

A Comparison of Epidural and Intramuscular Morphine in Patients Following Cesarean Section

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This randomized, double-blind study compared epidural (EP) and intramuscular (IM) morphine in 24 healthy parturients for 24 h after cesarean section. The 11 EP subjects received 5 mg of EP morphine and normal saline intramuscularly, and the 13 IM patients received 5 mg of IM morphine and normal saline epidurally. Both injections were given simultaneously just after delivery and then upon request with at least 30 min between each pair of injections. Blood pressure, visual analogue scale pain score, somnolence score, and presence of nausea, vomiting, or pruritus were assessed every 30 min for 1 h after each dose and then hourly. Oxyhemoglobin saturation (SpO_2) and respiratory rate (RR) and pattern were monitored continuously with pulse oximetry and respiratory inductive plethysmography. The EP group had significantly lower pain scores (less pain) than the IM (0.9 ± 0.3 vs. 3.3 ± 1.3 ; mean \pm SD; $P < 0.001$) with less morphine (0.3 ± 0.2 vs. 2.2 ± 0.6 mg patient⁻¹ h⁻¹; $P < 0.001$). There was no difference between groups for RR, SpO_2 , incidence or frequency of slow respiratory rate (SRR, 5-min mean RR < 10) and apneas (AP, ≥ 15 s of < 100 ml tidal volume), incidence of nausea and/or vomiting, pruritus, or hypotension, and hours asleep or drowsy. There were no major respiratory abnormalities. During control monitoring of nine EP and 11 IM subjects while asleep postoperatively, the RR, SpO_2 , and incidence and frequency of SRR and AP were similar to the study period in both groups. In conclusion, EP morphine was a more effective analgesic than IM morphine, but the side effects of both were similar. (Key words: Analgesia; postcesarean section. Analgesics: morphine. Anesthesia: obstetric. Anesthetic techniques: epidural. Complications: pain; respiratory depression. Pain: postoperative. Ventilation: apnea.)

FOR THE OBSTETRIC PATIENT who already has a functioning epidural catheter for her cesarean section, epidural morphine is an attractive form of postoperative analgesia. Although the efficacy in this situation has been well established,^{1,2} its safety with respect to respiratory depression has not.

In the obstetric population, respiratory depression has been reported infrequently.³⁻⁵ However, only a few

studies have used sensitive monitoring systems. Three studies employing continuous pulse oximetry⁶⁻⁸ produced conflicting results, and another study⁹ using the ventilatory response to CO_2 as a measure of respiratory depression demonstrated an up to 55% decrease in the ventilatory response.

In this randomized, double-blind study we compared the use of epidural (EP) and intramuscular (IM) morphine for 24 h after cesarean section. The analgesic efficacy and incidence and severity of side effects were examined. Respiration was monitored noninvasively and continuously by both pulse oximetry and respiratory inductive plethysmography for the entire study. These monitors were also employed in most of the subjects postoperatively during sleep to provide control measurements.

Materials and Methods

PATIENT SELECTION AND DRUG PREPARATIONS

The study was approved by the Institutional Review Board, and written informed consent was obtained from all participants. The study population consisted of 24 ASA Physical Status 1-2 parturients at term having an elective cesarean section with epidural anesthesia. Patients with a history of sensitivity to morphine or significant medical problems or maternal complications of pregnancy were excluded. The subjects were randomly assigned to either the EP or IM morphine group preoperatively. Double-blinding was achieved by simultaneously administering a 1 ml IM and a 10 ml EP injection. All ampules were prepared by the hospital pharmacy and labeled with the subject's identification number only. The 11 EP patients received 5 mg of EP morphine in 10 ml of normal saline plus 1 ml of normal saline IM and the 13 IM group subjects received 10 ml of normal saline through the EP catheter and 5 mg of morphine in 1 ml of normal saline IM. All EP solutions were preservative-free preparations.

INTRAOPERATIVE COURSE

After receiving 30 ml of 0.3 M sodium citrate and an iv infusion of 1-1.5 l of lactated Ringer's solution, continuous lumbar epidural anesthesia was initiated. Carbonated lidocaine with 1:200,000 epinephrine was administered to achieve a T4-6 sensory level (15-30 ml). During the surgery the patients were maintained supine with left uterine displacement and were monitored con-

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§ Leicht CH, Hughes SC, Dailey PA, Shnider SM, Rosen MA: Epidural morphine sulphate for analgesia after cesarean section: A prospective report of 1000 patients (abstract). ANESTHESIOLOGY 65:A366, 1986.

tinuously with a blood pressure cuff, ECG, and pulse oximeter. Oxygen was supplied by face mask at ≥ 6 l P.M. until delivery of the baby. Supplemental N_2O (50%) and iv drugs were used if necessary after delivery. The latter included 2.5–5.0 mg of diazepam, 50–100 μ g of fentanyl, or 0.625–1.25 mg of droperidol. The first dose of study drugs was given within 5 min after delivery. The epidural catheter was left in place at the end of the surgery.

POSTOPERATIVE COURSE

Analgesia was provided by injecting a pair of study drugs at the subject's request, with a minimum of 30 min between doses. No other analgesics were administered during the study.

One of the investigators (working in 12-h shifts) was with the patient and monitors for the entire study. The investigator and monitors were located just outside the patient's room to avoid disturbing the patient but allowing the investigator to see the patient and monitors at all times. Continuous monitoring by pulse oximetry (Nellcor N-100®) and respiratory inductive plethysmography (Respirace 300SC®, NIMS Inc, Miami Beach, Florida) was begun on arrival in the recovery room and performed for the remainder of the study. The hemoglobin oxygen saturation (SpO_2) was observed continuously and recorded every 30 min for 1 h after each dose of study drugs and then hourly, during all apneic episodes, and at any time the SpO_2 decreased to $<90\%$. The plethysmograph has been described previously.¹⁰ It was calibrated with the isovolume maneuver and validated using a wedge spirometer (Med Science 270®). Validation results of $\leq 10\%$ error were considered acceptable. It provided the mean respiratory rate (RR) and the number and duration of apneic episodes every 5 min. An apneic episode (AP) was defined as a period of ≥ 15 s with a tidal volume < 100 ml and a slow respiratory rate (SRR) as a 5-min mean RR of < 10 breaths/min.

The blood pressure, somnolence score, pain score, and presence of nausea, vomiting, or pruritus were recorded every 30 min for 1 h after each dose of study drugs and then hourly. If the subject was asleep at these times, she was not awakened. The somnolence score was also recorded whenever an AP or SRR episode occurred because only those episodes present during sleep or drowsiness were included in the data analysis. The somnolence score was graded as follows: 1 = wide awake, 2 = drowsy but easily aroused, and 3 = sleeping. The pain score was determined using a 10-cm visual analogue scale (VAS)¹¹ in which 0 cm = no pain and 10 cm = severe pain. The severity of pruritus, nausea, and vomiting was graded by the subjects as follows: 1 = mild, not needing treatment; 2 = moderate, requiring treatment; and 3 = severe, requiring treatment. Urinary retention was not assessed be-

cause every patient had a bladder catheter until the morning after the cesarean section. Side effects were treated upon request with iv injections of 10–20 mg of diphenhydramine (pruritus), 12.5–25 mg of dimenhydrinate (nausea), or 100 μ g increments of naloxone (excessive somnolence or respiratory depression).

The study was continued for 24 h after the initial intraoperative dose of study drugs. This was extended if necessary to ensure that the subjects in the EP group were fully monitored for 12 h after their last dose and discontinued earlier if all the doses of study drugs (total of 12) were used before then. The epidural catheter was removed at the end of the study and subsequent analgesia was supplied by IM meperidine until the third postoperative day when it was replaced by oral acetaminophen with codeine.

CONTROL RESPIRATORY MONITORING

Four to seven days postoperatively, when opioid analgesics were no longer used, nine EP and 11 IM subjects were monitored during nocturnal sleep with the pulse oximeter and plethysmograph. The others were excluded because they were still receiving opioids when discharged from the hospital. The SpO_2 , somnolence score, and plethysmography data were recorded as during the study period.

DATA ANALYSIS

The data were analyzed using ANOVA, Mann-Whitney U, Fisher-Yates exact, and Student's two-tailed *t* tests where appropriate. $P < 0.05$ was considered significant. The data are presented as mean \pm 1 SD unless otherwise indicated. The group means of the hourly SpO_2 , RR, pain scores, and morphine requirements are least squares means¹² to compensate for missing data (*e.g.*, when patients were not awakened for pain scores or when all the doses of study drugs were used before 24 h).

Results

DEMOGRAPHICS

There were 11 subjects in the EP and 13 in the IM group. The groups were similar for age, weight, height, study and control period durations, and time of day at study onset (table 1).

MORPHINE REQUIREMENTS

In the EP group six subjects received one dose of study drugs, four were given two doses, and one subject received three doses during the study period. The IM subjects received five to 12 doses. The study was discontinued prematurely in three of these (after 17, 19, and 20 h) because

TABLE 1. Demographics

	Epidural (n = 11)	Intramuscular (n = 13)	P value
Age (yr)	31 ± 5	33 ± 4	0.35
Weight (kg)	78 ± 10	76 ± 11	0.11
Height (cm)	156 ± 12	163 ± 9	0.66
Study duration (h)	24.2 ± 1.9	22.7 ± 2.4	0.10
Control duration (h)	7.3 ± 0.7	7.1 ± 1.7	0.73
Time of day at study onset (h)	11:12 ± 2.3	11:17 ± 2.1	0.93

There were no significant differences between groups.

all the available doses had been used. The mean hourly morphine requirement per patient for the entire study was significantly less in the EP than the IM group: EP, 0.3 ± 0.2 mg/h; IM, 2.0 ± 0.6 mg/h ($P < 0.001$) (fig. 1).

ANALGESIA

The mean VAS pain score for the entire study period was significantly less in the EP group: EP, 0.9 ± 0.3 ; IM, 3.3 ± 1.3 ($P < 0.001$). The hourly scores were also significantly lower in the EP group for most of the first 10 h ($P < 0.05$) (fig. 2).

RESPIRATORY MEASUREMENTS

Respiratory rate (RR). The mean RR for the entire study period was similar for the two groups (EP, 18 ± 2 ; IM 17 ± 3 breaths/min) ($P > 0.5$). The RR at each hour were also not significantly different ($P > 0.05$) (fig. 3).

Slow respiratory rate (SRR). The percentage of patients with at least one SRR episode did not differ between the groups: EP, 2 of 11 (18.2%); IM, 3 of 13 (23.1%)

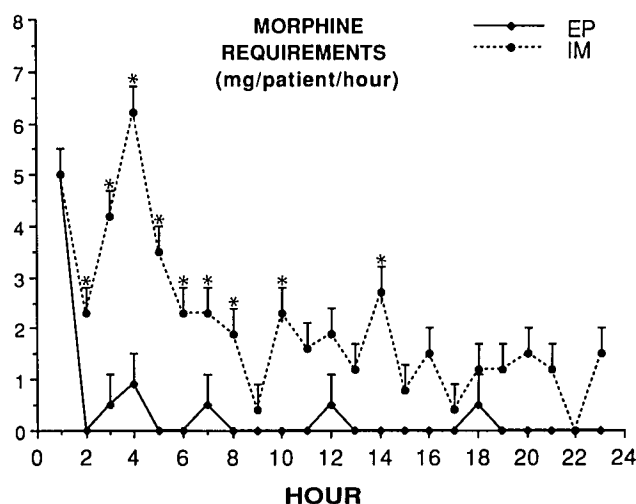


FIG. 1. Mean hourly morphine requirements per patient (mean \pm 1 SEM) for the EP and IM groups. The hours during which there was a significant difference between groups are indicated ($*P < 0.05$).

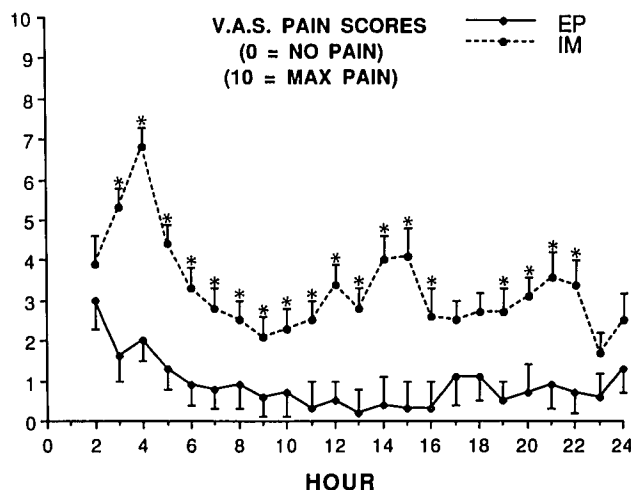


FIG. 2. Mean hourly VAS pain scores (mean \pm 1 SEM) for the EP and IM groups. The hours during which there was a significant difference between groups are indicated ($*P < 0.05$).

($P > 0.5$). The number of episodes is presented in table 2. The RR and duration of the episodes are shown in table 3.

Apneic episodes (AP). The percentage of subjects having at least one AP was not significantly different between the groups: EP, 3 of 11 (27.3%); IM, 5 of 13 (38.5%) ($P > 0.5$). The number of episodes is shown in table 2. The Sp_{O_2} and duration of the episodes are presented in table 4.

Oxygen saturation (Sp_{O_2}). The mean Sp_{O_2} for the entire study period was similar for the groups: EP, $98 \pm 1\%$; IM, $97 \pm 2\%$ ($P > 0.5$). The average minimum Sp_{O_2} also did not differ between groups: EP, $94 \pm 1\%$; IM, $93 \pm 2\%$ ($P = 0.19$). There was no $Sp_{O_2} < 90\%$ at any time in

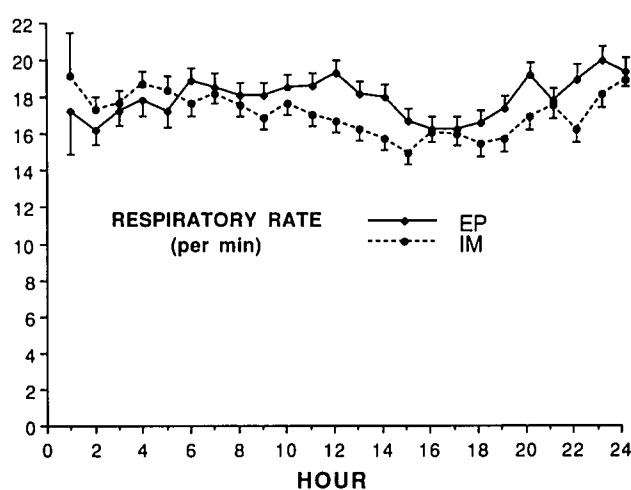


FIG. 3. Mean hourly respiratory rate (mean \pm 1 SEM) for the EP and IM groups. There were no significant differences between groups ($P > 0.05$).

TABLE 2. Incidence of Apneic (AP) and Slow Respiratory Rate (SRR) Episodes

	AP Total	AP per Hour Somnolent*	SRR Total	SRR per Hour Somnolent*
EP study (n = 11)	0.4 ± 0.7 (0-2)	0.1 ± 0.3	0.3 ± 0.7 (0-2)	0.04 ± 0.09
EP control (n = 9)	1.1 ± 0.6 (0-2)	0.2 ± 0.2	0	0
IM study (n = 13)	2.1 ± 5.0 (0-18)	0.2 ± 0.5	1.8 ± 4.1 (0-12)	0.2 ± 0.4
IM control (n = 11)	1.0 ± 1.3 (0-4)	0.3 ± 0.6	0	0

Values in parentheses are ranges. There were no significant differences between groups when comparing EP study *versus* EP control, EP study *versus* IM study, EP control *versus* IM control, and IM study *versus* IM control ($P > 0.2$ or larger for all comparisons).

* Somnolent = asleep or drowsy.

either group. The mean Sp_{O_2} at each hour was also similar for both groups ($P > 0.05$).

CONTROL RESPIRATORY MONITORING

RR. The mean RR for the entire control period was 19 ± 3 breaths/min in the EP group and 18 ± 4 breaths/min in the IM group.

SRR. There were no SRR episodes in any patient.

AP. At least one AP occurred in 6 of 9 (66.7%) EP subjects and 4 of 11 (36.4%) IM subjects. The number of episodes is presented in table 2. The Sp_{O_2} and duration of the episodes are shown in table 4.

Sp_{O_2} . The mean Sp_{O_2} for the entire period was EP $97 \pm 1\%$ and IM $97 \pm 2\%$. The average minimum Sp_{O_2} was EP $95 \pm 3\%$ and IM $93 \pm 3\%$. One episode of $Sp_{O_2} < 90\%$ occurred in one IM patient. The Sp_{O_2} decreased transiently to 88%, was not associated with an AP or SRR episode, and resolved with awakening her.

None of these respiratory parameters was statistically different between control groups (EP control *vs.* IM control) or when compared with their respective study groups (EP control *vs.* EP study; IM control *vs.* IM study) ($P > 0.2$ or larger for all except the mean Sp_{O_2} EP study *vs.* EP control comparison, which was 0.084).

The occurrence of pruritus, nausea, vomiting, hypotension, and somnolence is presented in table 5. The in-

TABLE 3. Slow Respiratory Rate Episodes: Duration and Respiratory Rate

	SRR Duration Mean (min)	SRR Duration Maximum (min)	SRR Rate Mean (breaths/min)	SRR Rate Minimum* (breaths/min)
EP study	10.0 ± 8.7	20	8 ± 1	7
IM study	11.1 ± 8.3	35	9 ± 1	7

* Lowest 5-min mean RR noted.

TABLE 4. Apneic Episodes (AP): Duration and Oxyhemoglobin Saturation (Sp_{O_2})

	AP Duration Mean (s)	AP Duration Maximum (s)	AP Sp_{O_2} Mean (%)	AP Sp_{O_2} Minimum (%)
EP study	17.1 ± 1.5	18.8	97 ± 2	95
EP control	18.9 ± 2.6	23.1	96 ± 2	94
IM study	17.5 ± 1.3	20.4	99 ± 2	94
IM control	17.4 ± 2.1	22.8	97 ± 3	91

cidence of these side effects was not significantly different between groups, although the pruritus comparison had a P value of 0.055. All pruritus, nausea, and vomiting episodes were mild or moderate in intensity.

After completion of the study the mean IM meperidine requirement was significantly greater in the IM group: EP, 130 ± 159 mg; IM, 287 ± 204 mg ($P = 0.047$). The groups did not differ in oral codeine use (EP, 398 ± 252 ; IM, 369 ± 279 mg; $P > 0.5$) or duration of hospital stay (EP, 6.4 ± 1.3 day; IM, 6.5 ± 1.3 day; $P > 0.5$).

Discussion

In this study we compared EP and IM morphine when used for analgesia after cesarean section, with emphasis on their respiratory effects. It is the first to continuously and intensively monitor both oxygenation and ventilation in this clinical setting.

The pulse oximeter and respiratory-inductive plethysmograph were chosen as our monitors because of their ability to provide data continuously and noninvasively. Intermittent monitoring systems may miss transient events, and those that disturb subjects will not reflect the natural, unmodified state. Of significance, there is a

TABLE 5. Nonrespiratory Side Effects

Side Effect	Epidural (n = 11)	Intramuscular (n = 13)	P value
Pruritus			
N (total)	10 (91%)	6 (46%)	0.055
N (treated)	4	2	
Nausea and/or vomiting			
N (total)	6 (55%)	6 (46%)	0.26
N (treated)	5	2	
Somnolence			
Time drowsy/asleep per patient (h)	6.0 ± 3.4	7.1 ± 3.9	0.49
N (treated)	0	0	
Hypotension (systolic blood pressure <90 mmHg)			
N (total)	1 (9%)	3 (23%)	0.59
Episodes per patient	2	1-5	
Minimum blood pressure (mmHg)	80/55	80/50	

N (total) = number of patients with side effect; N (treated) = number of patients requiring treatment.

"wakefulness" stimulus to breathe that is not present during sleep.¹³ For oxygenation the pulse oximeter is the ideal monitor and for ventilation the indirect methods of measurement are the most useful. Of these, respiratory-inductive plethysmography is probably the most accurate.^{14,15} Direct methods of measuring ventilation (e.g., spirometry) are uncomfortable, which disturbs patients and precludes long-term use. Assessing the ventilatory response to CO₂ requires patient cooperation and cannot be performed continuously.

The lack of oxygenation abnormalities in our EP or IM subjects is contrary to the results of two previous pulse oximetry studies in cesarean section patients receiving EP morphine. The incidence of SpO₂ ≤ 85% was 71% in 21 subjects⁶ and 50% in ten patients⁷ in the first 24 and 16 h after cesarean section, respectively. However, the isolated effect of EP morphine is unclear because both groups permitted supplemental analgesics (iv meperidine in the former study and unspecified in the latter). They also used computer and/or posthoc analysis of the pulse oximetry data to eliminate artifacts. In contrast, we had an investigator in constant attendance with the patient and monitors at all times to detect artifacts. We have noticed episodes of patient movement and partial dislodgement of the pulse oximeter probe, which have produced small and gradual SpO₂ changes. These changes would probably not have been identified as artifacts without direct examination of the patient.

Our oxygenation results are more similar to those of Ostman *et al.*,⁸ who examined six patients the night after receiving EP morphine during their cesarean section. They reported just one subject with a single episode of SpO₂ < 90%, which lasted 1 min and reached a minimum of 89%.

We also detected no significant ventilatory problems in our patients. Although a small number of AP and SRR episodes occurred, they were similar in frequency and incidence for the EP, IM, and control groups, and of no discernible physiologic consequence. Those episodes present while patients were wide awake were excluded because many activities during the normal awake state can disturb ventilation.¹³ A few episodes were noticed during coughing, talking, and eating (which did not produce a decrease in SpO₂).

Previous studies have indicated that the risk of respiratory depression with EP morphine used for analgesia after cesarean section is small. Potential reasons include the following: the stimulant effect of high progesterone levels in these patients,¹⁶ their lack of risk factors, such as old age and respiratory disease,¹⁷ and the low dose of morphine used¹⁷ (usually 4–5 mg after cesarean section *vs.* 15–20 mg/24 h after thoracotomy¹⁸). Two large epidemiologic studies have reported incidences of significant respiratory depression in this population of 0.07–0.2%.^{3,8}

However, both used intermittent counting of the respiratory rate to assess respiration, which has the major disadvantage of being discontinuous. In addition, the respiratory rate is not a reliable indicator of hypoxia and hypercarbia.^{19–21} Although we found no significant respiratory abnormalities in our study (despite continuous monitoring), the size of our study does not allow us to generalize our results to the entire obstetric population. Using the formula reported by Grayzel,²² we can only conclude that having had 11 consecutive EP and 13 consecutive IM patients with no respiratory depression, the true incidence in this population is no higher than 24% for EP and 21% for IM morphine (with 95% confidence limits). We also have no evidence to suggest that the common practice of monitoring these patients on the obstetric ward by intermittent assessment of the vital signs^{23,24} is unsafe. However, for the reasons explained previously, continuous measurement of oxygenation and/or ventilation would be a more optimal form of monitoring.

Our lower morphine requirements and better quality of analgesia with EP morphine supports the limited number of previous comparative studies.^{25,26} However, many of the IM subjects needed doses every 30 min for the first few hours, suggesting that 5 mg was not adequate. This may have contributed to the poorer pain scores at that time. A more appropriate IM dose would probably have been 7.5–10 mg, at least initially. Whether the EP or IM group's respiratory measurements would have remained similar if equivalent pain relief had been achieved is impossible to predict. The relationship between respiration and analgesia is complex. Inadequate pain relief may cause "splinting" of respiration resulting in decreased oxygenation due to a smaller functional residual capacity (FRC), AP and/or SRR episodes due to breath-holding, or an increased RR, in compensation for small tidal volumes. It may also produce sleep disturbances, with more time spent awake (with an increased RR and tidal volume compared with the sleep state²⁷), or in the early non-rapid eye movement (REM) stages of sleep (during which AP are common²⁷). Conversely, if excessive sedation accompanies good pain relief, more time is spent asleep. In addition, opioids may increase the percentage of time spent in the early non-REM stages,²⁸ and a potentiation of opioid-induced respiratory depression by sleep has been reported.²⁹ Of importance, our EP and IM groups did not differ in the time spent asleep or drowsy although there was much intragroup variability.

The incidences of nausea and/or vomiting and pruritus in our patients were similar to the higher values of those previously reported.^{5,30} This may have been due to our practice of directly questioning the subjects regarding these symptoms or adding epinephrine to the intraoperative anesthetic solution.³¹ Pruritus appeared to be more common in the EP group, similar to previous studies, but

this did not reach statistical significance due to the number of patients in our study.

In conclusion, EP morphine when used for analgesia after cesarean section provided better pain relief with fewer doses than that provided by IM morphine. There were no statistically significant differences in side effects between the two administration routes. Continuous and intensive monitoring by pulse oximetry and respiratory-inductive plethysmography revealed no significant respiratory abnormalities with either the EP or IM morphine.

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