A COMPARATIVE STUDY OF NEURAXIAL BLOCK FOR POST-CESAREAN ANALGESIA AND SIDE EFFECTS: INTRATHECAL VS EPIDURAL MORPHINE

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Abstract

Background: Neuraxial morphine can provide an effective post-cesarean analgesia with minimal systemic effects on the parturients. Our study aimed to compare two different neuraxial blocks-intrathecal and epidural injections in Cesarean section for post-operative analgesia and side effects.

Methods: This prospective observational study included 108 ASA I or II patients who underwent elective Cesarean section with central neuraxial block. The parturients either received intrathecal morphine (ITM) of 0.1 mg or epidural morphine (EDM) of 3mg via combined spinal/epidural block. An additional oral diclofenac sodium and paracetamol were also given as part of multimodal post-operative analgesia. The pain scores were assessed by using the 0-10 Verbal Numerical Rating Scale (VNRS), with rescue medication given to those with scores>4. Side effects were also recorded and treated accordingly.

Results: Both ITM and EDM groups showed equally good post-operative analgesic results with the highest median VNRS of only 1. There were no other additional rescue analgesics required. However, side effects were significantly higher in the ITM group as compared to the EDM group in terms pruritus (76.9% vs. 40.0%, p <0.001), nausea (35.9% vs. 10.0%, p=0.008) and vomiting (29.5% vs. 6.7%, p=0.012). None of the patients developed respiratory depression.

Conclusion: While both intrathecal and epidural morphine were equally effective as post-cesarean analgesia, epidural morphine was deemed to be more superior because of its lower incidence of side effects.

Introduction

Opioids are commonly used as an additive to local anesthetics in neuraxial blocks for Cesarean Section (C-S). It can enhance intra-and post-operative analgesia as well as minimize systemic effects on the lactating parturients[1]. Its analgesic effect is exerted via opioid receptors (principally μ receptors) in the substantial gelatinosa of the spinal cord; however side effects of pruritus,

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nausea, vomiting, and depression of ventilation have been reported[1,2].

Neuraxial opioids that are frequently used in C-S include fentanyl and morphine[2]. Siti et al showed that the overall post-operative pain score for 24 hours was significantly lower in the neuraxial morphine group as compared to the neuraxial fentanyl group[3]. Similarly, Dahl et al concluded that by using morphine neuraxially, it can prolong the time for the first additional analgesic requirement post-operatively[4]. In addition, Palmer et al showed that a single 3 mg epidural morphine injection provide up to 18 hours of post-operative pain relief without any significant respiratory depression in parturients who underwent C-S[5]. This prolonged analgesic effect was probably due to the lower lipid solubility property of morphine that allowed it to be concentrated in the CSF after a neuraxial injection[2]. Therefore, neuraxial morphine is used more frequently for prolonged post-cesarean analgesia.

In C-S, the two commonest routes for neuraxial morphine administration are either through the intrathecal or epidural blocks. Duale et al compared two different neuraxial blocks for post-cesarean analgesia-intrathecal morphine (ITM) and epidural morphine (EDM) injections. They found that the EDM group showed significant good post-operative analgesic results with reductions in the requirement for an additional parenteral morphine postoperatively. However, both techniques resulted in similar incidence of side effects[6]. Sarvela et al compared ITM and EDM injection groups and also found that they had equal good post-operative pain results with pruritus reported significantly higher in the ITM group[1].

Therefore, in view of these controversies regarding the more superior technique for the post C-S analgesic effect and side effects, we compared both intrathecal and epidural blocks by using an equipotent dose of morphine-0.1mg ITM and 3 mg EDM[5,7] to evaluate the efficacy and possible side effects.

Methods

This prospective observational study was conducted in the obstetric unit of Hospital Kuala Lumpur (HKL) from March 2016 to July 2016 after approval by the Dissertation Committee of the Department of Anesthesiology & Intensive Care, UKMMC, Medical Research & Ethics Committee of UKMMC(Project code: FF-2016-011) and Medical Research & Ethics Committee (MREC) of Ministry of Health Malaysia (NMRRID: 15-1463-26430).

Following written informed consent, patients with ASA physical status of I or II, aged 18-45 years who were scheduled for elective C-S with planned Pfannenstiel incision were studied. Patients who were morbidly obese, with contraindication for regional anesthesia and with known allergy to the drugs used in the study protocol were excluded. Intra-operatively, patients with inadequate or failed neuraxial blocks requiring additional local anesthetics or conversion to general anesthesia were excluded from the analysis.

Prior to the C-S, all patients were given oral ranitidine 150mg, metoclopramide 10mg and 30ml of mist sodium citrate 0.3M as premedication. Upon arrival to the operation theater, non-invasive monitoring with electrocardiogram, oxygen saturation, and non-invasive blood pressure were applied to all patients. They were also pre-hydrated with 500ml of Hartmann's solution as per local protocol. Intrathecal block or CSE was then performed based on the anesthetist's preference. Both types of neuraxial blocks were performed at the level of L3/L4 or L4/L5 interspaces with the patient in sitting position, skin disinfected with povidone-iodine and intradermal anesthesia achieved by using lidocaine 2%.

All intrathecal blocks were performed using a 27-gauge Pencan® spinal needle (B.Braun, Melsungen AG, Germany) with heavy bupivacaine 0.5% (pre-calculated volume according to the patient's height) (Appendix 1), 20mcg of fentanyl and 0.1mg morphine

Appendix 1
Dosage of intrathecal injection for heavy bupivacaine 0.5% 12:

Height	Heavy bupivacaine 0.5%
<140 cm	1.5ml
141-150cm	1.6ml
151-160cm	1.7-1.8ml
161-170 cm	1.9ml
>170cm	2.0-2.1ml

(total volume 2.0-2.6mls). As for the CSE block, the needle-through-needle technique was used with an Espocan® set (B.Braun, Melsungen AG, Germany) which contained an 18-gauge Touhy needle and a 27-gauge Pencan spinal needle. The pre-calculated volume of heavy bupivacaine 0.5% (Appendix 1) with an addition of fentanyl 20 mcg were given for the spinal component; while an additional of 3 mg morphine diluted with 3 ml of normal saline was given via the epidural catheter before the epidural catheters were removed at the end of the operation.

IV dexamethasone 8mg and ondansetron 4mg were also given to the patients for post-operative nausea and vomiting (PONV) prophylaxis once babies were delivered. Suppository diclofenac sodium 100 mg was given to all patients at the end of the surgery. The patients' pain scores were assessed by the nurses in the recovery room as well as before being discharged to the wards.

As part of the management of post-operative pain in the ward, all patients were given oral paracetamol 1 gram every 6 h and oral diclofenac sodium 50 mg every 8 h, which commenced 18 hours post-operatively for 3 days as well as IV injection of metoclopramide 10 mg every 8 h for one day as an addition for PONV prophylaxis. The patients' pain scores were assessed every 4 h until 24-h post-operatively by nurses in the ward. The overall pain score assessment was based on the 0-10 verbal numerical rating scale (VNRS). Rescue medication of oral tramadol 50 mg were prescribed to all patients if the pain scores were more than 4.

All side effects were recorded at an interval similar to the pain scoring assessments. The side effects included pruritus, nausea, vomiting and respiratory depression. Respiratory depression was defined as a respiratory rate of less than 8 breaths per min and/or the need for administrating 0.4 mg IV naloxone.

Sample size was calculated by using "Power and Sample Size Calculations" v.3.0.43 software (Vanderbilt Biostatistics, Nashville, TN, USA). With α value determined at 0.05, power of study at 80% and ratio of 0.38 (adjusted according to number of epidural subjects matched to each intrathecal morphine subject), this study required 78 patients for the ITM group and 30 patients for the EDM group after allowing dropout rate of 10% to detect a decrease of itching from 80% to 50% [1]. Statistical analysis was performed using SPSS v.23.0 software (International Business Machines Corporation [IBM], Armonk, NY, USA). Mann-Whitney U-test was used to compare the median VNRS score between the ITM and the EDM group. Chi-square was used to compare the categorical data. A p-value <0.05 was considered as statistically significant.

Results

A total of 110 patients were recruited into the study. However, two patients from the ITM group were excluded from the analysis as both patients required general anesthesia intra-operatively. One of them had a failed block while the other had prolonged surgery due to severe bowel adhesions. Therefore, a total of 108

Table 1

Demographic data. Values are expressed as mean ± standard deviation and numbers (%) as appropriate

	Intrathecal morphine (n=78)	**Epidural morphine (n=30)**	**p-value**
Age (years)	32.3±4.8	32.9±4.0	0.48
Weight (kg)	72.6±11.4	74.7±11.8	0.41
Height (m)	1.6±0.4	1.6±0.1	0.57
BMI (kg/m^2)	29.9±4.4	30.6±4.5	0.46
ASA status			
I	42 (53.8)	13 (43.3)	0.33
II	36 (46.2)	17 (56.7)	

BMI: Body Mass Index (kg/m^2), ASA: American Society of Anesthesiologists Physical Status Classification

Table 2
Pain score measured by VNRS. Values expressed as median [interquartile range]

	Intrathecal morphine (n=78)	Epidural morphine (n=30)	p-value
Upon arrival to recovery room	0	0	0.81
Upon discharge from recovery room Post-operative	0	0	0.30
4 hours	0[0-1]	0[0-0.25]	0.63
8 hours	0[0-1]	0[0-1]	0.71
12 hours	0[0-1]	0[0-1]	0.50
16 hours	0[0-1]	0[0-1]	0.83
20 hours	1[0-2]	1[0-2]	0.66
24 hours	1[0-2]	1[0-2]	0.57

VRNS: Verbal Numerical Rating Scale

Table 3
Side effects. Values expressed as numbers (%) of patients who described the side effects at least once over 24 hours

	Intrathecal morphine (n=78)	Epidural morphine (n=30)	p-value
Pruritus	60 (76.9)	12 (40.0)	<0.001
Nausea Vomiting Respiratory depression	28 (35.9) 23(29.5) 0	3(10.0) 2(6.7) 0	0.008 0.012 -

patients (78 patients from ITM group; 30 patients from EDM group) were included in the analysis.

Both ITM and EDM groups were comparable with respect to age, height, weight, and body mass index (BMI) and ASA status (Table 1). There were no significant differences in the median 24 hours VRNS pain score for both groups post-C-S. However, the highest median score was only 1 from both groups at the interval of 20th hour and 24th hour post C-S (Table 2).

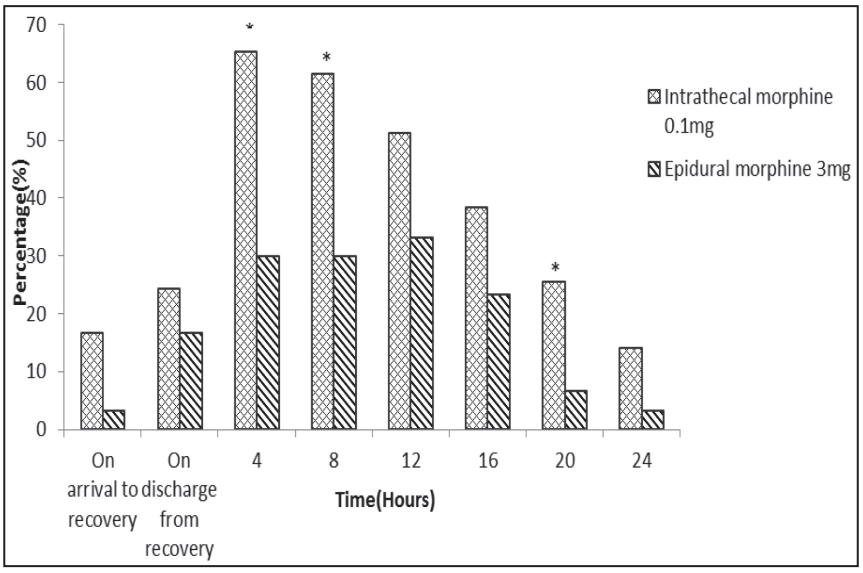
In terms of side effects, there were significantly higher incidences of pruritus (76.9% vs 40%, p≤ 0.001), nausea (35.9% vs 10.0%, p=0.008) and vomiting (29.5% vs 6.7%, p=0.012) in the ITM group as compared to the EDM group (Table 3). The peak incidence time for all side effects was at 4th hour after surgery in the ITM group and at 8th to12th hour post surgery in the EDM group (Figures 1, 2 and 3). There were no reported cases of respiratory depression in both groups of patients.

Discussion

Satisfactory post-cesarean analgesia is important in order to allow early maternal mobilization and discharge, as well as establishing maternal-child bonding. Our results showed that patients in both ITM and EDM groups were achieved comparable pain control for the first 24 hours post C-S with an overall median pain score <4. As part of the routine post-operative pain management in the ward, all patients received additional non-opioid analgesics i.e. oral diclofenac sodium and paracetamol. With this multimodal approach, good post-cesarean analgesia was achieved with no rescue analgesics required post-operatively. These results were consistent with the study by Duale et al in which the addition of non-opioids (propacetamol and ketoprofen) after neuraxial morphine injection significantly reduced post-operative parenteral morphine requirements[6]. Sun et al also concluded that the combination of EDM with intramuscular diclofenac resulted in more superior analgesic efficacy in C-S when compared to the EDM injection alone[8].

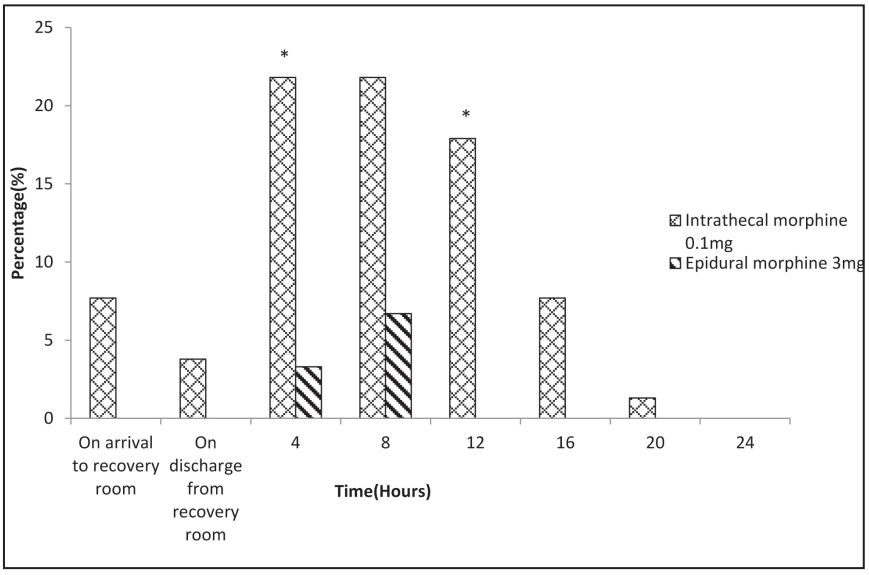
However, observed side-effects (pruritus, nausea and vomiting) were significantly higher in the ITM compared to the EDM group which could be explained by the pharmacokinetic profile of the opioid used. Most of the intrathecal morphine remained in the CSF with a lesser degree of vascular reabsorption, which allowed a considerable amount of it to be spread cephaladly in the spinal cord resulting in a higher incidence of side effects such as pruritus, nausea and vomiting[2,9,10]. On the contrary, in the presence of an extensive venous plexus, most of the epidural morphine were reabsorbed into the venous circulation before entering the CSF [2,9] which could explain the lower incidence of these side

Fig. 1
Incidence of pruritus in ITM and EDM patient groups



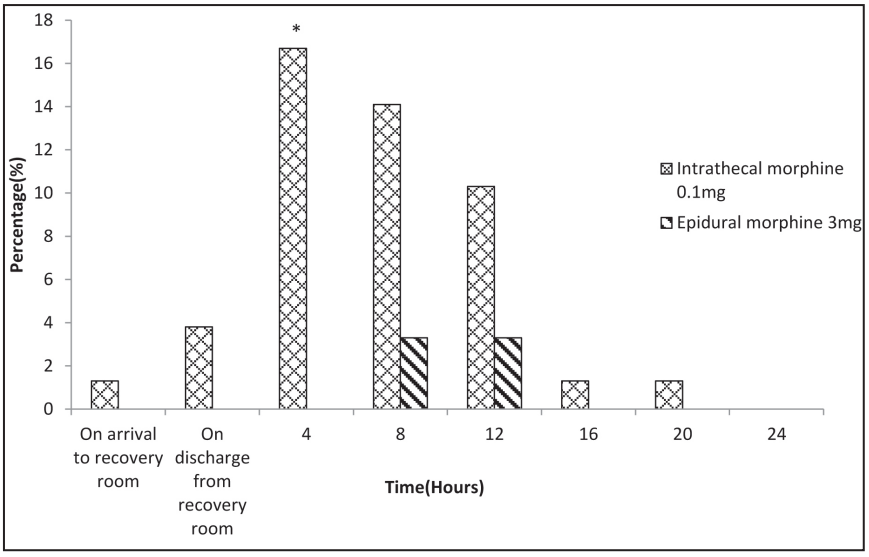
* p <0.05

Fig. 2
Incidence of nausea in ITM and EDM patient groups



\s* p <0.05

Fig. 3
Incidence of vomiting in ITM and EDM patient groups



\s* p <0.05

effects in the EDM group. The peak incidence time for all these three side effects in the ITM group occured at the 4th h post-C-S, which correlates with the time required for the cephalad spread of morphine in the CSF (within 1 to 5 hours)[9,10]. However, the delayed occurrence of side effects in the EDM group (at 8th to 12th hours post-C-S) was probably due the requirement of drug having to cross the dura before entering the CSF[9].

Appropriate pharmacological therapy plays an important role in preventing undesirable side effects of opioids. Koju et al showed that prophylactic administration of ondansetron-5-hydroxytryptamine-3 ($5HT_3$) receptor antagonist to parturients receiving intrathecal morphine could reduce the incidence of both PONV and pruritus[11]. In our study, all patients were prescribed with IV dexamethasone and ondansetron for the prevention of PONV, yet the incidence of side effects was relatively high especially in the ITM group. One of the possible reasons was that there was no scoring or grading done for the severity of the side effects observed in this study which could have resulted in an overestimation of its clinical significance. In addition, the timing of the prophylactic drugs administered in relation to neuraxial morphine may not have given the drug sufficient time to work. Therefore, we recommend more objective studies to be conducted to look into different modalities and timing of prophylactic intervention in relation to opioid administration in the prevention of its side effects.

In conclusion, both ITM and EDM injection techniques were equally effective in providing post-cesarean analgesia, and EDM injection technique was shown to be more superior in terms of lower incidence of side effects.

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