A comparative dose-response study on the efficacy and safety of intrathecal morphine effectiveness in post-cesarean patients under spinal anesthesia at a tertiary hospital

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Abstract

Introduction Intrathecal morphine, commonly administered at doses of 100 to 200 mcg, is a popular choice for post-cesarean analgesia; however, a trade-off between opioid analgesia and side effects exists. This study was conducted to determine the lowest dose of intrathecal morphine that will provide adequate analgesia with the least side effects among post-cesarean patients.

Methods Sixty term parturients for cesarean delivery under spinal anesthesia were randomized into three treatment groups to receive 50, 100 or 150 mcg of intrathecal morphine with a standard multimodal pain regimen and intravenous tramadol as needed. Pain scores, demand for rescue analgesic, and incidence of adverse effects (nausea, vomiting, and pruritus) during the first 24 hours' post-spinal anesthesia were recorded and compared between groups.

Results Pain scores and demand for rescue doses of tramadol were higher for the 50-mcg group as compared to the other groups. There was no significant difference in pain scores between the 100 and 150-mcg groups. No rescue dose of tramadol was necessary in the 100 and 150-mcg groups. No significant difference was seen in the incidence and severity of nausea and vomiting across treatment groups. The incidence and severity of pruritus were significantly higher in the 150-mcg group. No significant difference was noted in the incidence and severity of pruritus between the 50 and 100-mcg groups.

Conclusion A dose of 100 mcg of intrathecal morphine, in combination with a multimodal regimen, provides adequate analgesia with the least side effects.

Key words: Spinal anesthesia, intrathecal morphine, opioid analgesics, post-cesarean analgesia, cesarean section anesthesia, multi-modal pain management

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The effectiveness of intrathecal (IT) morphine for post-cesarean delivery analgesia is well established. Advantages of IT morphine include excellent postoperative analgesia for 14-36 hours with a decrease in total dose of opioid required, a low level of sedation, minimal accumulation of the drug in breast milk, facilitation of early ambulation, and early return of bowel function.[1-8] Though it is commonly administered at a dose of 100 to 200 mcg,

the optimal dose for pain control with the least side effects has yet to be established. Studies have shown that lower doses result in more patient discomfort and pain, however the incidence of side effects increases with higher doses.[9-17]

This study may serve as a reference for anesthesiologists regarding the use of low-dose intrathecal morphine to decrease unnecessary exposure to opioids and lessen side effects without decreasing the quality of post-operative analgesia, thus promoting patient satisfaction and comfort. In UERMMMC, the usual dose of IT morphine administered for post-cesarean pain control is 150 to 200 mcg. However, this is usually accompanied by pruritus commonly in the nasal and maxillofacial areas, with some patients having non-tolerable generalized pruritus. Hence, the purpose of this study was to determine the lowest dose of intrathecal morphine that would provide adequate analgesia with the least side effects among patients for cesarean section. Specifically, this study aimed to compare the pain scores at rest and upon movement of study groups (50 mcg, 100 mcg, 150 mcg) at 6, 12 and 24 hours post-spinal anesthesia, the incidence of IV opioid rescue dose demand in the first 24 hours across the study groups, and the incidence of side effects (i.e., nausea and vomiting, pruritus) across individual IT morphine doses.

Methods

This was a randomized trial comparing three doses of intrathecal morphine among women undergoing cesarean section. Participants were randomized to receive either 50, 100 or 150 mcg morphine during spinal anesthesia. Pain scores, the need for rescue doses of IV opioids and the incidence of side effects were determined and compared across the three study groups.

Sixty pregnant women aged 18 to 40 years at 37 weeks of gestation presenting for cesarean delivery under spinal anesthesia, who gave their written informed consent, were enrolled in this study. Those with any of the following characteristics or conditions were excluded: height of less than 147 cm, body mass index (BMI) greater than 45 kg/m^2, ASA Physical Status 3 or higher, allergy or contraindication to morphine, receiving analgesics or with an acute or chronic pain syndrome, history of neuropsychiatric disorder, and third trimester pruritus.

Each participant was randomized based on a computer-generated table of random numbers, with her dose assignment placed in a sealed numbered opaque envelope that was opened immediately before preparation of the spinal anesthetic dose. Patients were randomly assigned to one of three treatment groups to receive 50, 100 or 150 mcg of IT morphine with hyperbaric bupivacaine 0.5% 15 mg in a total volume of 3.2 mL with saline if necessary. The morphine and saline doses were drawn into a 1 mL syringe for accuracy and added to the spinal injection syringe containing 0.5% hyperbaric bupivacaine 15 mg/3 mL. Assigned doses were prepared by the assisting anesthesiologist. The patient, clinical care team, and the investigators performing all study-related assessments were blinded to the treatment group. The anesthesiologist who prepared the dose of morphine had no further involvement in the care or assessment of the patient.

All patients received crystalloid solution before anesthesia administration. Spinal anesthesia with the designated dose of morphine was administered with the patient in a lateral decubitus or sitting position depending on operator's preference, at an interspace judged to be L2-L3, L3–4 or L4–5 using a 25-gauge Quinckie spinal needle. Upon return of clear cerebrospinal fluid, bupivacaine 15 mg was injected with a morphine dose according to the patient's randomization. After injection, the patient was put in a supine position with left tilt. Surgery was started following temperature and/or pin-prick testing to the T4 level. Blood pressure was monitored every 2-3 minutes until delivery of the baby, after which blood pressure was monitored every 5 minutes at the provider's discretion. After delivery of the baby, oxytocin, using a standard concentration of 20 U in 1000 mL, and paracetamol 1g IV were infused. During closure of the subcutaneous layer, the patient received an intravenous dose of ketorolac 30 mg, or parecoxib 40 mg IV if the skin test to ketorolac was positive.

After surgery, all patients were provided with a standard set of pain medications of ketorolac 30 mg IV every 6 hours after a negative skin test and paracetamol 600 mg IV every 6 hours for the first 24 hours. Patients were also given a standing order of tramadol 50 mg IV every 6 hours as needed for breakthrough pain defined as a visual analog scale (VAS) score $\geq$ 6/10 or upon the patient's request. The pain score at the time of administration of tramadol was carried over to the next scheduled pain score assessment. The

incidence of IV tramadol demands was recorded for the first 24 hours' post-spinal anesthesia. Pain scores were recorded on an unmarked 100-mm line (at rest and with movement). Nausea and pruritus were each graded using a 4-point scale, where 0 = none, 1 = mild (requiring no treatment), 2 = moderate (responsive to treatment), and 3 = severe (unresponsive to treatment). Post-operative vomiting was assessed using a different 4-point scale as follows: 0 = none, 1 = 1 to 2 episodes, 2 = 3 to 4 episodes, and 3 = more than 4 episodes. Scores were collected by study personnel at the designated times (± 1 h).

Diphenhydramine 50 mg as first-line therapy for pruritus, nalbuphine 5 mg for refractory pruritus, and naloxone 0.4 mg for respiratory depression were available for treatment of side effects. First line treatment for nausea and vomiting was metoclopramide 10 mg IV; ondansetron 4 mg IV and dexamethasone 5 mg IV, respectively, were the 2nd and 3rd line treatments for unrelieved nausea/vomiting. Nurses administered the treatment based on the patient's reporting of symptoms and the nurses' clinical judgment within the order-set confines.

Data were analyzed using Stata version 13. Categorical data were expressed as counts and proportions and continuous data as mean and standard deviation or median and range, when appropriate. Baseline characteristics (age, BMI) were compared between treatment groups using one-way ANOVA. To determine significant differences in pain scores on the 6th, 12th and 24th hour post-spinal anesthesia between treatment groups, Kruskal Wallis one-way ANOVA with paired comparisons was used. To compare the need for rescue analgesics and the incidence and severity of side effects (e.g., nausea, vomiting and pruritus) between treatment groups, chi square test or Fishers exact test (for small samples) was done. A p-value < 0.05 was used as cut-off for significance.

Results

The mean age of the women was 29 years, the mean weight was 67 kg and the mean BMI was 27.8 kg/m^2. As seen in Table 1, there were no significant differences among treatment groups with respect to age, weight, height and BMI.

At rest and on movement, the mean and maximum pain scores were higher for the group receiving 50 mcg morphine. The pain scores decreased over time and were correspondingly lower in the higher morphine dose groups. Significant differences were noted in pain scores at rest between treatment groups on the 6th (p = 0.011) and on the 12th hour (p = 0.011) post-spinal anesthesia. By the 24th hour, pain perception was similar across treatment groups (p = 0.092) as shown in Table 2. Paired comparisons showed significant differences were between the 50 and 100 mcg groups (p = 0.020 on the 6th hour; p = 0.016 on the 12th hour) and between the 50 and 150 mcg groups (p = 0.005 on the 6th hour; p = 0.006 on the 12th hour). No significant differences were found between the 100 and 150-mcg groups at both time intervals (p = 0.624 and p = 0.728, respectively) as seen in Table 3.

On movement, pain scores differed significantly between treatment groups on the 6th (p = 0.002) and on the 12th hour (p = 0.030) but not on the 24th hour (p = 0.101) as seen in Table 2. These differences were noted between the 50 and 100-mcg groups (p = 0.005 on the 6th hour; p = 0.027 on the 12th hour) and between the 50 and 150-mcg groups (p = 0.004 on the 6th hour; p = 0.018 on the 12th hour).

Table 1. Baseline comparison among treatment groups.

Characteristics	Morphine dose groups*			p-value**
	50 mcg n = 20	100 mcg n = 20	150 mcg n = 20	
Age (yr)	30.2 ± 5.1	28.8 ± 6.1	28.9 ± 6.5	0.724
Weight (kg)	69.7 ± 6.7	66.7 ± 9.1	65.9 ± 7.5	0.290
Height (m)	1.6 ± 0.05	1.6 ± 0.06	1.6 ± 0.07	0.845
BMI (kg/m^2)	28.6 ± 2.2	27.4 ± 3.5	27.4 ± 2.2	0.257

* Data expressed as mean ± SD
** One-way ANOVA

Table 2. Comparison of post-operative pain scores at rest and on movement among treatment groups.

Time in hours post-spinal anesthesia	Morphine dose groups*			p-value**
	50 mcg	100 mcg	150 mcg	
At rest				
6th hour	2.0 (0, 8)	0 (0, 4)	0 (0, 4)	0.011
12th hour	0.5 (0, 8)	0 (0, 2)	0 (0, 2)	0.011
24th hour	0 (0, 8)	0 (0, 3)	0 (0, 5)	0.092
On movement				
6th hour	4.0 (0, 8)	1 (0, 8)	1.5 (0, 4)	0.002
12th hour	3.0 (0, 8)	0 (0, 4)	0 (0, 4)	0.030
24th hour	2.5 (0, 8)	0 (0, 4)	0.5 (0, 5)	0.101

* Data expressed as median (range)
** Kruskal-Wallis one-way ANOVA

Table 3. Pairwise comparison for significant differences between groups.

At rest	6th hour	12th hour
Between 50 and 100 mcg	0.020	0.016
Between 50 and 150 mcg	0.005	0.006
Between 100 and 150 mcg	0.624	0.728
On movement		
Between 50 and 100 mcg	0.005	0.027
Between 50 and 150 mcg	0.004	0.018
Between 100 and 150 mcg	0.798	0.868

Data in p-values

No significant differences were found between the 100 and 150-mcg groups in both time intervals ($p = 0.798$ and $p = 0.868$, respectively) as shown in Table 3. Six out of 20 patients in the 50-mcg group required rescue doses of tramadol, and none in the 100 and 150-mcg groups. As seen in Table 4, the difference was significant ($p = 0.009$).

The incidence and severity of nausea was 20-25% and did not differ significantly across treatment groups. The incidence of vomiting was highest at 20% in the 150-mcg group but the difference with the lower doses was not significant. The incidence and severity of pruritus was significantly higher in the 150-mcg group (vs 50 mcg, $p < 0.001$; vs 100 mcg, $p = 0.025$). The difference between the 50 and 100 mcg groups was not significant ($p = 0.077$) as seen in Table 5.

Discussion

It has been reported that more than 90% of obstetric anesthesiologists administer subarachnoid or epidural opioids to women undergoing cesarean deliveries under spinal, epidural or combined spinal-epidural anesthesia. Among the neuraxial opioids used, morphine has been described as having little intraoperative effect but is the opioid of choice for postoperative pain management.[10-11]

Intrathecal morphine appears to act principally on mu opioid peptide (MOP) receptors in the substantia gelatinosa of the dorsal horn by suppressing the release of excitatory neuropeptides from C fibers.[18] Due to morphine's high ionization and hydrophilic properties, morphine does not penetrate lipid-rich tissues as rapidly as fentanyl. It remains within the CSF for a prolonged period, spreading rostrally and reaching the trigeminal nerve distribution as early as three hours after intrathecal injection in healthy volunteers. It requires 45 to 60 minutes to achieve a peak effect, and the duration of analgesia is 14 to 36 hours depending on the dose.[2]

Intrathecal morphine is commonly used at doses of 100 to 200 mcg with excellent analgesic results;

Table 4. Differences in requirement for rescue doses of tramadol.

Requirement for rescue doses of tramadol	Morphine dose groups*			Comparison	p-value**
	50 mcg	100 mcg	150 mcg		
With	6 (30.0)	0	0	50 vs 100	0.009
Without	14 (70.0)	20 (100.0)	20 (100.0)	50 vs 150	0.009
				100 vs 150	> 0.999

* Data expressed as frequency (%)
** Fishers exact test

Table 5. Comparison of side effects between treatment groups.

Side effects	Morphine dose groups*			Comparison	p-value**
	50 mcg	100 mcg	150 mcg		
Nausea				50 vs 100	> 0.999‡
None	15 (75.0)	16 (80.0)	16 (80.0)	50 vs 150	> 0.999‡
Mild to moderate	5 (25.0)	4 (20.0)	4 (25.0)	100 vs 150	> 0.999‡
Vomiting				50 vs 100	0.605‡
None	19 (95.0)	17 (85.0)	16 (80.0)	50 vs 150	0.342‡
≥ 1 episode	1 (5.0)	3 (15.0)	4 (20.0)	100 vs 150	> 0.999‡
Pruritus				50 vs 100	0.077§
None	17 (85.0)	12 (60.0)	5 (25.0)	50 vs 150	< 0.001§
Mild to moderate	3 (15.0)	8 (40.0)	15 (75.0)	100 vs 150	0.025§

* Data expressed as frequency (%)
‡ Fishers exact test
§ Chi square test

however, many studies have different results on the adequacy of analgesia for post-cesarean patients. One study determined that the ED90 of IT morphine for post-cesarean analgesia is 150 mcg. The study also states that a 150-mcg dose is most effective when used in conjunction with a multimodal analgesic regimen.[14] Another study suggests that 50 mcg IT morphine produces analgesia similar to that produced by either 100 or 150 mcg.[12] On the other hand, Palmer studied patients receiving intrathecal doses from 25 to 500 mcg and found a ceiling effect with doses greater than 75 mcg, as measured by patient-controlled intravenous morphine use.[10] This study concluded that there is little justification for using more than 100 mcg IT morphine for post-cesarean analgesia.

Consistent with the findings of Palmer, the current study showed that a 100-mcg intrathecal morphine dose, with a multimodal analgesia regimen, provides sufficient post-cesarean analgesia for the first 24 hours. In the current study, pain scores at rest and upon movement were significantly higher in the 50-mcg group as compared to the other groups, while no significant differences were found on pain scores between the 100 and 150 mcg morphine dose groups in both time intervals. No rescue pain doses were needed for the 100- and 150-mcg dose groups while 30% of the 50-mcg dose group required rescue doses of tramadol.

Differences in pain scores among other studies may be secondary to cultural differences in pain perception and attitudes towards pain. One journal describing Filipino attitudes toward pain medications described Filipinos as stoic when it comes to pain. Some also have higher pain thresholds, while others fear becoming addicted to narcotics. This article also stressed that cultural generalizations will not fit every patient, but awareness of broad patterns may give practitioners a starting point from which to provide appropriate care.[19]

Neuraxial opioids have well-known side effects of which most are more annoying than life-threatening. Pruritus, nausea, and vomiting are the most common side effects of these agents that may cause a decrease in maternal satisfaction. Parturients are generally at risk for emetic symptoms due to the level of progesterone that causes smooth muscle relaxation, increase in gastrin secretion, decrease in gastrointestinal motility, and lower esophageal sphincter tones.[4] Side effects such as urinary retention and respiratory depression were not observed in this study since cesarean delivery patients typically have urinary catheters in place for the first 24 hours and respiratory depression is exceedingly rare at doses of 100 to 200 mcg.

Studies with dose response and side effects of intrathecal morphine differ in conclusion. In a qualitative and quantitative systematic review of randomized controlled trials on intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing cesarean section with spinal anesthesia, univariate logistic regression analysis showed that the relative risk of postoperative pruritus, nausea, and vomiting increased with higher doses of morphine.[11] On the other hand, some studies showed no significant differences in the incidence of nausea and vomiting across treatment groups given different doses and between treatment and control groups. These studies suggested that initial therapy for nausea or vomiting after cesarean delivery after intrathecal morphine of post-cesarean patients should perhaps be an antiemetic rather than an opioid antagonist.[10,12]

In the present study, the incidence and severity of nausea and vomiting were low to absent across treatment groups and did not differ significantly between groups. While studies showed an increased incidence and severity of pruritus with higher doses of morphine, only the 150 mcg group showed a significant difference when compared with the 50 and 100-mcg groups.[1,2,9,10] There was no difference in the incidence and severity of pruritus between the 50 and 100-mcg groups.

In summary, the dose-response relationship of intrathecal morphine for post-cesarean analgesia and side effects was investigated. The analgesic efficacy of 100 mcg intrathecal morphine is comparable to a dose of 150 mcg and superior to a dose of 50 mcg. The incidence and severity of nausea and vomiting were comparable across treatment groups. While the incidence and severity of pruritus between 50 mcg and 100-mcg group were comparable, the 150-mcg group had a higher incidence and greater severity. This study also highlights the importance of multimodal analgesia with the appropriate dose of intrathecal morphine as an ideal post-cesarean analgesic regimen that would provide consistent and high-quality pain relief with a low incidence of side effects and complications.[3,4,20] This regimen should not interfere with the maternal care of the newborn or with breastfeeding, and there should be minimal drug transfer to the breast milk and consequently minimal adverse effects on the newborn.[5-8] A dose of 100 mcg of intrathecal morphine, in combination with a multimodal regimen, provides adequate analgesia with the least side effects.

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