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Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases

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Abstract
Purpose. A low dose of morphine, given intrathecally is an effective postoperative analgesic technique and is widely used in cesarean section. Delayed respiratory depression is the most feared side effect of this technique. However, this side effect has not been thoroughly reported in the obstetric population. The aim of this study was to describe respiratory depression associated with intrathecal morphine in postcesarean women, and to estimate its incidence.
Methods. We retrospectively reviewed the obstetric anesthesia database at our institution from April 2000 to December 2006. Patients who were given 0.15 mg intrathecal morphine for cesarean section were identified. From this group, we identified patients who developed bradypnea (respiratory rate ≤ 10 breaths·min^{-1}) within 24 h after the intrathecal injection.
Results. Of 1915 women given 0.15 mg intrathecal morphine for postcesarean analgesia, 6 patients exhibited bradypnea within 24 h after the injection of morphine. Four of these 6 patients developed mild respiratory depression, which was treated with supplemental oxygen and/or encouragement of breathing. One patient had severe respiratory depression, and repeated episodes of oxygen desaturation below 90% and 30-s apneas were noted. Naloxone was required for this patient. One woman had obstructive sleep apnea which was not associated with the intrathecal morphine.
Conclusion. Of 1915 patients, 5 women (0.26%) developed bradypnea associated with 0.15 mg intrathecal morphine. The incidence of severe bradypnea requiring naloxone was 1/1915 (0.052%).

Key words Spinal anesthesia · Subarachnoid · Opioid

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Introduction

A low dose (0.1–0.25 mg) of morphine, given intrathecally is a very effective postoperative analgesic technique and is widely used in cesarean section [1–3]. Delayed respiratory depression is the most feared side effect of intrathecal morphine. There have been only two reports of mild respiratory depression induced by intrathecal morphine after cesarean section [4,5]. As this respiratory depression is a rare event, a large number of cases are required to determine its incidence. Abouleish et al. [6] found no cases of decreased respiratory rate induced by subarachnoid morphine in 856 postcesarean women. We therefore conducted a larger study to estimate the incidence of respiratory depression associated with intrathecal morphine in postcesarean women, and to describe its clinical features.

Patients, materials, and methods

Our division has an obstetric anesthesia database which contains information on the preanesthetic evaluation, anesthetic management, and postanesthetic course of all patients who receive anesthesia at our Center for Maternal, Fetal, and Neonatal Medicine. The database was established in April 2000 and since then has been consistently updated by one of the authors (K.T.). After we had obtained institutional approval, the obstetric anesthesia database from April 2000 to December 2006 was reviewed. Patients who were given 0.15 mg intrathecal morphine hydrochloride for cesarean section were identified from the database. From this subset of cases, we identified patients who developed bradypnea (respiratory rate ≤ 10 breaths·min^{-1}) within 24 h after the intrathecal injection.

Patients were premedicated with metoclopramide with/without famotidine. Either spinal or combined spinal-epidural anesthesia was chosen, at the discretion

of the anesthesiologist. A local anesthetic (2.0–2.4 ml bupivacaine or dibucaine) with 10 μg fentanyl was injected into the subarachnoid space with the morphine. An intravenous sedative (diazepam or midazolam) and/or an opioid (fentanyl or morphine), and/or an epidural local anesthetic were given to the patient during surgery, at the discretion of the staff anesthesiologist. Postoperatively, if patients complained of pain, they were given 15 mg intramuscular pentazocine, 0.2 mg intramuscular or rectal buprenorphine, 60 mg oral loxoprofen, an epidural local anesthetic with an opioid (fentanyl or morphine), or an epidural local anesthetic alone. Our routine postoperative monitoring included hourly respiratory rate (counted by nurses) and state of consciousness, and continuous oxygen saturation (Sp_{O_2}) and pulse rate determined by pulse oximetry. These parameters were recorded by nurses for 24 h after the subarachnoid injection of morphine. The nurses were given education about respiratory depression with intrathecal morphine, and instructed to call an anesthesiologist when the respiratory rate was 10 breaths·min^{-1} or less or when Sp_{O_2} was 95% or less.

Results

Intrathecal morphine was administered to 1915 patients from April 2000 to December 2006. Six women developed bradypnea within 24 h after the spinal injection (Table 1). Patients 1–4 and 6 had no past medical history that could have contributed to respiratory depression. None of them was obese; all had a body mass index (BMI) of 24.7–26.0 kg·m^{-2}. Patient 5 had a BMI of 34.7 kg·m^{-2} and a history of deep snoring. Patients 1–3, 5, and 6 underwent spinal anesthesia. Combined spinal-epidural anesthesia was chosen for patient 4. In all 6 patients, 12 mg hyperbaric bupivacaine (0.5%), 10 μg fentanyl, and 0.15 mg morphine were administered into the subarachnoid space. No additional sedatives or opioids were given during anesthesia, except to patients 1 and 3. None of the 6 women was given supplemental analgesic agents in the postoperative period prior to exhibiting bradypnea. All were asleep when they were found to be bradypneic.

Patient 1 was a healthy 38-year-old woman. Cesarean section was performed due to a history of uterine myomectomy. Ninety micrograms of intravenous fentanyl was given during surgery as supplemental analgesia. Her respiratory rate decreased to 10 breaths·min^{-1} 10 h after the spinal injection of morphine. Sp_{O_2} was 94%. Three liters per minute of oxygen, given via a face-mask, was started and she was verbally encouraged to breathe. Her respiratory rate and Sp_{O_2} were above 14 breaths·min^{-1} and 97%, respectively, for the remainder of the 24-h observation period.

Patient 2 was a 35-year-old woman with severe pre-eclampsia. She exhibited bradypnea 13.5 h after spinal anesthesia. Her respiratory rate and Sp_{O_2} were 7 breaths·min^{-1} and 94%, respectively. Arousal from sleep improved both the respiratory rate and Sp_{O_2}. The rest of the 24-h observation period was uneventful even during sleeping hours.

Patient 3 was 31 years of age and had a history of previous cesarean section. She was given 90 μg intravenous fentanyl during surgery. Bradypnea started 8 h after spinal anesthesia. Respiratory rate of 6 breaths·min^{-1} and a 15-s episode of apnea were noted. Sp_{O_2} was 94%. Two liters per minute of oxygen, given

Table 1. List of patients with bradypnea. Patients are listed in chronological order

Patient no.	Age (years)	Preoperative history	Respiratory depression	Onset time (h after morphine)	Treatment
1	38	Uterine myomectomy	RR, 10 breaths·min^{-1} Sp_{O_2}, 94%	10	Oxygen Breathing encouraged
2	35	Severe preeclampsia	RR, 7 breaths·min^{-1} Sp_{O_2}, 94%	13.5	Breathing encouraged
3	31	Previous C-section	RR, 6 breaths·min^{-1} Sp_{O_2}, 94%	8	Breathing encouraged Oxygen
4	29	Previous C-section	30-s apneas RR, 3–8 breaths·min^{-1} Sp_{O_2}, 78%	3	Breathing encouraged Oxygen Naloxone
5	29	Pregnancy induced hypertension BMI, 34.7 kg·m^{-2}; deep snoring	15- to 30-s obstructive sleep apneas Sp_{O_2} < 90% Similar respiratory depression episodes repeated on 4 consecutive nights	12	None
6	40	Uterine myomectomy	RR, 8–10 breaths·min^{-1} Sp_{O_2}, >95%	1	None

RR, respiratory rate

via nasal cannulae, was started. Although Sp_{O_2} was maintained above 96% with oxygen, her respiratory rate ranged from 8 to 10 breaths·min^{-1} for the next 7 h.

Patient 4 was a 29-year-old woman with a history of past cesarean delivery; 2.4 ml of 0.5% hyperbaric bupivacaine, 10 μg fentanyl, and 0.15 mg morphine were injected into the subarachnoid space at 10:55. No additional anesthetics were given during anesthesia. She vomited when she was sent back to the ward at 12:45. She remained nauseous and vomited a few times during the next 6 h. At 14:10, 3 l·min^{-1} of oxygen, given via a facemask, was started, because Sp_{O_2} was 93%. Sp_{O_2} dropped to 84% at 14:30. She was immediately encouraged to breathe by a nurse. An anesthesiologist was called in and found her respiratory rate to be 15–17 breaths·min^{-1}. Respiratory sounds were normal. She was encouraged to breathe more deeply, and Sp_{O_2} improved to 100%. Chest X-ray was normal. Sp_{O_2} then repeatedly dropped below 80%, respiratory rate was 3–8 breaths·min^{-1}, and episodes of 30-s apnea were observed. At 16:16, 0.05 mg intravenous naloxone was given, and her respiratory rate increased to 18 breaths·min^{-1}. She vomited again during the first postoperative ambulation at 17:40. At 18:25, 0.1 mg naloxone was administered because of decreased respiratory rate. She then complained of lower abdominal pain, and 9 ml of 0.25% bupivacaine was injected via the epidural catheter. Her respiratory rate remained at 12–18 breaths·min^{-1} and Sp_{O_2} was maintained above 96% with supplemental oxygen for the remainder of the 24-h observation period. A nasal capnogram was recorded after the first ambulation. Her records for Sp_{O_2} and respiratory rate by capnography, are shown in Fig. 1.

Patient 5 was a 29-year-old obese woman (153 cm; 81.2 kg; BMI, 34.7 kg·m^{-2}). She had a history of deep snoring. Cesarean section was performed due to the worsening of pregnancy-induced hypertension and edema. Twelve hours after the spinal anesthesia, when she was asleep, her respiratory rate decreased. She presented with 15- to 30-s episodes of obstructive apnea and consequent decreases in Sp_{O_2} to less than 90%. She then started breathing so that Sp_{O_2} rose above 95%. The same pattern was repeated several times during that night. We observed her overnight respiration for the next 3 days, and a similar pattern of respiratory depression was noted.

Patient 6 was a 40 year-old woman who underwent cesarean section because of a history of uterine myomectomy. Her respiratory rate was 9–11 breaths·min^{-1} during surgery and it had decreased to 6 breaths·min^{-1} at the end of surgery (1 h after the spinal injection). After returning to the ward, her respiratory rate was 8–11 breaths·min^{-1}. Sp_{O_2} was maintained above 95%. Mild bradypnea, which was not accompanied by Sp_{O_2} decrease, was noted until 12 h after the spinal injection. No treatment was given.

Discussion

In nonobstetric patients, a number of case reports describe respiratory depression caused by various doses of intrathecal morphine for postoperative analgesia [1,7–9]. There have been four relatively large-scale (number of subjects ≥ 100) studies [10–13]. The incidence of respiratory depression caused by intrathecal morphine ranged from 0.03% [11] to 3% [12].

Advanced age and coexisting disease have been suggested to be factors increasing the likelihood of respiratory depression [14]. The stimulatory effect of progesterone on ventilation is well established [15]. Hence, there has been a myth that young, healthy, and progesterone-abundant parturients may be less likely to develop respiratory depression [3,6]. Indeed, reports of respiratory depression in postcesarean patients are limited. The only large-scale study [6] reported no cases of bradypnea (respiratory rate ≤ 10 breaths·min^{-1}) in 856 women after 0.2 mg subarachnoid morphine. Eight women exhibited episodes of oxygen desaturation (Sp_{O_2} < 85%) during sleep. All of them were extremely obese (weight, 105.2 ± 2.1 kg; Broca index value, 1.82 ± 0.1) with a history of deep snoring; naloxone did not improve Sp_{O_2}. According to a systematic review of intrathecal

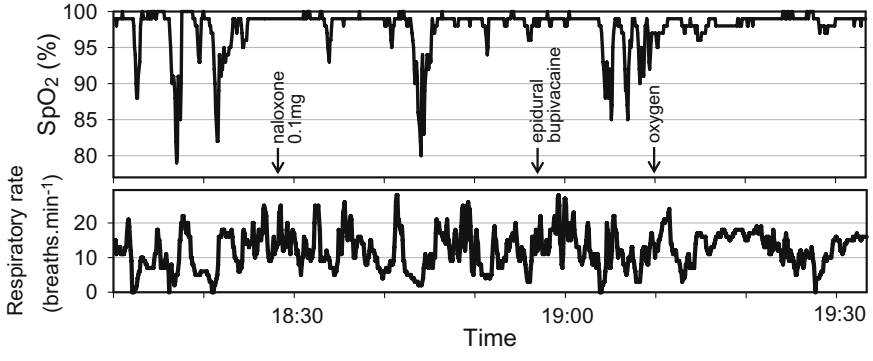

Fig. 1. Oxygen saturation (Sp_{O_2}) by pulse oximetry, and respiratory rate in patient 4. Respiratory rate, determined by nasal capnography, was recorded after postoperative ambulation (18:00). Neither bradypnean nor desaturation was noted after 19:30

opioids for cesarean section [1], one case of delayed respiratory depression was reported among 485 patients from 12 controlled studies. This patient had a respiratory rate of 7 breaths·min^{-1} after receiving 0.1 mg intrathecal morphine. Sp_{O_2} was 92%, and supplemental oxygen increased the Sp_{O_2} to 97%. Naloxone was not required [4]. In another controlled study, a mild decrease in respiratory rate (<12 breaths·min^{-1}) was noted after 0.075 mg intrathecal morphine [5].

The present study was based on data recorded since the opening of our Center for Maternal, Fetal, and Neonatal Medicine in April 2000. Of 1915 patients who were given 0.15 mg intrathecal morphine, 6 women developed bradypnea. Patient 4 presented with severe bradypnea and was treated with repeated doses of naloxone. Patient 5 was obese and had a history of deep snoring. As similar obstructive apnea and desaturation episodes were noted on 4 consecutive nights following surgery, the influence of intrathecal morphine on the respiratory event would seem to have been small in this patient. The respiratory depression in patients 1–4 and 6 was likely to have been caused by the intrathecal morphine, as no other causes were identified.

Intrathecal fentanyl and morphine exert their effects in 5 and 30 min, with durations of 2–3 and 12–24 h, respectively [3]. Patient 6 exhibited bradypnea 1 h after the spinal injection. Thus, the first few hours of her bradypnea could have been caused by fentanyl alone, morphine alone, or a combination of the two agents. However, it is almost certain that morphine was responsible for the latter part of her bradypnea, as the bradypnea lasted for 11 h.

The pathophysiological definition of respiratory depression is failure to respond to hypercapnia and/or hypoxia. It has been shown that intrathecal morphine depresses the response to both hypoxia and hypercapnia in humans [16,17]. But in clinical practice, it is not practical to assess the ventilatory responses of postoperative patients. In the present study, bradypnea was used to identify patients with respiratory depression. Decrease in Sp_{O_2} was not used as our definition of respiratory depression, because it is sometimes difficult to distinguish mild oxygen desaturation caused by opioid-induced respiratory depression from that associated with other causes, such as mild lung edema and pulmonary embolism. However, patients can be hypoxic or hypercapnic with a normal respiratory rate when respiration is depressed by morphine [3,14,18]. This is why we monitored not only the respiratory rate but also Sp_{O_2}, so as not to overlook respiratory depression arising from intrathecal morphine.

The severe respiratory depression in our patient 4 was identified not by respiratory rate decrease, but by pulse oximetry desaturation. Hourly respiratory rate monitoring alone would not have been enough to spot this respiratory depression. This is another reason why we monitored Sp_{O_2} continuously.

In conclusion, 5 of 1915 (0.26%) women at our center exhibited a decreased respiratory rate (≤10 breaths·min^{-1}) associated with 0.15 mg intrathecal morphine for postcesarean analgesia. One of them had severe respiratory depression, which required the repeated use of naloxone. The incidence of severe respiratory depression requiring naloxone was 0.052%.

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