frontiers | Frontiers in Anesthesiology

TYPE Original Research
PUBLISHED 18 February 2025
DOI 10.3389/fanes.2025.1521409

OPEN ACCESS

EDITED BY
Wael Saasouh,
Wayne State University, United States

REVIEWED BY
Firoozeh Madadi,
Shahid Beheshti University of Medical Sciences, Iran
Raghuraman M. Sethuraman,
Sree Balaji Medical College and Hospital, India

*CORRESPONDENCE
Brian A. Williams
✉ williamsba@anes.upmc.edu;
✉ brian.williams6@va.gov;
✉ williamsba@gmail.com

RECEIVED 01 November 2024
ACCEPTED 23 January 2025
PUBLISHED 18 February 2025

CITATION
Williams BA, Hall DE, Dalessandro C, Garbelotti KE and Ludden JM (2025) Patient-centered intrathecal morphine dose response in major abdominal surgeries when augmented by innovative five-drug antiemetic prophylaxis.
Front. Anesthesiol. 4:1521409.
doi: 10.3389/fanes.2025.1521409

Patient-centered intrathecal morphine dose response in major abdominal surgeries when augmented by innovative five-drug antiemetic prophylaxis

Brian A. Williams[1,2]*, Daniel E. Hall[1,2,3], Chelsee Dalessandro[4], Kelly E. Garbelotti[2] and John M. Ludden[5]

[1]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [2]Surgery Service Line, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, United States, [3]Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States, [4]Department of Pharmacy, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, United States, [5]Medicine Service Line, Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, PA, United States

Background: For abdominal surgery involving cephalad surgical trespass (such as sleeve gastrectomy and pancreatectomy), existing intrathecal morphine (ITM) recommendations of ≤150 μg may not achieve meaningful analgesia, potentially leading to side effects of intravenous opioids during or after surgery. This study aimed to present (i) an ITM dosing guideline to improve upon existing dosing guidelines (≤150 μg) and (ii) an analgesic duration predictor derived from the proposed vs. existing dosing guideline.

Methods: We used a mixed-method multi-hypothetical framework to demonstrate that five-drug antiemetic prophylaxis before spinal morphine administration may allow for ≥250 μg doses, which with further refinement may confer meaningful analgesia, downstream opioid sparing, *and* prevention of nausea/vomiting. A retrospective, case-matched quality improvement initiative was implemented, followed by multiple regression to (i) calculate successful spinal morphine dosing and (ii) predict analgesic duration in our Veteran patient population.

Results: As opposed to the currently recommended dose of ≤150 μg, 250 μg was the start-point for spinal morphine dosing, with adjustments for gender, height, and age. The 250 μg dose (and incremental adjustments) was associated with a 16 h baseline analgesic duration, while the <200 μg dose was associated with only 8 h; the latter analgesic duration (i.e., ≤8 h) was adversely influenced by factors that did not affect the ≥250 μg dose analgesic duration.

Conclusion: We achieved meaningful prophylaxis against nausea/vomiting with the five "keyword" drugs (all five drugs were used in 94% of our patients who received the ≥250 μg morphine dose). This seems to facilitate adherence to oral/enteral non-opioid analgesics after surgery, possibly contributing to analgesic duration. Conversely, *avoidance of usual intraoperative* (fentanyl, remifentanil, hydromorphone) *and postoperative* (hydromorphone, oxycodone,

hydrocodone) *opioids* may have prolonged perceived analgesic duration (and avoided nausea) by preventing opioid-induced hyperalgesia and/or tolerance. We presume that the ≥250 μg morphine dose had sufficient "cephalad reach" for various procedures, including those where endoscopic cases were converted to open. This approach may prevent reflexive intraoperative administration of usual intravenous opioids. Five-drug antiemetic prophylaxis may allow for improved analgesic outcomes and systemic opioid reductions, via patient-based parameters of a spinal morphine dose start-point of at least 250 μg, as opposed to the currently recommended dose of ≤150 μg.

KEYWORDS

palonosetron, perphenazine, aprepitant, diphenhydramine, dexamethasone, intrathecal morphine, postoperative nausea and vomiting

1 Introduction

Professional society guidance and/or consensus statements may not reflect recent innovations or important advances in "repurposing" viable therapeutic options, such as *intrathecal morphine* [ITM (1)]. For example, recommended opioid selection for intraoperative use, in light of the opioid epidemic, may not fully reflect important advances in determining *intravenous methadone* dose response, such as (i) incorporating a "single intraoperative dose that minimized pain and post-anesthesia care unit (PACU) opioid requirement (2)" separately for patients going home the same day (3) vs. those being planned for a 1-day hospital admission (2) and (ii) acknowledging "concentrations … below the minimum effective concentration, (for which) clinical benefit will not ensue, even with slow…elimination." (2) ITM likely shares similar threshold-based dose attributes as IV methadone. Recent professional society ITM dose–response guidance (4) seems to have recommended lower doses/concentrations than would still be meaningfully effective for transabdominal/truncal surgery. Another shared attribute of both IV methadone (2, 3) and ITM (1) is potent emetogenic effects in the absence of recently reported (1) multimodal nausea/vomiting prophylaxis. Avoidance of postoperative nausea/vomiting (PONV) now appears to be a 90%–95% achievable goal [on postoperative days (POD) 0–1 (1)] for patients receiving a five-drug combination regimen administered prior to procedural anesthesia, irrespective of conventional (5) PONV risk determination.

The *hypotheses generated* from this observational manuscript are as follows: (i) ITM (similar to IV methadone) appears to have a threshold dose in adults above which higher-quality analgesia can be achieved, (ii) current published guidelines/recommendations for ITM dosing [100–150 μg (4)] may be insufficient for transabdominal or adjacent surgery, (iii) five-drug PONV prophylaxis presented herein and previously published (1) may have indirect analgesic efficacy by allowing ongoing adherence to an oral/enteral non-opioid analgesic regimen during the ITM's window of efficacy, and (iv) antiemetic momentum may be sustained further into the hospital stay with "booster" dosing after initial pan-prophylaxis against PONV. The objective of this manuscript is to validate these hypotheses as potential guides for short-term practice adjustments. Moreover, our *specific aims* include presenting (i) an easily calculable ITM dosing guideline with likely better cephalad spread than the existing guideline doses (of 100–150 μg) and (ii) an analgesic duration predictor, while formulating long-term research agenda items for hypothesis confirmation and further care advances.

2 Materials and methods

2.1 Ethics approval

This report was an IRB-approved quality improvement initiative and was exempt from patient research consent above and beyond clinical surgery and anesthesia consent. Institutional approval (approval/exemption 1670098-1, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA) allowed for tracking and external reporting of outcome data, entailing general anesthesia (GA)/ITM data and GA (without ITM) case-matched controls.

2.2 External reporting precedents and guidance, patient identification/selection, and data collation

Following STROBE guidelines, we previously disclosed that our five-drug antiemetic prophylaxis was declared as the institutional standard of care for ITM recipients soon after our group's first case series was accepted for publication (which focused on addressing joint replacement surgery under spinal anesthesia including ITM) (6). In our subsequent publication (1), patients who received both ITM and GA were then case-matched as a second cohort as follows. We retrospectively reviewed and prospectively collected quality improvement data from a single US Veterans hospital. Institutional approval enabled our tracking and external reporting of GA patients receiving ITM and GA patients without ITM as case-matched controls. Case matching was based on the type of procedure (including Current Procedure Terminology codes, as applicable), procedure duration, gender, body mass index (BMI), and American Society of Anesthesiologists' Physical Status Classification. Our first (1) case queries included consecutive cases of non-smoking Veterans undergoing bariatric surgery ($n = 26$) and non-consecutive non-bariatric surgery cases ($n = 109$, with different smoking statuses

not tracked in real time). Case-matched historical or concurrent controls of GA cases (1) ($n = 135$ without ITM) were identified and analyzed, entailing cases occurring from 31 May 2016 to 31 August 2022. After these cases were analyzed and reported (1), 5 further retrospective unmatched GA/ITM cases (16 November 2021–11 July 2022) and 89 further prospective GA/ITM cases (9 September 2022–14 June 2023, unmatched) were added to the data pool to enhance outcome transparency; the latter 89 cases routinely included (i) antiemetic booster dosing (detailed later) and (ii) postoperative oral non-opioid analgesics such as acetaminophen, a COX-2 inhibitor, and dextromethorphan (7). Overall, 94 cases were incorporated and analyzed into the previously (1) published dataset for this current report.

2.3 Anesthesia procedure

All ITM doses were diluted in 2.5–3.0 ml of sterile water at the time of the procedure, instead of the previous uncited guidance (4) restricting intrathecal injectate to <2 ml volume [possibly driven (4) by concerns of co-administered local anesthetic and "high spinal"]. The ITM procedures in the present report were performed in a monitored block room, as previously reported (8, 9). Analgesic durations from the ITM procedures were determined from electronic medical records using methods previously reported (10–13). Hands-on anesthesia providers and/or attending anesthesiologists in the operating room were asked to not administer IV opioids (fentanyl, remifentanil, hydromorphone) during surgery when ITM was used, but this request was neither enforced nor enforceable. The presence and absence of such doses were tracked and analyzed.

2.4 Setting and participants, study size, and bias

The setting was a single US Veterans hospital, with matched cases having occurred no earlier than 31 May 2016 and prospective cases having occurred no later than 14 June 2023. All patients whose data were reviewed were either known in advance of surgery to be admitted to the hospital after surgery or were already hospitalized inpatients presenting for surgery. All prospective patients were ITM recipients. In other words, patients who refused the ITM procedure were not included in any data analysis (i.e., no one who refused the ITM procedure was analyzed as a "case–control"). The total case number reached was a convenience sample with no *a priori* power calculations. The absence of a further query of 94 additional control cases was related to no available further research support. No further efforts were made to address potential sources of bias other than those listed above.

2.5 Quantitative variables, and statistical methods

As reported (1, 6), the chief distinction in categorizing PONV prophylaxis was having received five categories of the described antiemetics, or less than five. The five antiemetics were perphenazine (as antidopaminergic), diphenhydramine (an antihistamine), dexamethasone, aprepitant (as neurokinin-1 antagonist), and either palonosetron or a minimum of 8 mg ondansetron (as 5-hydroxytryptamine type 3 antagonist). For the 89 latest (unmatched) cases (September 2022–June 2023), (i) palonosetron was exclusively used (not ondansetron) for prophylaxis, and (ii) all five prophylaxis drugs were given before patients were transported to the operating room.

Supplemental data (Supplementary Tables S1–S6) are serially presented as descriptive statistics and multivariable regression analyses, modeled to address this manuscript's objectives related to (i) ITM dose–response observations, (ii) verification of the potential value of the five-drug PONV prophylaxis, and (iii) augmentation of non-opioid analgesic-associated success, while putting forth efforts to avoid parenteral/oral opioids downstream from the ≥250 μg ITM dose, which is acknowledged as higher than currently (4) recommended (Table 1). Multivariable analyses were utilized to adjust for potential confounders driven by clinical judgment, to develop and strengthen the dose calculator and analgesic duration regression models, and to identify potentially independent associated predictors of outcome (for future research).

For the dose calculator, only ITM doses of >200 μg ($n = 166$) were incorporated into the model, while for the analgesic duration predictor, two separate duration models were created for >200 μg ($n = 166$) vs. ≤200 mcg ($n = 59$). For the described multivariable linear regression models, the variables considered were those listed in Supplementary Tables S1–S6. No sensitivity analyses were performed. All statistical analyses utilized IBM SPSS statistical software (version 29, IBM Corporation, Armonk, NY, USA).

2.6 Anatomic rationale for ITM dosing increase above existing recommendations

Acknowledging the detailed clinical factors presented in the Supplementary Material, the *specific aim* of this manuscript is to incorporate the described Supplementary Material findings into (i) a practical ITM dose calculator for transabdominal/truncal surgery and (ii) an analgesic ITM duration predictor model for the institution of origin, which could be applied and modified as needed for other patient populations. Both of these models, when implemented into practice, may offset the disadvantages of existing (4) ITM dose guidelines (of only 100–150 μg) that may render patients as undertreated, until further confirmatory or refinement studies are available. The present authors' disagreement with the 100–150 μg recommendation of Gustafsson et al. (2019) is further based on long-established (2008) ITM work in joint replacement orthopedic surgery which declared 200 μg as an optimal dose for knee replacement surgery (14), providing comparable knee analgesia as 300 μg ITM and superior analgesia over 100 μg ITM. Knee arthroplasty analgesia entails the L1–S3 nerve distribution and an intrathecal insertion typically at L2 or caudad. Anatomically,

TABLE 1 Potential effects of (i) intrathecal morphine (ITM), (ii) potentially synergistic five-drug PONV prophylaxis, and (iii) potentially antagonistic (i.e., *net hyperalgesic*) intravenous opioids given during GA, *when ITM is present at a ≥250 μg minimum dose*.

Paradigm challenge: An ample ITM dose [2–3 times above recent (4) recommendations of 100–150 μg] on "Day 0" may be more useful for providing opioid-sparing analgesic duration into POD 1, with no apparent POD 1 PONV burden in the setting of co-administered five-drug PONV prophylaxis with palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone.
Supplementary Table S1 addresses only bariatric cases ($n = 95$) with or without ITM, to better standardize ITM dose–response interpretations (with bariatric procedures primarily entailing upper abdominal endoscopic surgery, and not open procedures). Significant *factors predicting associated analgesic duration* included (i) whether ITM was used (16 h analgesic benefit, using linear regression, $P < 0.001$) and (ii) *no IV opioids at any time on the day of surgery* (additional 9 h, independent associated analgesic benefit, $P < 0.02$). Non-significant factors regarding analgesic duration that were analyzed (which may have been underpowered) included gender, length of surgery, five-drug PONV prophylaxis, BMI, sleeve gastrectomy (vs. Roux-en-Y gastric bypass), ITM dose above a 200 μg threshold, diabetes, volatile agents having been used, propofol having been used, and patient on baseline opioids before surgery.
Supplementary Table S2 addresses all recorded ITM cases ($n = 225$, therefore excluding non-ITM transabdominal cases) under GA to address either factors or potential statistical signals (2) that may be considered in future studies of dose response for *analgesic duration after ITM*. A significant factor reliably predicting associated analgesic duration was age (particularly, with each year over 70 predicting longer duration, using linear regression), while many signals were encountered warranting future study. These signals ($P \leq 0.1$) were (i) the *use of no IV opioids during or after surgery*, (ii) the use of five-drug PONV prophylaxis, and (iii) each ~25 μg increment above a 200 μg ITM threshold dose (all being favorable-contributing signals), *while baseline preoperative opioid use was an unfavorable contributing signal related to analgesic duration after ITM.*
Supplementary Table S3 addresses all recorded ITM cases ($n = 225$) of differing kinds of transabdominal surgery under GA, to address either factors or potential statistical signals that may be considered in future studies of ITM dose response and its effect on any *IV opioid dosing requirement* (yes/no, logistic regression) *after OR exit*. This table separately lists results for day of surgery, POD 1, and combined POD 0–1. For the latter (POD 0–1) time window, potentially important signals ($P < 0.05$) for future study of higher IV opioid requirements appear to be (i) any baseline opioid consumption, (ii) higher BMI, (iii) open (vs. laparoscopic) surgery, and (iv) *intraoperative fentanyl, remifentanil, or hydromorphone use.* Another potential adverse signal ($P < 0.1$) was the use of a volatile agent. *Note that* Supplementary Tables S1–S3 *each show an unwanted association of usual intraoperative opioids (fentanyl, remifentanil, and/or hydromorphone) with (i) adverse effects on ITM analgesic duration (i.e., shorter duration, or absence of duration prolongation), and (ii) higher opioid requirements despite the use of ITM.*
Supplementary Table S4 addresses only bariatric cases with ITM ($n = 58$), to determine whether the most common ITM dose range of ≥250 μg may favorably *influence postoperative IV opioid requirements* (yes/no, logistic regression). Of these 58 cases, 49 used ITM doses ≥250 μg, but all 58 ITM cases were included in this analysis. Only one significant factor predicted less likely IV opioid requirements on POD#1, that being the *absence of any IV opioids during or after surgery on Day 0* ($P = 0.003$). *In this small sample size (for a dichotomous variable), the question is raised regarding the common instinct of administering an IV opioid during surgery when it may not be necessary, and the possible triggering of downstream hyperalgesia and/or tolerance when doing so, as reported elsewhere.* (14)
Supplementary Table S5 addresses only bariatric cases with ITM ($n = 58$), *to determine whether PO/IV opioids on POD 0–1, including IV opioids in the OR, independently may contribute to PONV occurrence on POD 0–1*, along with other expected (or unexpected) factors. There were three significant factors ($P < 0.05$) associated with any PONV during this time window. First was sleeve gastrectomy, as previously reported (1, 15); second was an interaction term of no IV opioids on POD 0–1 *and* no PO opioids POD 0–1 (odds ratio 0.12). Finally, patients who were given POD 1 booster doses of perphenazine and aprepitant had associated profound PONV protection (OR = 0.06), compared with patients not receiving booster doses. In this small sample size for the PONV dichotomous yes/no variable, the question is raised regarding five-drug PONV prophylaxis, two-drug booster prophylaxis, *and* a sufficiently high ITM dose to render as sufficiently predictable not needing any further opioids, since these combined factors may allow for sufficient patient adherence to oral/enteral serial non-opioid analgesics started preoperatively and continued postoperatively, to also avoid the need for any further opioids (beyond the ITM). *In our sample, 10 cases of 58 total (17%) needed no subsequent opioids after the ITM was given.*
Supplementary Table S6 addresses only bariatric sleeve gastrectomy cases, with or without ITM, and with or without five-drug PONV prophylaxis ($n = 48$). For this highly emetogenic procedure (1, 15), we observed an overall PONV rate on POD 0 of 9/48 (19%), an overall PONV rate on POD 1 of 19/48 (40%), and an overall PONV rate either POD 0–1 of 21/48 (44%). *When considering patients without ITM and five-drug PONV prophylaxis ($n = 16$), we observed 63% PONV on POD 0–1; meanwhile, when considering patients receiving ITM, five-drug PONV prophylaxis, and a POD 1 perphenazine/aprepitant booster ($n = 24$), we observed only 25% PONV on POD 0–1* ($P = 0.0245$ by Fisher's exact test). These factors appear to support (i) a sufficient ITM dose (of a ≥250 μg start-point), representing 2–3 times above those (100–150 μg doses) previously (4) recommended, (ii) five-drug PONV prophylaxis before operating room entry, and (iii) POD 1 PONV booster dosing, as a potentially valuable integrated care plan that would theoretically also support enhanced non-opioid analgesic oral/enteral adherence, all in tandem aiming for downstream opioid-sparing objectives.

ITM, intrathecal morphine; PONV, postoperative nausea/vomiting; POD, postoperative day; BMI, body mass index; OR, operating room; PO, per os (per oral); IV, intravenous.
The authors acknowledge the limitation of cases available to analyze within the electronic medical record archive as a one-institution study and the necessary adjustment to sub-categorize each adjusted analysis in efforts to (i) generalize outcomes (e.g., "all available transabdominal procedures") and (ii) show enhanced process fidelity, when possible, with the most common available standardized procedures at a single institution (e.g., "only bariatric surgery" or "only sleeve gastrectomy").

it seems irrational to use a potentially underdosed (100–150 μg) amount of ITM for abdominal surgery with expectations of any meaningful analgesia as cephalad as T6, while creating usual procedural risks of ITM (bleeding, infection, nerve damage) in the process. Respiratory depression-related outcomes were tracked in real time using an open-ended "comments" field that was included in the cumulative data set for ITM cases (but not for historical controls).

3 Results

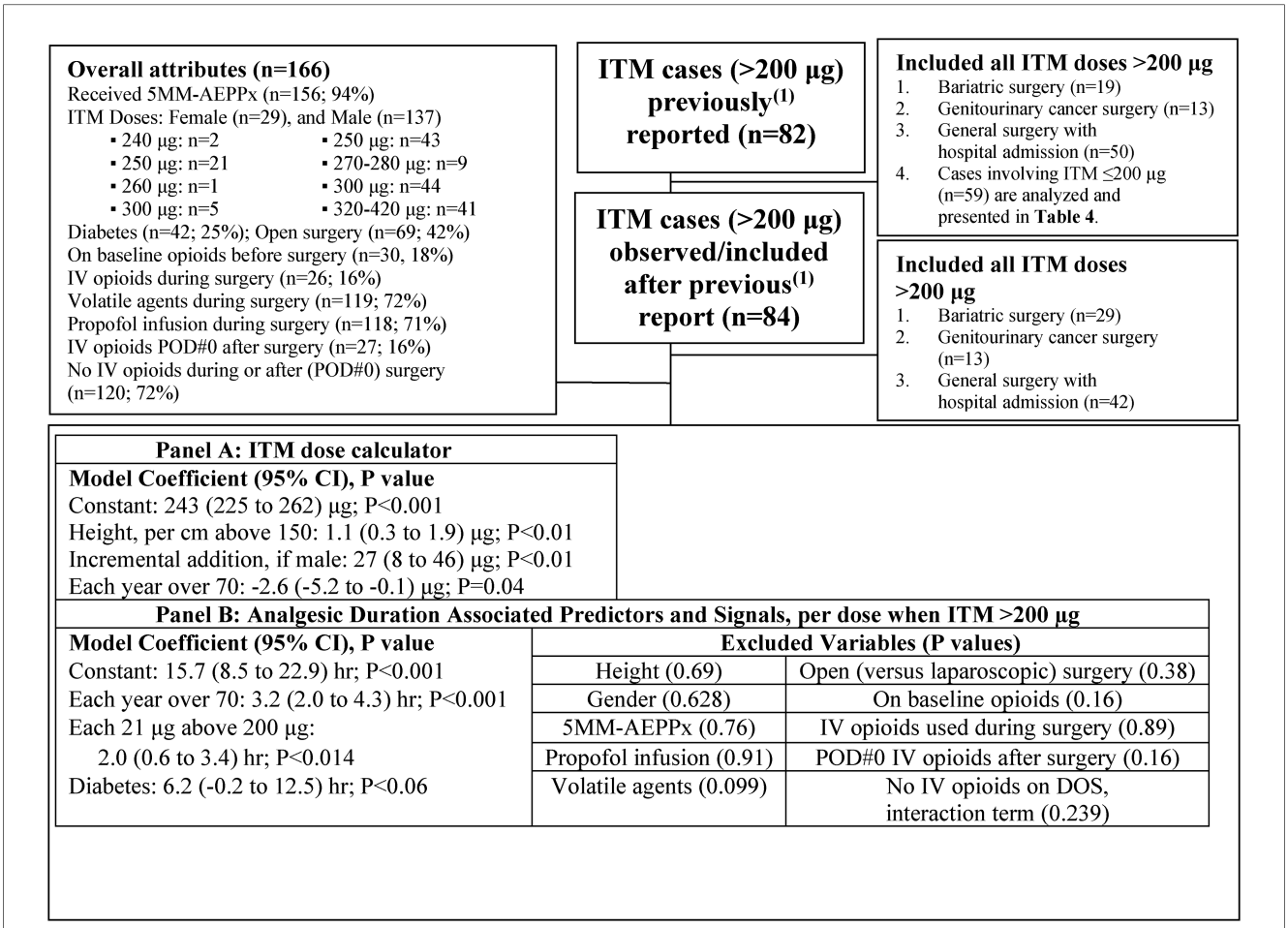
3.1 Participants and descriptive data

As itemized and detailed in Supplementary Tables S1–S6, the number of patients per analyzed observational condition is summarized in Table 2. To maximize data inclusion in the single-institution setting of only moderate-size caseloads, we present the available sample sizes (in CONSORT-like diagrams) associated with each analysis demonstrated in Figure 1, Table 3, and Supplementary Tables S1–S6. There

TABLE 2 Cases per analyzed condition and guide to data presentation locations.

Scenario and figure or table where data are presented	Sample size (*n*)
GA/ITM cases having received >200 μg ITM (Figure 1A,B)	166
GA/ITM cases having received ≤200 μg ITM (Table 3)	59
Bariatric GA cases with or without ITM, and with or without five-drug PONV prophylaxis (Supplementary Table S1)	95
All GA/ITM cases, with ITM doses ranging from 100 to 420 μg (Supplementary Tables S2, S3)	225
All bariatric cases that received ITM (Supplementary Tables S4, S5)	58
All sleeve gastrectomy bariatric cases (Supplementary Table S6)	48

GA, general anesthesia; ITM, intrathecal morphine; PONV, postoperative nausea/vomiting.



Panel A: ITM dose calculator

Model Coefficient (95% CI), P value
Constant: 243 (225 to 262) µg; P<0.001
Height, per cm above 150: 1.1 (0.3 to 1.9) µg; P<0.01
Incremental addition, if male: 27 (8 to 46) µg; P<0.01
Each year over 70: -2.6 (-5.2 to -0.1) µg; P=0.04

Panel B: Analgesic Duration Associated Predictors and Signals, per dose when ITM >200 µg

Model Coefficient (95% CI), P value	Excluded Variables (P values)	
Constant: 15.7 (8.5 to 22.9) hr; P<0.001	Height (0.69)	Open (versus laparoscopic) surgery (0.38)
Each year over 70: 3.2 (2.0 to 4.3) hr; P<0.001	Gender (0.628)	On baseline opioids (0.16)
Each 21 µg above 200 µg:	5MM-AEPPx (0.76)	IV opioids used during surgery (0.89)
2.0 (0.6 to 3.4) hr; P<0.014	Propofol infusion (0.91)	POD#0 IV opioids after surgery (0.16)
Diabetes: 6.2 (-0.2 to 12.5) hr; P<0.06	Volatile agents (0.099)	No IV opioids on DOS, interaction term (0.239)

FIGURE 1
Case selection diagram (for Panels A and B), to derive an ITM dose calculation formula (A) incorporating the ≥250 μg start-point dose for ITM, aiming for both clinically meaningful analgesic duration, and further opioid avoidance into postoperative day (POD) 1 (B). Linear relationships are not assumed outside the listed ITM dose range (240–420 μg). ITM, intrathecal morphine; 5MM-AEPPx, five-drug multimodal antiemetic prophylaxis with palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone; POD, postoperative day; CI, confidence interval; DOS, day of surgery; PONV, postoperative nausea/vomiting.

TABLE 3 Linear regression: analgesic duration predictors or signals, when ITM was dosed at ≤200 µg ($n = 59$).

Model coefficient (95% CI), *P*-value	Excluded variables (*P*-values)		
Constant: 8.3 (−6.6 to 23.1) h; $P = 0.27$	Height (0.47)	Propofol (0.15)	On baseline opioids (0.15)
No IV opioids on DOS: 11.4 (1.9–20.9) h; $P = 0.02$	Gender (0.88)	Volatile (0.46)	Yes POD 0 IV opioids after surgery (0.37)
Each year over 70: 1.4 (0.1–2.6) h; $P < 0.04$	Diabetes (0.91)	ITM dose (0.77)	
Five-drug PONV PPx: 14.2 (−0.6 to 28.9) h; $P < 0.06$	Yes IV opioids during surgery (0.65)		Open (vs. laparoscopic) surgery (0.95)

DOS, day of surgery; PONV, postoperative nausea/vomiting; PPx, prophylaxis; ITM, intrathecal morphine.

were no missing data among the 225 cases that received ITM (Supplementary Tables S2, S3), 58 of which were sub-analyzed as bariatric cases (Supplementary Tables S1, S4, S5). For the bariatric cases particularly in Supplementary Table S1, 37 historical control cases were retained and used from our previous (1) report (i.e., cases that did not receive ITM), for purposes of the described regression analysis. Although Roux-en-Y gastric bypass cases seem to generate more of a postoperative pain response than do sleeve gastrectomy cases (15), we opted to combine these bariatric case types for a more meaningful analysis of postoperative pain and analgesic duration prediction (while excluding more variable general colorectal and genitourinary cancer cases, from a postoperative pain perspective; Supplementary Table S1). Further following similar logic in bariatric case analysis, leading to our PONV-specific analysis (Supplementary Table S6), we retained all previously reported (1) bariatric sleeve gastrectomy cases, both ITM ($n = 18$) and historical controls ($n = 20$), and added newly available ITM-utilized sleeve gastrectomy case data ($n = 18$), based on the generally accepted clinical observation that sleeve gastrectomy patients experience more PONV (15) than those who underwent other types of gastric bypass procedures (i.e., which had been included in the pain/analgesia analyses of Supplementary Tables S4–S5).

3.2 Outcome data and main results

Case selection and other collated attributes are presented in Figure 1, wherein Panel A presents the suggested ITM dose calculator starting at a lower threshold of ~250 μg for non-orthopedic surgery, while Panel B presents associated analgesic duration predictors (and "signals" with $P < 0.1$), when the ITM dose was >200 μg.

Based on 166 GA/ITM cases with doses >200 μg, with ITM dosing aiming to minimize exposure to downstream opioids, a practical dosing formula that the authors recommend starts with ~250 μg, adding a further 25 μg for men, then adding ~10 μg for each ~9 cm above 150 cm in height (or ~10 μg for each ~3 inches of height above 5 feet tall; Figure 1A). An ITM duration prediction model was also generated for these $n = 166$ cases (Figure 1B), showing (i) an ~16 h duration constant, (ii) each year over an age of 70 being associated with 3 h of ITM/multimodal duration, and (iii) each ~20 μg above 200 μg being associated with an additional 2 h of ITM/multimodal duration. One signal of note, warranting future study, was a trend of an additional 6 h duration in patients with diabetes ($P < 0.06$). Therefore, if there are dosing concerns from a safety perspective, elderly patients and/or diabetic patients may not necessarily be harmed (from the perspective of analgesic duration) with slight ITM dose reductions from the proposed equation (Figure 1A), as indicated, if other potential comorbidities (e.g., ability to extubate at the end of a case) are being considered.

When analyzing the lower-dose GA/ITM cases of ≤200 μg, the prediction model (Table 3) generated an analgesic duration coefficient of ~8 h (as opposed to 16 h above in Figure 1B), with an additional 11 h of duration observed in patients that *did not receive IV opioids either during surgery or after the operating room on POD 0* (i.e., an interaction term, perhaps indicating that the ≤200 μg dose was, in fact, sufficient for some patients). With lower (≤200 μg) ITM doses, the age-based effect on duration above (i.e., as in Figure 1B) was not as robust. Meanwhile, having received five-drug PONV prophylaxis (with palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone) was an associated signal ($P < 0.06$) of 14 h analgesic prolongation, perhaps related to improved non-opioid oral/enteral non-opioid regimen adherence, while lower-dose (≤200 μg) ITM was still effective. Ten other factors (Table 3) appeared to be non-contributory but may have been underpowered.

3.3 Available data on respiratory depression, and underlying non-ITM probable causes

Four cases were annotated in real time as having respiratory depression issues prompting delayed extubation and/or early reintubation and forcing an intensive care unit (ICU) stay that seems likely to not have otherwise occurred.

3.3.1 First case (2021)

This male Veteran, age 50, BMI = 42 kg/m^2, received (i) 200 μg ITM, (ii) all five medications for PONV prophylaxis, and (iii) coinciding lidocaine- (0.5 mg/kg/h; 180 mg total) and propofol-only total intravenous anesthesia (5 g in total, encompassing induction and maintenance for a 160 min open hemicolectomy, with bispectral index values of 42–58 intraoperatively). Dexmedetomidine 10 μg IV was given by the hands-on anesthesia provider without consulting with the attending anesthesiologist 8 min before sugammadex reversal (400 mg). Absence of pain (from ITM) may have inhibited prompt emergence, and increments of naloxone to a total of 0.6 mg did not render the ITM effect as reversed, which shifted the differential diagnosis toward respiratory acidosis that had rapidly developed after the uninformed dexmedetomidine dose, soon after mechanical ventilation was converted to bag ventilation in a super-morbidly obese patient. The core temperature upon emergence was 35.9°. This patient was extubated the following morning in the ICU, reporting a pain score of zero and ultimately benefitting from an estimated ITM analgesic duration of 32 h.

3.3.2 Second case (2022)

This male Veteran, age 61, BMI = 36 kg/m^2, received (i) 300 μg ITM, (ii) all five medications for PONV prophylaxis, and (iii) a balanced volatile (sevoflurane, end-tidal 0.2%–0.6%)—propofol anesthetic (2 g in total), encompassing induction and maintenance for a 210 min laparoscopic cholecystectomy with planned hospital admission, exiting the operating room late into the evening (~11:30 p.m.). Bispectral index values were lower than above, ranging from 22 to 50 intraoperatively. Dexmedetomidine 10 μg IV was given 15 min before sugammadex reversal (400 mg). The absence of pain (from ITM) may again have inhibited prompt emergence, and increments of naloxone to a total of 0.2 mg did not render the ITM effect as reversed, This again seems to have shifted the differential diagnosis toward respiratory acidosis that had rapidly developed after the dexmedetomidine dose, soon after mechanical ventilation was converted to bag ventilation in a morbidly obese patient. This patient was extubated less than 3 h after arrival to the ICU.

3.3.3 Third case (2022)

This male Veteran, age 73, BMI = 28 kg/m^2, received (i) 250 μg ITM, (ii) three of five medications for PONV prophylaxis (neither dexamethasone nor diphenhydramine), and (iii) balanced sevoflurane/propofol for anesthetic maintenance (for a nearly 13 h laparoscopic-converted to open Whipple procedure). Extubation immediately after the case was neither considered nor attempted but was accomplished uneventfully 12 h after ~9:30 p.m. ICU arrival.

3.3.4 Fourth case (2023)

This male Veteran, age 75, BMI = 30 kg/m^2, received (i) 320 μg ITM, (ii) all five medications for PONV prophylaxis, and (iii) balanced sevoflurane (end-tidal 0.9%–1.1%) and propofol anesthetic [1.4 g in total, encompassing induction and maintenance for an 8 h robotic sigmoid colectomy and colorectal anastomosis (for symptomatic vesicointestinal fistula), with

bispectral index values of 48–60 intraoperatively]. Sugammadex reversal (300 mg) was not preceded by any end-of-case dexmedetomidine. However, the recorded core body temperature for 2 h before end-of-case and initial extubation was 33.9°. The patient was reintubated ~40 min later, presumably related to hypothermia (since no naloxone was used by the care team at the time), and was uneventfully extubated 12 h after the described reintubation the previous evening.

4 Discussion

The specific aims, using multivariable regression analyses, were to present (i) a practical ITM dose calculator for transabdominal/truncal surgery and (ii) an associated analgesic duration predictor. Such procedures included relatively cephalad trespass sites in the context of abdominal/axial anatomy, including bariatric surgery, nephrectomy, and pancreatic surgery. We were motivated to do so based on the existing guidelines (4) that seem to underdose ITM (100–150 µg recommendation), with the downstream potential of acute opioid escalation sequelae that include the development of tolerance, hyperalgesia, and/or PONV. Our models showed a ~250 µg start-point ITM dose to be seemingly rational, with adjustments available (based on both presented models, Figure 1 and Table 3) related to age (decrease ITM dose if over 70), gender (increase ITM dose if male), height (incremental ITM dose increase for achieving dermatomal objectives), and possibly diabetes (allowing for decrease of ITM dose if desired, in a diabetic patient). The 250 µg baseline dose (with associated incremental increases) was associated with a 16 h duration starting coefficient before other statistical adjustments, while the ≤200 µg dose was associated with only an 8 h duration starting coefficient, while being influenced by associated factors that did not influence the ≥250 µg dose duration.

Meanwhile, it seems probable that the five-drug PONV prophylaxis (palonosetron, perphenazine, aprepitant, diphenhydramine, and dexamethasone) may allow for better adherence to an oral/enteral non-opioid analgesic regimen, based on this latter (<200 µg) model. However, further study is needed to address both ITM dosing categories.

The four cases of unplanned inability to immediately extubate, or requirement to soon reintubate, indicate that there may be value to adding specific ITM-focused points above usual vigilance in intraoperative care. These include (i) avoiding unnecessary sedatives administered near the time of extubation, (ii) intraoperative euthermia, and (iii) acknowledging possible intraoperative acid–base shifts during IV fluid shortages, leading to normal saline default use and subsequent hyperchloremic metabolic acidosis that may lead to post-emergence early susceptibility to respiratory depression and rapidly mixed acidosis. The third point is based on personal observation (lead author BAW) in cases having occurred since the timeline of this collected data set. Another potentially useful consideration, when the described doses of ITM are used, is the delaying of switching the ventilator from mechanical mode to "bag mode" in the commonplace effort to stimulate respiratory effort via hypercarbia (and untreated pain). Recalling that pain is a potent stimulus to breathe, assisting emergence from anesthesia, the corollary is that the necessary ITM doses described to potentially affect the trajectory of the opioid epidemic (related to usual exposure to usual opioids) will commonly block the pain for many hours. As a result, the hands-on anesthesia provider at the bedside may do well to treat ITM patients quite differently to achieve prompt emergence. This could occur by allowing for extubation and PACU transfer to occur before any post-ITM opioid dosing in the OR; in contrast with the default of employing "usual" IV opioids and/or co-administered sedatives. In other words, delaying dexmedetomidine (e.g., for post-traumatic stress disorder-related emergence agitation risks) until PACU (i.e., after extubation) may be useful in ITM cases, particularly in those at risk for (or diagnosed with) obstructive sleep apnea. This was described in the first case and the second case above.

"Right-sized" ITM dosing compared to previous (4) recommendations seems to also involve preferable avoidance of probably unnecessary IV opioids during surgery [which could be potentially replaced by infused esmolol (16) or low-dose lidocaine, and delay the decision for further opioids to postoperative recovery after GA emergence]. Another factor potentially helpful for "right-sized" ITM dosing may incorporate the previously reported (1) and observationally successful five-drug PONV prophylaxis. Reticence to escalate ITM dosing to achieve desired analgesic effects (including considerations for relatively cephalad surgical sites) may be based, in part, on PONV avoidance. Therefore, to counteract PONV concerns, the five-drug (1) PONV prophylaxis seems to have the potential to allow for escalating ITM doses beyond current (4) recommendations. Based on recent observational work addressing IV opioid escalation intraoperatively (17), initial ITM underdosing that leads to reactive IV opioid supplementation intraoperatively may undermine ITM duration benefits (compared with ITM avoiding other intraoperative IV opioids such as fentanyl, remifentanil, and hydromorphone, as per Supplementary Tables S1–S5). Further research could explore whether supplemental intraoperative IV methadone, esmolol (16), or lidocaine (instead of fentanyl/remifentanil/hydromorphone) may be protective of ITM duration effects, when compared with our observations of possibly undermined ITM duration effects associated with intraoperative fentanyl/remifentanil/hydromorphone use.

5 Limitations

Veterans may be considered a low-risk population for PONV. However, Veterans have not been specifically studied in presented PONV consensus guidelines, nor have patients specifically receiving ITM. Therefore, forecasts of the five-drug PONV prophylaxis success in ITM cases may differ in the non-Veteran (with or without ITM) population. As a result, testing the five-medication technique may potentially offset some enthusiasm with the described combined strategies of ITM up-dosing before operating room entry. To offset this limitation, we allowed for

signals (with $P \geq 0.05$ but ≤ 0.1) into our final regression equations, often representing non-traditional but potentially interacting risk factors, to query for potential epidemiologic influence (or "bedside habit" influence) beyond traditional PONV risk factors.

Next, because postoperative bladder catheters were fairly ubiquitous in this postoperative patient population, issues regarding postoperative urinary retention will need to be separately addressed in future research. Importantly, our data did not account for potentially useful intrathecal adjuvants (e.g., preservative-free magnesium sulfate) or co-administered local anesthetics such as bupivacaine, including very low doses that might not be sufficient to be a self-sufficient anesthetic, but possibly being useful for meaningful antinociception.

Furthermore, we acknowledge that we were unable to derive and present expected *a priori* sample size determinations and power analyses. Our observations are limited to a single-center Veterans population, which may not generalize to broader, diverse patient populations. For this observational study, we could only "case-match" cases that were performed and assess similar historical control cases performed at the same institution in the described time periods as comparators. It is difficult to expand an observational sample size (with limited resource support) to cases that are neither present in one's institution nor present in the institution's medical record archive. Future work expanding the cohort and including non-Veteran populations are needed to enhance applicability. Using the described consecutive caseload, our goal was to provide preliminary data for external researchers to create their own cohorts (such as in non-Veteran populations) or prospective randomized study groups incorporating the described paradigm shifts, as soon as the significant findings and signals were noted in the analysis.

Finally, incorporating all described multimodal processes into an overarching enhanced recovery protocol (including the described five-medication multimodal antiemetic, and otherwise complete opioid avoidance until after extubation, and being stationed in PACU) may create a useful start-point for prospective study, which could include a head-to-head comparison of ITM 150 μg vs. either (i) ITM 250 μg or (ii) ITM dosed per the formula in Figure 1A.

6 Conclusions

We postulated, then validated, a 250 μg (as opposed to 100–150 μg) dose as a potentially viable and observationally tested start-point for ITM dosing, with additional dose adjustment opportunities based on gender, height, and age. The 250 μg start-point ITM dose (and its incremental adjustments) was associated with an unadjusted 16 h duration coefficient. Meanwhile, ITM doses <200 μg [such as those recommended (4) presently] were associated with only an unadjusted 8 h duration coefficient and were influenced by factors that did not affect the ≥250+ μg duration coefficient. PONV prophylaxis with the five described drugs seems to (i) allow for a more confident PONV-free postoperative course, (ii) be augmented by daily oral booster dosing of the two oral antiemetics (perphenazine and aprepitant), and (iii) allow for better patient adherence to oral/enteral non-opioid analgesics on a schedule [particularly agents such as dextromethorphan (18, 19) and celecoxib (20)], while the ITM is providing efficacious analgesia. There may be value in considering 24 and 48 h downstream effects on both pain and PONV recovery parameters when considering the merits of higher ITM doses recommended herein. Specifically, ITM in tandem with five-drug PONV prophylaxis, would be central to the preoperative phase. Thereafter, PONV oral booster dosing with perphenazine and aprepitant on POD 1 (as shown in Supplementary Table S5), *in tandem with postoperative and proactive*, enterally absorbed non-opioid analgesics such as acetaminophen, COX-2 inhibitors, and dextromethorphan, would seem central to the postoperative phase (instead of commonplace *reactive* dosing). Integrating these pre- and intra-/post operative maneuvers is intended to *avoid potentially any exposure to downstream opioids*. Our observed downstream opioid avoidance success presently approximates 17% with the described strategy (as shown in Supplementary Table S4), that perhaps other non-opioid analgesic/antinociceptive maneuvers (e.g., IV esmolol, IV lidocaine, and/or intrathecal magnesium) may improve, based on future research and/or clinical observation. Finally, "force of habit" and "unconscious biases" at the bedside in the operating room may need to be actively addressed preventatively, since the "margin for error" may significantly differ with *proposed* vs. *past-recommended ITM doses* (or no ITM at all).

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

This quality improvement report involving human participants was reviewed by the VA Pittsburgh Healthcare System Institutional Review Board, and was defined as an exempt protocol (1670098). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

BW: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. DH: Investigation, Methodology, Writing – review & editing.

CD: Conceptualization, Investigation, Methodology, Writing – review & editing. KG: Conceptualization, Investigation, Methodology, Writing – review & editing. JL: Conceptualization, Investigation, Methodology, Writing – review & editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

The authors are grateful to our Veterans for their service and that their understanding of the described maneuvers as a means to offset the risks of the opioid epidemic sufficiently resonated to receive the described procedures as part of our local recommended standard of care. We are also grateful for the clinical support of our chief anesthesiologist, James W. Ibinson MD, PhD, and our local surgeons, Drs. Ramesh Ramanathan (bariatric surgery), Gregory Watson, Robert Tessler, Robert Handzel, Christine Leeper, Brian Zuckerbraun, and Kelly McCoy (general surgery) and Amir Toussi (urology). Finally, we are grateful for the coordinating efforts of local general surgery physician assistants Megan White and Benjamin Purvis. This manuscript is dedicated to the contemporaneous Executive Director of the United States Veterans Administration National Surgery Office, Mark A. Wilson, MD, PhD.

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.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fanes.2025.1521409/full#supplementary-material

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