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Spring 2023

Impact Of Intrathecal Morphine On Patient Outcomes In Major Abdominal Surgery

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ANE-630: Research Practicum II

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Abstract

Colorectal enhanced recovery after surgery (ERAS) guidelines for patients undergoing major abdominal surgeries have started to include intrathecal morphine (ITM) as part of the protocol to improve patient outcomes. There is interest amongst other abdominal surgical disciplines in expanding the use of ITM. When used as a single bolus, ITM has shown to have an intravenous (IV) opioid sparing effect postoperatively, as well as improved pain scores for up to 24 hours (Koning et al., 2020). However, ITM coincides with unique considerations and side effects. There is a dose-dependent concern of ITM causing respiratory depression postoperatively that necessitates additional monitoring which should be considered with patient selection and dose (Gustafsson et al., 2019). Another less detrimental, albeit more common side effect, is a 30-60% increase in pruritus as compared to use of IV opioids (Wang et al., 2021). The intent of this literature review is to discuss the impact of ITM on pain scores and narcotic use across major abdominal surgery specialties, as well as postoperative side effects such as respiratory depression, pruritis, nausea, length of stay, and their impact on patient satisfaction. The mechanism of action and pharmacodynamics of ITM and how it compares to that of IV opioids will be reviewed.

Keywords: enhanced recovery, abdominal surgery, intrathecal morphine, patient satisfaction

Impact of Intrathecal Morphine on Patient Outcomes in Major Abdominal Surgery

Since 1979, intrathecal morphine (ITM) has been found to provide effective postoperative analgesia in patients undergoing major abdominal surgery (Koning et al., 2022). Today, colorectal Enhanced Recovery After Surgery (ERAS) guidelines for patients undergoing major abdominal surgeries have started to include ITM to improve patient outcomes, with increased interest in expanding the use of ITM across other surgical disciplines. The procedure involves a preoperative injection of morphine placed intrathecally into the cerebrospinal fluid which directly activates the mu-opioid receptors in the dorsal horn of the spinal cord (Pitre et al., 2018). Large doses of ITM, such as those greater than 500 micrograms (mcg), are associated with similar adverse side effects to IV morphine, however the intrathecal administration requires significantly smaller dosing (Pitre et al., 2018). When used as a single bolus, ITM is believed to have an IV opioid sparing effect postoperatively (Koning, Klimek et al., 2020).

Intrathecal morphine comes with a unique profile of considerations and side effects. There is a dose-dependent concern of ITM causing respiratory depression that necessitates additional monitoring postoperatively (Gustafsson et al., 2019). Another less detrimental, albeit more common, side effect is a 30-60% increase in pruritus as compared to use of IV opioids (Wang et al., 2021). There are additional concerns of increased nausea with ITM, as well as increased length of stay (LOS) in the hospital. Enhanced understanding and quantification of the IV morphine equivalent sparing effect of ITM in specific patient populations, as well as an understanding of the side effects and their impact on patient satisfaction, will assist providers in determining if ITM is the appropriate treatment modality for their patients across unique subspecialties for major abdominal surgery. Current studies of ITM are focused on the quantification of opioid reduction and expanded use across surgical specialties.

Background

Postoperative discomfort and pain are primary concerns for anesthesia providers when determining the plan of care for their patients. Surgical patients experience postoperative pain at a rate of up to 80%, with adequate pain control being achieved in less than 50% of patients (Pitre et al., 2018). After major abdominal surgeries, patients frequently report severe pain on a numbers rating scale (NRS) of 7-8 out of 10 (Pitre et al., 2018). Postoperative pain that is uncontrolled may result in a delay resuming physical activity. It is associated with increased morbidity, increased risk of chronic pain, increased postoperative narcotic use, and decreased patient satisfaction (Pitre et al., 2018). It is important to treat patients' pain to avoid such complications. However, there are deleterious side effects associated with increased opioid use such as postoperative nausea and vomiting, sedation, postoperative hyperalgesia, immunosuppression, and ileus; a painful obstruction of the intestine (Ioffe et al., 2021). Enhanced recovery after surgery protocols aim to design care pathways that decrease perioperative stress, maintain postoperative physiological function, and accelerate recovery after surgery (Gustafsson et al., 2019). Many ERAS protocols suggest implementation of multimodal protocols for the treatment of pain, as well as decreased narcotic usage.

An additional concern for providers and patients alike is the ongoing opioid epidemic. The World Health Organization (WHO) recognizes opioid misuse as an international issue and has declared that the world has been in an opioid epidemic since the 1990's (Cook, 2022). The Centers for Disease Control and Prevention (CDC) estimates an economic burden of prescription opioid misuse in the United States of $78.5 billion per year with costs accumulating from healthcare, lost productivity, addiction treatment, and criminal justice (Cook, 2022). The CDC estimates that approximately 35% of current opioid associated deaths can be attributed to

prescription opioid abuse (Ioffe et al., 2021). Pain that is inadequately or inappropriately controlled following major abdominal surgery affects patient outcomes and has broad population health and economic implications (Pirie & Traer et al., 2022). The exploration of multimodal therapies, such as ITM, is exceedingly important in the face of the opioid epidemic.

Pharmacodynamics and Pharmacokinetics of Intrathecal Morphine

There are three different primary sites where opioids work within the central nervous system, including the periaqueductal and periventricular gray matter, the ventromedial medulla in the brain, as well as directly on the spinal cord (Cummings et al., 2022). Morphine primarily interacts with the mu-receptor. These mu-receptor binding sites exist in the brain, but also within the substantia gelatinosa in the dorsal horn of the spinal cord (Cummings et al., 2022). Intrathecal morphine has the added benefit of delivering its analgesic medication directly to the site of action on the spinal cord, decreasing or blocking nociceptive transmission. The localized site of action of the opioid allows first-pass metabolism and interaction with the blood brain barrier to be bypassed (Deer et al., 2019). Additionally, because ITM is delivered directly to the spinal cord, a lower dose is required to be effective with less interactions on systemic opioid receptors, and potentially fewer systemic side effects (Deer et al., 2019).

The potency of morphine is exaggerated by intrathecal administration, with recommended dosing for postoperative and intraoperative analgesia ranging between 100-150 mcg of preservative free morphine or 300-500 mcg of diamorphine, as compared to the intravenous (IV) dose of 1-4 milligrams (mg; Gustafsson et al., 2019). Intrathecal morphine has an onset of action from 5 to 10 minutes (mins; Cummings et al., 2022). Morphine is ideal for intrathecal analgesia due to its hydrophilic nature as compared to other opioids, such as fentanyl, which allows for longer duration in the cerebrospinal fluid and increased duration of action (Pitre

et al., 2020). Intrathecal morphine's analgesic effects have been demonstrated to last

approximately 20 to 24 hours (hrs; Cummings et al., 2022). In the cerebrospinal fluid,

morphine's distribution is biphasic, with an early half-life of about 1.5 hrs and a late half-life of

approximately 6 hrs (Cummings et al., 2022). Intrathecal morphine is excreted primarily as the

conjugate morphine-3-glucuronide via the kidney, with about 2%- 12% unchanged in the urine

(Cummings et al., 2022).

Literature Review

Methods

A systematic literature search was performed in September and October of 2022 to

examine articles over the last 5 years. Databases used in search included Medline, PubMed,

CINAHL, and Google Scholar. Sources varied in level of evidence from large meta-analyses,

systematic reviews of the literature, and randomized control trials (RCTs), to prospective trials

and retrospective case studies. Population varied across all studies from $n = 7$ to $n = 2500$

patients, with 20 articles selected for review.

Inclusion criteria for this search were defined in accordance with a PICO question. The

population included all patients undergoing major abdominal surgery. Types of major abdominal

surgeries included in the literature review were colorectal surgeries, kidney surgeries, hepato-

pancreato-biliary surgeries, radical prostatectomies, and gynecologic procedures that were either

performed via open incision or laparoscopically. Cesarean section patients were excluded from

the search. The intervention was the administration of an intrathecal hydrophilic opioid, which

primarily included morphine, and diamorphine, with few studies including hydromorphone. The

search sought to compare outcomes for patients postoperatively who received ITM

preoperatively as compared to standard administration of IV opioids intraoperatively. Studies

that compared ITM to epidural morphine only were excluded. Primary outcomes of postoperative narcotic usage and pain scores were examined, as well as secondary outcomes of side effects such as respiratory depression, nauseas, pruritis, length of hospital stay and overall impact on patient satisfaction.

Key words combined for the literature search initially included "intrathecal morphine and abdominal surgery." To further evaluate specific effects of intrathecal morphine, it was combined in search terms with common themes that arose in the literature, "postoperative narcotic use," "pain scores," "respiratory depression," "pruritis," "patient satisfaction," "length of stay," "nausea," and "enhanced recovery," to assess for specific incidences of the most common side effects as well as patient dissatisfiers.

Postoperative Narcotic Usage and Pain Scores

Enhanced recovery after surgery protocols aim to design care pathways that decrease perioperative stress, maintain postoperative physiological function, and accelerate recovery after surgery (Gustafsson et al., 2019). Based on searches of the literature and reviews of national databases, Gustafsson et al. (2019) compiled recommendations for patients undergoing major colorectal surgery. Based on the search, Gustafsson et al. determined with moderate quality of evidence according to a standardized Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, that the use of multimodal stress-minimizing techniques were proven to reduce morbidity, improve recovery, and shorten length of stay (LOS) post colorectal surgery. Gustafsson et al. strongly recommended based on the literature and GRADE system the use of ITM as part of the ERAS protocol for laparoscopic colorectal surgeries. Gustafsson et al. concluded the addition of the long-acting opioids has the benefit of decreasing postoperative morphine requirements up to sixfold, allowing for significant stress-reducing effect and

postoperative opioid sparing. Other intraabdominal surgical specialties are following suit with research of ITM in hopes of expanding its use to improve patient outcomes.

Major Abdominal Surgery

Koning, Klimek et al. (2020) performed a large systematic search to examine patients undergoing major abdominal surgeries and developed a meta-analysis describing the outcomes for all intrathecal hydrophilic opioids, inclusive of ITM, and their side effect profile. The search included 40 trials and 2500 patients. The primary outcomes examined the consumption of IV morphine equivalents at the 24 and 48 hr time points postoperatively. Variations in dosing of ITM across the studies were limited, with 300 mcg being most common, and all but six studies varied between 100 mcg and 400 mcg (Koning, Klimek et al., 2020). The meta-analysis demonstrated that with the administration of ITM, there was a reduction in mean difference of IV morphine equivalent consumption. At the 24 hr mark, when ITM was administered, IV morphine equivalent consumption was -18.4 mg less (95% CI −22.3 to −14.4), and −25.5 mg less (95% CI −30.2 to −20.8) at the 48 hr mark (Koning, Klimek et al., 2020).

While the described reduction in morphine equivalents had been previously demonstrated in studies and did not come as a surprise to Koning, Klimek et al., the quantifiable difference of 18.4 mg proved clinical significance and quantified the extent of opioid sparing. In addition to morphine equivalents, Koning, Klimek et al. examined pain scores using a NRS from 0 to 10 at 24 and 48 hrs postoperatively during rest and exertion. Koning, Klimek et al. found that pain scores during rest and exertion were significantly reduced in the intrathecal opioid group up to the 24 hr mark (CI 95%, mean difference -0.9 & -1.2 respectively). At the 48 hr mark, pain scores were found to be lower with exertion, however there was no significant difference in pain scores at rest between the intrathecal and IV opioid groups (CI 95%, mean difference -0.4;

Koning, Klimek et al., 2020). Time until the first analgesic request postoperatively was longer in the ITM group than the IV opioid group, with requests for medication being on average 9.7 hrs sooner in the IV opioid group (95% CI; Koning, Klimek et al., 2020). Intraoperatively, sufentanil equivalents were reduced on average by -12.9 mcg with ITM (CI 95%), suggesting even further opioid sparing benefits (Koning, Klimek et al., 2020).

A systematic review and meta-analysis conducted by Pitre et al. (2020) similarly attempted to quantify the reduction in IV morphine when patients were administered ITM preoperatively. The study examined adults receiving general anesthesia for abdominal or thoracic surgery, however only one thoracic study was included in a population of seven RCTs and 353 patients (Pitre et al., 2020). The lone study of thoracic surgery accounted for 3.22% of the results. Patients were given ITM 300-500 mcg plus patient-controlled analgesia (PCA) with morphine, or PCA only. Morphine doses in the first 24 hrs postoperatively were assessed. The weighted mean difference of morphine between the ITM and PCA groups was -24.44 mg in favor of the ITM group (CI 95%; Pitre et al., 2020). A subgroup of patients who received a non-opioid medication postoperatively, acetaminophen, in addition to ITM and PCA showed no significant decrease in the weighted mean difference of morphine requirements (-25.93 mg, CI 95%), suggesting that the addition of acetaminophen did not improve postoperative analgesia when ITM is used (Pitre et al., 2020). No use of rescue analgesia was required after robot-assisted prostatectomy, and rescue analgesia was significantly reduced after open nephrectomy (Pitre et al., 2020). In agreement with Koning, Klimek et al. (2020), the findings of by Pitre et al. showed a significant, quantifiable opioid sparing effect for patients undergoing major abdominal surgery.

Colorectal Surgery

A retrospective study conducted by Young et al. (2021), included 283 patients, assessed the effectiveness of ITM and PCA compared to PCA alone in colorectal cancer surgery, stratifying between laparotomy and laparoscopy procedures. Patients received between 100 mcg-300 mcg of ITM + PCA. The ITM + PCA cohort contained 163 patients, with 52% being laparotomy and 48% laparoscopy. Additionally, 120 patients were included in the PCA only group; 58% laparotomy versus 42% laparoscopy (Young et al., 2021). Overall, there was a reduction found in morphine equivalents over the first 24 hrs in the ITM group, averaging 28.8 mg less than the PCA group (p = <.001; Young et al., 2021). When stratified to laparotomy versus laparoscopy; the doses were 32.7 mg lower, and 14.3 mg lower respectively in the ITM group versus the PCA only group, suggesting benefit in each population, with a larger dose reduction for laparotomy surgeries (Young et al., 2021). At 48 hrs, the difference in consumption of morphine equivalents became insignificant between the ITM and PCA groups. Interestingly, median pain scores between ITM and PCA groups in the first 24 hrs were similar for laparotomy (p >.05), but significantly lower for laparoscopy (p =.031; Young et al., 2021). Overall, the study showed that ITM could produce a similar analgesic effect after both laparotomy and laparoscopy in colorectal surgery, with benefit found in reducing opioid consumption postoperatively.

Laparoscopic Surgery

Koning et al. (2018) took an interest in the role of ITM when it came to laparoscopic surgeries. In a small, double-blind, single center RCT, 56 patients undergoing laparoscopic segmental colon resections were enrolled to receive a dose of ITM of 300 mcg preoperatively or a sham procedure, both were given an IV opioid PCA postoperatively (Koning et al., 2018). Pain scores on a NRS from 0 to 10 were collected from postoperative day (POD)-0-3. Interestingly, a difference in pain scores of 2 versus 1.5 in the control and intervention respectively during POD-

0 were observed ($p = .075$). However, Koning et al. (2018) did find a greater difference at POD-1 with average rating of 2.3 in the control and 0.3 in the ITM group ($p = .004$). It was estimated that use of ITM lasted approximately 20 hrs, as pain scores were not significantly different on POD-2 or 3 (Koning et al., 2018).

Despite significantly lower pain scores, Koning et al. (2018) found that opioid use was also significantly decreased with ITM. The doses were on average 9 mg piritramide in the ITM group versus 33 mg in the control in the first 20 hrs ($p =.001$), with decreased requirements extending to 48 hrs; 15 mg piritramide in the ITM group and 44 mg in the control ($p = <.001$; Koning et al., 2018). Just five patients required additional opioids after the PCA pump was removed, one in the ITM group, and four in the control, which demonstrated ITMs benefit to be opioid sparing (Koning et al., 2018).

Pirie, Doane et al. (2022) acknowledged the growing popularity of ITM in major abdominal surgeries and saw increased opportunity for expanding research to the laparoscopic population. They found no large studies focused on evaluating ITM in laparoscopic abdominal surgeries (Pirie, Doane et al., 2022). A multicenter double-blind RCT with a population of 51 patients was conducted across two tertiary hospitals to determine if ITM could decrease opioid consumption. Colorectal and urological surgery accounted for 69% of the procedures, and upper gastro-intestinal, gynecologic, and general surgery made up for the remainder (Pirie, Doane et al., 2022). The median dose of ITM was 175 mcg, with a range between 100-300 mcg (Pirie, Doane et al., 2022). Patients were randomly assigned to ITM or a sham injection of subcutaneous saline in the patient's lumbar region (Pirie, Doane et al., 2022). Both patient groups received IV PCA until at least POD-1 (Pirie, Doane et al., 2022). In Figure 1, Pirie, Doane et al. depicts how pain scores shift across the time from the post-anesthesia care unit (PACU) to POD-3. There was

a significant decrease in pain scores at rest and with movement in PACU, however after that,

Pirie, Doane et al. found only a significant difference with pain at rest during POD-1, and no

differences with movement.

Figure 1

Pain Scores at Rest and Dynamic in PACU and First 3 Days Postoperatively

Table 4 Postoperative recovery. Values are number (proportion), median (IQR [range]) or mean (SD).

	Intrathecal morphine group n = 23	Control group n = 22	p value
Rest pain; NRS			
PACU	2.8 (2.8)	6.4 (3.1)	0.04
Postoperative day 1	2.6 (2.3)	5.1 (2.5)	0.001
Postoperative day 2	2.3 (2.2)	3.4 (2.3)	0.43
Postoperative day 3	2.1 (2.1)	2.1 (2.1)	0.98
Across four time-points			0.007
Dynamic pain; NRS			
PACU	3.6 (2.9)	6.8 (3.2)	0.04
Postoperative day 1	5.6 (3.1)	6.7 (2.6)	0.33
Postoperative day 2	4.9 (2.3)	5.4 (2.6)	0.82
Postoperative day 3	2.6 (2.5)	3.8 (2.4)	0.56
Across four time-points			0.061
Hospital stay; days	4.0 (2.0–7.0 [1.0–19.0])	3.0 (2.0–5.0 [1.0–33.0])	0.48

QoR; quality of recovery 15, PACU; post-anaesthesia care unit, NRS; numerical rating scale.

Note. Figure produced by Pirie, Doane et al. (2022) detailing pain scores at rest and with movement in PACU and POD-1-3. From "Analgesia for major laparoscopic abdominal surgery: A randomised feasibility trial using intrathecal morphine." By Pirie, Doane et al., 2022, *Anaesthesia*, *77*(4), 428–437. https://doi.org/10.1111/anae.15651

Pirie, Doane et al. (2022) also observed that opiate administration was required by fewer

patients in the ITM group than the control in PACU (10 versus 17 respectively, *p* =.02). The

mean oral morphine equivalent in PACU was 8.6 mg in the ITM group versus 14.6 mg for the

control (*p* =.11). While the population in this study was small, the intent of this work was to aid

in the design of a future more definitive trial, where the outcomes could help further guide

research (Pirie, Doane et al., 2022).

Gynecologic Surgery

A prospective randomized double-blind study with 47 patients on how ITM affects

postoperative outcomes in laparoscopic hysterectomies was performed by Selvam et al. (2018).

Patients were randomized into three separate groups; Group B received subarachnoid

bupivacaine only, Group M received a subarachnoid block with bupivacaine and 200 mcg of morphine, and Group C received only local skin infiltration (Selvam et al., 2018). This study was unique in that it demonstrated the additive effect of morphine to bupivacaine only. Selvam et al. found that patients in Groups B and C both had significantly greater pain at rest and with movement postoperatively than patients in Group M. Doses of fentanyl postoperatively over 24 hrs in Group M were significantly lower at a cumulative of 175 mcg, compared to 350 mcg and 425 mcg in Group B and C respectively ($p =.0001$), demonstrating clear benefit to the opioid sparing ability of the addition of ITM (Selvam et al., 2018).

A retrospective chart review was completed by Ioffe et al. (2021) examining 315 patients undergoing open exploratory laparotomy on the gynecologic oncology service at a single center, all of whom were offered ITM. Of the patients in this study, 35% were given 200- 350 mcg of ITM with 20 mcg of intrathecal fentanyl, and the rest received IV opioids (Ioffe et al., 2021). Opioid requirements postoperatively were examined between 0-6 hrs, 6-12 hrs, and 12-24 hrs. Significant differences were found in morphine equivalents between 0-6 hrs, with 9.7 mg versus 14.3 mg ($p = <.0001$), and between 6-12 hrs with 2.7 mg versus 5.4 mg ($p =.0054$), in ITM and IV opioid groups respectively (Ioffe et al., 2021). The amount of IV opioid used in the 12–24 hr period did not differ significantly (Ioffe et al., 2021). Pain scores did not differ between the two groups despite lower morphine equivalent usage in the ITM group during the first 12 hrs (Ioffe et al., 2021). No difference was found in total morphine equivalents administered between the ITM and IV opioid groups over the cumulative 48 hrs studied (Ioffe et al., 2021). This study showed a shorter duration and overall benefit of ITM compared to prior studies. Ioffe et al. acknowledged the risk of self- selection bias where a patient with lower pain threshold may be more likely to opt for preoperative ITM, which is possible when conducting a retrospective study.

Radical Prostatectomy

To investigate the effect of ITM on the recovery post robot-assisted radical prostatectomy procedures, Koning, de Vlieger et al. (2020) examined pain scores and morphine use postoperatively in patients who either received ITM 300 mcg or a sham procedure plus IV opioid. Koning, de Vlieger et al. included 155 patients in their prospective double-blinded clinical trial. They found on POD-1, the number of patients who experienced extreme pain on a NRS was significantly decreased; with 13 less experiencing extreme pain in the ITM group and only 2 less in the control ($p = .002$). Additionally, the ITM group used less morphine overall during the admission at an average of 2 mg, versus 15 mg in the control ($p = <.001$), as well as less rescue medication (Koning, de Vlieger et al., 2020). The study only measured pain up to POD-1, unlike the studies performed by Pirie, Doane et al. (2022) and Koning et al. (2018), which measured through POD-3 but was significantly larger in population and provided strong evidence for a reduction in narcotics with ITM (Koning, de Vlieger et al., 2020).

Also interested in improving analgesia and outcomes for robotic prostatectomies, Bae et al. (2017) studied the use of ITM in a 30 patient prospective RCT. Patients were allocated to ITM 300 mcg with IV PCA or IV PCA alone as a control (Bae et al., 2017). On a NRS of 0 – 100 with 0 being pain free, and 100 being the worst pain imaginable, pain at 12 hrs postoperatively during rest was rated at 10 in the ITM group, and 50 in IV PCA group ($p <.001$) (Bae et al., 2017). With coughing at 12 hrs, pain was 20 and 60 in the ITM and IV PCA groups respectively ($p <.001$; Bae et al., 2017). At 24 hrs, pain at rest was 10 versus 40 ($p <.001$), and with coughing 20 versus 60 ($p = .001$) in ITM versus IV PCA respectively (Bae et al., 2017). No differences were observed with rest or coughing after 24 hrs (Bae et al., 2017). Morphine consumption postoperatively was lower in the ITM group at 12 and 24 hrs, with cumulative

consumption of 5 mg in the ITM group and 17 mg in the IV PCA group (Bae et al., 2017). Five

of the patients in the IV PCA group requested rescue analgesia during the 72 hrs postoperatively,

with no requests from the ITM group (Bae et al., 2017). Significant opioid sparing was observed,

with a reduction in pain for the first 24 hrs postoperatively.

Hepato-Pancreato-Biliary Surgery

Dichtwald et al. (2017) saw potential benefit with the use of ITM in the hepato-pancreatic

surgery population, where epidural catheters are commonly used for pain control, acknowledging

that coagulopathy can often delay epidural catheter removal due to the increased risk of epidural

hematomas in this population. Their RCT, comprised of 49 patients, compared the use of 4

mcg/kilogram (kg) ITM before skin incision to IV remifentanil infusion intraoperatively

followed by IV morphine 0.15 mg/kg 20-30 mins prior to incision closure, with both groups

receiving a PCA postoperatively (Dichtwald et al., 2017). Pain scores were evaluated in the

following 3 days postoperatively.

The ITM group had significantly lower pain scores than the IV group at most time points,

at rest and with coughing on POD- 1-2, and only while coughing during POD- 3 (Dichtwald et

al., 2017). There was a significant difference in the amount of rescue morphine requests with 12

patient requests in the control group and four in the ITM ($p =$.03; Dichtwald et al., 2017). The

morphine requirement was higher in the control group versus the ITM group; 14.7 mg versus 4.8

mg respectively. There was not a significant difference found in the demand and delivery of PCA

morphine across the 3- PODs (Dichtwald et al., 2017). Unlike the previously mentioned studies,

Dichtwald et al. found benefits in decreased pain scores through POD- 3, even though ITM

analgesic properties are known to only last about 24 hrs. The opioid sparing properties were

statistically significant ($p =$.03), with the added advantage of reducing the complication of

epidural hematoma during removal of a catheter in a potentially coagulopathic patient

(Dichtwald et al., 2017).

In another attempt to assess ITMs efficacy in the hepato-pancreatic population for the

reason of concern for coagulopathy with epidural removal, Niewiński et al. (2020) performed a

single-blind RCT with 36 patients. Patients received either IV PCA with preoperative ITM group

(400 mcg) or IV PCA without preoperative ITM (Niewiński et al., 2020). Pain scores were

collected over the first 3 days postoperatively at rest and with coughing. In contrast to previous

studies, the only time in which the ITM group had significantly lower pain scores, was at rest

during the first 24 hrs ($p =$.046). The rest of the time points, POD-1-3 at rest and with coughing,

showed no significant benefit with ITM in reduction of pain, as well as no benefit in the first 24

hrs with coughing (Niewiński et al., 2020). Also contradictory of previous studies, the number of

patients reporting episodes of clinically significant pain was identical in both groups (Niewiński

et al., 2020). Doses of cumulative morphine were also not clinically significant amongst the ITM

and IV control group, with 26 mg and 17 mg respectively ($p =$.257; Niewiński et al., 2020). The

study by Niewiński et al. (2020) was limited by the size, and differences in patient cohorts.

Patients who received ITM on average were younger, had lower American Society of

Anesthesiology (ASA) scores, and underwent major resections less than the IV group, with

primary liver malignancies occurring less frequently. Additionally, the patients and

anesthesiologists performing the injection were not blinded, and sham injections were not

provided in the control group, which could contribute to bias (Niewiński et al., 2020).

Tang et al. (2020) hypothesized that ITM would reduce postoperative opioid use and

enhance analgesia in patients undergoing open liver resection. Tang et al. conducted a

retrospective analysis of 216 patients at a single-center, 125 patients receiving ITM with doses

between 150-500 mcg, and 91 patients receiving what the authors defined as "usual care,"

meaning administering the medications which the provider would typically select if not included

in the study. In the PACU, the cumulative morphine equivalents were significantly lower in the

ITM group with none required, compared to usual care group at 6 mg (p =.001; Tang et al.,

2020). Opioid requirements were lower in the ITM group on POD- 0-1; 126.7 mg in the ITM

group versus 176.3 in the usual care (p =.04), with no statistically significant differences on

POD-2-3 (Tang et al., 2020). The median pain score on a NRS of 0-10 in the PACU was 1 in the

ITM group, compared to 4 in the usual care group (p =.001; Tang et al., 2020). At POD- 0,

median pain scores at rest were 3 versus 5 in the ITM group compared to the usual care group

respectively (p =.003; Tang et al., 2020). With movement on POD- 0, pain scores were 3 in the

ITM group versus 4 in the usual care group (p =.007; Tang et al., 2020). During POD-1-3, no

statistically significant difference in pain scores at rest were observed, and no differences were

found on POD- 2-3 (Tang et al., 2020).

No dose dependency was identified as there was not significant differences in pain scores

at rest or with movement in the doses observed between 150-200 mcg, 300 mcg, or 400-500 mcg

of ITM (Tang et al., 2020). Both oral morphine equivalents and pain scores in this study were

found to have significant reductions up to the 24 hr mark. The retrospective nature of the study

can produce a lack validity compared to a RCT, however the large sample size and the

congruence of the results with previous studies brings strength to the findings (Tang et al., 2020).

With acknowledgement of the benefit ITM has shown in RCTs and in ERAS protocols

for colorectal surgery, Liu et al. (2021) sought to study the benefit of ITM for patients

undergoing laparoscopic liver resection. A retrospective chart review was conducted at a single

center including 79 patients, comparing ITM (average dose 250 mcg) with PCA versus PCA

only (Liu et al., 2021). Postoperative pain and opioid consumption were measured over 48 hrs

showing a cumulative opioid consumption with a mean difference of -45.92 mg less in the ITM

compared to the PCA group (p =.015; Liu et al., 2021). The ITM group also demonstrated a

longer time before requiring opioids, 70 mins, versus 39 mins (p =.010; Liu et al., 2021). There

was no significant difference in pain levels assessed on a NRS at four time points: PACU,

discharge from PACU, ward arrival, and the 48 hrs postoperatively, despite lower opioid

consumption (Liu et al., 2021). Liu et al. found benefit in the findings of reduction in opioid

consumption, which they stress is particularly important in the setting of the opioid crisis.

Limitations for this study were the retrospective nature, potentially introducing selection bias, as

well as the small population size (Liu et al., 2021).

A large retrospective review with 233 patients was completed by Burchard et al. (2022)

investigating the effect of ITM on opioid consumption after pancreaticoduodenectomy. Patients

were categorized into three groups; no spinal anesthesia (36.5%), ITM (49.3%), or ITM with

transversus abdominus plane block (ITM + TAP; 14.2%; Burchard et al., 2022). Intrathecal

morphine doses ranged between 150 mcg to 300 mcg and were administered prior to induction

(Burchard et al., 2022). Total morphine equivalents were measured between POD- 0-3 and were

found lower for patients in ITM (121 mg) and ITM + TAP (132 mg), as compared to no spinal

(232 mg; p <.0001; Burchard et al., 2022). Unlike other studies, Burchard et al. found a decrease

in average daily morphine equivalents from POD-4 until discharge with lower doses for ITM

(18mg) and ITM + TAP (13.1 mg) as compared to no spinal (32.9 mg; p =.0016). After POD-3,

no additional opioids were requested in 23.5% of the ITM patients and 24.3% of the ITM + TAP

patients, compared to 2.3% of patients who did not receive any spinal analgesia (Burchard et al.,

2022). Postoperative pain scores were not found to be significantly different amongst the groups

between POD-0-3 (Burchard et al., 2022). This study was limited by its retrospective nature; however, it is the largest to date in examining ITMs effect on pancreaticoduodenectomy patients and calls for future prospective studies to gain insight on outcomes with ITM in this population (Burchard et al., 2022).

Respiratory Depression

As per the colorectal ERAS protocol developed, Gustafsson et al. (2019) stated that the main concern of using intrathecal opioids is the side effect of delayed respiratory depression. Due to the biphasic distribution of morphine, late respiratory depression is an adverse outcome that clinicians find concerning and may limit its use (Koning, Klimek et al., 2020). With the definition of respiratory depression being variable across studies, it can be a challenging data point to track. The meta-analysis performed by Koning, Klimek et al. (2020), defined respiratory depression as a situation when medical intervention such as mechanical ventilation or antagonistic medication was necessitated. Koning, Klimek et al. suggested a dose-dependent relationship between the risk of respiratory depression and dose of ITM. The incidence of respiratory depression was found to be 18 of 974 patients in the intrathecal opioid group, versus four of 888 patients in the control group (95% CI).

However, when two outlying studies with doses of >1,000 mcg of ITM were excluded from the evaluation, there was a similar incidence of respiratory depression between the two groups (CI 95%; Koning, Klimek et al., 2020). With the outlying high doses excluded, the majority of studies used ≤ 500 mcg, with a maximum dose of 800 mcg (Koning, Klimek et al., 2020). Koning, Klimek et al. suggested doses ≤ 500 mcg to reduce the risk of respiratory depression. To analyze further, subgroups were broken down into laparoscopic, laparotomic, addition of bupivacaine, and solely ITM, with no differences in respiratory depression found

amongst the groups (Koning, Klimek et al., 2020). Additionally, Koning, Klimek et al. suggests

avoiding benzodiazepines during the first 24 hrs, including coadministration for procedural

anxiolysis, because of a known side effect of potentiating respiratory depression.

An error from pharmacy which led to compounding morphine at 1000 mcg/milliliter (ml)

instead of the labelled 50 mcg/ml at a single center led Koning et al. (2022) to perform a

retrospective review of the six patients affected, then ultimately a systematic literature review

comprised of 104 studies. Typically, patients undergoing laparoscopic colonic resections at their

institution are given between 150 mcg- 250 mcg of ITM, with avoidance of benzodiazepines

(Koning et al., 2022). Of the six patients who received the erroneous batch of ITM, three were

found to have respiratory depression and somnolence with hypercapnia, with one experiencing

hypotension, and two having no detected adverse events (Koning et al., 2022). One patient had a

respiratory rate < 10, and one became hypoxic (Koning et al., 2022). Adverse events occurred

between 2-20 hrs post ITM and lasted up to 37 hrs, all resolving with supplemental oxygen and

opioid reversal with naloxone (Koning et al., 2022).

In their systematic review of the literature, Koning et al. (2022) found 54 episodes of

respiratory depression with the definition of respiratory depression being a respiratory rate < 10

breaths per min, or elevated $PaCO_2$. Thirty-eight patients required naloxone which resolved all

but two cases, and 12 needed ventilatory support (Koning et al., 2022). To further stratify the

dose dependent effect, life-threatening respiratory depression was categorized separately from

respiratory depression, and was found in 25 cases, with four recovering spontaneously, four

requiring mechanical ventilation, and 19 patients requiring opioid antagonism (Koning et al.,

2022). Figure 2 below from Koning et al. (2022) depicts the implication of dose on respiratory

depression. Hypoxemia was reported after doses of 4,000 mcg ITM, in addition to six other cases

which appeared cyanotic after doses of 10,000-15,000 mcg of morphine (Koning et al., 2022).

Severe respiratory rate depression of less than four breaths per min were reported in seven cases

after 3,000-15,000 mcg morphine (Koning et al., 2022).

Figure 2

Number of Cases with Somnolence and/or Respiratory Depression per Dose of ITM
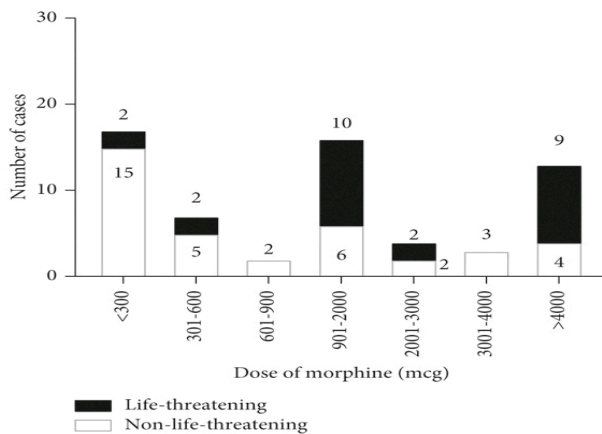
Note. Figure produced by Koning et al. (2022). Distribution suggests that more severe cases of respiratory depression are associated with higher doses of ITM, 15% of patients with doses <900mcg demonstrated life-threatening respiratory depression, versus 58% of patients with doses >900 mcg. From "Serious adverse events after a single shot of intrathecal morphine: A case series and systematic review" by Koning et al., 2022, *Pain Research & Management*, *2022,* 4567192. https://doi.org/10.1155/2022/4567192

Four cases of patients who received a dose < 900 mcg of ITM still met the criteria for

life-threatening respiratory depression, two of which had co-administration of benzodiazepines

(Koning et al., 2022). Flumazenil was able to resolve the respiratory depression in one of these

cases, while the other one resolved spontaneously (Koning et al., 2022). One of the four cases

had coadministration of continuous IV fentanyl in the post-operative period (Koning et al.,

2022). The other patient did not improve their Cheyne-Stokes breathing pattern with the

administration of naloxone (Koning et al., 2022). Through their systematic review and meta-

analysis, Koning et al. (2022) concluded that doses < 900 mcg of ITM have the potential to result

in respiratory depression with a risk of 15%, but found it only becomes life threatening with

coadministration of potentiating medications, while life-threatening respiratory depression is

associated with doses > 1,000mcg of ITM.

The multicenter double-blind RCT conducted by Pirie, Doane et al. (2022) assessed

respiratory depression over the first 12 hrs postoperatively, with oxygen saturation and

respiratory rate monitored twice an hour, along with level of sedation. A statistically greater

decrease in oxygen saturation (below 90%) was found in the control group with six adverse

events, and none detected in the ITM group, which had a median dose of 175 mcg of morphine

($p =$.049). Both groups were given an IV PCA of fentanyl postoperatively. Two events happened

in the PACU, with one patient requiring naloxone and high-flow oxygen. Another patient in the

control group had two episodes of low oxygen saturations while admitted and not receiving

supplemental oxygen (Pirie, Doane et al., 2022).

Many studies using lower range doses of ITM (<500mcg) found no greater risk of

respiratory depression associated with its use. Koning et al. (2018) used age dependent doses

between 240-300 mcg of ITM, with lower doses for the elderly, in their study of 56 patients

undergoing laparoscopic segmental colonic resections. Their study did not monitor respiratory

frequency or oxygen saturation during the first night but described "no clinically relevant

consequences of respiratory depression" by the medical staff observing the patients (Koning et

al., 2018). Burchard et al. (2022) found no difference in the rate of respiratory depression their

population amongst the ITM, ITM + TAP, and no spinal analgesia group, with a complication

rate of nine in 233 patients ($p >$.45). Likewise, the study by Selvam et al. (2018) found no

difference in respiratory depression across their population of subarachnoid bupivacaine only,

bupivacaine with ITM (200 mcg), or skin infiltration only groups. Liu et al. (2021) observed no

respiratory depression amongst two groups of ITM and PCA or PCA only in their study of 79

patients undergoing laparoscopic liver resection with a median dose from 230-270 mcg ITM.

Bae et al. (2017) administered 300 mcg of ITM plus IV PCA versus IV PCA postoperatively in

robotic prostatectomy patients and found no respiratory depression or need for naloxone. Tang et

al. (2020) observed no higher incidence of sedation and respiratory depression in their

retrospective study of 216 patients where patients received doses between 150-500 mcg of ITM.

No respiratory depression was found in either group of the study by Niewiński et al. (2020) with

36 patients undergoing liver resection who received IV PCA with preoperative ITM (400 mcg)

or IV PCA without preoperative ITM.

A RCT of patients undergoing hepato-pancreato-biliary surgery was constructed by

Cosgrave et al. (2020) with interest in prevention of respiratory depression after ITM. Higher

doses of ITM are required for procedures that necessitate upper abdominal incisions which

would increase the risk of dose dependent respiratory depression (Cosgrave et al., 2020).

Respiratory depression was defined as respiratory rate <10 breaths per min or oxygen saturation

<90%. At their hospital, Cosgrave et al. found a 31% incidence of respiratory depression using

the dose of 10mcg/kg of ITM, none of which required intubation, and 3% of patients were

administered naloxone. Because of the higher rates found at this facility, Cosgrave et al. studied

the use of a standardized low-dose naloxone infusion postoperatively. Patients were given the

usual dose of morphine, not to exceed 1,000 mcg, and were randomized to receive a naloxone

infusion postoperatively or saline as a control (Cosgrave et al., 2020). The incidence of

respiratory depression in the naloxone group was 10 in 48 patients, with the control being 21 in

47 patients ($p =.037$; Cosgrave et al., 2020). To its detriment, the naloxone therapy was found to

alter overall maximum pain scores, with a median score of 5 compared to the control group at 4

(*p* = <.001; Cosgrave et al., 2020). Additionally, postoperative fentanyl usage was significantly

higher in the naloxone group with a median dose of 100 mcg compared to the control at 20 mcg

(*p* = <.001; Cosgrave et al., 2020). While a low-dose naloxone infusion may decrease incidence

of respiratory depression after ITM, there is an increased need for postoperative narcotics and

still a chance of increased post-operative pain, which may be a greater dissatisfier for the patient

(Cosgrave et al., 2020). Naloxone infusions improve the safety profile of ITM, but case by case

considerations should be examined before deciding if it should be used as a prophylactic

medication or reserved for the treatment of respiratory depression if it occurs.

Pruritis

There is a significant difference in the incidence of pruritis in patients treated with

intrathecal versus systematic opioids of about of 30-60% versus 2-10% respectively (Wang et al.,

2021). In their large meta-analysis, Koning, Klimek et al. (2020) determined that the most

common undesirable side effect of ITM was pruritis with a relative risk ratio of 4.3 (CI 95%).

Additionally, a dose-dependent effect (CI 95%) was noted in the ITM ranges of 100-800 mcg

(Koning, Klimek et al., 2020). Pitre et al. (2020) identified a statistically higher incidence of

pruritis in their meta-analysis, with an odds ratio of 3.85 (CI 96%), between patients getting ITM

with PCA versus PCA alone. Pirie, Doane et al. (2022) found 15 incidences of pruritus in the

ITM group, with only five in the control group in their RCT of 51 patients (*p* =.007). Duration of

pruritis was monitored and patients were found symptomatic until POD- 2 (Pirie, Doane et al.,

2022). Koning, de Vlieger et al. (2020) evaluated pruritis on a NRS with 0 being none, and 10

being severe pruritis. Koning, de Vlieger et al. found increased pruritis in the ITM group with

an average rating of 4, versus none in the control (*p* =.000). Despite this, no treatment was

requested for pruritis in PACU, and it did not seem to affect any quality of recovery scores when

patients were interviewed (Koning, de Vlieger et al., 2020). In their RCT of 56 patients, Koning et al. (2018) found an incidence of 41% of patients experiencing pruritis versus only 8% in the control group, with the symptom only being present on POD- 1. Despite the incidence being so high, no patients in the study by Koning et al. (2018) requested treatment for pruritis, which is the same finding discovered by Koning, de Vlieger et al. (2020).

Dichtwald et al., (2017) observed only a slightly higher, rate of pruritus in their RCT of 49 patients, with five (22%) experiencing the symptom in the ITM group, and five (19%) in the IV opioid group, with the side effect only lasting during the first 4 hrs postoperatively. The results may be due to the small population, and the fact that the patients in the IV opioid group all received IV remifentanil intraoperatively with an IV bolus of morphine 0.15 mg/kg before the end of surgery, both known to increase the risk of pruritis. The prospective RCT by Bae et al. (2017) did not find a significant difference in rates of pruritis when assessed on a 4-point scale during the first 72 hrs postoperatively. Five patients (34%) of the ITM group versus two (14%) in the IV PCA group were symptomatic, with none reporting symptoms as severe (Bae et al., 2017). A higher morphine consumption was utilized the IV PCA group, which they believed accounted for less of a difference than what the rest of the literature had described (Bae et al., 2017). Additionally, the study by Bae et al. had a small population of 30 patients, making their results potentially insufficient to evaluate the effects of ITM on the incidence of pruritis.

Nausea

Large doses of IV opioids and ITM both possess the side effect profile of nausea. Nausea can lead to decreased dosing for analgesia and ultimately worse analgesia and prolonged recovery. The largest meta-analysis which included 2500 patients who were undergoing major abdominal surgery, open and laparoscopic, found no difference in the incidence of nausea

between ITM and IV opioids (Koning, Klimek et al., 2020). The comprehensive literature review by Pirie, Traer et al. (2022) confirmed the same findings. In the RCT of 51 people undergoing laparoscopic abdominal surgery, Pirie, Doane et al. (2022) found an incidence of nausea of 23 in the ITM group and 21 in the control ($p =$.31). Young et al. (2021) also did not find a significant difference in nausea in their retrospective study of 283 patients with 101 (80.8%) of patients experiencing the side effect in the ITM group, and 72 (79.1 %) of patients in the control. Young et al. attributed the finding to the fact that such large doses of opioids were required by the PCA group, which made up for the increased risk of nausea and vomiting that coincides with ITM. Additionally, Young et al. evaluated the incidence of nausea and vomiting requiring anti-emetics across different doses of ITM and did not find statistically significant increases in nausea as doses escalated; 150-200 mcg versus 300 mcg ($p =$.611), 300 mcg versus 400-500 mcg ($p =$.272), and150-200 mcg versus 400-500 mcg ($p =$.098).

Some studies did cite an increased incidence of nausea with ITM. The meta-analysis by Pitre et al. (2020), which included seven RCTs and 352 patients, was able to identify one study with higher rates of nausea and vomiting in the ITM with PCA group compared to the control ($p =$.016). Koning et al. (2018) observed more nausea during POD-1 for the ITM group, which reversed to the control group on POD-2 likely due to increased opioid use during that time. Antiemetics such as dexamethasone or scheduled 5hydroxytryptamine (5HT-3) receptor antagonists were not routinely utilized and Koning et al. (2018) acknowledged that their use may help decrease the risk of nauseas related to ITM. Preventative or scheduled used of antiemetics were not disclosed in the meta-analysis by Pitre et al. (2020), making it challenging to interpret the data as it is not standardized across the studies.

There were two smaller RCTs that observed a greater incidence of nausea in the IV opioid group. Dichtwald et al. (2017) observed six patients (26%) with nausea in the ITM group and eight (31%) in the IV opioid group in their population of 49 patients undergoing hepato-pancreatic surgery. Again, this study found significantly higher doses of morphine boluses IV postoperatively in the IV group than the ITM. Niewiński et al. (2020) observed nausea and vomiting in three patients (16.7%) in the ITM group and seven (38.9%) in the control group (p =.264). This data is difficult to interpret when it comes to total morphine dosing, as the study only quantified cumulative morphine doses across 3 PODs, finding a higher cumulative dose in the ITM group than IV only across the period. As such, it is challenging to correlate the data to total opioid dose at a given point in time, and Niewiński et al. (2020) describes it as a potentially accidental finding. Additionally, across the two groups, patients receiving ITM had overall lower ASA scores, underwent major resections less frequently, with fewer primary liver malignancies, which could skew the side effects and outcomes (Niewiński et al., 2020).

Length of Stay

Some, but not all studies cited shortened hospital stays with the use of ITM. Koning, Klimek et al. (2020) found lower pain scores with movement when ITM was used, which they concluded lead to early mobilization. Their large meta-analysis quoted a mean difference of -0.2 days, with an earlier fit for discharge at 0.3 days, which meant one out of every five patients would leave the hospital one day sooner (Koning, Klimek et al., 2020). Pirie, Traer et al. (2022) mirrored this sentiment across their literature search stating LOS was "marginally reduced." Koning et al. (2018) only found a marginal decrease in LOS, with a hospital stay of 4 days in the ITM and 5 days in the control (p =.270), however did observe an earlier fitness for discharge with the median being 3 days in the ITM group and 4 days in the control (p =.044). Niewiński et

al. (2020) found a slight reduction in LOS in their population of hepatectomy patients, with median being 6.5 days in the ITM group, and 7 days in the control (p =.044). The most significant benefit to LOS was the retrospective review of recovery after pancreaticoduodenectomy by Burchard et al. (2022), with a LOS with ITM+TAP of 6 days, ITM only of 7 days, and no spinal analgesia of 9 days. Days until functional recovery was assessed and found significant reductions in the ITM and ITM + TAP groups with a mean difference of - 0.57 days (p =.0018), as compared to no spinal analgesia with a mean difference of -0.9 days (p =.0003; Burchard et al., 2022).

In contrast, Ioffe et al. (2021) demonstrated a slight increase in LOS in their retrospective review of 315 gynecologic oncology patients, with the ITM group having a 17% increase, 6 versus 5 days, in their LOS (p =.02). Ioffe et al. acknowledged that this was not in agreement with other recent literature and studies and suggests that their results may be confounded by the retrospective nature. Young et al. (2021) also did not see a benefit in decreased LOS with ITM across laparotomy or laparoscopy patients undergoing colorectal surgery in their retrospective study of 283 patients. Laparotomy patients in the ITM group stayed on average 11 days versus 8 in the PCA group (p =.358), while the laparoscopy patients were 7.5 days versus 9 respectively (p =.756; Young et al., 2021). The limitations in this study with its retrospective nature allowed for potential confounding factors such as tolerance to opiates, pervious surgical history, and postsurgical complications (Young et al., 2021). In the retrospective study of patients undergoing open liver resection by Tang et al. (2020), the LOS was not found to be statistically different between ITM and the control group at 6 and 7 days respectively (p =.69). Additionally, Tang et al. observed patients in the ITM cohort had a longer median stay in the intensive care unit (ICU) at 17 hrs versus 10 hrs (p =.0001). This study was retrospective in nature and Tang et al. admits

it is subject to human error in interpretation and recording of data and may lack validity as compared to a RCT.

Discussion

Postoperative Narcotic Usage and Pain Scores

ITM has been integrated into ERAS protocols in colorectal surgery and has proven beneficial in decreasing postoperative opioid requirements, with vast interest across other major abdominal surgical specialties. The dosing of ITM used in the studies varied from 150-500 mcg, with only a few outlying higher unintentional dose administrations, and determined no evidence of a dose-dependent relationship to pain scores or narcotic usage. Most studies realized a reduction in pain scores and narcotic use during the first 24 hrs postoperatively. This data was strongly demonstrated and quantified in the meta-analysis by Koning, Klimek et al. (2020) across all major abdominal surgeries, in the colorectal population by Young et al. (2021), in the laparoscopic population by Pirie, Doane et al. (2022) and Koning et al. (2018), in the prostatectomy population by Koning, de Vlieger et al. (2020) and Bae et al. (2017), in the hepato-pancreato-biliary surgery population by Tang et al. (2020), and in the gynecologic population by Selvam et al. (2018).

Outlying data points for pain scores varied the most within the hepato-pancreato-biliary surgery population. Dichtwald et al. (2017) described an increased duration of ITM in their study of hepato-pancreatic patients, with lower pain scores in the ITM group through POD-2 and with coughing through POD-3 while observing significantly higher morphine requirements in the control group. Some studies saw no difference in pain scores postoperatively such as Liu et al. (2021), which could be a result of both groups receiving PCA in the postoperative period. Liu et al. did however observe an extended duration of benefit with opioid consumption being reduced

to the 48 hr time mark in the ITM group. Burchard et al. (2022) similarly found no difference in postoperative pain scores, however, did see a dramatic decrease in opioid use all the way through POD-4. Niewiński et al. (2020) found that the number of patients who reported clinically significant pain was similar between the ITM group and control, and there was not a significant difference in cumulative morphine dosing between the two groups. This outlying study is likely due to differences in the patient characteristics between the two groups, and the fact that neither patients nor clinicians were blinded.

In the gynecologic population, Selvam et al. (2018) demonstrated similar findings to the large metanalysis', however Ioffe et al. (2021) found only a significant reduction in opioid requirements during the first 6 hrs postoperatively, with more modest reductions between hours 6-12, and no significant difference between 12-24 hrs. Additionally, Ioffe et al. found no difference in pain scores between the two groups. The retrospective nature of the study could allow for skewed results, as well as the addition of fentanyl, where its additive relief would only be present during the first 6 hr period. The gynecologic population would benefit from a larger, prospective RCT to achieve more compelling results in the expansion of use for ITM.

Respiratory Depression

Provider concern of delayed respiratory depression has led to hesitation with use of ITM (Pirie, Traer et al., 2022). Studies using lower range doses of ITM generally found no increase in respiratory depression as compared to IV opioids. The study by Pirie, Doane et al. (2022) found significantly more respiratory depression in their cohort who received an IV PCA than the ITM. A dose-dependent increase in respiratory depression with ITM has been consistently observed across the literature, which providers should consider when choosing the optimal regimen for their patients. Based on the findings from their meta-analysis, Koning, Klimek et al. (2020)

suggested doses ≤ 500 mcg to reduce the risk of respiratory depression. The recommended

postoperative monitoring when patients are administered ITM is like that of patients receiving IV

PCA. Hourly monitoring should be performed and documented including respiratory rate,

oxygenation, and pain scores for the first 12 hrs post ITM, with two hourly readings for the

subsequent 12 hrs (Pirie, Traer et al., 2022). Koning et al. (2022) found 54 episodes of

respiratory depression in their study, where 38 patients required naloxone which resolved all but

two cases. Orders for opioid and benzodiazepine reversal such as naloxone and flumazenil

should be placed, and oxygen should be readily available (Pirie, Traer et al., 2022). Avoiding

medications that can potentiate ITM such as benzodiazepines is advised for approximately 24 hrs

(Koning, Klimek et al., 2020). Additionally, ITM should be used in caution with elderly patients

greater than 80 years of age, patients with obstructive sleep apnea, and those with chronic

respiratory and renal impairment (Tang et al., 2020).

Pruritis

The most consistent untoward effect of ITM across the literature was pruritis. Like with

respiratory depression, there was a dose-dependent relationship with the severity of pruritis,

however pruritis was never rated as severe. Most of the studies did not observe patients

requesting relief or treatment for the symptom. The duration of pruritis in major abdominal

surgeries likely lasts no longer than the time until discharge, with no studies reporting the side

effect past 48 hrs, and most declining after 24 hrs (Koning, Klimek et al., 2020). Two smaller

outlying studies did not find a significant increase in the incidence of pruritis, however both

studies utilized IV morphine at larger doses, which may have contributed to increased pruritis in

the control subjects. Further understanding on patients' perspective with pruritis may be

necessary and could be assessed with a patient driven quality of recovery review in larger trials (Pirie, Doane et al., 2022).

Nausea

Nausea varied across the studies, with the largest meta-analysis by Koning, Klimek et al. (2020) finding no difference between ITM and IV opioids in both laparoscopic and open approaches. Two studies cited increased nausea with ITM, one of which also had been given an IV PCA postoperatively, and the other found the symptom had reversed to the control group on POD-2, which was related to increased morphine requirements during that time. There were also two smaller RCTs that cited an increase in nausea in the control groups, both of which attributed this finding to higher doses of IV opioids postoperatively.

Length of Stay

There were inconsistencies in LOS data across the literature. Different metrics were used to track LOS such as time in the ICU, time until fitness for discharge, and actual LOS. The literature is pointing to a marginal reduction in overall LOS, and Koning, Klimek et al. (2020) attributed this to earlier time to mobilization due to lower pain scores. Additionally, the studies which did not observe a decreased LOS with ITM were retrospective and admit to confounding factors due to the nature. Given the necessity of increased monitoring when using ITM, it is important to consider the inpatient bed availability over the first 24 hrs. Even modest reductions in LOS can benefit patients and aid in decreasing hospital cost with enough volume.

Overall Satisfaction

Overall satisfaction is a challenging data point to track given its subjective nature and patients' unique experiences. It is more straight forward to compile data on specific side effects and assess severity of each rather than their effects on patient experience. Very few studies

tracked satisfaction as a data point. Koning et al. (2018) included satisfaction regarding pain

management on a scale of 0-3 with 3 being the most satisfied. On the day of surgery, they

observed that 40% of patients were satisfied with their pain management in the control group

versus 71% in the ITM group (p =.071), which on POD-1 became 48% and 61% respectively (p

=.401), and no difference in overall satisfaction was found (Koning et al., 2018). Koning, de

Vlieger et al. (2020) found no statistical difference on a NRS of 0-10, with 10 being most

satisfied, between the control group at 8, and the intervention group at 9 (p =.820). Koning, de

Vlieger et al. also quantified overall quality of recovery in their study, which on POD-1 there

was less of a reduction in quality of recovery in the intervention group at 10%, versus 13% in the

control (p =.019). These statistics, however, also showed no difference in quality of recovery for

the patients one week postoperatively (Koning, de Vlieger et al., 2020). Koning et al. (2018)

acknowledged that use of a quality of recovery questionnaire would be a beneficial adjunct to

measure patients overall experience, which is also recommended by the European Society of

Anesthesiology. The perspective of quality of recovery from a patient including the common side

effects would be a useful tool in gaining an understanding of patient satisfaction and experience.

Limitations and Gaps in the Literature

There is a degree of heterogeneity across the umbrella term of abdominal surgery which

adds to the complexity of evaluating the literature. Similar types of surgery were assessed for the

purpose of this literature review, including laparoscopic and open abdominal procedures,

colorectal surgeries, kidney surgeries, hepato-pancreato-biliary surgeries, radical

prostatectomies, and gynecologic procedures. There were five studies evaluating ITMs use in

hepato-pancreato-biliary surgery, where all but one identified opioid sparing properties. A lack

of studies with the use of ITM across gynecologic surgeries was found, with only one small

laparoscopic prospective RCT, and a larger retrospective review of open gynecologic oncology patients. The same is true for radical prostatectomies, with only one moderately sized prospective RCT, and one small prospective RCT. Both populations show promise in its use in reducing opioid requirements and call for larger RCTs.

When evaluating narcotic usage and pain, studies varied in the type and dose of control medications being used. Some studies dictated the opioids prescribed intraoperatively such as Niewiński et al. (2020) who administered 0.15 mg/kg of morphine IV prior to extubation, and Dichtwald et al. (2017) who infused remifentanil intraoperatively and dosed morphine 0.15 mg/kg IV at the end of surgery, while others such as Tang et al. (2020) described the control as "usual care," allowing the provider to select analgesic medications. Other studies, such as the retrospective review by Ioffe et al. (2021), included fentanyl in their intrathecal regimen which could skew pain scores in the PACU period. Quantification of IV morphine dose postoperatively was not collected across all studies, which is a valuable data point to determine if ITM is appropriate for a specific patient population. Not all studies followed pain scores on a NRS, and not all studied both pain scores and morphine equivalent dosing, which led to a wide variation in data points. Additionally, some studies tracked pain scores for 24 hrs, some up to 48 hrs, and others until POD- 3, with variation amongst potential duration of benefit. Only six of the studies evaluated pain with rest and with movement, which would be a valuable measurement to better understand the effect of ITM on patient satisfaction.

The incidence of nausea varied across the studies, with the largest meta-analysis finding no difference between ITM and IV opioids. The higher rates of nausea in the ITM cohort seemed to be linked to the addition of increased systemic opioids when the effects of the ITM waned,

thus confounding the relationship directly to ITM. There was no standardization in use of antiemetics across the studies which could make the data more challenging to interpret.

It is difficult to quantify overall effect on LOS due to the variation of surgeries studied. Most studies did demonstrate a marginally reduced LOS with two outlying retrospective studies reflecting increased LOS with ITM. This is another data point that warrants standardization across each specialty of abdominal surgery, especially given its impact on cost and patient satisfaction.

With proven beneficial use in colorectal surgery to be opioid sparing, more research with larger RCTs is justified to better understand how ITM effects specific populations, especially in the laparoscopic, gynecologic, and prostatectomy surgical populations. Patients' perspective in quality of recovery and acceptable side effects is lacking from the literature, with only three studies assessing it specifically in a questionnaire.

Conclusion

Throughout the literature there is clear evidence that ITM decreases opioid consumption and pain scores during the first 24 hrs after major abdominal surgery, which may facilitate enhanced recovery for patients postoperatively. There does not appear to be any benefit in improved pain management or duration of relief as doses of ITM escalate. The risk of delayed respiratory depression does exist, however with doses less than 500 mcg and avoidance of potentiating medications, the risk profile is greatly decreased (Koning, Klimek et al., 2020). Appropriate monitoring for respiratory depression should be routine for the first 24 hrs postoperatively, and orders for narcotic and benzodiazepine antagonists should be placed. Pruritis was increased with ITM over IV opioids, also in a dose dependent fashion, however most studies found that the irritation was tolerable and preferable for patients to achieve

increased pain relief and opioid reduction. The nausea risk profile was not found to be

significantly different between IV opioids and ITM. Length of stay is a data point that could be

evaluated in a more standardized manner to determine the exact benefit of the decrease, as the

studies show that there is a significant potential benefit for decreased LOS in reduction of

hospital costs and improved patient experience. The overall effect of ITM on patient satisfaction

has not been extensively studied and would be important information for practitioners to

understand to facilitate its use. With the negative consequences of pain postoperatively, as well

as the negative postoperative effects of opioid use and potential misuse that is exceedingly

problematic in society, ITM should be considered for patients undergoing major abdominal

surgery as an opioid sparing technique and for enhanced recovery after surgery. ITM has proven

beneficial in the literature for colorectal surgeries, with promising data of extended use in

laparoscopic abdominal procedures, prostatectomies, gynecologic surgeries, and hepato-

pancreato-biliary surgeries.

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