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Original Article

24-hour observation of patients after intrathecal morphine for lower segment caesarean section – Is it overrated? A prospective observational study

Thiruselvi Subramaniam, Shu Ning Kong, Shi Ting Tee, Muhammad Faiz Bin Ismail, Joanne Sue James, Hamitra Gandhi

Background: Side effects of intra-thecal (IT) morphine in lower caesarean section (LSCS) can be dangerous hence they are co-managed by the anesthesia pain team for a minimum of 24 hours. The aim of this study was to identify the side effects and consider the possibility of earlier discharge from the pain team to the parent team.

Methods: A prospective observational study was conducted on 323 patients who received IT morphine for LSCS. An interviewer-centered questionnaire was used to obtain data on the side effects.

Results: Side effects were experienced by 80% (n=259) of the patients, and none developed respiratory depression. Side effects occurred in first 6 hours in 94%(n=244) of the patients, 5% (n=13) within 6 to 12 hours and 1% (n=2) within 12 to 24 hours. Pruritus was the most common side effect (88%; n=227) and 93% (n=210) experienced it within the first 6 hours. Nausea and vomiting occurred in 54% (n=139) of the patients with side effects and 70% (n=97) of them experienced them within the first 6 hours. Kruskal-Wallis H test showed that Malays experienced more side effects, $\chi^2(2) = 3.363$, $p = 0.004$. No difference in pain scores was noted between races at 0-6 hours and 12-24 hours. However, Indians had higher scores at 6-12 hours ($\chi^2(1) = 4.31$, $p = 0.031$).

Conclusion: The most common side effect was pruritus, then nausea and vomiting with no respiratory depression. Most occurred in the first 12 hours suggesting possibility of earlier discharge by the pain team to the parent team. However, further research is needed as guidelines suggest 24 hours, fearing respiratory depression. Side effects in Malays and increased pain perception among Indians need exploration.

Keywords: *Caesarean Sections, Drug side effects, Intrathecal morphine, Race, Respiratory depression.*

Background

Neuraxial opioid refers to the epidural or intra-thecal administration of opioids. Intra-thecal and epidural opioids have today become part of a routine process for the management of post-operative pain. Intrathecal use of opioid for pain relief was reported as early as the 1900s in Romania and Japan and after a void it became increasingly used after Wang et al reported the treatment of cancer pain with intra-thecal morphine in 1979.[1, 2]

Intrathecal morphine (IT morphine) has been proven to improve the management of pain post- lower segment caesarean sections (LSCS) and other surgical procedures.[3-8] However, side effects of morphine can be dangerous and distressing to patients and clinicians, especially pruritus, nausea, vomiting, and respiratory depression.[9,10] The dreaded respiratory depression is the main reason why patients after IT morphine are followed up for up to 24 hours. According to the practice guidelines by the task force on neuraxial opioids, the American Society of Anesthesiologists and American Society of Regional Anesthesia and Pain Medicine, respiratory depression may be indicated by: (1) reduced respiratory rate to less than 10 breaths/min, (2) reduced oxygen saturation or (3) hypercapnia/hypercarbia. The guidelines also suggest other measures of respiratory

Department of Anaesthesia & Critical Care, International Medical University, No.126, Jalan Jalil Perkasa 19, Bukit Jalil, 57000 Kuala Lumpur, Malaysia

Address for Correspondence:

Dr Thiruselvi Subramaniam, Clinical Associate Professor, Department of Anaesthesia & Critical Care, International Medical University, Kuala Lumpur, Malaysia Email: thiruselvi_subramaniam@imu.edu.my

function like tidal volume or clinical signs such as drowsiness, sedation, periodic apnea, and cyanosis as indicators of respiratory depression.[11-13]

The practice by the Acute Pain Service (APS) team at our hospital is to follow up all post-LSCS patients who received intra-thecal morphine for the first 24 hours. This is to identify, prevent or manage life-threatening conditions like respiratory depression, other common side effects like pruritus nausea and vomiting. The question raised was, if the follow up duration of the IT morphine patients can be reduced, patients can then be discharged to parent team sooner for further continued management. Hence, we aimed to identify the side effects of IT morphine at 0-6 hours, 6-12 hours, or 12-24 hours after administration for LSCS. A minor objective was to also compare side effects among different races, considering the racial diversity of the patients in our hospital.

Methods

This is a prospective observational study conducted in the post-natal ward of a tertiary public hospital on patients (18 to 45 years of age) who were administered IT morphine during the induction of spinal anesthesia for the management of post-LSCS pain. A sample size of 384 was calculated based on a population size of 1000000, confidence interval of 5 and confidence level of 95%. However, we were able to recruit a total of only 323 patients in the time period of 6 months that we had for data collection. Patients who consented, signed a consent form agreeing to participate in the study and were informed that all information will be kept confidential. The study information was provided to all patients in a written form and verbal explanation was also provided.

Patients between the ages of 18-45 undergoing LSCS, who had no contraindication for spinal anesthesia and who received IT morphine, were included in the study. Patients who were excluded were those – 1) who refused participation, 2) had combined spinal epidural (having a catheter inserted epidurally for post-op pain, 3) had spinal anaesthesia without IT morphine, 4) morbid obesity, 5) allergy to morphine. An interviewer-centered questionnaire was used to obtain demographic information from patients. The questionnaire included demographics such as age, race and previous history of lower segment caesarean section with spinal anaesthesia, time to ambulation, the presence of pain over the incisional site, the presence of intrathecal morphine side effects and the sedation score.

The intrathecal cocktail used for lower section caesarean surgery was hyperbaric bupivacaine 12mg, fentanyl 10ug and 0.1mg morphine. Patients were monitored closely in the wards as per requirement of all post-operative patients but these group of patients had close monitoring of respiration and state of sedation as they had received IT morphine for their surgery. Post-operative evaluation of the patients for the research, however, was carried out at intervals of 0-6 hours, 6-12 hours and 12-24 hours using the questionnaire and was completed by patients with the assistance of the investigator. This time interval was chosen as it was convenient for the investigators and their availability to assess the patients, as well as to avoid frequent interruption and disruption of patients' post-operative recovery period. The targeted side effects were pruritus, sedation, nausea, vomiting and respiratory depression.

Pain score was assessed using modified Wong-Baker FACES Pain Rating Scale and pruritus was assessed using a score modified from the Wong-Baker visual pain score. Based on the protocol used in the hospital, respiratory depression was defined as respiratory rate of less than 8 breaths per minute. Sedation was assessed using the scoring system used routinely in the hospital.

Side effects targeted

a) Pruritus

Pruritus was categorised into localised pruritus and generalised pruritus. Localised pruritus meant a single area of itchiness and generalised pruritus meant more than one region of itchiness. The degree of pruritus was assessed as mentioned earlier, a score modified from the Wong-Baker visual pain score and pruritus intensity assessment questionnaire.

0 = no itch

2 = itch relieved by gentle rubbing

4 = itch relieved by scratching

6 = itch unrelieved by scratching

8 = itch unrelieved by scratching with excoriation

10 = itch affecting sleep

b) Respiratory depression

Respiratory rate of less than 8 breaths per minute was considered as respiratory depression.

c) Sedation

Sedation score was evaluated using the sedation score by the hospital, where 0 = none (patient is awake/ alert), 1 = mild (occasionally drowsy), 2 = moderate (frequently drowsy, easily roused), 3 = severe (difficult to rouse) and S = sleeping (easy to rouse).

d) Nausea and vomiting

Data analysis and Ethical clearance:

The data collected was analysed using SPSS and the statistical analysis was carried out using the Chi square test and Kruskal Willis test with statistical significance set at $p < 0.05$.

Ethical clearance was obtained from the International Medical University Ethical Joint Committee of Research and Ethics; ID No: CSc / Sem6(17)2015 and the National Malaysian Medical Research ethical committee.

Results

Patients' ages ranged from 18 to 43 with a mean of 30.3 years (SD=5.32) and they were categorised into three groups; 1) less than 29 years old (46%; n=149) 2) 30-39 years old (50%; n=160) and 3) more than 40 years old (4%; n=14). Most patients who had side effects were of ages between 30-39 years (80%; n=130). However, there was no statistically significant association between age group and the presence of side effects, $\chi^2(2) = 0.229a$, $p = 0.892$.

Of the 323 patients, 65% (n=209) were Malay, 10% (n=32) Chinese, 20% (n=65) Indian and 5% (n=17) were of other races which included the aboriginals and foreigners. Our study results show that 9% (n=29) of the patients began ambulating within 6 to 12 hours, 83% (n=269) by 12 to 24 hours and 8% (n=25) did not ambulate after 24 hours because they still had urinary catheters in-situ due to other obstetrical reasons. We found that 80% (n=259) of the patients experienced at least one side effect of IT morphine at some point in time during the post-operative review and 20% (n=64) did not experience any side effects at all (Fig. I). However, no patient developed respiratory depression. (Fig. II)

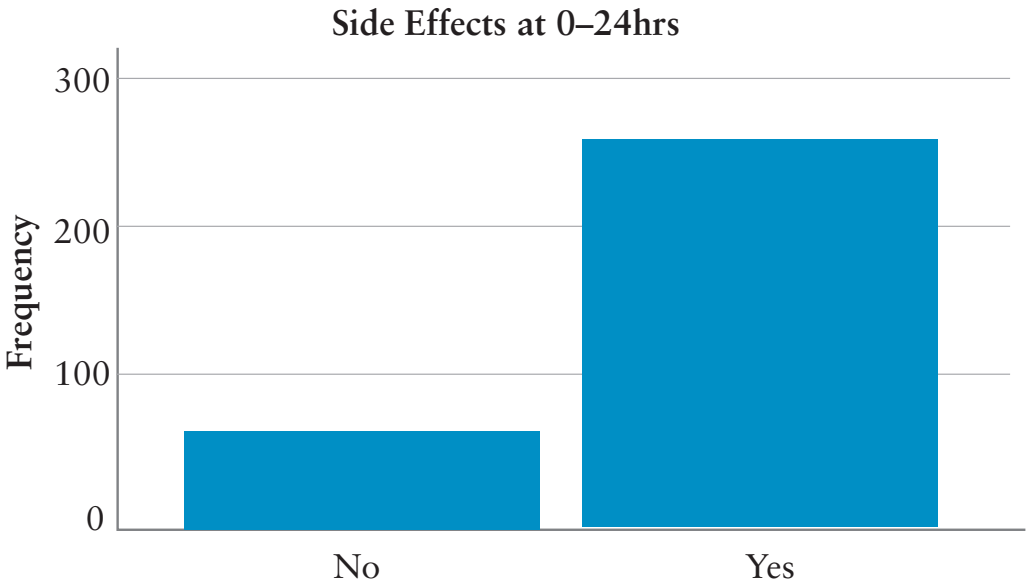

Figure I: Appearance of side effects in the first 24 hours

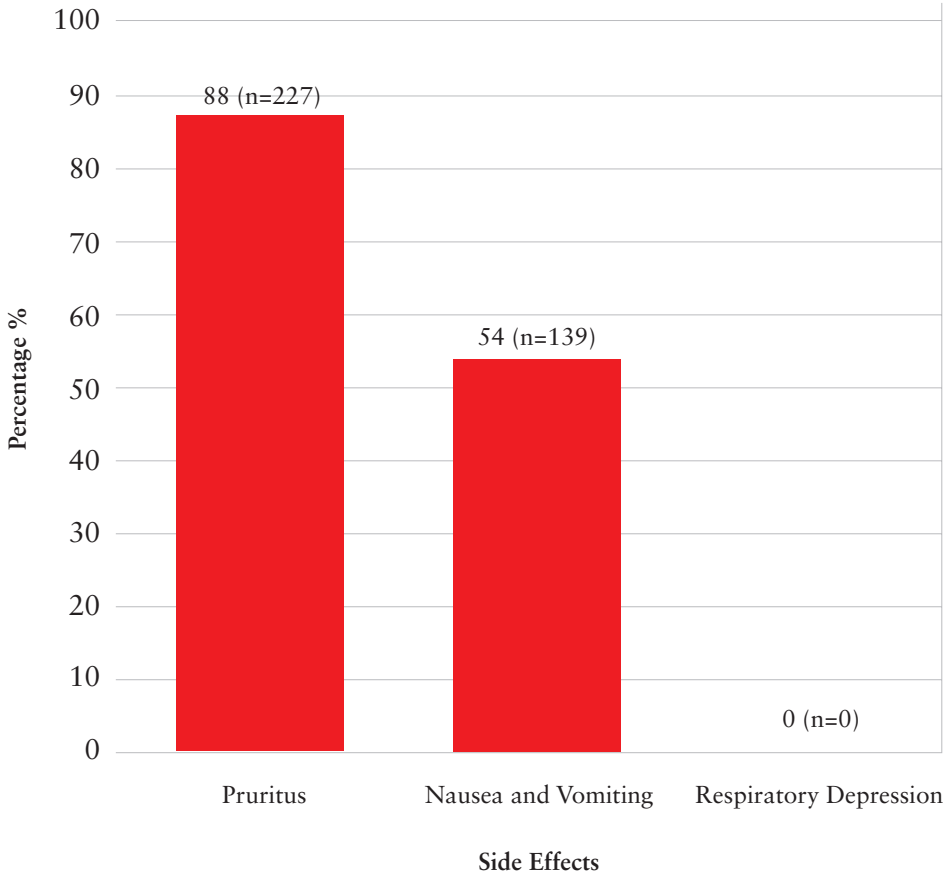

Figure II: The most common type of side effects identified in patients who developed side effects (n=259)

Kruskal-Wallis H test showed a statistically significant difference in side effects between the different races, $\chi^2(2) = 3.363$, $p = 0.004$, with a mean rank side effect of 170.05 for Malays, 148.58 for Chinese, 139.34 for Indians and 175 for Others. Interestingly we found that the Malay population experienced more side effects than the Chinese and Indians.

Side effects commonly occurred within the first 6 hours, as apparent in 94%(n=244) of the patients, 5% (n=13) within 6 to 12 hours and 1% (n=2) within 12 to 24 hours. (Fig. III) Pruritus was the most common side effect (88%; n=227) and majority (93%, n=210) of the patients experienced it within the first 6 hours. Among the Malays with side effects, pruritus appears to be the most common (90%; n=160).

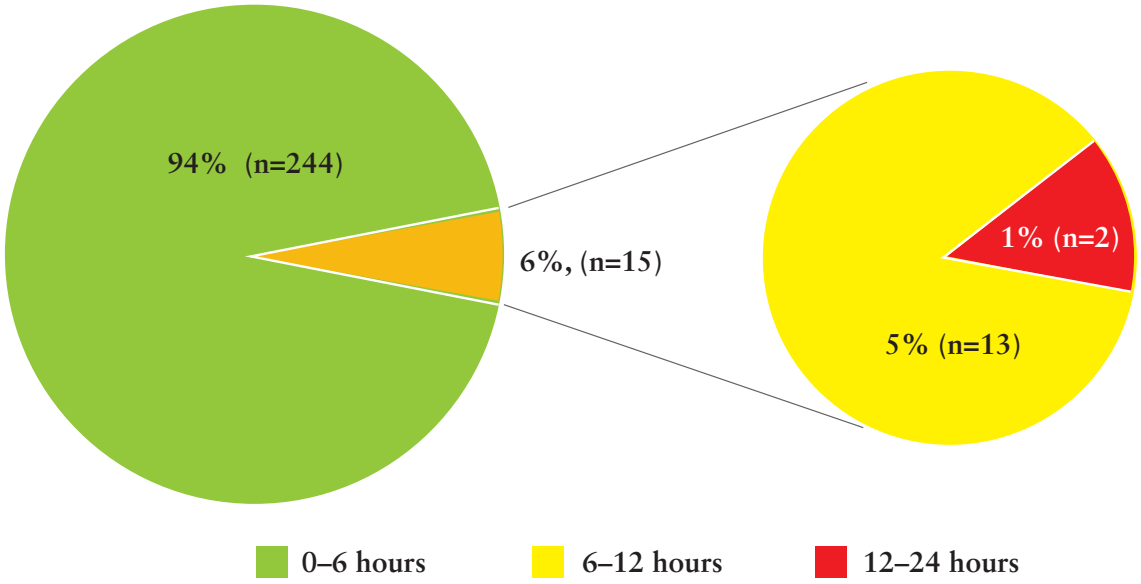

Figure III. Relationship of the onset of side effects and time

Of the total 210 patients with pruritus in the first 6 hours, 43% (n=90) had localised pruritus and 57% (n=120) had generalised pruritus. However, some (10%; n = 9) of the patients with localised pruritus in the first 6 hours eventually developed generalised pruritus. Of the 227 patients, the face was the most common location of pruritus (82%; n=186). Nausea and vomiting occurred in 54% (n=139) of the patients who had side effects and 70% (n=97) of them experienced this within the first 6 hours.

Pain

The mean pain score of the patients was the lowest during the first 6 hours (1.9 ± 2.1) and progressively increased in the 6-12-hour period (2.1 ± 2.0) and the 12-24-hour period (2.5 ± 1.9). However, the scores were generally within acceptable range. There was no difference in pain scores among the different races during the 0-6 hours, $\chi^2(1) = 1.39$, $p = 0.239$) and 12-24 $\chi^2(1) = 2.88$, $p = 0.090$) hours post IT morphine.

However, Indians had higher scores at 6-12 hours. $\chi^2(1) = 4.31$, $p = 0.031$) compared to the other races (Malays, Chinese and Others).

Sedation

None of the patients had a sedation score of more than 2 (drowsy but rousable), 63% (n=204) had a sedation score of 1 (occasionally drowsy-mild) and the rest, 37% (n=119) has either a score of 0 or S (sleeping). It was noted that that 97% (n=197) of those who were mildly sedated were so in the first 6 hours.

Discussion

Most of the side effects caused by IT morphine occurred within the first 12 hours of administration in our study. Nausea/vomiting was the second common side effect (54%; n-139) noted in our population of patients usually occurring in the first 6 hours, pruritus being the most common (88%; n=227). These findings were similar to other studies.[3, 14] Most studies identify pruritus, nausea, vomiting and urinary retention as common side effects of IT morphine though there appear to be inconsistencies regarding incidence of the most feared respiratory depression. The varied definitions about respiratory depression (respiratory rate of less than 8 or less than 10) could perhaps contribute to the inconsistencies in results from the various studies.[10, 12, 13, 15, 16]

This dose of morphine used at our premise is 0.1mg combined with fentanyl and bupivacaine. The dose of 0.1mg IT morphine is identified as optimal with minimal side effects for LSCS as evidenced in several research.[3, 10, 17, 18] Higher doses of IT morphine are known to provide adequate pain relief but at the expense of more side effects. The IT dose of 0.1mg morphine given intrathecally is found to have lesser side effects but with similar pain relief compared to higher doses.[4, 10, 19, 20, 21]

There have been debates about ethnicity and pain. Most studies on ethnicity and perception of pain are centered around the western population. A systematic review and meta-analysis by Kim et al found that Asians and Hispanics had higher pain sensitivity compared with non-Hispanic whites.[22] However, a study on perception to thermal pain among Indians, Chinese and Malays did not show any significance between the three groups. This could be because of the setting of the studies which were quite different and conducted in a controlled environment.[23] Knowledge about perception of pain among the different races will help in the improvement of post-IT morphine pain management. Earlier, routine administration of other form of pain medications would improve post-operative outcomes for the respective group of patients.

Our findings however, showed that, though there were no differences in pain scores in the 0-6 and 12-24 hours post IT morphine, there was significant difference in the 6-12 hour period, with Indians having higher scores (≥ 4 on the Wong- Baker's FACES Pain rating scale) compared to the other races (Malay, Chinese and Others) at 6-12 hours, $\chi^2(1) = 4.31$, $p = 0.031$). A study conducted on ethnic differences in pain perception and patient controlled analgesia usage post-LSCS where intrathecal morphine was used along with local anaesthetic had similar results.[24] A quantitative review of ethnic group differences in experimental pain response suggested that there are potentially important ethnic/racial group differences in the perception of pain. Demonstrating ethnic group differences, they felt would transfer to a more culturally competent clinical care. It would address and reduce pain treatment disparities among ethnically/racially diverse groups.[25] Furthermore, explorations into relevant psychological and socio-cultural factors may reveal more information

with regards to the relationship of pain perception and ethnicity.[23, 24, 25, 26, 27] The sample size in our study was a limitation that can be remedied in future by conducting a more focused research on perception of pain among these three major ethnic groups in our country.

The incidence of pruritus is 83% in postpartum patients and 69% in non-pregnant patients including males and females.[28, 29] Pruritus can cause significant discomfort to patients who receive IT morphine. Incidence of pruritus is noted to be related to higher doses of IT morphine. In our study pruritus appears to be a more common side effect than others like nausea and vomiting though we used relatively lower doses of morphine intrathecally. There are other studies that identify pruritus as a more common side effect in patients receiving intra-thecal opioids.[4] Mechanism of intrathecal opioid-induced pruritus is complex and the literature data on the pathogenesis is still not clear though there have been many discoveries and explanations to the cause.[30] Distribution of pruritus has been noted to be mainly in the upper half of the body, though in some cases it maybe generalised. In our case we found that most patients had pruritus on the face compared to other parts of the body.

Respiratory depression is one of the most dreaded side effects of intrathecal opioids. Swart et al reported 0.02% (n=1) incidence of respiratory depression (respiratory rate <10) in a study conducted on 60 patients who underwent LSCS with 0.1mg IT morphine.[3] In our study none of the patients developed respiratory depression, findings being similar to a retrospective study by Crowgey et al in 5036 obstetric patients.[31] However, the absence of respiratory depression does not imply the absence of this feared side effect in view of our sample size and thus may require further research. It is believed that the lack of a universally accepted definition and the variability of the IT doses used have prevented us from establishing the true incidence of respiratory depression.[12] A meta-analysis on side effects of morphine showed that the risk of respiratory depression seems not to be increased in patients receiving IT morphine < 0.3mg compared to placebo suggesting that using lower doses would provide a bigger safety margin with respiratory depression. In the obstetric patients, the higher levels of progesterone, a potent respiratory stimulant, makes it safer to use the neuraxial opioids. [12, 13, 31]

Conclusion

The results of our research suggest that 12-hour monitoring by APS team is adequate before discharging from the APS care and regular monitoring can be continued in the ward by the parent team. This will help in the redistribution of workload for the APS team and useful time management.

Further study with a bigger sample size may be needed to look at the predominance of side effects that were noted among Malays compared to the Chinese and Indian population in our study and reaffirm that respiratory depression is not the most dreaded side effect at low doses. Our study suggests that Indian women have a lower threshold for perception of pain, and it would be interesting to re-look at the racial differences using a bigger sample size.

Limitations

- The sample size was limited also by the duration available for the research.
- A bigger sample size would be required identify the significance of racial differences in perception of pain.

Conflict of interest and funding

There is no conflict of interest for the conduct of this study. No funding was needed.

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