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Intrathecal Morphine versus Extended Release Epidural Morphine for Postoperative Pain Control in Pediatric Patients Undergoing Posterior Spinal Fusion

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Abstract

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Background—Posterior spinal fusion for scoliosis is one of the most painful elective pediatric surgeries. Good postoperative pain control allows early ambulation and return of ability to tolerate oral intake. Options for analgesia in this patient population are suboptimal. We hypothesized that extended-release epidural morphine (EREM) would provide better pain control and less adverse effects compared to intrathecal (IT) morphine.

Methods—The primary outcome was total IV morphine consumption during 0–48 hours post-operatively. Secondary outcomes included time until first PCA demand, pain scores and adverse opioid effects. Seventy-one subjects undergoing posterior spinal fusion for idiopathic scoliosis completed the study. The subjects were randomly allocated to IT morphine 7.5 mcg/kg or EREM 150 mcg/kg. The final IT morphine and EREM groups contained 37 and 34 subjects, respectively. Post-operative pain was treated with morphine patient controlled analgesia (PCA), ketorolac, oral oxycodone and acetaminophen. Morphine consumption, pain scores, nausea and vomiting, pruritus, and respiratory depression were measured every 4 hours. Parents completed a caregiver questionnaire about their child's pain control regimen after the first post-operative day.

Results—There was no difference in total morphine consumption over the first 48 hours between subjects in the EREM and IT morphine groups: median (range) 42.2 (5.5–123.0) and 34.0 (4.5–128.8) mg, respectively ($p=0.27$). EREM and IT morphine groups had no difference in time until first PCA demand. Pain scores were no different between the groups from 8–24 hours after surgery. Compared to IT morphine, EREM subjects had lower pain scores from 28–36 hours after surgery. The reported incidence of pruritus was lower in the EREM subjects.

Conclusions—There was no difference in total morphine consumption or time until first PCA demand between the EREM and IT morphine groups. EREM provides a longer duration of analgesia after posterior spinal fusion for scoliosis and may be associated with less opioid induced pruritus.

Introduction

Postoperative pain control after posterior spinal fusion is an essential component in the care of patients with idiopathic scoliosis. Analgesic options include intravenous (IV) opioids via patient-controlled analgesia (PCA), epidural infusion of opioids with or without local anesthetic, or intrathecal (IT) morphine. Neuraxial opioids carry the benefit of decreased need for parenteral opioids, resulting in fewer systemic side effects in the post-operative period. Low-dose IT morphine supplemented by PCA morphine provides better analgesia than PCA morphine alone after spinal fusion in children.^{1,2} A single injection of epidural morphine has also been used successfully for analgesia after spinal fusion for scoliosis in children.³ Most of the literature regarding neuraxial intervention for spine fusion patients consists of retrospective reports or descriptions of a treatment group without comparison to another type of analgesia. The standard of care at our hospital is to give between 5 and 10 mcg/kg IT morphine prior to surgical incision to help decrease postoperative pain after spinal fusion surgery. One of the disadvantages of IT morphine is the short duration of action. The analgesic benefit wears off early in the morning on post-operative day 1. This increase in pain often coincides with the first physical therapy session. Another disadvantage is the adverse effects of pruritus, nausea, sedation, and respiratory depression. A pain

regimen that provides longer analgesia and fewer adverse effects could improve patient satisfaction and speed recovery by providing better pain control during physical therapy.

Extended-release epidural morphine (EREM) is a preservative-free sterile suspension of DepoFoam multivesicular liposomes (Pacira Pharmaceuticals) containing morphine. When compared to single shot plain epidural morphine, EREM has been shown to provide a longer duration of post-operative pain control after caesarean section,^{4, 5} lower abdominal surgery,⁶ and total hip arthroplasty.^{7, 8} After total knee arthroplasty, subjects treated with EREM used threefold less postoperative opioid compared to placebo.⁹ The adverse effect profile of EREM is similar to plain epidural morphine and includes nausea, vomiting, pruritus, and hypotension.

This randomized controlled double-blinded trial compared IT morphine with EREM for pain control after posterior spinal fusion for adolescent idiopathic scoliosis (AIS). The hypothesis was that EREM would be associated with less morphine consumption over the first 48 hours after surgery. Secondary outcomes included time until first analgesic request, pain scores, adverse reactions, days until discharge, and parent satisfaction.

Materials and Methods

The primary outcome was total IV morphine consumption during 0–48 hours post-operatively. Secondary outcomes included time until first PCA demand, pain scores and adverse opioid effects. The *a priori* assumption was that decreased total morphine post-operatively would demonstrate superior pain control. This study was designed in accordance with the CONSORT 2010 guidelines^{10, 11} as a randomized prospective double-blinded trial for transparency of recruitment and subject enrollment (Figure 1). We were granted an Investigational New Drug Application (IND) from the Food and Drug Administration for the use of epidural extended release morphine (EREM). After Institutional Review Board approval, the study was carried out at Children's Hospital Colorado over a three year period (ClinicalTrials.gov NCT00880607). All patients who met eligibility criteria were considered for participation. Inclusion criteria were males and females between 8–17 years-old, ASA status 1 or 2, who were undergoing thoraco-lumbar posterior spinal fusion for idiopathic scoliosis. There was a possibility that surgery at the level of epidural injection (lumbar) could disrupt the EREM medication. Approximately 12% of our AIS surgical population have spine fusions that do not extend past T12 into the lumbar region. There might be a disparity if some EREM patients had solely thoracic level surgery, with little chance for medication disruption, compared to patients who had thoracic and lumbar level surgery, which might disrupt the EREM. In order to avoid developing these two subpopulations in the EREM group, we elected to include only patients with surgery that extended into the lumbar region, L1 or lower. Exclusion criteria included neuromuscular scoliosis, allergy to morphine, history of OSA, abnormal pain thresholds, a contraindication to dural puncture, and cognitive deficits that would impair use of PCA (patient controlled analgesia). A total of 84 subjects were enrolled in this study. Thirteen subjects were withdrawn due to unblinding, inability to administer study medication, spinal fusion that did not extend below L1, or a change in health status after the time of consent. The final intrathecal (IT) morphine and EREM groups contained 37 and 34 subjects, respectively.

Once consent and subject assent, when appropriate, were obtained, the subject was randomly allocated by a pre-enrollment computer generated randomization table into one of two groups in a 1:1 ratio. The group that received IT morphine was given preservative-free morphine at a dose of 7.5 mcg/kg and the EREM group received a dose of 0.15 mg/kg. All surgeries were done by one of two orthopedic surgeons. All intrathecal/epidural injections were performed by the anesthesiologist before surgical incision. The subject and subject's parents, the surgeon, nurses and the investigator following the subject post-operatively were blinded as to study group. The research pharmacy sealed the medication in an envelope, preventing anyone but the anesthesiologist administering the medication from seeing which medication was given. A sealed envelope containing the information about which specific drug was administered went with the subject's chart in case of emergency.

Anesthesia and intrathecal (IT) morphine vs. extended-release epidural morphine (EREM) administration

Anesthesia was induced with propofol and/or sevoflurane. The use of ketamine was prohibited since the analgesic properties could potentially confound the study outcomes. At the start of surgery, subjects received a 2 – 5 mcg/kg bolus of fentanyl (maximum 250 mcg). After induction of general anesthesia and placement of an endotracheal tube, the subject was turned to the lateral decubitus position for lumbar IT or epidural injection, depending on the subject's randomization group. Standard aseptic technique was used. For Group ITM, a 24 gauge spinal needle was placed through the dura between levels L3–L5 to deliver the preservative free morphine at a concentration of 7.5 mcg/kg. For Group EREM, an 18 gauge Tuohy needle was used with standard loss of resistance technique to administer 0.15 mg/kg of EREM between levels L2–L5. The doses of IT morphine and EREM were selected with the goal of being equipotent based on previous studies; however, there is no head to head comparison of the two medications in the literature. The dose of IT morphine falls within reported ranges from published studies in this population.^{1, 2, 12, 13} The weight-based dose of EREM was chosen by extrapolating from recommended dosing in adults of 10–15 mg while assuming that an average adult weighs 70–80 kg.

Subjects received a total intravenous anesthetic with propofol infusion between 100 – 250 mcg/kg/min and remifentanyl infusions 0.05 – 0.5 mcg/kg/min titrated by the anesthesiologist as clinically indicated by monitoring vital signs and depth of anesthesia as observed with neuromonitoring.

Opioids used in the operating room included remifentanyl, fentanyl, morphine and/or hydromorphone. Opioids were titrated to respiratory rate, heart rate, and blood pressure at the discretion of the anesthesiologist. There was minimal variation between anesthetics and surgical technique; however, several anesthesiologists provided care for study subjects and intraoperative supplemental opioids as well as ketorolac were not standardized. The analgesic medications administered intraoperatively were recorded for analysis. Anti-emetic medications were used at the discretion of the anesthesiologist.

Postoperative pain management

All subjects had the same regimen for postoperative pain management: morphine patient controlled analgesia (PCA), scheduled acetaminophen, scheduled oxycodone started on post-operative day 1 and scheduled ketorolac which was given 24 hours after surgery. Subjects were given oral medication unless they were having frequent emesis. All subjects were monitored with continuous pulse oximetry, as is standard post-operative care for all patients that receive neuraxial opioids at our institution. The dosing of oxycodone, acetaminophen, and ketorolac were the same in both groups.

Measurement of Morphine Consumption, Pain Scores, and Side Effects

At four hour intervals, the following data were collected: IV morphine consumption, PCA demands and deliveries, pain score (Bieri Faces scale 0–10),¹⁴ presence of nausea and/or vomiting (scale of 0 – 2, no nausea =0, nausea = 1, emesis = 2), pruritus (present or absent), and respiratory depression ($\text{SpO}_2 < 88\%$). If the subject was sleeping at the time a score was due, they were not disturbed and a pain score was not recorded for that time point.

Caregiver satisfaction questionnaire

Parents were provided with a questionnaire on post-operative day 1 and the completed questionnaire was collected at 48 hours after surgery. The time frame of 24–48 hours was chosen because it is the interval during which we expected the largest potential difference in drug effect. ITM effect lasts approximately 16–24 hours, while EREM is reported to last 24–48 hours. If we had waited to ask the questions until the end of the hospital stay, the parents would be including the oral analgesic regimen in their assessment. Our study was designed to assess differences between the two medications during their anticipated duration of action. The questionnaire asked the following 1) Did your child itch a lot from the pain medication, 2) Did your child feel too sleepy from the pain medication, 3) Did the pain medicine make your child feel like throwing up, 4) Was your child in moderate to severe pain at any time after surgery, 5) Please circle a number to show the worst pain your child has had while lying quietly and resting (1–10), 6) Please circle a number to show the worst pain your child has had after getting up in bed or when out of bed (1–10), 7) Before surgery, how much pain did you think your child would have after surgery, 8) Overall, how satisfied were you with the pain relief your child received after surgery, 9) If your child needed surgery again, would you want the pain treated in the same way.

Statistics

SAS 9.3 (SAS Institute Inc., Cary, NC, USA.) was used for all the analyses. Comparison between two treatment arms in total post-operative IV morphine consumption was made using Wilcoxon rank sum test since the outcome variable was found to have a skewed distribution. Ninety-five percent confidence interval for between-treatment difference in median of total post-operative morphine consumption was calculated using Hodges-Lehmann estimation method. Log rank test in Kaplan-Meier analysis was used to compare the time to the first PCA demand request between treatment arms. Serial pain score data were analyzed using a linear mixed effects model with unstructured covariance where the fixed effects include measurement times and treatment as classification variable and their

interaction term. No adjustment for multiple comparisons was applied but all p-values of interest are reported. Adverse effects and survey data were analyzed using chi square test. P-value < 0.05 from a two tailed t-test was deemed to be statistically significant.

Power Analysis

No previous data is available for determining the potential effect size of the difference in morphine consumption between the two study groups in this subject population. Because it was anticipated that a small number of enrolled subjects would need to be excluded because of study protocol violation, the enrollment goal was set at 40 subjects per group, yielding an anticipated sample size of 36 subjects per group in the final analysis. With the sample size of 36 subjects per group, there would be 80% power at 5% level to detect the effect size of 0.67 times SD (Cohen's d) using two-tailed t test.

Gall et al.¹ reported that the mean and standard deviation of the first 24 h of PCA morphine consumption are both 12 mg for 10 children who had spinal fusion and received one dose of IT morphine (5 mcg/kg). Assuming these parameters for the IT group and common SD for the EREM group, the 0.67 Cohen's d corresponds to 8.04 mg between-group difference in total morphine consumption over 48 post-operative period (the primary outcome).

Results

A total of 71 subjects completed the study, 37 in the intrathecal (IT) morphine group and 34 in the extended release epidural morphine (EREM) group. The subject demographics are summarized in Table 1. Randomization into the two groups produced clinically similar subjects in terms of age, weight, number of levels fused, gender, and race/ethnicity. Both groups had more females than males, which is the normal distribution in this disease. Intraoperative dosing of IV opioids and ketorolac was not significantly different between the groups (Table 2).

Primary outcome

Subjects who received EREM had similar total morphine consumption over the first 48 hours compared to IT morphine: median (range) 42.2 (5.5–123.0) and 34.0 (4.5–128.8) mg, respectively (p=0.27). The Hodges-Lehman estimates of between-group median difference was 7.7 with 95% confidence interval of -5.8 to 21.2. (Table 3)

Secondary outcomes

Median time to first PCA demand was 0.99 hours for IT morphine and 0.92 hours for EREM group and the difference between two groups was not significant (p=0.42, Figure 2). There was a significant difference in the chronological pattern of self-reported pain scores between the IT morphine group and the EREM group (p<0.0001 for testing the interaction of time by treatment group). The pain scores reported immediately after surgery, and then 4 hours later, were significantly higher in subjects who received EREM compared with ITM (Figure 3). From 8–24 hours after surgery, the pain scores were similar in both groups, with the exception of 16 hours. At the 16 hour time point, EREM showed significantly lower pain scores. Starting at the 28 hour time point, EREM was associated with significantly lower

pain scores. This advantage of EREM over IT morphine was statistically significant at 28, 32 and 36 hours post-operatively. At the 40 hour time point, the pain scores of each group began trending back together.

The incidence of any type of adverse opioid effect was not statistically significant between the two treatment groups, EREM vs. IT morphine: nausea (26% vs. 46%, $p = 0.08$, difference (95% CI): 19% (-2.4% to 41.3%), emesis (15% vs. 24%, $p = 0.30$, Difference (95% CI): 9.6% (-8.6% to 27.9%), pruritus (62% vs. 81%, $p = 0.07$, Difference (95% CI): 19% (-1.3% to 40.0%)), and respiratory depression (15% vs. 24%, $p = 0.31$, difference (95% CI): 19% (-8.6% to 27.9%)) (Figure 4). It should be noted that nausea and pruritus had low p values, marginally significant ($p < 0.1$). There was no difference in the number of post-operative days until subjects were discharged from the hospital. There was no difference in the number of post-operative days between EREM and ITM: 4.9 (0.82) vs. 4.9 (1.3) respectively, $p = 0.96$. The 95% confidence interval for the between-group difference was -0.5 to 0.53 days.

Parent questionnaire results showed similar overall satisfaction with each pain control modality (Figure 5a-e). There was a significant difference in the response to the question "Did your child itch a lot from the pain medicine?" with more parents reporting itching with ITM than EREM (Figure 5b), 65% vs. 38% ($p = 0.02$).

Discussion

This study examines a new modality for controlling postoperative pain in spinal fusion patients: extended-release epidural morphine (EREM). Compared to standard treatment with intrathecal (IT) morphine, which gives pain control that lasts 18–24 hours, EREM is reported to provide analgesia for over 24 hours. With IT morphine, the loss of analgesic benefit often coincides with the time when a patient is beginning physical therapy on the first day after surgery. Pain can interfere with recovery if the patient is not willing to participate in physical therapy due to pain. Universally, patient outcomes and length of stay are improved when patients are able to get out of bed and participate in physical therapy. The pure physiologic changes related to pain are also important to consider. Poorly controlled pain can increase expression in inflammatory pathways and decrease healing.¹⁵ EREM continuously releases morphine into the epidural space for up to 48 hours; therefore, EREM has the potential to provide better pain control into post-operative days 1–2.

We hypothesized that EREM would be associated with less morphine use via PCA over the first 48 hours after surgery. There was no statistical difference in the primary outcome. We also evaluated the length of time until first PCA demand, a decrease in pain scores, adverse effects, days until discharge and improved parent satisfaction with EREM. Pain scores were different between the IT morphine and EREM groups. Immediately after surgery, subjects in the EREM group had higher pain scores. These observations could be explained by varied mechanisms of drug delivery. IT morphine attains a rapid effect since it is placed directly into the cerebrospinal fluid (CSF). However, EREM must diffuse out of the liposomes into the epidural space. Subjects who received EREM seemed to have poor pain control immediately postoperatively, suggesting that they had not attained a sufficient level of

epidural morphine by the end of surgery. In future studies with EREM, pain control during the first few hours after surgery might be improved with a dose of intrathecal fentanyl or larger intraoperative doses of IV opioids. The pain scores were similar after 8 hours and through the night. Interestingly, the pain reduction with EREM demonstrated a longer impact, extending into the second day after surgery. This is one of the most critical times in recovery. Postoperative day one activity entails the patient getting out of bed to the chair, and maybe a few steps in their room. On day two, the goal for physical therapy is ambulation for longer distances and navigation of stairs. Having the ability to maintain good pain control, as seen with EREM, is critical to accomplishing these goals.

IT morphine can cause high concentrations of morphine in the plasma and CSF, which can lead to opioid induced adverse effects. Because EREM releases morphine gradually, the maximum plasma morphine concentration is approximately 30% the concentration seen after an injection of IT morphine.¹⁶ Due to the lower plasma concentration, EREM might cause less opioid adverse reactions. In this study, parental reports of less itching with EREM were statistically significant. There was a trend towards less adverse effects (nausea and vomiting, itching, respiratory depression) in the EREM group; however, the differences were not statistically significant. Studying a larger set of subjects could elucidate if there is a statistically significant decrease in adverse effects with EREM.

One of limitations of this study includes the possibility that the doses of IT morphine and EREM were not analgesically equivalent. The chosen doses fall within the recommended ranges of each medication. There is no head to head comparison of the two medications in the literature. However, even though the doses of IT morphine and EREM may not be exactly equipotent initially, we can still expect to observe any extended benefit of longer analgesia with EREM compared to IT morphine. Not having a standardized intraoperative anesthetic technique is another weakness. Analysis of the intraoperative medications showed no statistical difference between the two groups. However, there may be some clinical significance in a trend toward higher doses of hydromorphone in the EREM group. Interestingly, the EREM subjects might benefit from more intraoperative analgesics as evidenced by the higher pain scores in the immediate post-operative period in the EREM subjects. Another limitation is the dropout of 13 subjects from 84 enrolled subjects. Accidental unblinding or failure of administration of the drug occurred in 7 subjects. Factors that could not be anticipated, such as a change in health status or surgery that did not extend past L1 (first lumbar vertebra) occurred in 6 subjects. Enrollment ended after only 34 subjects were included in the EREM group, as opposed to the planned 36, because the study medication was no longer produced by the manufacturer. Other limitations include the small sample size which may explain the lack of statistical significance in primary outcome and no type I error adjustment for multiple outcomes or multiple comparisons in analysis of pain scores. Therefore, caution should be taken when interpreting these results.

The subjects in this study had an average hospital stay of almost 5 days, which is longer than our institutions current average of 3–4 days. It is important to note that this study was done prior to implementation of our current system to fast track recovery and discharge at our hospital. The length of stay seen in this study was comparable to all spine fusion patients at

our institution in the past; therefore, these treatment modalities did not lengthen days until discharge.

Unfortunately, EREM is not commercially available in the United States at this time. If it is available in the future, then further research should be done to corroborate our findings of potentially improved pain control into postoperative day two after spinal fusion surgery. The potential benefit of sustained-release morphine might be simulated with infusion of morphine with an epidural catheter.

Postoperative pain management in pediatric scoliosis surgery remains challenging. Intense physical therapy usually begins around the time when the analgesia from IT morphine is wearing off. These findings suggest there is a longer duration of analgesia with EREM, which is especially important at the time when patients are starting to mobilize. The adverse effect profile of EREM is satisfactory compared with ITM and larger studies might confirm the finding of less pruritus. Extended-release epidural morphine is a promising alternative that may prolong the duration of pain control in the idiopathic posterior spinal fusion patient.

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FIGURE 1.

CONSORT Flow Diagram showing enrollment, randomization, withdrawal and analysis of subjects. IT = intrathecal; EREM = extended-release epidural morphine.

FIGURE 2.

Time until first PCA demand. IT morphine and EREM showed similar time until first PCA demand. IT = intrathecal; EREM = extended-release epidural morphine; PCA = patient-controlled analgesia.

FIGURE 3.

Pain scores vs. Time Post-operatively. Pain was assessed every 4 hours after surgery using the Bieri Faces scale 0–10. Data are presented as Mean $\pm$ SEM. * p-value < 0.05 was considered significant. IT = intrathecal; EREM = extended-release epidural morphine.

FIGURE 4.

Incidence of adverse opioid effects stratified by treatment group. Data on adverse opioid effects was collected every 4 hours post-operatively. Adverse effect categories included nausea and emesis, pruritus, and respiratory depression. IT = intrathecal; EREM = extended-release epidural morphine.

FIGURE 5.

FIGURES 5(a–e). Results of parent questionnaires. a) Parent satisfaction with the pain relief that their child received after surgery, b) parent rating of pruritus, c) parent rating of nausea, d) parent rating of somnolence, e), parent rating of the worst pain with ambulation experienced by their child. IT = intrathecal; EREM = extended-release epidural morphine.

TABLE 1

Demographics. Data are expressed as mean $\pm$ SD or count (%). IT = intrathecal; EREM = extended-release epidural morphine.

	IT morphine	EREM
Number of Subjects	37	34
Age (years) ^a	13.8 $\pm$ 1.9	14.2 $\pm$ 1.9
Weight (kg) ^a	53.6 $\pm$ 12.0	55.2 $\pm$ 10.4
Number of levels fused ^a	10.4 $\pm$ 2.7	10.5 $\pm$ 2.4
Gender		
Male ^b	9 (24%)	7 (21%)
Female ^b	28 (76%)	27 (79%)
Race		
Asian ^b	0	1 (3%)
Black ^b	3 (8%)	0
White ^b	29 (78%)	29 (85%)
Hispanic ^b	1 (3%)	3 (9%)
Other ^b	4 (11%)	1 (3%)

^aMean $\pm$ Standard Deviation (SD)

^bCount (percent of subjects)

TABLE 2

Total intraoperative analgesic medications administered. Data are expressed as mean $\pm$ SD. IT = intrathecal; EREM = extended-release epidural morphine.

	IT morphine	EREM	p-value
Intraoperative Fentanyl			
Total Fentanyl (mcg) ^a	152.7 $\pm$ 118.3	144.9 $\pm$ 111.3	0.775 ^b
Fentanyl per kg (mcg/kg) ^a	2.8 $\pm$ 2.1	2.8 $\pm$ 2.2	0.996 ^b
Intraoperative Hydromorphone			
Total Hydromorphone (mcg) ^a	67.6 $\pm$ 268.8	163.2 $\pm$ 340.1	0.191 ^b
Hydromorphone per kg (mcg/kg) ^a	1.0 $\pm$ 3.9	2.9 $\pm$ 6.1	0.131 ^b
Intraoperative Morphine			
Total Morphine (mg) ^a	1.1 $\pm$ 1.9	1.6 $\pm$ 2.3	0.280 ^b
Morphine per kg (mg/kg) ^a	0.02 $\pm$ 0.03	0.03 $\pm$ 0.04	0.300 ^b
Intraoperative Ketorolac Given ^c	8.1 (1.7–21.9%)	11.8 (3.3%–27.5%)	0.703 ^d

^a Mean $\pm$ SD

^b Two-sample t-test

^c % of subjects (95% CI)

^d Fisher exact test

TABLE 3

Total intravenous morphine consumption over 0–24 hours and 0–48 hours after surgery. Data are expressed as median (range) or midpoint of difference (95% CI). IV = intravenous, IT = intrathecal; EREM = extended-release epidural morphine.

	Total IV morphine ^a (mg)	p-value
0–24 hrs post-operative		0.17 ^b
IT morphine ^c	18.4 (0–68.0)	
EREM ^c	24.3 (2.1–87.0)	
Midpoint of difference (EREM – IT morphine) and 95% CI ^d	5.67 (–2.4 to 13.8)	
0–48 hrs post-operative		0.27 ^b
IT morphine ^c	34.0 (4.5–128.8)	
EREM ^c	42.2 (5.5–123.0)	
Midpoint of difference (EREM – IT morphine) and 95% CI ^d	7.7 (–5.8 to 21.2)	

^aAccounts for IV morphine only, not morphine equivalents

^btwo tailed p-values from Wilcoxon Rank Sum test

^cMedian (range)

^dHodges-Lehman estimates