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ORIGINAL ARTICLE

Incidence of respiratory depression after epidural administration of morphine for cesarean delivery: findings using a continuous respiratory rate monitoring system

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ABSTRACT
Background: Epidural morphine is widely used for postoperative analgesia after cesarean delivery. However, respiratory depression can occur after neuraxial administration of morphine. Previous reports describing respiratory depression in obstetric patients have relied on intermittent visual counting of the respiratory rate. In this study, we estimated the incidence of respiratory depression in patients who had received epidural morphine after cesarean delivery, using a continuous respiratory rate monitoring system with a finger sensor.
Methods: One hundred patients scheduled to undergo elective cesarean delivery and receive intraoperative neuraxial morphine between April and December 2016 were recruited for this single-center, prospective observational study. Postoperatively, all patients received epidural morphine 3 mg and were equipped with the Nellcor respiratory rate monitoring system. Respiratory depression was defined as both bradypnea (respiratory rate ≤10 breaths/min) and oxygen desaturation (mild ≤95%; moderate ≤90%; severe ≤85%) for longer than one minute. The number of patients with respiratory depression between administration of morphine and first ambulation was recorded hourly.
Results: Complete monitoring was obtained for 89 of 100 women. The median duration of monitoring was 19.0 hours. Forty-six patients (52%) developed mild respiratory depression at least once before ambulation, but only one (1%) developed moderate respiratory depression. None required supplemental oxygen or naloxone.
Conclusions: Approximately half the women experienced mild respiratory depression, but only one developed moderate respiratory depression. Continuous respiratory rate monitoring until ambulation may assist in early identification of respiratory depression after neuraxial administration of morphine.

Keywords: Cesarean delivery; Respiratory rate; Desaturation; Morphine; Epidural

Introduction

Epidural administration of morphine has been widely used as a postoperative analgesic technique, in women undergoing cesarean delivery, since the first report of its efficacy.[1] Respiratory depression can occur after neuraxial administration of morphine and intermittent respiratory rate monitoring is recommended by the American Society of Anesthesiologists.[2] The incidence of bradypnea has been reported to be as low as 0–0.25% with the use of epidural morphine doses of up to 5 mg and 0.07%–0.9% with intrathecal morphine doses of up to 0.2 mg after cesarean delivery.[3–7] However, such reports may underestimate the extent of opioid-induced respiratory depression because they are based on intermittent patient observation by a midwife and do not represent a continuous measurement. Moreover, manual counting is prone to observer error and not an efficient method for use by clinical staff.

The Nellcor respiratory rate monitoring system (Medtronic, Minneapolis, MN, USA) measures the respiratory rate derived from a pulse oximeter signal obtained from a finger sensor that can be attached to the patient after cesarean delivery. The respiratory rate derived from pulse oximetry has been shown to correlate well with the end-tidal carbon dioxide ($EtCO_2$) reference rate in different patient groups, including normal healthy adults and patients in a general medical ward.[8,9]

The aim of this study was to estimate the incidence of respiratory depression, as defined by both respiratory

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rate and oxygen desaturation for greater than one minute, using the Nellcor respiratory rate monitoring system in women who had received 3 mg of epidural morphine for post-cesarean delivery analgesia.

Methods

This prospective, observational study was approved by the institutional review board at Seirei Hamamatsu General Hospital in Shizuoka, Japan; registered at the UMIN Clinical Trials Registry (UMIN000022054); and conducted at Seirei Hamamatsu General Hospital. Women scheduled for elective cesarean delivery between April and December 2016 were approached to participate in the study, after their admission to hospital. The investigators obtained written informed consent from each patient preoperatively, having provided a verbal explanation and a patient information sheet. Our primary interest was the effect of epidural morphine on the respiratory rate in healthy women post-cesarean delivery. Therefore, women with an American Society of Anesthesiologists (ASA) physical status >2, a clinical history of obstructive sleep apnea, or a multiple birth, were excluded. Women with a contraindication to combined spinal-epidural anesthesia and emergency cases were also excluded.

Preoperatively, in the labor and delivery unit, a 20-gauge intravenous (IV) cannula was placed and lactated Ringer's solution was infused at a rate of 120 mL/h. The patient was positioned in the right lateral decubitus position. Dural puncture was performed at the L3/4 or L2/3 interspace according to the combined spinal-epidural anesthesia technique and 1.6 mL of 0.5% hyperbaric bupivacaine and 20 μg fentanyl were administered. Lactated Ringer's or colloid (6% hydroxyethyl starch) solution was rapidly infused. After completion of the anesthetic procedure, the patient was positioned supine with left lateral tilt. Phenylephrine or ephedrine was administered if necessary to maintain systolic blood pressure >80 mmHg.

After cesarean delivery, each patient received a mixture containing 3 mg morphine, 50 μg fentanyl, and 5 mL 1% mepivacaine via an epidural catheter. After completion of surgery, the patient was transferred to the maternity ward. The finger cuff of the Nellcor was wrapped around the index finger on the side opposite to that on which the blood pressure cuff was applied (Fig. 1). One gram of IV acetaminophen was administered as per the internal guidelines at our hospital. Routine observations, including blood pressure, pulse rate, and body temperature, were recorded at one-hourly intervals. The respiratory rate and oxygen saturation were continuously recorded until ambulation on the first postoperative day. For the purposes of the study, mild respiratory depression was defined as both bradypnea (a respiratory rate ≤10 breaths/min) and oxygen desaturation (an oxygen saturation (SpO_2) ≤95%) for >1-min; moderate respiratory depression as a respiratory rate ≤10 breaths/min and an SpO_2 ≤90%; and severe respiratory depression as a respiratory rate ≤10 breaths/min and an SpO_2 ≤85%. The number of respiratory depression events per hour was counted from the time of administration of morphine until ambulation. No alarms were set on the Nellcor device. If an SpO_2 ≤95% continued, midwives were allowed to visit, observe and encourage patients to breathe. The data were stored in the device and extracted later. Data analyses were performed after completion of data collection from all participants.

Fig. 1 The finger cuff of the Nellcor was wrapped around the index finger. Reproduced from the Covidien website (http://www.medtronic.com/covidien/en-us/products/pulse-oximetry/nellcor-spo2-adhesive-sensors.html) with permission

An unadjusted univariate analysis was performed and between-group differences were sought using *t*-tests for continuous variables and chi-square tests for categorical variables. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[10]

Results

One-hundred patients consented to participate in the study. Eleven patients were excluded because of intermittent recording failure, which was presumably caused by finger movement or speaking, leaving data for 89 participants available for analysis. The demographic data

are shown in Table 1. The median interval between epidural administration of morphine and application of the monitor was 52 min (interquartile range [IQR] 38–81). The median duration of monitoring was 19.0 h (IQR 17.0–20.4). Seventy-six women (85%) developed at least one episode of bradypnea and 46 (52%) developed mild respiratory depression. Eleven women (12%) developed moderate desaturation ($SpO_2 \leq 90\%$) but only one woman (1%) developed moderate respiratory depression. No patient developed severe respiratory depression. The median interval from administration of morphine to the first respiratory depression event was 3.2 h (IQR 2.1–5.5). The total number of patients with mild respiratory depression per hour did not decline until the point of first ambulation (Fig. 2). Thirteen patients received intramuscular tramadol for additional pain relief but none received supplemental opioids. No patient required supplemental oxygen or naloxone.

In univariate analysis, the mean patient age was slightly younger in the group of patients who did not experience respiratory depression (32.4 y vs 34.5 y, P=0.04). There was no significant difference in body mass index, gestational week, intraoperative fluid volume, or use of tramadol or droperidol, between the groups experiencing or not experiencing respiratory depression (Table 1).

Discussion

The most important finding of this study was that mild respiratory depression occurred in 52% of healthy young women who had received epidural morphine 3 mg as analgesia after cesarean delivery, although moderate respiratory depression was observed in only one woman (1%). Eighty-five percent of patients experienced at least one episode of bradypnea. Although the first respiratory depression event generally occurred several hours after

Table 1 Patient characteristics and univariate associations with at least one respiratory depression event

Variable	Without RD	At least one RD event	*P*-value
	n=42	n=47	
Maternal age, mean (SD)	32.4 (4.9)	34.5 (4.6)	0.04
Body mass index, mean (SD)	26.5 (3.6)	25.1 (3.1)	0.06
Gestational week (IQR)	38 (38–38)	38 (38–38)	0.18
Intraoperative fluid, mL (IQR)	1120 (955–1345)	1200 (1000–1350)	0.45
Droperidol, n (%)	4 (9.5%)	2 (4.3%)	0.42
Tramadol, n (%)	4 (9.5%)	9 (19.1%)	0.24
ASA physical status, n (%)			0.54
1	35 (83.3%)	42 (89.4%)	
2	7 (16.6%)	5 (10.6%)	
Indication for CD, n (%)			0.98
Breech position	15 (35.7%)	16 (34.0%)	
Repeat CD	25 (59.5%)	28 (59.6%)	
Other	2 (4.8%)	3 (6.4%)	

ASA: American Society of Anesthesiologists; CD: cesarean delivery; RD: respiratory depression; SD: standard deviation; IQR: interquartile range.

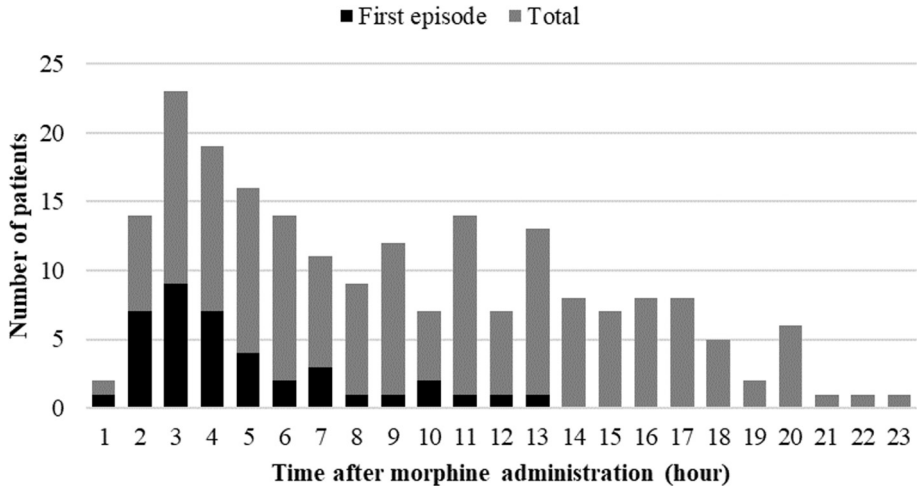

Fig. 2 The number of patients with respiratory depression per unit time after epidural administration of morphine. The black scales show the number of patients with a first episode and the gray scales show the total number of patients

epidural administration of morphine, the first event occurred as late as 13 hours after morphine had been administered.

Historically, the incidence of bradypnea after cesarean delivery, and epidural morphine postoperative analgesia could have been underestimated because the respiratory rate was counted manually. Fuller et al. reported that 12 (0.25%) of 4880 patients had a respiratory rate <10 breaths/min after cesarean delivery and epidural morphine doses in the range of 2–5 mg.[3] Palacios et al. reported that none of 23 women experienced a decrease in respiratory rate to <12 breaths/min after epidural administration of morphine 5 mg.[4] The incidence of bradypnea in this study was significantly greater than in the previous reports. We attribute this to the enhanced detection of events due to continuous monitoring of the respiratory rate.

In our study, we used the Nellcor respiratory rate monitoring system, which includes a pulse oximetry-derived respiratory rate (RR_{oxi}) algorithm. With regard to the accuracy of this method, the agreement between the RR_{oxi} and the end-tidal CO_2 reference rate (RR_{ETCO2}) has been studied in both healthy volunteers and in patients on a general care floor. In the healthy volunteers, the mean difference was −0.23 breaths/min, with a standard deviation (SD) of 1.14 breaths/min. In the patients under general care, the mean difference was −0.48 breaths/min with a SD of 1.77 breaths/min.[8,9] These data demonstrate that this algorithm is a potentially viable method for continuous monitoring of the respiratory rate.

In spite of the high incidence of bradypnea, none of the patients in this study required intervention, possibly because the midwives were allowed to encourage patients to breathe deeply when an SpO_2 ≤95% continued. Only one woman developed moderate respiratory depression and none developed severe respiratory depression.

There is no standard definition of respiratory depression[11] and recent studies of respiratory depression in patients post-cesarean delivery have used different continuous monitoring methods, such as pulse oximetry or transcutaneous measurement of CO_2 levels. Ladha et al. defined respiratory depression as an SpO_2 ≤90% and found an incidence of 23% in patients who had received 150 μg of intrathecal morphine.[12] Bauchat et al. defined respiratory depression as a transcutaneous CO_2 >50 mmHg, and in their study the incidence was 32% among patients who had received 150 μg of intrathecal morphine.[13] Dalchow et al. defined respiratory depression as an SpO_2 ≤90% and/or a transcutaneous CO_2 >7 kPa for greater than two minutes, and found an incidence of 17.8% in patients who had received 300 μg of intrathecal diamorphine.[14] In our study, the definition of respiratory depression included both bradypnea and oxygen desaturation. We thought that this definition enabled early intervention to prevent hypoxic events in the clinical setting. There is a potential for false-positive findings using this definition. However, we considered reducing false-negative findings more clinically useful because of the importance of early detection of respiratory depression. The incidence of respiratory depression was higher in our study than in previous reports as a result of our stringent definition. In contrast, if only moderate desaturation is considered, the incidence was 12% in our study and 23% in the study by Ladha et al.[14] This may reflect, at least in part, our early detection of mild respiratory depression and the encouragement of deep breathing by midwives.

After the introduction of neuraxial morphine into clinical practice in 1979, hourly monitoring of respiratory rate was deemed "totally unacceptable".[15] Although monitoring of the respiratory rate is recommended by the ASA,[2] an intermittent manual check by a nurse is prone to observer error and is not an efficient method in clinical practice. Pulse oximetry-derived counting of the respiratory rate enables continuous monitoring using a single non-invasive sensor, and may allow safer and more comfortable post-cesarean care for both patients and midwives.

The results of this study must be interpreted in the context of the study limitations. Firstly, it was not a blinded, randomized trial. For ethical reasons, it was not possible to include a placebo-treated control group, so how much of the bradypnea was attributable to the epidural morphine is unclear. Women who receive a lower dose of epidural morphine, or indeed no morphine at all, might still experience bradypnea using our definition, so further research is needed. Secondly, although we excluded patients who reported having obstructive sleep apnea, the actual prevalence of this disorder in our study population and how it might have affected our findings is unknown. Information about the conscious state at the time of the respiratory depression might provide useful clues about the trigger.

In conclusion, 52% of women who received 3 mg of epidural morphine for postoperative pain following elective cesarean delivery experienced mild respiratory depression, but only 1% developed moderate respiratory depression. Bradypnea alone was observed in 85% of the women. Continuous monitoring of both respiratory rate and oxygen saturation following cesarean delivery until ambulation is feasible and may contribute to early identification of respiratory depression after neuraxial administration of morphine.

Conflicts of interest

None.

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