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ORIGINAL ARTICLE • KNEE- ARTHROPLASTY

Safety and side-effect profile of intrathecal morphine in a diverse patient population undergoing total knee and hip arthroplasty

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Abstract
Intrathecal morphine (ITM) can be useful for postoperative analgesia following lower extremity joint arthroplasty, but concerns exist regarding potential dose-related side effects. In this study, we examined the safety and efficacy of ITM in patients undergoing lower extremity joint arthroplasty. We hypothesized that there would be (1) direct relationship between dosing and side effects, and (2) an inverse relationship between ITM dosing and 24-hour postoperative opioid requirement.

Keywords Intrathecal morphine · Neuraxial · Anesthesia · Spinal · Arthroplasty · Hip · Knee

Introduction

Modern-day arthroplasty procedures and perioperative management are evolving as providers seek better outcomes at lower costs. Hospital stays are becoming shorter, expectations are changing, and awareness of the implications of pain management choices is coming to light. Modern perioperative protocols utilize a multimodal pathway incorporating preemptive analgesia, intraoperative anesthetic selection, and postoperative pain control with a focus on regional anesthesia and non-opioid analgesics. Although general anesthesia is the classic anesthetic choice, neuraxial anesthesia is becoming more commonly employed and has been shown to be as equally effective in total joint arthroplasty procedures without any increase in comorbidities [1]. The addition of a long-acting intrathecal opioid such as morphine (ITM) is an option to provide postoperative pain control after total joint arthroplasty. Prior studies have confirmed its utility for both total hip arthroplasty (THA) and total knee arthroplasty (TKA) citing improved pain control postoperatively [2, 3].

The first published report on opioids for intrathecal anesthesia was in 1901 [4]. Since that time, there has been an increasing usage of neuraxial anesthesia, and in 1979, ITM was successfully used in humans [5]. ITM has demonstrated efficacy for anesthesia as a single dose in many different types of surgeries [6–12]. However, there are a number of side effects associated with ITM including sedation, urinary retention, pruritus, nausea and vomiting, and respiratory depression, which may be delayed in onset [6, 13–22]. These can be especially undesirable in the elderly, such as those undergoing total joint arthroplasty procedures of the hip or knee, who may be more prone to medication side effects.

In a meta-analysis of twenty-eight publications, Gehling and Tryba sought out to quantify these feared side effects [23]. They only looked at randomized, placebo-controlled studies in order to calculate risk ratios of the 790 patients who received ITM versus the 524 placebo patients who did not receive ITM. ITM dosages were broken down into < 0.3 mg and > 0.3 mg. They found that nausea (RR 1.4), vomiting (RR 2.9), and pruritus (RR 1.8) were at a statistically significant increased risk compared to placebo with ITM < 0.3 mg, while dosages of ITM > 0.3 mg significantly increased the risk of pruritus (RR 5.0) only. As it relates to respiratory depression, ITM dosages were not statistically

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significant; however, they trended toward increased rates with higher dosages when compared to placebo. Respiratory depression in the placebo group was 2%, compared to 3% (ITM < 0.3 mg) and 9% (ITM > 0.3 mg). This is compared to Gwirtz et al. who reported a respiratory depression incidence of 3% in an analysis of 5969 patients without a placebo control who received between 0.2 and 0.8 mg ITM [24].

The objective of this study was to examine the safety and efficacy of ITM in patients undergoing lower extremity joint arthroplasty. We hypothesized that there would be (1) direct relationship between dosing and side effects, and (2) an inverse relationship between ITM dosing and 24-hour postoperative opioid requirement.

Methods

Patient selection and data collection

We retrospectively reviewed the charts in a select group of patients approved by the Virginia Commonwealth University Health System institutional review board (IRB). All patients who underwent a hip or knee arthroplasty between January 2012 and December 2014 received ITM (unless contraindicated) as part of the standardized anesthesia pathway and were included in this study. The primary outcomes of this study were side effects associated with ITM including postoperative respiratory depression, postoperative nausea and vomiting (PONV), and pruritus within the first 24 h after surgery. Secondary outcomes included pain management within the first 24 h after surgery.

Postoperative respiratory depression was determined by the presence of any one of the following within the first 24 h after surgery: respiratory rate less than 10 breaths per minute, any pulse oximeter oxygen saturation (SpO2) less than 90%, naloxone administration, or the need for advanced level of care due to respiratory compromise. PONV and pruritus were evaluated by documentation and further quantified by the number of medications given within the first 24 h after surgery specific to the condition.

Demographic information and health characteristics, including age at surgery (years), sex (male, female), ethnicity (white, nonwhite), body mass index (BMI; kg/m^2), and American Society of Anesthesiologists class (ASA) were collected as potential associated variables. The dosage of ITM was categorized into dose ranges of < 0.3 mg, 0.3 mg, > 0.3 mg. Pre-surgery administration of celecoxib, acetaminophen, dexamethasone, transdermal scopolamine, and/or gabapentin was documented as yes or no. All patients had available a periarticular cocktail injection consisting of a mixture of 0.5% ropivacaine, 30 mg Toradol, 0.5 mg epinephrine, and 0.08 mg clonidine in normal saline that was injected into the soft tissues at the discretion of the surgeon. The need for narcotics within the first 24 h postoperatively was evaluated by documenting the time (hours) to the first narcotic pain medication and the total morphine equivalents (ME) required.

Statistical analysis

Medians and interquartile ranges or frequencies and percentages were used to summarize the study variables. Comparisons of side effects and postoperative 24-hour opioid requirements were performed using Pearson's Chi-square tests and Kruskal–Wallis tests. A multivariable logistic regression was used to identify demographic and clinical characteristics related to respiratory distress, pruritus, and PONV, separately. Odds ratios (OR) and 95% confidence intervals (CI) were reported for each association. All inference was performed at the 0.05 level.

Results

ITM side effects

A total of 1022 patients were included in the study. Patient information is presented in Table 1. Thirty-four (3%), 547 (54%), and 457 (46%) of patients experienced postoperative respiratory depression, PONV, and pruritus, respectively. No differences in the respiratory depression rates were observed and varied from 2.0% in the > 0.3 mg dosing group to 3.3% and 3.9% in each of the 0.3 mg and < 0.3 mg dosing groups, respectively ($P = 0.683$) (Table 2). Similarly, the PONV rate in each of the dosage groups was not found to be different, with 129 (56%), 366 (53%), and 52 (53%) in each of the < 0.3 mg, 0.3 mg, and > 0.3 mg dosage groups ($P = 0.624$). Postoperative pruritus was significantly less common in the < 0.3 mg dosage group ($N = 79$, 35%) than either of the 0.3 mg ($N = 334$, 48%) or > 0.3 mg ($N = 44$, 45%) groups ($P = 0.002$).

After adjusting for the demographic and clinical characteristics, dosage of ITM was related to pruritus ($P = 0.001$) but not respiratory depression ($P = 0.838$) or PONV ($P = 0.613$). Specifically, dosages of 0.3 mg and > 0.3 mg were more likely to produce itching than a dosage of < 0.3 mg (Table 3). Within the other characteristics, females were more likely than males to have PONV and pruritus. Patients with more severe ASA classifications were more likely to experience postoperative side effects, with respiratory depression reaching statistical significance ($P = 0.027$). Additionally, younger patients were more likely to have pruritus and PONV ($P = 0.008$; $P < 0.001$, respectively).

Table 1 Patient demographic and clinical characteristics

Variable	Level	Summary
Ethnicity	White	712 (70%)
	Black	278 (27%)
	Other	32 (3%)
Sex	Male	473 (46%)
	Female	549 (54%)
ASA class	1	31 (3%)
	2	669 (65%)
	3	314 (31%)
	4	7 (< 1%)
ITM dosage	< 0.3 mg	229 (22%)
	0.3 mg	695 (68%)
	> 0.3 mg	98 (10%)
Pre-surgery medications	Yes	166 (16%)
	No	856 (84%)
Age		62.7 [55.3, 70.0]
Morphine equivalents		30.0 [15.0, 60.0]
Number of antipruritics	0	565 (55%)
	1	299 (30%)
	2	138 (13%)
	3	16 (2%)
	4	4 (< 1%)
Number of antiemetics	0	481 (47%)
	1	229 (48%)
	2	55 (5%)

ME dosage in the first 24 h

Fifty-nine patients (6%) did not require additional analgesics in the first 24 h after surgery. An additional 87 (9%) patients had non-narcotic pain medications within the first 24 h. For those subjects that received narcotic pain medication after surgery, the median ME in the first 24 h after surgery was 30.0 [IQR 15.0, 57.5], 30.0 [IQR 15.0, 60.0], and 37.5 [IQR 15.0, 65.0] for ITM dosages of < 0.3 mg, 0.3 mg, and > 0.3 mg, respectively ($P = 0.053$). Patients who received any pre-surgery medications had identical median morphine equivalent values of 30.0 with interquartile ranges of [15.0, 60.0] and [15.0, 45.0] for the unmedicated and medicated groups ($P = 0.096$).

Discussion

The most feared side effect of ITM is respiratory depression. The peak onset of respiratory depression occurs 5–10 h after injection with an incidence of around 3% [3, 14, 23, 24]. This is similar to what we found in our study. A recent meta-analysis of randomized, placebo-controlled studies reported a 2% incidence of respiratory depression in a placebo group who did not receive ITM, compared to 3% in those that received < 0.3 mg ITM and 9% in those who received > 0.3 mg ITM; however, these were not significant [23]. In addition, we did not find a relationship between respiratory depression and any ITM dosage. Gwirtz et al. [24] also reported this finding in one of the largest, non-placebo-controlled studies analyzing ITM up to a dosage of

Table 2 Relationship between intrathecal morphine (ITM) dosage and side effects

ITM dosage	Respiratory depression	*P*	Nausea/vomiting	*P*	Itching	*P*
< 0.3 mg	9 (3.9%)	0.683	129 (56%)	0.624	79 (35%)	0.002
0.3 mg	23 (3.3%)		366 (53%)		334 (48%)	
> 0.3 mg	2 (2.0%)		52 (53%)		44 (45%)	

Table 3 Relationship between demographic and clinical characteristics with side effects

Variable	Difference	Respiratory distress		PONV		Itching	
		OR	*P*	OR	*P*	OR	*P*
ITM dosage	0.3–< 0.3	0.89 (0.40, 2.00)	0.781	0.86 (0.63, 1.17)	0.325	1.84 (1.33, 2.53)	< 0.001
	> 0.3–< 0.3	0.61 (0.12, 3.12)	0.553	0.90 (0.54, 1.49)	0.676	1.78 (1.06, 2.99)	0.031
	0.3–> 0.3	1.46 (0.33, 6.55)	0.621	0.95 (0.61, 1.48)	0.758	1.03 (0.66, 1.61)	0.883
ASA class	(3 or 4)–(1 or 2)	2.98 (1.13, 7.88)	0.028	1.26 (0.96, 1.66)	0.093	1.33 (1.00, 1.76)	0.047
Sex	Female–Male	1.33 (0.64, 2.77)	0.449	1.38 (1.06, 1.79)	0.015	1.64 (1.26, 2.14)	< 0.001
Race	White–Other	0.69 (0.32, 1.46)	0.330	0.98 (0.74, 1.30)	0.884	1.19 (0.90, 1.59)	0.229
Pre-surgery medications	Yes–No	1.39 (0.59, 3.27)	0.455	0.95 (0.68, 1.33)	0.758	1.39 (0.98, 1.95)	0.063
Age	(5 year decrease)	0.96 (0.82, 1.13)	0.632	1.08 (1.02, 1.15)	0.008	1.10 (1.03, 1.17)	0.002

0.8 mg. Other studies have suggested that dosages > 1 mg carry increased risk of respiratory depression [14].

The incidence of nausea and vomiting has been reported up to 100% in those who receive ITM [22]. In addition, orthopedic surgery has been shown to be an independent predictor of PONV [25]. ITM dosages greater than 0.3 mg may increase the risk of side effects, specifically PONV, pruritus, and respiratory depression [23]. In placebo-controlled trials, the incidence of nausea and vomiting is 28% and 12%, respectively, in patients who do not receive ITM, and in those who receive ITM there appears to be no dose–response relationship at it relates to nausea [23]. Our study also found that the incidence of PONV was not related to the ITM dose. This is in contrast to other studies that suggest there is a relationship. Cheah et al. [26] retrospectively looked at a group of 598 patients in a multimodal pain pathway and found that patients who received ITM were less likely to develop PONV compared to those that did not. They also found a trend for decreasing PONV in the females. Interestingly, however, we did find a statistically significant association between female gender and PONV. This is further supported in the literature by other studies [25, 27, 28].

Our study found that the incidence of postoperative pruritus increased with higher ITM dosages which is consistent with the previous literature [23]. Gwirtz et al. [24] looked at 5969 surgical patients and found that pruritus was the most common side effect. ITM naïve patients have a 12% incidence of pruritis when taking only systemic opioids compared to 37% in those who receive ITM [23, 24]. Pruritis had an incidence of 46% in our study of all comers and was second to PONV (54%) as the most common side effect. The exact mechanism of ITM-induced pruritus is unclear, and a recent study suggests a possible role of serotonin [29].

This study failed to demonstrate a relationship between the dosages of ITM and narcotic requirement during the first 24 h after surgery. We hypothesized that there would be an inverse relationship between ITM dosing and 24-hour postoperative opioid requirement. Previous studies have suggested the utility of ITM as an important adjunct to postoperative pain control [2, 3]. Fischer and Simanski reported on a collaboration of European anesthetists and surgeons whom conducted the first systematic review of randomized controlled trials of analgesic, anesthetic, and surgical interventions affecting postoperative pain control after THA [2]. This work group reached a consensus recommending general anesthesia with a peripheral nerve block or spinal anesthesia with the addition of an intrathecal narcotic along with NSAIDs and narcotics as needed for optimal management after THA. Dosages of 0.1 mg ITM have been proposed as a good balance between improved analgesia and decreased side effects [30] This is further supported by Rathmell et al. who showed that ITM dosages between 0.1 and 0.2 mg improved not only pain control but higher doses improved patient satisfaction [6]. Bowery et al. [3] looked at the relationship between postoperative pain control and its relationship to ITM dose after TKA as well as side-effect profile. In this randomized double-blind study, they found that 0.5 mg ITM dosages required less postoperative narcotics than those in the 0.2 mg ITM group. These are in contrast to the findings of our study that found no relationship between decreasing narcotic use and increasing ITM dosage.

There are several limitations to this study. First, this is a retrospective chart review that included manual extraction of data through the electronic health record. Data points may have been missed, or entry by nursing and medical staff may have been inaccurate. Second, we did not split the cohort of patients to evaluate differences between THA and TKA. Third, we did not have a control group. The anesthesia standard of care at our institution during this time period was for all arthroplasty patients to receive ITM. Additionally, it would not be reasonable to use historical controls prior to ITM due to the fact that the entire practice model had changed including the use of multimodal medications and periarticular cocktail injections. A prospective, randomized control study would be ideal to answer the true effect of ITM on post-op pain control in addition to the side-effect profile. Fourth, we did not analyze narcotic use beyond the 24-hour mark. Our review was not designed to evaluate overall opioid consumption focusing primarily on the side-effect profile. Given the use of multimodal analgesics, we could not control for morphine alone. Future studies are warranted to investigate this topic. Fifth, only a small subset of patients received medications prior to surgery (celebrex, tylenol, decadron, scopolamine patch, and/or gabapentin). Cheah et al. [26] showed that ITM used in a multimodal pathway decreased postoperative narcotic use. Sixth, there is no standard definition for respiratory depression, so we used multiple surrogates including any documented respiratory rate less than 10 breaths per minute, any pulse oximeter oxygen saturation (SpO2) less than 90%, any documented naloxone administration, or the need for advanced level of care due to respiratory compromise. Finally, length of stay, discharge destination, and patient satisfaction were not analyzed as it relates to ITM. These are important things to consider, and future research is warranted.

Conclusion

Intrathecal morphine may not have an effect on the opioid requirement in patients undergoing lower extremity arthroplasty in the first 24 h after surgery; however, pruritus increases at doses over 0.3 mg and is more prevalent in females. PONV and respiratory depression, the major safety concern, do not appear to have a dose response in this setting.

Compliance with ethical standards

Conflicts of interest Shane R. Hess, Laura A. Lahaye, Andrew C. Waligora, and Adam P. Sima have no conflicts of interest. William A. Jiranek discloses he is a paid consultant, receives royalties, had has stock with DePuy Synthes, and receives research support from DePuy Synthes and Stryker. Gregory J. Golladay discloses he is a paid consultant for OrthoSensor Inc., receives royalties and research support, has stock, and gives paid presentations for OrthoSensor Inc.; he is the deputy editor for Arthroplasty Today, on the editorial board for Journal of Arthroplasty, and is the publications committee chair for AAHKS.

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