **Table 2**). There were no statistically significant differences in the number of anti-glaucoma drugs used preoperatively and at the last follow-up between patients with and without NVG ($p = 0.893$ and $p = 0.443$, respectively, **Table 3**).

TABLE 3 | Comparison of IOP, BCVA, and number of anti-glaucoma drugs at different time points between NVG and non-NVG patients.

	NVG (n = 11)	Non-NVG (n = 10)	P-value
IOP (mmHg) Mean ± SD/Median (P25, P75)			
Pre-AGV	44.64 ± 12.53/45.00 (34.00, 60.00)	44.90 ± 13.43/47.50 (29.50, 60.00)	0.858
1 day	18.45 ± 7.81/16.00 (14.00, 22.00)	15.00 ± 2.11/15.00 (13.00, 17.25)	0.337
1 week	15.36 ± 4.39/13.00 (12.00, 20.00)	19.00 ± 7.85/15.50 (14.00, 21.25)	0.204
1 month	15.27 ± 4.03/16.00 (10.00, 20.00)	16.40 ± 4.72/15.00 (13.75, 17.25)	0.972
3 months	16.55 ± 3.39/16.00 (14.00, 20.00)	17.70 ± 5.58/16.00 (14.25, 24.25)	0.723
6 months	16.73 ± 3.44/17.00 (13.00, 19.00)	16.00 ± 4.64/15.00 (12.75, 17.50)	0.458
Last follow-up	17.64 ± 3.35/19.00 (14.00, 20.00)	16.50 ± 3.60/14.00 (15.00, 19.00)	0.374
BCVA (logMAR) Mean ± SD/Median (P25, P75)			
Pre-AGV	2.15 ± 0.56/2.30 (1.85, 2.60)	1.31 ± 0.78/0.87 (1.85, 2.30)	0.007
At discharge	2.01 ± 0.59/2.30 (1.70, 2.60)	1.04 ± 0.76/0.70 (0.52, 1.85)	0.005
Last follow-up	1.66 ± 0.65/1.70 (1.00, 2.30)	0.87 ± 0.77/0.52 (0.30, 1.74)	0.018
Number of anti-glaucoma drugs Mean ± SD/Median (P25, P75)			
Pre-AGV	2.73 ± 0.47/3.00 (2.00, 3.00)	2.70 ± 0.48/3.00 (2.00, 3.00)	0.893
Last follow-up	0.36 ± 0.51/0.00 (0.00, 1.00)	0.60 ± 0.70/0.50 (0.00, 1.00)	0.443
Corneal endothelial count (cells/mm^2) Mean ± SD/Median (P25, P75)			
1 week	1694.97 ± 360.89/1760.70 (1394.00, 1926.40)	1631.74 ± 418.87/1692.15 (1284.85, 1872.95)	0.680
6 months	1656.34 ± 366.65/1691.50 (1379.80, 1949.60)	1600.34 ± 396.58/1696.35 (1239.25, 1886.40)	0.717

NVG, neovascular glaucoma; AGV, Ahmed glaucoma valve; BCVA, best-corrected visual acuity; IOP, intraocular pressure; SD, standard deviation.

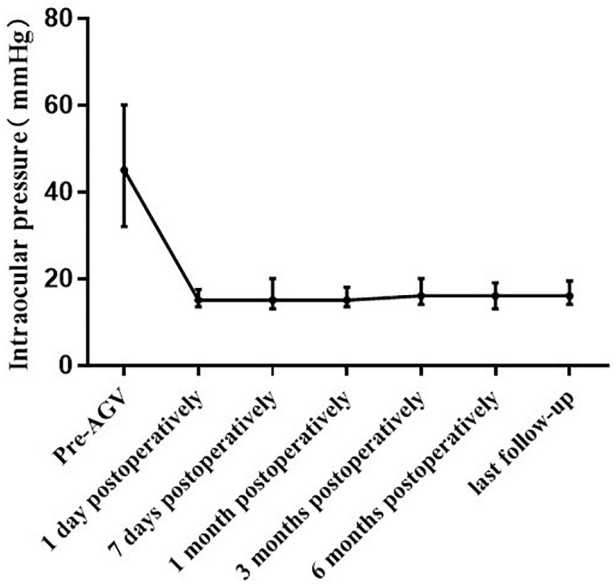

FIGURE 2 | Line chart of the intraocular pressure before and after pars plana Ahmed valve implantation, with postoperative assessments at 1 day, 7 days, 1 month, 3 months, 6 months, and last follow up.

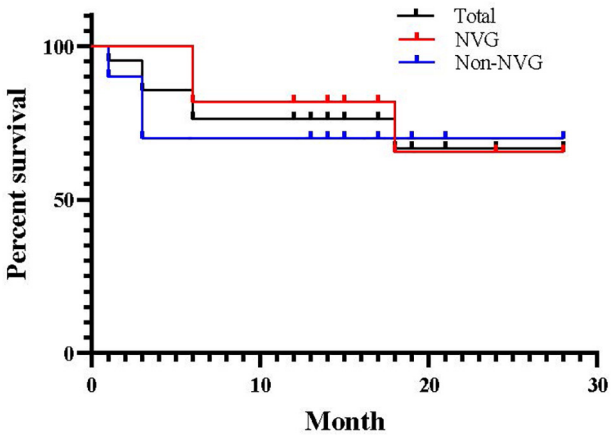

FIGURE 3 | Kaplan–Meier survival curve for success after pars plana Ahmed valve implantation. Success was defined as 8 mmHg ≤ postoperative intraocular pressure ≤ 21 mmHg without medication.

Corneal Endothelial Count

Corneal endothelial counts could not be preoperatively measured in two patients with trauma, two patients with malignant glaucoma, and 11 patients with NVG. Therefore, we measured the corneal endothelium count in all patients at 1 week postoperatively, but the results were still unavailable in two patients with trauma. There was no significant difference in the corneal endothelial count at 6 months postoperatively and 1 week postoperatively (p = 0.334, **Table 2**). There were no statistically significant differences in the corneal endothelial count at 6 months postoperatively and 1 week postoperatively between patients with and without NVG (p = 0.680 and p = 0.717, respectively, **Table 3**).

Complications

A 29-year-old woman with proliferative diabetic retinopathy underwent surgical treatment at 5 months postoperatively for

fibrous wrapping formed around the plate of the AGV, with the IOP at the last follow-up being 14 mmHg. Two patients with trauma underwent intraocular lens suspension at 6 months after Ahmed valve implantation, with stable postoperative ocular condition. Patients with retinal vein occlusion and proliferative diabetic retinopathy continued to receive postoperative anti-vesicular endothelial growth factor injections, as required. None of the patients showed other complications, including corneal endothelial decompensation, drainage tube shift, drainage tube exposure, drainage tube blockage, anterior chamber inflammation, or infectious endophthalmitis, during the follow-up period.

DISCUSSION

This retrospective case review assessed the pars plana Ahmed valve implantation in patients with refractory glaucoma post-vitrectomy from the Changshu city of Jiangsu province, China. Our findings indicated a significant improvement in IOP and medication consumption postoperatively. The BCVA of patients without NVG was better than that of patients with NVG at each time point. Our results suggest that pars plana Ahmed valve implantation is an effective treatment for vitrectomized eyes with refractory glaucoma, including NVG.

There has been considerable progress in PPV for treating posterior segment ocular disease (10). However, glaucoma remains a common complication after vitreoretinal surgery for various reasons. PPV is associated with an increased risk of open-angle glaucoma, and there is a risk of increased IOP after vitreoretinal surgery (11–15). Possible causes include increased oxidative stress in the vitreous cavity caused by post-vitrectomy trabecular injury, trabecular scarring caused by minor injuries during vitrectomy, progression of neovascularization, and the use of silicone oil in vitreoretinal surgery (13, 16, 17). However, the relationship between PPV and open-angle glaucoma remains unclear (18, 19).

Postoperative hypotony is a common complication of AGV implantation in vitrectomized eyes. Possible related factors include aqueous leakage from the drainage tube periphery and valve device destruction upon glaucoma valve implantation. However, after the formation of filtering blebs, most eyes return to normal (6, 8). The absence of early stage postoperative hypotony may be associated with the use of a 22-gauge needle to access the vitreous cavity at 3.5-4 mm behind the corneal limbus under the scleral flap and the use of 8–0 Vicryl sutures to intraoperatively fix the drainage tube on the sclera so that postoperative hypotony caused by leakage from the puncture tunnel into which the tube was inserted was unlikely to occur.

Choroidal detachment is also a common postoperative complication, mainly due to perioperative IOP fluctuations. It is more common in patients with persistent low IOP caused by preoperative hypertension and sudden drop of hypotension, excessive drainage, or puncture tunnel leakage intraoperatively (8). Therefore, intra- and postoperative IOP stabilization need to be emphasized. There was no postoperative hypotony in our cases. As a result, no complications, such as choroidal detachment, occurred postoperatively.

In our study, patients showed mild postoperative anterior chamber inflammatory response, with a stable anterior chamber and no postoperative hypotony and choroidal leakage or detachment. Complete peripheral vitrectomy is essential for the continued success of the AVG implantation procedure to avoid vitreous tube obstruction, which causes failure of IOP control or tearing due to the application of traction to the retina.

A previous study reported that the mean surgical interval was 1.8 $\pm$ 2.3 months and 12.41 $\pm$ 16.2 months in the NVG and non-NVG groups, respectively (6). NVG was found to occur 151 days after PPV, with 56% of the patients requiring surgery (16). Another study reported that the mean interval between PPV and AGV implantation was 7.5 $\pm$ 2.2 months (20). Our patients included both NVG and others; moreover, the overall mean interval between PPV and AGV implantations was 6.98 $\pm$ 11.20 (0.1–52) months, with a mean interval between PPV and AGV implantations of 4.10 $\pm$ 3.84 (0.10–12) months in the NVG group. In the non-NVG group, the mean interval between PPV and AGV implantations was 10.15 $\pm$ 15.54 (0.25–52) months.

Excessive fibrous wrapping of tenon's capsule around the drainage plate is the main reason for surgery failure, which affects filtration function (21). Patients with a high IOP during the early postoperative period were treated using ocular massage, which not only reduces IOP but also facilitates soaking of the fascia tissue by drained aqueous humor to prevent its proliferation. In the early postoperative period, ocular massage is an important measure for effectively preventing the blockage of the drainage tube head. After the function of the AGV is stabilized, intermittent ocular massage can prevent severe obstruction of the lumen caused by the accumulation of metabolic substances in the eye (8). Ocular massage was performed to avoid the drainage implantation site and cornea, as well as to avoid drainage tube displacement caused by direct compression (7). Since the drainage site in our patients was located in the superior temporal quadrant, we recommended that they look above and massage below. In our study, a young female patient with NVG developed a fibrous cyst formed around the plate of the AGV. We excised the outer cyst wall and strengthened postoperative eyeball massage, and the patient's IOP remained stable.

Corneal endothelial decompensation is also a serious complication of AGV implantations. The drainage tube in the anterior chamber is either in contact or proximal with the corneal endothelium; alternatively, it makes contact with the corneal endothelium when postoperatively massaging the eyeball. This causes corneal endothelial damage and functional decompensation. Specifically, the corneal endothelium of patients with a long-term shallow anterior chamber and high IOP is often in poor condition; additionally, these patients are prone to further postoperative damage. The drainage tube was implanted into the vitreous cavity from the pars plana to avoid touching and damaging the cornea. Moreover, stable fixation of the drainage tube is ensured to reduce its displacement when the eyeball is rotated or massaged, which can effectively prevent complications. In our study, the drainage tube was implanted and firmly fixed into the vitreous cavity to avoid possible contact

between the drainage tube and cornea, as well as to reduce disturbance to the anterior chamber caused by foreign bodies and surgery. Additionally, there was no significant difference in the corneal endothelial count preoperatively and at 6 months postoperatively.

In contrast to the thin-walled bleb after trabeculectomy, the bleb over the plate is far from the limbus. Furthermore, it has a thick and fibrous capsule, which could reduce the chances of bleb leaks or bleb-related infections (22). Exposure of drainage tubes can cause severe complications, including low IOP and endophthalmitis, which usually requires surgical repair (23). Pars plana tube implantation avoids the thin limbal region of the conjunctiva and reduces the extraocular tube length, which prevents complications (5). None of our patients showed drainage tube exposure. Furthermore, the tube could only be seen during dilation examination; therefore, it did not affect the patient's appearance.

Additionally, visual acuity is not considered in the success criteria of AGV implantation, since the treatment goal for refractory glaucoma is normalizing the IOP (24, 25). Visual acuity after glaucoma surgery varies according to glaucoma severity, surgical complications, and other factors. During the follow-up period, some of our patients continued anti-vesicular endothelial growth factor therapy and intraocular lens implantation, improving vision at the last follow-up compared with before surgery.

CONCLUSION

The present findings demonstrated the short-term efficacy of pars plana Ahmed valve implantation in vitrectomized eyes with refractory glaucoma. We observed that pars plana Ahmed valve implantation can be safely performed for managing vitrectomized eyes with refractory glaucoma, with low surgical requirements, large allowable space, and few complications. However, further studies are warranted to evaluate the long-term efficacy of the procedure.

Although all our patients showed post-vitrectomy refractory glaucoma, their conditions were heterogenous. Further, this was a retrospective study with a small sample size, no controls, and a short follow-up period. Therefore, there is a need for further studies, preferably randomized controlled trials, with large sample sizes and longer follow-up periods.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Changshu Hospital of Xuzhou Medical University (Changshu, China; approval number: 2016034). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XX, PX, JY, and ZH: conception and design. XX, PX, JY, and YC: data collection and collation. XX and TJ: data analysis and interpretation. XX: manuscript writing. XX and ZH: data interpretation and final review of the manuscript. All authors revised and approved the submitted manuscript.

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Applying Information Gain to Explore Factors Affecting Small-Incision Lenticule Extraction: A Multicenter Retrospective Study

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Purpose: This retrospective study aimed to identify the key factors influencing postoperative refraction after small-incision lenticule extraction (SMILE) using information gain.

Methods: This study comprised 2,350 eyes of 1,200 patients who underwent SMILE using a Visumax 500-kHz femtosecond laser (Carl Zeiss Meditec AG) in three ophthalmic centers: Tianjin Eye Hospital (center A), Jinan Mingshui Eye Hospital (center B), and Qingdao Eye Hospital (center C). Anterior segment features, including corneal curvature and central corneal thickness (CCT), were obtained from Pentacam HR (Oculus, Wetzlar, Germany). Information gain was calculated to analyze the importance of features affecting postoperative refraction.

Results: Preoperative and postoperative mean spherical equivalent (SE) refraction were −5.00 (−6.13, −3.88) D and 0.00 (−0.25, 0.13) D, respectively. None of the patients lost more than two lines of corrected distance visual acuity. The safety index was 1.32 ± 0.24, 1.03 ± 0.08, and 1.13 ± 0.16 in centers A, B, and C, respectively. The efficacy index was 1.31 ± 0.25, 1.02 ± 0.08, and 1.13 ± 0.17 in centers A, B, and C, respectively. At least 95% of the eyes were within ±1.00 D of the attempted correction. Postoperative refraction was related to preoperative spherical diopter refraction ($r = 0.369$, $p < 0.001$), preoperative SE ($r = 0.364$, $p < 0.001$), maximum lenticule thickness ($r = -0.311$, $p < 0.001$), preoperative uncorrected distance visual acuity ($r = 0.164$, $p < 0.001$), residual stromal thickness ($r = 0.139$, $p < 0.001$), preoperative mean anterior corneal curvature ($r = -0.127$, $p < 0.001$), preoperative flattest anterior corneal curvature ($r = -0.122$, $p < 0.001$), nomogram ($r = -0.100$, $p < 0.001$) and preoperative CCT ($r = -0.058$, $p = 0.005$).

Conclusions: SMILE was considered a safe and effective procedure for correcting myopia. Based on information gain, postoperative refraction was influenced by preoperative mean anterior corneal curvature, CCT, refraction, and residual stromal thickness.

Keywords: myopia, small-incision lenticule extraction, contributing factors, information gain, multicenter

INTRODUCTION

Small-incision lenticule extraction (SMILE) is a viable surgical option for the correction of myopia and astigmatism (1). Compared with laser-assisted *in situ* keratomileusis, the SMILE procedure was flapless. Because of no corneal flap, SMILE has the advantages of lower incidence of postoperative dry eye and better stability of corneal biomechanics (2, 3). There is a rising acceptance and recognition of SMILE surgery as a global surgical treatment option for refractive errors (4).Previous studies have reported that sex (5), age (6, 7), preoperative spherical equivalent (SE) (8), corneal curvature (9), optical zone (10), central corneal thickness (CCT) (11, 12), treatment nomogram (13), and laser energy (14, 15) affect visual outcomes after SMILE. While previous studies mostly analyzed the influence of a single factor, in this study, machine learning was used to analyze 20 different factors to determine the most important factors affecting SMILE.

Machine learning has been widely used for the diagnosis of corneal diseases (16), prediction of myopia progression (17), and diagnosis of keratoconus (18). Information gain allows the analysis of the correlation between different variables and their impact on outcomes. The impact of individual features on outcomes can be measured by the information gain (19). Information gain makes a comprehensive consideration of feature selection using the statistical properties of all samples and fitting non-linear data, while multiple linear regression is only capable of analyzing linear data. The purpose of this retrospective study was to explore the factors influencing postoperative refraction after SMILE in different ophthalmic centers using information gain.

METHODS

This retrospective study included patients who underwent SMILE surgery in three ophthalmic centers, namely, Tianjin Eye Hospital (center A), Jinan Mingshui Eye Hospital (center B), and Qingdao Eye Hospital (center C). The inclusion criteria were as follows: age $>$ 18 years, CCT $>$ 450 μm, corrected distance visual acuity (CDVA) of 20/25 or better, stable refraction for the past 2 years and patients demonstrate a keen desire to remove their lenses. Patients stopped wearing soft contact lenses for at least 2 weeks and hard contact lenses for at least 4 weeks before examination. The exclusion criteria were active ocular disease, previous ocular surgery or ocular trauma, keratoconus, psychiatric disorders, and systemic diseases. Informed consent was obtained from all patients. The study protocol was approved by the ethics committee of the Tianjin Eye Hospital (TJYYLL-201914). The study design adhered to the tenets of the Declaration of Helsinki.

Abbreviations: SMILE, small-incision lenticule extraction; CCT, central corneal thickness; SE, spherical equivalent; CDVA, corrected distance visual acuity; UDVA, uncorrected distance visual acuity; K1, flattest anterior corneal curvature; Km, mean anterior corneal curvature; Max, maximum lenticule thickness; Pre-UDVA, preoperative uncorrected distance visual acuity; Pre-SD, preoperative spherical diopter; Pre-SE, preoperative spherical equivalent; Pre-Km, preoperative mean anterior curvature; Pre-K1, preoperative flattest anterior corneal curvature; Pre-K2, preoperative steepest anterior corneal curvature, RST, residual stromal thickness.

Information Gain

In machine learning applications, information gain is often used for feature selection by evaluating the gain of each feature in the context of the target outcome. The greater the value of the information gain of a feature, the greater the relevance of the feature to the target outcome. The feature with the highest information gain is considered the best feature to be chosen, as it affects the target outcome the most. Information gain can examine the contribution of features to the whole system. It is suitable for the so-called "global" feature selection. In our study, we employed information gain to measure the relevance of some SMILE features, such as residual stromal thickness (RST) and preoperative mean anterior curvature (Pre-Km), to the target SMILE outcome, that is, postoperative SE. The higher the information gain value, the more important the feature is to the SMILE outcome.

Information gain is calculated by the reduction of information entropy, which quantifies the amount of information present in the target outcome.

$$IG(S,a) = H(S) - H(S|a)$$

where $IG(S, a)$ is the information gain for the outcome S with feature a, $H(S)$ is the entropy for the outcome S without feature a, and $H(S|a)$ is the conditional entropy for the outcome S given feature a. The entropy of S can be calculated from the probability distribution p_k, where k can be in K discrete states, and is written as the function $H(S)$:

$$H(S) = -\sum_{k}^{K} p_k log_{p_k}$$

The conditional entropy $H(S|a)$ can be calculated by splitting the dataset into groups for each observed value of a and calculating the sum of the ratio of examples in each group out of the entire dataset multiplied by the entropy of each group, that is,

$$H(S|a) = \sum_{v}^{a} \frac{Sa(v)}{S} H(Sa(v)),$$

TABLE 1 | Baseline information in the three ophthalmic centers.

	A	B	C	All	*P*
Eyes (*N*)	818	702	830	2350	-
Sex (male, %)	51.0	63.4	68.3	60.8	-
Age (years)	21 (9,25)	19 (18,22)	20 (18,23)	20 (18,24)	0.014
Pre-SD (D)	−5.00 (−6.25, −4.00)	−4.38 (−5.75, −3.25)	−4.50 (−5.50, −3.50)	−4.50 (−5.75, −3.50)	0.419
Pre-CD (D)	−0.75 (−1.25, −0.25)	−0.75 (−1.00, −0.25)	−0.50 (−1.00, 0.00)	−0.50 (−1.00, −0.25)	<0.001
Pre-SE (D)	−5.38 (−6.50, −4.38)	−4.75 (−6.13, −3.50)	−4.75 (−5.75, −3.75)	−5.00 (−6.13, −3.88)	0.122
Pre-CCT(μm)	551 (532, 573)	534 (516, 554)	550 (532, 571)	545 (528,568)	<0.001
Pre-Km(D)	43.1 (42.2, 44.0)	43.1 (42.2, 44.1)	42.7 (41.9, 43.6)	43.0 (42.1,43.9)	<0.001

A, Tianjin Eye Hospital; B, Jinan Mingshui Eye Hospital; C, Qingdao Eye Hospital; N, number of eyes; Pre-SD, preoperative spherical diopter; Pre-CD, preoperative cylinder diopter; Pre-SE, preoperative spherical equivalent. Data are represented as median (P_{25}, P_{75}). P < 0.05 was regarded as statistically significant.

TABLE 2 | Features affecting postoperative refraction.

A		B		C	
Feature	**Information gain value**	**Feature**	**Information gain value**	**Feature**	**Information gain value**
Pre-K1	0.0746	**Pre-Km**	0.0831	**Pre-SD**	0.0804
Pre-SE	0.0744	**Pre-K2**	0.0801	**OZ**	0.0777
Pre-Km	0.0741	**RST**	0.0779	**Nomogram**	0.0696
Pre-K2	0.0725	**Pre-SD**	0.0669	**Max**	0.0638
Age	0.0721	**Pre-K1**	0.0657	**RST**	0.0619
RST	0.0639	**Max**	0.0651	**Pre-SE**	0.0617
Max	0.0614	**Pre-CCT**	0.0643	**Pre-CCT**	0.0615
Pre-SD	0.0604	**Pre-SE**	0.0606	**Pre-Km**	0.0610
Pre-CCT	0.0593	**Pre-UDVA**	0.0536	**Pre-K1**	0.0594
Nomogram	0.0574	**Pre-IOP**	0.0527	**Pre-UDVA**	0.0547
Pre-axis	0.0535	**Nomogram**	0.05190	**Age**	0.0546
Pre-CD	0.0516	Pre-axis	0.0494	**Pre-IOP**	0.0510
Pre-UDVA	0.0505	OZ	0.0449	Pre-K2	0.0497
Laser energy	0.0481	Age	0.0446	Pre-axis	0.0495
Pre-IOP	0.0461	Pre-CD	0.0433	Pre-CD	0.0438
OZ	0.0453	Thickness	0.0314	Pre-CDVA	0.0359
Thickness	0.0202	Pre-CDVA	0.0228	Thickness	0.0347
Pre-CDVA	0.0147	Laterality (right/left)	0.0226	Laser energy	0.0291
Sex	0	Sex	0.0193	Sex	0
Laterality (right/left)	0			Laterality (right/left)	0

Information gain was used to determine the weight of the factors affecting surgical outcomes. The top common nine factors highlighted showed information gain values > 0.05 in all three centers.

A, Tianjin Eye Hospital; B, Jinan Mingshui Eye Hospital; C, Qingdao Eye Hospital; Pre-CCT, preoperative central corneal thickness; Pre-K1, preoperative flattest anterior corneal curvature; Pre-K2, preoperative steepest anterior corneal curvature; Pre-Km, preoperative mean anterior corneal curvature; Max, maximum lenticule thickness; OZ, optical zone; Pre-UDVA, preoperative uncorrected distance visual acuity; Pre-CDVA, preoperative corrected distance visual acuity; Pre-IOP, preoperative intraocular pressure; Pre-SD, preoperative spherical diopter; Pre-CD, preoperative cylinder diopter; Pre-axis, preoperative cylinder axis; Pre-SE, preoperative spherical equivalent; RST, residual stromal thickness; Thickness, cap thickness.

where $\frac{Sa(v)}{S}$ is the ratio of the number of examples in the dataset in which the variable a has the value v, and $H\,(Sa\,(v))$ is the entropy of the group of samples where the variable a has the value v.

In our data analysis, the postoperative SE at 3 months was discretized into three value ranges, 0, 1, and 2, defined as follows: 0:[−0.25,0.25] D, 1:[−0.50, −0.25) D or (0.25,0.50] D, and 2: <0.50 D or >0.50 D. Preoperative anterior segment features included flattest anterior corneal curvature (Pre-K1), steepest anterior corneal curvature (Pre-K2), mean anterior corneal curvature (Pre-Km), and preoperative CCT (Pre-CCT). The preoperative features included uncorrected distance visual acuity (UDVA), CDVA, intraocular pressure spherical diopter(Pre-SD), cylinder diopter, cylinder axis, SE, laterality, sex, and age. Surgical design parameters included RST, laser energy, maximum lenticule thickness (Max), cap thickness, optical zone, and treatment nomogram (Nomogram). Information gain values above 0.05 were considered significant.

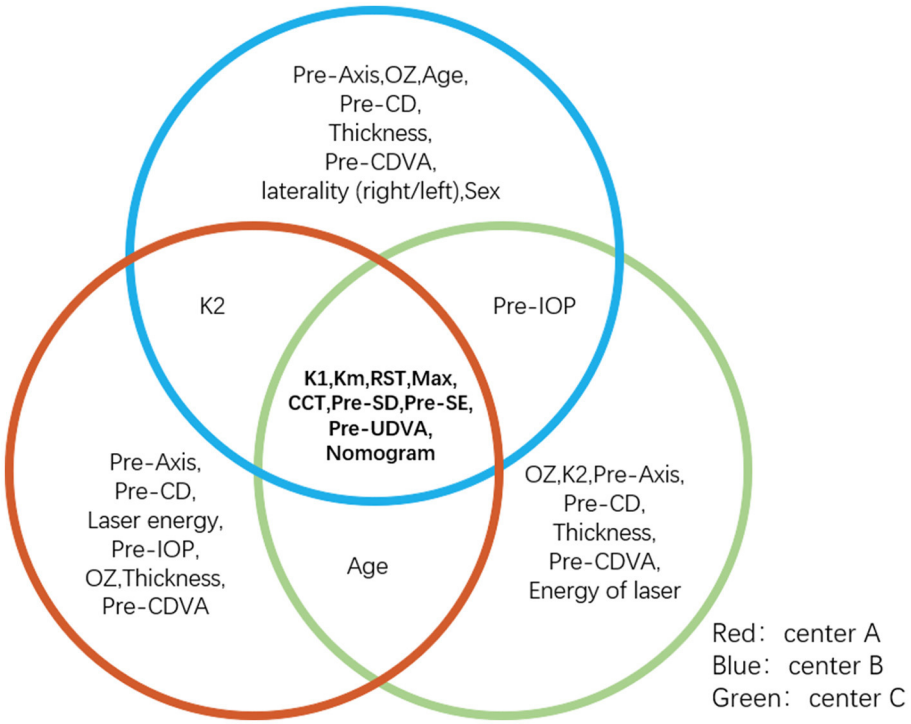


FIGURE 1 | The overlap part of the circle is the feature with three ophthalmic centers information gain values > 0.05, which are considered important factors affecting postoperative SE. K1, Km, RST, Max, CCT, Pre-SD, Pre-SE, Pre-UDVA, and nomogram make a large contribution to postoperative refraction after SMILE. CCT, central corneal thickness; K1, flattest anterior corneal curvature; Km, mean anterior corneal curvature; Max, maximum lenticule thickness; Pre-UDVA, preoperative uncorrected distance visual acuity; Pre-SD, preoperative spherical diopter; Pre-SE, preoperative spherical equivalent; SMILE, small-incision lenticule extraction; RST, residual stromal thickness.

Surgical Parameters

The SMILE procedure was performed using a Visumax 500 kHz femtosecond laser (Carl Zeiss Meditec AG) under topical anesthesia in all patients. In centers A, B, and C, the surgical parameters were optical zone 6.2-7.0 mm, cap diameter 7.2-8.0 mm, cap thickness 110-140 μm, and laser energy 125-145 nJ. The SMILE surgery was performed using a standard surgical technique (20) by experienced surgeons at each of the centers.

Postoperative Treatment and Follow-Up

All patients were prescribed 0.5% levofloxacin (Santen, Inc.) four times a day for 1 week, and 0.1% fluorometholone (Santen, Inc.) four times a day for 1-2 weeks postoperatively. UDVA, CDVA, manifest refraction, and corneal tomography (Pentacam HR, Oculus, Wetzlar, Germany) were performed. The follow-up period is 1 day, 1 week, 1 month, and 3 months after SMILE.

Statistical Analysis

All analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA) and SAS version 9.4 software (SAS Institute Inc., Cary, NC). The Kolmogorov-Smirnov test was used to test the normality of the data. The data that did not conform to the normal distribution were represented as median (P_{25}, P_{75}). The relationship between continuous variables, such as Pre-K1, Pre-Km, RST, Max, Pre-CCT, Pre-SD, Pre-SE, Pre-UDVA, Nomogram, and postoperative SE, were analyzed using the Spearman correlation analysis. A effect model was used to analyze the influencing factors. A p-value of <0.05 was regarded as statistically significant.

RESULTS

A total of 1,200 subjects (2,350 eyes) were included in this study (60.8% male, 50.6% right eye). The average age of the patients was 20 (18, 21) years. The preoperative SE was −5.00 (−6.13, −3.88) D. Demographic data from the different ophthalmic centers are shown in **Table 1**. Information gain was used to determine the weight of the factors affecting surgical outcomes. Factors influencing postoperative SE are presented in **Table 2**. Pre-K1, Pre-Km, RST, Max, Pre-CCT, Pre-SD, Pre-SE, Pre-UDVA, and Nomogram were found to significantly impact postoperative SE in all three centers (**Figure 1**). The top common nine factors highlighted showed information gain values > 0.05 in all three centers. Other variables, such as thickness, sex, laterality (right/left), and Pre-CDVA, had a smaller effect on postoperative SE.

Furthermore, since **Table 2** incorporates too many parameters, and each parameter gets a small weight, we repeated the information gain analysis using the nine features found to

TABLE 3 | Secondary information gain of the nine most influential feature (highlighted in **Table 2**) affecting postoperative refraction.

A		B		C	
Feature	**Information gain value**	**Feature**	**Information gain value**	**Feature**	**Information gain value**
Pre-Km	0.1761	**Pre-Km**	0.1584	Nomogram	0.1360
Max	0.1425	Pre-K1	0.1241	**Pre-SE**	0.1326
Pre-CCT	0.1209	**Pre-CCT**	0.1190	Max	0.1249
Pre-K1	0.1167	**Pre-SD**	0.1127	**Pre-SD**	0.1215
Pre-SD	0.1093	Pre-RST	0.1118	**Pre-Km**	0.1056
Pre-SE	0.1058	**Pre-SE**	0.1069	**Pre-CCT**	0.1001
Pre-UDVA	0.0959	Max	0.1047	Pre-K1	0.0992
Nomogram	0.0678	Pre-UDVA	0.0878	RST	0.0966
RST	0.0652	Nomogram	0.0747	Pre-UDVA	0.0836

*Information gain analysis again using the top nine parameters (highlighted in **Table 2**) obtained above. The features that showed high information gain values (>0.10) in all three centers are highlighted. The four top-ranking parameters (shown in bold) were selected as the most important factors affecting SMILE surgery.*
A, Tianjin Eye Hospital; B, Jinan Mingshui Eye Hospital; C, Qingdao Eye Hospital; Pre-CCT, preoperative central corneal thickness; Pre-K1, preoperative flattest anterior corneal curvature; Pre-Km, preoperative mean anterior corneal curvature; Max, maximum lenticule thickness; Pre -UDVA, preoperative uncorrected distance visual acuity; Pre-SD, preoperative spherical diopter; Pre-SE, preoperative spherical equivalent; RST, residual stromal thickness.

TABLE 4 | The result of the correlation analysis.

	Pre-K1	**Pre-Km**	**RST**	**Max**	**Pre-CCT**	**Pre-SD**	**Pre-SE**	**Pre-UDVA**	**Nomogram**
R	−0.122	−0.127	0.139	−0.311	−0.058	0.369	0.364	0.164	−0.100
Correlation	Negative	Negative	Positive	Negative	Negative	Positive	Positive	Positive	Negative
p	<0.001	<0.001	<0.001	<0.001	0.005	<0.001	<0.001	<0.001	<0.001

Spearman was applied to analyze the correlation of factors affecting the postoperative spherical equivalent in all three centers. $P < 0.05$ was regarded as statistically significant.
Pre-K1, preoperative flattest anterior corneal curvature; Pre-Km, preoperative mean anterior corneal curvature; RST, residual stromal thickness; Max, maximum lenticule thickness; Pre-CCT, preoperative central corneal thickness; Pre-SD, preoperative spherical diopter; Pre-SE, preoperative spherical equivalent; Pre-UDVA, preoperative uncorrected distance visual acuity.

TABLE 5 | The results of random effects estimation in laterality for the null model.

Cov Parm	**Subject**	**Group**	**Estimate**	**Standard error**	***t***	***P***
CHOL(1,1)	laterality	Group 0	0.4313	0.2974	4.38	0.143
CHOL(1,1)		Group 1	0		5.96	0.106
CHOL(1,1)		Group 2	0.5			

The null model was applied for random effects estimation in laterality.
Laterality represents the operation eye (Group 0, right eye; Group 1, left eye; Group 2, both eyes). $P < 0.05$ was regarded as statistically significant.

be significant in **Table 2** to obtain a greater weight (**Table 3**). In **Table 3**, we selected four out of the top six parameters (shown in bold), whose information gain values were higher than 0.10 in all the three centers. Finally, the result stated that Pre-Km, Pre-CCT, Pre-SD, and Pre-SE were the most influential features affecting postoperative refraction in all the three centers.

The result of the correlation analysis of the patients in all the three centers is displayed in **Table 4**. Postoperative SE was related to Pre-SD ($r = 0.369$, $p < 0.001$), Pre-SE ($r = 0.364$, $p < 0.001$), Max ($r = -0.311$, $p < 0.001$), Pre-UDVA ($r = 0.164$, $p < 0.001$), RST ($r = 0.139$, $p < 0.001$), Pre-Km ($r = -0.127$, $p < 0.001$), Pre-K1 ($r = -0.122$, $p < 0.001$), nomogram ($r = -0.100$, $p < 0.001$), and Pre-CCT ($r = -0.058$, $p = 0.005$).

The results of random effects estimation for the null model is shown in **Table 5**. The null model is the first step for building mixed effect model and is used to determine whether the construction of the mixed effect model is necessary. The results of null model indicate that the correlation in laterality is not statistically significant ($p1 = 0.143$, $p2 = 0.106$). It means that there is no significant difference between right eye, left eye and binocular.

Standard Refractive Analyses

Standardized graphs of surgical outcomes after SMILE are displayed in **Figures 2–4**. There was no intraoperative or postoperative complications in all centers.

Center A

None of the eyes lost two or more lines of CDVA. The safety index was 1.32 ± 0.24. Throughout the follow-up, the UDVA was 20/20

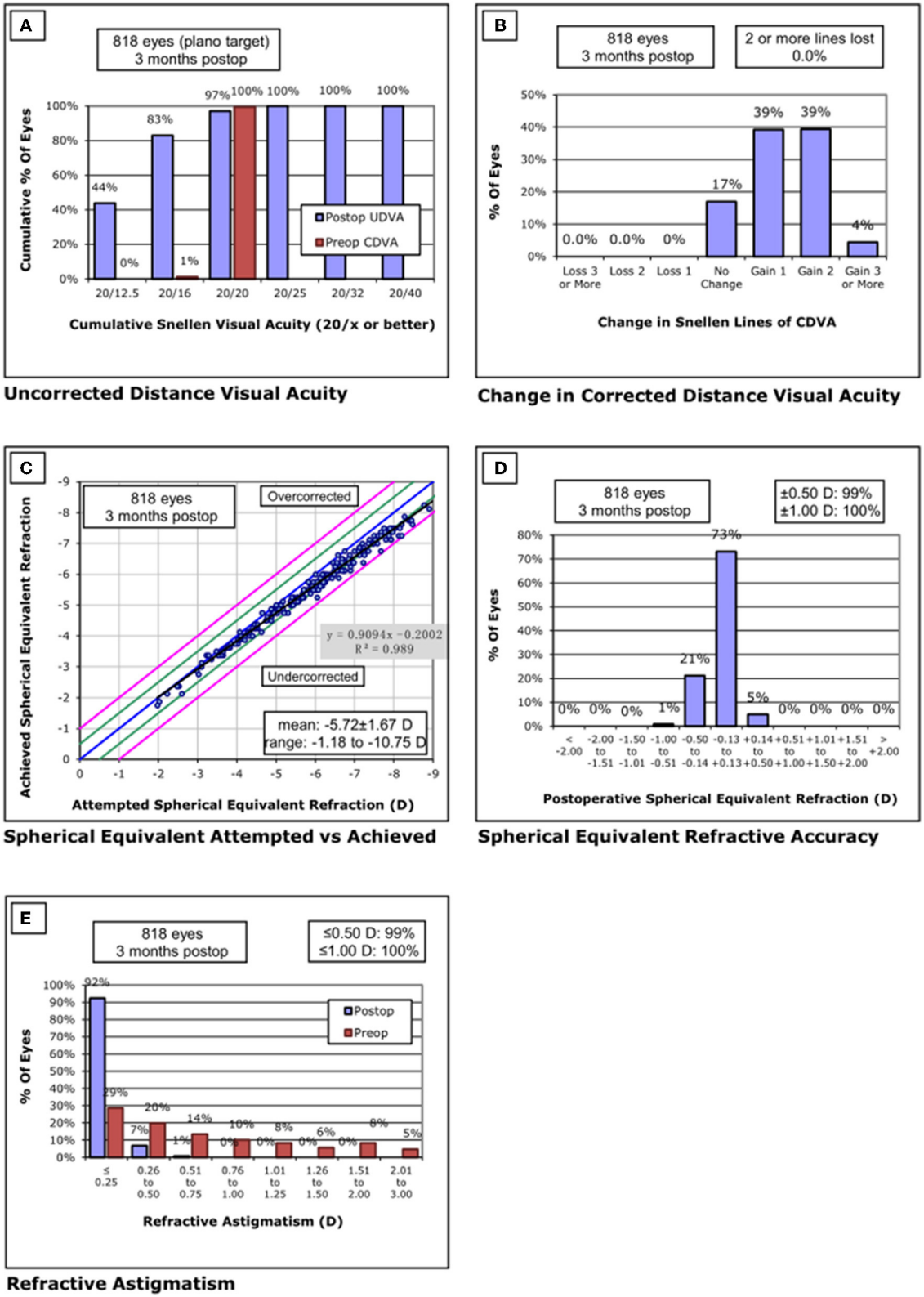


FIGURE 2 | Standard graphs of refractive surgery visual and refractive outcomes for 830 eyes at 3 months post-SMILE in center A. **(A)** Uncorrected distance visual acuity. **(B)** Change in corrected distance visual acuity. **(C)** Spherical equivalent attempted vs. achieved. **(D)** Spherical equivalent refractive accuracy. **(E)** Refractive astigmatism. SMILE, small-incision lenticule extraction.

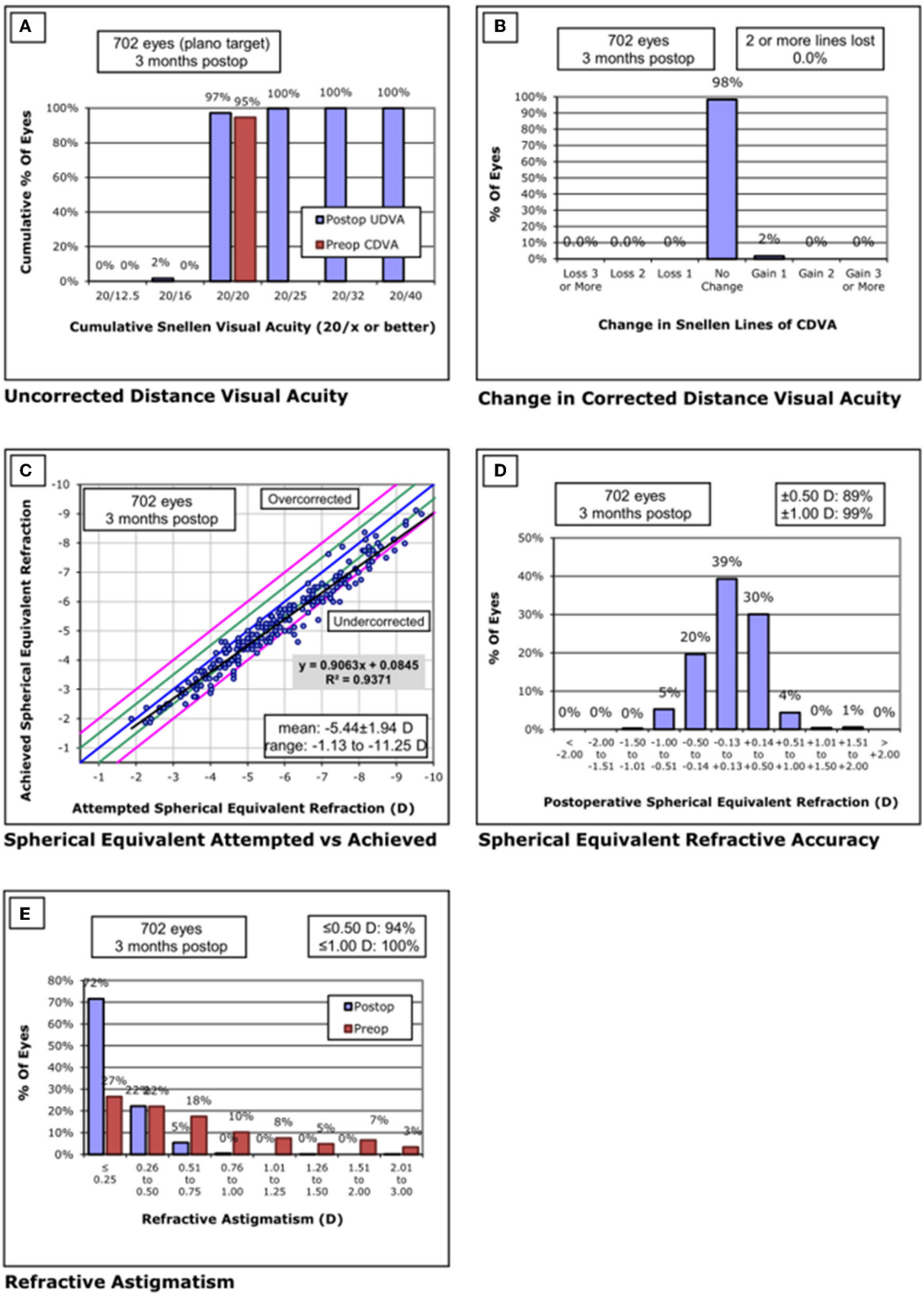
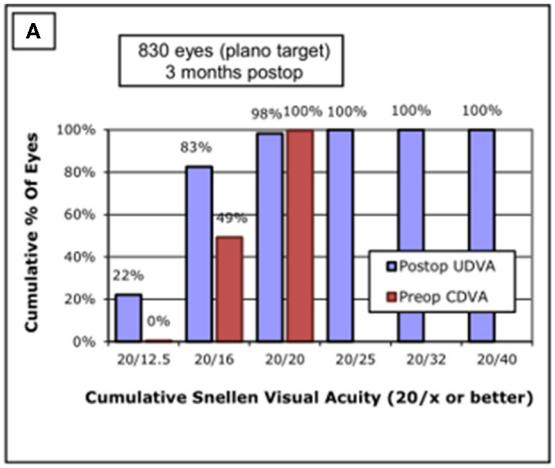
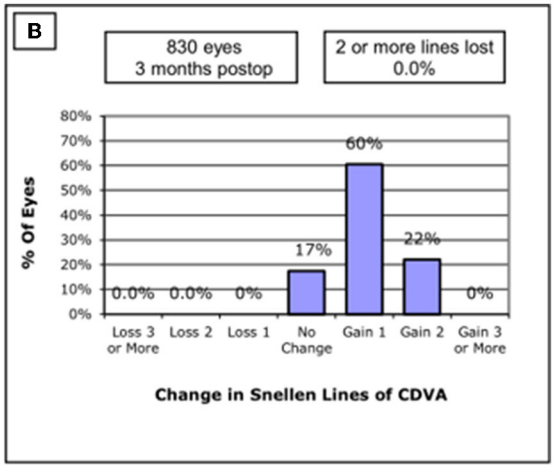


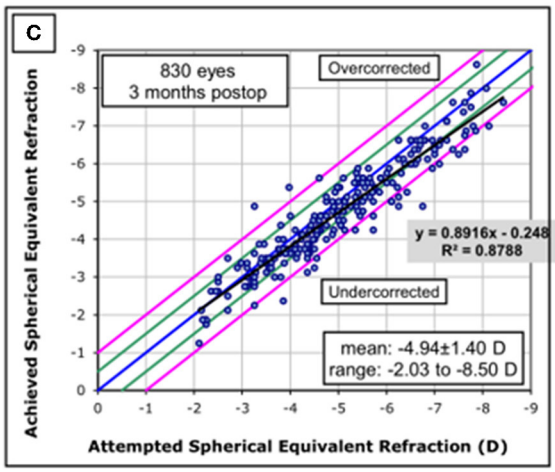
FIGURE 3 | Standard graphs of refractive surgery visual and refractive outcomes for 702 eyes at 3 months post-SMILE in center B. **(A)** Uncorrected distance visual acuity. **(B)** Change in corrected distance visual acuity. **(C)** Spherical equivalent attempted vs. achieved. **(D)** Spherical equivalent refractive accuracy. **(E)** Refractive astigmatism. SMILE, small-incision lenticule extraction.



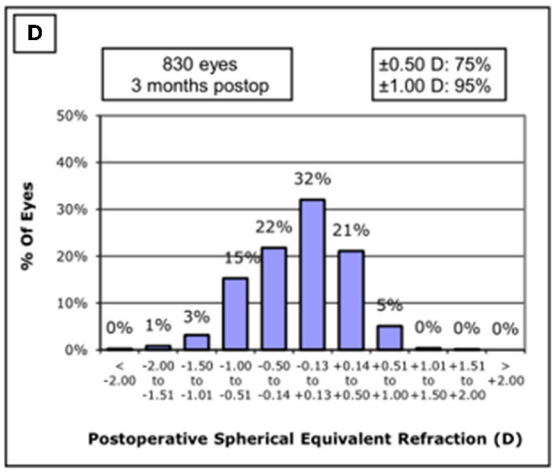
Uncorrected Distance Visual Acuity



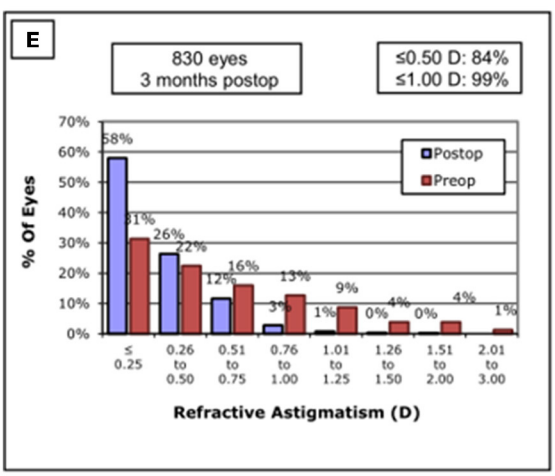
Change in Corrected Distance Visual Acuity



Spherical Equivalent Attempted vs Achieved



Spherical Equivalent Refractive Accuracy



Refractive Astigmatism

FIGURE 4 | Standard graphs of refractive surgery visual and refractive outcomes for 830 eyes at 3 months post-SMILE in center C. **(A)** Uncorrected distance visual acuity. **(B)** Change in corrected distance visual acuity. **(C)** Spherical equivalent attempted vs. achieved. **(D)** Spherical equivalent refractive accuracy. **(E)** Refractive astigmatism. SMILE, small-incision lenticule extraction.

or better in 794/818 eyes (97%) and equal to or better than the preoperative CDVA in 818/818 eyes (100%). The efficacy index was 1.31 ± 0.25. The postoperative SE was within ±0.50 D of the attempted correction in 99% of eyes and within ±1.00 D in all the eyes.

Center B

None of the eyes lost two or more lines of CDVA. The safety index was 1.03 ± 0.08. Throughout the follow-up, the UDVA was 20/20 or better in 682/702 eyes (97%) and equal to or better than the preoperative CDVA in 702/702 eyes (100%). The efficacy index was 1.02 ± 0.08. Postoperative SE was within ±0.50 D of the attempted correction in 89% of the eyes and within ±1.00D in 99% of the eyes.

Center C

None of the eyes lost two or more lines of CDVA. The safety index was 1.13 ± 0.16. Throughout the follow-up, the UDVA was 20/20 or better in 816/830 eyes (98%) and equal to or better than the preoperative CDVA in 830/830 eyes (100%). The efficacy index was 1.13 ± 0.17. Postoperative SE was within ±0.50 D of the attempted correction in 75% of the eyes and within ±1.00D in 95% of the eyes.

DISCUSSION

The safety, efficacy, and predictability of SMILE were confirmed in all the patients in our study. After analyzing a total of 20 parameters, including anterior segment features, preoperative parameters, and surgical design parameters, valuable and interesting results were obtained. Corneal curvature, CCT, SD, SE, UDVA, RST, maximum lenticule thickness, and nomogram were the factors affecting postoperative refraction after SMILE. In addition, mean anterior corneal curvature, CCT, SD, and SE were the most influential features of postoperative refraction among the nine common features.

There are various factors that impact the SMILE procedure in order to obtain better vision outcome. In the study, the contribution of each parameter was obtained by combining the data in multicenter, so that the top factors influencing the surgery were acquired. The factors that influence the postoperative refraction of SMILE include not only corneal parameters but also preoperative refraction and surgical parameters. Our findings indicate that preoperative corneal parameters, including Pre-Km ($r = -0.127$, $p < 0.001$), Pre-K1 ($r = -0.122$, $p < 0.001$), and Pre-CCT($r = -0.058$, $p = 0.005$), play a crucial role in postoperative refraction after SMILE. The diverse ocular biometric parameters are interactive. This result is consistent with that of a previous study in which in the eyes with low myopia, a steeper corneal curvature could lead to a greater undercorrections after SMILE (9), suggesting that a steeper corneal curvature is often associated with high myopia, which tends to be undercorrected after SMILE (22, 23). In the current study, the entire corneal thickness was negatively correlated with the postoperative SE. This might be attributed to the differences in corneal biomechanics based on corneal thickness (24).

Our study showed that preoperative refraction parameters, including Pre-SD ($r = 0.369$, $p < 0.001$), Pre-SE ($r = 0.364$, $p < 0.001$), and Pre-UDVA ($r = 0.164$, $p < 0.001$), had a positive correlation with postoperative SE after SMILE. A higher preoperative SD or SE is associated with a greater postoperative SE after photorefractive keratectomy, laser-assisted *in situ* keratomileusis, or SMILE (21, 25, 26). In addition, in our study, the higher the preoperative UDVA, the greater the postoperative SE, demonstrating that preoperative UDVA is somewhat predictive of postoperative surgical outcomes. Cui et al. (13) indicated that preoperative UDVA can affect the nomogram in SMILE, which may explain why preoperative UDVA plays a role in postoperative SE. Much more attention should be paid to the patient's preoperative UDVA in future studies to improve surgical outcomes.

Among surgical parameters, RST ($r = 0.139$, $p < 0.001$), Max ($r = -0.311$, $p < 0.001$), and nomogram ($r = -0.100$, $p < 0.001$) were noted to influence postoperative SE after SMILE. Ogasawara et al. (27) suggested that RST correlated with regression of myopia after laser-assisted *in situ* keratomileusis during long-term follow-up and that adequate RST is important to preserve a good UDVA. Nevertheless, there was no obvious correlation between UDVA and postoperative SE. In this study, preserving more RST was beneficial in obtaining a greater postoperative SE. It is worth noting that the maximum lenticule thickness represents the actual corneal ablation depth. A tendency for undercorrection after surgery for high myopia compared to mild to moderate myopia is well documented (21). Evidence indicates that the nomogram plays an important role in the safety, efficacy, and predictability of corneal refractive surgery (28). In the eyes with high myopia 1 year after SMILE, the SE was significantly worse. Adjustment of the nomogram to 0.13 × attempted SE (D)-0.66 D has been suggested (23). In summary, more degrees need to be added in high myopia for correction.

Corneal cap thickness, sex, laterality (right/left), laser energy, and preoperative CDVA did not affect postoperative refraction in our cohort. Liu et al. (12) have demonstrated that a 110-μm cap thickness had better visual outcomes postoperatively compared with a 150-μm cap thickness. In contrast, another study found that postoperative refraction was not significantly affected by cap thickness of 100 and 120 μm in SMILE (11). In our study, cap thickness ranged from 110 to 140 μm, which may have led to different results. In contrast with a previous study on the impact of the energy setting on visual outcomes after SMILE (14), the influence of laser energy was clinically insignificant in our study. Although a Visumax 500 kHz femtosecond laser was used in all patients, the temperature or humidity settings might have been different in the three centers. In addition, the large number of parameters analyzed might explain why laser energy contributed less to postoperative refraction.

The current study has both strengths and limitations. Due to the strong covariance of the data, the linear model is not effective at the beginning of this study. However, Applying information gain, a ranking of the importance of 20 features affecting postoperative SE was derived in the study. In particular, although its design was retrospective, this study included a large number of eyes from three ophthalmic centers. However,

different surgical setups may result in measurement errors. In addition, further statistical analysis in the study revealed that no correlation was found between monocular and binocular, which may reduce the possible risk of wrong results due to the violation of the assumption of independence. Finally, the outcomes in center A varied widely compared to those of centers B and C. The reason for this is that the surgeon in center A has extensive experience and has been performed more than 10,000 SMILE procedures since 2011.

In summary, our study assessed factors affecting postoperative refraction after SMILE. Among 20 parameters evaluated in three ophthalmic centers, preoperative mean anterior corneal curvature, CCT, SD, and SE significantly affected postoperative refraction. A larger preoperative Km and CCT is associated with a smaller preoperative SD and RST and a smaller postoperative SE. These findings can be used to optimize the outcomes of SMILE surgery. The refractive surgery surgeons should pay more attention to the patient's preoperative Km, CCT, SD and RST in the daily routine to obtain great outcome for postoperative refraction.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Eye Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YW, SL, SJ, MC, and YLe designed and performed the research. SL and XL organized the manuscript writing. XL, SJ, and YLi analyzed the data. JH, ML, HZ, YP, and ZM collected the data. VJ and YW reviewed the manuscript. YW obtained funding. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Management of Cystoid Macular Edema in Retinitis Pigmentosa: A Systematic Review and Meta-Analysis

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Background: To date, various treatments for cystoid macular edema (CME) in retinitis pigmentosa (RP) have been reported. We performed a systematic review and meta-analysis to evaluate the efficacy and safety of current treatments for RP-CME.

Methods: PubMed, Embase and the Cochrane library were searched from inception to August 2021. ClinicalTrials.gov, WHO ICTRP and ISRCTN were also searched for relevant studies. Only studies published in English were included. The RoB 2 tool was used to evaluate the risk of bias of randomized controlled trials (RCTs), and the MINORS scale was used to assess the methodological quality of non-RCTs. Review manager (Revman) was used to pool the data. The primary outcomes included the change of central macular thickness (CMT) and best-corrected visual acuity (BCVA) from baseline. The secondary outcomes included fluorescein angiography (FA) leakage, rebound of CME and adverse effects.

Results: Thirty-two studies were included in the current systematic review and 7 studies were used for meta-analysis. Treatments for RP-CME included oral and topical carbonic anhydrase inhibitors (CAIs), systematic and local steroids, anti-VEGF therapy, NSAIDS, grid LASER photocoagulation, subliminal micropulse LASER, vitrectomy, lutein supplement and oral minocycline. CAIs and local steroids were proved to be effective in reducing CMT. The effects of anti-VEGF reagents varied among studies. Regarding other treatments, only one study for each method fitted the inclusion criteria, so the evidence was very limited.

Conclusion: Topical CAIs, oral CAIs and local steroids are effective in treating RP-CME. However, due to the overall inferior design and small patient number of the included studies, the quality of evidence was poor. Systematic steroids, LASER, NSAIDS and vitrectomy may also be effective, nevertheless, considering the limited number of studies, no conclusion could be drawn regarding these treatments. More well-designed and conducted studies are needed in this field.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021273979, identifier CRD42021273979.

Keywords: retinitis pigmentosa, cystoid macular edema, carbonic anhydrase inhibitors, steroids, systematic review, meta-analysis

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INTRODUCTION

Retinitis pigmentosa (RP) is an inherited retinal dystrophy that primarily involves the rod photoreceptors, leading to low vision and blindness. The incidence of RP is 1 in 4,000 (1). To date, over 100 RP-causing genes with diverse mutations have been identified (2). At the early stage, RP is characterized by the constriction of visual field, while the central vision might be reserved. Cystoid macular edema (CME) is observed in 10–50% of RP patients when searched with optical coherence tomography (OCT) (3, 4), with the pathological mechanisms include the blood-retina barrier (BRB) breakdown, retinal pigment epithelium (RPE) pumping dysfunction, inflammatory responses and vitreous traction (4). When macular edema occurs in RP patients, the central vision will be impaired.

In 1988, Cox et al. reported the application of acetazolamide (AZM) in a group of patients with CME due to different diseases. Among the 6 included RP-CME patients, 4 responded to the drug, as indicated by improved visual acuity (VA) and reduced fluorescein angiography (FA) leakage in the macular region (5). Later, Fishman et al. reported the efficacy of oral methazolamide and topical dorzolamide in the treatment of RP-CME (6, 7). Nowadays, carbonic anhydrase inhibitors (CAIs) including AZM, methazolamide and dorzolamide are recommended as the first-line choice of drugs for RP-CME (4, 8). On the other hand, steroids were also believed to be useful. Oral and local steroids were reported to be effective in reducing central macular thickness (CMT) as well as improving visual acuity (VA) in RP-CME patients (9, 10). In recent years, the application of slow-releasing intravitreal steroids has proved beneficial, with minimal systematic side effects (11). Other treatments for RP-CME including anti-VEGF therapy, LASER treatment and vitrectomy have also been reported, with varied results in clinical trials.

Two systematic reviews and one meta-analysis have been published regarding the treatment of RP-CME, with results of studies up to 2016 summarized and analyzed (4, 8, 12). Nevertheless, during the past 5 years, more evidence has been published on the application of CAIs (13–18), steroids (10, 11, 13, 14, 16, 19), anti-VEGF therapy (20), and LASER treatment (21). Therefore, we conducted this updated systematic review and meta-analysis, to summarize the existing evidence on the treatment of RP-CME.

MATERIALS AND METHODS

Protocol and Registration

The current systematic review and meta-analysis was conducted according to the PRISMA guideline (**Supplementary Data Sheet 1**) (22). This work was registered in PROSPERO (registration number CRD42021273979).

Search Strategy

We searched PubMed, Embase and the Cochrane library from inception to August 2021. The websites of ClinicalTrials.gov, WHO ICTRP and ISRCTN were also searched. Combinations of various forms of the keywords "retinitis pigmentosa" and "macular edema" were used in the search process, and the detailed search strategy was in **Supplementary Data Sheet 2**. Duplicates were identified and removed by the Endnote software (Clarivate Analytics, USA), followed by removal of irrelevant records by manual screening of the titles and abstracts. For remaining records, the full texts were retrieved and assessed against the inclusion criteria. Two reviewers (Chen and Liu) searched the databases and screened the records independently. Disagreements were solved by consulting the third reviewer (Peng).

Inclusion and Exclusion Criteria

The inclusion criteria (PICOS) were: (1) Participants (P): RP patients with CME. (2) Interventions (I): any intervention that aimed to treat CME. (3) Comparison (C): both comparative studies and single-arm studies were included. (4) Outcomes (O): primary outcomes included the change of CMT and best-corrected visual acuity (BCVA) from baseline. Secondary outcomes included FA leakage, rebound of CME and adverse effects. (5) Type of study (S): any study, prospective or retrospective, that approached the management of RP-CME were included.

The exclusion criteria were: (1) Studies that had <5 patients; (2) Studies published in languages other than English.

Data Extraction and Quality Assessment

The following data were extracted from each included study: first author, publication year, location where the study was conducted, study type, participants, age, interventions, number of patients/eyes, follow-up duration and outcome measurements. For randomized controlled trials (RCTs), the updated Cochrane risk-of-bias tool (RoB 2) was used to assess the methodological quality (23). For non-randomized comparative studies and single-arm studies, the methodological index for non-randomized studies (MINORS) was used to evaluate the study quality (24). The ideal MINORS score was 16 for single-arm studies and 24 for comparative studies. Two reviewers (Chen and Liu) performed data extraction and quality assessment independently. Consensus was reached by consulting the third reviewer (Peng).

Statistical Analysis

Because of substantial heterogeneity among the included studies, we only pooled the data from several single-arm trials exploring the efficacy of CAIs treatment. CMT values at the last visit were used for analysis. Data from prospective and retrospective studies were pooled separately. For steroids treatment, the data from different studies were put together in a diagram for clarity, but were not pooled due to heterogeneity. For other treatments including anti-VEGF therapy, LASER treatment, vitrectomy, lutein supplement and NSAIDS eyedrops, a systematic review was performed instead of meta-analysis. Review manager (the Cochrane Collaboration, UK) was used to pool the data and generate the figures. Mean Difference (MD) (for CMT change) or Risk Difference (RD) (for responder proportion) was calculated. Subgroup analysis was carried out regarding different means of CAIs treatment (oral or topical). The heterogeneity among included trials was assessed with I^2 statistics. If the heterogeneity

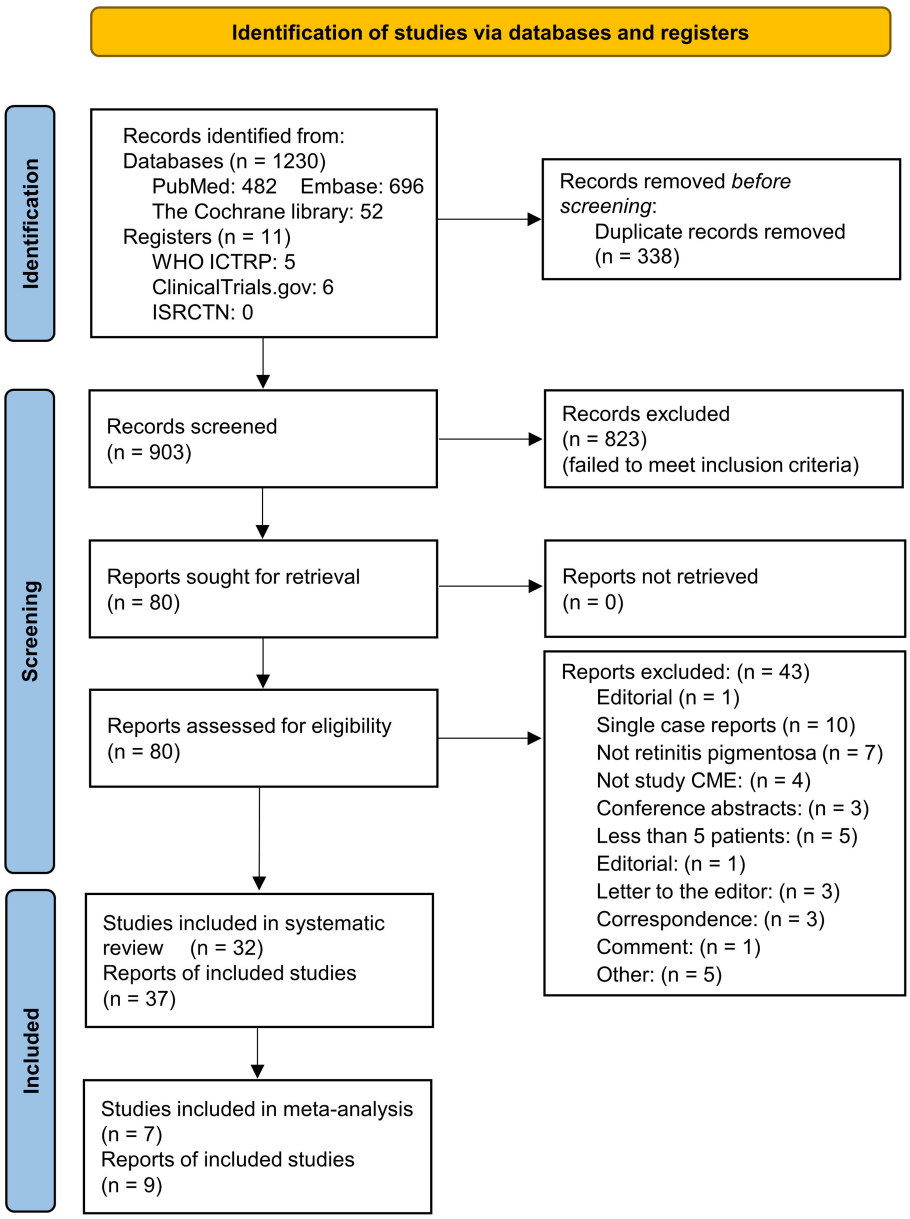

FIGURE 1 | Flow diagram of literature search and records screening.

was low (I^2 < 50%), fixed effect model was employed to pool the data. If the heterogeneity was substantial (I^2 > 50%), random effect model was used. A $p < 0.05$ was considered statistically significant for treatment effects.

RESULTS

Study Characteristics

During databases and registers searching, 1,241 records were identified. After removal of 338 duplicates, 903 titles and abstracts were screened. Eighty full-text records were evaluated according to the inclusion criteria, and 43 records were excluded with reasons (see **Figure 1**). A total of 32 studies (37 reports) were included in the qualitative synthesis, and 7 studies (9 reports) were used for meta-analysis (**Figure 1**). Among the included studies, 6 were RCTs (5 crossover and 1 parallel design), 3 were prospective comparative studies, 2 were prospective paired-eye studies, 15 were prospective single-arm studies, and 6 were retrospective single-arm studies (**Figure 2A**). Treatments for RP-CME included CAIs (14 studies), steroids (6 studies), CAIs compared with steroids (2 studies), steroids (betamethasone) additional to CAIs (1 study), CAIs compared with NSAIDS (ketorolac) (1 study), anti-VEGF therapy (3 studies), LASER treatment (2 studies), pars plana vitrectomy (PPV) (1 study),

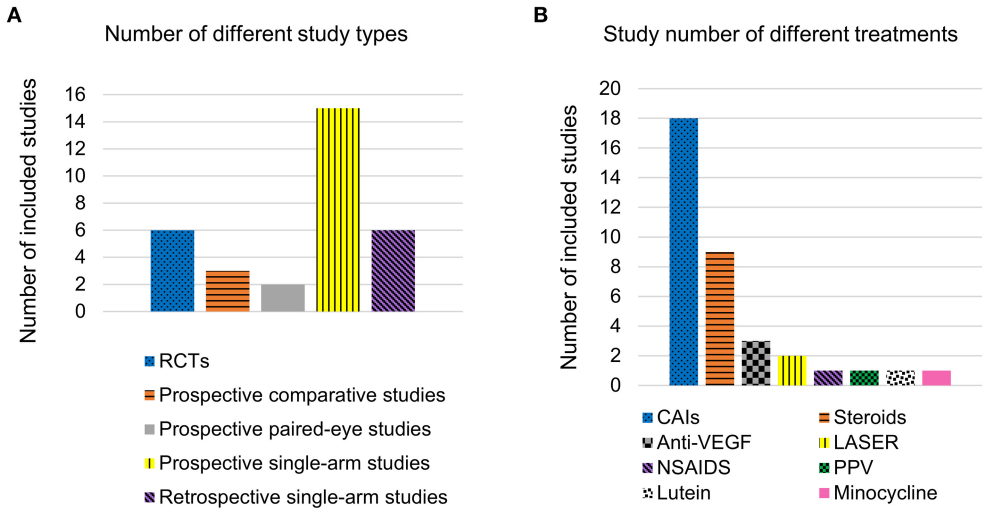

FIGURE 2 | Distribution characteristics of included studies. **(A)** Number of different study types; **(B)** Study number of different treatments.

lutein supplement (1 study) and oral minocycline (1 study) (**Figure 2B**). Detailed study characteristics were presented in **Table 1**.

Quality Assessment

For methodological quality assessment, the 6 RCTs were evaluated with the RoB2 tool, and the remaining 26 studies were assessed using the MINORS scale. Of the 6 RCTs, 1 was determined to be at low risk of bias, 3 were determined to be of some concerns because of potential bias in the randomization process (1 of the 3 also had potential bias in deviations from intended interventions and measurement of the outcome), 2 were determined to be at high risk of bias due to the selection of the reported result (**Figure 3**). By MINORS scale, the 5 prospective comparative studies (including the 2 paired-eye studies) were scored 15–20 out of an ideal score of 24. The 15 prospective single-arm studies were scored 8–13, and the 6 retrospective single-arm studies were scored 5–8 out of an ideal score of 16 (**Table 2**).

Primary Outcome: Change in CMT

In our included studies, macular thickness was entitled diversely as central macular thickness (CMT), central foveal thickness (CFT), foveal zone thickness (FZT), central subfield thickness (CST), or central retinal thickness (CRT). Here we use CMT throughout this paper for consistency. In the OCT era, macular edema is assessed by OCT measurements of the CMT. In the pre-OCT era, macular edema was evaluated by FA leakage in the macular region. Of the included studies, 22 reported the CMT change after treatment, 8 reported the change in FA leakage, and 2 reported both outcomes.

CAIs have been used in clinical trials to treat RP-CME for over 30 years (4, 5, 38). Pooled data from 4 prospective single-arm studies including 41 patients (78 eyes) demonstrated a significant decrease in CMT from baseline after CAIs treatment (CMT values at the last visit were used for analysis) (mean difference: −58.8 μm, 95% CI: −75.76 μm, −41.85 μm, I^2 = 36%, P <0.00001). Data from 3 retrospective cohort studies including 138 patients (254 eyes) also revealed a similar effect of the CAIs (mean difference: −38.16 μm, 95% CI: −44.82 μm, −31.49 μm, I^2 = 31%, P <0.00001) (**Figure 4A**). Regarding different administration methods, both oral CAIs and topical CAIs significantly decreased CMT (**Figure 4B**). Generally, CAIs decreased CMT by 45.64 μm from baseline, as demonstrated by the meta-analysis including 5 studies (139 patients and 261 eyes, P <0.00001) (**Figure 4B**).

To be consistent with other studies (7, 17, 34, 36), we define eyes with more than 11% reduction of baseline CMT after treatment as "responders." The pooled responder proportion for CAIs was 50% in prospective single-arm studies (95% CI: 35%, 64%, I^2 = 0%) (n = 2 studies, 25 patients, 46 eyes), and 36% in retrospective cohort studies (95% CI: 30%, 42%, I^2 = 0%) (n = 3 studies, 138 patients, 254 eyes) (**Figure 5A**). The responder proportion was 40% for oral CAIs, and 38% for topical CAIs (**Figure 5B**). The overall responder rate for CAIs was 39% (pooled data from 3 studies, 123 patients, 229 eyes) (**Figure 5B**). Shimokawa et al. defined eyes with more than 20% reduction of CMT after 1.0% topical dorzolamide treatment as responders, and they reported a higher responder rate of 59.1% and 63.5% in two publications (15, 18).

Local steroids were also reported to be useful in treating RP-CME. The average change of CMT varied from −58.56–−320.62 μm after different local steroids treatments, as shown in **Figures 6A,B**. Moreover, in 2 comparative studies, intravitreal dexamethasone implant (0.7 mg, Ozurdex) showed better results in reducing CMT than the CAIs (14, 16). **Figure 7** is a representative of RP-CME treated with dexamethasone implant, illustrating the macular change by OCT during the treatment and follow-up [figure reproduced from Veritti et al. (14)].

The efficacy of anti-VEGF therapy in RP-CME varied among studies. Artunay et al. reported that a single intravitreal injection of ranibizumab (0.5 mg) significantly reduced CMT at 1, 3, 6

TABLE 1 | Characteristics of included studies.

Treatment	First author /year	Location	Study design	Participants	Age (year) (mean, range)	Intervention	Patients/Eyes	Follow-up duration	Outcome measurements
CAIs	Cox, 1988	UK	Prospective single arm study	CME due to various reasons (6 RP-CME)	28–84 for responders	Oral acetazolamide 500 mg/d, then cyclopenthiazide 0.5 mg/d	Total 41 patients (RP-CME: 6/12)	16 w	BCVA, FA grade of CME
	Fishman, 1989	US	RCT (crossover design)	RP-CME	45 (29–79)	Oral acetazolamide 500 mg/d vs. placebo	12/24	4 w-21 w	BCVA, FA grade of CME, subjective improvement
	Orzalesi, 1993	Italy	Prospective single arm study	RP (7 RP patients, 5 have CME)	23–60	Oral acetazolamide 500 mg/d, tapered to 125 mg every 3 days	5/9	3 w-16 m	BCVA, FA grade of CME, macular threshold
	Fishman, 1994 Fishman 1993	US	RCT (crossover design, multicenter)	RP-CME	NR (inclusion criteria 18–65)	Oral methazolamide 50 mg bid vs. placebo	17/34	10 w-5 m	BCVA, FA grade of CME, subjective improvement
	Grover, 1997	US	RCT (crossover design)	RP-CME	44 (37–53)	Topical 2% dorzolamide vs. placebo, then oral acetazolamide 500 mg/d	5/10	26 w	BCVA, FA grade of CME
	Moldow, 1998	Denmark	RCT (crossover design)	CME due to RP and US (9 patients, 7 have CME)	38.7 (24–63)	Oral acetazolamide 250 mg bid vs. placebo	7/14	4 w	BCVA, FA grade of CME, penetration ratio of fluorescein, AEs
	Chung, 2006	Korea	Prospective single arm study	RP-CME	28–66	Oral acetazolamide 125 mg or 250 mg daily for 4–12 m	10/20	4–12 m	CFT, BCVA, FA leakage
	Apushkin, 2007	US	Prospective single arm study	RP-CME	21–48	Oral acetazolamide 500 mg/d for 8–12 w	6/12	8–22 w	BCVA, FT, FZT
	Grover, 2006 Fishman 2007	US	Prospective single arm study	RP-CME	38 (16–62)	topical 2% dorzolamide tid	15/28	1–15 m	BCVA, FT, FZT
	Genead 2010	US	Retrospective single arm cohort study	CME due to RP and US	38.2 (19–67)	Topical 2% dorzolamide tid	32/64	6–58 m	BCVA, CFZ thickness, responder proportion
	Ikeda, 2012 Ikeda 2013	Japan	Prospective single arm study	RP-CME	43 (20–60)	topical 1% dorzolamide tid	10/18	12–18 m	BCVA, CST, MD and macular sensitivity
	Liew, 2015	UK	Retrospective single arm cohort study	RP-CME	Oral: 36.0 topical: 45.4	oral acetazolamide 250 mg bid or 500 mg qd, or topical 2% dorzolamide tid	Oral: 17/32 topical: 64/115	1.5–12 m	BCVA, CSF thickness, responder proportion
	Reis, 2015	Portugal	RCT	CME due to RP and US	Dorzolamide: 43.54 ketorolac: 41.80	2% dorzolamide 3 drops daily vs. 0.5% ketorolac 4 drops daily	18/28 (dorzolamide: 9/13 ketorolac: 9/15)	12 m	BCVA, FT, FZT

(Continued)

TABLE 1 | Continued

Treatment	First author /year	Location	Study design	Participants	Age (year) (mean, range)	Intervention	Patients/Eyes	Follow-up duration	Outcome measurements
CAIs	Strong, 2019	UK	Retrospective single arm cohort study	RP-CME	48 (17–79)	Oral acetazolamide 250 mg bid or topical dorzolamide/brinzolamide tid	25/43 (acetazolamide: 4 eyes, dorzolamide/ brinzolamide: 39 eyes)	3–9 m	CMT, BCVA change, responder proportion, CME fluid distribution
	Shimokawa, 2020; Shimokawa, 2021	Japan	Retrospective single arm cohort study	RP-CME	53	1.0% dorzolamide eyedrop tid	47/66	0.8–10.1 y	Responder proportion, CME fluid distribution, macular sensitivity
	Veritti, 2020	Italy	Prospective, non-randomized, propensity-score-matched, comparative study	RP-CME, with CRT>350 μm	Dexamethasone implant: 38.3 oral acetazolamide: 36.7	Oral acetazolamide 500 mg/day vs. dexamethasone implant (0.7 mg, Ozurdex)	60/60 (oral acetazolamide: 30/30, dexamethasone implant: 30/30)	12 m	CRT, BCVA, number of injections, AEs
	Park, 2020; Park, 2021	Korea	Randomized, non-controlled, paired-eye, single crossover study	RP with bilateral CME, CMT>250 μm	51.5 (34–66)	Topical 2% dorzolamide vs. intravitreal dexamethasone implant (0.7 mg, Ozurdex)	14/28	12 m	CMT, BCVA, IOP
Steroids	Giusti, 2002	Italy	Prospective single arm study	RP-CME	42.7	Oral deflazacort 30 mg/d, tapered for a total 12 m	10 patients	12 m	BCVA (far and near), FA grade of CME, MD and retinal sensitivity
	Ozdemir, 2005	Turkey	Prospective single arm study	RP-CME unresponsive to oral acetazolamide	33.2 (25–41)	Intravitreal injection of 4 mg (0.1 ml) triamcinolone acetonide	5/5	6–8 m	VA, CMT
	Scorolli, 2007	Italy	Prospective, non-randomized, controlled study	RP-CME	treatment: 40.2 (28–54) control: 39.5	Intravitreal injection of 4 mg (0.1 ml) triamcinolone acetonide vs. observation	Treatment: 20/20 control:20/20	12 m	CMT, BCVA, IOP
	Sudhalkar, 2017	India	Prospective single arm study	RP-CME with incomplete or no response to CAIs	43–56	Intravitreal dexamethasone implant (0.7 mg, Ozurdex)	5/6	2 y	CDVA, CST, IOP, number of injections
	Mansour, 2018	Lebanon	Retrospective single arm multicenter study	RP-CME (previously untreated or treated)	32.7 (16–57)	Intravitreal dexamethasone implant (0.7 mg, Ozurdex)	34/45	1–48 m	CMT, BCVA, IOP
	Kitahata, 2018	Japan	Retrospective single arm cohort study	Persistant RP-CME	39.4 (16–51)	Topical 0.1% betamethasone tid or qid (in addition to previous topical dorzolamide or brinzolamide/bromfenac)	10/16	3–58 m	BCVA, CFT
	Karasu, 2020	Turkey	Prospective single arm study	RP-CME unresponsive to CAIs	36.25 (13–63)	Subtenon triamcinolone acetonide (1 ml: 40 mg)	42/48	4–6 m	CMT, BCVA, IOP

(Continued)

TABLE 1 | Continued

Treatment	First author /year	Location	Study design	Participants	Age (year) (mean, range)	Intervention	Patients/Eyes	Follow-up duration	Outcome measurements
Steroids	Veritti, 2020	Italy	Prospective, non-randomized, propensity-score-matched, comparative study	RP-CME CRT>350 μm	Dexamethasone implant: 38.3 oral acetazolamide: 36.7	dexamethasone implant (0.7 mg, Ozurdex) vs. oral acetazolamide 500 mg/day	60/60 (oral acetazolamide: 30/30, dexamethasone implant: 30/30)	12 m	CRT, BCVA, number of injections, AEs
	Park, 2020; Park, 2021	Korea	Prospective, paired-eye, crossover study	RP with bilateral CME, CMT>250μm	51.5 (34–66)	Intravitreal dexamethasone implant (0.7 mg, Ozurdex) vs. 2% topical dorzolamide	14/28	12 m	CMT, BCVA, IOP
Anti-VEGF	Artunay, 2009	Turkey	Prospective, non-randomized, controlled study	RP with persistent CME despite previous medication	Treatment: 36.6 (29–52) control: 39.6 (26–55)	intravitreal ranibizumab 0.5 mg (single injection) vs. observation	Treatment: 15/15 control:15/15	6 m	BCVA, CFT
	Yuzbasioglu, 2009	Turkey	Prospective single arm study	RP with persistent CME despite previous medication	44.14 (25–69)	Intravitreal bevacizumab (1.25 mg/0.05 ml)	7/13	6–14 m	CMT, VA, number of injections
	Strong 2020	UK	Prospective single arm study	RP-CME	43.3	Intravitreal aflibercept (50 μl, 2 mg) (3+TAE)	30/30	12 m	CMT, BCVA, retinal sensitivity, AEs
LASER	Newsome, 1987	US	Prospective paired-eye study	RP-CME	34.2 (19–60)	Grid laser photocoagulation	16/16	4–21 m	BCVA, FA leakage
	Arslan, 2021	Turkey	Prospective single arm study	RP-CME unresponsive to CAIs, CMT>500 μm	38.8 (18–67)	Subliminal micropulse yellow laser	29/32	12 m	CMT, BCVA, subjective improvements
Vitrectomy	Garci'a-Arumi', 2003	Spain	Prospective single arm study	RP-CME unresponsive to oral acetazolamide	26–48	Pars plana vitrectomy + inner limiting membrane removal + gas tamponade	8/12	12 m	BCVA, foveal thickness, FA leakage
NSAIDS	Reis, 2015	Portugal	RCT	CME due to RP and US	Ketorolac: 41.80 dorzolamide: 43.54	0.5% ketorolac 4 drops daily vs. 2% dorzolamide 3 drops daily	18/28 (ketorolac: 9/15 dorzolamide: 9/13)	12 m	BCVA, FT, FZT
Lutein	Adackapara, 2008	US	RCT (crossover design)	RP	51 (23–67)	Oral lutein 10 or 30 mg/d vs. placebo	Total 39/77 RP-CME 19/36	48 w	BCVA, central thickness
Minocycline	NCT02140164 PI: Dr Cukras, completed 2016	US	Prospective single arm study (phase I/II clinical trial)	RP-CME	27.7	Oral minocycline 100 mg bid for 12 m	7 participants, 5 completed	12 m	Change of CMT, microperimetry, visual field and VA. AEs

CAIs, carbonic anhydrase inhibitors; RCT, randomized controlled trial; RP, retinitis pigmentosa; CME, cystoid macular edema; BCVA, best-corrected visual acuity; FA, fluorescein angiography; CMT, central macular thickness; CFT, central foveal thickness; FT, foveal thickness; FZT, foveal zone thickness; CFZ, central foveal zone; MD, mean deviation; CSF, central subfield; IOP, intraocular pressure; CST, central subfield thickness; CDVA, corrected distance visual acuity; CRT, central retinal thickness; AE, adverse events; VA, visual acuity.

FIGURE 3 | Summary of risk of bias assessment for randomized controlled trials (RCTs) employing RoB 2 tool.

months post injection in 15 patients (32). Also, Yuzbasioglu et al. reported a significant reduction of CMT after single or multiple intravitreal injections of bevacizumab (1.25 mg) in 7 patients (13 eyes) (33). However, in a recent study approaching the efficacy of intravitreal aflibercept (2 mg) with a 3+TAE protocol, the treatment failed to achieve a significant overall reduction of CMT, although all the 30 eyes responded after the 1st injection. The responder rate was 37.9% in this study (20).

Regarding other treatments for RP-CME, one session of subliminal micropulse yellow laser treatment was reported to reduce the mean CMT from 651.3 to 247.7 μm in 29 RP patients (32 eyes) at 12 months after the treatment (21). Also, vitrectomy with inner limiting membrane peeling and gas tamponade (40) was reported to reduce the average CMT from 478 to 260 μm in 8 patients (12 eyes) at 6 months post operation. On the other hand, ketorolac eyedrops (41) and lutein supplement (10 or 30 mg/d) (3) failed to decrease the average CMT. Oral minocycline treatment (100 mg bid for 12 m) (NCT02140164) reduced CME in 2 out of 5 patients, and achieved a CMT change of −16.7 ± 42.16 μm and −37.3 ± 52.90 μm at 6 and 12 months (mean ± SD).

Primary Outcome: Change in BCVA

Improvement or stability of the visual acuity (VA) is the goal of all treatments. All included studies, except a retrospective cohort study (15, 18), have reported VA or BCVA before and after treatment. The reported forms of the change of BCVA after treatment varied among studies, so the data cannot be pooled.

Regarding oral CAIs, acetazolamide (AZM) was the most extensively studied drug to treat RP-CME. In 1988, Cox et al. reported that among 6 RP-CME patients treated with 500 mg/d AZM, 4 had improved VA (5). In 1989, Fishman et al. reported that 10 out of 12 patients had improved VA after AZM treatment (38). Also, Orzalesi et al. reported that among the 5 RP patients who showed leakage in macular on FA, 4 had improved vision after oral AZM therapy (26). However, data from later studies seemed to be less encouraging. In 1998, Moldow et al. observed only small improvements (≤5 ETDRS letters) of VA by AZM treatment (42). Also, Veritti et al. reported an average improvement of only 1.6 ETDRS letters in 30 RP-CME eyes treated with AZM (14). On the other hand, methazolamide has also been used to treat RP-CME. In 1994, Fishman et al. reported a significant VA improvement in a group of 17 patients after methazolamide treatment (50 mg bid). However, an improvement of more than 2 lines (10 ETDRS letters) compared to placebo was only seen in 3 patients (6).

Regarding topical CAIs, Grover et al. reported that 3 out of 15 patients had an improved BCVA of 7 letters or more (Snellen chart) in at least one eye after topical 2% dorzolamide treatment (30). Besides, Genead et al. reported that 10 out of 32 patients (31%) had improved VA by 7 or more letters in at least one eye, and the mean average LogMar VA improved from 0.33 to 0.28 after 2% dorzolamide treatment (34). Also, Reis et al. reported a significant increase in BCVA from baseline at 1, 3, 6 months, but not at 12 months after topical 2% dorzolamide treatment, with 7 eyes (54%) had an improvement of 7 letters or more (Snellen

TABLE 2 | Quality assessment of non-RCT studies using the MINORS scale.

References	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Appropriate follow-up period	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	MINORS Score
Newsome and Blacharski (25)	2	0	2	2	2	1	2	0	1	2	1	2	17/24
Cox et al. (5)	2	2	2	2	0	1	1	0	0	0	0	0	10/16
Orzalesi et al. (26)	2	0	2	2	0	1	2	0	0	0	0	0	9/16
Giusti et al. (9)	2	0	2	2	0	2	0	0	0	0	0	0	8/16
García-Arumí (40)	2	2	2	2	0	1	2	0	0	0	0	0	11/16
Ozdemir et al. (27)	2	0	2	2	0	1	2	0	0	0	0	0	9/16
Chung et al. (28)	2	2	2	2	0	1	2	0	0	0	0	0	11/16
Apushkin et al. (29)	2	0	2	2	2	1	2	0	0	0	0	0	11/16
Grover et al. (30), Fishman and Apushkin (7)	2	1	2	2	1	1	2	0	0	0	0	0	11/16
Scorolli et al. (31)	2	0	2	2	0	2	0	0	1	2	2	2	15/24
Artunay et al. (32)	2	2	2	2	2	1	1	0	1	2	2	2	19/24
Yuzbasioglu et al. (33)	2	0	2	2	0	1	2	0	0	0	0	0	9/16
Genead and Fishman (34)	2	0	0	2	0	1	2	0	0	0	0	0	7/16
Ikeda et al. (35)	2	2	2	2	0	2	1	0	0	0	0	0	11/16
Liew et al. (36)	2	0	0	2	0	1	1	0	0	0	0	0	6/16
Sudhakar et al. (19)	2	2	2	2	0	2	2	0	0	0	0	0	12/16
Mansour et al. (11)	2	0	0	2	0	1	0	0	0	0	0	0	5/16
Kitahata et al. (37)	2	0	0	2	0	1	1	0	0	0	0	0	6/16
Stong et al. (17)	2	2	0	2	0	0	2	0	0	0	0	0	8/16
Karasu (10)	2	2	2	2	0	1	0	0	0	0	0	0	9/16
Shimokawa et al. (15, 18)	2	0	0	1	0	2	2	0	0	0	0	0	7/16
Strong et al. (20)	2	0	2	2	1	2	2	2	0	0	0	0	13/16
Veritti et al. (14)	2	0	2	2	0	2	2	2	2	2	2	2	20/24
Arslan (21)	2	0	2	2	0	2	2	0	0	0	0	0	10/16
Park (13, 16)	2	0	2	2	1	1	1	0	1	1	2	2	15/24
NCT02140164	2	0	2	2	0	2	1	0	0	0	0	0	9/16

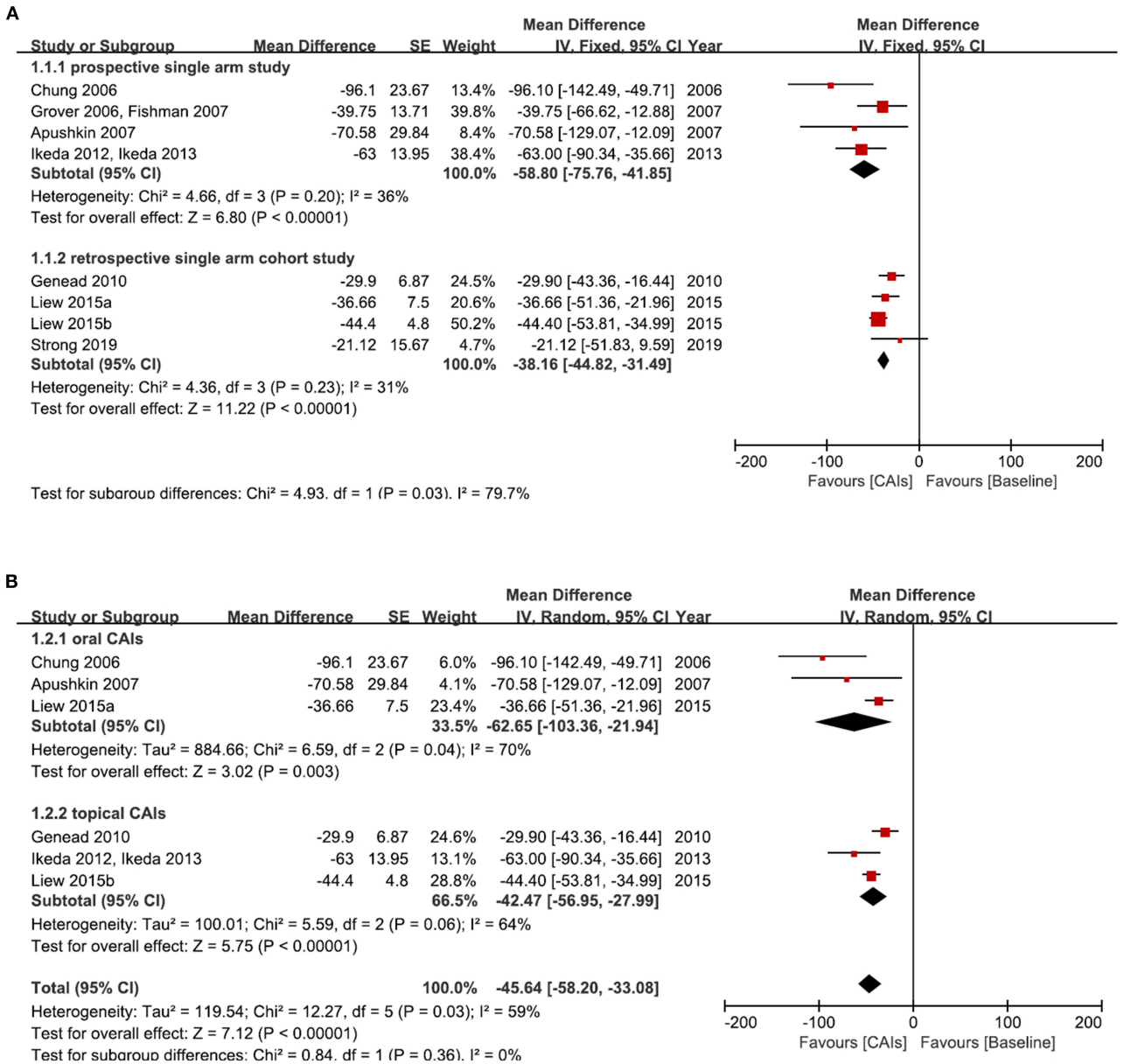

FIGURE 4 | Forest plots for the meta-analysis of change of central macular thickness (CMT) (μm) from baseline after carbonic anhydrase inhibitors (CAIs) treatment. **(A)** Meta-analysis of different study types; **(B)** Subgroup analysis according to different administration methods of CAIs. [For the studies Chung et al. (28), Grover et al. (30)/Fishman and Apushkin (7), Apushkin et al. (29), and Ikeda et al. (35, 39), the change of CMT was calculated from published original individual data; For the study Genead and Fishman (34), the change of CMT was calculated from the mean/standard deviation data before and after treatment; For the study Liew et al. (36), the change of CMT was calculated from the mean/95% CI of CMT reduction in responders and non-responders; For the study Strong 2019, the change of CMT was calculated from the mean/standard deviation data which was extracted from the box plot from the original article by Photoshop software] [*The study Strong 2019 was used for analysis in **(A)** but not in **(B)** because oral and topical CAIs treatment data cannot be separated in this study. The study Grover et al. (30)/Fishman and Apushkin (7) was used for analysis in **(A)** but not in **(B)** because this study may share some same patients with the study Genead and Fishman (34)].

chart) (41). However, in 3 other studies, topical dorzolamide treatment failed to achieve a significant improvement in VA (16, 35, 39, 43).

Different treatments of steroids also showed varied effects in VA improvement, among which intravitreal dexamethasone implant (0.7 mg, Ozurdex) seemed promising. Sudhalkar et al. reported a significant improvement of corrected VA in 5 patients underwent dexamethasone implant treatment (19). The result was further confirmed by a later study including 45 eyes from 34 patients, which observed an improvement of mean BCVA from 0.61 to 0.37 ($P = 0.012$) (11). Furthermore, two studies published in 2020 reported that intravitreal dexamethasone

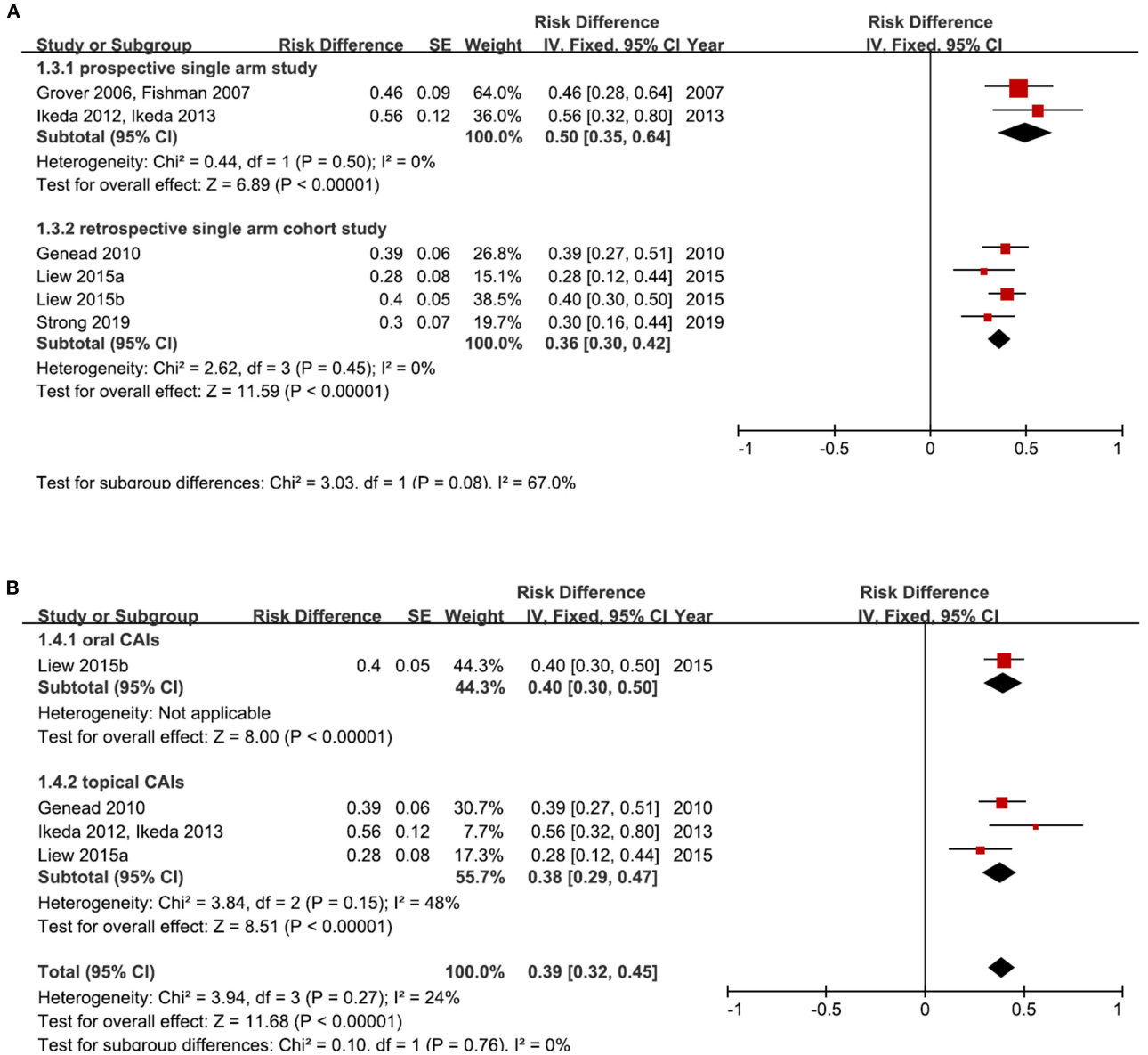

FIGURE 5 | Forest plots for the meta-analysis of the responder proportion after carbonic anhydrase inhibitors (CAIs) treatment**. (A)** Meta-analysis of different study types; **(B)** Subgroup analysis according to different administration methods of CAIs. [Ikeda et al. defined the responder as CMT decreased 20% from baseline. We calculated the 11% decrease of CMT from their published original data; The responder rate of the study Grover et al. (30)/Fishman and Apushkin (7) was calculated from their published original data; Other studies reported the 11% reduction rate directly] [*the study Strong 2019 was used for analysis in **(A)** but not in **(B)** because oral and topical CAIs treatment data cannot be separated in this study. The study Grover et al. (30)/Fishman and Apushkin (7) was used for analysis in **(A)** but not in **(B)** because this study may share some same patients with the study Genead and Fishman (34)].

implant was superior to CAIs in BCVA improvement (14, 16).

Oral deflazacort was evaluated in one study, with the near BCVA improved significantly ($p < 0.01$) while the far BCVA improved slightly ($p < 0.05$) (9). Intravitreal triamcinolone acetonide (IVTA) (4 mg) was reported to transiently improve VA in 2 out of 5 patients at 1 month after injection, but not at 3 and 6 months post injection (27). While in another study, no significant change of BCVA was observed over a 12 months period after IVTA (4 mg) (31). However, subtenon TA (40 mg) was reported to improve VA in all participants, with a change of LogMAR BCVA from 1.09 at baseline to 0.54 at 3 months post injection (10). Last, topical 0.1% betamethasone treatment failed to improve BCVA in RP-CME (37).

A single dose of intravitreal ranibizumab (0.5 mg) was reported to improve BCVA in 9 out of 15 treated eyes, however, the mean BCVA change was not significantly different between ranibizumab and control group (32). In the meantime,

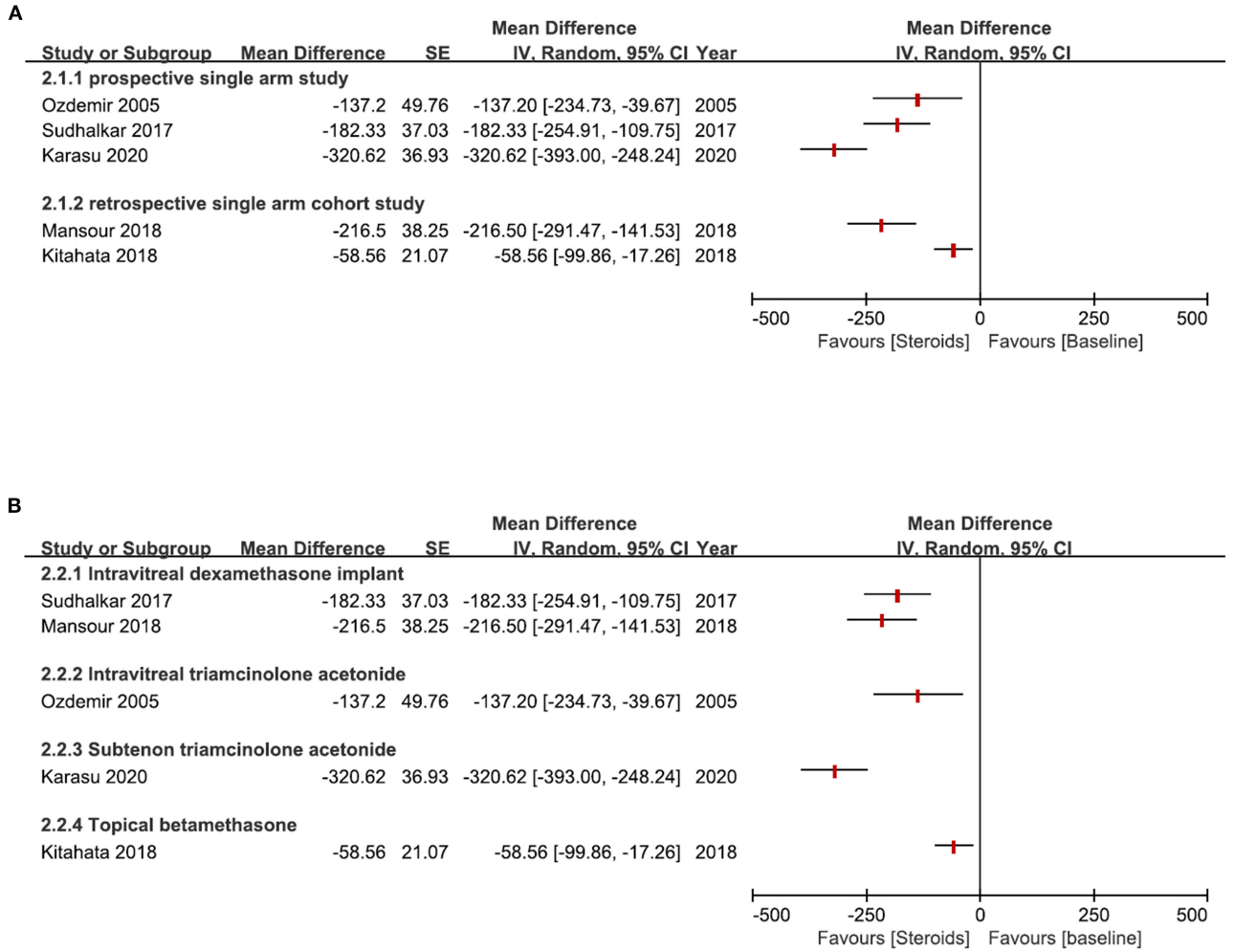

FIGURE 6 | Plots for the change of central macular thickness (CMT) (μm) from baseline after steroids treatment. **(A)** CMT change (μm) in different study types; **(B)** CMT change (μm) of different administration methods of steroids. [for the studies Ozdemir et al. (27) and Sudhalkar et al. (19), the change of CMT was calculated from published original individual data; For the study Kitahata et al. (37), the change of CMT was calculated from the mean/standard deviation data before and after treatment; For the studies Karasu (10) and Mansour et al. (11), the change of CMT was reported in the article].

intravitreal bevacizumab (1.25 mg) was reported to improve VA from 5/400–20/100 to 20/200–20/63 in 13 treated eyes (33). However, intravitreal aflibercept (2 mg) administrated with a 3+TAE protocol failed to show any help in BCVA (20).

Regarding LASER treatment, Newsome et al. reported an improvement of VA in 6 out of 16 eyes treated with grid photocoagulation. Authors also found this method to be effective in preventing worsening of VA (25). On the other hand, subliminal micropulse yellow laser was reported to improve median BCVA from 66.8 ETDRS letters to 70.0 letters ($p = 0.18$), with subjective improvement of central vision, color vision and contrast sensitivity in 68% of patients (21).

In 2003, Garci'a-Arumi' et al. reported that PPV improved the mean VA from 20/115 to 20/45. The VA improved in 10 out of 12 treated eyes, with an average improvement of 3 lines (ETDRS chart, $p = 0.028$) (40). Meanwhile, Reis et al. reported that ketorolac eyedrops improved LogMAR BCVA from 0.37 ± 0.17 at baseline to 0.27 ± 0.18 at 6 months ($p = 0.03$), and to 0.28 ± 0.16 at 12 months ($p = 0.02$) (41). Lutein supplement and oral minocycline didn't show any help in VA (3).

Secondary Outcome: Change in FA Leakage

Evaluation of CME by FA leakage is subjective to some extent, however, in the pre-OCT era, assessment of FA leakage in the macular area provided useful information about macular edema. Overall, 10 of our included studies reported changes in FA leakage after treatment, with different criteria to grade the leakage. Seven of these studies approached the CAIs treatment, 5 of which studied the efficacy of AZM on RP-CME. The ratio of reduced FA leakage in the macular region was reported to be 33% (2 out of 6 patients) (5), 50% (6 out of 12 patients) (38), 0% (0 out of 5) (26), 43% (3 out of 7) (42) and 20% (1 out of 5) (28) after AZM treatment. Meanwhile, methazolamide

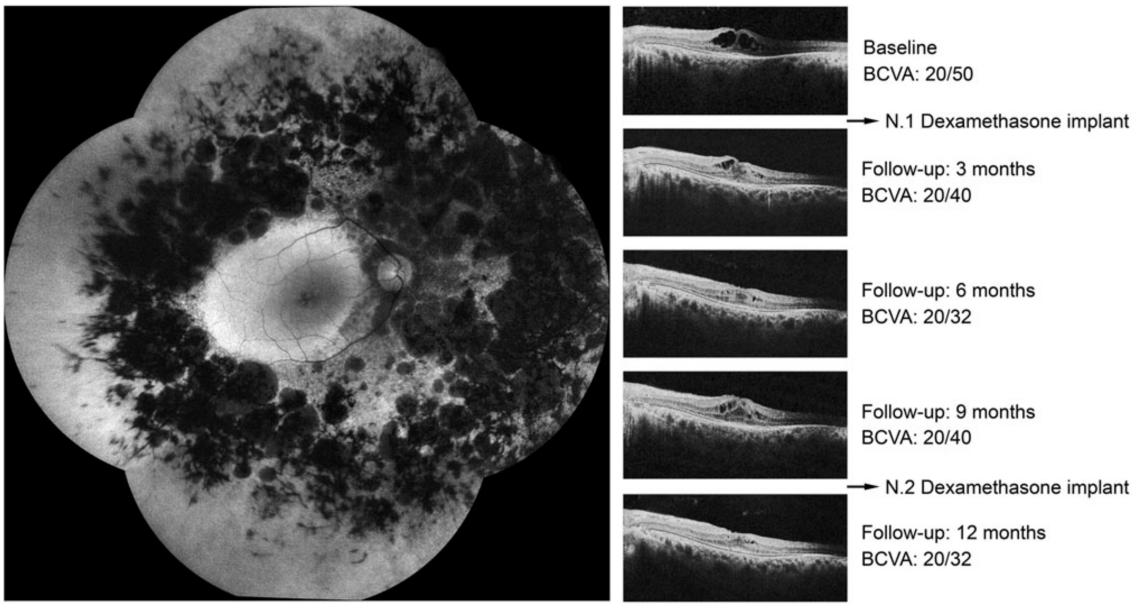

FIGURE 7 | Autofluorescence and optical coherence tomography (OCT) images of a 41-year-old woman affected by macular edema after retinitis pigmentosa (RP) and treated with 1 injection of dexamethasone implant at baseline and at month 9. At baseline, BCVA (Snellen equivalent) was 20/50, and the presence of intraretinal fluid was detected by OCT. At months 3 and 6, BCVA improved, and a reduction in CRT was observed. At month 9, a gradual visual loss and an increase of intraretinal fluid were noted. An additional intravitreal dexamethasone implant was performed at month 9. At 12 months, BCVA improved to 20/32, and no fluid was detected by OCT. This figure was reproduced from Veritti et al. (14). The publisher for this copyrighted material is Mary Ann Liebert, Inc. publishers.

was reported to decrease FA leakage in 9 out of 17 patients (6), and topical dorzolamide treatment reduced leakage in 2 out of 5 patients (43).

In 1987, Newsome et al. reported that grid photocoagulation reduced FA leakage in the macular area in 13 out of 16 treated patients (25). In 2002, Giusti et al. reported that oral deflazacort reduced FA macular leakage in 47% of participants at the study end (12 m) (9). And vitrectomy was reported to reduce macular leakage in 75% of patients (40).

Secondary Outcome: Rebound of CME

Rebound of CME was not rare in spite of continual use of medications. Apushkin et al. reported that 3 out of 6 patients had recurrent CME during prolonged treatment of AZM for 8–12 weeks (29). Also, Fishman et al. reported that all 3 patients that had oral methazolamide (50 mg bid) for prolonged 6–12 weeks experienced rebound of CME (44). For topical dorzolamide, the recurrence rate was reported to be 27% (4 out of 15 patients) (30), 28% (5 in 18 eyes) (39), and 35% (14 in 40 patients) (18). Regarding steroids treatment, Giusti et al. reported that oral deflazacort tapering therapy resulted in reduction of FA leakage in 100% patients at 4 months, while the reduction was observed in only 47% patients at 12 months compared to baseline (9). For IVTA (27), subtenon TA (10) and intravitreal dexamethasone implant treatments (11, 16, 19), multiple injections were needed because of recurrence of CME. Repeated injections were also common in anti-VEGF therapy for RP-CME (20, 33).

Secondary Outcome: Adverse Effects

Among the included studies, adverse effects were reported in 14 studies, and were reported as not present in 13 studies, and were not mentioned in other studies. The side effects of oral AZM and methazolamide included tingling of the extremities, gastrointestinal tract upset, fatigue, dizziness and altered taste sensation (6, 29, 38, 42). Also, Veritti et al. reported that one patient developed aciduria and one patient developed kidney stones after continual use of AZM for 9 and 11 months, respectively (14). Besides, dorzolamide eyedrops was reported to cause a burning and stinging sensation right after administration (30, 43).

No side effects were reported for oral deflazacort, however, regarding local steroids, elevation of intraocular pressure (IOP) and cataract formation was reported (9–11, 16, 19, 37). On the other hand, in the 7 patients treated with oral minocycline (100 mg bid for 12 m), 15 adverse events (3 ocular and 12 non-ocular) were recorded within 16 months after the beginning of treatment (NCT02140164). No adverse effects were reported in anti-VEGF therapy, LASER therapy, PPV, ketorolac eyedrops and lutein supplement for the treatment of RP-CME (3, 20, 21, 25, 32, 33, 40, 41).

DISCUSSION

In the present study, we systematically review the existing treatments for RP-CME on the aspects of efficacy and safety. From the pooled data, we found that CAIs (including oral

and topical CAIs) significantly decreased CMT, with the mean change of −45.64 μm. And the responder proportion was 39% (reduction >11% initial CMT). Multiple mechanisms are implicated in the therapeutic effects of the CAIs in RP-CME. Moldow et al. reported that AZM decreased passive permeability and stimulated unidirectional permeability for fluorescein in the retina of 7 RP-CME patients (42), and they pointed out that AZM reduced retinal vascular leakage and increased active transport through the BRB. In animal models, AZM was demonstrated to accelerate subretinal fluid absorption and promote the adhesion between neuroretina and pigment epithelium, and this effect was attributed to the influence on the carbonic anhydrases located at both apical and basal surfaces of the RPE (1, 45, 46). Regarding spatial distribution of CME, Strong et al. revealed that all RP-CME had fluid in the inner nuclear layer (INL), while all responders to CAIs had coexisting fluid in the outer nuclear layer (ONL). However, not all patients presented with coexisting INL and ONL fluid responded to CAIs (17). They also found that epiretinal membranes had minimal influence on drug efficacy, possibly because the CAIs had better access to the basal surface of the RPE than the neuroretina (17).

Carbonic anhydrases (CA) are ubiquitously distributed in multiple organs and tissues and are involved in various physiological processes (47). CAIs have been used clinically to treat epilepsy, obesity, glaucoma, altitude sickness, idiopathic intracranial hypertension, and some tumors (48). AZM and methazolamide are non-selective CA inhibitors, thus when administrated systematically, they bring about side effects (47), which restricted the long-term use of these drugs. Moreover, it's noteworthy that drug allergy occurs in ∼7.4% of patients exposed to sulfonamide antibiotics (49). CAIs are non-antimicrobial sulfonamides (50). Although cross-reaction between antimicrobial and non-antimicrobial sulfonamides is still controversial (50), application of CAIs in individuals with history of sulfonamide allergy is not recommended, especially when other therapeutic options exist.

Steroids were employed in the treatment of RP-CME on the basis that inflammatory responses were implicated in the pathogenesis. In 1988, Newsome et al. detected the presence of various subsets of T lymphocytes including T helper, T suppressor lymphocytes and natural killer cells from the vitreous sample of RP patients (51). Besides, Yoshida et al. observed inflammatory cells in the anterior vitreous cavity of 37.3% RP patients. Also, they found the levels of proinflammatory cytokines were increased in both the aqueous and vitreous samples of RP patients compared to the control (52). Moreover, Heckenlively et al. detected the existence of serum antiretinal protein antibodies in 27 out of 30 RP patients with macular edema, but only in 4 out of 30 RP patients without macular edema (53), indicative of the implication of inflammation process in RP-CME. Current evidence demonstrated that steroids were beneficial in the management of RP-CME, with the average change of CMT from baseline varied from −58.56 to −320.62μm by different steroids treatments (10, 11, 19, 27, 37). In the 2 studies compared the treatment of intravitreal dexamethasone implant to CAIs (AZM and topical dorzolamide, respectively), the dexamethasone implant was reported to be more effective in reducing CMT as well as improving VA (14, 16). However, the risk of increased IOP and the development of cataract need to be considered, and aphakic or pseudophakic eyes may benefit more from local steroids. Although no side effects of oral deflazacort were observed during a 12-months period (9), we don't recommend oral steroids for RP-CME because of potential risk of infection and adrenal crisis associated with systematic steroids (54).

The rationale for anti-VEGF therapy in RP-CME is still debatable. VEGF has been identified as a neuroprotective factor, which plays an important role in neuron survival and in the functional maintenance of retinal ganglion cells, photoreceptors and Muller cells (55, 56). Salom et al. reported that the aqueous level of VEGFA was 94.9 ± 99.8 pg/ml in eyes of RP patients, and 336.5 ± 116.8 pg/ml in control eyes ($p < 0.001$). They speculated that the inadequate VEGF level may contribute to the degeneration of retinal vasculature in RP patients, and questioned the validity of anti-VEGF therapy in RP-CME (56, 57). In the present systematic review, 3 included studies approached the efficacy of different anti-VEGF reagents in RP-CME. Ranibizumab significantly reduced mean CMT in 15 included eyes, but the BCVA improvement was not significant compared to control (32). Bevacizumab was reported to be effective in reducing CMT as well as improving BCVA in 7 patients (33). Aflibercept failed to reduce mean CMT or improve BCVA in a group of 30 patients, in spite of an initial response after the first injection in all patients (20). Based on existing evidence, anti-VEGF therapy may not be suitable for treating RP-CME.

Grid photocoagulation was reported to reduce FA leakage in 13 out of 16 treated eyes and improve VA in 6 out of the 16 eyes (25). However, due to possible deterioration of the severely constricted visual fields in RP patients after treatment, the validity of grid photocoagulation is questionable (58). In contrast, micropulse LASER may be more suitable in treating RP-CME. The length of each LASER pulse is 100–300 μs, so that the RPE cells are only stimulated, instead of being destroyed by thermal heat (59). The stimulation of RPE cells induces an altered profile of gene expression, which is beneficial for tissue healing and repair of the inner BRB (59). Micropulse LASER was reported to reduce CMT significantly in RP-CME. Although the change in BCVA was not significant, 86% of participants had subjective improvement of vision (21). Possessing the non-invasive, safe and repeatable properties, micropulse LASER treatment may be promising in the treatment of RP-CME. However, more clinical studies are needed to verify the efficacy and safety of this treatment approach.

Vitrectomy was employed to treat RP-CME on the hypothesis that vitreous traction played a role in the pathogenesis. Vitrectomy with internal limiting membrane removal and gas tamponade was reported to reduce CMT and significantly improve VA in 12 RP-CME eyes (40). However, this is the only study approached the efficacy and safety of vitrectomy in RP-CME, with small number of patients. Concerning its invasive

nature and the potential risk of complications, vitrectomy should not be considered when other methods are effective and available.

It is noteworthy that although some of our included studies reported the CMT reduction along with the significant improvement of BCVA (10, 11, 14, 16, 19, 40), several other included studies reported that the remarkable reduction of CMT accompanied only minimal improvement of BCVA (17, 27, 28, 32, 39). Chung et al. attributed this to the irreversible photoreceptor cell loss and permanent functional damage due to chronic macular edema and the genetic degenerative nature of the photoreceptor cells in RP patients (28). Two recent studies found that the duration of CME did not affect the positive anatomical change after treatment (13, 20). Nevertheless, Strong et al. pointed out that the intactness of the photoreceptor layer and the ellipsoid zone within the macular was important for the improvement of VA after treatment (20). Thus, early management of CME may be vital in preserving the vision in RP patients.

Rebound of RP-CME was reported in some treatment approaches including subtenon TA, intravitreal TA and intravitreal dexamethasone implant (10, 11, 16, 19, 27, 31). In these studies, patients responded well to retreatments, indicating that the rebound was due to drug elimination. However, in several included studies, rebound of RP-CME was observed in spite of continual use of the drugs (AZM, methazolamide and dorzolamide included) (29, 30, 39, 44). Although rebound of CME might be partially attributed to poor patient compliance (18, 44), the underlying mechanisms were unknown. A recent study found that the high baseline CMT value was significantly associated with recurrence of CME in topical dorzolamide treatment (18). Authors also reported that in rebound RP-CME under dorzolamide treatment, additional topical steroids was useful to reduce CMT (18).

The most common measurements for evaluating RP-CME include BCVA, CMT measured by OCT, and FA leakage. Chung et al. reported that among the included 10 patients who had macular cyst change in OCT, 5 had fluorescein leakage in FA (28). OCT is more sensitive in detecting RP-CME, because OCT detects the fluid accumulation both from RPE pumping dysfunction and BRB breakdown, while FA only detects the latter (57). Moreover, inconsistency between OCT and FA may also rise from that FA detects the real-time vascular or RPE leakage and the accumulation of dye during the examination, while OCT detects the intraretinal fluid accumulating from a relatively long period of time. On the other hand, the macular sensitivity detected by Humphrey field analyzer 10–2 program may also be helpful in evaluating the visual function change in RP-CME (35).

Compared with the previous systematic reviews (4, 8), our study included meta-analyses in order to evaluate the extent of the change of CMT after CAIs treatment. While compared with the previous published meta-analysis (12), our study added data from recently published studies, as well as calculated the pooled responder rate. However, the current study has limitations. Most of our included studies had small patient number, due to the relatively low incidence of RP-CME. The 6 RCTs included in our study had a patient number of 5–39, and 5 of the RCTs were crossover designed studies. More than half of the included studies lacked a control group. Moreover, the follow-up period of all included prospective studies were no more than 2 years, which is insufficient regarding the refractory and recurrent nature of RP-CME.

Another limitation of our study was the heterogeneity among the included trials, which restricted the pooling of data. For example, some of the included studies measured visual acuity (VA) as the therapeutic outcome (27, 33), while other studies measured the best corrected visual acuity (BCVA), which was more accurate for evaluating the visual function. Also, the grading system for FA leakage was different among studies (5, 28, 38). Moreover, the measurement of CMT was not consistent among the studies we used for meta-analysis. Some of the studies measured the foveal thickness (FT) (28, 37), while some other studies measured the central subfield thickness (CST) or foveal zone thickness (FZT) which was defined as the mean thickness of the central 1,000 μm diameter area of the macula (11, 34, 35, 39). Some studies didn't mention their definition of CMT at all (10, 17, 19, 27, 36), while some other studies reported both FT and FZT (for these studies we used FZT values for analyzing) (7, 29, 30). The inconsistency in CMT measurement decreased the accuracy of our data pooling.

Last but not the least, in most of our included studies, RP was diagnosed by typical clinical signs and symptoms (night-blindness, restricted visual field, pale optic disc, retinal vessel attenuation and bone spicule pigments) as well as the change of electroretinography. Nevertheless, genetic mutation test was not routinely carried out, even in recent years. Twelve of the included studies recorded the inheritance pattern of RP (autosomal dominant, autosomal recessive, X-linked recessive or sporadic) (5, 9–11, 15, 20, 30, 34, 36, 37, 40, 43), while only 3 studies reported the specific mutation of genes (20, 30, 34). Liew et al. reported that the macular edema of autosomal recessive RP responded better to topical dorzolamide than autosomal dominant RP (36). However, Strong et al. found no association between inheritance pattern and response to intravitreal aflibercept (20). As diverse genetic types of RP may respond differently to therapy, genetic tests are recommended in future studies, which will add to our knowledge of RP-CME.

Because of the limitations mentioned above, no high-quality evidence could be provided based on existing reports. More controlled clinical trials are needed in future, since single-arm studies cannot rule out the influence of natural progression of the disease. Topical CAIs, local steroids, topical NSAIDS and micropulse LASER are worthwhile for more clinical trials as the side effects of these treatments are milder compared to oral CAIs and systematic steroids. Thus, these treatments may be used for a relatively long period, or can be repeated (retreated). On the other hand, standard measurements, for example, BCVA (in logMAR or in ETDRS letters) and CST (the average thickness of the central 1,000 μm diameter area of the macular) are recommended in future studies.

To sum up, topical CAIs, oral CAIs and local steroids were proved to be effective in treating RP-CME. However, due to the overall inferior design and small patient number of the included studies, the grade of evidence was very low. Systematic steroids, LASER, NSAIDS and PPV may also be effective, nevertheless, considering the limited number of studies, no conclusion could

be drawn regarding these treatments. More well-designed and conducted studies, especially RCTs, are desperately needed.

DATA AVAILABILITY STATEMENT

The original data are presented in the article and online supplementary files. Further inquiries can be directed to the corresponding author XP (74000041@ccmu.edu.cn) or to CC (chenchenmd@aliyun.com).

AUTHOR CONTRIBUTIONS

XP and CC conceived and designed the project. CC and XL performed the literature search, data extraction, study quality assessment, and data analysis. CC drafted the manuscript. XP critically revised the paper. All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.895208/full#supplementary-material

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Comparison of Intravitreal Anti-VEGF Agents With Laser Photocoagulation for Retinopathy of Prematurity of 1,627 Eyes in China

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Purpose: To compare the efficacies and treatment outcomes of intravitreal anti-VEGF agents and laser therapy in retinopathy of prematurity (ROP).

Methods: A retrospective, non-randomized, comparative study of patients diagnosed with type 1 ROP or aggressive posterior ROP (A-ROP) treated with intravitreal anti-VEGF agents or laser therapy as primary treatment at the People's Hospital of Peking University.

Results: A total of 1,627 eyes of 862 patients were included. In **Group 1**, 399 eyes of 204 patients were diagnosed with A-ROP or zone I type 1 ROP. The initial regression of the anti-VEGF subgroup was better than that of the laser subgroup, and the reactivation rate and rate of progression to retinal detachment were lower than those of the laser subgroup. In **Group 2**, 1,228 eyes of 658 patients were diagnosed with zone II type 1 ROP. The reactivation rate of the laser subgroup was lower than that of the anti-VEGF subgroup. No significant differences were found in the initial regression and the probability of developing retinal detachment. Among the anti-VEGF agents, the reactivation rate in eyes treated with conbercept was much lower than that in eyes treated with ranibizumab. The spherical power and spherical equivalents of eyes treated with laser were significantly higher than those of eyes treated with anti-VEGF agents 1 year after initial treatment.

Conclusions: In contrast to laser therapy, anti-VEGF agents as primary treatments have potential advantages for eyes with zone I type 1 ROP and A-ROP. For eyes with zone II type 1 ROP, laser photocoagulation and anti-VEGF agents therapy showed similar efficacy; however, the rate of reactivation with laser therapy was significantly lower than that with anti-VEGF agents. Among the anti-VEGF agents, the reactivation rate was much lower in eyes treated with conbercept than in eyes treated with ranibizumab. Compared to anti-VEGF agents, laser treated eyes had greater trend to myopia.

Keywords: retinopathy of the prematurity, type 1 ROP, APROP, anti-VEGF (vascular endothelial growth factor), laser

INTRODUCTION

Retinopathy of prematurity (ROP) is one of the leading causes of childhood blindness in both developing and developed countries and is associated with premature birth and oxygen intake (1). Aggressive retinopathy of prematurity (A-ROP) is considered to be a subtype in premature infants (2–5), characterized by rapid progression instead of following the typical stages of the disease.

Treatment of ROP has undergone changes in the last 30 years. Initially, studies (6–11) such as the CRYO-ROP trial (11) confirmed the effectiveness of cryotherapy. Later, studies (12–17) such as the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial (17) showed the efficacy of diode laser therapy. To date, laser therapy is still the classic treatment of ROP. With the in-depth study of the pathogenesis of ROP and many reports of the drawbacks of laser treatment of ROP, anti-VEGF therapy has also entered the treatment stage. A number of studies, such as the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study (BEAT-ROP study), has confirmed the efficacy of anti-VEGF agents in ROP treatment [bevacizumab (IVB) (18–21); ranibizumab (IVR) (22–24); conbercept (IVC) (25–27)]. In the last decade, the use of anti-VEGF therapy has increased significantly. However, considering the advantages and disadvantages of laser and anti-VEGF agents, the optimal treatment options remain controversial.

Our hospital is one of the first units to carry out ROP screening and treatment in China. We have experienced the evolution of treatments from external cryotherapy to laser therapy and then to anti-VEGF agents, including bevacizumab (IVB), ranibizumab (IVR) and conbercept (IVC). Here, we summarize our own ROP treatment data between 2010 and 2018 of cases diagnosed with type 1 ROP or A-ROP, treated with anti-VEGF agents (including bevacizumab, ranibizumab, conbercept) or laser photocoagulation primarily at our eye center, and followed for at least 6 months. In this study, we compared the efficacies and treatment outcomes of anti-VEGF and laser coagulation, including the rate of initial regression, reactivation requiring retreatment, retinal detachment, refractive status.

METHODS

This was a retrospective study that was conducted in a tertiary hospital, namely, People's Hospital of Peking University, Beijing, China. The research was approved by the Clinic Institutional Review Board and complied with the Declaration of Helsinki. All patients enrolled in the retrospective study were diagnosed with type 1 ROP or A-ROP, were treated with anti-VEGF agents (bevacizumab, ranibizumab, conbercept) or laser photocoagulation primarily within 72 h of diagnosis (A-ROP within 24 h) between 2010 and 2018 at the Eye Center in People's Hospital of Peking University, and had at least 6 months of follow-up. ROP was diagnosed and classified according to the International Classification of ROP (3). Type 1 ROP was defined as zone I any stage with plus, zone I stage 3 without plus, or zone II stage 2 or stage 3 with plus according to the Early Treatment Retinopathy of Prematurity Study (17). A-ROP was defined as increased dilation and tortuosity of the posterior pole vessels in all four quadrants with a new vascular network between vascularized and non-vascularized retina in zone I and posterior zone II (3). After we communicated with the parents of ROP infants, the parents choosed treatment method. For patients who cannot withstand general anesthesia, they can only be treated with anti-VEGF injection.

For anti-VEGF injection, topical anesthesia or inhalation anesthesia was used. The eyelid was opened with an eyelid speculum, 10% povidone-iodine was instilled, anti-VEGF agents [bevacizumab (IVB) at a dose of 0.625 mg/0.025 ml; ranibizumab (IVR) at a dose of 0.25 mg/0.025 ml; and conbercept (IVC) at a dose of 0.25 mg/0.025 ml, which was half of the adult dose for treating age-related macular degeneration (AMD)] were injected with a sterile 0.5-inch needle 1 mm posterior to the limbus.

For laser photocoagulation, inhalation anesthesia or intubation anesthesia were used. After an eyelid speculum was placed into the eyelid, an indirect laser was used to photocoagulate the entire avascular retina.

All the patients who underwent anti-VEGF injection or laser photocoagulation were reexamined the next day to assess infection, returned to our hospital 1 or 2 weeks (one week after the injection or 2 weeks after the laser therapy) to assess the efficacy of treatment, and then returned to the clinic according to the gestational age and eye condition as evaluated by our ophthalmologists. The supplementary treatment in the follow-up process included reinjection, laser treatment, external compression, vitrectomy with or without lensectomy.

In some patients, cycloplegic refraction 6 months after primary treatment was obtained during an examination under anesthesia.

The main outcome measures in this study included initial regression, reactivation requiring retreatment, and retinal detachment. Initial regression was defined as follows: plus disease or a ridge regressed partially or completely after the first treatment. Reactivation requiring retreatment was defined as plus disease or ridge reappearance; retinal detachment was defined as ROP worsening into stage 4a or 4b or stage 5 requiring external compression or vitrectomy with or without lensectomy.

The following information about the patients in this study was collected and recorded: gender, gestational age at birth, birth weight, ROP zone, ROP stage, plus disease, presence or absence of A-ROP, age at primary treatment, follow-up period, presence or absence of reactivation, and additional treatment.

Classification of Patients

We classified all the eyes into 2 groups according to the ROP zone and ROP type: group 1 consisted of A-ROP and zone I ROP which meets type 1 diagnostic criteria, and group 2 consisted of zone II stage 2 or stage 3 ROP with plus disease. Each group was classified into two subgroups: one subgroup was treated with anti-VEGF agents, and the other was treated with laser photocoagulation. We compared the rate of initial regression, reactivation requiring retreatment, and rate of retinal detachment requiring surgery between the two subgroups in each group. In addition, refractive data was compared between these two treatments.

TABLE 1 | Demographics of the infants enrolled.

	Zone I ROP and APROP			Zone II ROP		
	Anti-VEGF group	**Laser group**	***P*-values**	**Anti-VEGF group**	**Laser group**	***P*-values**
Patients, *n*	133	71	/	509	149	/
Male, *n* (%)	53 (39.8%)	31 (43.7%)	0.655	277 (54.4%)	87 (58.4%)	0.391
GA, weeks	29.5 ± 2.1	29.2 ± 2.1	0.246	28.7 ± 2.0	30.2 ± 2.3	<0.001
	(range: 25–37)	(range: 25–36)		(range: 20–36)	(range: 28–32)	
Bw, g	1334.7 ± 374.9	1282.2 ± 258.9	0.200	1252.5 ± 368.4	1410.9 ± 374.6	<0.001
	(range: 800–3,000)	(range: 850–2,035)		(range: 500–3,100)	(range: 850–2,700)	
PMA, weeks	36.5 ± 2.7	36.2 ± 2.3	0.427	39.7 ± 3.9	38.6 ± 3.2	<0.001
	(range: 30–47)	(range: 32–46)		(range: 28–57)	(range: 33–48)	
Follow-up months	20.3 ± 12.0	13.2 ± 1.6	0.063	17.8 ± 11.3	21.24 ± 18.7	0.044
	(range: 6.6–85.7)	(range: 9.47–107)		(range: 6.0–86.6)	(range: 6.0–83.0)	

GA, gestational age; BW, birth weight; PMA, postmenstrual age.

Statistical Analysis

The data were analyzed using SPSS (version 22; SPSS Science, Chicago, IL). The Mann-Whitney *U*-test and Student's *t*-test were used to compare the quantitative data. Qualitative data were analyzed with the Chi-square test. A generalized estimating equation (GEE) method using the SAS procedure GENMOD (version 9.4, SAS Institute, Cary, NC) that allows for intereye correlation was used for analysis of binary treatment outcomes for zone II type ROP. Values of $p < 0.05$ were considered statistically significant.

RESULTS

A total of 1,627 eyes of 862 patients were included. **Group 1** contained 399 eyes of 204 patients, including 137 eyes of 71 patients with laser therapy and 262 eyes of 133 patients with anti-VEGF therapy. **Group 2** contained 1,228 eyes of 658 patients, including 266 eyes of 149 patients with laser therapy and 962 eyes of 509 patients with anti-VEGF therapy.

1. Comparison between anti-VEGF agents and laser therapy for ROP, including rate of initial regression, reactivation requiring retreatment and retinal detachment.

For **group 1 (A-ROP and zone I ROP),** no significant differences were observed between the two subgroups in terms of gestational age, birth weight, sex distribution, postmenstrual age at treatment and follow-up period (shown in **Table 1**).The comparison of treatment outcomes were shown in **Table 2**; the initial regression of anti-VEGF subgroup was significantly better than that of the laser subgroup ($P < 0.001$), and the reactivation rate and the probability of developing to retinal detachment were significantly lower than those of the laser subgroup ($P < 0.001$, $P = 0.001$, respectively).

For **group 2 (zone II ROP)**, significant differences were observed between the two subgroups in terms of gestational age, birth weight, postmenstrual age at treatment and follow-up period, but the overall distribution was similar. The sex distribution showed no difference (shown in **Table 1**). Therefore, a GEE was used for multivariate analysis of the difference in initial regression, reactivation rate, and proportion of retinal detachment between the two subgroups. The comparison of treatment outcomes of group 2 is shown in **Table 2**. There was no significant difference in the initial regression or probability of developing retinal detachment between the two subgroups ($P = 0.406$, $P = 0.136$, respectively). However, the reactivation rate of the laser subgroup was significantly lower than that of the anti-VEGF subgroup ($P = 0.009$).

2. Comparison between the two anti-VEGF agents (ranibizumab vs. conbercept) for ROP.

A total of 916 eyes treated with intravitreal ranibizumab (IVR), 283 eyes treated with intravitreal conbercept (IVC) and 25 eyes treated with intravitreal bevacizumab (IVB) were included in our study. Among them, no significant differences were observed between eyes with IVR and those with IVC in terms of gestational age, birth weight, sex distribution, postmenstrual age at treatment and follow-up period. The comparison of treatment outcomes of IVR and IVC are shown in **Table 3**. No statistically significant differences in the initial efficacy or the rate progression to retinal detachment were found. However, the reactivation rate of IVC was lower than that of IVR: for zone I ROP and A-ROP, the reactivation rate of IVC was 23%, much lower than the 49% for IVR ($P = 0.006$). For zone II ROP, the reactivation rate of IVC was 12%, much lower than the 23% for IVR ($P < 0.001$).

3. Comparison of refractive errors between ROP patients treated with anti-VEGF agents and laser photocoagulation.

Refractive data were collected from 212 eyes of 110 ROP patients with regressed ROP 6 months after receiving laser or anti-VEGF injection. There was no significant difference in baseline data such as GA, BW, PMA between the two groups. In total, 121 eyes of 61 ROP patients received anti-VEGF injection only, and among them, 2 eyes had zone I ROP, 4 eyes had A-ROP, and the others had zone II ROP; the mean spherical refractive error was 1.51 ± 1.26 D, the mean astigmatism 0.79 ± 1.33 D, and the mean spherical equivalent was 1.90 ± 1.42 D. Ninety-one

TABLE 2 | The comparison of efficacies and treatment outcomes.

	Zone I ROP and APROP			Zone II ROP		
	Anti-VEGF group	**Laser group**	***P*-values**	**Anti-VEGF group**	**Laser group**	***P*-values**
Eyes, *n*	262	137	/	962	266	/
Initial regression-no. of eyes (%) regression	223 (85%)	97 (71%)	<0.001	933 (97%)	263 (99%)	0.406
Reactivation-no. of eyes (%)	123 (47%)	90 (66%)	<0.001	202 (21%)	21 (8%)	0.009
Retinal detachment-no. of eyes (%)	26 (10%)	30 (22%)	0.001	8 (0.8%)	3 (1.1%)	0.136

TABLE 3 | The comparison of efficacies and treatment outcomes of IVR and IVC.

	Zone I ROP and APROP			Zone II ROP		
	IVR group	**IVC group**	***P*-values**	**IVR group**	**IVC group**	***P*-values**
Eyes, *n*	220	35	/	696	248	/
Initial treatment efficacy-no. of eyes (%) regression	187 (85%)	33 (94%)	0.091	675 (97%)	240 (97%)	0.781
Reactivation of ROP- no. of eyes (%)	108 (49%)	8 (23%)	0.006	160 (23%)	30 (12%)	<0.001
Retinal detachment- no. of eyes (%)	22 (10%)	2 (6%)	0.392	5 (0.7%)	3 (1.2%)	0.485

eyes of 49 ROP patients received laser therapy only, and among them, 4 eyes had zone I ROP, and the others had zone II ROP; the mean spherical refractive error was 1.61 ± 1.77 D, the mean astigmatism 0.65 ± 1.54 D, and the mean spherical equivalent 1.8 ± 1.99 D, No significant difference were found between these two groups ($P = 0.617$, $P = 0.480$, $P = 0.691$, respectively). However, refractive data from eyes of regressed ROP patients after 1 year of anti-VEGF injection or laser therapy were significantly different. The mean spherical refractive error of eyes (71 eyes/36 patients, 2 eyes had zone I ROP, 2 eyes had A-ROP, and the others had zone II ROP) treated with anti-VEGF agents was 1.20 ± 1.31 D; the mean astigmatism was 0.19 ± 1.51 D, and the mean spherical equivalent was 1.8 ± 1.99 D. The mean spherical refractive error of eyes (53 eyes/32 patients: 2 eyes had zone I ROP, and the others had zone II ROP) with laser therapy was 0.34 ± 1.16 D, and the mean astigmatism was −0.37 ± 1.62. Statistical differences were found between these two groups. The spherical and spherical equivalents were significantly higher in eyes treated with laser than in eyes treated with anti-VEGF agents ($P = 0.06$, $P < 0.001$, respectively). No difference was found in the power of astigmatism ($P = 0.201$). The above results are shown in **Table 4**.

DISCUSSION

To the best of our knowledge, this is the largest sample size for a comparative study on the efficacy of intravitreal anti-VEGF agents and laser photocoagulation for ROP. As one of the earliest centers to carry out ROP screening and treatment in China, we reported the use of intravitreal injection of anti-VEGF agents or laser photocoagulation as first-line therapy among a total of 1,627 eyes of 862 premature infants from 2010 to 2018 in our center.

For our initial treatment options, we had used laser therapy for ROP patients before 2010, then IVB was started from 2011, IVR from 2011 and IVC from 2015. Most of the cases treated with laser and IVB happened before 2013. Later, as the anti-VEGF agents being used more widely in ROP, laser has been used relatively less frequently. However, in our center, for the patients who came from distant provinces or had difficulties in keeping long-term follow-up, we tended to choose laser therapy. In all of our cases, we had communicated fully with the parents of ROP patients, and the vast majority had chosen anti-VEGF treatment for its convenience, safety and efficacy. For ROP patients who could not tolerant general anesthesia, only anti-VEGF treatment could be selected. Thus, we observed that in zone II ROP, gestational age, birth weight and postmenstrual age in anti-VEGF group were all smaller than those in laser group. Moreover, for ROP cases accompanied by fibrous tissue on the ridge, we tended to choose laser instead of anti-VEGF injection, because our long-term clinical observations showed that in ROP cases with fibrotic proliferation, the treatment of anti-VEGF injection was more likely to aggravate retinal pulling and increase the risk of retinal detachment than laser therapy. This might be attributed to the role of anti-VEGF drugs played in fibrotic proliferation.

For our additional treatment options, the above factors were still very important. Besides, for ROP cases that recurred after first injection, if the avascular area was large, which meant the lesion was located posterior, we tended to choose anti-VEGF drugs because laser treatment would cause a definite visual field defect for patients. However, if ROP cases reactived after two injections, although there was still a large avascular zone, we would choose laser therapy.

Our clinical study showed the efficacies of both anti-VEGF agents and laser therapy as primary monotherapy for type 1 ROP and A-ROP.

1. anti-VEGF agents had advantages in zone I type 1 ROP and A-ROP.

Initial regression was an important observation indicator. In our study, for zone I ROP and A-ROP, the initial regression rate of

TABLE 4 | Comparison of refractive errors between ROP patients treated with anti-VEGF and laser.

	6-month follow-up			1-year follow-up		
	Anti-VEGF group	**Laser group**	***P*-values**	**Anti-VEGF group**	**Laser group**	***P*-values**
Eyes, *n*	121	91	/	71	53	/
Mean spherical refractive error (D)(D) eyes (%) regression	1.51 ± 1.26	1.61 ± 1.77	0.617	1.20 ± 1.31	0.34 ± 1.16	0.060
Mean astigmatism (D)	0.79 ± 1.33	0.65 ± 1.54	0.480	0.19 ± 1.51	−0.37 ± 1.62	0.201
Mean spherical equivalent (D)	1.90 ± 1.42	1.8 ± 1.99	0.691	1.8 ± 1.99	0.19 ± 1.53	<0.001

the anti-VEGF agent group was 86%, which was obviously higher than that (71%) of laser ablation ($P < 0.001$). The initial response reflected whether the disease could be controlled quickly. It was well-established that anti-VEGF agents had a fast onset, whereas laser therapy worked relatively slowly. Moreover, the low initial regression rate of laser therapy for zone I ROP and A-ROP might be attributed to the fact that it was a more difficult operation than intravitreal injection. Pupil rigidity in some eyes would make it harder to expose the avascular area, which was much larger than that in eyes with zone II ROP, thus increasing the difficulty for laser surgery. Inadequate laser treatment could not effectively prevent ROP progression, so the rate of initial regression was low. Similarly, the sooner ROP disease was controlled, the better would be the prognosis. Our research had also confirmed this. Because of the fast-progression of zone I type 1 ROP and A-ROP, if the initial treatment could not control ROP in time, the rate of progression to retinal detachment in the anti-VEGF agent group was 10%, significantly lower than that (22%) in the laser group ($P = 0.001$).

Reactivation after the first effective treatment of ROP was also an important observation indicator. In our study, comparing the reactivation of eyes treated with laser or anti-VEGF agents, we found that in zone I ROP and A-ROP, eyes treated with anti-VEGF agents (47%) were less likely to experience reactivation than those treated with laser ablation (66%, $P < 0.001$), which was in accordance with the BEAT-ROP study (21) (3.2 vs. 35% for zone I ROP).

Therefore, from the three points of initial regression, the probability of progressing to retinal detachment and rate of reactivation, anti-VEGF agents had advantages in zone I type ROP and A-ROP when compared with laser therapy.

2. Laser photocoagulation and anti-VEGF agents therapy showed similar efficacy for eyes with zone II ROP, however, the rate of reactivation with laser therapy was significantly lower than that with anti-VEGF agents.

For zone II ROP, anti-VEGF agent group and laser ablation group both showed a high initial regression rate (97, 99%, respectively), which were much higher than those for zone I group and A-ROP (85, 71%, respectively), and no significant difference was found between the two groups ($P = 0.406$). This might be attributed to the relatively simpleness of laser operations for Zone II type 1 ROP. The sooner ROP disease was controlled, the better would be the prognosis. Because of the high initial regression of ROP cases in two groups, the rate of progression to retinal detachment were both low (anti-VEGF agent group 0.8%, laser group 1.1%) and no significant difference was found between them ($P = 0.136$).

However, the reactivation rate of eyes treated with anti-VEGF agents was 21%, which was much higher than those eyes treated with laser therapy (8%) ($P = 0.009$), which was opposite to the BEAT-ROP study (21) (anti-VEGF agents 5.1% vs. laser 11.2% for posterior zone II ROP). Unlike the BEAT-ROP study, reactivation requiring retreatment in our study was defined as plus disease or ridge reappearance, not neovascularization. Also, the composition ratio of ROP types was not the same. The BEAT-ROP study eliminated anterior zone II ROP, but we included all the zone II ROP, which met the type 1 ROP diagnostic criteria. As described above, the laser treatment for ROP which located posterior was relatively difficult, so the reactivation rate of ROP treated with laser in BEAT-ROP study was higher than that in our group.

Moreover, the ROP population was different. All individuals in the present study population were Asians, but those of the BEAT study were various ethnicities.

We believed that laser treatment in zone II ROP had a relatively high success rate, and it was easier to perform sufficient ablation. Once the peripheral retina was sufficiently photocoagulated, the damaged retina would no longer cause elevated VEGF concentrations in the eye. However, anti-VEGF agents had a metabolic cycle in the eye. During the continuous growth of the vasculature of the peripheral retina, the fluctuation of VEGF could still cause ROP reactivation, and therefore, the reactivation rate of the laser group was lower than that of the anti-VEGF agent group.

3. Reactivation rate of IVC group was lower than that of IVR.

A total of 916 eyes with IVR, 283 eyes with IVC and 25 eyes with IVB were included in our study. Among them, no statistically significant differences in the initial regression or rate of progression to retinal detachment were found between eyes treated with conbercept and those treated with ranibizumab. However, the reactivation rate of eyes treated with conbercept was much lower than those treated with ranibizumab. This might be attributed to the differences in structure of the two drugs. Ranibizumab is a well-established recombinant, humanized monoclonal G1 kappa isotype antibody Fab fragment that is structurally derived from the light chains of bevacizumab and is designed to bind all isoforms of VEGF-A. Conbercept is a recombinant soluble fusion protein composed of the second Ig domain of

VEGFR1 and the third and fourth Ig domains of VEGFR2 with the Fc portion of human IgG (28). The receptor portion has a high affinity for all VEGF-A isoforms, PIGF 1 and 2, and VEGF-B (29). Most likely, because of more targets of conbercept than of ranibizumab, the effect of conbercept may be faster and more powerful. Thus, the reactivation rate in conbercept-treated eyes may be lower than eyes treated with ranibizumab.

4. The refractive results after 1 year of primary treatment showed that laser treatment had a greater effect on the change in refractive power than anti-VEGF injection had, and the refractive power was 1 D lower with anti-VEGF treatment than with laser treatment. Therefore, lasers were more likely to cause myopia and advances in pre-existing myopia, which were comparable with the effects observed in other studies. There was no difference in refractive data obtained over 6 months, which might be because the eyeball is still developing as the patient ages and the effect of laser on refractive power may gradually emerge.

In summary, our study demonstrated that for initial treatment in eyes with zone I ROP and A-ROP, anti-VEGF agents seemed to have potential advantages in contrast to conventional laser therapy. For eyes with zone II ROP, anti-VEGF agents and laser photocoagulation showed similar efficacy, however, the reactivation rate of eyes treated with laser therapy was significantly lower than those treated with anti-VEGF agents. Among the anti-VEGF agents, the reactivation rate of eyes treated with conbercept was much lower than those treated with ranibizumab. Lasers were more likely to cause advances in myopia.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Beijing University People's Hospital Medical Ethics Committee Peking University People's Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

JL: conceptualization, supervision, and writing—review and editing. JL and DL: methodology. JL, HY, MZ, YJ, and XL: cases provider. DL, YC, XZ, and XD: data collection and data curation. DL and YC: data formal analysis. DL: writing—original draft. All authors contributed to the article and approved the submitted version.

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One-Year Outcomes of Modified Technique for Scleral Fixation of a Three-Piece Intraocular Lens Without Conjunctival Opening

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Purpose: This study aimed to present the 1-year follow-up of a modified technique for scleral fixation of three-piece intraocular lens (IOLs) without conjunctival incision.

Materials and Methods: A retrospective chart review of a consecutive series of 10 eyes of nine patients who underwent scleral IOL fixation using the modified technique was performed. Data were collected 1 year after surgery for all patients.

Results: The range of follow-up time was between 1 year and 31 months. At the last follow-up point, the IOL was well-positioned and the visual acuity was good (as limited by primary diseases). Short-term complications included pupillary IOL capture (n = 1) and decreased intraocular pressure (n = 1), and no long-term complications were observed.

Conclusion: Outcome data support this technique as a viable option for the management of secondary IOL fixation with flexible usage of more designs of IOLs.

Keywords: intraocular lens, three-piece, scleral fixation, Hoffman pockets, outcomes, modified technique

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INTRODUCTION

Scleral fixation of posterior chamber intraocular lens (PCIOLs) is a widely accepted way to restore aphakic eyes without enough capsule, such as congenital and acquired zonular weakness, posttraumatic subluxation, and post lensectomy. Although several sutureless scleral fixation methods have been reported in recent years, such as the flanged haptic technique (1) and the scleral tunnel approach (2, 3), the scleral suture fixation of PCIOL is still one of the most effective methods and offers relatively easy management of potential surgical complications (4).

CZ70BD IOL (Alcon Laboratories, Inc., Fort Worth, United States) is a commonly used scleral-sutured IOL that is made of polymethyl methacrylate (PMMA) and has an optic diameter of 7 mm. While such a sizable rigid IOL requires a large incision and risks intraoperative damage and postoperative complications (5), the use of foldable IOL refines this surgery into a small incision; however, most of the IOLs reported for scleral fixation in previous studies were specially designed with closed-loop haptics, such as Akreos AO IOL (Bausch & Lomb, Inc., Rochester, United States) (6, 7) with four eyelet haptics and C-flex IOL (Rayner Intraocular Lenses Ltd., East Sussex, United Kingdom) with two closed-loop haptics (8). The options of foldable IOLs for scleral fixation are still limited. Therefore, developing novel fixation techniques for flexible usage of various designs of IOLs represents a general trend and fits in with different conditions.

In this study, we propose a modified technique for the scleral fixation of a secondary foldable three-piece PCIOL, which demonstrates surgical success in ten eyes. The long-term outcomes are presented to evaluate the reliability and reproducibility of this novel technique.

SUBJECTS AND METHODS

Institutional Review Board approval and Ethical Review Board approval were obtained from Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. The study adhered to the principles of the Declaration of Helsinki. A retrospective chart review consisting of 10 eyes of nine patients who underwent modified transscleral suture fixation of a 3-piece pre-loaded PIOL (PY60AD, HOYA Medicals, Tokyo, Japan) between December 2018 and July 2020 was performed. Patients were followed up for at least 1 year after surgery.

Data collected included surgical indications, primary surgery (if applicable), the time interval between the present and primary surgery, and relevant ocular and systemic history. Complete ophthalmic examination was conducted for all the patients, including best-corrected visual acuity (BCVA), intraocular pressure (IOP), refraction, slit-lamp biomicroscopy, dilated fundus examination, axial length, and corneal endothelial density (ECD) preoperatively and at 1 month and the last visit postoperatively. The presence of postoperative complications was also recorded. IOL tilt and decentration were measured and calculated automatically with swept-source anterior segment optical coherence tomography (SS-ASOCT, CASIA2; Tomey Corp., Nagoya, Japan) under the mode of a 3-dimensional (3D) scan at the last visit under mydriatic conditions using a mixture of 0.5% tropicamide and 0.5% phenylephrine hydrochloride (Mydrin-P, Santen Pharmaceutical, Osaka, Japan) according to the method previously described (9, 10). Briefly, CASIA2 uses a swept-source laser with a 1,310-nm wavelength at a frequency of 0.3 s and provides higher resolution images of IOLs. Using the IOL scan mode, 8 distinct ASOCT images from 8 different angles (namely 0–180, 90–270, 23–203, 113–293, 45–225, 135–315, 68–248, and 158–338) are obtained and a 3D image is created (9). IOL tilt and decentration are directly generated by the built-in software (Version SS2000) relative to the visual line, and the detailed extent and azimuth (the orientation of IOL tilt and decentration in degree) are present beside the image.

Surgical Technique

The step-by-step surgical procedure was demonstrated in **Figure 1**. After the external incision of the superior scleral tunnel is made 2 mm posterior to the limbus at 11 o'clock, an ophthalmic marker is placed and pressed on the cornea, making two location imprints at 3 o'clock and 9 o'clock. Using a crescent blade, two partial-thickness grooves (300 μm-depth, 3.0 mm-long) are made on the corneal limbus at the two imprints, followed by dissection of two scleral pockets posteriorly from these limbal grooves. The pockets are extended perpendicular to the limbus and continued for 3.0 mm, maintaining a uniform depth in the sclera. Then, a paracentesis is made at 8 o'clock by a 15-degree lance tip blade for 20-G infusion, and another paracentesis is made using a 3.0 mm sharp-tip keratome to complete the superior sclerocorneal incision.

Afterward, a double-armed 9-0 polypropylene suture (Mani Inc., Tochigi, Japan) with two straight needles (or one straight needle and one curved needle) is used for IOL fixation. Two puncture points are marked by calipers at the middle line of the pocket beds 2.0–2.5 mm posterior to the limbus on both sides. The straight needle is introduced at one puncture point at 9 o'clock through the conjunctiva and full thickness of the Hoffman pocket, passing through the anterior chamber to the opposite side, then docked into the opening of a 27-G needle, which is introduced at the other puncture point at 3 o'clock and then removed externally. Afterward, the straight needle is again passed backward through the conjunctiva and the full thickness of the scleral pocket 1.0–2.0 mm adjacent to the first pass of the needle, threading through the anterior chamber and docked again with the 27-G needle, and guided out in the same way 1.0–2.0 mm adjacent to the puncture point at 9 o'clock. When visualized in the pupillary area, the pairs of sutures are retrieved externally through the superior incision by a Sinskey hook (or forceps) and cut into two halves, leaving two double-sutured ends for IOL fixation.

Next, the leading haptic of the preloaded PIOL is pushed out of the cartridge and tied with one end of the double sutures at the junction of the enlarged haptic end. After the leading haptic and the folded IOL optic are injected into the anterior chamber, the trailing haptic left externally is tied with the other end double sutures and then pushed subsequently into the eye by the Sinskey hook. By removing the two needles linked to the suture ends passed at 3 o'clock and cutting the suture-loop at 9 o'clock into two single suture ends, each suture end is retrieved through the scleral pocket opening by placing the Sinskey hook into the pocket and pulling and externalizing the trailing suture end. After the PCIOL is placed at the exact position behind the iris, the pairs of sutures at each pocket are knotted *via* a tension adjustable knot to center the optic of the IOL. Each knot is tied into the scleral pocket, and the suture ends were laid flat into each pocket. Finally, the superior incision is sutured, and the 20-G infusion tip is removed with this incision watertight.

The video demonstrates the procedures (**Supplementary Video 1**). All surgeries were performed by one experienced surgeon (PZ) under general anesthesia for patients under 13 years old or retrobulbar anesthesia for the others. For cases with lens subluxation, lensectomy and complete pars plana vitrectomy (PPV) were performed prior to IOL fixation.

RESULTS

Ten eyes of nine patients who underwent the procedure were enrolled. All the eyes met the criteria for scleral fixation of PIOL with obviously better preoperative BCVA. The mean patient age was 23.4 ± 22.89 years at the time of the surgery. Four patients had subluxation lens because of Marfan Syndrome (MFS) and received lensectomy and complete PPV before IOL fixation (5 eyes, 50%). The lens in four patients (4 eyes, 40%) were extracted in previous surgeries. One patient (1 eye, 10%) suffered aphakia secondary to ocular rupture. The average axial

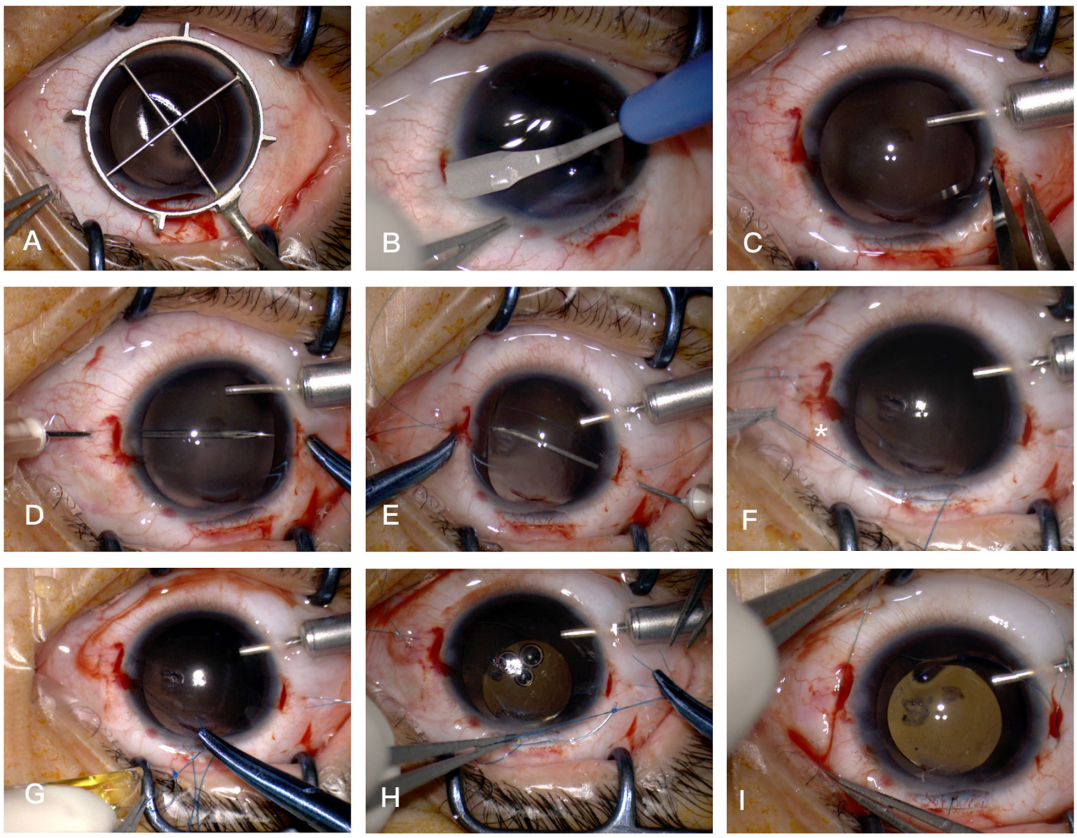

FIGURE 1 | Surgical steps. **(A)** Two location imprints at 3 o'clock and 9 o'clock are made by an ophthalmic marker. **(B)** Two scleral pockets are dissected by a crescent blade posteriorly from the limbus, achieving a thickness of 300 μm and a length of 3.0 mm. **(C)** After anterior chamber infusion, puncture points are marked at the middle line of the pocket beds 2.0–2.5 mm posterior to the limbus on both sides. **(D)** The straight needle of a double-armed 9-0 polypropylene suture (with two curved needles) is introduced at one puncture point at 9 o'clock through the conjunctiva and full thickness of the Hoffman pocket, passing through the anterior chamber to the opposite side, then docked into the opening of a 27-G needle, which is introduced at the other puncture point at 3 o'clock, then removed externally. **(E)** The straight needle is again passed backward through the conjunctiva and the full thickness of the scleral pocket 1.0–2.0 mm adjacent to the first pass of the needle, threading through the anterior chamber and docked again with the 27-G needle, and guided out in the same way 1.0–2.0 mm adjacent to the puncture point at 9 o'clock. **(F)** The pairs of sutures are retrieved externally through the superior incision and cut into two halves. The star symbol demonstrates one end of the double sutures to tie on the leading haptic. **(G)** The leading haptic of the pre-loaded PIOL is pushed out of the cartridge and tied with one of the double sutures at the junction of the enlarged haptic end. **(H)** After the leading haptic and the folded IOL optic is injected into the anterior chamber, the trailing haptic left externally is tied with the other double sutures. **(I)** The two pairs of suture ends are retrieved through the scleral pocket opening pulled out by the Sinskey hook and knotted *via* tension adjustable knot to center the optic of the IOL.

length was 24.43 ± 1.05 mm. The mean follow-up time was 19.6 ± 7.04 months. Detailed individual patient data are provided in **Table 1**.

As **Table 2** demonstrates, the patients' BCVA ranged from counting fingers to 20/25 preoperatively and 20/125 to 20/20 at the last postoperative follow-up time. The IOP and ECD remained in the normal range before and after surgery. Throughout the follow-up period, one child patient with MFS experienced pupillary capture of IOL optic on the first day after surgery, which was repositioned after pupillary dilation and supine positioning. Another child patient suffered decreased IOP caused by suspected incision leakage on the first day after surgery and was successfully treated with pressure bandaging for 2 days. No other intraoperative or postoperative complications were recorded. The IOL was well-positioned at the last follow-up time (see **Table 3**).

DISCUSSION

Scleral suture fixation of PCIOL is the most widely accepted method and plays an important role in the visual restoration of eyes with inadequate capsule support. In our present study, we for the first time described a modified approach of the scleral Hoffman pocket fixation technique (11), combined with HOYA PCIOL. The clinical observation for at least 1 year demonstrated improved BCVA and a low rate of complication. No patient presented suture knot exposure, suture breakage, or severe IOL tilting or decentration. There were no severe intraoperative or postoperative adverse events during the follow-up period.

The application of the Hoffman pocket technique provides several advantages. Dissection of this pocket starts from a clear corneal incision, avoiding the need for scleral cautery and preserving the integrity of the conjunctiva. This surgical

TABLE 1 | Individual patient characteristics.

Case	Age, years	Gender	Laterality	Axial length, mm	Indication for surgery	Ophthalmolmic comorbidities	Follow-up time, months
1	4	Female	Right	25.33	Crystalline lens subluxation	Marfan syndrome	12
2	5	Male	Right	24.80	Crystalline lens subluxation	Marfan syndrome	21
3			Left	24.68			12
4	7	Male	Left	23.55	Crystalline lens subluxation	Marfan syndrome	24
5	10	Male	Right	23.20	Crystalline lens subluxation	Marfan syndrome	31
6	12	Female	Right	25.98	Traumatic aphakia	Ocular rupture	28
7	27	Male	Left	24.86	Postoperative aphakia	Penetrating injury	21
8	48	Female	Left	25.02	Postoperative aphakia	Vitreous hemorrhage	22
9	52	Male	Left	22.52	Postoperative aphakia	Traumatic RD	12
10	64	Male	Left	24.35	Postoperative aphakia	Traumatic RD and CD	13

RD, retinal detachment; CD, choroidal detachment.

TABLE 2 | Comparison of clinical data before and after surgery.

Case	BCVA (Snellen)		IOP, mmHg		ECD, cells/mm^3		Postoperative complications
	Pre	Post	Pre	Post	Pre	Post	
1	20/100	20/80	13	10	3275	3045	None
2	Uncooperative	20/67	Tn	13	Uncooperative	3201	Decreased IOP
3	Uncooperative	20/100	Tn	14	Uncooperative	2996	Pupillary IOL capture
4	20/50	20/40	18	17	3509	3385	None
5	CF/30 cm	20/100	15.6	18.2	3086	3056	None
6	20/25	20/20	13	14	3322	3124	None
7	20/200	20/125	13.2	14.2	1919	1890	None
8	20/25	20/20	23	18.2	2646	2632	None
9	20/133	20/100	13	10.1	2703	2700	None
10	20/67	20/50	15	14.6	1783	1659	None

BCVA, best-corrected visual acuity; CF, counting fingers; IOP, intraocular pressure; ECD, endothelial cell density; IOL, intraocular lens.

TABLE 3 | Parameters of intraocular lens position at the last follow-up time.

Case	Tilt, degree	Azimuth, degree	Decentration, mm	Azimuth, degree
1	1.8	312	0.10	28
2	2.4	320	0.18	105
3	2.8	304	0.14	118
4	3.5	352	0.11	127
5	2.3	308	0.08	24
6	5.0	342	0.14	52
7	6.3	326	0.19	46
8	1.4	338	0.04	182
9	6.8	314	0.17	42
10	7.7	51	0.20	16

procedure creates a larger surface area for suture passes than traditional triangular scleral flaps (12), allowing the needles to exit inside the dissected pocket as long as they are at a proper distance from the limbus (13). Most remarkably, burying the suture knot in the pocket prevents erosion of the overlying conjunctiva with the potential risk for endophthalmitis and avoids suture breakage and the ensuing IOL malposition or dislocation. In addition, using this technique, the conjunctiva can be preserved at maximum, which is particularly desirable for the patients who previously received or who needed to receive glaucoma infiltration surgery (14). Postoperative complications, such as surgical induced astigmatism (SIA) and corneal edema, are also less likely to happen, and the patients' comforts are largely improved.

Scleral fixation with the Hoffman pocket technique has been applied for various types of IOLs, while most of the IOLs are used with closed-loop haptics or designed eyelets on the haptics, through which sutures can easily be passed for IOL fixation (15–17). On the other hand, seldom had the 3-piece IOLs been reported to be fixated with this technique, except that Domingues

et al. (18) described a cupid technique to perforate and knot at the body of the 3-piece subluxated IOL with 10-0 polypropylene suture. In this study, we for the first-time used Hoffman's technique in the fixation of a 3-piece pre-loaded IOL, which provides several significant improvements: first, the pre-loaded foldable design of the IOL allows the implantation through a smaller incision, associating with better intraoperative IOP control and less postoperative SIA. Next, the haptics of this IOL, namely HOYA PY60AD, are made of PMMA. The rigid material as well as the C-loop posteriorly angulated thin configuration of its two haptics largely minimize iris chafing, reducing the risk for uveitis-glaucoma-hyphema (UGH) syndrome, pigment dispersion syndrome, and increased IOP. Most distinctively, the end of haptics is designed as an enlarged cone shape, which enables the suture to fixate directly on the haptics by knotting at the junction of haptic ends and at the same time avoid suture slippage (19). Our method provides an effective, simple, safe, and a minimally invasive way for scleral suture fixation with more IOL options.

Concerning complications, pupillary IOL capture was observed in one patient with MFS 1 day postoperatively, and the IOL was reposited followed by pilocarpine therapy without repeated captures. The pupillary capture rate was reported much higher in the pseudophakic eyes of patients with MFS (20–22) because the myopathy of pupil constrictors and dilators in this population gives rise to pliable iris and reverse pupillary block (23, 24). To deal with this situation, preventative intraoperative surgical iridectomy (preferably with small gauge vitrectomy) or postoperative laser iridectomy are recommended (25). We also modified the technique, retreating the fixation plane from 2.0 to 2.5 mm posterior to the limbus for patients with MFS, which noticeably decreased the rate of pupillary IOL capture (not mentioned in this study). Another child patient also suffered from decreased IOP 1 day postoperatively. The Seidel test was done to exclude leakage of the incision, and the IOP returned to normal after pressure bandaging for 2 days. Significantly, the tilt azimuth quite differed in Case 10 compared with other cases, as demonstrated in **Table 3**. This patient suffered from ocular rupture, resulting in superior temporal traumatic aniridia. The inadequate anterior support of the iris might be the reason for his unique azimuth.

CONCLUSION

This surgical technique offers an alternative approach to the management of secondary IOL fixation with flexible usage of more designs of IOLs for patients with insufficient capsular support, achieving a reliable and reproducible procedure with improved anatomical and visual outcomes, reduced complications, and decreased surgical times. However, the limitations of this study include its small sample size and relatively short follow-up period. Future studies with longer follow-up observation are needed to determine its standing among other documented techniques.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board approval and Ethical Review Board approval were obtained from Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HY conceived and designed the analysis and wrote the manuscript. HY, SZ, and WM collected the data and performed the analysis. HY, SZ, PF, and PZ contributed to data collection. PZ carried out final editing and approval. All authors agreed to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.856800/full#supplementary-material

Supplementary Video 1 | The surgical procedures of the technique.

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SYSTEMATIC REVIEW
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Trabeculectomy With Antimetabolite Agents for Normal Tension Glaucoma: A Systematic Review and Meta-Analysis

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Background: Evidence regarding the impact on visual field (VF), intraocular pressure (IOP), and antiglaucoma medications from trabeculectomy with antimetabolites for normal tension glaucoma (NTG) is conflicting because of insufficient study sample sizes. The aim of this study is to systematically assess VF progression rate, IOP control and antiglaucoma medication use after trabeculectomy with antimetabolites for progressing NTG.

Methods: We searched published articles on PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials from database inception to March 21, 2022. We selected studies that reported VF data before and after trabeculectomy with antimetabolite agents for NTG. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guidelines. Data were extracted by 2 independent reviewers, and a random-effects model was employed for the meta-analysis. Study outcomes were VF progression rates measured using the pooled mean deviation (MD) slope, changes in antiglaucoma medications, and IOP. Subgroup analyses of the MD slope according to mean age (over or under 65 years), baseline MD (over or under –12 dB), and baseline IOP (over or under 15 mmHg) were performed to determine the results' robustness.

Results: We included 7 retrospective observational studies (Japan: 6 studies, United States: 1 study) comprising a total of 166 eyes. Mean preoperative VF MD slopes ranged from –0.52 to –1.05 dB/year. The meta-analysis demonstrated significant MD slope improvement after trabeculectomy (pooled mean difference: 0.54 dB/year, 95% CI: 0.40 to 0.67, I^2 = 9%). Mean age, baseline MD, and baseline IOP subgroup analyses revealed MD slope results were consistent with those of the main analyses.

The mean IOP (pooled mean difference: –5.54 mmHg, 95% CI: –6.02 to –5.06, I^2 = 0%) and mean number of antiglaucoma medications (pooled mean difference: –1.75, 95% CI: –2.97 to –0.53, I^2 = 98%) significantly decreased after trabeculectomy. The most frequently reported early complications after trabeculectomy were hypotony, hyphema, and shallow anterior chamber.

Conclusion: This systematic review and meta-analysis indicated that trabeculectomy with antimetabolites is beneficial for progressing NTG; it preserves visual function by alleviating the MD slope and reducing antiglaucoma medication use. However, several post-trabeculectomy complications should be monitored.

Keywords: trabeculectomy, normal tension glaucoma, systematic review, meta-analysis, mean deviation slope

INTRODUCTION

Glaucoma, the second leading cause of blindness worldwide for adults aged older than 50, (1) is characterized by retinal ganglion cell apoptosis with specific glaucomatous optic neuropathy with or without elevated intraocular pressure (IOP). Primary open-angle glaucoma (POAG) is the predominant subtype of glaucoma affecting 1.4% of Caucasians, 5.2% of those of African descent and 2.2% of south-east Asian populations aged over 60 years old. (2) Normal tension glaucoma (NTG), a form of open-angle glaucoma, accounts for up to 92% PAOG cases in Asian countries, (3–7) compared to about 31% in the United States. (8) NTG is defined as IOP consistently lower than 21 mmHg and generally presents with progressive optic nerve damage with unknown patho-mechanisms and visual field (VF) impairment (9).

The current standard treatment for glaucoma consists of IOP reduction, including medical and laser treatment, and surgical interventions. Clinical trials involving NTG have demonstrated that 30% IOP reduction is beneficial for VF progression, in comparison to untreated controls. (10, 11) Anti-glaucoma medications, such as topical beta blockers and prostaglandin analogues (PGA), are mainstream treatment options for managing NTG in clinical practice (12–15). However, if NTG progresses despite topical medical treatment, other advanced interventions, such as filtration surgery, aka trabeculectomy, may be recommended to achieve the IOP reduction target.

Trabeculectomy surgery with the wound healing modulating agents, anti-metabolites like 5-Fluorouracil (5-FU) and Mitomycin C (MMC), remains the established and most performed fistulizing procedure for NTG refractory to medical treatment. (16–18) However, with the reduction of IOP to single digits, the efficacy of VF progression rates with MD slope following trabeculectomy with antimetabolite agents on NTG differs. For example, the mean difference of MD slope was 0.8 dB/year in the Iverson et al. study with nine participants, and 0.18 dB/year in the Nakajima et al. study with 28 participants. (17, 19) Given that previous individual studies usually included small sample sizes leading to inconsistent findings, (17, 19–24) it would be important to conduct a systematic review and meta-analysis to summarize the overall operative effects, especially as regards VF progression rates, IOP, and the number of antiglaucoma medication changes, after trabeculectomy with an antimetabolite in patients with progressing NTG.

METHODS

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (**Supplementary Table 1**) and the Meta-Analysis of Observational Studies in Epidemiology guidelines. Two authors (C Lai and YH Chen) independently performed study selection, data extraction, and risk-of-bias assessments. Another senior author (Shao SC) resolved any disagreements. The study protocol has been registered on PROSPERO (CRD42021281699).

Literature Search

We searched PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials for relevant studies published from inception to March 21, 2022, by using the free-text keywords of normal tension glaucoma and trabeculectomy with appropriate MeSH terms and abbreviations. The search strategy is presented in **Supplementary Table 2**.

Study Selection

We selected the studies using the following inclusion criteria: (1) The studies were observational studies (including prospective or retrospective case series or cohorts) or randomized controlled trials (RCTs). (2) They included participants with a diagnosis of NTG. (3) They included participants who had received trabeculectomy with antimetabolite agents, including MMC, applied during operation or with 5-FU as an adjunct. Finally, since the preoperative MD slope may vary among NTG patients, we included only studies with pre- and postoperative MD slope outcome data to appropriately reflect the treatment effects.

We excluded the following studies: (1) Other types of publications (e.g., conference abstracts, case reports, reviews, editorials, guidelines, trial registrations, or viewpoint papers). (2) Those not specifically focused on participants with NTG subtypes. (3) Non-English-language articles. For studies with overlapping populations from the same study source (e.g., the

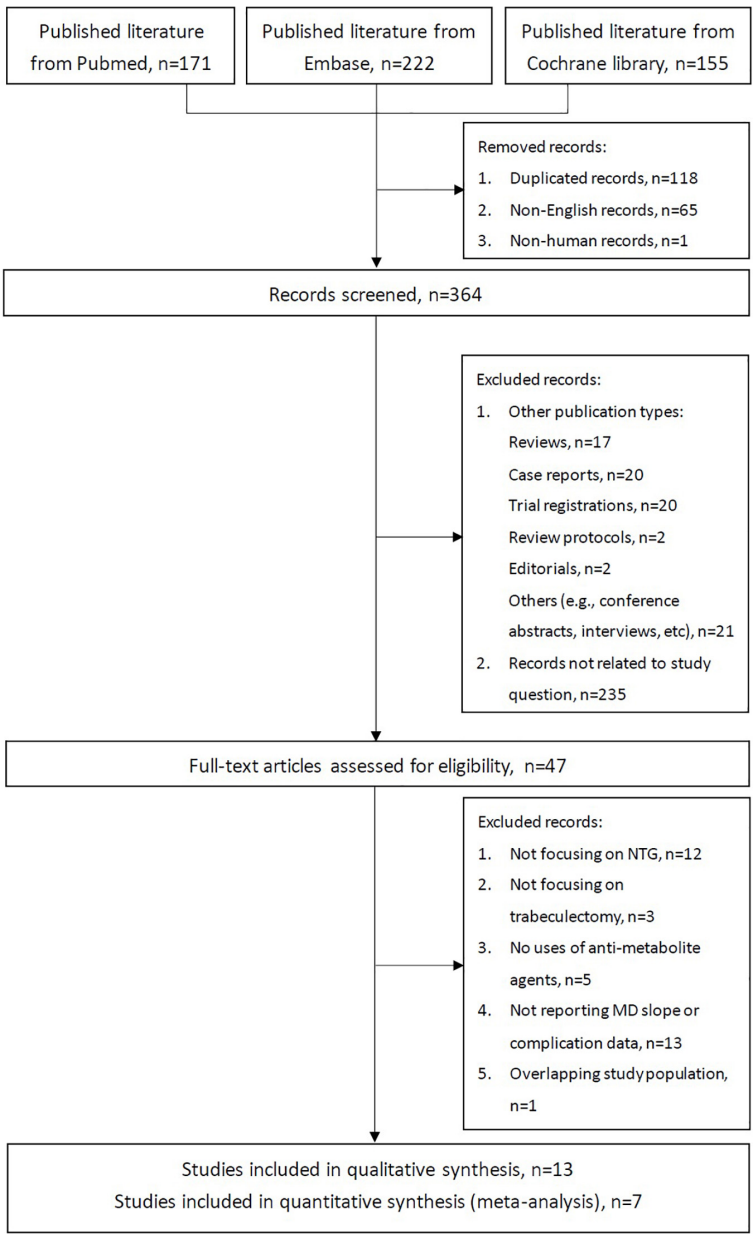

FIGURE 1 | PRISMA flowchart.

same hospitals), we excluded the study with the shorter follow-up period.

Data Extraction and Risk-of-Bias Assessment

We extracted study data, including study characteristics (e.g., first author name, study design, publication year, study country, sample size, mean age, and follow-up time length), visual characteristics (e.g., baseline MD, MD slope prior to and after trabeculectomy, and IOP prior to and after trabeculectomy), and treatment characteristics (e.g., the mean number of antiglaucoma medications prior to and after trabeculectomy and complications prior to and after trabeculectomy). For studies that reported visual outcome data at different follow-up times, we extracted only the data with the longest follow-up as the post-trabeculectomy data. The risk of bias for the included studies was assessed using the Quality Assessment Tool for Before-After (Pre–Post) Studies with No Control Group developed by the National Institutes of Health (25).

Statistical Analysis

We conducted meta-analyses using Review Manager Version 5.4 (26) to investigate the changes in the MD slope before and after trabeculectomy with antimetabolite drugs. We also measured the

changes in IOP and the number of antiglaucoma drugs if the data were available. We used a random-effects model in our meta-analysis because we anticipated clinical heterogeneity within the included studies. We used the I^2 value to quantify the statistical heterogeneity across the studies. To investigate the predisposing factors that affect the treatment effects of trabeculectomy with antimetabolite agents, we conducted several subgroup analyses, including age group (mean ages older or younger than 65 years) and baseline disease severity (pre-trabeculectomy MD: over or under −12 dB (27) and pre-trabeculectomy IOP: over or under 15 mmHg). We also summarized the reported complications after trabeculectomy through descriptive analyses.

RESULTS

Characteristics and Risk of Bias in Included Studies

The PRISMA flowchart for the study is presented in **Figure 1**. We initially identified 548 records from our search of three electronic biographic databases. Overall, only seven were retrospective studies, which included a total of 166 subjects from Japan (six studies, 151 eyes) and the United States (1 study, 15 eyes). These seven studies were included in this meta-analysis based on the predefined inclusion and exclusion criteria. Among these seven studies, five used MMC with a concentration of 0.2 to 0.5 mg/ml and exposure time of 1 to 5 min. (17, 19, 20, 22, 23) The other two studies used MMC at 0.4 mg/ml with exposure time of 3 to 5 min, or adjunctive use of 5-fluorouracil. (21, 24) The post-trabeculectomy follow-up periods in the studies ranged from 4.51 to 15.6 years. The details of the included studies, participants, and visual and treatment characteristics are listed in **Table 1**. The risk-of-bias assessment for the studies is presented in **Supplementary Table 3**.

Visual Field

After data extraction in the included studies with complete MD slope data of the VF examination, the meta-analysis of seven retrospective studies comprising 156 eyes demonstrated a significant improvement in the MD slope after the patients underwent trabeculectomy, with small statistical heterogeneity (pooled mean difference: 0.54 dB/year, 95% CI: 0.40 to 0.67, I^2 = 9%; **Figure 2**). Subgroup analyses indicated that the MD slope improved in different age (pooled mean difference in younger than 65 years: 0.52 dB/year, 95% CI: 0.35 to 0.68, I^2 = 33%; pooled mean difference in older than 65 years: 0.65 dB/year, 95% CI: 0.28 to 1.02, I^2 = 0%; test for subgroup differences: P = 0.53; **Supplementary Figure 1**), baseline MD (pooled mean difference in under -12 dB: 0.40 dB/year, 95% CI: 0.20 to 0.60, I^2 = 17%; pooled mean difference in over −12 dB: 0.69 dB/year, 95% CI: 0.44 to 0.93, I^2 = 0%; test for subgroup differences: P = 0.08; **Figure 3**), and baseline IOP groups (pooled mean difference in under 15 mmHg: 0.55 dB/year, 95% CI: 0.33 to 0.76, I^2 = 31%; pooled mean difference in over 15 mmHg: 0.52 dB/year, 95% CI: 0.33 to 0.70, I^2 = 0%; test for subgroup differences: P = 0.82; **Supplementary Figure 2**).

IOP

The meta-analysis of seven retrospective studies comprising 166 eyes indicated a significant decrease in IOP with no statistical heterogeneity after trabeculectomy (pooled mean difference: −5.54 mmHg, 95% CI: −6.02 to −5.06, I^2 = 0%; **Figure 4**). The subgroup analysis results for IOP changes according to age, baseline MD, and baseline IOP were consistent with those of the main analyses (**Supplementary Figures 3–5**).

Number of Antiglaucoma Medications

After data extraction in the included studies with complete antiglaucoma medication records, the meta-analysis of 4 retrospective studies comprising 77 eyes indicated a significant decrease in the mean number of antiglaucoma medications with high statistical heterogeneity after trabeculectomy (pooled mean difference −1.75, 95% CI: −2.97 to −0.53, I^2 = 98%; **Supplementary Figure 6**).

Trabeculectomy Complications in NTG

After data extraction in the included studies with reported surgical complications after antimetabolite-adjunctive trabeculectomy, we included 7 studies (330 patients with NTG) for qualitative synthesis in this systematic review. (16, 18, 22, 28–31) Early complications after trabeculectomy, i.e., hypotony (2–48%), (18, 28, 30) hyphema (1–20%), (18, 28, 30) and shallow anterior chamber (1–16%) (28–30) were frequently reported. Among late complications, hypotonous maculopathy (3–18%) (16, 18, 22, 29–31) and bleb leak (1–19%) (16, 18, 22, 28–30) were frequently reported. Laser suturelysis, bleb needling or glaucoma eyedrops were applied in 5 studies and conservative management for other complications was noted during the follow-up period. (17, 19–21, 24) The details of the reported complications are listed in **Supplementary Table 4**.

DISCUSSION

In this systemic review and meta-analysis from seven observational studies, our findings indicated that trabeculectomy with antimetabolite drugs could significantly improve the MD slope in patients with progressing NTG. Subgroup analyses of age, baseline IOP, and baseline MD groups demonstrated results consistent with those of the main analysis and no significant differences between subgroups. Furthermore, IOP and the mean number of medications significantly decreased after trabeculectomy. Because trabeculectomy with antimetabolite drugs is a mainstream treatment strategy for patients with progressing NTG, our findings could reconfirm the treatment benefits of this procedure.

Previous studies have demonstrated the natural course of VF progression in NTG by reporting the mean MD slope, with slopes ranging from −0.33 to −0.41 dB/year. (32–34) If NTG patients are treated with adequate anti-glaucoma medications, VF progression could supposedly be alleviated, according to the findings of RCTs (12, 13, 15). However, one cohort study from De Moraes et al. demonstrated that 31% of their participants had VF progression with a slope more than −1.0 dB/year after

TABLE 1 | Characteristics of included studies.

Study	Region	Study design	Sample size [N(eyes)]	Age (years, mean ± SD)	Baseline MD (dB, mean ± SD)	Pre-op MD slope (follow-up) [dB/year, mean (years)]	Post-op MD slope (follow-up) [dB/year, mean (years)]	Pre-op IOP (mmHg, mean ± SD)	Post-op IOP (mmHg, mean ± SD)	IOP reduction	Pre-op medication number	Post-op medication number
Shigeeda et al. (24)	Japan	Retrospective	23	62.8 ± 10.3	N/A	−1.05 (N/A)	−0.44 (6.0)	16.2 ± 1.8	6.0 ± 1.7 (mean follow-up time: 3 years)	33%	N/A	N/A
Mataki et al. (21)	Japan	Retrospective	34	57.7 ± 9.6	−12.7 ± 5.5	−0.7 (4.6)	−0.25 (5.7)	15.7 ± 1.7	10.3 ± 2.7 (mean follow-up time: 5.7 ± 1.2 years)	34%	N/A	N/A
Naito et al. (22)	Japan	Retrospective	17	69.5 ± 7.6	−18.9 ± 4.2	−0.91 (4.3)	−0.32 (5.0)	13.9 ± 0.9	8.1 ± 2.9 (mean follow-up time: 5.0 ± 1.3 years)	42%	3.0 ± 0.4	0.8 ± 1.5
Nakajima et al. (19)	Japan	Retrospective	28	57.9 ± 10.1	−13.7 ± 7.2	−0.52 (6.3)	−0.34 (6.0)	13.9 ± 3.1	9.0 ± 4.6 (mean follow-up time: 6 years)	35%	2.6 ± 0.5	0.1 ± 0.4
Iverson et al. (17)	United States	Retrospective	15	71.8 ± 7.5	−9.5 ± 6.5	−1.05 (7.6)	−0.25 (5.4)	13.1 ± 1.5	8.5 ± 3.5 (mean follow-up time: 5.7 ± 2.3 years)	35%	2.5 ± 1.3	0.8 ± 1.3
Oie et al. (23)	Japan	Retrospective	17	55.8 ± 7.9	−11.8 ± 5.0	−0.86 (5.9)	−0.19 (15.6)	14.7 ± 1.3 (mean at follow-up)	9.1 ± 2.0 (mean follow-up time: 15.6 ± 3.2 years)	38%	0.9 ± 0.3	0.3 ± 0.4
Daugeliene et al. (20)	Japan	Retrospective	32	56.9	N/A	−0.97 (3.8)	−0.32 (4.5)	14.7 ± 1.6	8.7 ± 2.4 (mean follow-up time: 4.5 ± 1.1 years)	41%	1.5 ± 0.7	N/A

MD, mean deviation.
IOP, Intraocular pressure.
N/A, not available.

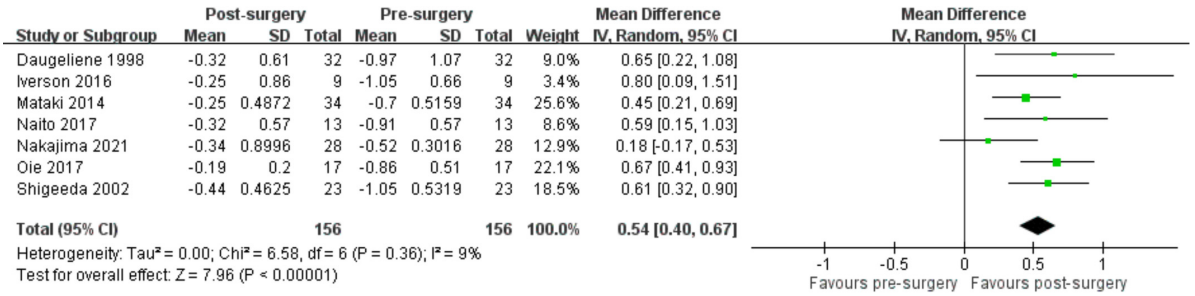

FIGURE 2 | VF progression with MD slope in patients with NTG after trabeculectomy.

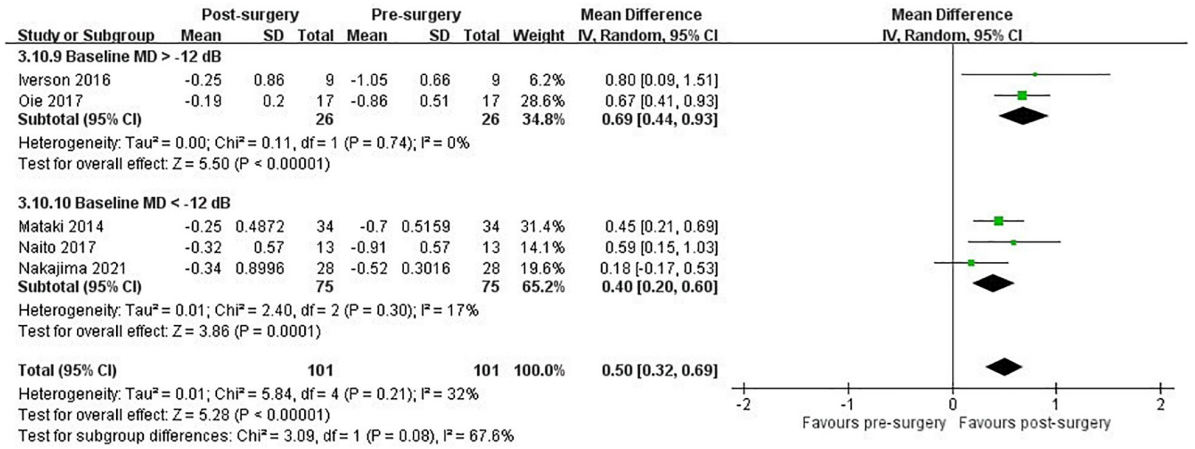

FIGURE 3 | Subgroup analysis: VF progression with MD slope in patients with NTG after trabeculectomy, stratified by baseline MD group.

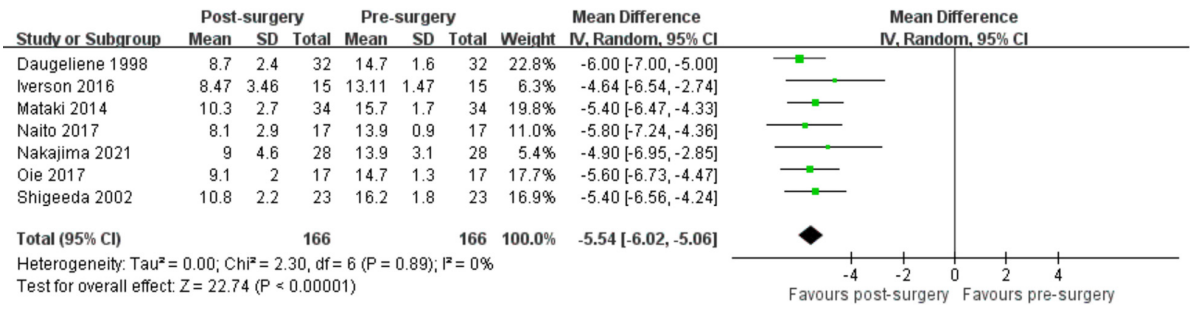

FIGURE 4 | Mean change in IOP in patients with NTG before and after trabeculectomy.

receiving drug treatment. (13) Therefore, advanced interventions may be required to further lower IOP and prevent VF progression in progressing NTG patients. Our systematic review and meta-analysis concluded that trabeculectomy with antimetabolite drugs effectively slows VF progression, measured through the MD slope (pooled mean difference: 0.54 dB/year) in NTG patients with progressing MD slopes (-0.52 to –1.05 dB/year). This finding is especially notable because of the consistent treatment benefits across age, baseline IOP, and baseline MD groups. Although the differences of MD slope between the baseline MD groups (baseline MD under –12 dB: 0.40 dB/year and baseline MD over –12 dB: 0.69 dB/year) did not reach statistical significance (test for subgroup differences: $P = 0.08$) probably due to the suboptimal statistical power, our results may suggest a trend of patients with more favorable baseline VF conditions demonstrating more surgery-related improvement in MD slopes. The detailed mechanisms to explain these findings remain unclear, so future prospective studies are required to verify our observations.

The IOP-lowering effects of trabeculectomy with antimetabolite drugs in patients with progressing NTG have previously been reported. (16–24, 28–31) Consistent with

the results of these studies, our findings quantified the mean reduction of IOP as about 5.54 mmHg after trabeculectomy, which may also explain a significant decrease in the use of antiglaucoma medications after trabeculectomy. Taking together these findings, we suggested that trabeculectomy with antimetabolite drugs was beneficial for the IOP modulation of progressing NTG. In addition to the MD slope improvement attributed to effective IOP controls after trabeculectomy with antimetabolite drugs in NTG, our findings support that low tolerance of IOP may be one patho-mechanism of NTG; (9) that is, reaching the targeted IOP reductions could prevent the visual function deterioration in NTG. However, more aggressive IOP-lowering effects following trabeculectomy with antimetabolite drugs potentially cause other ocular complications, so ophthalmologists may be very cautious when considering surgeries for progressing NTG. Although the reported complications from the included studies largely varied, we found early hypotony and late hypotonous maculopathy may occur in 2–48% and 3–18% of NTG patients after trabeculectomy, respectively. These complications may be attributed to the use of antimetabolites during ocular surgery, and careful observation and supportive treatments are often sufficient. (35) Frequent follow-up for close monitoring and timely management of possible ocular complications in progressing NTG patients after trabeculectomy with antimetabolite drugs are suggested (28).

To the best of our knowledge, this is the first systematic review and meta-analysis to evaluate the treatment effects before and after trabeculectomy with antimetabolite drugs in patients with progressing NTG. By utilizing the designs of systematic review and meta-analysis, we were able to summarize the current evidence from seven observational studies to prove the beneficial effects of this surgery on progressing NTG. This has previously remained inconsistent, probably due to insufficient sample sizes within the different individual studies. However, we must acknowledge several limitations in the present study. First, we did not identify RCTs on this topic; potential residual confounders may affect the treatment effects of trabeculectomy with antimetabolite drugs. Second, both 24–2 and 30–2 programs were used to evaluate VF progression in the included studies, but the measurement variability between these 2 programs was minor, based on a previous report. (36) Third, we found 2 included studies did not report the details on topical antiglaucoma medication use before and after trabeculectomy, which may affect the comprehensive evaluation of the surgery effects. Fourth, the clinical heterogeneity among the included studies, such the various surgical techniques of trabeculectomy, should be noted before interpreting our findings. Fifth, we excluded non-English-language articles from this systematic review, but these excluded studies were mostly from Japan. Because we included several Japanese studies published in English in this meta-analysis, we considered the potential influence of language restrictions on our findings to be minor. Finally, most of the included studies were from Japan, so we suggested further studies from other countries to confirm our findings.

This systematic review and meta-analysis suggested that trabeculectomy with antimetabolite drugs may significantly improve VF by alleviating the MD slope in progressing NTG, regardless of age, baseline IOP, and baseline MD. This surgery could also lower IOP and reduce antiglaucoma drug use. However, several surgery complications, such as early hypotony and late hypotonous maculopathy, should be clinically monitored.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CL and L-HC: concept and design, full access to all the data in the study, and responsibility for the data integrity and analysis accuracy. CL, S-CS, Y-HC, and L-HC: acquisition, analysis, or interpretation of the data. CL, S-CS, and L-HC: drafting of the manuscript. CL: statistical analysis. L-HC: supervision. All authors contributed in critical revision of the manuscript for important intellectual content.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.932232/full#supplementary-material

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Endoscopic dacryocystorhinostomy with short-term, pushed-type bicanalicular intubation vs. pulled-type monocanalicular intubation for primary acquired nasolacrimal duct obstruction

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Dacryocystorhinostomy (DCR) has been a primary treatment for adults with nasolacrimal duct obstruction, while the optimal approach and technique remain controversial. With the advancement of endoscopic DCR and the silicone stents, an update of the surgical outcomes and preferable approaches is required. This study aims at comparing the surgical outcomes of endoscopic DCR using pushed bicanalicular intubation (BCI) to pulled monocanalicular intubation (MCI) in adults with primary acquired nasolacrimal duct obstruction (PANDO). Forty five eyes of 45 patients were enrolled, including 22 eyes of 22 patients treated with endoscopic DCR with pulled MCI and 23 eyes of 23 patients with pushed BCI from January 2014 to June 2021. The success rates at stent removal, 1 month and 3 months after removal were 95, 91, and 82%, respectively, in the MCI group, and 100, 87, and 87% in the BCI group. The BCI group had better success rates but failed to reach a significant difference ($p = 0.49$, $p = 0.67$, $p = 0.24$, respectively). After analyzing with binary logistic regression, the implant material was demonstrated as the predictive of surgical success ($p = 0.045$). There was no significant difference in success rates between patients with dacryocystitis and those without dacryocystitis. We conclude that endoscopic DCR with pushed BCI is easily manipulated and has a promising surgical outcome over pulled MCI. Stent indwelling duration as well as history of dacryocystitis have less influence on the success rates.

KEYWORDS

dacryocystorhinostomy, endoscopic dacryocystorhinostomy, pulled monocanalicular intubation, pushed bicanalicular intubation, nasolacrimal duct obstruction

Introduction

Since dacryocystorhinostomy (DCR) was modified in the late nineteenth and early twentieth century (1, 2), it has been an effective treatment for adults with nasolacrimal duct obstruction. DCR was categorized into two major approaches, namely external or endoscopic approach, and with various techniques described, such as laser assisted endoscopic DCR and the utilization of different silicone stents. It was previously believed that external DCR had better success rates over endoscopic DCR (3, 4), yet with the improvement of endoscopic technology, endoscopic DCR had been reported a comparable result in recent reports (5, 6). Leong et al. conducted a meta-analysis for DCR outcomes, which showed a success rate ranging from 64 to 100% in external DCR, 84 to 94% in endoscopic DCR, and 47 to 100% in laser-assisted DCR (7).

It has long been debated regarding the best approach or technique. There were randomized studies as well as meta-analysis comparing the success rates of endonasal with external DCR (5, 8), and DCR with or without intubation (9–11). However, few comparative studies focused on the outcomes of endoscopic DCR with different devices and optimal duration of silicone stenting. This study aims to compare the surgical outcomes of endoscopic DCR with pulled monocanalicular intubation (MCI) to pushed bicanalicular intubation (BCI) in adults with primary acquired nasolacrimal duct obstruction (PANDO).

Materials and methods

We retrospectively reviewed medical records of adult patients diagnosed with PANDO and received endoscopic DCR as treatment with pulled MCI (Monoka®, FCI, Paris, France) or pushed BCI (Nunchaku®, FCI, Paris, France) from January 2014 to June 2021 at the Ophthalmology Department of National Cheng Kung University Hospital in Tainan, Taiwan. The diagnosis of PANDO was obtained when meeting both complete nasolacrimal duct obstruction *via* lacrimal duct irrigation and the subjective symptoms with epiphora. The pulled MCI is covered by National Health Insurance in Taiwan, while pushed BCI is not. Thus, the tube selection with MCI or BCI was determined by the patient's decision. Patients with minimum of 3 months follow-up after stent removal were included. Exclusion criteria included patients with trauma of lacrimal system, lacrimal system tumor, abnormal lid position, early silicone tube loss, follow-up duration <3 months and inadequate record information. All procedures were performed by the same ophthalmologist, Dr. Chun-Chieh Lai. Informed consent was obtained from all enrolled patients before invasive interventions performed. This study was approved by an institutional review board at National Cheng Kung University Hospital and in accordance with the ethical standards of the Declaration of Helsinki.

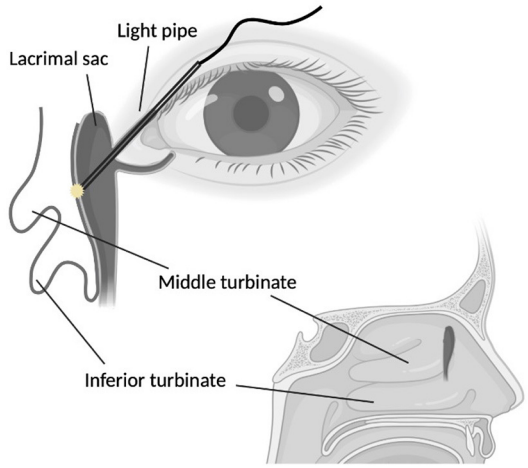

FIGURE 1
Intraoperative endoscopic dacryocystorhinostomy. The light pipe was inserted from the upper canaliculus into the lacrimal sac. The illumination of lacrimal sac located in front of the middle turbinate.

Procedure technique

All procedures were performed under general anesthesia. We disinfected the nasal cavity and operation site with povidone-iodine, and decongested the nose using 1% lidocaine with 1:100,000 epinephrine. Lacrimal probing was done with a Bowman probe for assessing the patency of lacrimal system. Next, an endonasal endoscopy was performed with 30-degree Karl Storz endoscope. An illuminator, 23-gauge pars plana vitrectomy light pipe, was inserted to the upper canaliculus to help guide the lacrimal sac location, which was usually located along the maxillary line between the frontal process of maxilla and lacrimal bone. The light pipe illumination in the lacrimal sac usually located in front of the middle turbinate from endonasal view (Figure 1). We incised the overlying nasal mucosa from bone under the optic light guide. Thereafter, a bone window was created with a Kerrison bone punch to expose the lacrimal sac. The lacrimal sac was open with relaxing incision. After hemostasis, a pulled MCI or pushed BCI was performed from the canaliculus to nasal cavity. The monocanalicular stent was inserted through the lower canaliculus, pulled into the nasal cavity, and fixed in the punctum. The bicanalicular stent was pushed from lower and upper puncta together with a metallic guide. Noteworthily, no knots or suture were needed to fix the pushed BCI stent (Figure 2). There was no antimetabolite use in our procedure.

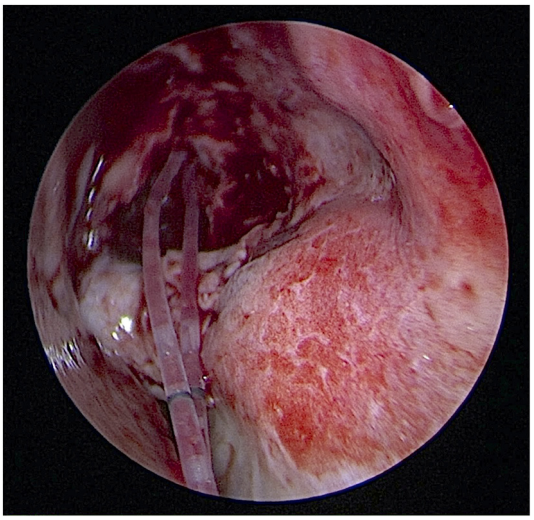

FIGURE 2
The pushed-type bicanalicular silicone stent (Nunchaku®) was pushed through the lower and upper pucta into the nasal cavity. No knots or suture were needed for fixation.

Post-operative care and outcome measurements

All patients were prescribed with topical 0.3% gentamicin and 0.1% betamethasone four times daily for 2 weeks postoperatively, followed by sulfamethoxazole and 0.1% fluorometholone four times daily. The postoperative follow-up was arranged 1 week after the operation, and further appointments were arranged every 2 weeks to every month until the stent removal. The MCI was placed for ∼4 months as most previous studies suggested. Due to lack of strong evidence of the intubation duration regarding the new type of pushed BCI, as well as our attempts to relieve the discomfort of stent intubation, BCI was placed with shorter duration around one month. The stents were removed by pulling the monocanalicular stent from the punctum or pulling the bicanalicular stent from the upper and lower puncta under topical anesthesia. After the stents were removed, appointments were arranged monthly to every 3 months, and we performed lacrimal irrigation at every appointment afterwards. The surgical outcomes were evaluated with the irrigation results at the time the stent removed, around 1 and 3 months after silicone stent removal. Patients' reflections after the surgeries were also documented in the medical records. Success was defined as both subjective improvement of epiphora after the surgery and a patent lacrimal system on nasolacrimal irrigation at the outpatient visits. Due to the assumption of independence in the traditional statistics, only one eye was selected in each patient. If both eyes were manipulated and included in current study, the results were defined by the eye with more severe symptoms or with underlying dacryocystitis.

TABLE 1 Patient characteristics.

Variable	MCI ($N = 22$)	BCI ($N = 23$)	p-value
	Mean or N	Mean or N	
Age (min-max) (years)	63 (23–86)	67 (38–78)	0.51[a]
Gender			>0.99[b]
Male	4 (18%)	4 (17%)	
Female	18 (82%)	19 (83%)	
Laterality			0.29[c]
OD	8 (36%)	12 (52%)	
OS	14 (64%)	11 (48%)	
Stent indwelling duration (min–max) (month)	3.90 (2.63–6.70)	1.2 (0.4–1.9)	<0.001[a*]
Medical history			
Dacryocystitis	10	11	
Diabetes mellitus	1	4	
Hypertension	3	6	
Sinusitis	3	0	
NTM infection	0	2	
Head and neck tumor	3	0	
Breast cancer	0	1	
Previous operation			
Balloon dacryocystoplasty	13 (59%)	18 (78%)	
Incision and drainage	6 (27%)	6 (26%)	

[a]Mann-Whitney U test, [b]Double-tailed Fischer exact test, [c]Double-tailed Chi-square test. The * symbol indicates the statistical significance.

Statistics

Statistical analysis was performed using software Statistical Product and Service Solutions (SPSS), version 20.00. Data were presented as median (minimum–maximum) in quantitative variables and frequencies in categorical variables. Since the sample size was small and data were not normally distributed, nonparametric tests were applied. Mann-Whitney U test was used for calculating quantitative variables, and Fischer exact test as well as Chi-Square test were applied for comparing the categorical variables. To further examine the relative contribution of potential predictor to the success rate, implant material, stent indwelling duration, age and gender were included in a binary logistic regression model. Adjusted odds ratios (AOR) and the significance of AOR were calculated. P-value <0.05 was defined as statistically significant.

TABLE 2 Surgical outcomes of endoscopic DCR with MCI and BCI.

Variable	MCI ($N = 22$)	BCI ($N = 23$)	p-value
	Mean or Number	Mean or Number	
Success rate			
At stent removal	21 (95%)	23 (100%)	0.49[a]
1 month after removal	19 (91%)	21 (87%)	0.67[a]
3 months after removal	17 (82%)	21 (87%)	0.24[a]

[a]Double-tailed Fischer exact test.

TABLE 3 Binary logistic regression analysis of predictors of surgical success in patients with primary acquired nasolacrimal duct obstruction at 3 months after stent removal.

	Variable	*B*	SE	Wald Chi-Square	*p*	AOR
Implant	Nunchaku	3.68	1.834	4.022	0.045*	39.554
	Monoka	(Ref)				
Stent indwelling duration		0.692	0.489	1.998	0.157	1.997
Age		−0.041	0.046	0.786	0.375	0.960
Gender	Male	1.106	1.063	1.082	0.298	0.331
	Female	(Ref)				

SE, standard error; p, p-value; AOR, adjusted odds ratio.
The * symbol indicates the statistical significance.

TABLE 4 Surgical outcomes of endoscopic DCR with MCI with or without previous dacryocystitis.

Variable	MCI without dacryocystitis ($N = 12$)	MCI with dacryocystitis ($N = 10$)	*p*-value
	Mean or Number	Mean or Number	
Success rate			
At stent removal	11 (92%)	10 (100%)	>0.99[a]
1 month after removal	9 (83%)	10 (100%)	0.22[a]
3 months after removal	8 (67%)	9 (90%)	0.32[a]

[a]Double-tailed Fischer exact test.

TABLE 5 Surgical outcomes of endoscopic DCR with BCI with or without previous dacryocystitis.

Variable	BCI without dacryocystitis ($N = 12$)	BCI with dacryocystitis ($N = 11$)	*p*-value
	Mean or Number	Mean or Number	
Success rate			
At stent removal	12 (100%)	11 (100%)	–
1 month after removal	11 (92%)	10 (91%)	>0.99[a]
3 months after removal	11 (92%)	10 (91%)	>0.99[a]

[a]Double-tailed Fischer exact test.

Results

Sixty one eyes of 53 PANDO patients were reviewed. Five eyes were excluded due to short follow-up duration <3 months, 1 eye due to the traumatic mechanism, 1 eye due to abnormal lid position and trauma-related nasolacrimal duct obstruction, and 4 eyes due to no documented time of stent removal. Five patients had PANDO and treated with DCR with silicone stents in both eyes, and only the eye with more severe symptoms or with underlying dacryocystitis was selected. Forty five eyes of 45 PANDO patients were enrolled in current study. Among them, 22 eyes of 22 patients were performed with endoscopic DCR with pulled MCI, while 23 eyes of 23 patients were with pushed BCI. Characteristics were listed in Table 1. The median age was 63 [23–86] in MCI group and 67 [38–78] in BCI group. There was no significant difference in age ($p = 0.51$), gender ($p > 0.99$) and laterality ($p = 0.29$) between the MCI and BCI group. Stent indwelling duration in the BCI group was significantly shorter than that in the MCI group ($p < 0.001$). Nearly half of the enrolled patients had history of dacryocystitis. Previous lacrimal procedures including balloon dacryocystoplasty (59% in MCI and 78% in BCI group) as well as incision and drainage (27% in MCI and 26% in BCI group) were presented in our study.

Surgical outcomes were reported in Table 2. Improvement of the symptoms reported by patients and patent lacrimal system with lacrimal irrigation were observed mostly at the visit when the stent removed (95% in the MCI and 100% in the BCI group), and gradually decreased by time. No significant difference was obtained throughout the follow-up. Nevertheless, there was a higher success rate in the BCI group at 3 months after stent removal (87% in the BCI vs. 82% in the MCI group).

To evaluate the predictors of surgical success, implant material, stent indwelling duration, age and gender were incorporated into the binary logistic regression model (Table 3). Only the implant material reached a statistical significance ($p = 0.045$) with AOR 39.554 as a predictor of the surgical success at 3 months after stent removal.

We performed subgroup analysis of previous dacryocystitis listed in Tables 4, 5. There was no significant difference between the success rates of endoscopic DCR in PANDO patients with or without previous dacryocystitis either in the MCI or BCI group.

There was no immediate complication, such as tube loss, puncta complications or corneal abrasion in our study. Only one patient in the BCI group suffered from post-operative infection of surgical site and failed to maintain a patent lacrimal system at 1 month after stent removal. Some patients had mild nasal bleeding after surgery but controlled easily without the need of additional hemostasis.

Discussion and conclusion

Endoscopic DCR has gained popularity over the last few decades. It has several advantages over external DCR, namely the cosmetic benefit with no facial scar formation, shortened wound recovery time and hospitalization period, less blood loss, better visualization of endonasal anatomy, the ability to correct endonasal abnormality such as a hypertrophic turbinate and deviated nasal septum simultaneously, and applicability when acute dacryocystitis (6, 10, 12–15). Disadvantages of endoscopic DCR includes more expensive equipment and steep learning curve that a thorough understanding of endonasal anatomy is required (6, 12, 13).

The issue of whether to place stents during endoscopic DCR was frequently discussed. Endoscopic DCR with stents had no significant superiority in success rates over that without stents in previous studies (10, 11, 16). Nevertheless, the recent meta-analysis reported a tendency of improving success rate for endoscopic DCR with silicone intubation after 2012 (17). Due to the rapid recovery, cosmetic benefit and promising outcomes, we performed mostly endoscopic DCR with silicone stents in substitution of external DCR in our institution in recent 7 years.

In current study, PANDO mostly affected our patients around their sixth decades, characterized with female predominant and history of dacryocystitis, which was compatible with previous studies (6, 18, 19). The pathophysiology of PANDO seemed to be multifactorial. It might result from the smaller diameter of nasolacrimal duct in women (20, 21), hormonal change especially in postmenopausal female (22), and derangement of lacrimal drainage-associated lymphoid tissue in chronic dacryocystitis (23).

To manage PANDO, DCR is recognized as the treatment of choice. External approach and endonasal approach with various devices and techniques were reported (12). Rather than using Crawford or Ritleng stent for endoscopic DCR with BCI in previous comparative studies (24, 25), we used a Nunchaku-style silicone tube with a push-to-insert technique. Since the Nunchaku-style silicone tube was introduced by Katsuaki Kurihashi in 1993 (26, 27), it has become another choice of bicanalicular stent other than Crawford stent, which was a more commonly used and historical stent in western countries. The Nunchaku-style silicone tube is characterized by the bilateral thicker tube segments connected with a central rod segment, named after the shape of Nunchaku (26, 27). This design gives the bicanalicular stent a good stability in the lacrimal passage; therefore, there is no need of knots to anchor the stent and consequently it is easy to be removed from puncta. The unnecessity of tying knots avoids the excess tension that might damage or distort the puncta. Noteworthily, there was no BCI dislocation in our study. To date, the Nunchaku-style silicone stent is mostly applied as simple lacrimal system intubation than accompanied with endoscopic DCR in lacrimal duct obstruction. The success rate of solely Nunchaku-style silicone tube intubation was ranged from 63.6 to 95.1% in nasolacrimal duct obstruction in previous studies (19, 27–29).

As illustrated in this study, the success rate of endoscopic DCR with pushed BCI were slightly higher than that in the pulled MCI group at 3 months after stent removal (87 vs. 82%). Moreover, the implant material (the pushed BCI) served as a significant predictor of success. Kashkouli et al. first compared the success rate of endoscopic DCR with pulled MCI to that with pulled BCI using Ritleng stent for adults with nasolacrimal duct stenosis, and reported a similar success rate of 61.53 vs. 59.09%, respectively (25). Andalib et al. reported an equivalent result of 76% success rate in endoscopic DCR with pulled MCI using a Monoka Fayet tube and 76.2% in pulled BCI using a Crawford stent for adults with nasolacrimal duct stenosis (24). The success rates were also reported with no significant difference in the MCI and BCI in congenital nasolacrimal duct obstruction (30–32). The better success rate in pushed BCI might be resulted from the thicker stenting. It was ∼0.94 mm of the outer diameter of each thick segment in the Nunchaku stent, in contrast to 0.64 mm of the outer diameter in the Monoka stent. The thicker diameter of the tube provided a lower resistance and increased the lacrimal outflow according to the Poiseuille Law, which states that resistance is inversely proportional to the fourth power of the path radius (33–35). Additionally, the increased outflow may maintain the enlarged passage as named reverbed phenomenon in Moscato's study (35).

In the binary logistic regression, there was no significant difference of the success rate in the stent indwelling duration in current study. The optimal time for stent removal was controversial over time and the recommendation for stent indwelling duration varied from 4 weeks to 6 months. Higher success rate was reported when the stents placed longer in the lacrimal system (36, 37). However, Walland et al. suggested early removal of intubation due to the increased failure rate caused by granulomatous formation when prolonged intubation (38). Charalampidou et al., Kashkouli et al. and Jung et al. stood for an opposite opinion and reported that the timing of tube removal did not influence the success rate (25, 39, 40). Similarly, Zilelioğlu et al. found no correlation between the indwelling duration and the patency of the lacrimal system (41). Increased risks of complications such as granulation tissue formation of the puncta was reported in prolonged intubation, but good biological tolerance within 6 months of intubation length was documented (39, 41). Our study provided another evidence of early removal of silicone stent at 4–6 weeks might be noninferior and not detrimental. Meanwhile, it might reduce the duration of stent irritation and ease patients' discomfort.

In subgroup analysis, we reported no significant difference of the success rates in patients with or without previous dacryocystitis. Seider et al. revealed a lower success rate in patients with chronic dacryocystitis and treated with external DCR (42). However, recent studies showed a comparable surgical result regardless of dacryocystitis (43, 44). There was

no significant difference in surgical outcomes of external DCR in patients with and without history of dacryocystitis reported by Rabina et al. (43). Keren et al. studied the failure factors of endoscopic DCR and reported no correlation between previous dacryocystitis and the success rate (44). Current study is the second one that compared the surgical outcomes of endoscopic DCR with or without previous dacryocystitis other than Keren's study.

To our knowledge, this study is the first comparative literature focusing on endoscopic DCR with pulled MCI using Monoka® and pushed BCI using Nunchaku® with dacryocystitis subgroup analysis in adults with PANDO. Meanwhile, we provide evidence of shorter stent indwelling duration might not be inferior than prolonged stenting, which had been rarely discussed in a comparative study. Our study is also strengthened with one competent surgeon, which minimizes the operator bias.

There are limitations in the current study. First, this study was in a retrospective manner, and the grading of epiphora was not included. There was relatively small sample size that might amplify the statistic bias. Moreover, since most patients with primary acquired nasolacrimal duct obstruction received endoscopic DCR with stenting in our hospital, we compared the outcomes of two stents yet lacked a control group without stent. Furthermore, we studied cases up to 3 months after stent removal. A longer follow-up duration is required to obtain a long-term outcome. Further prospective, large-scaled and long-term study is needed to strengthen the evidence of the potential of endoscopic DCR with pushed BCI.

Conclusively, endoscopic DCR with silicone stenting is an effective surgical approach for patients with PANDO, and the surgical outcomes are not significantly influenced by previous dacryocystitis. The utility of the pushed BCI with Nunchaku® might possess a better surgical outcome than the pulled MCI with Monoka®. Early removal of the silicone stent after 1 month is noninferior to prolonged intubation after 4 months, and may reduce biofilm colonization as well as patients' discomfort caused by prolonged stent intubation.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of National Cheng Kung University Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

C-CL conceptualized, designed the study, reviewed, and revised the manuscript. Y-CC collected and analyzed the data, drafted, and revised the manuscript. All authors approved the final manuscript and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Diagnosis, Management, and Treatment of Vernal Keratoconjunctivitis in Asia: Recommendations From the Management of Vernal Keratoconjunctivitis in Asia Expert Working Group

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Vernal keratoconjunctivitis (VKC) is an underdiagnosed and underrecognized ocular surface disease with limited epidemiological data in Asia. It is more prevalent in warm, dry, and windy climates, and often has a substantial impact on a patient's quality of life. In rare cases, VKC can be associated with vision loss, either through corticosteroid overuse or inadequate treatment of persistent inflammation. As a potentially severe and complex disease, there is variability with how VKC is managed across Asia and among the various allergic eye diseases. Diagnosis and treatment of patients with VKC is a challenge for many ophthalmologists, since no precise diagnostic criteria have been established, the pathogenesis of the disease is unclear, and anti-allergic treatments are often ineffective in patients with moderate or severe disease. In addition, the choice of treatment and management strategies used for patients varies greatly from country to country and physician to physician. This may be because of a lack of well-defined, standardized guidelines. In response, the Management of Vernal Keratoconjunctivitis

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in Asia (MOVIA) Expert Working Group (13 experts) completed a consensus program to evaluate, review, and develop best-practice recommendations for the assessment, diagnosis, and management of VKC in Asia. The expert-led recommendations are summarized in this article and based on the currently available evidence alongside the clinical expertise of ophthalmologists from across Asia with specialism and interest in the ocular surface, VKC, and pediatric ophthalmology.

Keywords: vernal keratoconjunctivitis (VKC), ocular surface, ocular allergy, cyclosporine A (CsA), corticosteroids, MOVIA, consensus, recommendations (guidelines)

INTRODUCTION

The key findings and best-practice recommendations of the MOVIA Expert Working Group, as shown in **Table 1** (with a summary of a stepwise management approach according to disease severity shown in **Figure 1**), are based on the available literature, evidence, and clinical experience at the time of writing. All relevant information and literature pertaining to the discussions exchanged in the consensus program are detailed hereafter. These expert-led, best-practice recommendations are not intended as clinical practice guidelines.

Background

Definition

Vernal keratoconjunctivitis (VKC) is a recurrent form of ocular allergy characterized by severe and often bilateral chronic inflammation of the ocular surface, which can result in permanent injury or visual disabilities if not adequately recognized and treated. VKC is a T-lymphocyte-mediated disease with subsequent immunoglobulin (Ig)E-mediated chronic inflammation involving eosinophils, mast cells, lymphocytes, and structural cell activation (1–4).

Epidemiology

Allergic conjunctivitis alone has an estimated worldwide prevalence of 6–30% in the general population and is estimated to occur in up to 30% of children, either alone or in association with allergic rhinitis (5). VKC is an underdiagnosed and underrecognized ocular surface disease and epidemiological data are limited. VKC is most frequent in Asia, Central and West Africa, and South America, but is also common in the Mediterranean area, North America, and Australia (1, 6–9). A recent epidemiological survey has provided insight into the frequency of VKC across Europe, where a prevalence of <1–3.2/10,000 overall and 0.8/10,000 with corneal complications has been reported (9). In Japan, a prevalence of 1.2% has been described, and in African countries prevalence ranges from 4.0 to 11.1% (8). However, the prevalence of VKC in much of Asia is currently unknown and current estimates may be inaccurate (6)—this is because the clinical form is generally mild and self-limiting, and access to care varies significantly among Asian countries, meaning that many patients do not present to a clinic. In addition, many ophthalmologists categorize VKC as an ocular allergy, and therefore estimates can be misleading and underrepresent the true prevalence of the condition. Depending on geography and climate, the prevalence of VKC can vary widely across Asia, including within countries and regions. There remains an unmet need for ophthalmologists to accurately diagnose VKC and for precise estimates of prevalence, including differences in clinical presentation, across Asia.

VKC occurs mainly in children and young adults, with onset often occurring in the first decade of life (predominantly 5–10 years) (9). While it is considered a long-term disease with an average duration of 4–8 years (9), VKC generally subsides before or just after puberty, but can leave permanent lesions in patients with severe disease (7). The disease is more common among males than females, with a ratio of 3:1, but this difference may become less at older ages of onset (7, 10).

Environmental factors play an important role in the development of VKC, with increased frequency in warm, dry, and windy climates, and worsening severity as a result of air pollution and Asian dust storms (1, 7, 11, 12). The MOVIA Expert Working Group previously recognized that despite a typically seasonal trend, perennial forms of VKC are more widely reported (50–100% of the VKC population across different regions of Asia) with acute exacerbations in the spring–summer period; seasonal forms are more commonly reported in Hong Kong (up to 50% of patients with VKC) and to a lesser extent in South Korea (20%). The type of allergen responsible for aggravating VKC may explain its seasonal or perennial nature. For example, pollen may be responsible for seasonal VKC, while dust mites (or other indoor allergens) could be responsible for the perennial form.

Pathophysiology

VKC is a T-helper-2 (Th2) lymphocyte-driven disease characterized by infiltration of the conjunctiva by a number of inflammatory cell types, including eosinophils, mast cells, and T lymphocytes (3, 4). This differs from atopic keratoconjunctivitis (AKC), which has been shown to involve both Th1 and Th2 inflammatory cascades (13). Increased levels of tumor necrosis factor (TNF) alpha, histamine, tryptase, IgE, and IgG antibodies are observed on pathologic examination of tears (14). It is believed that the exaggerated IgE response observed with VKC in response to common allergens may be a secondary event (4). Mast cells and basophils cause the immediate reaction (through the release of histamine) and the recruitment of inflammatory cells (lymphocytes and eosinophils). This results in the release of a number of pro-inflammatory cytokines, including (but not limited to) interleukin (IL)-4, IL-5, and IL-13, as well as other toxic cell mediators (such as eosinophil cationic protein, eosinophil-derived neurotoxin/eosinophil protein X

TABLE 1 | Expert-led recommendations from the MOVIA Expert Working Group.

Assessment and diagnosis
• Slit-lamp examination and eversion of eyelids.
• Ocular surface staining, tear film stability, and breakup pattern; if available.
• Adjunctive tests should be considered in the context of a multidisciplinary team approach, if required and if locally available.
Management should follow a stepwise approach with active patient education
• Address triggers and aggravating factors (e.g., environment and allergens).
• Maintain ocular health, including frequent hand, face, and hair washing.
• Use of ocular lubricants and cold compresses should always be considered.
Several treatments are effective for reducing the symptoms of VKC *(For the use of any eye drops on the ocular surface, it is recommended to use preservative-free compounds, where possible, to minimize ocular surface toxicity)*
Conventional topical anti-allergic drugs
○ Dual-acting agents, antihistamines, and mast cell stabilizers are all effective for reducing signs and symptoms of mild or moderate VKC.
○ Dual-acting agents should be considered ahead of monotherapy with antihistamines or mast cell stabilizers.
Cyclosporine CsA 0.1% cationic emulsion (CsA 0.1% CE)
○ Topical CsA 0.1% CE should be considered for patients with in moderate-to-severe or persistent VKC.
○ Patients should be instructed on how to apply CsA eye drops to minimize stinging or burning on instillation, such as using artificial tears prior to instillation.
Topical corticosteroid eye drops
○ In patients with only conjunctival involvement, topical corticosteroids should be reserved for use after loss of control or persistence of symptoms with immunomodulators (such as CsA).
○ Topical corticosteroids are effective for the management of acute exacerbations, or when the cornea is involved, and preferably only introduced in patients with more severe disease. In these individuals, corticosteroids should be used in combination with CsA to account for the fact that CsA may require ≥1 week to act.
○ Because of an increased risk of adverse events/or vision loss with chronic use, topical corticosteroid eye drops should be used in short pulses (alone or in combination with CsA) under the supervision of an ophthalmologist and tapered rapidly.
Tacrolimus
○ In regions where available, tacrolimus should be reserved for patients with severe VKC that is refractory to CsA. It can be considered as a treatment for moderate-to-severe VKC in patients with allergy of the eyelid, but please note this may be off-label.
Vasoconstrictors
○ Vasoconstrictors are not recommended for the treatment of VKC.
○ If used to address hyperemia, vasoconstrictors should be used with caution and only for a short period due to adverse events.
Non-steroidal anti-inflammatory drugs (NSAIDs)
○ NSAIDs are not recommended as they do not target the specific inflammatory mechanism associated with VKC.
Systemic antihistamines
○ Second-generation systemic antihistamines are preferred over older first-generation antihistamines.
Allergen-specific immunotherapy
○ Allergen-specific immunotherapy is only recommended when clearly defined systemic hypersensitivity to an identified allergen exists.
○ Patients requiring allergen-specific immunotherapy should be referred to an allergist or specialist ophthalmologist.
In selected patients with ocular complications or persisting symptoms following prior treatments
○ Surgery, oral corticosteroids (short pulses) or corticosteroid lid injection, or systemic treatment with immunomodulators or biologics may be appropriate options for use by corneal specialists.

[EDN/EPX]) that result in corneal damage (4, 15). Release of these factors mediates the remodeling, ocular inflammation, and itch that are commonly associated with VKC.

Management strategies should continue to be focused on tackling specific aspects of the clinical presentation and pathophysiology of VKC.

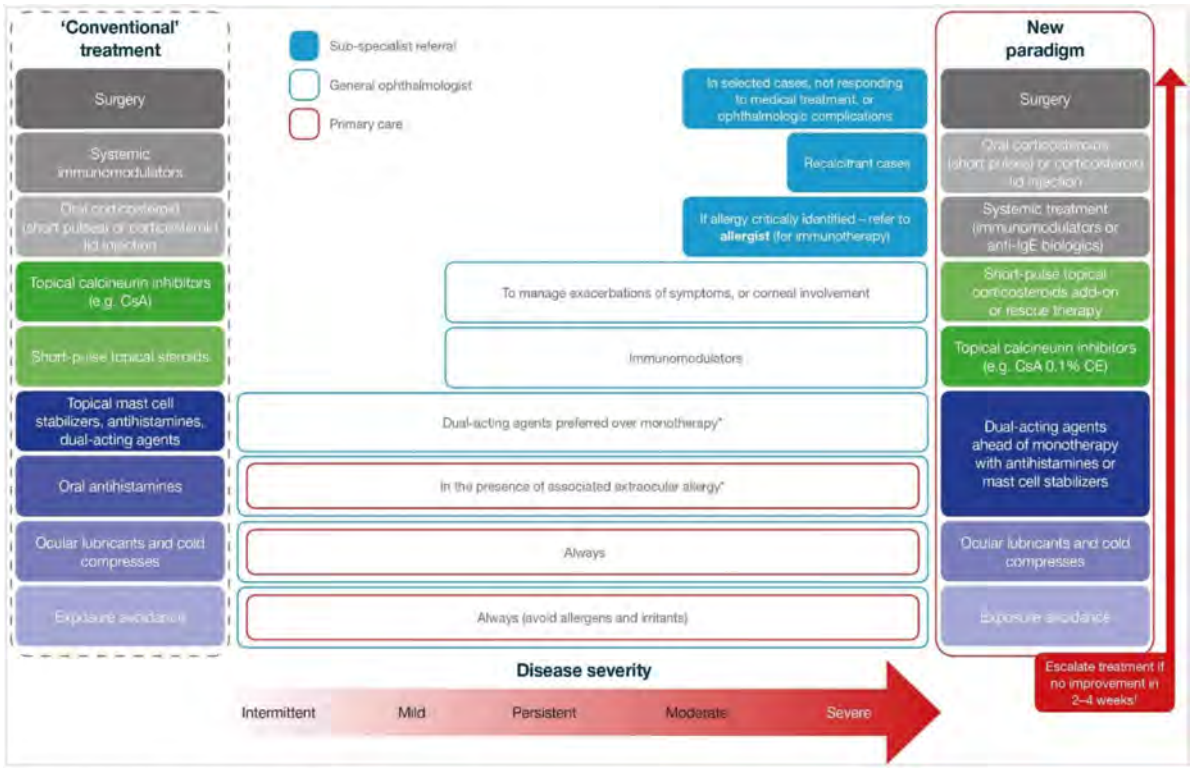
Clinical Forms

Clinical signs of VKC include a papillary reaction of the upper tarsal conjunctiva and throughout the limbus. The disease can be classified into three clinical subtypes based on the location of the papillae: tarsal (palpebral; see **Figure 2**), limbal (bulbar; see **Figure 3**), or mixed form (3).

The tarsal form is characterized by large, cobblestone-like papillae on the upper tarsal conjunctiva. These can differ in shape and size, but are usually defined as >1.0 mm in diameter (1, 3). The limbal form typically involves Horner–Trantas dots, indicating lymphocytic and eosinophilic infiltration of the limbal conjunctiva (1, 3). The mixed form is characterized by the presence of both tarsal and limbal subtypes in only one eye (as signs are often heterogeneous between eyes) (1). According to the MOVIA Expert Working Group, the most common form of VKC seen in clinics across Asia is the tarsal form; however, up to one-third of patients are assumed to have the mixed form. The limbal form of VKC is considered less common in Asia (based on clinical experience).

Disease-Related Signs, Symptoms, and Complications

The most common ocular features of VKC are initially itching, redness, and tearing. Other common features include blurred vision, photophobia, burning, and a characteristic ropey, stringy



- **Patient education**; with avoidance of triggers, good hygiene, and use of cold compresses/ocular lubricants
- **Dual-acting agents**; ahead of monotherapy with mast cell stabilizers or antihistamines
- **Topical cyclosporine A (CsA)** (immunomodulators; preferably commercial formulations)
  - Steroids should only be used in short pulses, as rescue therapy when CsA alone appears ineffective in cases of conjunctival involvement, or in combination with CsA in patients with moderate-to-severe disease with corneal involvement or acute exacerbations
  - Non-ocular systemic antihistamines should only be considered if an allergy is critically identified
  - Allergen-specific immunotherapy is suitable when clearly defined systemic hypersensitivity is known, and must be referred to an allergist and specialist ophthalmologist

FIGURE 1 | A new paradigm for the stepwise management of VKC based on disease severity. Adapted from Leonardi et al. (28). *In the case of associated rhinitis, consider treatment according to Allergic Rhinitis and its Impact on Asthma (ARIA) protocol; †No improvement is defined as no improvement in symptoms or changes in conjunctival, papillary or ocular surface clinical signs. CE, cationic emulsion; CsA, cyclosporine A; IgE, immunoglobulin E.

mucus, and/or serous discharge (1, 16). Other typical signs and symptoms include moderate-to-intense conjunctival hyperemia, mild-to-moderate chemosis, foreign-body sensation, and pain, all of which can be very intense upon awakening, causing what is called "the morning misery" (1).

Severe VKC can result in sight-threatening complications. Ocular surface damage as a result of repetitive eyelid trauma and VKC-associated inflammatory activity can lead to corneal complications such as superficial punctate keratopathy (SPK), shield ulcers, corneal scarring, keratoconus, dry eyes, limbal stem-cell deficiency, and secondary infections (1, 6, 17, 18). Shield ulcers, which can be self-limiting or associated with bacterial keratitis, usually form on the upper third of the cornea, and can lead to loss of vision (see **Figure 4**) (3). Plaques can also form when inflammatory debris accumulates at the base of a shield ulcer (17), and can be particularly resistant to topical therapy or require surgical intervention (3). Limbal stem-cell deficiency can occur with longstanding inflammation (3). Keratoconus and irregular astigmatism can result from frequent eye rubbing in the pediatric population (10, 19, 20). In these patients, there is a fine balance between the benefits of corticosteroids and the risk for vision loss as a result of overtreatment. Patients with severe VKC may also develop lid complications and acquire ptosis (often with atopic dermatitis). The variable severity of these complications in each patient presents a challenge to ophthalmologists to not only manage acute episodes, but also to prevent reappearances.

Despite the limbal form of the disease being rare in Asia, a new clinical sign of VKC has been reported in patients from India and China—perilimbal hyperpigmentation. In these case reports, patients with VKC (ranging across all grades of disease, including remission) were observed to have fine, golden brown spotty pigmentations, mostly located in the perilimbal bulbar conjunctiva. With abundant melanocytes and mast cells around the limbus and complex immune mechanisms involved in VKC, it may be that any perilimbal conjunctival pigmentation is a by-product of these interactions and pathways. Whether

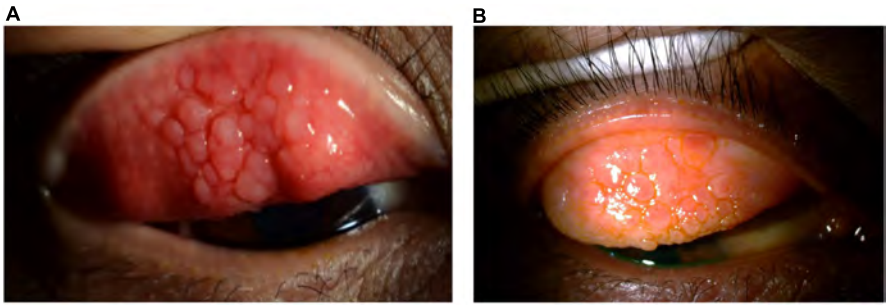


FIGURE 2 | Clinical subtypes of VKC: *Tarsal form*. The tarsal form is characterized by large, cobblestone-like papillae on the upper tarsal conjunctiva. **(A)** Image courtesy of Jodhbir S. Mehta; **(B)** image courtesy of Douglas K. Lam.

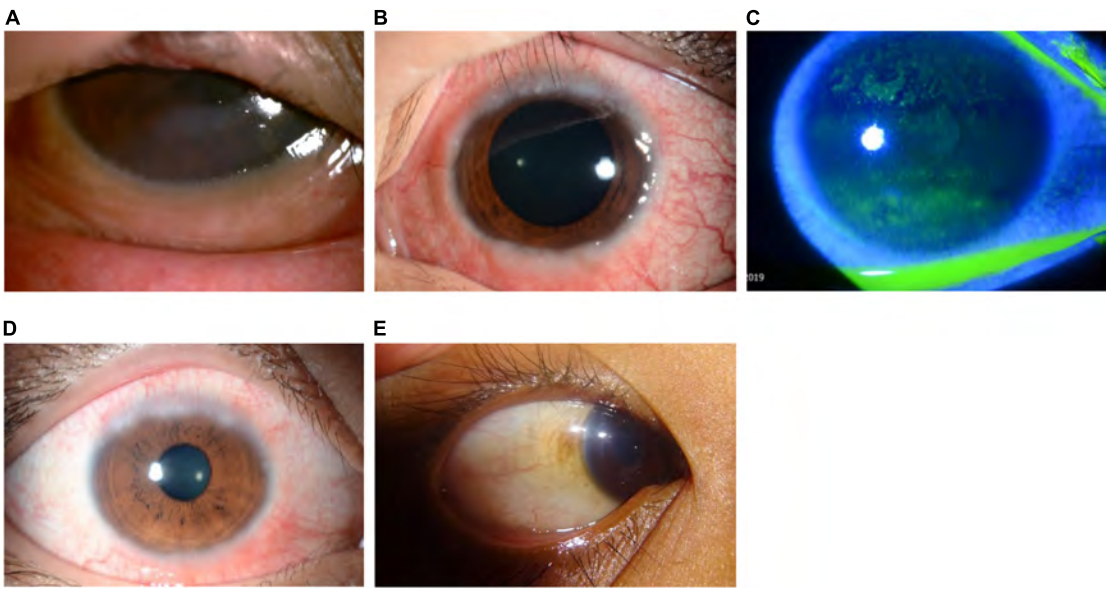


FIGURE 3 | Clinical subtypes of VKC: *Limbal form*. The limbal form typically involves Horner–Trantas dots (see **Figure 5**), indicating lymphocytic and eosinophilic infiltration of the limbal conjunctiva. The mixed form is characterized by the presence of both tarsal and limbal subtypes in only one eye. **(A)** Image courtesy of Wei-Li Chen; **(B–D)** images courtesy of Jodhbir S. Mehta; **(E)** image courtesy of Florence Manurung.

environmental or racial factors have a role in the presence and/or distribution of the pigmentation remain to be solved. Immunopathological studies of conjunctival specimens from patients with VKC may provide additional information. More research is required to understand whether this sign is a consistent clinical finding, and whether this may be a useful diagnostic sign in patients with early or mild disease when signs and symptoms are subtle (21).

VKC usually resolves after puberty or adolescence. This means VKC can evolve and even spare the cornea, with only occasional presentation of symptoms during seasonal periods. However, without adequate treatment, the seasonal form can evolve into a chronic perennial inflammation after a mean of 3 years from disease onset (4). By contrast, children diagnosed with AKC will suffer from manifestations throughout their life, and may develop more severe complications, as the condition is progressive (22).

Burden of VKC

VKC is associated with a substantial impact on quality of life and daily living. Symptoms, which can be exacerbated by exposure to allergens or irritant stimuli, can lead to sleep deprivation and the inability to be outdoors (23). The latter has significant negative consequences for the daily life and social interactions of children, including playing sports, meeting friends, and attendance at school.

VKC also negatively impacts quality of life in adult patients (24). An increased disease duration and considerable inflammatory state (atopic sensitivity) associated with adult VKC can significantly impact the life and daily activities of individuals, with an additional economic burden (24). In patients with severe VKC, psychological support may be required.

Inadequate counseling and unrealistic expectations, often resulting in the overuse, misuse, and self-use of corticosteroids, can be associated with complications. Overmedication with

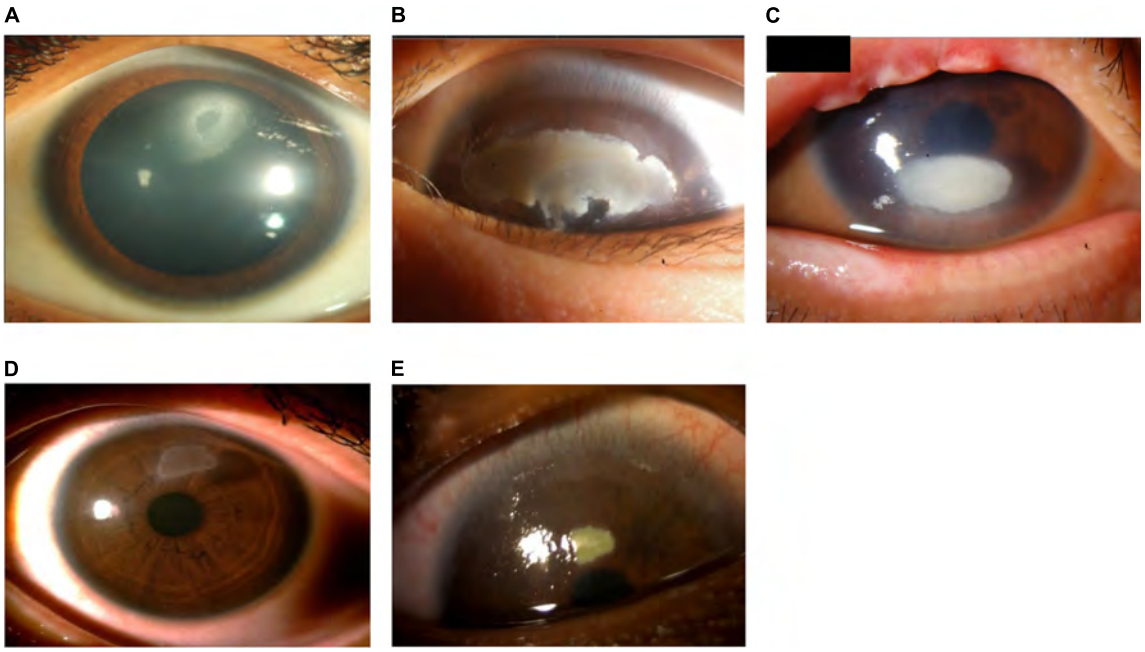


FIGURE 4 | Patients with shield ulcer formation. Shield ulcers usually form on the upper third of the cornea. Plaques can also form when inflammatory debris accumulates at the base of a shield ulcer. **(A)** Image courtesy of Ramesh Kekunnaya; **(B,C)** images courtesy of Wei-Li Chen; **(D)** image courtesy of Leo Seo Wei; **(E)** image courtesy of Dominique Bremond-Gignac.

corticosteroids can cause vision loss, as can undermedication (although uncommon) and persistent inflammation resulting in corneal scarring and stem-cell damage (25). The long-term use of corticosteroids by patients is often unsupervised and can be associated with raised intraocular pressure (IOP) and glaucoma, cataracts and opportunistic infections (10, 18–20, 26). Patients who are overtreated with corticosteroids may live with vision impairment for years, with an increased financial burden to treat the aforementioned complications (20).

Rationale and Objectives

The aim of these expert-led recommendations is to provide general ophthalmologists in Asia with guidance for the diagnosis and management of VKC in order to inform clinical decisions and improve patient outcomes. The recommendations aim to incorporate the best available evidence into clinical practice to close the gap between the current standard of care and what the literature supports. The management recommendations are intended to progress clinical practice across Asia from a "conventional" approach to an evidence-based paradigm to provide patients with the greatest disease control as early as possible.

METHODS

The recommendations and information stated herein are based on the best available evidence as interpreted by an expert panel of 12 ophthalmologists from across Asia (Hong Kong SAR, India, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam) and one expert from France, all of whom have specialism and interest in the ocular surface, VKC, and pediatric ophthalmology. Gaps were identified and recommendations suggested by the expert group based on clinical expertise and available literature at the time of writing. The consensus program and development of this article followed an iterative process, led by two co-chairs of the MOVIA Expert Working Group (Prof. Jodhbir S. Mehta and Prof. Dominique Bremond-Gignac), with regular review and input from all members. Consensus was confirmed in a MOVIA Expert Working Group meeting held in October 2020 with every member of the group formally agreeing on the recommendations and paradigm presented. Voting included a five-way Likert scale to ascertain the certainty and strength for each—comprising the following options: "Weak" (associated with a score of –1), "Neutral" [0], "Moderate" [1], "Strong" [2], and "Very strong" [3]. The values of the votes were averaged, and the strength of the recommendation determined—with scores $\geq$2.5 were categorized as "Very strong" [+++]; $\geq$1.6 to $<$2.5 as "Strong" [++]; and $\geq$0.8 to $<$1.6 as "Moderate" [+]. Any recommendations with score $<$0.8 were not included.

UNMET NEEDS IDENTIFIED

The MOVIA Expert Working Group identified key unmet needs, including:

- Diagnosis and treatment of patients with VKC—this is a challenge for many ophthalmologists, since no precise diagnostic criteria have been established, the pathogenesis

of the disease is unclear, and anti-allergic treatments are often ineffective in patients with moderate or severe disease (27).
- Choice of treatment and management strategies—currently, those used for patients with the same severity of disease varies greatly from country to country and physician to physician across Asia. This is because of a lack of well-defined, standardized guidelines and grading systems (25).
- Safety and iatrogenic complications (28).
- Optimal dosing regimens of pharmacological treatments (28), including supervision and compliance of readily available options.

Providing Clarity in the Diagnosis of VKC

VKC forms part of a spectrum of ocular allergic disorders—termed allergic conjunctivitis—that affect the eyelid and conjunctiva (14). Other clinical forms that belong to this collection of diseases include contact blepharoconjunctivitis (CBC), seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), AKC, and giant papillary conjunctivitis (GPC) (14). Corneal involvement is typically restricted to the two most severe forms of ocular allergy, VKC and AKC, which require particular care in their diagnosis and management, with careful documentation of the patient's clinical history and the use of slit-lamp examination for key clinical signs (28–30). The diagnosis has to be made as early as possible in order to specify the individual's prognosis: regression in VKC (usually disappearing at adolescence) and progression in AKC (into adulthood) (31).

While the differential diagnosis of diseases belonging to the allergic conjunctivitis family can be challenging, VKC is relatively easy to diagnose by clinical examination. Horner–Trantas dots (see **Figure 5**) and large cobblestone papillae (see **Figure 6**) are indicative of the disease (1, 3). On the other hand, AKC in children can be misdiagnosed as the presentation appears similar. However, atopic dermatitis or eczema often accompany this ocular allergy, with signs of thickened dry skin, and can be used to differentiate AKC from VKC. Particular attention can be given at first examination to the extent of atopic dermatitis across the skin, elbow, neck or canthus (31).

VKC can be differentiated from other ocular allergic conditions or drug-induced conjunctivitis (which can occur following instillation of eye drops, e.g., topical antiglaucoma agents, mydriatics, or alpha-adrenergic agonists commonly used as decongestants in over-the-counter anti-allergy eye drops) through a comprehensive clinical history and ophthalmic examination (28). No single clinical feature viewed in isolation can accurately differentiate AKC and VKC—a multifactorial assessment of key clinical signs presented, taking into consideration the presence of AKC-specific clinical features and the absence of VKC-related clinical features, in combination with a history of eczema and conjunctivitis/keratitis, may promote accurate diagnosis in children (31).

Table 2 includes clinical features that can assist the differential diagnosis of VKC vs. other common forms of ocular allergy. The diagnosis is generally based on the signs and symptoms of the disease, but in difficult instances can be aided by conjunctival scraping to demonstrate the presence of infiltrating eosinophils (4). Recently published guidelines in Japan include a diagnostic flowchart for allergic conjunctival diseases (in keeping with **Table 2**) which highlights key diagnostic differentiators for VKC, AKC SAC, PAC, and GPC. These include the absence or presence of conjunctival proliferation, seasonality of the condition, use of contact lenses, and absence or presence of atopic dermatitis, alongside the common symptom of ocular itching and hyperemia (32).

The MOVIA Expert Working Group highly recommend the use of slit-lamp examination and the inversion and examination of the eyelids in the initial diagnostic approach for VKC, as many of the key clinical features appear on the eyelid or palpebral conjunctiva. Fluorescein staining may also help to identify sight-threatening corneal involvement in patients with moderate or severe disease.

Outside of ocular allergy and drug-induced conjunctivitis, other key differential diagnoses include:

- Pediatric blepharokeratoconjunctivitis—commonly misdiagnosed as ocular allergy in children of the same age range who present with blepharitis (33).
    - This can be differentiated from AKC and VKC through assessment of symptomology and corneal changes (31). It is important to consider that in patients with blepharokeratoconjunctivitis, crusting of the lids may ensue in the morning, but discharge is not a major feature. In addition, there is frequently a history of recurrent chalazia. However, the condition may occasionally be asymptomatic until the presentation of photophobia, reduced vision and corneal opacities. Notable corneal changes in blepharokeratoconjunctivitis can include punctate epithelial erosions, peripheral (or marginal) keratitis, central or paracentral opacities with and without scarring, and secondary corneal vascularization (34).
    - The presence of subconjunctival (cholesterol) oil crystals may also be a specific sign for blepharokeratoconjunctivitis (35).
- Infectious ulcers—the prevalence of which is anecdotally increasing among children in Asia due to the occurrence of orthokeratology lens-related corneal infections and trauma (36).
    - It is important to differentiate ulcers from VKC, as treatment with corticosteroids can worsen the condition.
- Scleritis (episcleritis).
    - Look for localized or widespread edema and purplish erythema, which indicate a serious cause, such as scleritis.
- Chlamydial infection (or trachoma)—distinguished by the presence of tarsal scarring (line of Arlt) and scarring of limbic follicles (Herbert's pits).
- Corneal foreign body—where removal can leave acute epithelial defects.

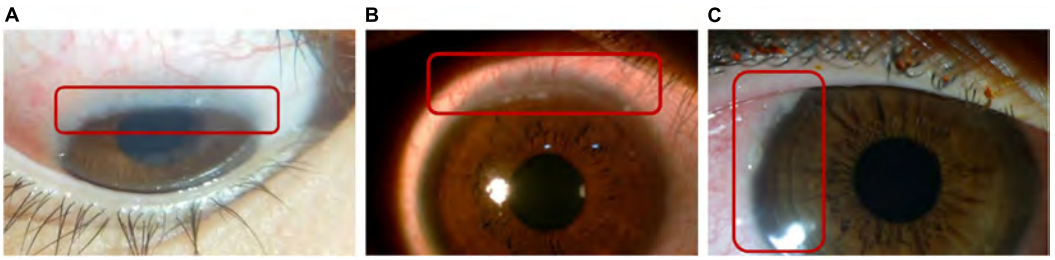


FIGURE 5 | Horner–Trantas dots. Peri-limbal Horner–Trantas dots are focal white dots consisting of degenerated epithelial cells and eosinophils and are indicative of VKC. **(A)** Image courtesy of Florence Manurung; **(B)** image courtesy of Leo Seo Wei; **(C)** image courtesy of Dominique Bremond-Gignac.

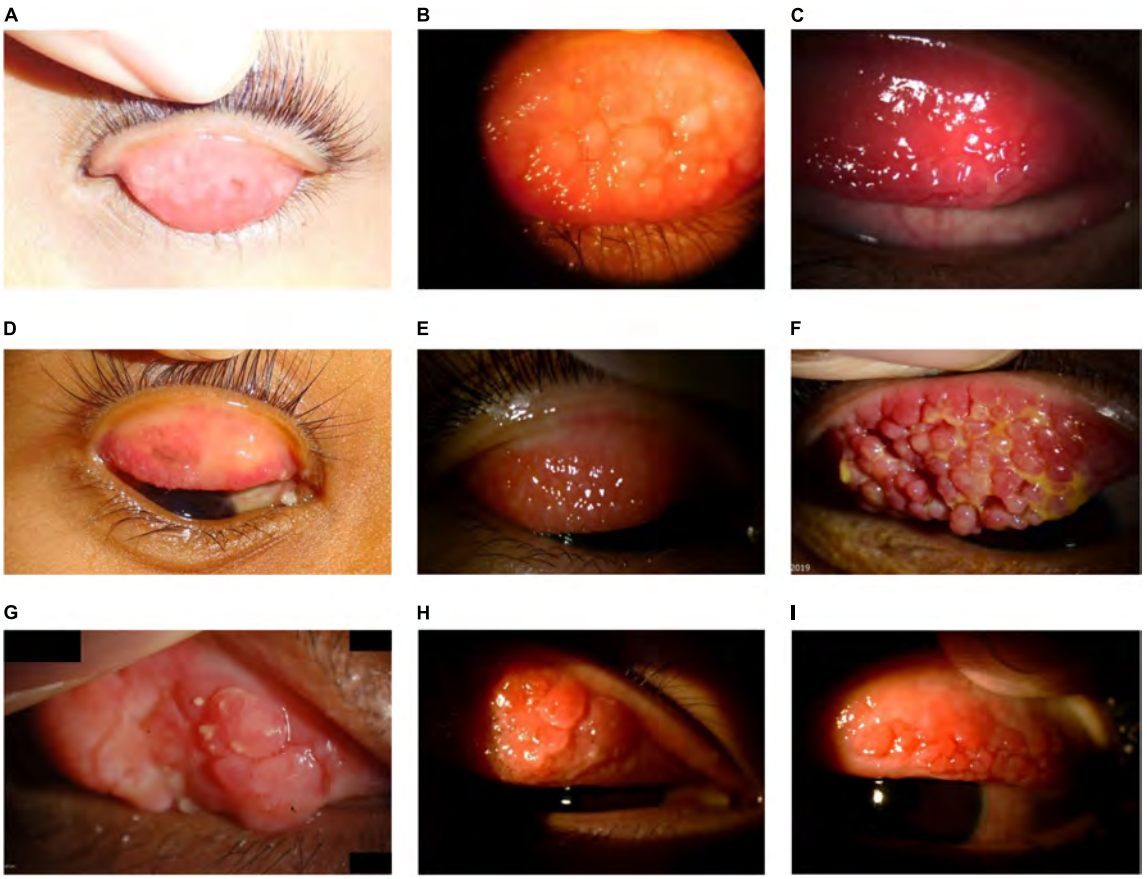


FIGURE 6 | Large cobblestone papillae. Upper tarsal giant papillae are typical of VKC. These have characteristically flattened tops which sometimes demonstrate stain with fluorescein. Giant papillae can sometimes be seen near the limbus and, while relatively uncommon, symblepharon formation and conjunctival fibrosis can occur. **(A–D)** Images courtesy of Florence Manurung; **(E)** image courtesy of Douglas K. Lam; **(F)** image courtesy of Jodhbir S. Mehta; **(G)** image courtesy of Wei-Li Chen; **(H-I)** images courtesy of Leo Seo Wei.

Slit-lamp examination and eyelid eversion should allow the identification of clinical features related to VKC. The following areas should be prioritized to understand the nature of the ocular allergy:

- Conjunctiva—papillae (small conjunctival elevations with central vessels), follicles, chemosis (swelling), and membranes. Pull on the lower eyelid and evert the upper lid to examine the palpebral conjunctiva.
- Cornea—look for SPK, ulceration, opacities, and Horner–Trantas dots. Keratoconus and astigmatism, as well as vernal plaques, may present in patients with moderate-to-severe VKC or AKC.
- Eyelids—look for discharge, swelling, inflammation, loss of lashes (may present in VKC and AKC), lice infestation, or blepharitis.
- A dull blue discoloration below the eye (sometimes called the "allergic shiner") resulting from venous congestion may

TABLE 2 | Clinical features of major ocular allergy syndromes, including the underlying hypersensitivity mechanism and ophthalmological presentation (68).

	VKC	AKC	CBC	GPC	PAC	SAC
Clinical presentation	Persistent ± intermittent exacerbations	Chronic	Chronic ± intermittent exacerbations	Persistent	Persistent	Intermittent
Allergic mechanism(s)	IgE- or non-IgE-mediated	IgE- or non-IgE-mediated	Non-IgE-mediated	Non-allergic	IgE-mediated	IgE-mediated
Background	**Childhood** ± atopic	Adult atopic	Non-atopic	Atopic or non-atopic	Atopic	Atopic
Eyelids	Edema, pseudoptosis	Eczema + meibomitis, blepharitis, Dennie–Morgan folds	Erythema, eczema	–	± Edema	Edema
Conjunctiva	**Giant papillae, hyperemia**	Papillae ± fibrosis	± Hyperemia, follicles	Giant papillae	Follicles and/or papillae	Follicles and/or papillae
Limbus	± Thickened + **Horner–Trantas dots**	± Thickened ± Horner–Trantas dots	–	Hyperemia	–	–
Cornea	SPK ± shield ulcer ± vernal plaque ± keratoconus	SPK, shield ulcer, plaque, opacities, scars, neovascularization ± keratoconus	–	Rare	–	–

Clinical features in bold are key differentiators from other ocular allergic conditions. Adapted from Leonardi et al. [69]. AKC, atopic keratoconjunctivitis; CBC, contact blepharoconjunctivitis; GPC, giant papillary conjunctivitis; PAC, perennial allergic conjunctivitis; SAC, seasonal allergic conjunctivitis; SPK, superficial punctate keratopathy; VKC, vernal keratoconjunctivitis.

be present in some people with allergies. This is often related to allergic rhinitis and should not be confused with Dennie–Morgan folds in the lower eyelid, which is a common sign of AKC.

Supplementary ophthalmic examinations, although non-essential in the context of ocular allergy assessment, include:

- Visual acuity—compare with previous levels of visual acuity, if possible.
- IOP—it remains important to monitor IOP in a condition where steroids may be used and associated with IOP-increasing adverse events.

If available, tear film stability and breakup patterns can be assessed using fluorescein application, and the cornea can be examined for abnormalities, such as small branching corneal dendrites (characteristic of herpes simplex keratitis), single or multiple dendrite-like epithelial or subepithelial lesions (pseudodendrites), and corneal ulcers. VKC should also be assessed with respect to dry eye disease, as the two conditions often coexist (1).

Adjunctive tests should be considered in the context of a multidisciplinary team approach, if needed and locally available. These include skin-prick tests, blood tests, examination by allergists (for asthma, dermatitis, rhinitis, eczema), and conjunctival allergen provocation tests. Two VKC populations can be defined according to the diagnostic criteria:

1. Those with positive test results, who generally also present with some other allergic manifestation, such as asthma, rhinitis, or eczema;
2. Those with negative test results, and a negative personal and familial history of atopy.

Importantly, while skin-prick tests are useful for allergen detection (and results may be positive), VKC is not always closely related to allergen exposure, and climate is an equally critical factor (1).

Conjunctival scrapings or tear cytology may be useful to indicate increased leukocytes in the conjunctiva, particularly eosinophil levels (1). However, biochemical markers are not a requisite for diagnosis. In many cases, patients should be referred to a corneal specialist or specialist pediatrician to receive treatment without the need for full diagnosis (1, 30).

Research has suggested that dendritic cells play an essential role in VKC, with higher numbers reported in patients with VKC compared with normal eyes. The dynamic changes of dendritic cells at the conjunctiva and cornea, such as density, morphology, and distribution, may be observed with *in vivo* confocal microscopy (37). This could help the assessment, diagnosis, and monitoring of the disease. However, the application in everyday practice across Asia may be limited to specialists and/or research purposes, due to access and availability.

Current Practice in Clinical Grading and Assessment of Severity

Symptomatic or clinical grading criteria can provide general ophthalmologists (and pediatricians) with clearly defined parameters that can guide referral of the patient to a corneal specialist or allergist for diagnostic confirmation (7).

The finding of papillary hyperplasia (see **Figure 7**) is mandatory for the diagnosis of VKC, and there is agreement on classifying the disease based on the part of the conjunctiva involved (tarsal, limbal, or mixed form). Papillae are variable in size, ranging from 0.1 to 5.0 mm in diameter (7). However, there is no consensus on the threshold that distinguishes giant from small papillae, with proposed cut-offs ranging from 1.0 to 3.0 mm in diameter (7).

With regard to the severity of the disease, some models of combined evaluation of symptoms have been proposed. Across Asia, the most widely used model is the Bonini scale (27), on which the most frequent grades of VKC seen in ophthalmology clinics is understood to be moderate and severe.

This Bonini grading is based on the clinical signs and symptoms of ocular surface inflammation to help classify the severity of disease (7, 27). **Figure 8** outlines this grading system.

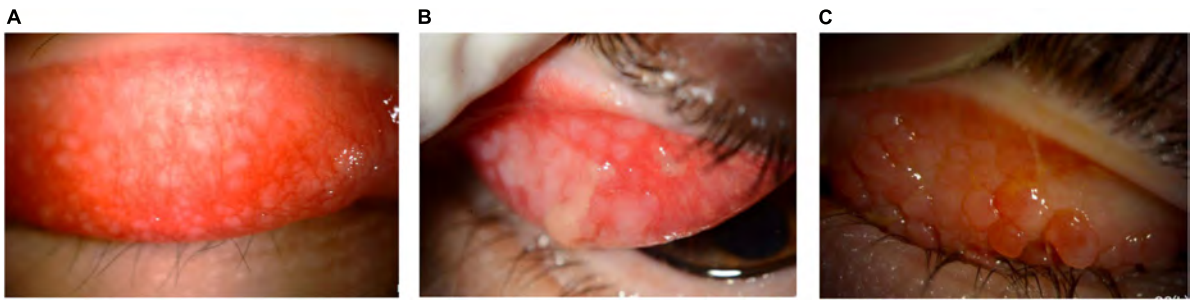


FIGURE 7 | Characteristic papillary hyperplasia in VKC. The conjunctiva often shows hyperplasia, with infiltration of lymphocytes and eosinophils. **(A)** Image courtesy of Wei-Li Chen; **(B)** image courtesy of Jodhbir S. Mehta; **(C)** image courtesy of Dominique Bremond-Gignac.

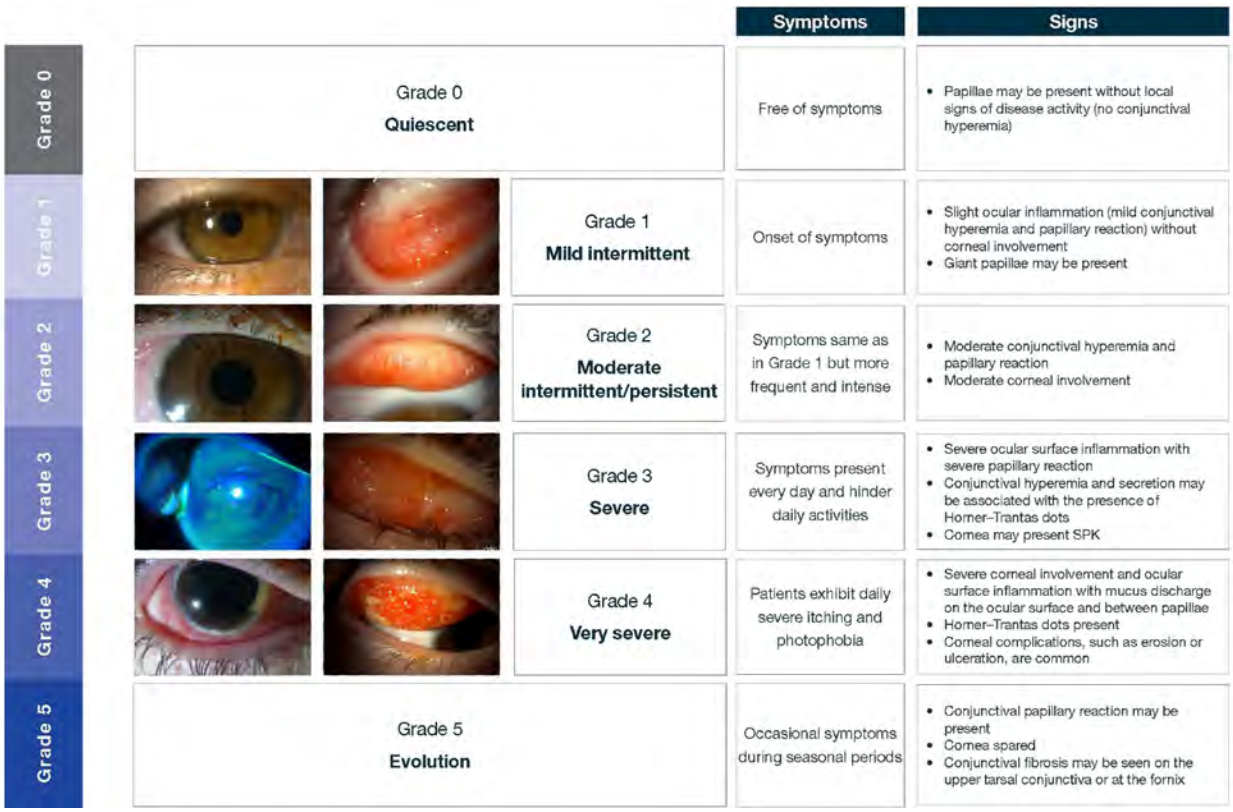


FIGURE 8 | Levels of severity of VKC, based on the Bonini grading scale. Adapted from Bonini et al. (27). Images courtesy of Dominique Bremond-Gignac. SPK, superficial punctate keratopathy.

A variety of other grading schemes are available but are not as widely used in Asia. Pucci et al. developed a grading score of subjective ocular symptoms (itching, photophobia, tearing, foreign body, and burning sensation) ranging from 0 (no symptoms) to 15 (severe clinical picture) (38). Several other grading schemes may be available to estimate corneal involvement in VKC, such as the new VKC-Collaborative Longitudinal Evaluation of Keratoconus study (VKC-CLEK) system, which aims to better evaluate limbal and tarsal epithelial damage in patients with VKC (39). Although the Bonini scale is in common use across Asia, many ophthalmologists simply use personal clinical notetaking to assess the progression of the condition and treatment effects.

The severity of VKC is often used as an indicator for treatment escalation, where no improvement in symptoms or signs within 2–4 weeks results in a step up in the management approach.

Coming to Consensus for the Management of VKC

Non-pharmacological Management

Where possible, first-line management of VKC should involve the identification of relevant allergens and avoidance of non-specific

environmental factors that aggravate the disease (1), particularly during periods of exacerbation, such as sunlight, wind, and salty water. Frequent hand, face, and eye washing, alongside lid hygiene, is also strongly recommended (28). Furthermore, artificial tears (ocular lubricants) can aid in stabilizing the tear film to provide a better mucosal barrier against allergens, acting as an eyewash and diluting the concentration of mediators in the tear film in contact with the ocular surface (28). Products with herbal extracts, such as chamomile-containing eye drops, should be avoided as they may cross-react with allergens (e.g., *Artemisia vulgaris*) (28). Cold compresses are also recommended for use as a decongestant (1, 28).

Patients and caregivers should be given educational support regarding the anticipated duration and prognosis of the disease (see **Table 3**), and the possible complications from suboptimal control. In addition, it must be made clear that unsupervised or overuse (self-medication) of certain treatments for VKC, such as corticosteroids, must be avoided as this can lead to impaired vision or blindness (25, 26). Psychological support may be necessary for patients with severe VKC.

Where possible, a collaborative approach between the family doctor and medical specialists should be considered (1). VKC often requires a multidisciplinary approach—immunologists, pediatricians, and allergists should all be consulted as and when appropriate (1). Despite varying considerably between and within Asian countries, access to care remains important for patients with allergies to receive an assessment promptly to manage any seasonal flares, rather than refer to self-medication.

Pharmacological Management

Controlling the signs and symptoms of VKC can be a challenge for even experienced ophthalmologists. Given the chronicity and severity of the disease, non-pharmacological treatment options, such as avoiding specific and non-specific triggers and lifestyle planning, should be accompanied by pharmacological treatments (1).

This article includes a comprehensive overview of the currently approved treatments for VKC; however, it may not include all therapies that are currently available in Asia, under evaluation, or in the early stages of research. Available topical drugs include antihistamines, mast cell stabilizers, dual-acting agents (combination of antihistamines and mast cell stabilizers), alpha-adrenergic agonists (vasoconstrictors), non-steroidal anti-inflammatory drugs (NSAIDs; prostaglandin inhibitors), immunomodulators [e.g., cyclosporine A (CsA)], and corticosteroids. **Table 4** summarizes some of the available and commonly used treatments (28). Additional information on available treatments and dosing by region are provided in **Supplementary Tables 1–6**.

In patients with a history of VKC, pharmacological treatment should be planned early and started at the beginning of spring or continued all year, depending on allergen exposure and duration of symptoms (1). While treatment approaches may differ in regions or countries in Asia with seasonal variation, specific treatment recommendations should depend on the disease severity and cause. The sequence and combination of therapies should be determined on the patient's needs and preferences, and the treating ophthalmologist's medical judgment. Any treatment decisions should be made on an individual patient basis after evaluating the benefits and risks of available therapies.

Figure 1 summarizes the MOVIA Expert Working Group's recommended stepwise management approach according to disease severity. For the use of any eye drops on the ocular surface, it is recommended to use preservative-free compounds, where possible, to minimize ocular surface toxicity. The pharmacological strategies presented here align with that presented in the recent Japanese guidelines for allergic conjunctival diseases (32).

Conventional Topical Treatments

a. Antihistamines

Antihistamines act *via* histamine receptor antagonism to block the inflammatory effects of endogenous histamine and relieve any associated signs and symptoms. Most antihistamines used in the treatment of ocular allergy are H1 receptor antagonists, although some agents have affinity for other subtypes. H2 antagonists have been shown to modulate both cell growth and migration. Animal model studies have shown that antihistamines may even reduce infiltration of eosinophils and thus reduce the clinical aspects of the late-phase reaction (1).

Overall, topical antihistamines (instilled four times daily) appear to be safe and well tolerated in patients with VKC. Alongside mast cell stabilizers and dual-acting agents, they are often the first-choice treatment and are effective in reducing the signs and symptoms of VKC (28). Antihistamine drugs with ocular activity are a good therapeutic option for patients with allergic conjunctivitis, including VKC, since they can inhibit pro-inflammatory cytokine secretion from conjunctival epithelial cells (40).

First-generation antihistamines are well tolerated and associated with a favorable long-term safety record, but are associated with instillation pain, short duration of action, and limited potency (41). They remain available in over-the-counter products, particularly in combination with vasoconstrictors. While newer antihistamines are also H1 antagonists, they have a longer duration of action (4–6 hours) and are better tolerated than their predecessors (1).

b. Mast cell stabilizers

Alongside antihistamines and dual-acting agents, mast cell stabilizers (instilled two to four times daily) form the first line of treatment and are effective in reducing the signs and symptoms of disease. Mast cell stabilizers have been shown to act on multiple cells involved in allergic inflammation, including eosinophils, neutrophils, macrophages, mast cells, and monocytes. For example, lodoxamide is known to have an effect on eosinophil activation (shown in studies by measuring tear eosinophil cationic protein before and after therapy), while N-acetyl-aspartyl glutamic acid (NAAGA) is known to inhibit leukotriene synthesis and release of histamine by mast cells (1).

Overall, they are generally well tolerated (especially preservative-free options); however, there are tolerability

TABLE 3 | Summary of patient education and preventive measures in the management of VKC.

Patients/caregivers should be advised that:
• VKC is a chronic, recurrent condition that usually improves with age.
• Rubbing itchy eyes can make the condition worse.
• Sunlight, wind, salty water, dust, and heat can exacerbate VKC, so the use of sunglasses, hats, visors, and swimming goggles should be considered.
• Common allergens can exacerbate VKC. Frequently washing hands, face, and hair can reduce exposure to these allergens.
• Cold compresses and preservative-free artificial tears can provide symptomatic relief.
• Vacations in locations with unsuitable climates should be avoided.
• An air-filtration system in the home may provide relief.

TABLE 4 | Overview of pharmacological options currently available across Asia for the management of VKC (28)*.

Class	Drug	Standard dosing	Indication	Considerations
Topical antihistamines (second generation)	Antazoline Emedastine Levocabastine	QID	Relief of itching Relief of signs and symptoms	• Short duration of action • Frequently not enough alone to treat the entire disease
Mast cell stabilizers	DSCG Lodoxamide NAAGA Pemirolast potassium	BID to QID	Relief of signs and symptoms	• Long-term use • Slow onset of action • Prophylactic dosing • Frequently not enough alone to treat the entire disease
Dual-acting agents (antihistamine + mast cell stabilizers)	Alcaftadine Azelastine Bepotastine Epinastine Ketotifen Olopatadine	QD QD to BID BID BID BID to QID BID	Relief of itching Relief of signs and symptoms	• Side effects • Bitter taste (azelastine) • Frequently not enough alone to treat the entire disease
Immunomodulators (calcineurin inhibitors)	Cyclosporine A Tacrolimus	QD to QID QD	Treatment of severe VKC and AKC not responding to anti-allergic drugs	• Pharmacy-compounded preparations vary from center to center • Quality control and availability of pharmacy-compounded preparations are poor • Tacrolimus is largely used off-label in ocular allergy (tacrolimus is approved for VKC only in Japan)
Corticosteroids	Betamethasone Desonide Dexamethasone Fluorometholone Hydrocortisone Loteprednol Prednisolone Rimexolone	As required (up to 7 days)	Treatment of allergic inflammation Use in moderate-to-severe forms	• Risk for long-term adverse events • No mast cell stabilization • Potential for inappropriate patient use • Requires close monitoring
Vasoconstrictors (vasoconstrictor–antihistamine combinations)	Naphazoline/pheniramine	BID to QID	Episodic itching and redness	• Rapid onset but short duration of action • Only addresses hyperemia • Associated with a range of side effects • Potential for inappropriate patient use

The table was correct as of January 2021.
**Availability and access to treatments may vary across clinics, hospitals, regions, and countries. Each treatment option should be considered in accordance with the level of evidence available at the time.*
AKC, atopic keratoconjunctivitis; BID, twice daily; DSCG, disodium cromoglycate; NAAGA, N-acetyl-aspartyl glutamic acid; QD, once daily; QID, four times daily; VKC, vernal keratoconjunctivitis.

concerns with some agents, including burning and stinging sensations upon instillation, blurred vision, and an undesirable aftertaste. Data on long-term efficacy and safety are lacking (28).

c. Dual-acting agents

The combination of mast cell stabilizing properties and histamine receptor antagonism (instilled twice daily) has shown clear benefits in treating forms of ocular allergy. A key benefit of these agents is the provision of rapid symptomatic relief by alleviating itching and redness (1). Olopatadine and ketotifen, for example, have shown to be effective in relieving itching, tearing, conjunctival hyperemia, mucus discharge, and photophobia (42).

Dual-acting agents are well tolerated and are not associated with significant ocular drying effects (1), and should be preferred over monotherapy with antihistamines or mast cell stabilizers alone.

Recommendations

- All of the topical anti-allergic drugs mentioned here are effective for reducing signs and symptoms of mild or moderate VKC [++].
- Dual-acting agents should be considered ahead of monotherapy with antihistamines or mast cell stabilizers [+++].

Topical Immunomodulators

Topical calcineurin inhibitors are frequently prescribed for patients with VKC (28). They are recommended in patients with

acute-phase or persistent, moderate or severe VKC that is not responding to anti-allergic drugs (28).

a. Cyclosporine A

Topical CsA is effective in controlling ocular surface inflammation in VKC and is thought to work by inhibiting Th2 proliferation and IL-2 production, and by reducing levels of immune cells and mediators acting on the ocular surface and conjunctiva (25).

Different concentrations of CsA, ranging from 0.05 to 2.0%, are currently available in different countries with different clinical indications (43, 44). The 0.1% cationic emulsion (CE) formulation increases the bioavailability of CsA in the tear film compared with available oil-based (often used when CsA is pharmacy-compounded) or anionic emulsion CsA formulations (45). Clinical studies on the efficacy of topical CsA 0.1% CE for treating VKC have consistently shown a beneficial effect of the drug, with safety and efficacy demonstrated for up to 7 years and comparable with those seen in patients with dry eye disease (25, 46–48).

There is no consensus on the minimum effective concentration of CsA to treat VKC (1), as this can depend on the emulsion vehicle. Currently, CsA 0.1% CE is approved based on significant improvements in signs, symptoms, and quality of life in patients with severe VKC, and is commercially available across Asia. It is recommended that CsA 0.1% CE should be initiated twice daily for patients with mild-to-moderate disease and four times daily for those with moderate-to-severe disease for up to 6 months. Other commercially available CsA formulations exist but are not approved for use in VKC (as of December 2020). In addition, CsA may be compounded in hospital-based pharmacies to provide variable concentrations and formulations; however, its quality may be compromised, and availability is limited to specialist centers.

The most commonly associated adverse event with CsA is a stinging or burning sensation on instillation, and no new safety issues were identified in long-term follow-ups (25, 46–48). Instillation pain can be minimized by following a standard technique for ophthalmic drop instillation, which includes using artificial tears prior to instillation (avoiding any potential washout effect of the subsequently administered CsA, by waiting at least 10 minutes between administrations), followed by one drop into the lower conjunctival sac of each eye in the morning, at noon, in the afternoon, and in the evening, approximately 4 hours apart (48). Patients should also be counseled to expect stinging and burning when the drops are applied, but that the sensation should taper off with regular use as prescribed.

After long cycles of treatment, CsA can allow control of symptoms without corticosteroids. There is a trend in the Asia-Pacific region, as shown by these expert-led recommendations, in using CsA as a first-line treatment for patients who present with moderate-to-severe or persistent VKC. In patients presenting with conjunctival involvement only, CsA alone is recommended for treatment, while corticosteroids should only be prescribed (as short pulses) if there is an inadequate response to CsA. Otherwise, CsA can be used in combination with corticosteroids in patients with corneal complications (or limbitis) or acute exacerbations, in the understanding that CsA may take over a week to act due to its immunosuppressive mechanism of action.

b. Tacrolimus

Tacrolimus is a strong, non-steroidal immunosuppressant that binds to FK506-binding proteins in T lymphocytes and inhibits calcineurin activity (49). Tacrolimus has been investigated in a small randomized controlled trial in VKC, where it demonstrated improvements in symptoms of itching, foreign-body sensation, and photophobia, as well as in signs of limbal inflammatory activity and keratitis, with maintenance of disease control (50, 51). Tacrolimus may be administered as eye drops or an ointment; however, the eye drop formulation is not approved for use in many countries in Asia. The use of tacrolimus (0.03%) ointment in ophthalmic and dermatologic form is currently off-label in Asia for patients with VKC. However, there are findings in published studies of small population sizes demonstrating effectiveness and tolerability (50–55).

Similar to CsA, tacrolimus may be associated with instillation pain (49). As a strong immunosuppressant, topical tacrolimus may be associated with an increased risk for corneal infections with prolonged use, and close monitoring of patients on long-term therapy is necessary (55). Topical tacrolimus (0.02–0.1%) should be reserved for patients with severe VKC involving allergy of the eyelid (in countries where it is currently available) or whose disease is refractory to CsA (28).

Recommendations

- Topical CsA 0.1% CE should be considered for patients with moderate-to-severe or persistent VKC [+++].
- Patients should be instructed on how to apply CsA eye drops to minimize stinging or burning on instillation, such as using artificial tears prior to instillation [+++].
- In regions where available, tacrolimus should be reserved for patients with severe VKC that is refractory to CsA. It can be considered as a treatment for moderate-to-severe VKC in patients with allergy of the eyelid, but please note this may be off-label [++].

Corticosteroids

Topical corticosteroid eye drops should be used as short, pulsed therapy to provide symptomatic relief in patients with more persistent VKC or acute exacerbations, or when the cornea is involved (e.g., patients with shield ulcers or hyperplasia in limbal VKC), and under an ophthalmologist's monitoring (28). Topical corticosteroids can be administered at a low or high dose, depending on the severity of VKC, and can be given up to four times daily with or without CsA. Corticosteroids act by suppressing the late-phase reaction in both experimental and clinical settings. They, in part, limit the inflammatory cascade by inhibiting phospholipase A2, and consequently act to prevent migration of leukocytes, release of hydrolytic enzymes, growth of fibroblasts, and lead to changes in vascular permeability (56).

Moderate-to-severe VKC may require repeated topical corticosteroid treatment to downregulate conjunctival inflammation (1). Persistent and severe symptoms, thick mucus discharge with moderate-to-severe corneal involvement,

numerous and inflamed limbal infiltrates, and/or giant papillae may indicate a need for corticosteroids in addition to CsA use (1). However, use of corticosteroids as first-line therapy is not recommended in those with only conjunctival involvement (1).

Corticosteroids with low intraocular absorption ("soft steroids"), such as hydrocortisone, fluorometholone and loteprednol, may be preferred (1). Dosages are chosen based on the inflammatory state of the eye, with therapy prescribed in pulses of 3–5 days (1). Loteprednol is usually indicated for 7–8 days in the treatment of the acute phase (1). Prednisolone, dexamethasone, and betamethasone are sometimes considered only as second-line options, or as first-line treatment in more severe cases, due to their potential effect on intraocular pressure (1). Steroid–antibiotic combination eye drops are not recommended, since VKC is an allergic inflammation and not an infection (1).

Corticosteroids are not recommended for long-term use because of the increased risk for ocular adverse events, including increased IOP, glaucoma, cataracts, and susceptibility to infection (1). These adverse events depend, in part, on the structure of the steroid, the dose, and duration of treatment (57). Treatment with corticosteroids requires careful monitoring for the development of IOP, which should be promptly brought under control to prevent deterioration or loss of vision (58).

Supratarsal corticosteroid injections have demonstrated some value in treating adults with VKC but may not be an appropriate approach for children or for application by general ophthalmologists (58, 59). For more specialist ophthalmologists, this may be an option in children with refractory, severe, or challenging VKC.

Recommendations

- In patients with only conjunctival involvement, topical corticosteroids should be reserved for use after loss of control or persistence of symptoms with immunomodulators (such as CsA) [++].
- Topical corticosteroids are effective for the management of acute exacerbations, or when the cornea is involved, and preferably only introduced in patients with more severe disease. In these individuals, corticosteroids should be used in combination with CsA to account for the fact that CsA may require ≥1 week to act [+++].
- Because of an increased risk for adverse events and/or vision loss with chronic use, topical corticosteroid eye drops should be used in short pulses (alone or in combination with CsA) under the supervision of an ophthalmologist and tapered rapidly [+++].

Vasoconstrictors

Topical vasoconstrictors can be effective at alleviating hyperemia but offer little to no relief from itchiness and have a short duration of action. Vasoconstrictors may cause several side effects including rebound redness, chronic follicular conjunctivitis, and tachyphylaxis. Vasoconstrictors are rarely used in the pediatric population. It is recommended that these agents should be avoided. If used, they should be used with caution and only for a short period (no longer than 5–7 days) because of adverse events and tachyphylaxis (28).

Topical decongestants do not reduce the allergic response because they do not antagonize any of the mediators of allergic inflammation. Burning or stinging on instillation is a common adverse event, and prolonged use and/or discontinuation following longer-term use can lead to rebound hyperemia and conjunctivitis medicamentosa (60). These events are usually associated with topical combinations of vasoconstrictors and first-generation antihistamines, such as pheniramine and antazoline, which are available as over-the-counter products.

Recommendations

- Vasoconstrictors are not recommended for the treatment of VKC [++].
- If used to address hyperemia, vasoconstrictors should be used with caution and only for a short period due to adverse events [+++].

Topical Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of ocular allergy typically inhibit cyclooxygenase (COX)-1 and COX-2 enzymes (1). Some have demonstrated a slight effect in the treatment of ocular allergy, by targeting itching, intercellular adhesion molecule-1 expression, and tear tryptase levels (1, 28). However, use of NSAIDs is not encouraged in VKC because of their local side effects, such as burning or stinging after application, increased risk of inducing keratitis on the ocular surface, and because they do not target the specific inflammatory mechanism associated with VKC.

Recommendations

- NSAIDs are not recommended as they do not target the specific inflammatory mechanisms associated with VKC [++].

Systemic Pharmacological Treatment

Systemic treatment with oral antihistamines or antileukotrienes can reduce the severity of flare-ups and generalized hyperreactivity (1). Newer second-generation antihistamines are preferred over older first-generation antihistamines, in order to avoid the sedative and anticholinergic effects that are associated with first-generation agents (61).

Recommendations

- Second-generation systemic antihistamines are preferred over older first-generation antihistamines [++].

Allergen-Specific Immunotherapy

Allergen-specific immunotherapy is indicated only when a clearly defined systemic hypersensitivity to an identified allergen exists (28), and should be managed by an allergist or specialist ophthalmologist. The combination of clinical history with the results of a skin-prick test and specific serum IgE should be taken into consideration when the choice of immunotherapy is made (28). There are currently no robust studies of allergen-specific immunotherapy in VKC (28). A meta-analysis of several double-blind, randomized, placebo-controlled trials investigating sublingual immunotherapy for allergic conjunctivitis, reported a significant reduction in total ocular symptom scores and ocular

signs (redness, itchiness, and tearing) vs. placebo in pollen-induced allergic conjunctivitis, but not in allergic conjunctivitis associated with house dust mites, in the pediatric population (62).

Recommendations

- Allergen-specific immunotherapy is only recommended when clearly defined systemic hypersensitivity to an identified allergen exists [++].
- Patients requiring allergen-specific immunotherapy should be referred to an allergist or specialist ophthalmologist [+++].

Surgery

Case reports and ongoing clinical practice have indicated that, in rare instances, specialist surgical management may be beneficial in patients with VKC. Surgical approaches that focus on conjunctival cobblestone papillae, shield ulcers, corneal plaques, limbal insufficiency, and other ocular surface presentations that do not respond to medical treatment can be beneficial (63–65).

Surgical approaches can include excision of giant papillae, debridement of the corneal plaque to remove cytotoxic cells, and amniotic membrane transplantation (66). Surgical treatment, especially corneal plaque removal, may be appropriate for patients with ulcers of moderate-to-severe severity, because short-term re-epithelialization rates are higher and the number of complications is lower than that associated with medical therapy (66). Other reports suggest surgical treatment, such as giant papillae excision, may be appropriate in cases of corneal involvement and in the presence of coarse giant tarsal papillae resulting in ptosis (or mechanical pseudoptosis) (1, 67). Amniotic membrane transplantation following keratectomy has been described as a successful treatment for deep ulcers, in severe allergic patients with slight stromal thinning (68).

Patients with VKC who may benefit from surgical intervention should be referred to a corneal specialist first. Leonardi et al. have suggested that cryotherapy and/or giant papillae excision papillae should otherwise be avoided because they only treat the complications of VKC and not the underlying disease, and may induce unnecessary scarring (1).

CONCLUSION

VKC is an underdiagnosed and underrecognized chronic form of ocular allergy that is an important public health problem in Asia, imposing a substantial burden on both patients and healthcare professionals managing their care. Chronic disease management remains a clinical unmet need; if inadequately treated, VKC can result in significant damage to the cornea and conjunctiva, with the potential for vision impairment. Adequate and continuous treatment through good patient education and regular, long-term follow-up are essential.

Treating VKC should entail a stepwise approach, identifying triggers, educating patients/caregivers on good ocular health, and addressing symptoms. In a new paradigm of management, the use of immunomodulators (e.g., topical CsA) should be considered early to tackle the inflammatory and chronic nature of VKC, with topical corticosteroids reserved as an add-on, short-pulse therapy for persistent disease, during acute exacerbations, or in patients with corneal involvement. Any use of corticosteroids requires tapering once symptoms have been controlled to avoid adverse events. For patients with an identified allergy, referral to an allergist is recommended for additional systemic treatment. In the rare patients who do not respond to medical treatment, surgery may be required.

DISCLOSURES

This article includes a comprehensive overview of the currently approved treatments for VKC; however, it may not be inclusive of all therapies for VKC that are currently available in Asia, under evaluation, or in the early stages of research. Availability of assessment tools, diagnostics, and treatments may differ between countries across Asia, as well as within regions and clinics. References to specific drugs, instruments, and other products are made for illustrative scientific purposes only and are not intended to constitute an endorsement of such. The expert-led recommendations are intended to generally meet the needs of most ophthalmologists and patients; they cannot possibly meet the needs of all. Any treatment decisions should be made on an individual patient basis after evaluating the benefits and risks of available therapies.

ETHICS STATEMENT

All authors who have provided images for use in this article have obtained appropriate declarations of informed consent from the patient or legal guardian.

AUTHOR CONTRIBUTIONS

All authors were involved with the conceptualization, investigation, resources, validation, and writing (both original and draft presentation, review, and editing), and read and approved the submitted version of the manuscript. JSM and DBG provided supervision.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.882240/full#supplementary-material

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Clinical application of the CO_2 laser in Ab externo Schlemm's canal surgery

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Purpose: This study aimed to investigate the clinical application of laser as a knife in Ab externo Schlemm's canal (SC) surgery and compare the efficacy and safety of the CO_2 laser with the conventional procedure using a surgical knife.

Methods: Patients who underwent either canaloplasty or trabeculotomy with CO_2 laser system which was used to locate and ablate the outer wall of SC at the time interval between May 2020 and May 2021 were identified, their medical files were reviewed, and their results were compared with conventional surgery group who underwent canaloplasty or trabeculotomy with conventional surgical knife at the same time period. The following datas were conducted and compared: age, sex, intraocular pressure (IOP), number of drugs, best-corrected visual acuity (BCVA), mean deviation and pattern standard deviation of visual field examination, SC opening related complications.

Results: A total of 49 patients (49 eyes) were included in this study, including 23 in the Laser surgery group and 26 in the conventional surgery group. Time for SC opening was 49.33 ± 25.23 s and 116.50 ± 31.79 s for laser surgery group and conventional surgery group, respectively. This difference between the two groups was statistically significant ($P < 0.01$). Hemorrhage occurred in five eyes during ablation for the laser surgery group and in 24 eyes for the conventional surgery group. In addition, anterior chamber penetration occurred in two cases for the laser surgery group and in six cases for the conventional surgery group. The success rate of identifying and opening outer wall of SC was 91.30% (21 eyes) for the laser surgery group and 76.92% (20 eyes) for the conventional surgery group. The difference between preoperative and postoperative intraocular pressure for each group was statistically significant ($P < 0.01$), and there were no statistically significant differences across the two groups in terms of postoperative IOP ($P = 0.238$) and BCVA ($P = 0.389$).

Conclusion: Compared with the conventional procedure using a surgical knife, CO_2 laser-assisted ablation of the outer wall of SC was less time-consuming and less technically challenging. CO_2 laser-assisted ablation also resulted in fewer complications. Furthermore, it had a shorter learning curve and a higher success rate of identifying and opening SC.

KEYWORDS

primary open-angle glaucoma, CO_2 laser, complications, Schlemm's canal, success rate

Introduction

As a critical link in the outflow pathway, normal Schlemm's canal (SC) is indispensable for maintaining normal intraocular pressure (IOP) (1). SC surgery primarily reduces intraocular pressure by increasing internal drainage. Compared with traditional anti-glaucoma surgery, it does not rely on filtering blebs to reduce IOP, with high patient comfort and easy postoperative management. SC surgery includes external and internal SC surgery. Ab externo SC surgery, including viscocanalostomy or canaloplasty, has been highlighted (2). As a bleb-independent surgical approach, it has shown good results in IOP reduction (3, 4). Precise location and correct dissection (SC outer wall) are important to achieve successful SC surgery, which requires a long learning curve, and such processes are technically challenging in conventional SC surgery using a surgical knife. The CO_2 laser has been applied in glaucoma surgery and shown excellent efficacy and safety, for example, CO_2 laser-assisted sclerectomy surgery (CLASS) (5). The CO_2 laser is suitable for use in non-penetrating surgery because of its certain inherent characteristics: The laser effectively ablates the dry scleral tissue and is absorbed in water or aqueous solution within a short penetration depth (5). In this study, the CO_2 laser-assisted system was used in ab externo SC surgery, and it achieved successful ablation of the SC outer wall, leading to satisfactory surgical results. Moreover, the clinical practice was summarized and reported.

Methods

Baseline information

In this retrospective study, 49 patients (49 eyes) with primary open-angle glaucoma hospitalized in Fuzhou Eye Hospital from May 2020 to May 2021 were enrolled. They were divided into laser surgery group (23 cases, 23 eyes) and conventional surgery group (26 cases, 26 eyes). In accordance with the tenets of the Declaration of Helsinki, all patients were informed of the operative procedures and related issues, and signed informed consent was obtained from the patients. This study received approval from the Institutional Review Board of the Fuzhou Eye Hospital in Fuzhou, China.

Perioperative management

IOP was decreased pre-operatively as close to 21 mmHg as possible to mitigate the effect of high preoperative IOP on the collapse of the inner wall. IOP reduction was achieved by administering hypotensive eye drops or conducting anterior chamber paracentesis. Preoperative routine examinations were conducted, including best corrected visual acuity (BCVA), gonioscopy, ultrasound biomicroscopy (UBM), retinal nerve fibre layer (RNFL), mean deviation (MD) and pattern standard deviation (PSD) for the visual field examination. The examination results confirmed open-angle glaucoma. The surgeries were performed by a single experienced surgeon. Data were recorded, including the time needed to open the outer wall of the canal and the complications (such as hemorrhage and penetration) during the opening of the canal.

Surgical approach

All surgeries were performed by a single experienced surgeon. Canaloplasty was applied in all surgeries firstly and then trabeculotomy was introduced as the alternative approach when the suture could not advance for 360 degrees. The CO_2 laser-assisted system contained a beam micromanipulation system (OT-135P2, IOPtima Ltd., Israel) and a CO_2 laser (SmartXide, DEKA, Italy). In the case of penetration, compound trabeculectomy was performed as an alternative. Success in identifying and opening the canal was indicated by the advancement of the blue prolene suture within SC using a gonioscope (regardless of the results of 360 degrees advancement). Details of the surgery are as follows.

Laser surgery group

The patient lay in a supine position. The procedure was routinely sterilized, and a sterile surgical towel was laid out. After local anesthesia, the eyelid was opened. A limbal traction suture was placed to fixate the eyeball. A fornix-based conjunctival flap was created along the cornea limbus. Then a limbal-based flap measuring 4 × 4 mm with one-half scleral thickness was created, extended by 1-1.5mm into the clear cornea. A side cut was made at 10 o 'clock position with a side cutter to drain a small amount of aqueous humor. The CO_2 laser system was employed. The laser beam, measuring 1 × 2 mm (length × width), conducted perpendicular ablation in the middle of corneoscleral junction until a channel structure and continuous aqueous humor percolation were observed, which marked the successful opening of the canal's outer wall and suggested that the ablation should be halted (Figure 1). A 6-0 prolene suture with a previously processed tip was inserted into SC from the surgical opening in a clockwise/counterclockwise fashion. An advancing blue prolene suture detected using gonioscope suggested the success of both identifying and opening the canal's outer wall (Figure 2). After the 360-degree journey in the canal was accomplished, the prolene suture came out from the other end of the canal. Next, a 10-0 polypropylene suture was tied to the tip of the 6-0 prolene suture, which would be withdrawn, pulling the 10-0 polypropylene suture into the

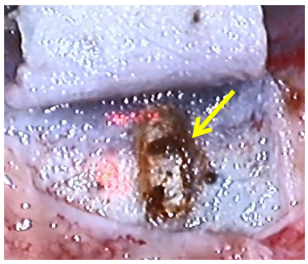

FIGURE 1
Laser-ablated outer wall of SC.

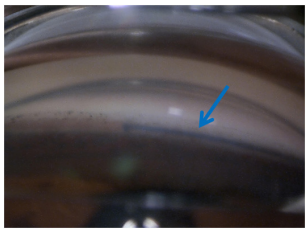

FIGURE 2
An advancing blue prolene suture was observed using gonioscope.

canal. After the 6-0 prolene was completely retracted, the 10-0 polypropylene, which was kept within SC, was then tied to itself. The scleral flap was closed tight with 10-0 nylon sutures, and the conjunctival flap was closed with interrupted 10-0 nylon sutures.

Conventional surgery group

The patient lay in a supine position. The procedure was routinely sterilized, and a sterile surgical towel was laid out. After local anesthesia, the eyelid was opened. A limbal traction suture was placed to fixate the eyeball. A fornix-based conjunctival flap was created along the cornea limbus. Then a limbal-based flap measuring 4 × 4 mm with one-half scleral thickness was created, and it was extended by 1–1.5mm into the clear cornea. A side cut was made at 10 o 'clock position with a side cutter to drain a small amount of aqueous humor. A deeper scleral flap (1.0 × 2.0 mm) was dissected under the superficial flap. It should be deep enough to enable the sight of the pigment of the choroidal tissue. In the process of extending it forward to the corneoscleral junction, SC was identified and the outer wall was excised (Figure 3). Aqueous percolation could be seen, suggesting that the outer wall of the canal was opened. The deep scleral flap was then excised. A 6-0 prolene suture with a blunted tip was inserted into SC from the surgical opening

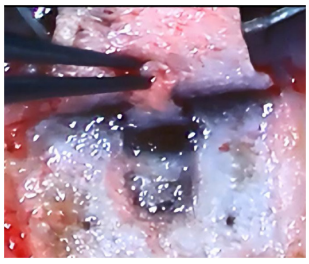

FIGURE 3
Manually dissected outer wall of SC.

in a clockwise/counterclockwise fashion. The rest steps of the surgery were the same with those in the laser surgery group.

Timing method

For the laser surgery group, timing started from the first laser shot by the CO_2 laser-assisted system; for the conventional surgery group, timing started from the first cut when dissecting the deeper scleral flap. The terminal time was marked by a channel structure, and aqueous percolation was observed in the surgical field. Furthermore, timing in the laser surgery and conventional surgery groups was recorded.

Statistical analysis

The cases which penetration occurred and resulted in failed opening of the SC would be excluded from the statistical analysis of the time required to locate and open the outer wall of the SC (hereinafter referred to as canal opening). Cases that will be included in postoperative statistical analysis of BCVA, IOP and anti-glaucoma medications should meet the following criteria: (1) the canal was successfully identified; (2) subsequent steps were successfully performed; (3) the 10-0 polypropylene suture was retained in the canal and tied to itself.

SPSS 25.0 (IBM, IL, USA) was used for statistical analysis. Descriptive results were presented as N (%) for categotical variables or mean (standard deviation) for continuous variables. Normality of the measurement data was evaluated using the Shapiro-wilk test. A paired t test was used to compare preoperative and postoperative values of parameters, for normally distributed differences in both groups, or via the paired Wilcoxon tests, in other cases. Independent samples t test was used for between-group comparisons (for normally distributed differences in both groups) or Wilcoxon Mann-Whitney tests (otherwise). Chi-square test (with Yates' corrected) or Fisher's exact test was used to compare between different percentages. Data were considered statistically significant when $P < 0.05$.

TABLE 1 Preoperative baseline information for both groups.

	Laser surgery group ($N = 23$) N (%)		Conventional surgery group ($N = 26$) N (%)		p^*
Sex					
Male	14 (61%)		15 (58%)		0.821
Female	9 (39%)		11 (42%)		
	Laser surgery group		**Conventional surgery group**		
	Mean (SD)	**Median** (P_{25}, P_{75})	**Mean (SD)**	**Median** (P_{25}, P_{75})	p
		($N = 23$)		($N = 26$)	
Age	60.30 (15.22)	63 (52, 73)	59.23 (13.86)	60 (52.5, 70.3)	0.703†
IOP (mmHg)	19.31 (6. 41)	17.7 (14.4, 25)	22.36 (7.27)	21.7 (15.9, 26.6)	0.128&
Medications	3.00 (0. 74)	3 (2, 4)	3.04 (0.82)	3 (2, 4)	0.856†
		($N = 19$)		($N = 22$)	
MD (dB)	−18.4 (8. 97)	−18.4 (−26.9, −9.8)	−18.2 (9.11)	−19.1 (−26.1, −10.7)	0.935&
PSD (dB)	7.23 (2. 98)	6.8 (5.2, 9.5)	8.56 (3.61)	9.1 (5.5, 11.8)	0.212&

*Chi-squared test; &Independent samples t test [intraocular pressure (IOP) normally distributed in both groups].
†Wilcoxon Mann-Whitney tests (age and drugs non-normally distributed in any group).
SD, standard deviation; IOP, intraocular pressure. MD, mean deviation for the visual field examination; PSD, pattern standard deviation for the visual field examination.

Results

Baseline information

The current study enrolled 49 patients (49 eyes), including 29 males (29 eyes) and 20 females (20 eyes). All 49 patients were corrected the information of the age, sex, preoperative IOP, and medications. However, only 41 patients were corrected the information of MD and PSD for the other eight patients can't finished the visual field examination due to the poor visual acuity. Results showed that the two groups had no statistically significant differences with regard to sex (Chi-squared test: $P > 0.05$), mean age (Wilcoxon Mann-Whitney tests: $P > 0.05$), preoperative IOP (Independent samples t-test: $P > 0.05$), medications (Wilcoxon Mann-Whitney tests: $P > 0.05$), MD (Independent samples t-test: $P > 0.05$) and PSD (Independent samples t-test: $P > 0.05$) (Table 1).

Complications in opening SC

Based on our definition of success in identifying and opening the canal, the outer walls of the SC from 21 eyes in laser surgery group were all successfully opened. Of the 21 eyes, two encountered suture blockage, and trabeculotomy was introduced as an alternative approach. For the conventional surgery group, the outer walls of the SC from 20 eyes were successfully opened. Of the 20 eyes, three encountered suture blockage; thus, trabeculotomy was introduced as the alternative approach. The penetration rate in the laser group was lower than that in the manual group, but the Chi-square test with Yates' corrected showed that the difference was not statistically significant ($P > 0.05$, Table 2). Chi-square test (c) showed that statistically significant differences in intraoperative bleeding between the two groups ($P < 0.01$, Table 2). Severe complications, such as shallow anterior chamber, vitreous incarceration, explosive suprachoroidal hemorrhage and massive intraocular hemorrhage, did not occur during the surgery.

TABLE 2 Complications in identifying and opening SC for both groups.

	Laser surgery group ($N = 23$) N (%)	Conventional surgery group ($N = 26$) N (%)	p
Hemorrhage (eyes)	5 (22%)	24 (92%)	< 0.001*
Penetration (eyes)	2 (9%)	6 (23%)	0.331‡

*Chi-squared test; ‡Chi-square test with Yates'corrected.

Time needed to open the outer wall of SC

Twenty-one cases (21 eyes) and 20 cases (20 eyes) were included for statistical analysis of the laser surgery and

TABLE 3 Time needed to open SC for both groups. Excluding the cases wherein penetration occurred and resulted in failed identification of the canal.

	Laser surgery group ($N = 21$)		Conventional surgery group ($N = 20$)		$p^{\dagger}$
	Mean (SD)	Median (P_{25}, P_{75})	Mean (SD)	Median (P_{25}, P_{75})	
Time needed to open the canal (second)	49.33 (25.23)	40.0 (30.0, 65.0)	116.50 (31.79)	111.5 (93.3, 139.8)	<0.001

†Wilcoxon Mann-Whitney tests (Time needed to open the canal non-normally distributed in any group).

TABLE 4 Pre-operative BCVA and BCVA at post-operative 1 week for both groups. Excluding the cases wherein compound trabeculectomy or trabeculotomy was performed as the alternative approach.

BCVA	Laser surgery group ($N = 19$) N (%)	Conventional surgery group ($N = 17$) N (%)	$p^{\uparrow}$
Stabilised or slightly improved	12 (63.16%)	9 (52.94%)	0.389
At least one line lost	7 (36.84%)	8 (47.06%)	

$^{\uparrow}$Fisher's exact test.

conventional surgery groups, respectively. Time to open the outer wall of SC for the laser surgery and conventional surgery groups was 49.33 ± 25.23 s and 116.50 ± 31.79 s, respectively. Wilcoxon Mann-Whitney tests showed that the difference in canal opening time between the two groups was statistically significant ($P < 0.01$, Table 3).

The postoperative statistical analysis included 19 cases (19 eyes) for the laser surgery group and 17 cases (17 eyes) for the manual surgery group

BCVA

Table 4 shows information about the BCVA before the operation and at 1 week after the operation. For the laser surgery group, 12 eyes (63.16%) showed stabilized or slightly improved BCVA at postoperative 1 week, whereas, seven eyes (36.84%) showed decreased BCVA. For the conventional surgery group, nine eyes (52.94%) had stabilized or slightly improved BCVA at postoperative 1 week, whereas eight eyes (47.06%) had decreased BCVA. No statistical difference was found between the BCVA prior to the operation and that at postoperative 1 week using Fisher's exact test. ($P = 0.389$).

IOP

As shown in Table 5, the preoperative IOP for the laser surgery group and conventional surgery group was 18.63 ± 6.24 mmHg and 20.81 ± 6.42 mmHg, respectively, whereas the IOP at postoperative 1 week was 13.47 ± 2.83 mmHg and 14.72 ± 3.45 mmHg, respectively. Paired t-test showed that for each group, the difference between preoperative IOP and IOP at postoperative 1 week was statistically significant ($P < 0.01$). However, Independent samples t-test showed that the IOP of the laser surgery group and that of the conventional surgery group was not statistically significant at Preoperative and postoperative 1 week ($P > 0.05$), indicating that laser-assisted surgery had no negative effect on postoperative IOP reduction compared with the conventional procedure.

Anti-glaucoma medications

The number of anti-glaucoma medications before the surgery was 3.00 ± 0.75 (2–4 drugs) and 3.24 ± 0.75 (2–4 drugs) for the laser surgery and conventional surgery groups, respectively. In postoperative 1 week, the number of anti-glaucoma medications was 0.26 ± 0.65 (0–2 drugs) and 0.76 ± 1.15 (0–3 drugs), respectively. Paired Wilcoxon tests showed significant differences between the preoperative number of medications and medications in one post-operative week for both groups ($P < 0.01$). Wilcoxon Mann-Whitney tests results showed no significant differences in the number of administered medications in post-operative 1 week between the two groups ($P = 0.144$, Table 5).

Discussion

As an anti-glaucoma surgery for reconstructing physiological aqueous outflow channel, external SC surgery has fewer complications than classical trabeculectomy because it does not rely on filtering blebs. External SC surgery, such as canaloplasty and trabeculotomy, has been proven to have a good IOP-lowering effect, and it is safe in patients with open-angle glaucoma (6–8). Nevertheless, many doctors are still reluctant to perform this kind of surgery because of its high technical requirements, and this surgery requires surgeons with relevant surgical experience. During surgical operation related to external SC surgery, locating and opening the outer wall of the SC are important. Locating and cutting the outer wall of the SC by manual dissection is the traditional way of

TABLE 5 Pre-operative values and values post-operative 1 week for both groups. Excluding the cases wherein compound trabeculectomy or trabeculotomy was performed as the alternative approach.

	Laser surgery group ($N = 19$)		Conventional surgery group ($N = 17$)		$P^{\downarrow}$
	Mean (SD)	Median (P_{25}, P_{75})	Mean (SD)	Median (P_{25}, P_{75})	
Pre-operative IOP (mmHg)	18.63 (6.24)	17.00 (13.3, 25)	20.81 (6.42)	20.2 (15.4, 24.5)	0.310[&]
Post-operative IOP (mmHg)	13.47 (2.83)	12.6 (11.3, 14.8)	14.72 (3.45)	13.6 (12.1, 18.4)	0.238[&]
$p^{\#}$	0.001[•]		0.003[•]		
Pre-operative Medications	3.00 (0.75)	3.00 (2, 4)	3.24 (0.75)	3.00 (3, 4)	0.340[†]
Post-operative Medications	0.26 (0.65)	0 (0, 0)	0.76 (1.15)	0 (0, 2)	0.144[†]
$p^{\#}$	0.004[▶]		0.001[▶]		

[#]Intragroups analysis: [•]A paired t test (drugs normally distributed in both groups), [▶]Paired Wilcoxon tests (IOP non-normally distributed in any group) .
[↓]Intergroups analysis: [&]Independent samples t-test (drugs normally distributed in both groups), [†]Wilcoxon Mann-Whitney tests (IOP non-normally distributed in any group).

opening the canal. However, mastering this surgical technique requires a long learning curve because of many factors such as the complexity of anatomical factors. In addition, experienced surgeons have high variability in whether they can successfully dissect the SC (3, 9, 10). Therefore, glaucoma doctors must find a tool to replace manual operation, simplify canal opening, improve the safety and effectiveness of SC opening and shorten the learning cycle of surgeons.

In China's medical market, CLASS surgical equipment (CO_2 laser-assisted system), as a mature ophthalmic CO_2 laser equipment, is increasingly developed. It uses a CO_2 laser to ablate dry tissue and coagulate blood vessels, and the energy can be completely absorbed by a small amount of liquid. It repeatedly ablates deep scleral tissue in a controllable and standardized way, which shortens the learning cycle of manual doctors and improves the safety of surgery compared with classic non-penetrating deep sclerectomy (NPDS) (11–14). In recent 10 years, domestic and foreign researchers in CLASS surgery have also confirmed the feasibility of CO_2 laser ablation of the deep sclera and the outer wall of the SC (15–18).

At present, little research is conducted on CO_2 lasers in external SC surgery. We creatively applied the platform to external SC surgery and found that it is convenient to use in identification and opening the outer wall of SC, which can reduce the operation difficulty and shorten the operation time and learning curve of this kind of surgery. On the contrary, CLASS surgery is often parallel to the angle when ablating the outer wall of the SC. The size of the laser (3 × 1 mm) at the scleral margin is used to ensure an effective penetration area of a certain length, but the width of 1 mm has high requirements for positioning, and for some patients whose gray-blue junction is not evident or whose limbal structure is abnormal, the size of the laser may not be able to cover the outer wall of the SC. In the early stage of our research, the size of the laser spot is 3 × 3 mm; thus, the laser irradiation area can cover the SC. The outer wall of the SC can be ablated by careful separation. With rich surgical experience, the size of the laser spot gradually transits to 2 × 2 mm or 1 × 2 mm. We found that the 2 mm diameter is perpendicular to the corneoscleral edge, and the outer wall of the SC can also be dissected smoothly. This change can reduce the shallow scleral flap and show the impact on intraoperative astigmatism. The long-term results need to be followed up.

The canal opening time of the laser surgery group (49.33 ± 25.23 s) is significantly shorter than that of the conventional surgery group (116.50 ± 31.79 s). The main reason for the laser group to have a shorter canal opening time is the application of CO_2 laser-assisted external wall ablation of SC, which does not need to manually dissect the deep scleral flap and locate the external wall of SC as the traditional operation, and the canal like structure after ablation in the laser group is obvious. Once the external wall is successfully ablated, aqueous humor exudation can be seen basically, with less intraoperative bleeding and clearer visual field Clear (see Figure 1 at the yellow arrow). In addition to bleeding disturbing the visual field, in the manual group, it is considered that the outer wall of the SC cannot be exposed due to the uneven depth of manual incision of the deep scleral flap, which cannot accurately reach the reliable depth of the incision. Therefore, the deep scleral flap needs to be dissected repeatedly. At the same time, if the outer wall is not fully opened, the adjacent tissue needs to be carefully removed under the deep scleral flap to be more satisfactory. The outer wall of the SC, and in this case, the removal of adjacent canal tissue, is easy to cause anterior chamber penetration, resulting in difficult subsequent steps. Compared with the laser group, it significantly increases the operation time and intraoperative operation load, and puts forward higher requirements for the operator's operation ability.

Hemorrhage occurred in only five cases (five eyes) for the laser surgery group and in 24 cases (24 eyes) for the conventional surgery group during canal opening time. The reason for the difference may be that the CO_2 laser played a

role in blood coagulation and thus reduced the incidence of hemorrhage (19).

Anterior chamber penetration occurred in two cases (two eyes) for the laser surgery group and in six cases (six eyes) for the conventional surgery group. The penetration rate of the laser group is only 8.7%, which is obviously lower than that of the manual group, but the Chi-square test with Yates' corrected showed that the difference was not statistically significant, which may be due to the small sample size, which needs to be further expanded in the future. This could be accounted for by the following reasons for the difference in the incidence of penetration. For one thing, it may be caused by a disadvantageous operative field as a result of hemorrhage, which resulted in a higher incidence of penetration. For another, after the ablation of the canal's outer wall was completed and the ablation came to a halt, the superfluous CO_2 laser energy could be absorbed by the percolated humor (10). In this case, the internal wall of SC and the trabecular meshwork could be kept intact, reducing the incidence of penetration. However, ablation of the outer wall of the SC with the aid of the CO_2 laser still has the risk of anterior chamber penetration. The reason for anterior chamber penetration in the laser group is analyzed. It may be that the marginal surface of the corneoscleral membrane to be ablated is not completely perpendicular to the laser beam, resulting in a slope like ablation. The ablation depth of tissue in the 1×2 mm area is unbalanced. Therefore, excessive penetration of front-end ablation into the anterior chamber occurs before aqueous humor exudation, so the intraoperative 1×2 mm is adjusted. There is no anterior chamber penetration after the surgical wound is perpendicular to the laser angle. Other researchers suggest that the laser energy can be appropriately reduced when deep ablation is performed near the outer wall of the SC (14); or the SC of some glaucoma patients has been blocked, and there is no liquid flow in the SC. Even if the outer wall of the SC is ablated, there may still be no liquid outflow. At this time, simple SC surgery may not be able to reduce IOP, so trabeculectomy can be considered directly.

There was no significant difference in BCVA, IOP and the number of anti-glaucoma drugs used between the two groups at 1 week after the operation. The average IOP at 1 week after operation in the laser group and the manual group decreased compared with the baseline IOP, and the difference was statistically significant. The range of IOP reduction in the laser group was lower than that in the manual group at 1 week after the operation, but there was no significant difference (27.70% and 29.26%, respectively), it may be related to the lower baseline IOP in the laser group than in the manual group. The mean IOP (14.72 ± 3.45) mmHg in the manual group 1 week after operation is similar to that reported by Ramesh s and Juliane matlach (the latter two are 13.7 ± 6.4 mmHg and 15.0 ± 6.7 mmHg, respectively) (20, 21).

The advantage of this study is to directly compare the application of the CO_2 laser and traditional manual dissection in external SC surgery. To our knowledge, this is the first study to directly compare the effectiveness of the CO_2 laser and manual dissection in locating and opening the outer wall of SC in glaucoma patients. External SC surgery requires high surgical technology and experience. If the surgical experience is insufficient or the technology is poor, and the operation is easy to fail due to the complexity of manual dissection or intraoperative bleeding, which reduces the operator's confidence in the operation and causes some difficulties for the development of this operation. With the assistance of CLASS platform laser, the most critical canal opening step in operation can be simplified, and the operation mode of the CO_2 laser-assisted system is simple and easy to learn, which is beneficial to the doctor's operation experience and operation experience. The technical requirements are relatively lower, which is a good alternative to manual operation.

In conclusion, the application of the CO_2 laser in external SC surgery has advantages over traditional manual sectioning and canal opening, which can improve the safety and effectiveness of such surgery and shorten the learning cycle of operators. Therefore, more ophthalmologists may be willing to choose to try external SC surgery, which will help promote the development of SC related surgery and provide a better basis for the treatment of glaucoma patients and doctors.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

Study concept and design, supervision, and critical revision of the manuscript: JZ, LZ, YY, QL, and YL. Data collection: LZ, QL, and YL. Analysis and interpretation of data, writing the manuscript, statistical expertise, and administrative, technical, or material support: JZ and LZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

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Simple new technique for macular pucker peel without forceps

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Purpose: This study aimed to describe the effectiveness and evaluate the anatomical and functional results of surgery for macular pucker (MP) peel using a 25-gauge pars plana vitrectomy (PPV) cutter without forceps.

Methods: This study assessed a prospective consecutive case series of 14 eyes of 14 patients who underwent 25-gauge PPV for MP. The surgical procedure was performed using the new peeling technique. The edge of the membrane was engaged at the opening of the cutter by gradually increasing the vacuum. The peeling process was finished by holding a stable vacuum or regrasping the membrane in the same manner.

Results: The study included six women and eight men patients with a mean age of 72.3 (range 59–84) years. MP peel was achieved in all cases without the need for microforceps. Patients were followed for at least 6 months. Visual acuity and retinal thickness were obtained 6 months after the surgery. Best corrected visual acuity improved from a mean pre-operative 0.6 on a logMAR scale to post-operative 0.23 ($P < 0.001$). Mean pre-operative Central Retinal Thickness was significantly reduced from 489.7 to 377.6 μm post-operatively ($P < 0.001$). There were no intra- or post-operative complications.

Conclusion: MP peel with a 25-gauge vitrectomy probe could be an alternative simple and safe technique. The technique does not require extra instrumentation. It results in anatomic and functional improvement in all cases.

KEYWORDS

epiretinal membrane, macular pucker peel, pars plana vitrectomy, best corrected visual acuity, central retinal thickness

Introduction

Epiretinal membranes (ERM) are a collection of cells and an extracellular matrix that grow on the inner surface of the retina, mainly localized on the central retina or the macula lutea (1). In the optical coherence tomography (OCT) definition by Hubschman et al., the ERM is considered to be an irregular and hyperreflective layer over the inner limiting membrane (ILM) frequently associated with the presence of hyporeflective spaces between the ERM and the ILM, and with signs of wrinkling of the underlying retina (2).

ERMs may be located peripherally and have little or not any impact on visual function (3). More commonly, they have central foveal or perifoveal localization leading to significant visual impairment and worsening the quality of life (4). The prevalence of ERM increases with age (5). Most often, ERMs occur in individuals older than 50 years, approaching the incidence of 20% of the total population by the age of 70 years (4).

There are different classification schemes of ERMs, but in general, more traction on the fovea causes more disruption to the macular anatomy, more severe visual acuity impairment, and more symptoms like reduced visual acuity, blurred vision, metamorphopsia, loss of stereopsis, and aniseikonia (6).

Gass JDM was the first to propose a clinical classification of ERMs based on the ophthalmoscopic appearance and distortion of the central retina by the membrane (7). Despite modern classifications with various OCT classification schemes, in clinical practice, the most often used is the two-stage classification scheme, which categorizes the ERMs as *cellophane maculopathy* (with an early, translucent form of ERM without distortion of the inner retina) and *macular pucker* (MP; with a late, opaque form of ERM having a distortion of the inner retina) (6, 8–11).

Currently, there are no medical treatment options for MP. The management consists of either observation or surgical intervention. The modern surgical approach for treating MP consists of sutureless transconjunctival three-port (23-, 25-, or 27- gauge) pars plana vitrectomy (PPV) and peeling of the ERM and/or ILM usually performed under a higher magnification lens (6). ERM peeling usually starts with a "pinch and peel" technique by using ILM or any other microforceps. Beside ILM forceps, there are other tools that can be used either to start or to complete the peeling, including micro-vitreoretinal blades, needle picks, diamond-dusted scrapers, and flex loops (12). Since multiple attempts in order to engage and peel the membrane are necessary, iatrogenic damage by the instrumentation may happen. Unintentional and accidental pinches to the nerve fiber layer and contusional retinal pigment epithelial cells lesions as well as multiple focal retinal hemorrhages have also been described (12).

Herein, we report a simple, cost- and time-saving technique for MP peeling without using micro-forceps or any other instrumentation except the simplest standard PPV tools.

Abbreviations: ERM, epiretinal membrane; OCT, optical coherence tomography; MP, macular pucker; ILM, inner limiting membrane; PPV, pars plana vitrectomy; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; CRT, central retinal thickness; MH, macular hole; ELM, external limiting membrane; EZ, ellipsoid zone; RPE, retinal pigment epithelium; SF, subretinal fluid.

Subjects and methods

Fourteen patients having MP who underwent surgery from May 2020 to August 2021 at the Eye Hospital, University Medical Center Ljubljana, Slovenia, were included in the study. The study design was prospective interventional non-comparative case series. Enrolled were only patients with idiopathic MP in which membrane peeling was performed using only a vitreous cutter. Patients with a history of other ocular diseases, macular diseases, retinal dystrophies, previous vitreoretinal surgeries, and myopia of more than 5 diopters were excluded. The indication for surgery in each of the cases was decreased visual acuity and metamorphopsia.

Prior to surgery, all patients underwent a complete ophthalmological examination including Snellen best corrected visual acuity (BCVA), intraocular pressure measurement (IOP), slit lamp anterior segment examination, and dilated funduscopic examination. The Snellen acuity was converted into a logarithm of the minimum angle of resolution (logMAR) equivalent. Optical Coherence Tomography (Swept-source OCT, DRI OCT Triton, Topcon) was performed and used for evaluation of the macular area, MP edges, and morphological structural changes on the retinal layers. The following pre- and post-operative parameters were analyzed on OCT: central retinal thickness (CRT), presence of ERM, presence of macular hole (MH), continuity or discontinuity of external limiting membrane (ELM), ellipsoid zone (EZ), and retinal pigment epithelium (RPE), as well as presence or absence of subretinal fluid (SF). We considered the following primary outcomes: mean change in BCVA in the studied eye between baseline and 6 months after the surgery, change in the mean CRT, and complications related to the surgical technique. Secondary outcomes were the following: recurrence of ERM during the follow-up period, MH occurrence, post-operative ELM, EZ, and RPE continuity, and presence of SF.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before surgery and all of them had a proper follow-up.

Surgical technique

In all cases, the surgical technique involved a 25-gauge three-port PPV. Surgeries were performed with the Constellation platform (Alcon Laboratories, Fort Worth, TX, USA) under sub-tenon's anesthesia. In cases with nuclear sclerosis or significant cataract, phacoemulsification with single piece IOL in-the-bag implantation was carried out together with vitrectomy. In all patients, Brilliant Peel Dual Dye (Fluoron GmbH, Germany) was used for staining the ERM. The proper edge of the ERM was first identified. After completing the vitrectomy, the opening of the

TABLE 1 Characteristics of the studied patients.

Number of patients	Age (years; mean (range))	Gender: female vs. male (ratio)	Pre-op BCVA (logMAR; median (IQR), range)	Post-op BCVA (logMAR; median (IQR), range)	Pre-op CRT (μm; mean ± SD)	Post-op CRT (μm; mean ± SD)
14	72.3 (59–84)	6:8	0.7 (0.4–0.7) 0.3–1.0	0.15 (0.1–0.3) 0.0–1.0	489.71 ± 57.22	377.64 ± 41.05
Number of patients	**Eye (Right/Left) (ratio)**	**IOP Pre-op vs. Post-op (mmHg; mean ± SD)**	**Lens status Phakic/IOL at last follow-up (ratio)**	**Axial length (mm; mean ± SD)**	**Surgical time (min.; mean (range))**	**Previous cataract surgery (N)**
14	8:6	16.1 ± 2.8 vs. 14.3 ± 2.02	3:11	23.32 ± 0.76	19.43 (16.49–26.32)	4

BCVA, best corrected visual acuity; CRT, central retinal thickness; IOP, intraocular pressure; IOL, intraocular lens, IQR, interquartile range, SD, standard deviation.

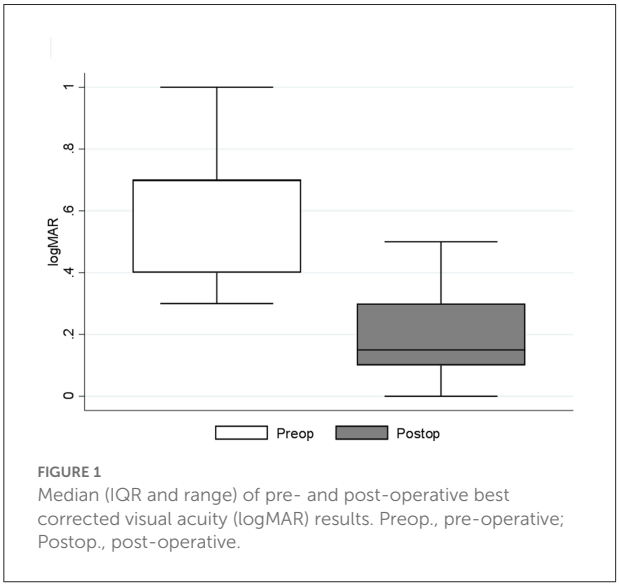

FIGURE 1
Median (IQR and range) of pre- and post-operative best corrected visual acuity (logMAR) results. Preop., pre-operative; Postop., post-operative.

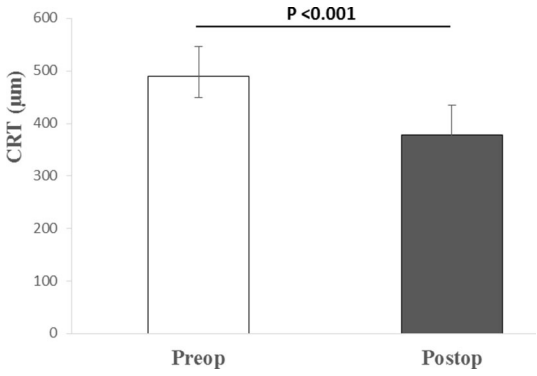

FIGURE 2
Median (IQR and range) of pre- and post-operative central retinal thickness. Preop., pre-operative; Postop., post-operative; CRT, central retinal thickness; μm, micrometers.

25-gauge cutter was oriented toward the edge of the MP. The cutting function was turned off from the foot pedal. By stepping gently on the pedal and increasing gradually the vacuum, it was possible to see the engaged edge of the membrane on the cutter. The proper engagement was achieved at a 300 mmHg vacuum. By holding the stable vacuum, we started to elevate the edge of the membrane. In case the vacuum level was not sufficient to continue peeling, the aspiration was gradually increased up to 500 mmHg. Once the edge was elevated, then stable vacuum was maintained, while the membrane was carefully elevated. During this maneuver, several times it was necessary to release the edge of the membrane by stopping the aspiration on the foot pedal or activating the reflux with the foot pedal, then reengaging the membrane in the next location in order to finish the peeling. After complete removal of the MP, Brilliant Peel Dual Dye was injected again. If there was no ERM seen on the inner surface of the retina, no further manipulation was performed. At the end of the surgery, only BSS was left inside the eye (see video, Supplementary materials 1, 2).

Statistical analysis

The analysis of the data was performed by descriptive statistical analysis; ratio, mean ± standard deviation (SD), median and interquartile range (IQR), and range are presented. Normality of the continuous variables was tested using a histogram and the Shapiro-Wilk test. Paired sample *t*-test was used to compare the means of the two dependent, continuous, numerical variables when the normality assumption was satisfied; otherwise, Wilcoxon Signed Rank Test was used, when the normality assumption was not satisfied. The

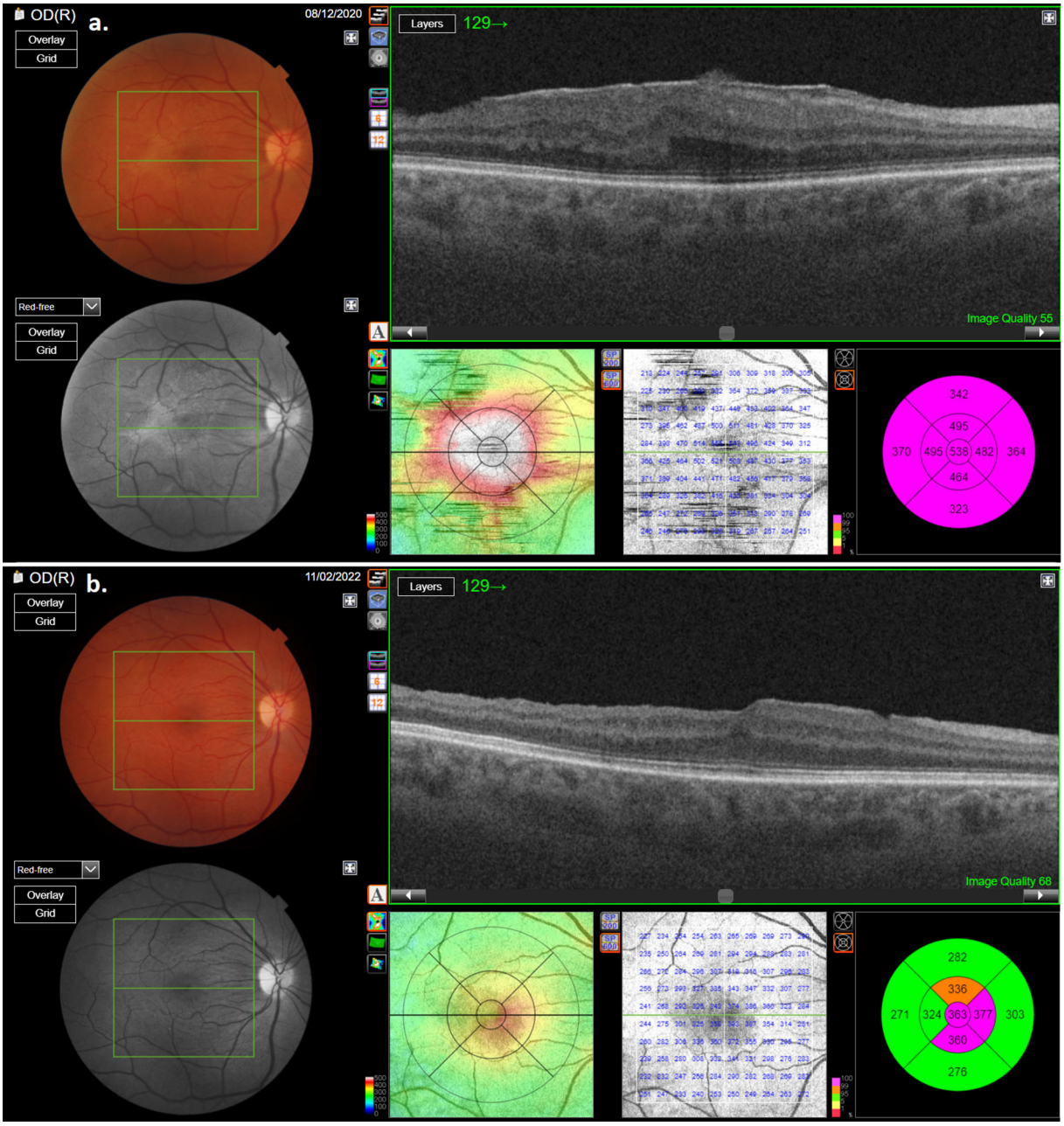

FIGURE 3
OCT scan of one of the patients with macular pucker: **(a)** pre-operative OCT scan showing thick macular pucker; **(b)** OCT scan of the same patient after surgery.

significance limit was set as $P < 0.05$. All statistical analyses were performed using the Statistical Package for STATA (Stata version 14; College Station, TX, USA) was used.

Results

A total of fourteen eyes of fourteen patients were included in the study and further evaluated. There were six women and eight men patients. The mean age of the patients was 72.3 (range 59–84) years (Table 1).

The median pre-operative BCVA was 0.7 (IQR: 0.4–0.7; range 0.3–1) on a logMAR scale. The mean ± SD of the pre-operative CRT was 489.71 ±_57.22 μm. The patients had normal pre- and post-operative intraocular pressure, while the axial length was on average 23.32 ± 0.76 mm (Table 1). In one case the eye was amblyopic, while the systemic disease was present in 11 cases (most commonly arterial hypertension, hyperlipidemia,

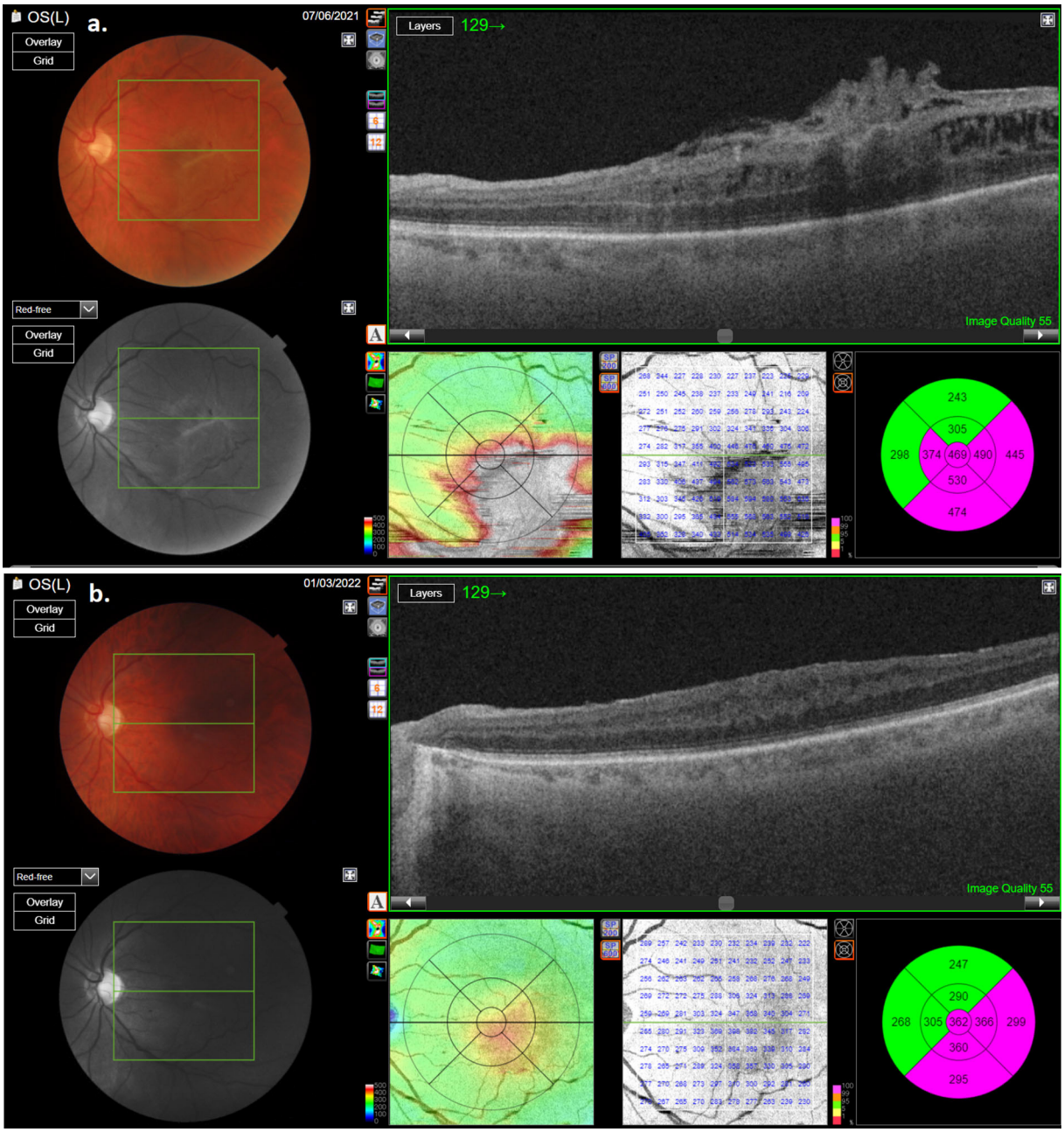

FIGURE 4
OCT scan of the second patient with macular pucker: **(a)** pre-operative OCT; **(b)** post-operative OCT showing reduction of retinal thickness.

and diabetes mellitus without signs of diabetic retinopathy; least commonly: osteoporosis, benign prostatic hyperplasia, and cardiac disease). Combined phacoemulsification and vitrectomy were performed in five cases. In all cases, the MP was peeled off with the vitrectomy probe without the need for micro-forceps and without the need for additional procedures. Vitrectomies were finished without intraocular bleeding. All patients had follow-ups for at least 6 months. There were no intra- or post-operative complications registered. No cases of post-operative retinal detachment or glaucoma were registered. During the follow-up period, 2 patients had additional cataract surgery in the operated eye because of progressive nuclear sclerosis. The median post-operative BCVA 6 months after the surgery improved to 0.15 (IQR: 0.1–0.3; range: 0–1). Statistically significant median difference ($P < 0.001$) between the pre- and post-operative logMAR values was detected (Figure 1). The

mean value of the post-operative CRT was 377.64 ± 41.05 μm. Statistically significant mean difference ($P < 0.001$) was detected between the pre- and post-operative CRT (Figure 2).

During the post-operative follow-up period, no recurrence of ERM in any of the patients could be found (Figures 3, 4). In none of the cases did MH appearance occur. ELM and EZ continuity were post-operatively present in 13 out of 14 cases. SR was not detected in the study cases. RPE continuity was preserved in all patients (Figures 3, 4).

Discussion

Surgery for ERM is one of the more common interventions in vitreoretinal surgery. As in any other surgical procedure, the main goal is to perform a complete removal of the pathologic tissue in as much as possible atraumatic manner. Many times, this is difficult. Even in the hands of experienced surgeons, iatrogenic damage by the different sharp tips of the instruments can happen (12).

In this pilot study, we present a novel surgical approach for MP removal without the need for extra instrumentation. The technique enables surgeons to simply engage the edge of the MP, then gradually increase the vacuum to achieve peeling of the membrane without the need for multiple pinches. Fewer pinches made reduce the possibility of iatrogenic damage to the central or peripheral retina.

In this case series, we have successfully removed complete MP without the need for forceps. Our experience with this approach is longer, but this is the first time we did a prospective analysis of the results of surgery. In all cases, the surgery was finished fast and without complications. Our impression is that the technique is simple and safe. In each case, the patient did well. BCVA improved in all cases. Morphological improvement was seen on OCT in all cases with reduced CRT.

None of the patients had IOP rise or developed glaucoma after the surgery. There are also previous reports that uncomplicated PPV for idiopathic ERM does not increase the risk of ocular hypertension or open-angle glaucoma development in long-term observations (13). However, Lin GC et al. found high IOP at baseline or during follow-up to be a significant factor associated with limited visual outcomes (14).

Surgery for ERM is generally considered safe and effective. Even in cases with very good pre-operative visual acuity, the treatment results in significant improvement in vision (15). Significant improvement of visual acuity after PPV for ERM has also been found in the analysis of Kishi et al. 3 months after the surgery, which was maintained over the 5-year follow-up period (16).

The ILM peeling procedure during surgery for ERM is being increasingly used by retinal surgeons. However, the effectiveness of the ILM peeling is uncertain and debatable. There are different and also contradictory reports on the outcomes of such peeling. In a meta-analysis by Chang et al., they found a more efficacious reduction of CRT in patients without ILM peel in comparison to patients with ERM and ILM peel. However, the long-term follow-up showed better functional improvement and a lower recurrence rate in patients with ILM peel (17). Another meta-analysis showed that patients without ILM peel had better visual improvement in the long-term than patients after both ERM and ILM peel (18). In a randomized multicenter clinical trial, Ripandelli et al. evaluated the retinal sensitivity, frequency of microscotomas, and other microperimetric parameters in patients with idiopathic MP—they found better outcomes in patients without ILM peel after a 12-month follow-up (19).

The fact is that ILM is a much more fragile, thinner, and less elastic structure compared to ERM, and our technique is probably less suitable for ILM alone. But in our opinion, this question remains to be answered in future studies and analyses. Since this is a pilot study and with the aim of eliminating potential dilemmas about the impact of ILM peeling on the final treatment outcomes, we decided to perform only ERM peeling.

In our hands, this technique works better with the 25-gauge system. It is possible to perform it with 23 and 27 gauge as well. But 23-gauge cutter has a wider opening, which can represent a higher chance of aspirating and accidentally engaging the retina. On the other hand, a 27-gauge cutter is more flexible and sometimes it can extensively bend during the peeling procedure.

Neither in this case series nor before we could not detect any complication related to the technique. We are aware that any surgical approach can go wrong and every surgical procedure can result in a bad outcome. However, in our opinion, at least in some cases, this approach may work well in reducing the costs for the management of MP, and also improving outcomes of the treatment.

Conclusions

This technique could offer an alternative and safe approach for MP surgery without the need for extra instrumentation. In all cases, it was possible to remove the membrane in a safe, and cost-saving manner. In all cases, we achieved good functional and morphological outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Medical Ethics Committee of the Republic of Slovenia (Approval No. 91/05/11). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XL, BP, and GP did the literature review and wrote the manuscript. XL performed surgeries. BEP defined methodologies and performed statistical analysis. GP contributed to conception and design of the study. All authors contributed to the article and approved the final submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.947578/full#supplementary-material

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Modified tarsorrhaphy versus gold weight implant technique for paralytic lagophthalmos treatment in patients with leprosy: One-year observation of a randomized controlled trial study

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Trial design: This study was a multicenter, Prospective Randomized Open-label Blinded-Endpoint (PROBE) clinical trial, parallel-group study conducted in Indonesia (three sites).

Methods: The aim of this study was to compare the effectivity and efficiency of modified tarsorrhaphy (MT) and gold weight implant (GWI) techniques in the surgical treatment of paralytic lagophthalmos in patients with leprosy. The study sample consisted of 23 eyes, with 11 eyes in the MT group and the remaining 12 eyes in the GWI group—the control group.

Results: The central eyelid margin distance (lagophthalmos distance) decreased when gentle pressure was applied in the MT (3.09 mm to 0.43 mm) and GWI groups (3.21 mm to 0.83 mm) at postoperative year 1. The Ocular Surface Disease Index score, the tear break-up time, and the Schirmer test without and with anesthesia in the MT and GWI groups showed a p-value of > 0.05. Epitheliopathy improvement occurred in 54.55% of the MT group and 58.33% of the GWI group. Corneal sensitivity change in the inferior quadrant of the MT group (50.00 to 51.30 mm) and in the GWI group (49.61 to 52.93 mm) resulted in a $p > 0.05$. Postoperative complications occurred in 15% of patients in the GWI group. In addition, the surgery duration of both

techniques was similar. Furthermore, the surgery cost in the MT and GWI groups yielded a $p < 0.05$.

Conclusion: The MT technique is as effective as the GWI technique but more efficient than the GWI technique as a surgical treatment for paralytic lagophthalmos in patients with leprosy.

Clinical trial registration: [www.ClinicalTrials.gov], identifier [NCT04944498].

KEYWORDS

Hansen's disease, paralytic lagophthalmos, surgical intervention, epitheliopathy, corneal exposure

Introduction

Lagophthalmos is a condition in which eyelids are incapable of closing completely. This condition can be divided into paralytic and cicatricial based on the etiology. Several factors could induce paralytic lagophthalmos, such as idiopathic nerve paralysis (e.g., Bell's palsy), infection, trauma, or neoplasm. Paralytic lagophthalmos is one of the most common eye disorders in patients with leprosy caused by *Mycobacterium leprae* invasion on the peripheral endings of the facial cranial nerve, which innervates orbicularis muscles of the eyelids. *Mycobacterium leprae* invasion causes disturbance in axon conduction and nerve demyelination. These disruptions are associated with laminin 2 protein and dystroglycan, which can be found in the peripheral nerve endings of CN VII. When *Mycobacterium leprae* is ligated by neuregulin receptors (ErbB2, ERK 1, and ERK 2), nerve inflammatory responses form. If zygomatic and temporalis branches of CN VII are affected, orbicularis oculi muscles will be paralyzed, resulting in paralytic lagophthalmos.

To date, about 200,000 new leprosy cases are diagnosed worldwide every year. In 2019, the highest number of new leprosy cases is from India (114,451), followed by Brazil (27,863) and Indonesia (17,439). The World Health Organization (WHO) stated that leprosy still required global attention; therefore, the WHO implemented Global Leprosy Strategy 2021-2030 (1). Lagophthalmos might cause corneal opacities, which lead to decreasing visual acuity and blindness (2). The WHO grades visual impairment in leprosy as grade 0, no eye problem due to leprosy; grade 1, eye problems due to leprosy, but vision is not severely affected [visual acuity (VA) 6/60 or better; can count fingers at 6 m]; and grade 2, severe visual impairment (VA worse than 6/60; inability to count fingers at 6 m), including lagophthalmos, corneal anesthesia, and iridocyclitis (3).

The presence of blindness along with another form of disability (extremities, such as hands and feet) will significantly reduce the quality of life of patients with leprosy. In order to prevent such conditions, surgical treatment is considered necessary. In this case, the upper eyelid loading technique is the most commonly used surgical procedure for paralytic lagophthalmos, mainly using the gold weight implant (GWI) technique. Although this technique has a high success rate in the management of paralytic lagophthalmos, the GWI has a fairly high complication rate in patients with leprosy, such as implant extrusion found in six of 12 (50%) patients between 3 and 12 months during the observation period (4). The modified tarsorrhaphy (MT) technique could be considered a treatment in leprosy cases. This technique is more simple to perform and can be carried out even in rural areas with limited availability of oculoplastic surgeons. Furthermore, since patients with leprosy in most cases are from a low socioeconomic class, the cost of surgery needs to be considered. The modified tarsorrhaphy technique might be a more accessible technique than the GWI technique to use for paralytic lagophthalmos in patients with leprosy, but the effectivity and efficiency between the two techniques have not been studied before. This study aims to compare the effectivity and efficiency of the MT and GWI techniques as surgical treatment for paralytic lagophthalmos in patients with leprosy.

Materials and methods

Study design and sampling

A multicenter Prospective Randomized Open-label, Blinded-Endpoint (PROBE) clinical trial was conducted in three hospitals in Indonesia. The sample size was determined using a two-tailed hypothesis test, which predicted a minimum number of 12 eyes for each group.

$$n = \frac{Sd^2(Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu_0 - \mu_a)^2}$$

$$n = \frac{1.19^2(1.96 + 0.842)^2}{(1)^2}$$

$$n = 12$$

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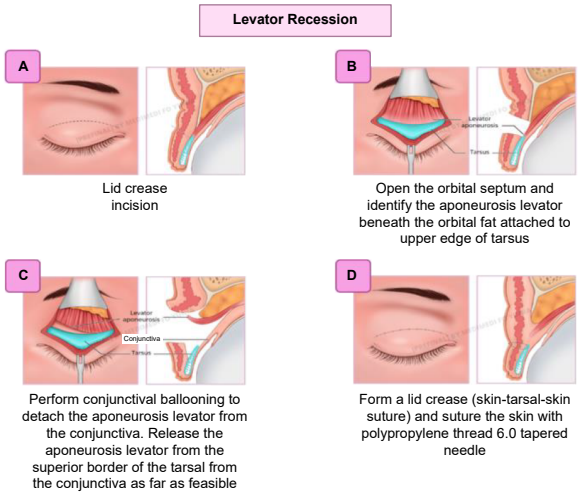
where n = total sample, Sd = standard deviation of mean difference (1.19), $Z_{1-\alpha/2}$ = type 1 error (1.96), $Z_{1-\beta}$ = type 2 error (0.842), and $\mu_0 - \mu_a$ = mean significant difference between both groups (1 mm represents significance).

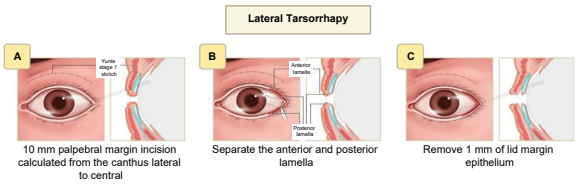
Anticipating a dropout, the researchers added 20% of the total sample. Research team members assigned treatment on all samples *via* randomization with a blocking restriction size of 2. A researcher as the oculoplastic surgeon (YI) acknowledged the treatment assigned to each eye based on randomization. Also, the outcomes were measured by three oculoplastic surgeons with equal clinical experiences (HD, TR, and AP), who had been trained to reduce data bias.

The inclusion criteria were patients with paucibacillary (PB)- or multibacillary (MB)-type leprosy with unilateral/bilateral lagophthalmos, who had not undergone eyelid reconstruction, aged 18 years or older, and who could undergo surgery with local anesthesia. The exclusion criteria were patients with acute leprosy reaction (<6 months) and under steroid medication, and patients with an eyelid laxity > 8 mm. The dropout criteria were patients who had not attended follow-up appointments as determined by researchers and patients who resigned during the study period. Patients who were willing to participate in this study were asked to sign a written consent form. Those in the intervention group received the MT, which was carried out in three steps (Yunia technique):

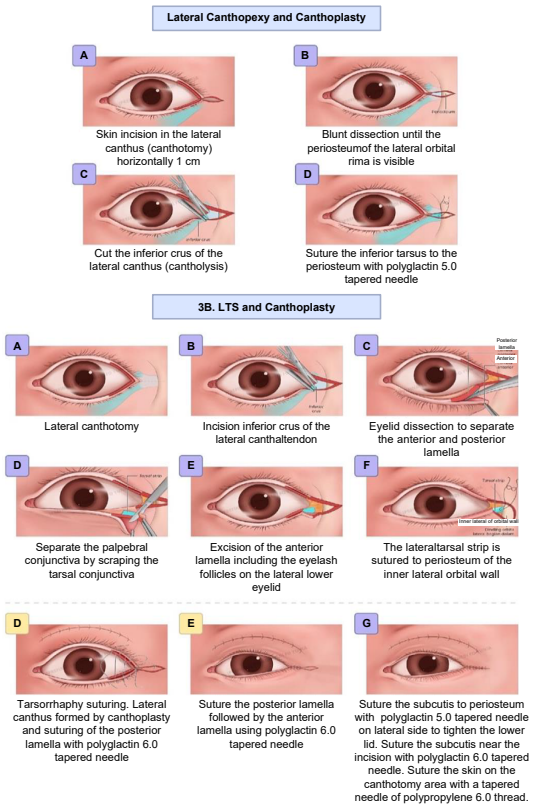
(1) **Levator recession:** This technique involves (a) an aseptic procedure, eyelid skin crease marking, and local anesthesia injection in the upper eyelid and lateral side; (b) skin crease incision and orbicularis dissection until the tarsal plate, and then conjunctival eversion and ballooning; (c) levator recess; and (d) perform lid crease suture.



(2) **Lateral tarsorrhaphy:** This technique involves canthotomy, lateral cantholysis, and excision of upper and lower lid margins as long as 10 mm from the lateral canthus to the central area, followed by permanent lateral tarsorrhaphy.



(3) **Canthopexy and canthoplasty or lateral tarsal strip and canthoplasty** were performed according to the horizontal eyelid laxity. The canthopexy/lateral tarsal strip (LTS) used Vicryl 5-0 and canthoplasty with Vicryl 6-0, and (9) skin suture with Prolene 6-0 at skin crease.



The control group received GWI which was performed with the following steps: (1) aseptic procedure; (2) eyelid skin crease marking; (3) subcutaneous local anesthesia injection in the upper eyelid; (4) skin crease incision and orbicularis dissection; (5) orbital septum opening in the superior tarsal midline; (6) conjunctival eversion and ballooning; (7) placing the gold weight inferior to the levator insertion on the tarsal plate, followed by suturing the implant on the tarsal plate with Prolene 6-0; and (9) suturing pretarsal and preseptal orbicularis muscles with Vicryl 6-0 to cover implant, followed by suturing the skin with Prolene 6-0.

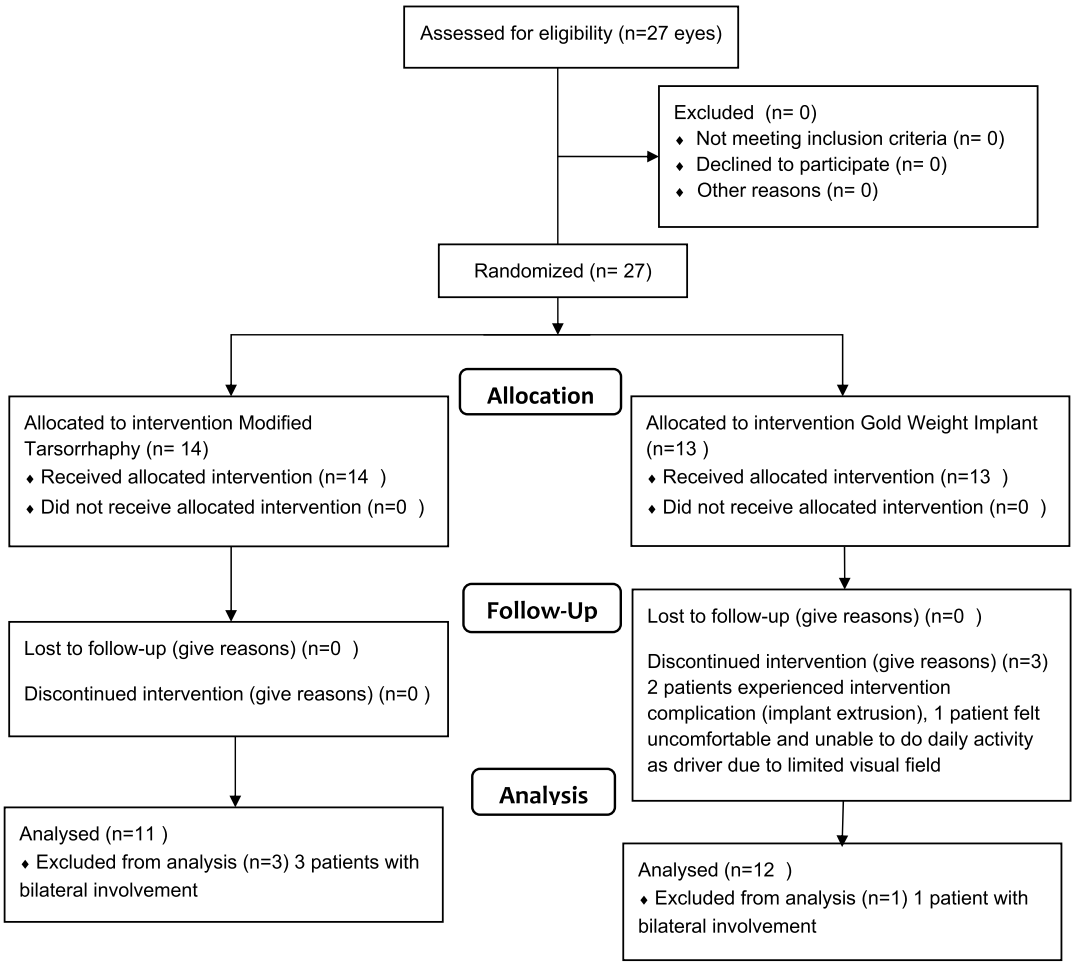


FIGURE 1
Flow diagram of subject recruitment and group allocation (18–20).

Data collection

Anticipating a dropout, the researchers added 20% of the total sample. The research team members assigned treatment for all the samples *via* randomization with a blocking restriction size of 2. One of the researchers, an oculoplastic surgeon (YI) acknowledged the treatment assigned to each eye based on randomization. Outcomes were measured by three oculoplastic surgeons with equal clinical experiences (HD, TR, and AP), who had been trained to reduce data bias.

The inclusion criteria were patients with paucibacillary (PB)- or multibacillary (MB)-type leprosy with unilateral/bilateral lagophthalmos who had not undergone eyelid reconstruction, patients aged 18 years or older, and who could undergo surgery with local anesthesia. The exclusion criteria were patients with an acute leprosy reaction (<6 months) and under steroid medication, and patients with an eyelid laxity >8 mm. The dropout criteria were patients who did not attend follow-up appointments as determined by researchers and patients who resigned during the study period. Patients who were willing to participate in this study were asked to sign a written consent form. The total sample was 23 eyes, with 11 eyes in the MT group (intervention group) and 12 eyes in the GWI group (control group) (Figure 1).

Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20 developed by International Business Machines (IBM). A univariate analysis was performed to obtain an overview of the frequency distribution. To analyze a normal distribution of data, the Shapiro–Wilk test was used. A bivariate analysis was conducted using an independent *t*-test, the Wilcoxon homogeneity test, and the Mann–Whitney test. In addition, a *p*-value of 0.05 was used as the cutoff point of significance.

Ethical consideration

For ethical reasons, researchers were blinded to the results. This study was approved by the Medical and Health Research Ethics Committee (MHREC) of the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada—Dr. Sardjito General Hospital, Yogyakarta, Indonesia, with the reference number KE/FK/0557/EC/2018 and extended with the reference number KE/FK/0525/EC/2019. This study complies with the 2013 WMA Declaration of Helsinki. Written informed consent was obtained from all the patients after the aim of the study and the nature of their participation were explained to them.

Results

Subject and clinical characteristics

A total of 23 eyes from 23 patients were randomly grouped into the MT group (11 eyes) as the intervention group and the GWI group (12 eyes) as the control group. All the participants were observed for 1 year without losses or exclusions after randomization. In this study, 18 patients (78.3%) were male. The patients' ages ranged from 40 to 77 years (55.45 ± 9.5). Patient characteristics are shown in Table 1.

Almost all patients had MB-type leprosy (21 patients or about 91.3%), and most of them had been diagnosed with leprosy for more than 5 years. Table 2 shows that both groups had similar clinical characteristics.

Treatment effectivity and efficiency

Lagophthalmos distances at the central area measured with gentle pressure decreased significantly ($p < 0.05$) after the surgery compared with the preoperative result until the 3-month observation period both within the MT and GWI groups. In the MT group, the lagophthalmos distance with pressure significantly decreased until the 3-month observation at the nasal area ($p < 0.05$), and until the 1-month observation at the temporal area ($p < 0.05$). In the GWI group, the lagophthalmos distance with pressure significantly decreased until 1-year observation at the nasal area ($p < 0.05$), and until 3-month observation at the temporal area ($p < 0.05$).

Lagophthalmos distances without pressure between the MT and GWI groups are shown in Table 3. Table 4 shows lagophthalmos distances with gentle pressure in both groups. The MT and GWI techniques showed no significant difference in decreasing lagophthalmos distances with or without gentle pressure at nasal, central, and temporal areas.

This study took account of confounding variables such as age, gender, level of education, leprosy type, and duration of leprosy. In the multivariate analysis, these variables significantly affected the lagophthalmos distance without pressure. Meanwhile, the lagophthalmos distance with gentle pressure was significantly affected by age and level of education.

The TBUT improved significantly ($p < 0.05$) in the GWI group after 1-year observation; meanwhile, in the MT group, no significant improvement was found in TBUT during the observation. In the GWI group, the Schirmer test without anesthesia only showed significant improvement at 1-day observation, and the Schirmer test with anesthesia had significant improvement at 1-day observation as well as at 3-month observation ($p < 0.05$). In the MT group, no significant improvement was found in the Schirmer test without anesthesia, but the Schirmer test with anesthesia showed significant improvement after 1-year observation ($p < 0.05$) (Table 5).

TABLE 1 Patient characteristics.

Patient characteristics	Total patients ($N = 23$)	Percentage (%)
Age (years)		
Mean ± SD	(55.45 ± 9.5)	
Range	40–77	
Sex		
Male	18	78.3
Female	5	21.7
Occupation		
Unemployed	10	43.5
Freelance	13	56.5
Education level		
None	9	39.1
Primary School	8	34.8
Junior High School	2	8.7
Senior High School	4	17.4

SD, standard deviation.

TABLE 2 Clinical characteristics.

Clinical characteristics	MT group no. of patients (%)	GWI group no. of patients (%)	*P*-value
Total eyes	11 (47.8)	12 (52.2)	0.686
Leprosy type			
Paucibacillary	1 (4.3)	1 (4.3)	0.455
Multibacillary	10 (43.5)	11 (47.8)	
Leprosy duration			
<2 years	0 (0.0)	1 (4.3)	0.560
2–5 years	3 (13.0)	2 (8.7)	
>5 years	8 (34.8)	9 (39.1)	
Leprosy treatment			
Not finished yet	0 (0.0)	0 (0.0)	N/A
Finished	11 (47.8)	12 (52.2)	
Unfinished	0 (0.0)	0 (0.0)	
Lagophthalmos distance in central area preoperative (mm)			
Without pressure	5.42 ± 2.54	4.82 ± 2.40	0.873
Gentle pressure	3.21 ± 1.99	3.09 ± 2.91	0.925

TABLE 3 Lagophthalmos distance without pressure (mm) in the MT and GWI groups.

Area	Follow up time	MT group				GWI group				*P*-value
		Mean/Median	SD/IQR	Δ	Range	Mean/Median	SD/IQR	Δ	Range	
Nasal	Pre	3.23	2.56		0–7	3.71	2.45		1–9	
	PostD1	0.36	0.67	2.87	0–2	1.29	2.07	2.42	0–5	0.724[a]
	PostD7	0.95	1.00	2.28	0–2.4	1.00	0.85	2.71	0–2	0.680[a]
	PostM1	1.55	1.83	1.68	0–6	0.75	0.97	2.96	0–3	0.264[a]
	PostM3	2.35	1.89	0.88	0–5.9	1.00	1.12	2.71	0–3	0.148[a]
	PostY1	1.71	1.50	1.52	0–4	1.00	1.00	2.71	0–2	0.168[a]
Central	Pre	4.82	2.40		1–8	5.42	2.54		1–10	
	PostD1	0.28	0.47	4.54	0–1	0.92	1.83	4.50	0–6	0.961[b]
	PostD7	0.84	1.02	3.98	0–3	1.00	1.21	4.42	0–3	0.617[b]
	PostM1	1.97	3.08	2.85	0–9	1.08	2.07	4.34	0–7	0.139[b]
	PostM3	2.99	2.85	1.83	0–9	1.25	1.29	4.17	0–3	0.044[b]
	PostY1	1.43	1.27	3.39	0–3	1.64	1.84	3.78	0–5	0.383[b]
Temporal	Pre	2.91	2.81		0–10	2.50	1.83		0–5	
	PostD1	0.00	0.00	2.91	0–0	0.46	0.9	2.04	0–3	0.487[a]
	PostD7	0.28	0.47	2.63	0–1	0.28	0.47	2.63	0–1	0.928[a]
	PostM1	0.68	1.35	2.23	0–4	0.68	1.35	2.23	0–4	0.833[a]
	PostM3	1.06	1.63	1.85	0–4.7	1.06	1.63	1.85	0–4.7	0.740[a]
	PostY1	0.57	0.79	2.34	0–2	0.57	0.79	2.34	0–2	0.805[b]

SD, standard deviation; Δ,delta; Pre, preoperative; PostD1, postoperative day 1; PostD7, postoperative day 7; PostM1, postoperative month 1; PostM3, postoperative month 3; PostY1, postoperative year 1; [a]independent *t*-test; [b]Mann–Whitney test.

TABLE 4 Lagophthalmos distance with gentle pressure (mm) in the MT and GWI groups.

Area	Follow up time	MT group				GWI group				*P*-value
		Mean/Median	SD/IQR	Δ	Range	Mean/Median	SD/IQR	Δ	Range	
Nasal	Pre	2.18	2.28		0–8	2.29	1.54		0–4.5	
	PostD1	0.13	0.32	2.05	0–1	0.66	1.61	1.63	0–5	0.671[a]
	PostD7	0.39	0.76	1.79	0–2	0.29	0.62	2.00	0–2	0.203[b]
	PostM1	0.41	1.20	1.77	0–4	0.50	0.67	1.79	0–2	0.334[a]
	PostM3	1.06	1.96	1.12	0–5	0.58	0.66	1.71	0–2	0.520[a]
	PostY1	1.00	0.89	1.18	0–2	0.42	0.78	1.87	0–2	0.085[a]
Central	Pre	3.09	2.91		0–9	3.21	1.99		0–6	
	PostD1	0.00	0.00	3.36	0–3	0.83	1.94	2.38	0–5	0.547[a]
	PostD7	0.28	0.90	3.14	0	0.75	1.48	2.46	0–5	0.736[a]
	PostM1	1.04	2.12	2.07	0–6	0.42	0.90	2.79	0–3	0.316[b]
	PostM3	1.33	2.01	3.14	0–5	0.75	0.86	2.46	0–2	0.382[a]
	PostY1	0.43	1.27	1.57	0–3	0.83	1.84	2.38	0–5	0.238[a]
Temporal	Pre	2.04	2.49		0–8	1.29	1.30		0–3	
	PostD1	0.18	0.60	1.86	0–2	0.00	0.00	1.29	0–0	0.976[b]
	PostD7	0.09	0.30	1.95	0–1	0.83	0.28	0.46	0–1	0.786[b]
	PostM1	0.41	0.97	1.63	0–3	0.83	0.28	0.46	0–1	0.833[b]
	PostM3	0.72	1.27	1.32	0–4	0.16	0.39	1.13	0–1	0.786[b]
	PostY1	0.78	0.78	1.26	0–2	0.85	1.07	0.44	0–3	0.535[b]

SD, standard deviation; Δ,delta; Pre, preoperative; PostD1, postoperative day 1; PostD7, postoperative day 7; PostM1, postoperative month 1; PostM3, postoperative month 3; PostY1, postoperative year 1; [a]independent *t*-test; [b]Mann–Whitney test.

TABLE 5 Subjective and objective tear assessments using OSDI (total score), TBUT (seconds), and Schirmer tests (millimeter) of patients in the MT and GWI groups.

Test	Follow up time	MT group			GWI group			*P*-value
		Mean/Median	SD/IQR	Δ	Mean/Median	SD/IQR	Δ	
OSDI	Pre	29.74	5.83		31.33	11.11		
	PostD1	19.45	9.27	-10.28	21.33	12.62	-10	0.941[a]
	PostD7	14.00	6.58	-15.74	14.83	8.77	-16.5	0.809[a]
	PostM1	11.27	8.94	-18.47	16.17	9.48	-15.16	0.400[a]
	PostM3	8.09	7.94	-21.65	9.75	7.43	-21.58	0.880[b]
	PostY1	11.50	8.58	-18.24	15.09	12.44	-16.24	0.226[a]
TBUT	Pre	4.20	3.04		2.10	0.73		
	PostD1	5.0	2.98	0.80	3.09	1.86	0.99	0.566[b]
	PostD7	4.0	3.09	-0.20	2.41	1.56	0.3‘	0.614[a]
	PostM1	3.81	1.47	-0.39	3.08	1.78	0.98	0.258[a]
	PostM3	5.10	3.24	0.90	4.0	1.78	1.9	0.494[a]
Schirmer without anesthesia	Pre	20.45	9.06		12.5	9.66		
	PostD1	24.36	9.32	3.91	20.18	10.13	7.68	0.685[a]
	PostD7	19.82	10.08	-0.63	13.16	9.23	0.66	0.771[a]
	PostM1	20.27	8.92	-0.18	15.58	10.06	3.08	0.495[a]
	PostM3	12.10	10.71	-8.35	13.18	11.66	0.68	0.127[a]
	PostY1	19.66	7.76	-0.79	17.14	11.67	4.64	0.564[a]
Schirmer with anesthesia	Pre	16.64	9.68		14.25	10.64		
	PostD1	21.09	10.68	4.45	22.16	10.93	7.91	0.539[a]
	PostD7	21.36	9.31	4.72	18.66	6.44	4.41	0.943[a]
	PostM1	19.54	9.34	2.90	18.58	8.67	4.33	0.760[a]
	PostM3	19.40	10.52	2.76	18.36	7.00	4.11	0.788[a]
	PostY1	25.33	11.36	8.69	18.28	10.30	4.03	0.141[a]

SD, standard deviation; Δ,delta; Pre, preoperative; PostD1, postoperative day 1; PostD7, postoperative day 7; PostM1, postoperative month 1; PostM3, postoperative month 3; PostY1, postoperative year 1; [a]independent *t*-test; [b]Mann–Whitney test.

Epitheliopathy was observed pre- and post-surgery. Epitheliopathy improvement occurred in 13 of 23 eyes, 6 of which (54.55%) were in the MT group and 7 (58.33%) were in the GWI group, with no significant difference between both groups. No epitheliopathy was found at pre- and post-surgeries in one eye (4.3%), whereas nine eyes (39.1%) experienced this condition with no improvement after a 3-month observation period (Table 6).

Corneal exposure was observed to assess part of the cornea exposed while the eyes were closed. Table 7 shows that the corneal exposure degree at pre- and post-surgery follow-up appointments in the MT group and the GWI group indicates no significant difference between both groups. The results showed improvement after surgery on the first and seventh days in both groups, but the degree of exposure increased in the first month in the MT group and in the third month in the GWI group.

Table 8 shows corneal sensitivity pre- and post-surgery in all four quadrants between the MT and GWI groups. Corneal sensitivity improvement in both groups was insignificantly different.

Surgical technique safety, duration of surgery, and cost of surgery were observed to determine procedure efficiency. In addition, the complication was evaluated from the first day to 12 months post-surgery to rate surgical technique safety. The observation result showed that there was no complication found in the MT group, while two eyes (15%) in the GWI group experienced implant extrusion. Furthermore, the surgery duration for those in the MT group (44,61 ± 11,29 min) was insignificantly different from those in the GWI group (43,81 ± 15,03 min). In terms of cost, the mean cost of surgery in the MT group was 1.488.357, 14 ± 18.156,82 IDR, while that in the GWI group was 1.488.357, 14 ± 18.156,82 IDR. Only two patients who had implant extrusion underwent the MT technique as a reparative procedure. The final mean cost

TABLE 6 Epitheliopathy improvement between the MT and GWI groups.

Follow up time	MT group *N* = 11	GWI group *N* = 12	*P*-value
Post D1	0 (0.00%)	3 (25.00%)	0.124[a]
Post D7	3 (27.27%)	4 (33.33%)	0.556[a]
Post M1	5 (45.45%)	5 (41.67%)	0.593[a]
Post M3	6 (54.55%)	7 (58.33%)	0.593[a]

PostD1, postoperative day 1; PostD7, postoperative day 7; PostM1, postoperative month 1; PostM3, postoperative month 3; [a]chi-square test.

TABLE 7 Corneal exposure degree (mm) between the MT and GWI groups.

Follow up time	MT group			GWI group			*P*-value
	Mean	SD	Δ	Mean	SD	Δ	
Pre	0.50	0.24		0.33	0.18		
Post D1	0.00	N/A	0.50	0.00	N/A	0.33	0.873
Post D7	0.00	N/A	0.50	0.00	N/A	0.33	0.873
Post M1	0.18	0.12	0.32	0.00	N/A	0.33	0.873
Post M3	0.27	0.14	0.23	0.08	0.08	0.22	0.866

SD, standard deviation; Δ,delta; Pre, preoperative; PostD1, postoperative day 1; PostD7, postoperative day 7; PostM1, postoperative month 1; PostM3, postoperative month 3; Mann–Whitney test.

TABLE 8 Corneal sensitivity between the MT and GWI groups.

Corneal quadrant	Follow up time	MT group			GWI group			*P*-value
		Median	Range	Δ	Median	Range	Δ	
Superior	Pre	60	(45–60)		60	(40–60)		
	PostM3	60	(40–60)	0.00	60	(40–60)	0.00	0.562
Nasal	Pre	60	(40–60)		60	(35–60)		
	PostM3	60	(40–60)	0.00	60	(45–60)	0.00	0.754
Temporal	Pre	60	(45–60)		60	(50–60)		
	PostM3	60	(45–60)	0.00	60	(50–60)	0.00	0.377
Inferior	Pre	60	(50–60)		60	(50–60)		
	PostM3	60	(40–60)	0.00	60	(25–60)	0.00	0.295

SD, standard deviation; Δ,delta; Pre, preoperative; PostM3, postoperative month 3; Mann–Whitney test.

of those in the GWI group after complication correction was significantly higher (3.017.437,54 ± 560.823,97 IDR) than of those in the MT group ($p < 0.05$).

Discussion

In this study, in general, lagophthalmos is found in patients with MB-type leprosy. According to a previous study, patients with 100% leprosy who experienced ocular complications were diagnosed with the MB type (borderline and lepromatous leprosy types) (5). This was related to the ability of *Mycobacterium leprae* to invade the Schwann cells at facial cranial nerve (CN) VII endings. These peripheral nerves innervate the orbicularis muscles of the eyelid.

This study showed a decrease in the lagophthalmos distance after the surgery without significant differences between the MT and GWI groups. Modified tarsorrhaphy was performed with a combination of three procedures: levator recess, lateral tarsorrhaphy of 10 mm, and lateral canthopexy/lateral tarsal strip (LTS). This was performed at the temporal side due to its large area; therefore, patients' vision field would not be limited. Tarsorrhaphy was carried out at about 10 mm from the lateral canthus to provide an adequate visual function, and this technique yielded more aesthetically pleasing and more comfortable results. Moreover, it would not disrupt the tear flow into the medial punctum. Another study reported a permanent lateral tarsorrhaphy procedure in four lagophthalmos eyes (2–3.5 mm) with the lower lid retracted laterally and the upper lid retracted medially. This technique resulted in a smaller palpebral width and limited vision field (6). A significant difference in the lagophthalmos distance without pressure was only found in the third-month follow-up ($p = 0.044$). In the MT group, no weight was placed on the eyelids, and after 3 months of the wound-healing process, the swelling of the eyelid reduced, and there was a significant difference in the lagophthalmos distance compared with the GWI group.

The ideal GWI weight could be calculated preoperatively by putting trial weight on the pretarsal lid from 0.6 g and adding 0.2 g gradually until the lagophthalmos is reduced by 50% without inducing ptosis more than 2 mm (7). Another study suggested adding 0.2 g from the ideal weight to obtain better eyelid closure (8). In this study, the GWI group preoperative mean eyelid margin distance was 5.38 ± 2.43 mm. To make the implant easier to obtain, the researchers used 1.5-g gold weight for all patients as the average load as opposed to implants with a different ideal weight for each eye. In the GWI group, the lagophthalmos distance decreased significantly with a more stable result. The patients in this group experienced limited

vision field when the eyes were open due to the weight in their upper lids.

A study on dry eyes in patients with leprosy is currently developing. This dry eye condition in patients with leprosy is related to several mechanisms, such as decreasing tear component secretion and increasing evaporation. Subjective dry eye symptoms were evaluated through OSDI questionnaires. The OSDI score showed significant improvement from pre- to post-surgery within each group, with no significant difference between them. A decrease in the lagophthalmos distance leads to reduced evaporation and a more comfortable experience after undergoing the surgery, as indicated by the OSDI score (9).

In addition, lagophthalmos could cause conjunctival goblet cell impairment, which leads to a decrease in mucin production. A study showed that human goblet cells did not have nerve endings, but their secretion could be activated with sympathetic and parasympathetic nerve stimulation (10). Patients with leprosy had a high prevalence of Meibomian gland dysfunction due to *Mycobacterium leprae* infiltration and infection. Meibomian gland dysfunction could lead to gland atrophy, increasing tear osmolarity and reducing defense of the anterior surface of the cornea (11). *Mycobacterium leprae* could also directly invade lacrimal glands, causing a reduction in aqueous component production (12). Objectively, tear film stability was evaluated by using the TBUT, and the Schirmer test with and without anesthesia. The test results showed that the tear film stability was less than normal, in both groups at preoperative assessment, but this increased insignificantly post-surgery. A study also showed that the TBUT in patients with MB-type leprosy was significantly lower than that in normal eyes (13). Schirmer tests pre- and post-surgery were still in the normal range, suggesting a normal function of the lacrimal gland in this study. This result was similar to that of a previous study where there was no significant difference in the Schirmer test results between the patients with MB- or PB-type leprosy and the control group comprising normal eyes (13).

A previous study suggested that male individuals have a greater lower eyelid pressure, which results in relatively a slow healing of epitheliopathy (14). The weight of the implant put pressure on the upper eyelid, which was likely to cause less epitheliopathy improvement for those in the GWI group.

The corneal exposure improvement in the GWI group was due to the gold implant placed on the upper eyelid, which is similar to a previous study that showed that the corneal function remained constant in 99.5% of the patients in the 2-year evaluation (15). Meanwhile, in the MT group, the lagophthalmos distance increased after the healing process was complete.

A decrease in corneal sensitivity in patients with leprosy is caused by *Mycobacterium leprae* invasion to the maxillary branch of CN V, which innervates the corneal surface. Corneal sensitivity decreases over time as, in general, it is found in patients with MB-type leprosy and causes nerve atrophy, sensory function disruption, and lagophthalmos, which lead to corneal xerosis and tear film instability, and also indirectly causes corneal microtrauma (16). According to the systematic review of seven studies, impaired corneal sensitivity incidence varied between 8.1 and 59.2%, depending on disease duration and anterior segment abnormalities (17).

Postoperative complications were found in two patients (15%) in the GWI group after 1-year observation, whereas no complication was found in MT group patients. A previous study reported 50% of patients experienced extrusion after 1-year observation, from 3 to 12 months (4). However, in this study, a different GWI technique was used to prevent extrusion as the implant was placed above the tarsal lid under the aponeurosis levator muscle. Those two patients in the GWI group with implant extrusion underwent the MT procedure as repair surgery, and they felt satisfied with the results. One of the patients who belonged to the GWI group expressed discomfort with the implant after the 3-month evaluation. The patient experienced a very limited vision field, which interfered with his job as a motorbike driver, and requested to receive the MT surgery. Therefore, the MT technique to replace the previous GWI technique was performed on the patient's eyes, and the patient felt more comfortable after the second surgery. Another common complication in the GWI group was allergic reactions. Gold has an inert nature, but it can trigger allergic reactions in some patients. Therefore, an allergy examination is necessary, particularly for patients with a previous history of gold or metal allergy.

The duration of surgery was insignificantly different for both groups. Even though the MT technique consisted of a three-step procedure, more procedures than those used in the GWI technique, both techniques had the same level of difficulty when suturing the implant to the tarsal plate. The GWI technique had to be performed carefully to avoid the pretarsal orbicularis muscle tear as the implant was placed above the tarsal plate, underneath the levator aponeurosis. Another consideration is the cost of surgery; the cost was significantly higher in the GWI group since gold as the implant material, which is a higher value, was used in the GWI surgery, even though the surgery preparation cost (laboratory examinations, radiology imaging) of both MT and GWI procedures were similar. Moreover, for two patients who experienced implant extrusion and underwent an additional MT procedure, the total cost of surgery in the GWI group was higher. The surgery cost is important to be considered when deciding on lagophthalmos treatment in patients with leprosy since the patients in most cases are from a low socioeconomic class. Therefore, the MT technique is recommended as an alternative treatment for paralytic lagophthalmos in patients with leprosy as this technique was as effective as the GWI technique but more efficient than the GWI technique. The MT group showed no complication and felt more satisfied with the results than those in the GWI group.

Conclusion

The effectiveness of the MT technique was similar to that of the GWI technique in decreasing the eyelid margin distance (lagophthalmos distance) with and without gentle pressure, ameliorating subjective and objective tear assessments, improving epitheliopathy occurrence, decreasing corneal exposure, and improving corneal sensitivity. However, the MT technique was more efficient, had no complication, and had a lower cost of surgery than the GWI technique. The duration of surgery for both techniques was similar. Modified tarsorrhaphy can be considered appropriate for paralytic lagophthalmos surgical treatment in patients with leprosy.

Limitation

Lagophthalmos in patients with leprosy typically occurs over a long period of time, which allows them to adjust. Although patients with lagophthalmos are numerous, it might be challenging to locate patients who are willing to undergo surgery at community-based health institutions. Moreover, this study was held during the COVID-19 pandemic. Consequently, the number of samples was limited.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada – Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YI designed the concept, planned the study, and led the project administrations. YI and MN obtained the data collection and performed the data analysis. YI, MN, TG, ID, and HS were involved in data interpretation and validation. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.941082/full#supplementary-material

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A simple marking system for accurate intraoperative monitoring and adjustment of cyclotorsion strabismus surgery

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Ocular cyclotorsion is treatable only with surgery. The surgical procedure must be tailored individually to the specific etiologies causing the horizontal and vertical strabismus and its torsional components. An adjustable surgical approach is often used for postoperative or intraoperative adjustments. However, the methods currently used have some limitations. In this study, we propose a simple intraoperative marking system for all cyclotorsion correction surgery. The proposed marking system used three sets of surface markers: external horizontal markings, ocular horizontal markings, and surgical torsion markings, drawn in sequence. We retrospectively analyzed the surgical results using this novel marking system in this single-center, single-surgeon study. Fifteen patients with cyclotorsion who underwent treatment using the proposed marking system as an intraoperative aid between August 2019 and August 2021 were included. The medical charts were thoroughly reviewed, and the pre-and postoperative subjective and objective cyclotorsion were analyzed. Among the study subjects (10 males, 5 females; age range: 6–89 years), 13 had excyclotorsion and 2 incyclotorsion. Preoperative mean net subjective cyclotorsion measured by the double Maddox rod (DMR) test was 6.0° (standard deviation: 10.8°) and mean net disc-to-fovea angle (DFA) was 20.23° (13.21°). The postoperative net DMR and DFA were 0.2° (2.1°) and 14.09° (5.97°), respectively. The mean absolute net DMR and DFA being treated were 9.8° (4.8°) and 9.76° (4.61°). Overall, the proposed intraoperative marking system is a simple and quantitative method to assess, monitor, and adjust the torsional aspect for all strabismus surgeries.

KEYWORDS

cyclotorsion, disc-fovea angle, double Maddox rod, ocular torsion, torsional strabismus, surgical markings

1. Introduction

Ocular torsion, or cyclodeviation, is the rotation of the eye along its anteroposterior axis, causing a torsional misalignment between the eyes in the primary position. Various disorders involving the cyclovertical extraocular muscles could result in cyclodeviation, including traumatic or ischemic superior oblique palsy (SOP), secondary strabismus caused by thyroid-associated orbitopathy, and skew deviation from brainstem lesions (1–3). Other possible causes are primary oblique muscle overaction with A- or V-pattern strabismus (4–6), inferior oblique paresis (7) or other vertical muscle palsies (8) from oculomotor nerve palsy, Brown syndrome (9), iatrogenic postoperative cyclotorsion from retrobulbar anesthesia (10, 11), and surgically induced cyclotorsion from macular translocation surgery (12), scleral buckling procedure (13), or consecutively from prior strabismus surgery (14–17). The resulting torsional misalignment may cause severe debilitating symptoms of cyclodiplopia to these patients in the acute state (18), which cannot be alleviated by any prism or orthoptic treatment, except for omitting vision entirely by occlusion or through sensory adaptation mechanisms (19) in chronic conditions. Surgical treatment is then the only possible means to restore correct vision.

The available surgical options vary based on the underlying specific disorder and anatomy. The surgical goals are achieved by targeting all six extraocular muscles and their pulleys to treat the causative vertical and/or horizontal deviations and the accompanied cyclotorsion, reducing all alterations (20). For excyclotorsion commonly caused by SOP, the oblique muscles are usually targeted through direct manipulation of the superior oblique (SO) muscles with strengthening procedures, such as SO tucking or the Harada-Ito technique (21), whereas the inferior oblique (IO) muscle can be weakened by myotomy or myectomy (22). In rarer cases of incyclotorsion, the SO can be treated with weakening procedures, such as tenectomy (23) or tendon spacer (24), or, more rarely, the IO strengthened with tucking or advancement techniques (25).

However, the resulting cyclo-alleviating effect of the same muscle procedure can vary greatly, and the outcome is often unpredictable with different etiologies and individual anatomical conformations (26, 27). Surgical techniques allowing postoperative (28–30) or intraoperative adjustments under local anesthesia (31) have been proposed. However, these modified techniques can be burdensome for young children and uncooperative adult patients, rendering them occasionally unsuitable. Herein, we propose a simple torsion marking system for intraoperative adjustment, providing an individualized, tailored, and targeted cyclotorsion surgery applicable to any procedure, which can be easily implemented under general anesthesia in all patients with torsional strabismus.

2. Materials and methods

2.1. Patients

This case series retrospectively analyzed patients with cyclotorsion who underwent strabismus surgery at the Ophthalmology Department of the Tri-Service General Hospital in Taipei, Taiwan between August 2019 and August 2021. The study protocol was approved by the Institutional Review Board (No: C202105113) of the Tri-Service General Hospital. The requirement for informed consent was waived by the review board according to the guidelines for a retrospective study. All patients were followed up for at least 6 months after the surgery.

The inclusion criteria were documented cyclotorsion and surgical treatment using the proposed technique. The data collected included demographic and clinical information, diagnosis, pre- and postoperative ophthalmic and strabismus examination results, the strabismus surgery performed, and pre- and postoperative fundus photographs. Patients with incomplete information were excluded from the study.

2.2. Examinations

The standard strabismus examinations included a prism alternate cover test to determine the angle of deviation in the primary and nine cardinal positions, a 3-step test, and a double Maddox rod test (DMR; **Figure 1A**), according to the protocol proposed by Liebermann et al. (32) to measure subjectively the cyclodeviation of the patient. Color fundus photographs (**Figure 1B**) were routinely acquired pre- and postoperatively to document the difference in the objective cyclodeviations, and the degree of the disc-fovea angle (DFA) was calculated using the online software Cyclocheck (33).

2.3. Surgical procedure

The procedure and surgical correction required were determined preoperatively by Dr. Chien, who performed all the strabismus surgeries under general anesthesia. All chosen surgical procedures were performed with an adjustable suture technique. The degree of cyclodeviation to correct was calculated based mainly on the subjective measurements from the DMR test, supported by the calculated objective DFA from color fundus photography (**Figures 1A, B**).

The proposed surgical technique for accurate intraoperative torsional adjustment is a simple marking system. First, the patient was asked to fixate directly ahead while staying in an upright head-straight position before inducing general anesthesia. With the guide of a simple toric reference marking device (Cionni Toric Reference Marker, Duckworth & Kent

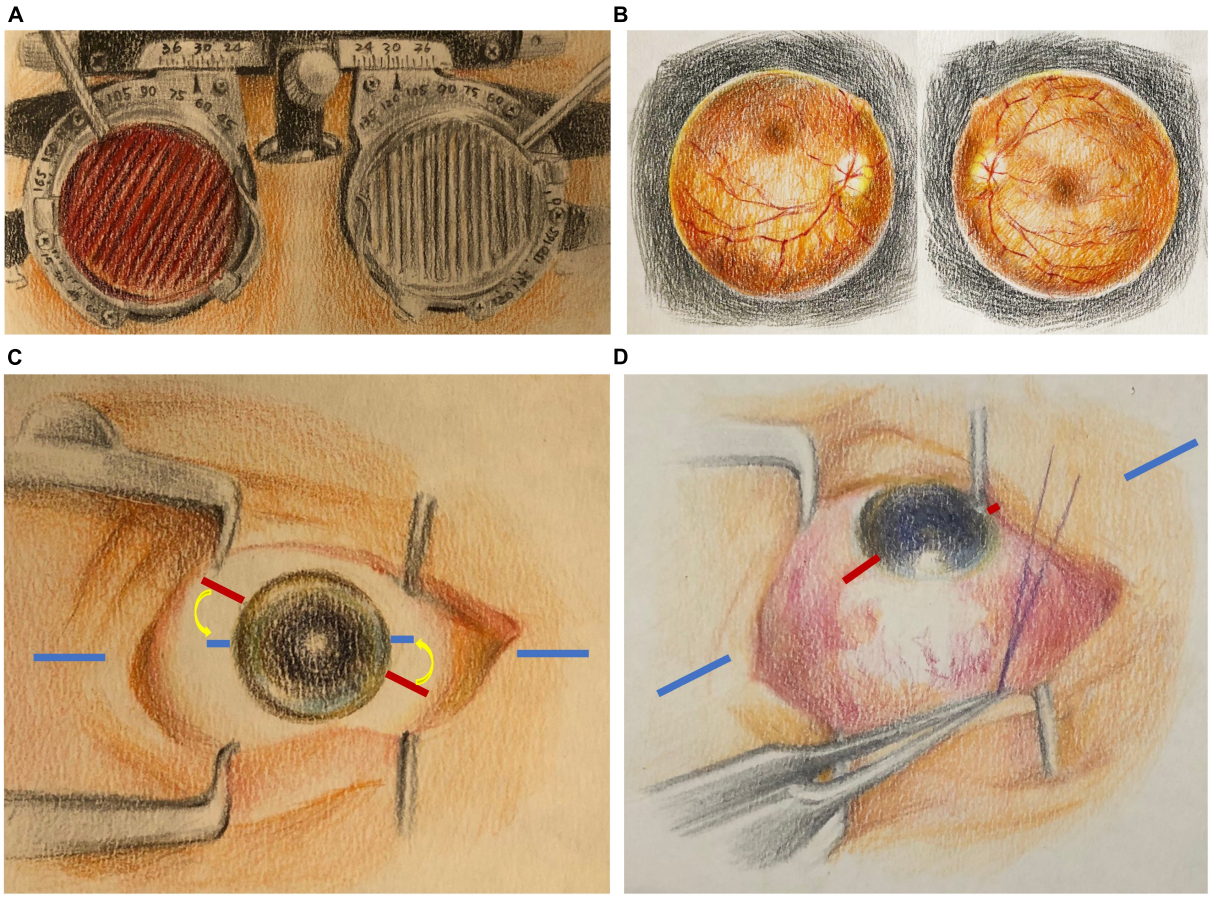

FIGURE 1
Pre- and intraoperative preparation for the simple torsion markings technique. In this instance, a significant incyclotorsion was measured subjectively with the double Maddox rod test **(A)** and confirmed objectively with the color fundus photography **(B)**. **(C)** The amount of cyclodeviation to be corrected was determined from the preoperative exams **(A,B)** and marked on the ocular surface before the surgery (red lines, indicating the surgical torsion markings) clockwise above the ocular and external horizontal markings (blue lines). For example, in a patient with a 15° incyclotorsion in the right eye, a surgical torsion marking should be marked 15° clockwise above the original ocular horizontal markings. In contrast, for a patient with excyclotorsion in the right eye, counter-clockwise surgical torsion markings should be placed below the original ocular horizontal markings, and vice versa with the left eye. **(D)** The surgical goal was to realign the surgical torsion markings (red lines) until parallel to the external horizontal markings (blue lines) using any adjustable surgical approach, which eventually achieved an excyclotorted correction.

Ltd., Baldock, United Kingdom), the eye's horizontal axis, parallel to the floor through the pupil, was marked using a marking pen able to withstand the disinfection procedures, preferably on the cornea, which is not affected during strabismus surgery. A horizontal line was also marked on the skin of the periocular region to add an external horizontal reference line for intraoperative adjustments. In this first step, the ocular horizontal markings and external horizontal markings should be aligned or parallel to each other. Second, the patient was placed in the supine position for anesthesia preparation and instructed to look straight ahead, alternatively with each eye if both eyes required surgery, to examine the ocular markings for significant cyclotorsion induced by postural change. If significant torsional change induced by the supine position was present, the ocular horizontal marking was updated to align or be parallel to the external horizontal markings. After the patient was anesthetized and properly draped, we ensured that the previous external and ocular horizontal markings were visible and adequate as a reference. Third, we marked the predetermined correcting degree for cyclodeviation on the ocular surface using a toric axis marking device (Cionni Toric Axis Marker, Duckworth & Kent Ltd.) with degree measurements (Figure 1C). Finally, the chosen strabismus surgery to correct any horizontal and/or vertical deviation and cyclodeviation was performed. Before the conclusion of the surgery, the surgical torsion markings were supposed to be aligned or parallel to the external horizontal markings. If the desired position was not achieved through the approach originally planned, adjustments were performed immediately to align the surgical torsion markings to the

external horizontal markings (Figure 1D). Adjustments could be obtained with a modifiable suture technique or additional muscle surgery.

2.4. Main outcomes and statistical analysis

All postoperative data presented in Table 1 were obtained at 3 months postoperatively. Descriptive statistics were calculated using Microsoft Excel and expressed as mean (standard deviation, [SD]). The pre-and postoperative DMR and DFA were analyzed with their net value from the sum of the right and left eye.

3. Results

3.1. Main outcomes

Fifteen patients (10 male and 5 female) met the inclusion criteria and underwent surgery with the proposed marking system for torsion correction between August 2019 and August 2021. The mean (SD) age was 47.29 (28.15) years, and three patients were under 18 years (Patients 3, 7, and 15), whereas the oldest was 89 years old. Etiologies contributing to the torsional aspect of the strabismus included ischemic (n = 5) or traumatic (n = 1) trochlear nerve palsy, congenital SOP with inferior oblique overaction (IOOA) (n = 2), primary IOOA (n = 2), thyroid-associated orbitopathy (n = 1), and other types of strabismus (n = 4). The surgical approach for each case differed according to the underlying etiologies; the clinical presentations are listed in Table 1.

There were 13 cases of net exyclotorsion and 2 of net incyclotorison preoperatively. The preoperative DMR ranged from 36° of incyclotorsion to 13° of excyclotorsion. The overall mean (SD) of the preoperative net DMR was 6.0° (10.8°), and the mean (SD) DMR was 0.8° (9.3°) for the right eye and 5.2° (5.1°) for the left eye, respectively. The preoperative overall mean (SD) net DFA was 20.23° (13.21°), and the mean (SD) DFA was 7.08° (9.84°) for the right eye and 13.16° (6.13°) for the left eye. The overall mean (SD) of the postoperative net DMR was 0.2° (2.1°), and the mean (SD) DMR was 0.1° (1.8°) for the right eye and 0.1° (1.1°) for the left eye. The postoperative mean (SD) net DFA was 14.09° (5.97°), and the mean (SD) DFA was 5.98° (4.84°) and 8.11° (2.91°) for the right and left eyes, respectively. The mean absolute net DMR and DFA being treated were 9.8° (4.8°) and 9.76° (4.61°), respectively. Patients 1, 9, and 15 are discussed here to illustrate the simplicity and the advantages of this marking system for intraoperative adjustment to correct the torsion degree simultaneously with other surgical treatments, such as for vertical strabismus or IOOA.

3.2. Case presentation

Patient 15 was a 7-year-old boy with a significant right head tilt. Left hypertropia with 4 prism diopters and grade-2 IOOA were observed, and the 3-step test was positive for left SOP. The DMR test revealed subjective excyclotorsion of 5° in the left eye only. The objective calculated DFA from color fundus photography using Cyclocheck was 9.32° in the right eye and 14.07° in the left eye, for an overall 4.75° excyclotorsion in the left eye, consistent with the result of the subjective DMR test. Hence, a surgical 5° incyclotorsional effect was predetermined for surgical torsion marking. A 10-mm IO recession was performed to correct the primary vertical deviation, IOOA, and excyclotorsion, using the surgical markings described in the Section "Materials and methods." Intraoperatively, the IO muscle was disinserted and repositioned on the sclera at the intended 10-mm recession position, then temporarily tied only with a slip knot for possible adjustments. The surgical effect was assessed to determine whether the recession was sufficient to align the surgical torsion marking with the external horizontal markings. The markings were aligned, and the suture was then tied securely to complete the surgery. The 3-month postoperative strabismus examination revealed orthotropia with grade-1 IOOA and no subjective torsion on DMR testing which remained stable throughout follow-up. The DFA calculated with Cyclocheck in the left color fundus photograph revealed a reduction in cyclotorsion to 4.57°compared to the preoperative DFA (Figures 2A, B).

Patient 9 was a 66-year-old male with acute vertical, and subsequent torsional, diplopia. Initial strabismus examination revealed 8 prism diopters of right hypertropia and 6 prism diopters esotropia were noted. The 3-step test was inconclusive. A diagnosis of idiopathic orbital inflammation with right superior rectus muscle hypertrophy, causing secondary strabismus was made. Medical treatment with systemic steroids was prescribed. During the treatment and observation period of 6 months, the disease was relatively quiescent, and the strabismus stabilized on a right hypertropia of 20–25 prism diopters at the simultaneous prism cover test with fusion, and 30 prism diopters on the DMR test. However, a net right incyclotorsion of 8° was also revealed by the DMR test, with symptoms under a corrected prism. The preoperative DFA was −2.86° in the right eye and 2.26° in the left eye (Figure 3A). A strabismus surgical correction was then planned with superior rectus muscle recession, using the hang-back technique, and muscle biopsy for tissue proof. The proposed torsion marking system was applied intraoperatively to monitor the torsional effect of the muscle biopsy combined with the corrective muscle-weakening procedure. Eventually, the surgical torsion marking was set approximately 8°clockwise to the external horizontal markings to correct 8° of incyclotorsion. At the 3-month follow-up, the DFA was 1.45° in the right eye and 4.61° in the left eye (Figure 3B), and the patient was orthotropic

TABLE 1 Summarized torsional characteristics.

No.	Age (years)/Sex	Diagnosis	Operation	Pre-op cover test	Post-op cover test	Pre-op DMR† OD/OS (°)	Post-op DMR† OD/OS (°)	Pre-op DFA‡ OD/OS (°)	Post-op DFA‡ OD/OS (°)	Overall corrected DMR (°)§	Overall corrected DFA (°)¶	Follow-up months
1*	49/F	Iatrogenic bilateral asymmetric CN3 palsy, consecutive torsional strabismus, OD	Multiple surgeries*	RET 14∧, RHoT 5∧*	RET 20∧, RHoT6∧*	−27/0	−4/0	−20.54/5.58	0.40/5.18	23	20.54	23.4
2	88/M	SOP, ischemic, OD	Recession of IO to the IR insertion with anterior transposition, OD	RHT 4∧	Ortho	5/2	−1/2	4.55/5.95	−0.15/6.58	−6	−4.07	9.3
3	6/F	Alternating esotropia with primary IOOA, OS > OD status post prior strabismus surgery with residual IOOA, OS > OD	Recession of IO (4 mm), OD and posterior displacement of IO (4 mm posterior to IR), OS	IOOA (OS 2+ > OD 1+); right head tilt	No more head tilt and IOOA	−3/13	−1/0	0.19/22.47	1.23/9.21	−11	−12.22	6.5
4	89/M	SOP, ischemic, OS	Recession of SR (2 mm) + disinsertion of IO, OS	LHT 16∧; 3-step: LRL	Ortho	0/12	−1/−2	8.30/15.66	5.96/2.62	−15	−15.38	6.2
5	51/M	SOP, ischemic, OD	Recession of IO inferiorly (4 mm) and medially (2 mm), OD	RHT 2∧; 3-step: RLR	Ortho	5/0	−1/0	6.43/11.22	5.56/6.42	−6	−5.64	9.4
6	57/M	Consecutive hypertropia, OS	Recession of IO (4 mm), OS	LHT 2∧; 3-step: negative	LHoT 1∧	1/6	1/0	11.37/15.40	10.23/9.67	−6	−6.87	9.7
7	6/M	Congenital SOP with secondary IOOA, OS status post prior strabismus surgery with residual left hypertropia with IOOA and right head tilt	IO myotomy + recession SR (2 mm), OS	LHT 6∧; IOOA 3 + (OS); right head tilt	Ortho but still mild right head tilt; IOOA 2+ (OD, reversal)	1/4	0/−1	12.26/10.41	8.91/7.31	−6	−6.45	10.2

(Continued)

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TABLE 1 (Continued)

No.	Age (years)/Sex	Diagnosis	Operation	Pre-op cover test	Post-op cover test	Pre-op DMR† OD/OS (°)	Post-op DMR† OD/OS (°)	Pre-op DFA‡ OD/OS (°)	Post-op DFA‡ OD/OS (°)	Overall corrected DMR (°)§	Overall corrected DFA (°)¶	Follow-up months
8	63/F	SOP, ischemic, OS	Recession of SR (8 mm), OS	RHoT 25∧; 3-step: LRL	Ortho	0/12	0/0	7.99/20.45	7.64/8.34	−12	−12.46	6.2
9	66/M	Idiopathic orbital inflammation with secondary hypertropia, OD	Recession of SR (7 mm) + muscle biopsy, OD	RHT 30∧	Ortho at primary; ET 8∧ with LHoT 6∧ at down gaze	−7/−1	−1/0	−2.86/2.26	1.45/4.61	7	6.66	12.1
10	49/F	Alternating exotropia with left hypotropia and strong right eye preference	Recession of IR (5 mm), OS	LXT 6∧, LHoT 15∧	Ortho	4/8	2/0	14.84/17.28	12.35/10.24	−10	−9.53	6.2
11	58/F	TAO, OU with secondary hypertropia and esotropia, OD	Recession of IR (10 mm) and MR (6 mm), OD	RHoT 30∧, RET 40∧; mild limitation of upper gaze (OD)	Ortho	8/0	1/0	16.54/7.82	9.13/7.14	−7	−8.09	8.3
12	19/M	Traumatic SOP with secondary IOOA, OD	Resection of IO (8 mm), OD	RHT 8∧; IOOA 1.5+ (OD); 3-step: RLR	Ortho	12/0	2/0	7.08/12.53	−2.9/13.34	−10	−9.17	6.1
13	27/M	Congenital SOP with IOOA, OS and right head tilt	Recession of IO + recession of SR (1.5 mm), OS	LHT 4∧; IOOA 3 + (OD); right head tilt,	Ortho	13/5	4/0	22.47/13.71	12.38/8.30	−14	−15.5	9.6
14	73/M	SOP, ischemic, OS with VR surgery for RD 3 months prior	Recession of IO (10 mm) + recession SR (3 mm), OS	LHT 4-6∧	Ortho	0/12	0/3	8.19/22.54	8.48/13.52	−9	−8.73	15.4
15	7/M	Congenital SOP with secondary IOOA, OS	Recession of IO (10 mm), OS	LHT 4∧; IOOA2 + (OS)	Ortho	0/5	0/0	9.32/14.07	9.09/9.15	−5	−5.15	6.7

CN, cranial nerve; DFA, disc-center-fovea angle; DMR, double Maddox rod; ET, esotropia; HoT, hypotropia; HT, hypertropia; IO, inferior oblique; IOOA, inferior oblique overaction; IR, inferior rectus; MR, medial rectus; OD, right eye; OS, left eye; OU, both eyes; RD, retinal detachment; TAO, thyroid-associated orbitopathy; SOP, superior oblique palsy; SR, superior rectus; VR, vitreoretinal; XT, exotropia.

†Pre-and postoperative cyclotorsions were measured with the subjective double Maddox rod test and were the main factor determining the surgical markings. Positive numbers indicate excyclotorsion and negative numbers incyclotorsion.

‡The pre-and postoperative DFA was calculated using the online software Cyclocheck and used to confirm the subjective torsion measured.

§The difference between the pre-and postoperative DMR sum of the right and left eye was calculated to represent overall correction.

¶The difference between the pre-and postoperative DFA sum of the right and left eye was calculated to represent overall correction.

*Patient 1 had multiple surgeries and was presented in detail in the text.

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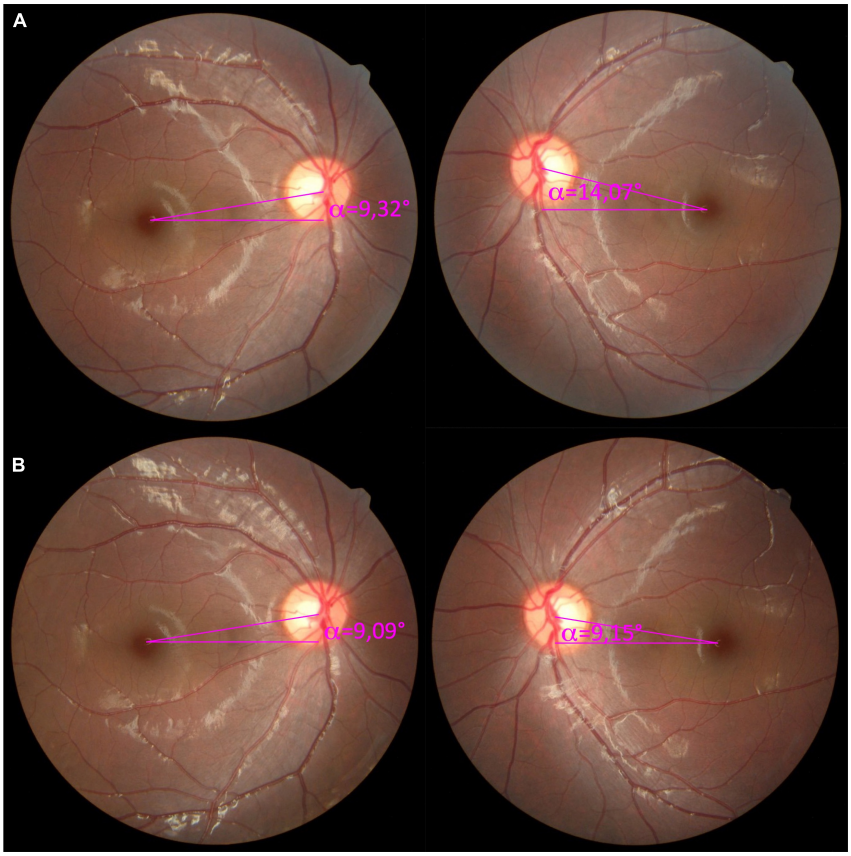

FIGURE 2
Pre- and postoperative color fundus photographs for Patient 15. **(A)** The preoperative color fundus revealed a disc-fovea angle (DFA) of 9.32° in the right eye and 14.07° in the left eye, with 5° of excyclotorsion in the left eye measured with the double Maddox rod (DMR) test. **(B)** At the postoperative 3-month follow-up, the DFA was 9.09° in the right eye and 9.15° in the left eye with no subjective torsion at the DMR test.

in the primary position with 1° subjective incyclotorsion in the right eye, with an incomitant esotropia and left hypotropia on downward gaze.

Patient 1 was a 49-year-old woman who suffered from intraoperative bleeding during endoscopic transnasal transphenoid removal of an invasive pituitary macroadenoma with clival involvement 5 years earlier. Postoperatively, the patient experienced a bilateral asymmetric oculomotor nerve palsy with secondary strabismus. Multiple strabismus surgeries were attempted to treat the different aspects of the ever-evolving secondary strabismus, from a marked exotropia to a consecutive esotropia, with evident right hypotropia, and a significant 40° incyclotorsion due to secondary SO overaction. However, previous attempts failed to correct the debilitating symptomatic cyclodiplopia. The patient was then referred to Dr. Chien with a constant right esotropia, hypotropia, and significant incyclotorsion measuring 27° on DMR testing and −20.54° DFA on the color fundus photographs (Figure 4A). Owing to the severe conjunctival scarring, the surgical plan was devised after meticulous dissection of the conjunctival scar tissue. Scarred muscle and scar tissue complexes were identified on the eyeball at several attachment sites and detached, then secured with 6-0 Vicryl (Ethicon, Raritan, NJ, USA) for adjustment. The surgical torsion markings were targeted for an excyclotorsion effect of 30°, marked clockwise above the horizontal reference line. Eventually, a transposition of the medial rectus muscle to the lateral side of the original inferior rectus muscle insertion was performed, with transposition of the inferior rectus muscle to the inferior side of the lateral rectus muscle. The 1-month postoperative result was temporarily satisfactory with 3° of incyclotorsion on DMR testing and −1.17° of DFA (Figure 4B). Unfortunately, after 5 months, the incyclotorsion increased to 10° on DMR testing with −5.00° DFA (Figure 4C). A second operation with transposition of the superior and lateral rectus muscle insertion was performed to correct the residual torsion. The intraoperative torsion correction was targeted to 10° excyclotorsion effect using the proposed surgical torsion marking system; however, due to the poor muscle tone and severe scarring noticed intraoperatively, the outcome was unsatisfactory, with a residual 5-10° incyclotorsion on DMR testing and −1.04° to −2.09° DFA (Figures 4D–F). After 3 months we attempted another reoperation. The residual

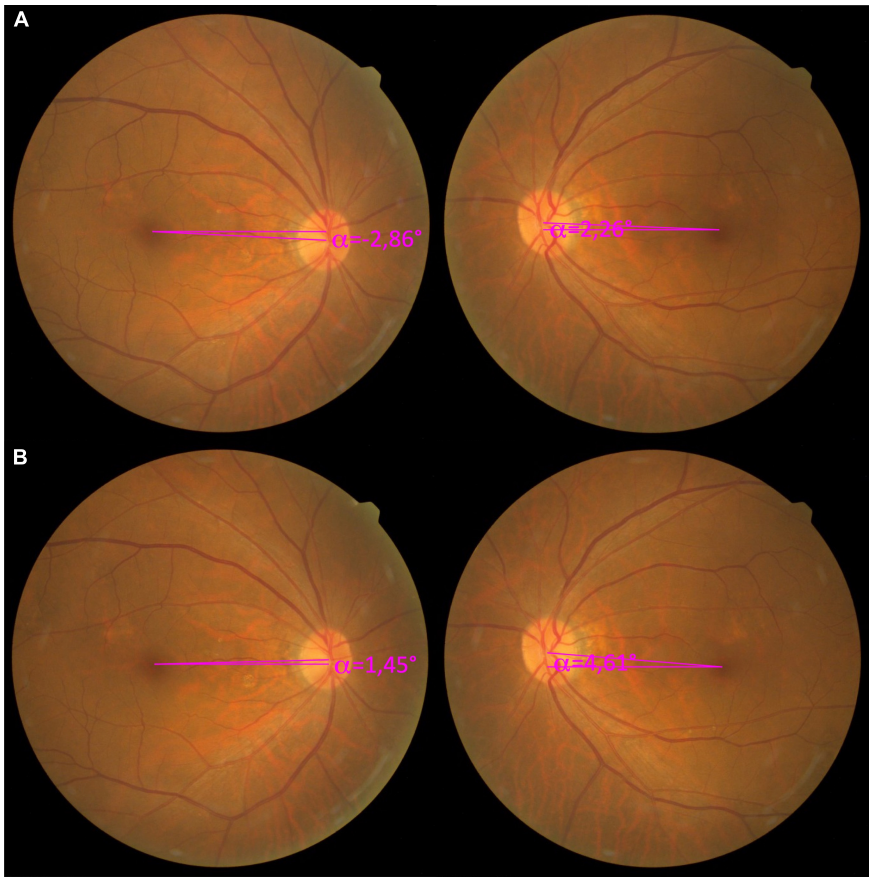

FIGURE 3
Pre- and postoperative color fundus photography of Patient 9, with a right superior rectus muscle hypertrophy due to idiopathic orbital inflammation. **(A)** The preoperative color fundus photograph showed a relatively small disc-fovea angle (DFA) in both eyes with an easily missed incyclotorsion of the right eye, with a −2.86° DFA, and a 2.26° DFA in the left eye. However, the subjective net incyclotorsion was 8° measured by the double Maddox rod (DMR) test. **(B)** The 3-month follow-up fundus photograph showed a net reduction of 4.31° excyclotorsional effect from the superior rectus recession, with the right DFA being 1.45° and the left DFA 4.61°.

muscles and scar tissues were temporarily fixated and adjusted solely based on the effect that could align the surgical torsion markings to the external horizontal markings. The primary surgical aim to correct the symptomatic cyclodiplopia and treat the residual horizontal and vertical strabismus using a prism was achieved. The patient had no residual cyclodiplopia one month postoperatively (Figure 4G). At the 5-month follow-up, the patient had a 4° incyclotorsion on DMR testing and 0.40° DFA, with constant right esotropia and hypotropia corrected by prism (Figure 4H). The patient was symptom-free with fusion and satisfied with the surgical outcome.

4. Discussion

We presented a simple marking system to monitor and adjust the torsional effect with ease while treating cyclodeviation during strabismus surgery. The proposed marking system does not require specific additional tools in the operating room, only a marking pen and toric marking devices for routine astigmatic correction. The markings are drawn in three parts: first, a cutaneous horizontal marking for external reference; then, an ocular horizontal marking to indicate the supine torsional effect and guide to mark for the predetermined surgical correction; and finally, a surgical torsion marking showing the required torsional correction. The proposed marking system follows a sequence of simple steps to ensure accuracy and consistency and can be applied to all types of cyclotropia and implemented in any procedure to correct, assess, or monitor the surgical torsional effect. Using this marking system during the correction of cyclotorsion strabismus, we demonstrated an overall mean absolute net 9.8° (4.8°) subjective cyclotorsion correction, achieving satisfactory results of an average of net DMR 0.2° (2.1°) postoperatively.

The success of a cyclotorsion correction is determined by the preoperative assessment and the surgery itself. Hence, an adequate and accurate cyclotorsion quantification is paramount.

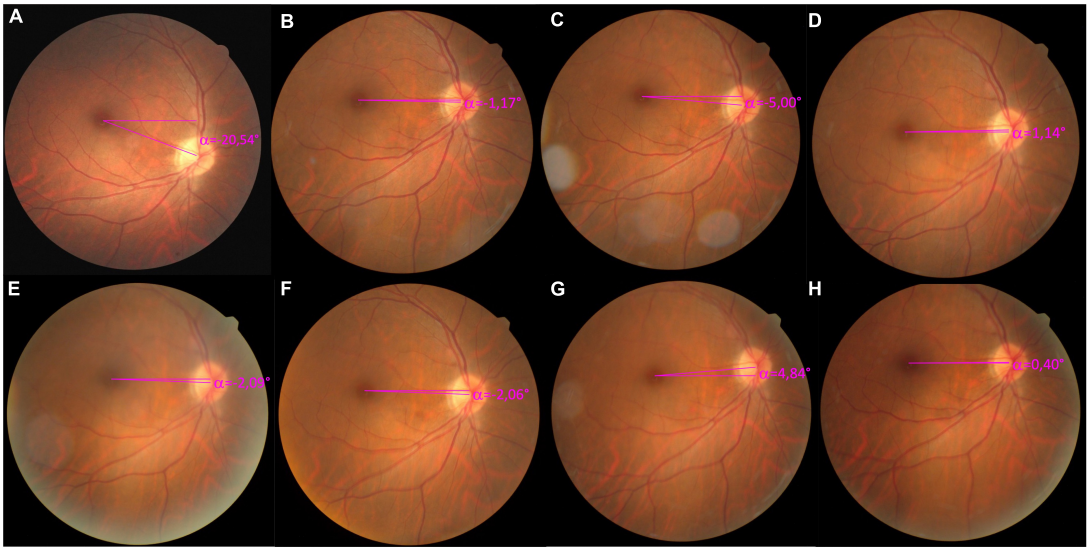

FIGURE 4
Serial objective cyclotorsion changes of the right eye for Patient 1 depicted by color fundus photography. **(A)** Photograph acquired before the first attempted surgery with the proposed marking system, with 27° of incyclotorsion measured with the double Maddox rod (DMR) test and a −20.54° of disc-fovea angle (DFA). **(B)** The 1-month postoperative results of the first surgery showed a marked improvement with the DMR test showing 3° of incyclotorsion and a markedly reduced DFA (−1.17°). **(C)** Five months after the first reoperation, a residual subjective incyclotorsion of 10° with a −5° DFA was noted. A second surgical procedure was then performed. **(D)** One month after the second surgery. **(E)** Two months after the second surgery. **(F)** Three months after the second surgery, a residual of 10° incyclotorsion measured with the DMR test was noted. A third procedure of scar revision and transposition of scar and residual muscle was performed to correct the torsion. **(G)** One month after the fifth reoperation. **(H)** Five months after the fifth reoperation. The DMR test revealed a 4° of incyclotorsion and the DFA was 0.40°.

Cyclotorsion measurement includes objective and subjective methods. Objective methods measure the anatomical torsion, defined as the position of the fovea relative to the optic disc, classically quantified using the nominal Guyton's grading system with an indirect ophthalmoscope or fundus photography (34). Other techniques involve using the retinal vascular arcades (35), retinal temporal raphe (36), iris recognition (37, 38), and scleral blood vessels (39). A more accurate numerical measurement most accepted by clinicians, the DFA, is defined as the angle between a horizontal line and a line drawn through the fovea and the center of the optic disc. The DFA can be measured using fundus photography (40, 41), perimetry (42), scanning laser ophthalmoscopy (43), or optical coherence tomography (44, 45). Anatomic variations of the DFA in normal subjects can range from −0.4° to 12.76°, with a mean of 6.39° (2.72°), and the angle is typically slightly larger in the left than in the right eye (46). Furthermore, because of sensory adaptation, ocular dominance, anomalous retinal response, and other mechanisms, the objective measurement may differ from the subjective torsional perception (19, 47, 48).

Subjective methods to measure cyclotorsion include the Bagolini striated lens test (49), single (50) and double Maddox rod (DMR) test (32), synoptophore test (51), and Lancaster red-green test (52). However, these methods have different procedural protocols and may yield different results (53, 54). Furthermore, while subjective cyclotorsion in healthy subjects is relatively low, around 1° of excyclotorsion, the cyclofusional amplitude can range from 7° of incyclotorsion to 9° of excyclotorsion (55). Hence, the motor-defective cyclovergence accounting for the symptomatic cyclodisparity should be the main treatment target when determining the degree of surgical correction required to alleviate the cyclodiplopia since the intended corrective influence of a stress-lessened cyclofusion and other sensory neuroadaptation mechanisms are usually still active. Accordingly, the subjective DMR test was chosen in our study as the main tool for treatment assessment for its reliability and repeatability, low cost, wide availability, and dissociative nature (32).

Cyclotorsion correctional surgery is not a standardized procedure and is usually planned based on the individual's cyclovertical manifestation and the surgeon's preference. Surgery usually warrants some modifications or adjustments to the individual anatomy or pathology to achieve a satisfactory result. The most common approach is to adopt an adjustable suture technique and adjust the correction postoperatively within a day based on a subjective measure, such as a DMR test (28, 29). Intraoperative one-stage adjustment under topical anesthesia had been proposed by Xie et al. achieved positive results (31); however, this approach is challenging in children or uncooperative adult patients. Furthermore, the patient is usually required to be in an upright position for the subjective measurement either under local anesthesia or general

anesthesia with an intraoperative awake phase (56), which poses additional challenges.

Hence, as strabismus surgery is usually performed under general anesthesia, intraoperative adjustments must be monitored using objective methods, namely, observation of the fundus torsion using an indirect ophthalmoscope (24, 27). However, this presents some challenges. First, intraoperative fundus rotation evaluation is a subjective skill requiring considerable surgical experience, with differences among surgeons. Second, a relative head tilt of the patient or surgeon while performing the indirect ophthalmoscopy would complicate the assessment (57). Moreover, the supine position in general anesthesia induces 5° or more postural cyclotorsion in either direction in over 40% of these patients, confounding the results (58, 59). Furthermore, the objective anatomical torsion often differs from the subjective target cyclotropia correction; and lastly, the method used to measure the cyclotorsion should be the same in the assessment process before, during, and after surgery, for consistent results.

Therefore, an intraoperative torsion monitoring method that can be performed under general anesthesia without the deficiencies of the objective indirect ophthalmoscopy, such as the proposed marking system, has great potential. Previous studies proposed using limbal markings at the 12 and 6 o'clock positions in complicated multiple-muscle surgery to monitor the torsional effect, with great success (60, 61). Our proposed method has three sets of markings: an ocular marking placed horizontally with the patient in upright position, which can be adjusted in supine position while alternating fixation in case of posture-induced ocular torsion; an added external horizontal marking on the skin for standard reference, together with the ocular marking serve as the corrective guide for exotropia eye position often seen in deep general anesthesia; and surgical torsion markings, showing the subjective correction required directly on the ocular surface rather than on the fundus. Hence, the surgeon can further quantitatively monitor, assess, and adjust the torsional effect during any procedure with ease and accuracy.

Our study has some limitations. First, the markings may be altered or deleted by scrub solution, intraoperative heme, or other factors. Hence, other techniques using VERION Image Guided System (Alcon Laboratories, Ft. Worth, TX, USA) or other iris recognition systems can be used to adapt this technique to microscope oculars for augmented reality viewing during strabismus surgery (62). Second, in patients with combined large-angle exodeviations or vertical deviations, the two markings on the ocular surface may be difficult to assess under general anesthesia, which resumes both eyes into their resting position farther apart. Hence, the second ocular horizontal reference marking should be drawn carefully, and the patient should be instructed to fixate alternately with each eye looking straight forward while sitting upright and in the supine position before anesthesia. This ensures the accuracy of the ocular horizontal reference as the base for the surgical torsion markings in these significantly deviated eyes. Then, using a new method proposed by Fu et al., the immediate target endpoint at the conclusion of the surgery can be assessed (63). Third, the sample size was relatively small; however, our results demonstrate the utility of the proposed marking system in several clinical scenarios. Further research should involve larger and more diverse groups.

In conclusion, the proposed marking system can be used in all types of strabismus surgery at any age and for any presentation, under local or general anesthesia, allowing the correction of subjective cyclotorsion and posture-induced ocular torsion. This simple system applies basic techniques and modalities to provide quantitative intraoperative assessment and guide adjustments during cyclotorsion correction and can be utilized by all strabismus surgeons at any level of experience.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (No: C202105113) of the Tri-Service General Hospital. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

K-HC: conceptualization, methodology, writing—review and editing, and funding acquisition. L-CL, H-CC, and K-HC: formal analysis and investigation. L-CL: writing—original draft preparation. Y-HC and K-HC: resources and supervision. All authors read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1059790/full#supplementary-material

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