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Short-term effects of ophthalmic topical 0.01% atropine on the ocular surface, pupil size, and subsequent subjective quality of vision in young myopic Chinese adults

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Background: Daily use of low concentrations of atropine is recommended for children undergoing myopia control therapy. While the benefits of controlling myopia progression have been confirmed, the potential unwanted side effects on the ocular surface, pupil size, and quality of vision following the administration of 0.01% atropine have not been investigated.

Objective: This single-arm, self-control study aimed to investigate the short-term effects of 0.01% atropine topical eye drop (He Eye Hospital Co., Ltd., Shenyang, China) on pupil size and subjective quality of vision in participants with myopia. Each 3 mL vial of eye drops contains atropine (0.01%), sodium chloride (0.9%), and benzalkonium chloride (0.005%) in an aqueous solution.

Methods: Thirty-three adults (66 eyes) were recruited for the study. The mean age of the participants recruited for this study was 24.91 ± 3.36 years. This study is registered with ClinicalTrials.gov (NCT06071260). Assessments were performed at baseline and 10 h, 14 h, and 18 h following the administration of 0.01% topical atropine drop (TAD). Mesopic pupil diameter (MPD), photopic pupil diameter (PPD), higher order aberration (HOA), non-invasive tear breakup time (NITBUT), tear meniscus height (TMH), tear film lipid layer (TFLL), and Redness score (RS). Subjective assessments included the quality of vision (QoV) and the ocular surface disease index (OSDI) questionnaires.

Results: Following the use of 0.01% atropine, PPD significantly increased at all the time points ($p < 0.001$); MPD increased significantly at 10 h and 14 h ($p < 0.001$ and $p < 0.05$, respectively). A decrease in TMH and an increase in the OSDI questionnaire scores were observed up to 10 and 14 h, respectively, after using atropine ($p < 0.001$). Glare ($p = 0.004$ at 10 h and $p = 0.003$ at 14 h), blurred vision ($p < 0.0001$ at 10 h and $p = 0.035$ at 14 h), and focusing difficulties ($p < 0.0001$ at 10 h and $p < 0.0001$ at 14 h) were significantly higher at both 10 h and 14 h after using atropine. No significant changes were observed in the HOA, NITBUT, and RS scores (all $p > 0.05$) at all time points.

Conclusion: Decreased TMH, dry eye symptoms, and visual symptoms will likely persist overnight but often diminish within 18h after using 0.01% atropine eye drops.

KEYWORDS

atropine, pupil size, quality of vision, dry eye, OSDI questionnaire

Highlights

- Both subjective and objective signs and symptoms of dry eye were evaluated, and measurements of pupil size and visual quality were taken before and after the use of 0.01% atropine.
- Objective instrumental measurements and subjective questionnaires were used for data collection.
- The sample size was not large enough, and bias may have occurred.
- Lack of corneal fluorescence staining to assess corneal status.
- The present study specifically examined myopic individuals in their youth, rather than children.
- The study assessed short-term immediate changes; a longer-term follow-up study is warranted.

1 Introduction

Myopia has become a global health issue due to its growing prevalence, earlier onset, and progression (1, 2). Myopia progression is significantly linked to eye Axial length (AL) (3–5). Several treatments, including low-concentration topical atropine eye drops, have been reported to significantly slow down axial elongation (6, 7). While the safety and efficacy of topical atropine have been documented to be optimal, adverse events have not been stringently reported by all articles (8–10). As stated by North et al. in 1987, there are a myriad of adverse effects (AEs) related to topical administration of atropine (11).

Furthermore, the effect of atropine on the progression of myopia is proportional to its concentration, with greater effects and more pronounced side effects, including photophobia, impaired near vision, and increased intraocular pressure (IOP) (12–14). Atropine at 1% concentration is used in clinical practice for pharmacological dilation of the pupil and paralysis of the ciliary muscle (15, 16). The use of low-concentration topical atropine for myopia control in children is linked to certain ocular AEs, such as mydriasis, photophobia, and reduced accommodation. These effects may manifest as symptoms of glare and blur, specifically during activities involving close visual work (17, 18). Though typically of a mild nature, subjective side effects have the potential to impede academic and outdoor pursuits, thus serving as a notable factor contributing to the discontinuation of treatment.

Polling et al. documented that the most negative occurrences were photophobia (72%), followed by difficulties with reading (38%), and headaches (22%) when 0.5% atropine was used to treat myopic children (19, 20). In contrast, side effects such as photophobia can be resolved by outdoor use of sunglasses in children (15, 21). On the other hand, reports suggest that 0.01% atropine had no significant AEs on contrast sensitivity in myopic adults (22). As daily use of low concentrations of atropine is recommended for children undergoing myopia control therapy,

there is concern about the potential development of dry eye with prolonged atropine administration (23, 24). Therefore, the current study is intended to assess the short-term changes in ocular surface parameters, pupil size, and quality of vision in young adults treated with 0.01% concentration of atropine.

2 Methods

2.1 Study design and participants

This investigation was conducted under the supervision of the Institutional Review Committee of He Eye Hospital in Shenyang, China, as per the Declaration of Helsinki (approval number: IRB (2022) K011.01) and registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT06071260). After thoroughly explaining the nature of the study and its potential repercussions, written consent was obtained from every participant. Participants' information was collected between 1 December 2023 to 20 December 2023. Thirty-three adults (66 eyes) were recruited for the study. All the participants met the following inclusion and exclusion criteria.

Inclusion criteria comprised the following: (i) participants who provided consent; (ii) age ≥ 18 years old; (iii) IOP between 10 and 21 mmHg; (iv) refractive error < -6.00 diopter (D) and astigmatism ≤ 1.50 D; and (v) best-corrected visual acuity (BCVA) of 20/20 or above. Exclusion criteria: (i) any keratopathy, fundus lesion; (ii) strabismus, amblyopia, or eye muscle dysfunction caused by any reason; (iii) previous eye surgery; (iv) refusal to use topical 0.01% atropine eye drop; (v) exposure to any ocular drug within the past 30 days; (vi) allergic to atropine; and (vii) inability to follow the examiner's request.

2.2 Patients and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

2.3 Experimental design

This single-arm self-control study assessed participants before and after administering one drop of 0.01% atropine in each eye. Each 3 mL vial of eye drops contains atropine (0.01%), sodium chloride (0.9%), and benzalkonium chloride (0.005%) in an aqueous solution. On day 1, baseline measurements were assessed by a trained clinician; participants were sent back with a bottle of 0.01% topical atropine drop (TAD) and instructed to put one drop in each eye and mark the time on their diary. On day 2 (the following day), 10h, 14h, and 18h following the use of 0.01% TAD, subjective and objective tests were performed by a trained clinician (Figure 1).

2.4 Assessments

The OPD Scan III assessed all mesopic pupil diameter (MPD), photopic pupil diameter (PPD), and higher order aberration (HOA) by the same ophthalmologist in the same dark room setting (0.63 lux) (14). All the participants were required to stay in the darkroom for at least 5 min to adapt to the dark condition before the examination. Then, the test was performed 3 times, and the mean value was recorded (25, 26).

The Keratograph 5M Topographer (OCULUS, Germany) assessed the tear film stability. Parameters of the ocular surface included non-invasive tear breakup time (NITBUT), tear meniscus height (TMH), and RS (redness score) (27, 28).

The quality of vision (QOV) questionnaire consists of (i) symptom frequency, (ii) severity, and (iii) bothersomeness for (a) glare, (b) halo, (c) starbursts, (d) hazy vision, (e) blurred vision, (f) distortion, (g) multiple images, (h) visual fluctuations, (i) difficulty focusing, and (j) difficulty judging distance or depth perception. Respondents use a scale of 0 to 3, where zero (0) denotes “none,” one (1) “a little,” two (2) “quite a bit,” and three (3) “very much.” Furthermore, on a scale from 0 to 10, patients were asked to provide Likert ratings for “daytime” and “nighttime” quality of vision (0 denoting the poorest vision, while 10 indicating the best vision) (29, 30).

The ocular surface disease index (OSDI) questionnaire is widely used to assess the dry eye symptoms of participants. It includes 12 items, divided into three parts (items 1–5 refer to ocular pain and visual difficulties; items 6–9 are about visual functionality; and items 10–12 assess environmental factors). The total OSDI score can range from 0 to 100, with the higher score indicative of worse symptoms of dry eye (31).

2.5 Statistical analysis

Statistical Package for Social Sciences (SPSS, version 26, IBM Corp, United States) for macOS software was used to analyze the data. Shapiro–Wilk tests were performed to determine whether the data were normally distributed. A chi-square test was performed on the counting data, and a repeated-measures analysis of variance (ANOVA) was used to evaluate changes before and after medication. An analysis was performed between before treatment and after treatment. A *p*-value of <0.05 was considered statistically significant.

3 Results

3.1 Patient characteristics

Table 1 displays the demographic characteristics of the study participants. The mean standard deviation (SD) age of the 33 participants (22 women and 11 men) was 24.91 ± 3.36 (range: 21 to 35 years), mean spherical equivalent were −3.78 ± 2.33 diopters, mean cylinders were −0.72 ± 0.7 diopters, and the BCVA was 1 ± 0.03 (decimal notation).

3.2 Objective parameter index

Table 2 displays the PPD at baseline was 4.78 ± 0.75 mm, and following the administration of 0.01% atropine, PPD was found to

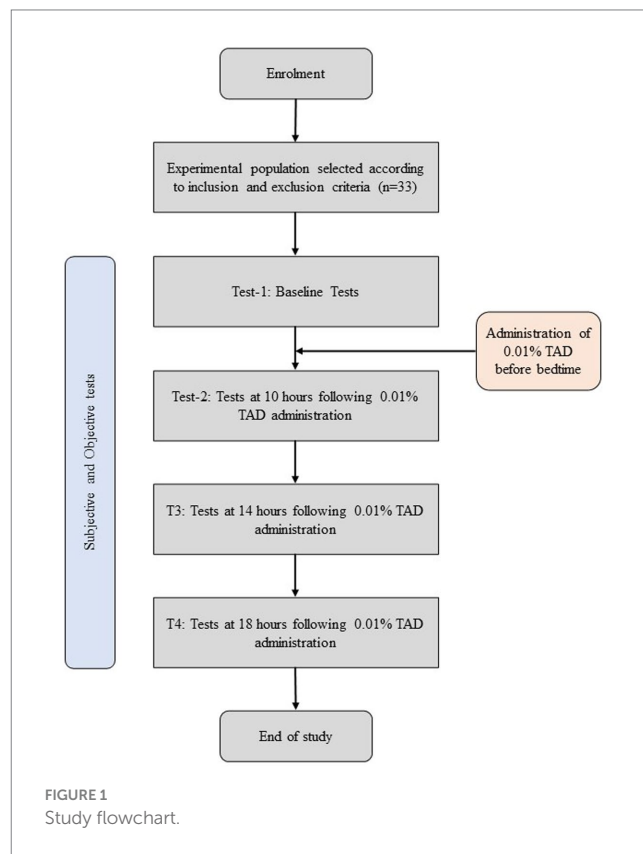


TABLE 1 Demographic characteristics of participants in the study.

Variable	
Sex, female (%)	22 (66.7%)
Age, mean ± SD (years)	24.91 ± 3.36
BCVA (Decimal notation)	1.0 ± 0.03
SE	−3.78 ± 2.33
C	−0.72 ± 0.7

SD, standard deviation; BCVA, best-corrected visual acuity; SE, spherical equivalent; C, cylinder.

be 5.83 ± 0.88 mm (*p* < 0.001) at 10 h, 5.52 ± 0.86 mm (*p* < 0.001) at 14 h, and 5.12 ± 0.91 mm (*p* < 0.005) at 18 h and were all significantly larger than baseline measurements. The MPD at baseline was 6.72 ± 0.81 mm. After administration of 0.01% atropine, the PPD was 7.25 ± 0.74 mm (*p* < 0.001) at 10 h, 7.02 ± 0.92 mm (*p* < 0.005) at 14 h, and 6.87 ± 0.80 mm (*p* < 0.244) at 18 h. Measurements at 10 h and 14 h were significantly larger than the baseline measurements (Table 2).

HOA at baseline was found to be 2.65 ± 2.36 μm and remained significantly (*p* > 0.05) unchanged at 10 h (2.42 ± 1.23 μm), 14 h (2.44 ± 1.19 μm), and 18 h (2.38 ± 1.17 μm). First NITBUT at baseline was 9.47 ± 5.9 s, 8.14 ± 6.27 s at 10 h, 8.75 ± 7.18 at 14 h, and 8.31 ± 5.90 s at 18 h. While a decreasing trend was found in the first NITBUT measurements following the use of atropine, all changes were not statistically significant compared to the baseline measurements (*p* > 0.05). Average NITBUT at baseline was 14.14 ± 12.07 s, 10.50 ± 6.31 s at 10 h, 10.88 ± 5.48 at 14 h, and 10.95 ± 6.09 s at 18 h. Similar to the first NITBUT, all changes were not statistically significant when compared

to the baseline measurements ($p > 0.05$). TMH at baseline, at 10h, 14h, and 18h was recorded to be 0.20 ± 0.07 mm, 0.17 ± 0.05 mm, 0.17 ± 0.05 mm, and 0.18 ± 0.05 mm, respectively. Statistically significant differences were found when comparing the baseline with 10h ($p = 0.007$) and the baseline with 14h ($p = 0.002$). Finally, we compared the variations in RS prior to and following the use of eye drops and found no significant difference ($p > 0.05$) (Table 2).

3.3 Subjective parameter index

In the QOV questionnaire, there was a statistically significant difference between patients before and 10h and 14h after receiving 0.01% atropine ($p < 0.001$, $p = 0.003$). After 18h, there was no significant difference ($p = 1.00$) (Table 3).

We then evaluated the prevalence, severity, and impact of specific visual phenomena prior to and following atropine administration. The results for the symptoms reported by patients 10h and 14h after atropine use differed significantly from those reported before atropine use: glare ($p = 0.004$ 10h and $p = 0.003$ 14h), blurred vision ($p < 0.0001$ 10h and $p = 0.035$ at 14h), and focusing

difficulties ($p < 0.0001$ 10h and $p < 0.0001$ 14h). Additionally, there were significant differences in hazy vision and vision fluctuation before and 10h after atropine use ($p = 0.003$ and $p = 0.023$, respectively) (Table 3; Supplementary Figure S1).

In order to assess the change in subjective dry eye symptoms before and after the use of 0.01% atropine eye drops, the OSDI questionnaire was administered at baseline, after 10h, 14h, and 18h. According to the findings (Table 4), there was a statistically significant difference between 0.01% atropine 10h after usage and before use ($p < 0.001$).

4 Discussion

This study aimed to examine the immediate impact of administering 0.01% atropine drops on both the ocular surface and visual quality. The findings indicate that a single dose (one drop in each eye) of 0.01% atropine had a discernible impact on the ocular surface and quality of vision in adult patients with myopia that lasted overnight and returned to initial values after 18h. While there is no notable disparity in the impact on the NITUBT and RS scores. The study observed a significant rise in dry eye symptoms, particularly within 8h of dosing. However,

TABLE 2 Characteristics of participants at baseline and after using 0.01% atropine.

Groups		Test 1 (Baseline)	Test 2 (10 h)	p-value ¹	Test 3 (14 h)	p-value ²	Test 4 (18 h)	p-value ³
Pupil size	Photopic	4.78 ± 0.75	5.83 ± 0.88	0.0001**	5.52 ± 0.86	0.0001**	5.12 ± 0.91	0.005**
	Mesopic	6.72 ± 0.81	7.25 ± 0.74	0.0001*	7.02 ± 0.92	0.05*	6.87 ± 0.80	0.244
HOA		2.65 ± 2.36	2.42 ± 1.23	0.952	2.44 ± 1.19	0.941	2.38 ± 1.17	0.897
NITBUT-F		9.47 ± 5.9	8.14 ± 6.27	0.586	8.75 ± 7.18	0.976	8.31 ± 5.90	0.621
NITBUT-A		14.14 ± 12.07	10.50 ± 6.31	0.144	10.88 ± 5.48	0.204	10.95 ± 6.09	0.252
TMH		0.20 ± 0.07	0.17 ± 0.05	0.007*	0.17 ± 0.05	0.002*	0.18 ± 0.05	0.198
RS		1.00 ± 0.26	1.05 ± 0.37	0.747	1.18 ± 0.83	0.378	1.06 ± 0.27	0.211

* $p < 0.05$, ** $p < 0.001$. Test 1: baseline tests; Test 2: tests after 10h; Test 3: tests after 14h; Test 4: tests after 18h. HOA, higher order aberration; NITBUT-F, first non-invasive breakup time; NITBUT-A, average non-invasive breakup time; TMH, tear meniscus height; RS, redness score.

TABLE 3 Characteristics of participants at baseline and after using 0.01% atropine.

Groups	Test 1 (Baseline)	Test 2 (10 h)	p ¹	Test 3 (14 h)	p ²	Test 4 (18 h)	p ³
Glare	0.52 ± 1.06	1.55 ± 2.42	0.004*	1.33 ± 2.10	0.003*	0.70 ± 1.23	0.744
Halo	0.21 ± 0.73	0.36 ± 1.05	0.932	0.15 ± 0.56	0.996	0.12 ± 0.54	0.967
Starbursts	0.39 ± 1.14	0.64 ± 1.57	0.801	0.45 ± 1.19	0.999	0.30 ± 1.01	0.976
Hazy	0.79 ± 1.03	1.94 ± 2.61	0.003*	1.27 ± 1.74	0.085	0.64 ± 1.19	0.888
Blurred	0.97 ± 1.30	2.33 ± 2.57	0.0001**	1.64 ± 1.94	0.035*	1.09 ± 1.41	0.965
Distortion	0.00 ± 0.00	0.12 ± 0.69	0.646	0.00 ± 0.00	-	0.00 ± 0.00	-
Multiple vision	0.39 ± 0.89	0.73 ± 1.41	0.244	0.24 ± 0.61	0.799	0.30 ± 0.76	0.980
Fluctuation	0.27 ± 0.76	0.64 ± 1.21	0.023*	0.36 ± 0.812	0.943	0.18 ± 0.52	0.857
Focusing difficulties	0.55 ± 1.03	2.55 ± 2.38	0.0001**	1.58 ± 1.67	0.0001**	0.91 ± 1.58	0.479
Depth perception	0.00 ± 0.00	0.15 ± 0.61	0.261	0.06 ± 0.35	0.646	0.00 ± 0.00	-
Day	9.03 ± 1.00	7.52 ± 2.35	-	8.27 ± 1.43	-	8.55 ± 1.51	-
Night	8.67 ± 1.00	-	-	-	-	-	-

* $p < 0.05$, ** $p < 0.001$. Test 1: baseline tests; Test 2: tests after 10h; Test 3: tests after 14h; Test 4: tests after 18h. P1, p-value for Baseline vs. 10h; P2, p-value for baseline vs. 14h; P3, p-value for baseline vs. 18h.

TABLE 4 OSDI questionnaire scores at different time.

Groups	Overall score
Test 1 (Baseline)	11.21 ± 11.52
Test 2 (10h)	27.41 ± 21.11
<i>p</i> -value ¹	0.0001**
Test 3 (14h)	19.58 ± 16.97
<i>p</i> -value ²	0.001**
Test 4 (18h)	13.04 ± 11.90
<i>p</i> -value ³	0.667

* $p < 0.05$, ** $p < 0.001$. Test 1: baseline tests; Test 2: tests after 10 h; Test 3: tests after 14 h; Test 4: tests after 18 h.

these symptoms returned to their initial levels after 18 h. Moreover, the size of the pupil (in both the presence of light and darkness) showed a significant increase. In particular, even after 18 h, the pupil size in the presence of light remained significantly different from the initial measurement. The symptoms of QOV, including difficulty in focusing, glare, and blurred vision, remained for a duration of 14 h and thereafter faded after 18 h. The symptoms of hazy vision and fluctuation in vision persisted for a duration of 8 h.

The use of topical 0.01% atropine eye drops in clinical practice primarily focuses on mitigating the progression of myopia (22, 32–35). Studies have successfully demonstrated the efficacy of atropine impeding the AL growth in myopic children (36, 37). While the endpoint goals of such studies typically focus on monitoring AL growth and visual acuity, they often do not specifically assess the subjective quality of vision and dry eye symptoms. Although some studies have reported complications or AEs such as photophobia, blurred near vision, eye irritation/discomfort, allergic reactions, headache, stye/chalazion, glare, and dizziness, these are generally characterized as complications or AEs (38).

Currently, there is no definitive conclusion on whether long-term use of atropine in children affects the meibomian glands and tear film, thereby causing dry eye. Animal experiments have shown that 1% atropine eye drops can quickly induce dry eye symptoms in rabbit eyes, this effect is weakened after a few weeks (39). However, the abovementioned articles did not include human subjects nor were ocular surface and visual quality indicators assessed.

Patients typically utilize low-concentration atropine for months or even years for myopia control. The current study only observed the changes in the eye within 1 day of the patient's use. While long-term use is a rational way to validate the effects of low-concentration atropine. Therefore, from the current study, we cannot fully ascertain whether the short-term effects found in this study will persist in real-world settings. According to Luo et al. (40), adult users of 0.01% atropine for 14 days found notable variations between the NITBUT-first and NITBUT-average. On the other hand, the differences receded when the treatment was stopped, which could be related to the low concentration of the atropine eye drop. However, prolonged applications (years) could lead to cumulative or transient effects. Therefore, future studies will aim to assess long-term use and quality of vision changes (41).

The research is limited by the small sample size of the trial and by the fact that data were collected at only one site. The attainment of statistical significance with a limited sample size for both indications and symptoms underscores the importance of the findings (41).

Moreover, the present study specifically examined myopic individuals in their youth, rather than children in general. As a result, these findings cannot be extrapolated to the broader population of children. It is evident that younger individuals may exhibit similar indications and symptoms as adults (42, 43). However, adults are likely to provide a more discerning evaluation of the side effects compared to children. Nevertheless, subsequent investigations will focus on expanding the sample size, including younger individuals, and implementing a randomized controlled approach. Furthermore, formulations with low amounts of atropine commonly include BAK as a preservative. It is important to note that Benzalkonium chloride (BAK) is known to be harmful to the corneal epithelium and has been linked to the development of dry eye syndrome. Several investigations have specifically emphasized the harmful effects of it on the retinal tissue (44, 45). While preservative-free low-dose atropine is commercially not available, future studies will aim to compare preservative-free and BAK low-dose atropine drops (17, 46).

5 Conclusion

The findings in this research support the notion that a low concentration of atropine (0.01%) temporarily impacts both subjective and objective dry eye tests and subjective visual quality. However, these evaluations revert to their original levels approximately 18 h after their application. This finding may suggest how persistent changes to the ocular surface and quality of vision might impact children and adolescents. Ultimately, more investigation and longer follow-up examinations are necessary for myopic patients who undergo long-term therapy with low-concentration atropine.

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 humans were approved by Institutional Review Committee of He Eye Hospital in Shenyang, China. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ML: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. YC: Writing – review & editing, Data curation, Formal analysis. JC: Methodology, Project administration, Validation, Visualization, Writing – review & editing. GQ: Formal analysis, Methodology, Project administration, Writing – review & editing. LL: Formal analysis, Software, Visualization, Writing – review & editing. WH: Funding acquisition, Project

administration, Supervision, Writing – review & editing. SY: Writing – review & editing. XH: Visualization, Writing – review & editing. EP: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LX: Funding acquisition, Project administration, Resources, Supervision, Writing – review & editing.

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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.2024.1436551/full#supplementary-material>

SUPPLEMENTARY FIGURE S1

Change in QoV questionnaire score at various time points.

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