Original Article

Incidence of Respiratory Depression and Other Side Effects of 0.2 mg Intrathecal Morphine for Cesarean Section: A Review of 17,659 Cases at Thailand's Tertiary Referral Center

Raviwon Atisook MD[1], Saowapark Chumpathong MD[1], Vimolluck Sanansilp MD[1]

[1] Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: Intrathecal morphine is routinely given for post-cesarean section analgesia. The most serious side effect of intrathecal morphine in this setting is delayed respiratory depression. The aim of the present study was to investigate the incidence of respiratory depression and other side effects within the first 24 hours after administration of 0.2 mg intrathecal morphine to control post-cesarean section pain.

Materials and Methods: Electronic medical records of 17,659 parturients who underwent cesarean section under spinal anesthesia with bupivacaine and concurrent administration of 0.2 mg intrathecal morphine to control post-cesarean section pain at Siriraj Hospital during July 2011 to June 2016 were retrospectively reviewed.

Results: No cases of respiratory depression that required naloxone reversal in the first 24 hours post-cesarean section were observed in the present study. At rest, most patients had a verbal numerical rating score [VNRS] of 1 to 3 (52.8%). During movement, the majority of parturients had a VNRS of 4 to 6 (42.6%). Vomiting and pruritus occurred in 34.7% and 34.5% of patients, respectively. Women with advanced maternal age (≥35 years) had significantly lower pain scores both at rest and on movement (p<0.001), significantly less pruritus (p<0.001), but significantly more vomiting (p<0.001) than women aged less than 35 years.

Conclusion: No incidence of delayed respiratory depression was observed among the 17,659 parturients who received 0.2 mg intrathecal morphine to control post-cesarean section pain in the present study. Although the vast majority of patients had good pain control at both rest and during movement, one-third of patients experienced vomiting and/or pruritus.

Keywords: Cesarean section, Intrathecal morphine, Respiratory depression, Side effects, Spinal anesthesia

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Spinal bupivacaine with low-dose intrathecal morphine provides effective anesthesia and postoperative analgesia in cesarean section[1]. Although intrathecal morphine has side effects that include nausea, vomiting, pruritus, and delayed respiratory depression, the last of these is of most concern to physicians. Studies in delayed respiratory depression from intrathecal morphine in cesarean section have reported an incidence of 0% to 1%, with variation in morphine dose (0.1 to 0.25 mg), obstetric population (e.g., race, age, and body mass index [BMI]), and definition of delayed respiratory depression (e.g., reduced respiratory rate, reduced oxygen saturation, or need for naloxone reversal)[2]. In addition to the rarity of delayed respiratory depression in this setting, its consequence can be severe if there is a delay in diagnosis or treatment[3].

At our hospital, which is Thailand's largest national tertiary referral center, 0.2 mg intrathecal morphine has been used for post-cesarean section

Correspondence to:
Chumpathong S. Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4197978, **Fax:** +66-2-4113256
E-mail: saowapark.chu@mahidol.ac.th

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analgesia for more than two decades, but there have been very few studies which investigated the side effects of this anesthesia protocol[4]. Accordingly, the aim of the present study was to investigate the incidence of respiratory depression and other side effects within the first 24 hours after administration of 0.2 mg intrathecal morphine to control post-cesarean section pain.

Materials and Methods

The protocol for this retrospective descriptive study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Si. 077/2017). Electronic medical records of 17,659 parturients with American Society of Anesthesiologist [ASA] physical status I-III who underwent either elective or emergency cesarean section under spinal anesthesia with bupivacaine and concurrent administration of 0.2 mg intrathecal morphine to control post-cesarean section pain at Siriraj Hospital during the July 2011 to June 2016 study period were included. Patients having one or more of the following were excluded: combined spinal-epidural anesthesia, or combined spinal-general anesthesia; ASA physical status IV; spinal anesthesia with other doses of intrathecal morphine; and/or, incomplete medical information.

All parturients received lumbar spinal anesthesia with 11 mg of 0.5% hyperbaric bupivacaine with 0.2 mg preservative-free morphine. Surgery was started after loss of sensation at least the 4th thoracic vertebra level. Hypotension was treated with either ephedrine or norepinephrine. Intra-operative antiemetic and antipruritic medications were given at the discretion of the attending anesthesiologist. No premedication or intra-operative analgesic medication was given. The post-intrathecal morphine standing protocol was followed, which included hourly monitoring of vital signs, oxygen saturation (SpO_2), and sedation score (SS) ranging from 0 to 3 (0 = wide awake; 1 = easy to arouse; 2 = easy to arouse, but unable to stay awake-early respiratory depression; 3 = somnolence, difficult to arouse-severe respiratory depression) for 12 hours, and then every 2 hours until 24 hours. If any sign of respiratory depression was detected (respiratory rate <10 breaths per minute or SpO_2 <92% at room air), a physician would be notified and a decision would be made whether to assist ventilation or to give naloxone reversal. Pain scores at rest and on movement were monitored using verbal numerical rating score (VNRS; range 0 to 10). Rescue medication for breakthrough pain (VNRS >3 and SS <2) was intravenous pethidine 20 mg every 2 hours. In cases with vomiting, ondansetron 0.15 mg/kg was given intravenously and the number of vomiting episodes was recorded. Presence of pruritus and whether treatment was required or not was recorded. In cases requiring treatment, chlorphenira mine 10 mg was given intravenously. Other oral and/or intravenous analgesic medications were prescribed at the discretion of each obstetrician (varying from acetaminophen to non-steroidal anti-inflammatory drugs [NSAIDs]), and given around the clock or as needed. Baseline maternal characteristics, including age, height, BMI, and ASA physical status, were collected and recorded. Postoperative naloxone administration was identified in inpatient documents, pharmacy department medication records, and anesthetic risk management records. Data specific to pain scores at rest and on movement, vomiting, pruritus, and medications given during the first 24 hours after cesarean section were obtained from nurse anesthetist postoperative round records.

Statistical analysis

Sample size calculation was based on the results of a previous study[5] that used 0.15 mg intrathecal morphine in cesarean section, and that found a 0.052% incidence of delayed respiratory depression within the first 24 hours. Using an estimated incidence of delayed respiratory depression of $\pm$0.1% and a 95% confidence interval [CI] of 0.05 to 0.15, a minimum sample size of 17,574 was required using PASS Sample Size Software version 14.0.11 (NCSS, LLC, Kaysville, UT, USA).

Data analysis was performed using PASW Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics are presented as mean $\pm$ standard deviation [SD] or number and percentage. Association between side effects of intrathecal morphine and maternal age, BMI, and pain score was assessed using chi-square test. A *p*-value less than 0.05 was considered statistically significant.

Results

From a total of 21,227 women who underwent cesarean section during July 2011 to June 2016, 17,975 (84.7%) received spinal anesthesia, 2,121 (10%) general anesthesia, 941 (4.4%) epidural anesthesia, and 190 (0.9%) combined general and regional anesthesia. None of the patients in the present study received combined spinal and epidural anesthesia. Of the 17,975 patients who underwent cesarean section under spinal

anesthesia, 17,795 patients (99%) received concurrent administration of 0.2 mg intrathecal morphine. Of these, 136 patients with incomplete medical information were excluded. The remaining 17,659 women were included in the final analysis (Figure 1).

Baseline maternal characteristics are shown in Table 1. Approximately one-third (31.6%) of patients were of advanced maternal age (≥35 years), and 34.7% of patients underwent emergency cesarean section. Mean BMI at delivery was 26.8 kg/m^2.

No intra-operative or immediate postoperative respiratory event was reported among our study population. Inpatient data and our review of pharmacist medication records revealed no cases of delayed respiratory depression that required naloxone reversal within the first 24 hours after cesarean section.

Postoperative pain control during the first 24 hours compared between at rest and during movement was, as follows: no pain (VNRS 0; 34.3% vs. 6.2%), mild pain (VNRS 1 to 3; 52.8% vs. 38.3%), moderate pain (VNRS 4 to 6; 11.3% vs. 42.6%), and severe pain (VNRS 7 to 10; 1.6% vs. 12.9%), respectively. Vomiting and pruritus occurred in 34.7% and 34.5% of patients, respectively. With regard to the incidence of vomiting, 29.5% of parturients vomited 1 to 2 times, and 5.2% vomited >2 times. Only 3.5% of parturients who had pruritus required treatment.

Women with advanced maternal age (≥35 years) had significantly lower pain scores both at rest and on movement (p<0.001), significantly less pruritus (p<0.001), but significantly more vomiting (p<0.001) than women aged less than 35 years (Table 2). No significant association was observed between BMI and any of pain score at rest or on movement, pruritus, or vomiting.

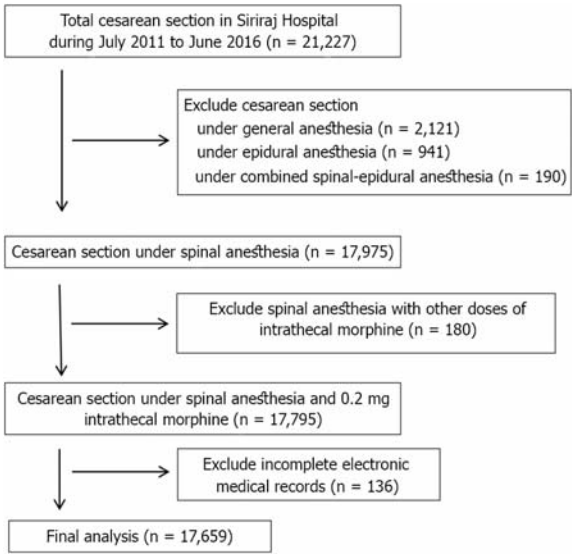

Figure 1. The diagram showing enrollment and exclusion.

Table 1. Baseline maternal characteristics

Parameter	n = 17,659
Age (year) (n = 17,623)	31±6
Age ≥35 year	5,571 (31.6)
BMI at delivery (kg/m^2) (n = 17,360)	
<18.5	85 (0.5)
18.5 to 24.9	4,207 (24.2)
25.0 to 29.9	7,897 (45.5)
30.0 to 34.9	3,763 (21.7)
35.0 to 39.9	1,050 (6.0)
≥40.0	358 (2.1)
ASA Physical status	
I	3,421 (19.4)
II	13,761 (77.9)
III	458 (2.6)
Emergency cases	6,134 (34.7)

The data are presented as mean ± standard deviation or n (%)
BMI = body mass index; ASA = American Society of Anesthesiologist

Discussion

The present study in 0.2 mg intrathecal morphine for post-cesarean section pain control revealed 0% incidence of delayed respiratory depression that required naloxone reversal within the first 24 hours in 17,659 cases over a 5-year period. Although the vast majority of patients had good pain control both at rest and during movement, one-third of patients experienced vomiting and/or pruritus.

The most serious side effect of neuraxial opioid is delayed respiratory depression. Death or permanent brain damage has been reported in some cases[6]. Early and delayed respiratory depression after intrathecal morphine can occur within 2 hours and during 6 to 24 hours, respectively. The pharmacokinetics of neuraxial opioid, including rostral spread in cerebrospinal fluid, vascular uptake by subarachnoid venous plexuses, and slow penetration into the brainstem respiratory center, caused patient failure to respond to hypercapnia and/or hypoxia[7]. A lower incidence of respiratory depression was found among obstetric patients due to the relatively younger age of parturients and an increased level of progesterone, which is a respiratory stimulant[8]. Kato et al studied

Table 2. Proportion of patients with pain, vomiting, and pruritus by age group

		Age (year)		*p*-value
	n	<35	≥35	
Pain at rest	17,623	12,082	5,541	<0.001*
None (VNRS = 0)		3,987 (33.0)	2,060 (37.2)	
Mild (VNRS = 1 to 3)		6,500 (53.8)	2,813 (50.8)	
Moderate (VNRS = 4 to 6)		1,402 (11.6)	580 (10.5)	
Severe (VNRS = 7 to 10)		193 (1.6)	88 (1.6)	
Pain on movement	17,623	12,082	5,541	<0.001*
None (VNRS = 0)		700 (5.8)	393 (7.1)	
Mild (VNRS = 1 to 3)		4,555 (37.7)	2,177 (39.3)	
Moderate (VNRS = 4 to 6)		5,230 (43.3)	2,277 (41.1)	
Severe (VNRS = 7 to 10)		1,597 (13.2)	694 (12.5)	
Vomiting	17,307	11,854	5,453	<0.001*
None		7,942 (67.0)	3,365 (61.7)	
1 to 2 times		3,330 (28.1)	1,772 (32.5)	
≥3 times		582 (4.9)	316 (5.8)	
Pruritus	17,219	11,790	5,429	<0.001*
None		7,628 (64.7)	3,654 (67.3)	
Yes, treatment not required		3,761 (31.9)	1,585 (29.2)	
Yes, treatment required		401 (3.4)	190 (3.5)	

The data are presented as n (%)
* $p<0.05$ indicates statistical significance
VNRS = verbal numerical rating score

1,915 parturients who received 0.15 mg intrathecal morphine[5]. Five patients (0.26%) developed bradypnea (respiratory rate <11 breaths per minute), and only one patient (0.052%) required naloxone reversal. None of these five patients had BMI more than 35 kg/m^2. Dalchow et al defined respiratory depression as transcutaneous carbon dioxide level >7 kPa for >2 minutes, oxygen saturation <90%, or the need for medical intervention, and found an incidence of 17.8% when using 0.3 mg intrathecal diamorphine in cesarean section[9].

Crowgey et al reviewed 5,036 parturients (mean BMI = 34 kg/m^2) who received neuraxial morphine doses ranging from 0.05 to 0.25 mg for cesarean section, and no respiratory depression requiring naloxone administration was found[10]. The finding of no delayed respiratory depression requiring naloxone reversal in the present study may be attributable to the post-intrathecal morphine standing protocol that we have had in place at our center for more than two decades. Our parturients were also not obese, with only 8.17% of them having a BMI at delivery of ≥35 kg/m^2. Although the incidence of respiratory depression is low, factors that increase the risk of this event continue to be a matter of concern, including history of obstructive sleep apnea, morbid obesity, receiving magnesium sulfate for treatment of preeclampsia as seizure prophylaxis, and sedative medications (e.g., diphenhydramine, chlorpheniramine)[6]. Different definition of respiratory depression is also a cause of variation in incidence among many studies.

Patients could be hypoxic or hypercapnic with a normal respiratory rate when respiration is depressed by morphine[3,5,11]. Although monitoring of SpO_2 and end-tidal CO_2 might facilitate early detection of respiratory depression[12], these methods are not practical in routine clinical practice at our center. Regular assessments and vigilant nursing observations of respiratory effort, respiratory rate, and unusual somnolence are probably adequate in low-risk obstetric patients[13].

Neuraxial morphine had an analgesic efficacy ceiling, with no observed benefit at doses higher than 0.2 mg, and some authors suggested a dose range of 0.075 to 0.2 mg[1-3]. Using intrathecal morphine 0.2 mg in this study, we found 34.3% and 52.8% of parturients had no pain and mild pain at rest, respectively. Pain on movement was found in nearly equal proportions in

the mild and moderate pain groups (38.3% and 42.6%, respectively). Severe pain on movement was found in only 12.9% of parturients, as we had a standing order to give a small dose of intravenous pethidine as needed every 2 hours. The low proportion of severe pain may also be due to the effect of oral analgesics given early in the first 24 hours after surgery. Unfortunately, the postoperative round records did not indicate the amount of pethidine used. Multimodal analgesia has been associated with superior pain relief and decreased opioid usage[14]. Acetaminophen has opioid-sparing effect of approximately 20%. NSAIDs have a 30% to 50% opioid-sparing effect, but they should be used with caution in preeclampsia with renal impairment. A single dose of dexamethasone before surgery significantly decreased the incidence of nausea and vomiting, and improved analgesia on the first postoperative day[15]. We do not routinely give intraoperative or postoperative dexamethasone at our center. No evidence of the effectiveness of gabapentin for pain relief in cesarean delivery was observed[14].

Age influences pain perception. Wandner et al reported that young adults (aged 17 to 28 years) had more pain sensitivity than middle-ages adults (30 to 45 years)[16]. In contrast, Nazare et al reported that women aged 18 to 33 years had no difference in pain threshold than women aged 34 to 49 years[17]. Other factors that influence individual pain perception include pain experience, socio-economic factors, and education. However, data relating to these factors were not available in the medical records of included patients.

Incidence of postoperative vomiting in cesarean section varied from 12% to 58%[18]. Intrathecal morphine moves rostrally in 5 to 6 hours after administration to the chemoreceptive trigger zone in the medulla oblongata, which has various emitogenic receptors, including the dopamine-2 [D_2] receptor, histamine-1 receptor, opioid receptor, 5-hydroxy-tryptamine-3 [5-HT3] receptor, acetylcholine receptor, neurokinin-1 receptor, and cannabinoid receptor-1 receptor[19,20]. Recent consensus guidelines for the management of postoperative nausea and vomiting [PONV] suggest using a different multimodal medication class for each receptor[21]. Imeh et al found that prophylaxis consisting of combination dexamethasone and ondansetron in parturients receiving 0.2 mg intrathecal morphine for cesarean section significantly reduced the incidence of PONV compared with dexamethasone alone (9.3% vs. 37%; $p = 0.003$)[22].

To our knowledge, no previous study has investigated the relationship between age and PONV in parturients undergoing cesarean section under spinal anesthesia. Lien et al reported that patients aged ≥65 years (not BMI or pain score) had a higher incidence of vomiting than patients aged <65 years after spinal anesthesia (24.7% vs. 15.6%, respectively; $p<0.0001$)[23].

Compared with non-parturients, the incidence of intrathecal morphine-induced pruritus varied from 60% to 100% in parturients due to the interaction between estrogen and opioid receptors[24]. Various recent studies have suggested the serotonin 5-HT3 receptor as the mechanism by which opioid is activated[25]. Koju et al reported that prophylactic administration of ondansetron to parturients receiving 0.2 mg intrathecal morphine for cesarean section provided a significant reduction in pruritus and nausea and vomiting. Their incidence of pruritus in the placebo group (88%) was higher than the incidence in the present study (34.5%)[26]. We do not routinely give prophylactic antiemetic or antipruritic at our center. Not all parturients were cured from pruritus with 5-HT3 receptor antagonists alone due to other explained mechanisms including dorsal horn activation, antagonism of inhibitory transmitters, mu receptor, D_2 receptor antagonists and the involvement of prostaglandins. It is not caused by the histamine release due to the ineffective treatment of antihistamine drug[25]. Naloxone, propofol (which acts at the dorsal horn of spinal cord), NSAIDs and pentazocine, were also used for treatment of intrathecal morphine-induced pruritus[27].

Although patients with advanced maternal age had statistically significantly lower pain scores both at rest and on movement, a lower incidence of pruritus, and a higher incidence of PONV than the younger age group in this retrospective study ($p<0.001$), further prospective randomized controlled study is needed to identify any clinical significance between maternal age and the analgesic efficacy and side effects of intrathecal morphine.

Limitations

The present study has some mentionable limitations. First and consistent with the retrospective nature of this study, some patient data may be missing or incomplete, such as time to first analgesics, and the amount of either intravenous or oral analgesics given. Second, the patients enrolled in this study were from a single center. Third, naloxone reversal was the only definition of delayed respiratory depression that we used in this study. This may be in contrast with other

studies that used other definitions, such as episodic minor hypoventilation or desaturation that did not require intervention or need for respiratory assistance. Although our definition does not account for some early signs of delayed respiratory depression, we chose these criteria because they are clinically significant. Fourth, some parturients received medical prophylaxis for nausea and pruritus intraoperatively. Importantly, the strength of this study is that this data reflects real-world experience in a large study population over a 5-year period at Thailand's largest medical center.

Further studies with a prospective, randomized controlled design are needed to identify the optimal dose (effective pain control with minimal side effects) of intrathecal morphine in this patient population, as well as to identify the factors that might influence side effects and the intended effects of prophylactic medications.

Conclusion

No incidence of delayed respiratory depression was observed among the 17,659 parturients who received 0.2 mg intrathecal morphine to control post-cesarean section pain in the present study. Although the vast majority of patients had good pain control both at rest and during movement, one-third of patients experienced vomiting and/or pruritus.

What is already known on this topic?

Low-dose intrathecal morphine provides effective anesthetic technique and postoperative analgesia in cesarean section. Although intrathecal morphine has side effects that include nausea, vomiting, pruritus, and delayed respiratory depression, the last of these is the most serious side effect and its consequence can be severe if there is a delay in diagnosis or treatment.

What this study adds?

The current incidence of respiratory depression and other side effects of 0.2 mg intrathecal morphine for cesarean section at Siriraj Hospital has been established. The results of the present study will help anesthesiologist to identify the optimal dose. (effective pain control with minimal side effects) of intrathecal morphine, as well as to identify the factors that might influence side effects and the intended effects of prophylactic medications.

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Trial registration

Thai Clinical Trials Registry as TCTR201801 26004.

Potential conflicts of interest

The authors declare no conflict of interest.

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