

CME Respiratory Depression After Neuraxial Opioids in the Obstetric Setting

Brendan Carvalho, MBBCh, FRCA Neuraxial opioids have contributed significantly to improved labor and postcesarean delivery analgesia. In the obstetric population, epidural and intrathecal opioids are associated with a very low risk of clinically significant respiratory depression. Although rare, respiratory depression is a serious risk; patients may die or suffer permanent brain damage as a consequence. This review discusses the mechanism and incidence, as well as the prevention, detection, and management of respiratory depression with morphine, extended-release epidural morphine, and lipophilic opioids in the labor and cesarean delivery setting.

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Pain associated with delivery is the most important anesthetic-related concern for expectant mothers.¹ Compared with systemic opioids or regional techniques that use local anesthetics alone, neuraxial opioids provide superior labor and postcesarean analgesia.²⁻⁴ Most cesarean deliveries are performed with spinal or epidural anesthesia⁵; 60%–70% of women in the United States receive neuraxial analgesia during labor.^{6,7} Although rare, respiratory depression is a potentially serious risk after epidural and intrathecal opioid administration. Recent closed-claim data report 16 cases of respiratory depression involving neuraxial opioids, with 73% of these patients dying or suffering permanent brain damage.⁸ This review discusses the mechanism and incidence, as well as the prevention, detection, and management of respiratory depression after neuraxial opioid administration in the obstetric setting.

MECHANISM AND PHARMACOKINETICS

Neuraxial opioids depress the respiratory centers in the brainstem via direct and/or indirect mechanisms,

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as shown in Table 1.⁹⁻¹⁵ Respiratory depression after neuraxial morphine is biphasic¹⁶: it can occur early (30–90 min) after epidural administration of hydrophilic morphine due to systemic vascular absorption,¹⁰ or it can occur late (6–18 h) after epidural or intrathecal morphine due to rostral spread in cerebrospinal fluid and slow penetration into the brainstem.¹⁷ In contrast, lipophilic opioids (e.g., fentanyl and sufentanil) do not cause delayed respiratory depression, but they may cause early-onset respiratory depression, typically within 30 min due to significant vascular uptake, rostral spread via cerebrospinal fluid, and potentially by direct transit in epidural veins.^{9,12}

INCIDENCE

Nonobstetric studies report an incidence of respiratory depression after neuraxial opioids of 0.01%–7%.^{18,19} Retrospective, observational studies may under-estimate the true incidence. Also, the fact that there is no standard definition of respiratory depression²⁰ may contribute to misestimating the incidence. Respiratory rate, hypercarbia, low SpO₂, sedation, depressed ventilatory response to hypoxia or hypercarbia, and naloxone treatment have all been used as indicators of respiratory depression.²⁰

MORPHINE SULFATE

Cesarean Delivery

Morphine is currently the “gold-standard” neuraxial opioid for postcesarean analgesia. It provides effective postoperative analgesia for 12–24 h.²¹ The incidence of respiratory depression after neuraxial morphine administration ranges from 0% to 0.9% (Table 2).²²⁻²⁶ No studies reported serious sequelae, although some patients required naloxone administration.^{22,23}

Early reports suggested that intrathecal morphine was more likely to cause delayed respiratory depression than epidural morphine.¹⁰ However, this fact likely reflected the higher intrathecal morphine doses (1–5 mg) reported in early clinical studies.²⁷ More

Table 1. Mechanisms by which Neuraxial Opioids Cause Respiratory Depression⁹⁻¹⁵

Mechanism
Vascular uptake by the epidural or subarachnoid venous plexuses and circulation to brainstem respiratory center
Arachnoid penetration and movement into the spinal cord
Rostral spread via the aqueous cerebrospinal fluid to the brain stem
Rostral spread via direct perimedullary vascular channels

recently, smaller doses of intrathecal morphine have been found to provide effective analgesia with a low risk of respiratory depression. In one study, neither 0.1 nor 0.25 mg intrathecal morphine affected minute ventilation or the ventilatory responses to CO₂, whereas both measurements were depressed for 3 h after 8 mg subcutaneous morphine.²⁸

Labor Analgesia

In isolation, the efficacy of intrathecal (0.5–2 mg) or epidural (up to 7.5 mg) morphine for labor analgesia is limited by a long latency (15–60 min), incomplete analgesia, and maternal side effects.^{29–32} In combination with lipophilic opioids and local anesthetic, intrathecal morphine in small doses (0.1–0.3 mg) may prolong or improve labor and postpartum analgesia.^{33–38} However, side effects (e.g., nausea, vomiting, and pruritus) and concerns for respiratory depression limit neuraxial morphine's role in a labor setting.^{39,40} In community hospitals with limited anesthesia services, neuraxial morphine for labor analgesia is still occasionally used.⁴¹ The incidence of respiratory depression in a community practice was reported as 1.3%,³³ but it is likely that respiratory depression is under-reported in this setting. Although a case of postpartum respiratory depression was reported 7 h after 1 mg intrathecal morphine administration in labor,⁴² investigators in several studies using smaller intrathecal doses (0.1–0.5 mg) did not report respiratory depression.^{34–37}

EXTENDED-RELEASE EPIDURAL MORPHINE (EREM)

Single-dose epidural or intrathecal morphine provides effective analgesia for 12–24 h postcesarean,²¹ shifting peak pain levels to the second postoperative day.⁴³ EREM (DepoDurTM) delivers standard morphine via multi-vesicular lipid, sustained-release,

drug-delivery technology.^{44–46} A single, 10-mg dose of EREM compared with standard epidural morphine 4–5 mg significantly reduced opioid consumption and pain for 48 h postcesarean delivery without significant respiratory depression in this young, healthy population.^{47,48} However, small sample sizes used in these studies do not allow the respiratory depression incidence to be accurately calculated. Respiratory depression has been reported with larger EREM doses (15–30 mg) administered for hip and knee arthroplasty and lower abdominal surgery.^{49–51} The dose-related incidence of respiratory depression ranged from 2% to 16%, with 8% to 21% of patients requiring naloxone to reverse opioid-related adverse events.^{49–52} Compared with obstetric patients, the surgical patients were higher risk, older, and many received general anesthesia. In the obstetric setting, cautious use of EREM is prudent in high-risk patients (e.g., those with obesity or obstructive sleep apnea, or those who receive magnesium).

LIPOPHILIC OPIOIDS

Labor Analgesia

Lipophilic drugs alone or in combination with bupivacaine are used as a single-dose spinal, part of a combined-spinal epidural technique, and/or combined with epidural local anesthetic solutions to improve analgesia, reduce local anesthetic use and decrease motor block. Respiratory depression after administration of lipophilic opioids in a labor setting is very rare. A few case reports describe respiratory depression or arrest after intrathecal sufentanil 10–15 µg,^{53–59} fentanyl 10 µg (after 100 µg of epidural fentanyl),⁶⁰ and meperidine 50 mg.⁵⁹ Cases typically occur within 4–20 min after intrathecal dosing, and respiratory depression was often associated with prior systemic opioid administration and repeated neuraxial doses. A retrospective analysis of 4870 patients who received intrathecal sufentanil 10 µg for labor analgesia found the risk of respiratory depression was 0.02% (1 of 4870, 95% CI: 0%–0.06%).⁵⁵ Evidence from nonpregnant patients suggests that plasma levels of fentanyl (and, to a lesser extent, of sufentanil) increase progressively during continuous epidural administration and may decrease ventilatory response to CO₂ and increase PaCO₂.^{61,62} However, despite widespread use of epidural opioids in modern obstetric practice, this author is unaware of reports of significant respiratory depression

Table 2. Incidence of Respiratory Depression After Administration of Neuraxial Morphine for Cesarean Delivery

Author	Numbers studied	Route administration	Outcome measure	Respiratory depression incidence (%)
Fuller et al. ²²	4880	Epidural 2–5 mg	RR <10	0.25
Leicht et al. ²³	1000	Epidural 5 mg	RR <10	0.4
Kotelko et al. ²⁴	276	Epidural 5 mg	RR <10	0
McMorland et al. ²⁵	3000	Epidural	RR <10	0.07
Abouleish et al. ²⁶	856	Intrathecal 0.2 mg	SaO ₂ ≤85% and/or RR <10	0.9

RR = respiratory rate.

in this setting. In one retrospective study, no patients (0 in 10,047, 95% CI: 0%–0.03%) who received continuous labor epidural infusions containing bupivacaine with 1.45 $\mu\text{g}/\text{mL}$ fentanyl had respiratory depression.⁵⁵

Cesarean Delivery

Neuraxially administered lipophilic opioids (e.g., fentanyl 10–15 μg) improve intraoperative analgesia and reduce nausea and vomiting during cesarean delivery.⁶³ The incidence of clinically significant respiratory depression after lipophilic drugs in the cesarean delivery setting is unknown, but probably very low. In one case, respiratory depression requiring naloxone reversal occurred 25 min after spinal anesthesia that included intrathecal fentanyl 15 μg .⁶⁴ Epidural fentanyl 100 μg or sufentanil 10–50 μg added to lidocaine for cesarean delivery caused statistically significant changes of respiratory rate and end-tidal CO_2 .⁶⁵ In another study, intrathecal fentanyl 20 μg added to bupivacaine for cesarean delivery improved the quality of neuraxial blockade, but it did not cause deterioration in peak expiratory flow rate or vital capacity.⁶⁶ Respiratory depression has been described after epidural fentanyl 90–100 μg for cesarean delivery.^{67,68} Epidural sufentanil (30–50 μg) depressed ventilatory response to CO_2 after cesarean delivery, although overt respiratory depression did not occur.¹²

PREVENTION

Identify Patients at Risk

Respiratory depression risk factors in the nonobstetric setting include advanced age, morbid obesity, cardiopulmonary disease, obstructive sleep apnea, and preoperative opioid tolerance.¹⁸ Although obesity is common, obstetric patients are relatively young and healthy. They rarely present with significant pulmonary disease or other risk factors for respiratory depression. Pregnant women also have increased progesterone, a respiratory stimulant that may further decrease the risk of respiratory depression. However, because opioid-induced respiratory depression occasionally occurs in healthy patients without comorbidity who receive standard doses of neuraxial opioid,⁸ we must expect this rare, but hazardous event in our obstetric population.^{8,69}

In morbidly obese patients, increased surveillance after administering neuraxial morphine is necessary. In one study of 856 patients, all 8 who experienced respiratory depression after intrathecal morphine for cesarean delivery were markedly obese.²⁶ Before neuraxial opioids are administered, a history and physical directed at identifying sleep apnea and coexisting disease should be performed. Because hypermagnesemia can cause respiratory depression, extra vigilance is needed with pre-eclamptic women receiving magnesium sulfate for seizure prophylaxis. Caution should be exercised when any other opioids or sedative drugs (e.g.,

diphenhydramine) are administered because they may increase the risk of respiratory depression.⁸ Multiple order sets prescribing parenteral or oral opioids to treat breakthrough pain pose a particular hazard to patients who have received neuraxial opioids.

Limit Opioid Dose and Distribution

In the past, large opioid doses were common and the respiratory depression incidence was more frequent. In the obstetric setting, neuraxial morphine has an analgesic efficacy ceiling.^{70,71} Large neuraxial opioid doses increase side effects without significant prolongation of analgesia. For cesarean delivery, intrathecal doses of morphine >100–200 μg ^{21,70} and epidural doses >2–4 mg⁷¹ are unnecessary. There is a similar analgesic ceiling with lipophilic opioids in labor; doses >2.5–7.5 μg sufentanil or >10–25 μg fentanyl may increase the risk of respiratory depression and other side effects without significantly improving analgesia.^{72–75} Although respiratory depression risk is dose-related and larger doses (intrathecal sufentanil ≥ 10 μg or fentanyl ≥ 50 μg) are more likely to cause respiratory depression, small doses can also cause respiratory depression.^{60,76}

Plain bupivacaine and opioid mixtures (e.g., sufentanil and fentanyl) are hypobaric.⁷⁷ Rostral spread of lipophilic opioids may be minimized by limiting the duration spent in the sitting position after block placement.⁷⁸ Hyperbaric local anesthetic solutions may decrease rostral spread of the opioid, but provide inferior labor analgesia compared with plain (hypobaric) solutions.⁷⁹

MONITORING, DETECTION, AND TREATMENT

Use Appropriate Methods of Respiratory Monitoring

A recent closed-claim analysis estimated that 56% of respiratory events after neuraxial opioids could have been prevented.⁸ The American Society of Anesthesiologists (ASA) approved guidelines in 2007 that address respiratory depression associated with neuraxial opioid administration.¹⁸ These guidelines are scheduled to be revised in 2008. However, these general guidelines do not specifically address obstetric patients in labor or postcesarean delivery.

Opioid effects on respiration include decreased minute ventilation (decreased respiratory rate, tidal volume or both), decreased response to hypoxia, and a rightward shift and depression of the CO_2 response.^{80,81} All patients receiving neuraxial opioids should be monitored for adequacy of ventilation, oxygenation, and level of consciousness. Unfortunately, current monitoring technology and clinical observation practices are unreliable and yield both false positives and negatives.⁸ Intermittent evaluation of clinical signs (respiratory rate, level of sedation, pupil size) are often unreliable predictors of respiratory depression. The respiratory rate of patients with sleep apnea may be misleading, as there may be

chest-wall movement without ventilation due to airway obstruction.⁸ Pulse oximetry, a noninvasive monitor of oxygenation, has poor sensitivity to detect hypoventilation and hypercarbia, especially when supplemental oxygen is administered. Increased surveillance is warranted in patients at high risk of respiratory depression who are receiving oxygen. Brief episodes of desaturation are common 24 h postcesarean delivery. In one study, 71% of patients had ≥ 1 episode of oxyhemoglobin saturations $< 85\%$ after epidural morphine 5 mg administration for cesarean delivery.⁸² Continuous pulse oximetry is inconvenient and impractical for the postpartum patient due to frequent motion-artifact alarms and lack of central monitoring on most postpartum units. Similarly, apnea monitors, associated with frequent, annoying false alarms, do not detect hypoventilation. End-tidal P_{CO_2} monitoring in unintubated patients has significant limitations, and it is not yet universally available.

There are sparse outcome data to guide the selection and frequency of respiratory monitoring. Routine continuous pulse oximetry (while appropriate for the obstetric patient with risk factors such as obesity) may be unnecessary in healthy postcesarean patients when small doses of opioids (e.g., intrathecal morphine ≤ 0.2 mg, epidural morphine ≤ 4 mg) are used. Although intermittent respiratory monitoring may miss transient episodes of desaturation and bradypnea, respiratory depression typically progresses slowly, often preceded by increasing maternal sedation. Regular assessments (e.g., hourly) and vigilant nursing observations of respiratory effort, respiratory rate, or unusual somnolence are probably adequate in low-risk obstetric patients.^{22,83–85} Nursing staff should be adequately trained in detecting and treating opioid-induced respiratory depression, and an anesthesia care provider should be readily available to manage complications that may arise.

Monitor Respiration for an Appropriate Duration

CO_2 responsiveness was depressed for up to 24 h postcesarean delivery after administration of 5 mg epidural morphine.⁸⁶ Thus, it is prudent to continue respiratory monitoring for about 24 h after administering neuraxial morphine. The recently approved ASA guidelines recommend that respiratory monitoring after single-dose neuraxial morphine should occur at least every hour for the first 12 h, then every 2 h for the next 12 h. Patients receiving continuous infusions of neuraxial opioids should be monitored for the duration of the infusion. Because of the potential risk of delayed respiratory depression beyond 24 h, the ASA Task Force recommends that patients receiving epidural EREM should be monitored for up to 48 h.¹⁸ Prolonged monitoring currently recommended for EREM^{18,83} may be overly conservative, as respiratory depression beyond 24 h with single-dose EREM in doses ≤ 10 mg has not been reported.^{48,52}

Early-onset respiratory depression associated with lipophilic opioids usually occurs within 30 min of administration and is likely to occur in a high-visibility, controlled setting (e.g., operating or labor room). The ASA Task Force recommends that after neuraxial administration of lipophilic opioids (e.g., fentanyl), continual respiratory monitoring should be performed for a minimum of 2 h after administration or discontinuation of the infusion. These recommendations are not specific to the obstetric setting and may be overly conservative and impractical to implement in a busy labor suite after discontinuation of an epidural infusion. However, continuous respiratory monitoring for 2–4 h after bolus doses of lipophilic opioids for cesarean delivery should be performed. Investigators reported respiratory depression 100 min after 100 μ g epidural fentanyl for cesarean delivery.⁶⁷ In another study of ventilatory changes after 200 μ g of epidural fentanyl, investigators found that it took 180 min to return to baseline.⁹

Treat Respiratory Depression

Physicians and nursing staff must be educated to prevent, recognize, and treat respiratory depression. Treatment protocols and mechanisms to ensure a rapid response to respiratory events should be in place. Patients who display altered level of consciousness, bradypnea, or hypoxemia require treatment and more intensive monitoring until symptoms have resolved. Although supplemental oxygen should be available, its routine use is not recommended, because it may increase the duration of apnea and reduce the sensitivity of pulse oximetry for detecting hypoventilation.⁸ Naloxone is indicated in patients with more than transient somnolence and respiratory depression that does not respond to arousal. If naloxone fails to reverse severe respiratory depression or arrest, prompt mask ventilation and/or endotracheal intubation should be performed. An intravenous infusion of naloxone (2–10 mg over 24 h) should be maintained for as long as the patient remains symptomatic.^{87–90} The routine administration of prophylactic naloxone is not recommended.⁸⁵ Patients already using continuous positive airway pressure devices should continue to do so postpartum.

IN SUMMARY

Neuraxial opioids have contributed to improved analgesia during labor and after cesarean delivery. The analgesic benefits derived from neuraxial opioids far outweigh the risks of a rare respiratory depression event; a risk that is not significantly increased with neuraxial compared with parenteral opioid administration. In the obstetric population, although neuraxial opioids are associated with a very low risk of clinically significant respiratory depression, it does occur, and may have fatal consequences.⁸ If we identify patients at risk and adequately monitor their ventilation, oxygenation, and level of consciousness, we will be able to decrease the

risk of adverse outcomes. Despite the rarity of respiratory depression in the obstetric population, we must be prepared to diagnose and treat this potentially deadly complication.

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