PSUMJ
PSU MEDICAL JOURNAL

Original Article

Different Doses of Intrathecal Morphine on Postoperative Analgesia and Pruritus after Cesarean Section: a Prospective Randomized Triple-Blinded Trial

Orarat Karnjanawanichkul, M.D., Jatuporn Pakpirom, M.D., Thitiporn Pueaksuwan, M.D., Sasikaan Nimmaanrat, M.D., Niranuch Siripunt, B.N.S., Sukanya Kaewsridam, B.N.S.

Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

ABSTRACT

Objective: Intrathecal morphine (ITM) is an effective postoperative analgesia provided after Cesarean section. However, pruritus is an undesirable side effect that disrupts maternal breast feeding. This study aimed to evaluate the effects of three different doses of ITM added to spinal bupivacaine on postoperative analgesia and opioid-related side effects in Cesarean section.

Material and Methods: This prospective randomized, triple-blinded trial was conducted in 321 patients undergoing Cesarean section. They were allocated to receive either; one intervention group; intrathecal morphine 50 mcg (IT50 group, N=98), 100 mcg (IT100 group, N=100), or 200 mcg (IT200 group, N=101), added to spinal bupivacaine for Cesarean section. The primary outcome was the incidence of pruritus in the recovery room, and then every 4 hours for 24 hours. The secondary outcomes were the pain scores at rest and during activities, time to the first analgesia, 24 hours of morphine consumption and the incidence of postoperative nausea and vomiting (PONV).

Results: Patient characteristics between the three groups were comparable. Both of the IT50 and IT100 groups had a lower incidence of pruritus, when compared with the IT200 group at all-time points, with the exception of at 24 hours; wherein, there were no differences between the three groups. Pain scores during activities were not different between the three groups. However, at rest the IT50 group had a higher pain score than those in the IT100 and IT200 groups; at 4, 8, and 16 hours. Time to the first analgesic requirement was shorter in the IT50 group (2 hours) than in the IT100 (2.4 hours) and IT200 (2.6 hours) groups (p-value=0.03). Moreover, the median [IQR] of morphine consumption in 24

Corresponding author: Jatuporn Pakpirom, M.D.
Department of Anesthesiology, Faculty of Medicine, Prince of Songkla University,
Hat Yai, Songkhla 90110, Thailand.
E-mail: pakpirom013@gmail.com
doi: 10.31584/psumj.2022255472
https://he01.tci-thaijo.org/index.php/PSUMJ/

PSU Med J 2022;2(3):109-120
Received 12 April 2022
Revised 4 May 2022
Accepted 6 May 2022
Published online 28 September 2022

hours was higher in the IT50 group [17 mg (9, 29.8)] than those in the IT100 [13 mg (5, 23.2)] and IT200 [12 mg (4, 17)] groups (p-value<0.001). However, the incidence of PONV was lower in the IT50 group compared to other groups. **Conclusion:** This study demonstrates that reducing the dose of ITM to 100 mcg added to spinal bupivacaine is effective to maintain postoperative analgesic effects. Additionally, it reduces the incidence of postoperative pruritus compared to ITM at 200 mcg.

Keywords: Cesarean section; intrathecal morphine; PONV; postoperative analgesia; pruritus

INTRODUCTION

A single dose of intrathecal morphine (ITM) is an effective technique to provide excellent postoperative analgesia after a Cesarean section.[1,2] ITM doses commonly range from 75 mcg to 500 mcg[3]; however, some studies have shown that a lower dose of ITM, as 25 mcg added to spinal bupivacaine, was still effective for controlling postoperative pain for Cesarean sections.[4,5] The analgesic efficacy of ITM has ceiling characteristic effects; hence, the present evidence is still controversial concerning doses of less than 100 mcg.[3-6] Many studies have found that smaller doses of ITM at 100 mcg, were comparable in effectiveness for postoperative analgesia, when compared with higher doses of more than 100 mcg.[6-9]

On the other hand, undesirable side effects related to ITM are common, and have been associated with the doses of morphine administered intrathecally.[9] Pruritus is the most common side effect, which effects maternal satisfaction, and has often been reported as being associated with a high dose of ITM.[3-10] Although, the evidence for prevention of pruritus, induced by ITM, is still unproven[11-12] low doses of ITM for postoperative analgesia after a Cesarean section are recommended to reduce the incidence of side effects; especially pruritus, nausea and vomiting.[13] However, the optimal dose of ITM for postoperative analgesia after Cesarean section for minimizing any side effects is still unknown. Hence, the aim of this study was to evaluate the lowest effective doses of ITM added to spinal bupivacaine on postoperative analgesia and opioid-related side effects in Cesarean section.

MATERIAL AND METHODS

Population

The study protocol (EC. 56-148-08-1-2) was approved by the Human Research Ethics Committee, from the Faculty of Medicine, Prince of Songkla University. In total, 321 patients with American Society of Anesthesiologists (ASA) II, and those undergoing Cesarean delivery under spinal anesthesia, were recruited to participate in this study; from August 2013 to May 2014. Informed consent was obtained at the ward during the preoperative visit for the elective surgery, or in the operating theater for emergency cases, by the anesthesiologists. Patients who had any allergies to the study drugs (morphine, ibuprofen), complicated pregnancy (i.e.: abnormal placenta adherence, abnormal fetal condition, or preterm labor less than 28 weeks), fasting of less than 6 hours before the procedure, changes to general anesthesia (for any reason) during the procedure, inadequate spinal anesthesia, repeat spinal anesthesia or additional opioids and/or sedative drugs and unplanned hysterectomy have been excluded from this study.

Randomization and blinding technique

After patients were recruited into the study protocol, they were randomized to receive one dose of ITM; ITM 50

mcg (IT50), 100 mcg (IT100), or 200 mcg (IT200) added to spinal bupivacaine during spinal anesthesia for Cesarean section. A computer-generated randomization sequence was performed, and randomization lists were created and kept in sealed-envelopes by a third party. These were opened by the nurse assistant when patients were recruited into the study.

The anesthesiologists performing spinal anesthesia along with the surgeons in the operation room, and the outcome assessors; who were the ward nurses, were blinded. Additionally, the patients were also unaware of their group allocation.

Intervention

All subjects received the same preparation during the preoperative period; including, fasting for at least 6 hours, and receiving 30 ml of sodium citrate orally at the operating room before the start of anesthesia. Before spinal anesthesia, standard monitoring included; non-invasive blood pressure, electrocardiogram, and pulse oximeter was instituted. Oxygen 8-10 liters/minute was given via an oxygen mask with a bag, and isotonic solution fluid was loaded with at least 10 ml/kg. After this, patients were asked to lie down in a lateral position with bent knees to the chest to prepare for spinal anesthesia.

The spinal anesthesia drugs were prepared by an assigned anesthesist nurse, who was not involved in the outcome assessments. Morphine (10 mg/ml) was diluted with 0.5% hyperbaric bupivacaine into 1 mg/ml, using an insulin syringe, and then by 0.05 ml (50 mcg) for the IT50 group, 0.1 ml (100 mcg) for the IT100 group, and 0.2 ml (200 mcg) for the IT200 group. These were mixed with 0.5% hyperbaric bupivacaine of up to final 2.2 ml (11 mg of bupivacaine) as the identical spinal anesthesia drug for all patients in the three groups. The spinal anesthesia drugs were identical in volume and color, so they could not be differentiated between group allocations.

Standard monitoring; including, non-invasive blood pressure, electrocardiogram, and pulse oximeter were used during the intraoperative period. The sensory blockade was checked using “pinprick sensation” and reported as the highest sensory level blockade. Ephedrine was administered when the patient’s blood pressure was reduced by more than 20%, or when the mean blood pressure was less than 60 mmHg. The incidence of hypotension and shivering along with other complications were recorded.

Morphine (0.5 mg/ml) intravenous patient-controlled analgesia (PCA) (bolus 1 mg, lock-out 5 minutes and 4 hours limit 40 mg), was given to relieve pain during the postoperative period of 24 hours. Acetaminophen of 1 gram orally every 6 hours, and ibuprofen at 400 mg every 8 hours were started after the patient could tolerate an oral liquid diet. To treat the pruritus 10 mg of chlorpheniramine was given intravenously, and 8 mg of ondansetron was given for postoperative nausea and vomiting (PONV).

Outcomes

The primary outcome was a pruritus incidence, which used a pruritus score of 4 levels: 0-3, 0=none, 1=mild (no treatment required), 2=moderate (responsive to treatment), and 3=severe (unresponsive to treatment). These assessments were made by a recovery room nurse and/or the ward nurses, who were all trained in grading the pruritus score. The scores were recorded at the recovery room at 4, 8, 12, 16, 20 and 24-hour periods after spinal anesthesia.

The secondary outcomes; including PONV score, VAS and 4-hr-morphine consumption, were assessed regularly every 4 hours for 24 hours after the spinal block at: 4, 8, 12, 16, 20 and 24 hours. The visual analog scale (0-10; 0=no pain, 10=worst pain) was used to measure pain levels at rest and during movement and deep breathing at 4, 8, 12, 16, 20 and 24 hours after spinal anesthesia. Four hours-morphine consumption was acquired from the

PCA machine. PONV used a 4 point-scale to grade the severity[14]: 0=none, 1=mild nausea (no treatment required), 2=moderate (responsive to treatment), and 3=severe (unresponsive to treatment or requesting repeat treatment) was recorded. The first-dose morphine requirement to rescue postoperative analgesia (recorded by the PCA machine) and patient's satisfaction using 5 scores (0-5; 0=very unsatisfaction 5=vary satisfaction) were also acquired.

Statistical analysis

The sample size was calculated using two independent proportions of pruritus incidence from: 1) Anesthesiology department annual report (pruritus incidence with ITM 200 mcg=76%), and 2) from a previous study[2] (pruritus incidence with ITM 100 mcg=56%). As a result, 291 subjects (97 patients per group) were required, and a further 10% were added to compensate for any loss in follow-up of patients and/or incomplete information. The final 321 subjects (107 per group) were required to have a 95% confidence level, and power of 80 to detect any differences between groups.

Statistical analysis was performed using R program, version 3.1.1. The Shapiro-Wilk test was used to test the normality distribution of continuous variables. The normal distribution variables were presented as mean and standard deviation (SD), and the non-normal distribution variables were presented as median and interquartile range (IQR). Kruskal-Wallis test and ANOVA tests were used to test the association between groups. Categorical data were presented in number and percentage, and the Chi-square test or Fisher's exact test were used to compare between the three groups. The pruritus and PONV scores were grouped to dichotomous data (pruritus and PONV scores=0 were changed to "no" and >0 were changed to "yes") Logistic regression was then used to describe the effects of ITM doses on pruritus and PONV. The Mann-Whitney test was used for further intergroup analysis, as an indication to compare between groups. A p-value less than 0.05 was considered a statistically significant level.

RESULTS

In total, 817 patients were assessable during the period of study. However, only 321 patients were enrolled into the study (39.3%), with 107 patients being randomized into each group. The consort diagram shows the flow of participants through each stage of the randomized trial (Figure 1). A total of 22 patients were withdrawn from analysis during the intraoperative period. This included: 9 patients in the IT50, 7 patients in the IT100, and 6 patients in the IT200; the reasons are described in Figure 1. Finally, 299 patients remained for the analysis; 98 patients in the IT50, 100 patients in the IT100, and 101 patients in the IT200.

There were no differences in patient demographic characteristics, and intraoperative complications between the three groups (Table 1). The highest sensory blockade was at the T6 dermatome level in the three study groups (p-value>0.05).

The incidence of postoperative pruritus in the recovery room at 4, 8, 12, 16, 20 and 24 hours postoperatively in the three groups are shown in Table 2. There was an association between the incidence of postoperative pruritus and ITM doses at all times of follow-up (p-value<0.05); except at the 24-hour time period (p-value=0.13). The odds of postoperative pruritus in the recovery room were reduced by; 54% in IT100 (OR 0.46, 95% CI 0.24-0.89), and 86% in IT50 (OR 0.14, 95% CI 0.06-0.36) compared to IT200, respectively. Additionally, the odds of postoperative pruritus were also reduced significantly at; 4, 8, 12, 16, 20 hours postoperatively in the IT100 and IT50 groups; as shown in Table 2.

There was a significant association between incidences of PONV and ITM doses at all-times of follow-up; except for in the recovery room, and at 16 and 24 hours postoperatively (Table 3). The IT100 and the IT50 group

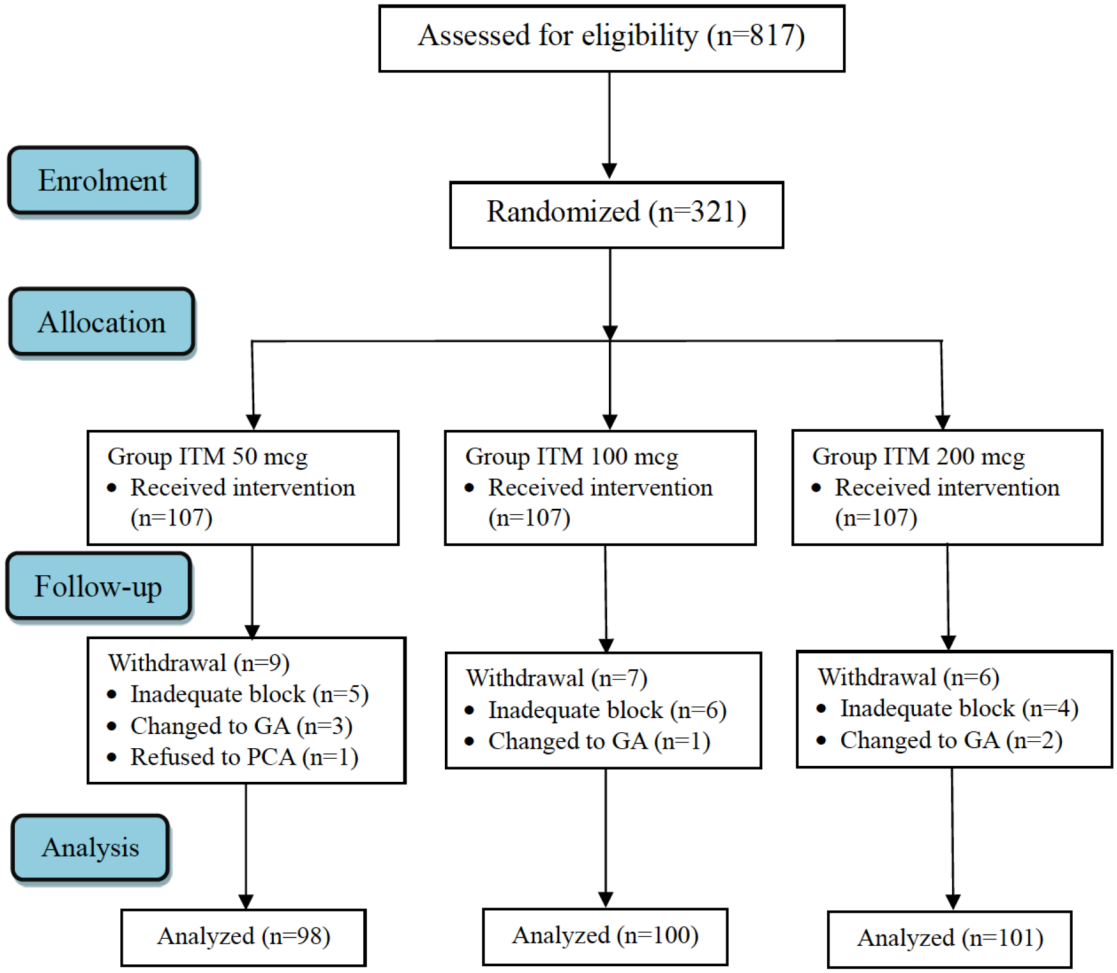


Figure 1 CONSORT flow diagram

had significantly reduced incidences of PONV at 4, 8, 12, and 20 hours comparing to the IT200 group (Table 3).

The pain score, assessed by VAS at rest and during activities is presented in Figure 2 and Figure 3. The IT50 group had higher VAS scores at rest than the IT200 groups at 4, 8 and 16 hours, and the IT100 group at 4 and 16 hours (Figure 2). There was no difference in the VAS score during activities between the three groups at all follow-up time points (Figure 3).

The median [IQR] time to the first dose of morphine requirement was 2 hours [1.6,3.2] for IT50, 2.4 hours [1.8,3.2] for IT100, and 2.6 hours [1.8,4.5] for the IT200 group; there was a statistically significant difference between the groups (p-value=0.031).

Postoperative 4-hr-morphine consumption was statistically different between the groups at 4, 8, 12 and 20 hours (p-value<0.05) (Figure 4). Post-hoc analysis of 4-hr-morphine consumption found that the IT50 group required a higher dose of morphine than the IT100 group at 8, 12, and 20 hours as well as in the IT200 group at 4, 8, 12, and 20 hours. The median [IQR] of 24-hr morphine consumption in the IT50 group 17 mg [9,29.8] showed a

Table 1 Patients, surgical and intraoperative characteristics

Total	IT50 (n=98)	IT100 (n=100)	IT200 (n=101)	p-value
Age (years)	31.7±4.6	31.3±4.8	30.6±5.5	0.27
Weight (kg)	68 (61.0,75.0)	70 (64.0,78.2)	70 (62.0,79.0)	0.11
Height (cm)	158 (154.0,160.0)	157 (154.0,160.0)	157 (152.0,160.0)	0.79
Surgical incision				0.67
low midline; n (%)	24 (24.5)	26 (26.0)	21 (20.8)	
low transverse; n (%)	74 (75.5)	74 (74.0)	80 (79.2)	
Intraoperative complications				
Hypotension; n (%)	63 (64.3)	64 (64.0)	70 (69.3)	0.67
Shivering; n (%)	4 (4.1)	8 (8.0)	6 (5.9)	0.51

Data are presented as mean±S.D.; median (IQR) or n(%); IT50 = intrathecal morphine 50 mcg group; IT100 = intrathecal morphine 100 mcg group; IT200 = intrathecal morphine 200 mcg group; kg = kilogram; cm = centimeter

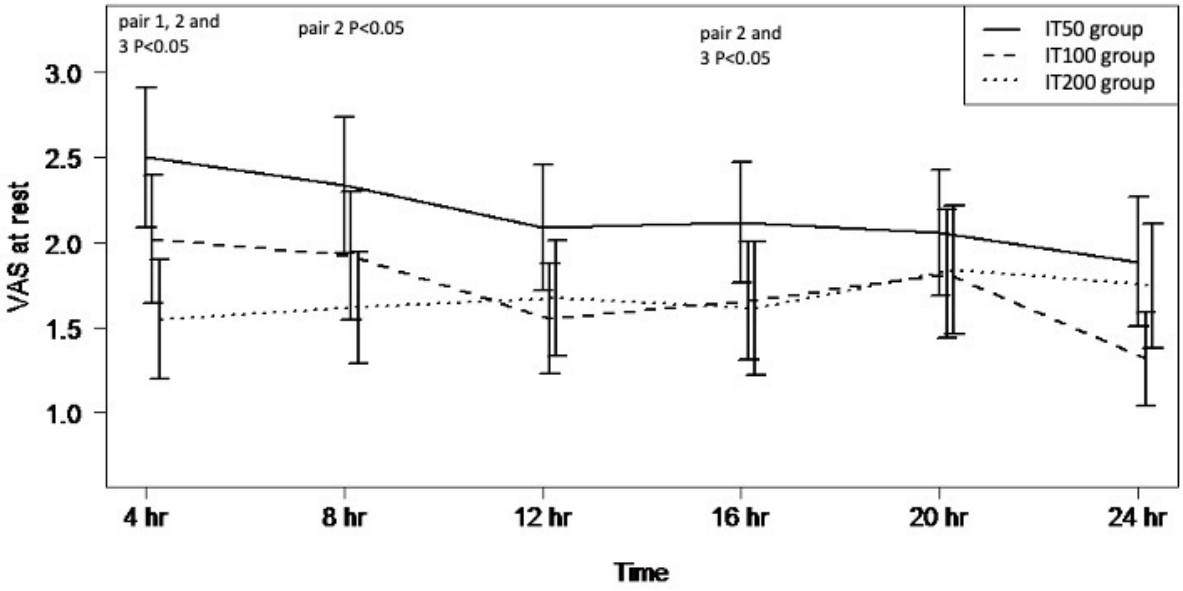


Figure 2 The visual analog scale (VAS) score at rest at the follow-up time after cesarean section among the three groups. Data are presented as median [IQR]. Pair 1; IT200 vs. IT100, pair 2; IT200 vs. IT50 and pair 3; IT100 vs. IT50

Table 2 Incidence of postoperative pruritus

Group	Incidence n (%)	OR (95% CI)	p-value (LR-test)
at RR (N=282)*			
IT200 (n=89)	33 (33.7)	reference	<0.001
IT100 (n=95)	18 (18.9)	0.46 (0.24–0.89)	
IT50 (n=98)	6 (6.7)	0.14 (0.06–0.36)	
at 4 hr (N=299)			
IT200 (n=101)	74 (73.3)	reference	<0.001
IT100 (n=100)	55 (55.0)	0.45 (0.25–0.81)	
IT50 (n=98)	36 (36.7)	0.21 (0.12–0.39)	
at 8 hr (N=299)			
IT200 (n=101)	76 (75.2)	reference	0.002
IT100 (n=100)	54 (54.0)	0.39 (0.21–0.70)	
IT50 (n=98)	54 (55.1)	0.4 (0.22–0.74)	
at 12 hr (N=299)			
IT200 (n=101)	70 (69.3)	reference	<0.001
IT100 (n=100)	54 (54.0)	0.52 (0.29–0.93)	
IT50 (n=98)	41 (41.8)	0.32 (0.18–0.57)	
at 16 hr (N=299)			
IT200 (n=101)	73 (72.3)	reference	<0.001
IT100 (n=100)	55 (55.0)	0.47 (0.26–0.84)	
IT50 (n=98)	43 (43.9)	0.3 (0.17–0.54)	
at 20 hr (N=299)			
IT200 (n=101)	63 (62.4)	reference	0.034
IT100 (n=100)	49 (49.0)	0.58 (0.33–1.02)	
IT50 (n=98)	44 (44.9)	0.49 (0.28–0.87)	
at 24 hr (N=299)			
IT200 (n=101)	46 (45.5)	reference	0.134
IT100 (n=100)	41 (41.0)	0.77 (0.44–1.34)	
IT50 (n=98)	32 (32.7)	0.56 (0.31–0.99)	

Data are present as n (%) and 95% CI. * 17 cases bypassed the recovery room; n = number in each group; N = total number at each time follow-up; OR = odd ratio; p-value (LR-test) = p-value of a likelihood-ratio test

significantly higher analgesic requirement than those in the IT100 13 mg [5,23.2] and IT200 12 mg [4,17] groups (p-value<0.001). However, the patient's satisfaction with pain control in IT50, IT100, and IT200 groups as well as the patient's satisfaction with pruritus were not different between the three groups.

DISCUSSION

This present study showed that minimal doses of ITM 50 mcg and 100 mcg, added to spinal bupivacaine, reduce the postoperative incidences of pruritus, significantly, at all follow-up time points when compared to ITM 200 mcg after Cesarean section. ITM 100 mcg added to spinal bupivacaine for Cesarean section can maintain postoperative analgesia;

Table 3 Incidence of postoperative nausea and vomiting (PONV)

Group	Incidence n (%)	OR (95% CI)	p-value (LR-test)
at RR (N=282)*			
IT200 (n=89)	14 (14.3)	reference	0.682
IT100 (n=95)	12 (12.6)	0.87 (0.38–1.99)	
IT50 (n=98)	9 (10.1)	0.68 (0.28–1.65)	
at 4 hr (N=299)			
IT200 (n=101)	30 (29.7)	reference	0.002
IT100 (n=100)	19 (19.0)	0.56 (0.29–1.07)	
IT50 (n=98)	10 (10.2)	0.27 (0.12–0.59)	
at 8 hr (N=299)			
IT200 (n=101)	18 (17.8)	reference	0.012
IT100 (n=100)	9 (9.0)	0.46 (0.19–1.07)	
IT50 (n=98)	5 (5.1)	0.25 (0.09–0.70)	
at 12 hr (N=299)			
IT200 (n=101)	14 (13.9)	reference	0.041
IT100 (n=100)	11 (11.0)	0.77 (0.33–1.78)	
IT50 (n=98)	4 (4.1)	0.26 (0.08–0.83)	
at 16 hr (N=299)			
IT200 (n=101)	11 (10.9)	reference	0.192
IT100 (n=100)	5 (5.0)	0.43 (0.14–1.29)	
IT50 (n=98)	5 (5.1)	0.44 (0.15–1.32)	
at 20 hr (N=299)			
IT200 (n=101)	5 (5.0)	reference	0.020
IT100 (n=100)	1 (1.0)	0.19 (0.02–1.69)	
IT50 (n=98)	0 (0.0)	0 (0–Infinity)	
at 24 hr (N=299)			
IT200 (n=101)	2 (2.0)	reference	0.113
IT100 (n=100)	0 (0.0)	0 (0–Infinity)	
IT50 (n=98)	0 (0.0)	0 (0–Infinity)	

Data are present as n (%) and 95% CI. * 17 cases bypassed the recovery room; n = number in each group; N = total number at each time; OR = odd ratio; p-value (LR-test) = p-value of a likelihood-ratio test

whereas, ITM 50 mcg added to spinal bupivacaine has lower analgesic effects than ITM 100 mcg and 200 mcg. There was also evidence of a higher pain score at rest, higher morphine consumption within the first 12 hours, and a requirement for earlier analgesic drugs for rescue pain compared to other groups.

This present study found an association between the incidence of postoperative pruritus (37% vs 47% vs 62%) and ITM doses (50 mcg vs 100 mcg vs 200 mcg) in a direct proportion. This finding was supported by the Palmer et al[3] and Girgin et al[7] studies that reported the linear association and dose-responsiveness between pruritus and ITM doses.[3,7,15] However, this relationship disappeared when the dose of ITM was lower than 60 mcg.[16]

The aim of this study was to reduce the incidence of pruritus by reducing the ITM doses. In general, most of

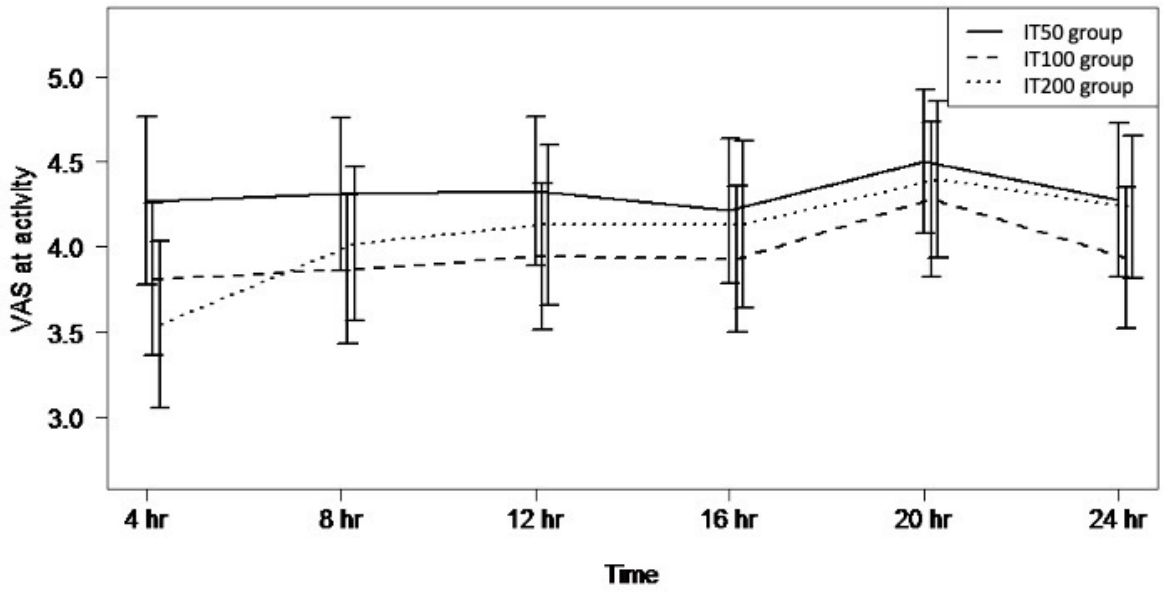
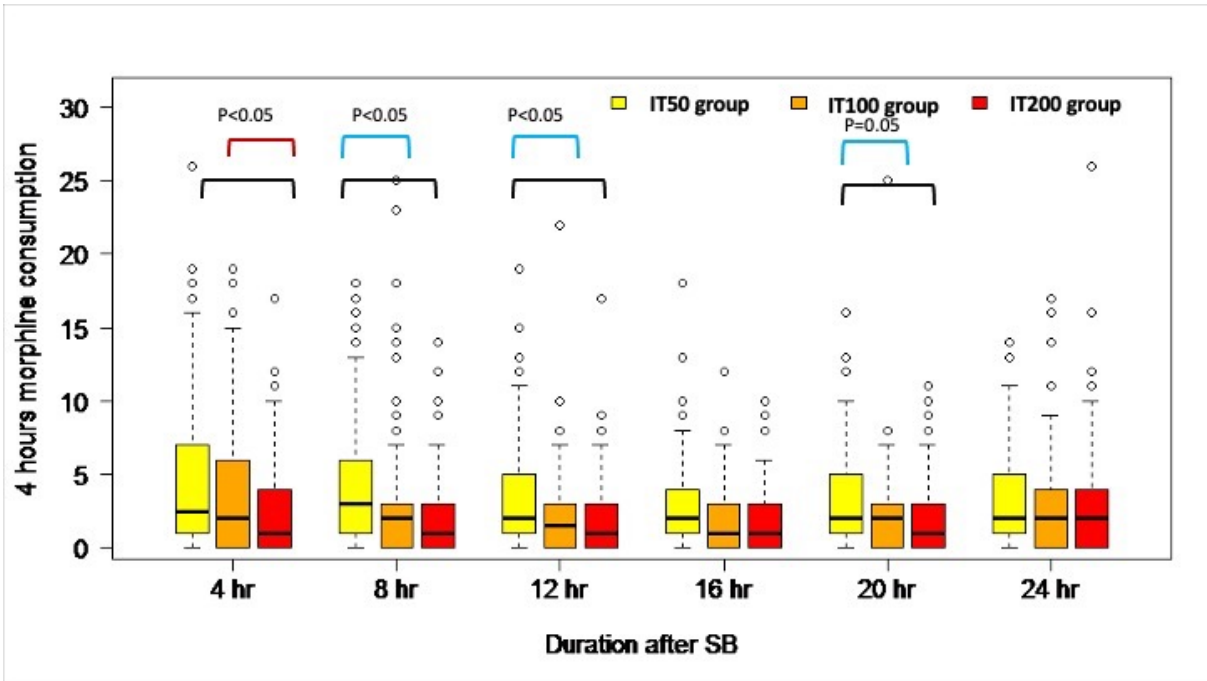


Figure 3 The visual analog scale (VAS) score during activity at the follow-up time after cesarean section among the three groups. Data are presented as median [IQR]



SB = spinal block

Figure 4 Four-hour-morphine consumption at different follow-up times between the three groups. Data are presented as median [IQR]

the hospitals in Thailand add ITM 200 mcg during spinal anesthesia, and have reported the incidence of pruritus as approximately 56-60%.[17,18] The analgesic efficacy to control pain after Cesarean section is dose-dependent, and has ceiling effects. Palmer et al[3] demonstrated that increasing the dose of ITM by more than 100 mcg did not increase analgesic effects. In this study, we evaluated the analgesic efficacy between three doses of ITM, and found that the analgesic efficacy of ITM 200 mcg was not different from ITM 100 mcg in all aspects, while ITM 50 mcg had inferior analgesic profiles compared to ITM 200 mcg and 100 mcg. This result was similar to the previous studies[7,15], which found that ITM 100 mcg had low incidences of postoperative pruritus, and produced analgesia compatible with a higher dose of more than ITM 100 mcg. Palmer et al[3] also reported that ITM doses higher than 75 mcg increased the incidences of postoperative pruritus without the benefit of the analgesia. This study found that a very small dose of ITM 50 mcg, still provided analgesia, but was inferior to ITM of 100 mcg and 200 mcg for postoperative pain control. However, Carvalho and colleague[19] stated that ITM 50 mcg provided a similar quality of postoperative analgesia with ITM 100 mg, while it induced fewer side effects. Therefore, they recommended ITM between 50-100 mcg should be adequate for controlling postoperative analgesia in Cesarean section. On the other hand, some studies found that ITM at 200 mcg was superior to ITM at 100 mcg.[20,21] Therefore, they suggested using ITM at 200 mcg for postoperative analgesia after Cesarean section.

To strike a balance between the analgesic effects and the risk of ITM-induced side effects, the optimal dose of ITM has been evaluated to compare a high-dose of ITM (100-250 mcg) and a low-dose of ITM (50-100 mcg). It has been reported that a high dose ITM provided a longer duration of analgesia; with a mean difference of 4.5 hours; however, it was associated with an increase in the risk of pruritus at 2.9 times as well as for nausea and vomiting at 2.3 times compared to low-dose ITM (50-100 mcg).[22] Therefore, according to our results, we agree with the previous studies[2,5,7,8] that recommended an ITM dose of 100 mcg, so as to minimize the risk of pruritus; while still maintaining the analgesic effects.

In this study, the incidence of ITM-induced PONV in patients undergoing Cesarean section had a relationship with the ITM doses during the first 12 hours after spinal anesthesia. Our results were in contrast with a previous study by Palmar[3], in which they found a direct proportion with the ITM-doses only for pruritus, but not for PONV. In contrast, Uchiyama[15] studied a variety of ITM-doses in patients undergoing Cesarean section and found that the incidences of PONV were dose-dependent with ITM-doses.

Apart from ITM, intrathecal fentanyl, sufentanil or a fentanyl-morphine combination has been evaluated for providing postoperative analgesia after Cesarean section. However, these intrathecal, additive drugs have a short duration as well as inferior analgesic effects compared to ITM.[23] In addition, those drugs added to spinal bupivacaine also produce neuraxial opioid-induced pruritus and PONV, which does not differ from ITM.[23] Hence, morphine is recommended, rather than short-acting opioids, to be added to spinal bupivacaine for providing postoperative analgesia after Cesarean section. Although, the quadratus lumborum block might be a technique to replace, and avoid ITM-induced side effects in Cesarean delivery, evidence showed that it did not have additive analgesic effects when combined with ITM; additionally, it was inferior to ITM when used alone in patients undergoing Cesarean section[24-25]

Although, we could not eliminate intrathecal morphine-induced side effects to zero, we could reduce them as much as possible by reducing the dose of ITM. However, this will reduce the analgesic effects as well. Thus, using multimodalities to reduce the incidence of ITM-induced side effects; such as pruritus and PONV, prophylaxis, and implementing multimodal analgesia techniques to compensate with the ITM dose reduction is recommended. Additionally, the benefits of a multimodalities

approach can improve patients' quality of life, and satisfaction in patients undergoing Cesarean section, and is therefore warranted.

The limitation of this study, were that the primary and secondary outcomes were measured by a number of nurses, with some of them having not been trained in acute pain care. This might have effects on validation of the outcome measurements. However, all participants were trained to use the PCA machine, and how to grade their pain and pruritus score by the research team. The strengths of this study were that this study was conducted as a triple-blinded study, which can reduce some bias during data collection, and it had a large sample size, for each group. Additionally, all participants followed the study protocol.

CONCLUSION

This study demonstrates that reducing the ITM dose from 200 mcg to 100 mcg added to spinal bupivacaine is substantially effective in reducing postoperative pruritus. Additionally, it maintains postoperative analgesia after Cesarean section. Therefore, we recommend an ITM of 100 mcg as the choice of dosage to minimize ITM-induced pruritus.

FUNDING SOURCE

This study was supported by the Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Gadsden J, Hart S, Santos AC. Post-Cesarean delivery analgesia. Anesth Analg 2005;101(Suppl 5):S62-9.
2. Swart M, Sewell J, Thomas D. Intrathecal morphine for caesarean section: an assessment of pain relief, satisfaction and side-effects. Anaesth 1997;52:373-7.
3. Palmer CM, Emerson S, Volgoropolous D, Alves D. Dose-response relationship of intrathecal morphine for post-Cesarean analgesia. Anesthesiology 1999;90:437-44.
4. Cardoso MM, Carvalho JC, Amaro AR, Prado AA, Cappelli EL. Small doses of intrathecal morphine combined with systemic diclofenac for postoperative pain control after Cesarean delivery. Anesth Analg 1998;86:538-41.
5. Gerancher JC, Floyd H, Eisenach J. Determination of an effective dose of intrathecal morphine for pain relief after Cesarean delivery. Anesth Analg 1999;88:346-51.
6. Dahl JB, Jeppesen IS, Jorgensen H, Wetterslev J, Moiniche S. Intraoperative and postoperative analgesic efficacy and adverse effects of intrathecal opioids in patients undergoing Cesarean section with spinal anesthesia: a qualitative and quantitative systematic review of randomized controlled trials. Anesthesiology 1999;91:1919-27.
7. Girgin NK, Gurbet A, Turker G, Aksu H, Gulhan N. Intrathecal morphine in anesthesia for Cesarean delivery: dose-response relationship for combinations of low-dose intrathecal morphine and spinal bupivacaine. J Clin Anesth 2008;20:180-5.
8. Milner AR, Bogod DG, Harwood RJ. Intrathecal administration of morphine for elective Caesarean section. A comparison between 0.1 mg and 0.2 mg. Anaesthesia 1996;51:871-3.
9. Gehling M, Tryba M. Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. Anaesthesia 2009;64:643-51.
10. Kjellberg F, Tramer MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. Eur J Anaesthesiol 2001;18:346-57.
11. George RB, Allen TK, Habib AS. Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing Cesarean delivery with intrathecal morphine: a systematic review and meta-analysis. Anesth Analg 2009;109:174-82.
12. Abboud TK. Mini-dose intrathecal morphine for analgesia following Cesarean section. Anesthesiology 1988;69:805.
13. Sarvela J, Halonen P, Soikkeli A, Korttila K. A double-blinded, randomized comparison of intrathecal and epidural morphine for elective Cesarean delivery. Anesth Analg 2002;95:436-40.
14. Pakpirom J, Asampinwat T, Nuanjun K, Watanayomnaporn E. A randomized control trial of a multimodal antiemetic management for the prevention of postoperative nausea and vomiting in patients undergoing ambulatory gynecologic endoscopic surgery. J Med Assoc Thai 2017;100:549-57.

15. Uchiyama A, Nakano S, Ueyama H, Nishimura M, Tashiro C. Low dose intrathecal morphine and pain relief following caesarean section. Int J Obstet Anesth 1994;3:87-91.
16. Raffaeli W, Marconi G, Fanelli G, Taddei S, Borghi GB, Casati A. Opioid-related side-effects after intrathecal morphine: a prospective, randomized, double-blind dose-response study. Eur J Anaesthesiol 2006;23:605-10.
17. Chinachoti T, Nilrat P, Samarnpiboonphol P. Nausea, vomiting and pruritus induced by intrathecal morphine. J Med AssocThai 2013;96:589-94.
18. Nimmaanrat S, Yunuswanjsa Q. The analgesic and adverse effects of intrathecal opioids for Cesarean section: 11 years' experience in 10,061 cases. Br J Med Med Res 2014;4:2112-18.
19. Carvalho FA, Tenorio SB. Comparative study between doses of intrathecal morphine for analgesia after caesarean. Braz J Anesth. 2013;63:492-9.
20. Terajima K, Onodera H, Kobayashi M, Yamanaka H, Ohno T, Konuma S, et al. Efficacy of intrathecal morphine for analgesia following elective Cesarean section: comparison with previous delivery. J Nippon Med School 2003;70:327-33.
21. Wong JY, Carvalho B, Riley ET. Intrathecal morphine 100 and 200 mug for post-Cesarean delivery analgesia: a trade-off between analgesic efficacy and side effects. Int J Obstet Anesth 2013;22:36-41.
22. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective Cesarean delivery: A meta-analysis. Anesth Analg 2016;123:154-64.
23. Seki H, Shiga T, Mihara T, Hoshijima H, Hosokawa Y, Hyuga S et al. Effects of intrathecal opiods on Cesarean section: a systematic review and Bayesian network meta-analysis of randomized control trials. J Anesth 2021;35:991-27.
24. Pangthipampai P, Dejarkom S, Poolsuppasit S, Luansritisakul C, Tangchittam S. Bilateral posterior quadratus lumborum block for pain relief after Cesarean delivery: a randomized control trial. BMC Anesthesiol 2021;21:90.
25. Tan HS, Taylor C, Weikel D, Barton K, Habib AS. Quadratus lumborum block for postoperative analgesia after Cesarean delivery: A systematic review with meta-analysis and trial-sequential analysis. J Clin Anesth 2020;67:110003.