Society for Obstetric Anesthesia and Perinatology Consensus Statement: Monitoring Recommendations for Prevention and Detection of Respiratory Depression Associated With Administration of Neuraxial Morphine for Cesarean Delivery Analgesia

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The majority of women undergoing cesarean delivery in the United States receive neuraxial morphine, the most effective form of postoperative analgesia for this surgery. Current American Society of Anesthesiologists (ASA) and American Society of Regional Anesthesia and Pain Medicine (ASRA) recommend respiratory monitoring standards following neuraxial morphine administration in the general surgical population that may be too frequent and intensive when applied to the healthy obstetric population receiving a single dose of neuraxial morphine at the time of surgery. There is limited evidence to support or guide the optimal modality, frequency, and duration of respiratory monitoring in the postoperative cesarean delivery patient receiving a single dose of neuraxial morphine. Consistent with the mission of the Society for Obstetric Anesthesia and Perinatology (SOAP) to improve outcomes in pregnancy for women and neonates, the purpose of this consensus statement is to encourage the use of this highly effective analgesic technique while promoting safe practice and patient-centered care. The document aims to reduce unnecessary interruptions from respiratory monitoring in healthy mothers while focusing vigilance on monitoring in those women at highest risk for respiratory depression following neuraxial morphine administration. This consensus statement promotes the use of low-dose neuraxial morphine and multimodal analgesia after cesarean delivery, gives perspective on the safety of this analgesic technique in healthy women, and promotes patient risk stratification and perioperative risk assessment to determine and adjust the intensity, frequency, and duration of respiratory monitoring. (Anesth Analg 2019;129:458–74)

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Accepted for publication March 21, 2019.

Funding: None.

The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000004195

PURPOSE OF THIS CONSENSUS STATEMENT

Cesarean delivery is the most commonly performed inpatient procedure in the United States with the majority of women receiving neuraxial morphine for postoperative analgesia. The purpose of this document is to provide expert consensus recommendations on the monitoring of obstetric patients following neuraxial morphine administration. The primary aims of this document are as follows:

1. Support the mission of the Society for Obstetric Anesthesia and Perinatology (SOAP) to improve pregnancy-related outcomes for women and neonates;
2. Encourage the use of a highly effective analgesic technique following cesarean delivery by reducing resource burden for unnecessary respiratory monitoring;
3. Promote patient-centered care by reducing the burden of excessive respiratory monitoring in healthy mothers recovering from cesarean delivery; and
4. Focus clinical vigilance and intensive respiratory monitoring on those women at high risk for respiratory depression following neuraxial morphine administration.

This writing group was appointed and selected by the SOAP board and comprised a representative group of clinical experts in obstetric anesthesiology who conduct research or have a special interest in respiratory monitoring or neuraxial opioid administration. The writing group consisted of 7 members: Jeanette R. Bauchat, Carolyn F. Weiniger, Pervez Sultan, Ashraf S. Habib, Rie Kato, Ronald B. George, and Brendan Carvalho (chair). Craig M. Palmer provided valuable input into the document, and Kazuo Ando and John J. Kowalczyk conducted the SOAP member survey and provided valuable input into the document. This statement represents the consensus of the writing committee and was approved by the SOAP board of directors. In generating its consensus, several committee members conducted a systematic review.[1] Selected articles from this review and any additional articles identified by committee members were then selected based on relevance for this consensus statement. The committee reviewed systematic reviews, meta-analyses, randomized controlled trials, retrospective trials, and case reports primarily in the obstetric patient population. For topics where there are no data specific to the obstetric population, the writing group referenced best available literature collected in nonobstetric populations.

DERIVATION OF THIS CONSENSUS DOCUMENT

In writing a consensus document, it is recognized that consensus recommendation does not mean that there was complete agreement among all writing group members. Email surveys and personal meetings of the entire writing group were used to identify areas of consensus. The American College of Cardiology and American Heart Association Clinical Practice Guideline Recommendation Classification System was used for classes of recommendation and strength of evidence[2] (see details of the classification system in Supplemental Digital Content 1, Document, http://links.lww.com/AA/C801). Authors used the class of recommendation and strength of evidence as agreed on by greater than or equal to two-third (5 of 7 members) of the Task Force writing group. If the class recommendation was not agreed on by greater than or equal to two-third, then we moved to a lower class of recommendation and strength of evidence until greater than or equal to two-third agreement was obtained by the Task Force writing group.

APPROPRIATE USE OF THE CONSENSUS DOCUMENT

The ultimate judgment regarding care of an individual patient must be made by the physician anesthesiologist and other health care providers in conjunction with the patient. Construction of the optimal postpartum analgesic plan should incorporate the patient's medical condition and preferences, the institutional management options available (which may be limited in low-resource environments), and the relative risks and benefits of available analgesic options. The physician anesthesiologist working in a low-resource environment must consider the capabilities and limitations of their setting before implementation of neuraxial opioid analgesia (Box 1). This document focuses on the management of obstetric patients who are receiving low-dose intrathecal or epidural morphine for postoperative analgesia as part of a multimodal analgesic regimen following cesarean delivery. The writing committee expanded the American Society of Anesthesiologists (ASA) and American Society of Regional Anesthesia and Pain Medicine (ASRA) recommendations for respiratory monitoring following neuraxial opioid administration,[3] specifically addressing patient risk stratification, dosing of intrathecal or epidural morphine, as well as modality, duration, and frequency of perioperative respiratory monitoring.

Box 1. Considerations for Use of Neuraxial Opioid Analgesia in a Low-Resource Environment

A physician anesthesiologist in the low-resource environment must evaluate the appropriateness of neuraxial opioid use in their setting including

- Availability of medical providers who can evaluate underlying patient comorbidities and risk factors that may increase the likelihood of respiratory depression
- System to ensure reliable and accurate administration of nonopioid multimodal medication
- Availability of postpartum nurses who can detect respiratory depression
- Emergency response team in the event of unexpected respiratory depression, which may result from undiagnosed comorbidities and/or drug error

What Other Statements or Guidelines Are Available Regarding This Topic?

The ASA/ASRA have developed Practice Guidelines for the Prevention, Detection and Management of Respiratory Depression Associated with Neuraxial Opioid Administration for all surgical patients.[3] These guidelines codify recommendations to identify patients at risk for respiratory depression and to prevent, detect, and manage respiratory depression associated with neuraxial opioids in the general surgical population.[3] However, the guidelines do not distinguish between the obstetric population receiving single-shot neuraxial morphine for postcesarean delivery analgesia and the general surgery population receiving neuraxial morphine for postoperative analgesia.

Why Was This Consensus Statement Developed?

This consensus statement was developed by SOAP to provide recommendations for strategies surrounding the prevention and detection of respiratory depression associated with neuraxial morphine specifically in the obstetric population following cesarean delivery. Opioid-induced ventilatory impairment is under scrutiny at a national level.[4] The ASA/ASRA guidelines for postoperative monitoring following neuraxial opioid administration were perceived by many to be overly rigorous for the healthy obstetric population, given the low risk of respiratory depression utilizing contemporary neuraxial morphine dosing strategies.[3] Moreover, the ASA/ASRA guidelines may inadvertently reduce the utilization of intrathecal morphine, a highly effective postcesarean delivery analgesic, due to high resource requirements imposed by the included recommendations for respiratory monitoring.[5,6] The ASA/ASRA guidelines recommend frequent and prolonged duration of postoperative assessments for respiratory monitoring without differentiation for populations at risk.[3] Healthy obstetric patients who receive low doses of neuraxial morphine have a reduced risk of respiratory depression when compared with older patients and other vulnerable populations. Moreover, breastfeeding already interrupts sleep, so the necessity of monitoring should be considered against the risk of further sleep disruption and impact on maternal and neonatal welfare. Finally, the requirement for unnecessary respiratory monitoring for all postcesarean patients may detract from monitoring vigilance for those patients at high risk of respiratory depression.

How Does This Consensus Statement Differ From Existing Guidelines?

This statement interprets and applies aspects of the recommendations from the ASA/ASRA Practice Guidelines that were updated in 2016 as they relate to postcesarean delivery analgesia in the obstetric population.[3] The ASA/ASRA guidelines considered all forms of neuraxial opioid administration (single shot, intrathecal, epidural, continuous, patient controlled), all doses, and all patients as equivalent.[3] Unlike the ASA/ASRA guidelines, this consensus statement does not address all modes of neuraxial drug administration (ie, continuous, patient-controlled epidural analgesia) or cover neuraxial lipophilic opioids (eg, fentanyl or sufentanil). This consensus document bases its recommendations on obstetric women undergoing cesarean delivery who are generally younger, not sedated and have fewer comorbidities than other surgical populations, and receive a neuraxial technique using a low-dose “single-shot” administration of neuraxial morphine.

SUMMARY POINTS

SOAP Task Force Summary Points Based on Literature Review

1. Neuraxial opioids have been safely administered to millions of women for cesarean delivery for several decades. Reports in the literature or registries of severe morbidity or mortality in the healthy obstetric population due to respiratory depression from neuraxial morphine administration are exceedingly rare.
2. There is limited evidence to support or guide the optimal modality, frequency, and duration of respiratory monitoring required to detect or prevent adverse respiratory events after cesarean delivery in women receiving neuraxial morphine.
3. Monitoring should be appropriately adjusted for high-risk patients with comorbidities or with risk factors predisposing them to respiratory depression. Monitoring for respiratory depression can be intrusive, disturb sleep, increase nursing workload, interfere with newborn care, and increase health care cost. Overly aggressive monitoring for respiratory depression in the setting of low-dose neuraxial morphine in low-risk parturients may impact resource allocation and patient-centered postcesarean delivery care without improving safety.
4. Neuraxial morphine provides superior analgesia compared to systemically administered opioids and should be utilized preferentially for postoperative analgesia after cesarean delivery. Neuraxial opioids do not increase the risk of respiratory depression compared to systemic opioids after cesarean delivery with neuraxial anesthesia. Low-dose neuraxial morphine combined with multimodal analgesics (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], acetaminophen) provides effective analgesia while minimizing the risk for side effects such as pruritus, nausea/vomiting, and possibly respiratory depression.

RECOMMENDATIONS

SOAP Task Force Recommendations for Frequency and Modality of Respiratory Monitoring Following Neuraxial Morphine Administration for Postoperative Analgesia After Cesarean Delivery

1. Scientific literature findings: frequency and modality of respiratory monitoring
   a. The literature is insufficient to assess whether any monitoring interval or duration of monitoring is optimal for detecting respiratory depression or reducing risks associated with respiratory depression (level C-EO).
   b. The literature is insufficient to assess whether any modality of respiratory monitoring is optimal for detecting clinically relevant respiratory depression (level C-EO).
2. Recommendation
   a. The Task Force members agree that frequency and modality of respiratory monitoring should be based on patient risk stratification, neuraxial morphine dose administered, and clinical setting (see Table 1; Figure).

SOAP Task Force Recommendations for Respiratory Monitoring Based on Neuraxial Morphine Dose

1. When using ultra–low-dose intrathecal morphine (≤0.05 mg) or epidural morphine (≤1 mg) in low-risk, healthy parturients: The Task Force members agree that it is reasonable to have no additional respiratory monitoring beyond routine institutional postoperative cesarean delivery monitoring (clinical decision tool in Table 1; class 2A). (Ultra–low-dose of neuraxial morphine may provide less optimal analgesia when compared to higher doses. If ultra–low-dose morphine is used in combination with a nonopioid multimodal analgesic regimen, this approach may be a reasonable option in low resource settings with limited postoperative respiratory monitoring but must be evaluated in the context of all potential limitations of a low resource environment [Box 1].)
2. When using low-dose intrathecal morphine (>0.05 to ≤0.15 mg) or epidural morphine (>1 mg to ≤3 mg) in low-risk, healthy parturients: The Task Force members agree that in addition to routine institutional postoperative cesarean delivery monitoring, it is reasonable to monitor with respiratory rate and sedation measurement every 2 hours for 12 hours postoperatively (class 2A).
3. When using higher doses of intrathecal morphine (>0.15 mg) or epidural morphine (>3 mg) in low-risk, healthy parturients: The Task Force members agree that it is reasonable to monitor based on ASA/ASRA Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration[3] (class 2A).

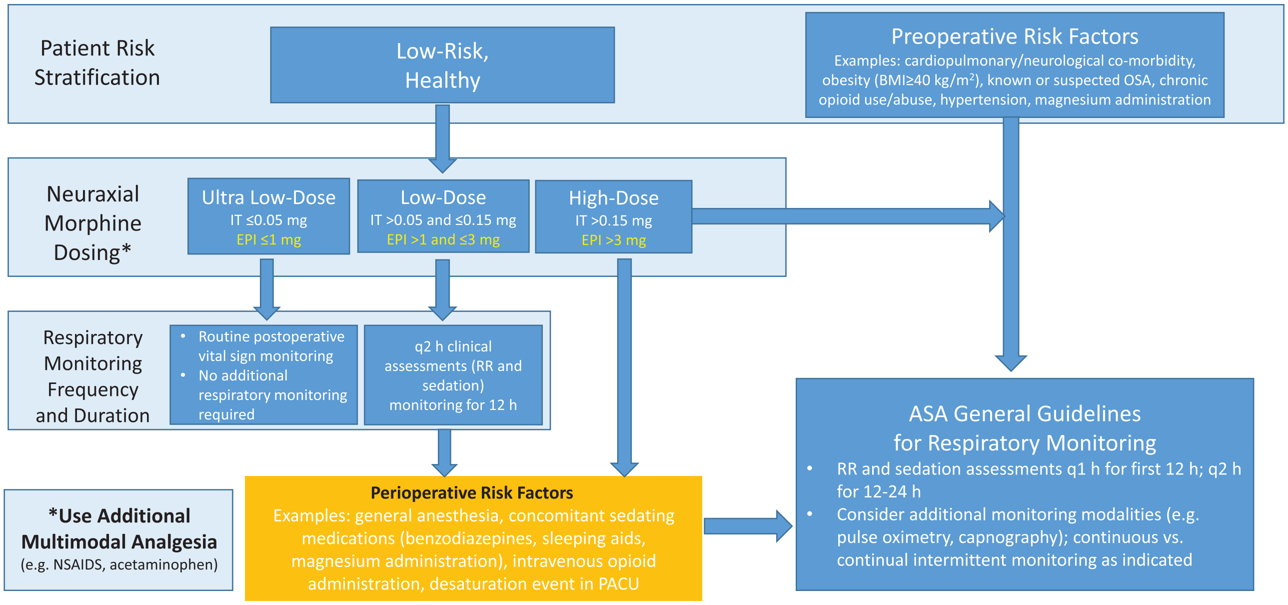

Figure. Respiratory monitoring algorithm following neuraxial morphine administration for postcesarean delivery analgesia. BMI indicates body mass index; EPI, epidural; IT, intrathecal; Mg, magnesium; NSAIDs, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnea; PACU, postoperative anesthesia care unit; Q, every; RR, respiratory rate.

Table 1. Suggested Clinical Decision Tool for Risk Stratification Using Neuraxial Morphine

	Neuraxial Morphine Dose		
Risk Factors	**Intrathecal**	**Epidural**	**Postoperative Respiratory Monitoring Recommendation**
None (healthy, normal BMI)	≤0.05 mg	≤1 mg	No further respiratory monitoring needed in addition to institutional guidelines for postoperative monitoring in this patient population
	>0.05 and ≤0.15 mg	>1 and ≤3 mg	Q 2 h for 12 h RR and sedation checks
	>0.15 mg	>3 mg	Follow ASA/ASRA guidelines[3]: 1. RR and sedation assessments for Q 1 h for first 12 h; Q 2 h for 12–24 h 2. Consider additional monitoring modalities (eg, pulse oximetry, capnography); continuous versus continual intermittent monitoring as indicated
Patient risk factors examples Cardiopulmonary/neurological comorbidity Class III obesity (BMI ≥40 kg/m²) Known or suspected OSA[a] Chronic opioid use Hypertension Peri/postoperative risk factors examples General anesthesia Supplemental IV opioid Concomitant sedating medications[b] Magnesium administration Desaturation event in the PACU	≤0.05 mg	≤1 mg	No further respiratory monitoring needed in addition to institutional guidelines for postoperative monitoring in this patient population
	>0.05 mg	>1 mg	Follow ASA/ASRA guidelines[3]: 1. RR and sedation assessments for Q 1 h for first 12 h; Q 2 h for 12–24 h 2. Consider additional monitoring modalities (eg, pulse oximetry, capnography); continuous versus continual intermittent monitoring as indicated

Abbreviations: ASA, American Society of Anesthesiologists; ASRA, American Society of Regional Anesthesia and Pain Medicine; BMI, body mass index; OSA, obstructive sleep apnea; PACU, postanesthesia care unit; Q, every; RR, respiratory rate; EPI, epidural; IV, intravenous.

[a]All patients with risk factors for OSA (ie, obesity > 30 kg/m², hypertension, etc) should be screened using any or a combination of STOP, STOP-BANG, the ASA checklist, Flemons Index Berlin, or the Epworth Sleepiness Scale.[7–12] Additionally consider these OSA screening questions: BMI > 35 kg/m², falling asleep while talking with someone, and history of treatment for hypertension.[13,14]

[b]Examples include general anesthetics, benzodiazepines, and sedating antiemetics.

SOAP Task Force Recommendation for Patient Risk Stratification for Postoperative Respiratory Depression After Cesarean Delivery

1. Scientific literature findings: Patients may have comorbidities or postoperative circumstances that increase their risk of developing respiratory depression:

   a. Risk factors in the nonobstetric population that are relevant to the obstetric population include obesity, known or suspected obstructive sleep apnea (OSA), chronic opioid use or abuse, additional sedative medications (eg, benzodiazepines, antihistamines), concomitant systemic opioid use, significant respiratory, cardiac or surgical comorbidities, and detection of an adverse respiratory event after opioid administration intraoperatively or in the postanesthesia care unit (PACU) (level B-NR).

   b. Additional risk factors in the obstetric population may include preeclampsia and administration of magnesium sulfate (level C-EO).

2. Recommendation based on risk stratification (Table 1):

   a. Elective and nonurgent clinical situations: Task Force Members strongly agree that it is reasonable to evaluate women with a focused history and physical examination for identification of those who may be at increased risk of respiratory depression for neuraxial morphine administration (class 2A). Members agree that women undergoing cesarean delivery may require opioid analgesia via any route during the perioperative period, and therefore, all women who present for cesarean delivery, irrespective of whether intrathecal morphine will be administered, should be assessed and screened for respiratory depression risk factors (class 2A).

   b. Urgent clinical situations: Task Force members strongly agree that when the urgency of a cesarean delivery may not allow for patient risk stratification before neuraxial morphine administration, a focused history and physical examination is reasonable in the postoperative period for evaluation of appropriate respiratory monitoring (class 2A).

   c. The Task Force members agree that in low-risk women, with no risk factors for respiratory depression, for routine cesarean delivery, it is reasonable for neuraxial morphine dose to guide the frequency, duration, and modality of respiratory monitoring (class 2A).

   d. The Task Force Members agree that in higher-risk women with ≥1 comorbidities and other perioperative circumstances that place them at higher risk of respiratory depression (Box 2), it is reasonable for the frequency, duration, and modality of respiratory monitoring to be guided by clinical judgment of the physician anesthesiologist, institutional guidelines, and/or the ASA/ASRA Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration.

Box 2. Examples of Patient and Postoperative Risk Factors for Respiratory Depression in the Obstetric Population

Perioperative	General anesthesia
	Desaturation event in PACU
	Coadministration of intravenous opioid
	Coadministration of sedatives (intra/postoperative)
	Coadministration of magnesium
Patient	Cardiopulmonary or neurological comorbidities
	Class III obesity (BMI ≥ 40 kg/m^2)
	Obstructive sleep apnea
	Chronic opioid use
	Hypertension

Abbreviations: BMI, body mass index; PACU, postanesthesia care unit.

SOAP Task Force Recommendation for Neuraxial Compared to Systemic Morphine Administration

1. Scientific literature findings: neuraxial morphine compared to systematic administration:

   a. Numerous studies demonstrate the superior analgesic efficacy of neuraxial (epidural or intrathecal) opioid analgesia compared to systemic opioid administration (eg, intravenous [clinician bolus or patient controlled], oral or intramuscular analgesia) for postcesarean delivery analgesia (level B-R).

   b. Studies demonstrate the superior analgesic efficacy of neuraxial (epidural or intrathecal) opioid analgesia compared to local anesthetic techniques (eg, transversus abdominis plane block or wound infiltration) for postcesarean analgesia (level B-R).

   c. Respiratory depression with neuraxial opioids is no greater than with systemic opioids in the general surgery population (level B-R).

2. Recommendations: The SOAP Task Force members strongly agree that neuraxial morphine should be the preferred method for postcesarean delivery analgesia in healthy women (class 1). These recommendations are in accordance with the ASA Practice Guidelines for Obstetric Anesthesia recommendations.[15]

SOAP Task Force Recommendations for Neuraxial Morphine Dosing for Postcesarean Delivery Analgesia

1. Scientific literature findings: neuraxial (intrathecal and epidural) morphine dose selection for postcesarean delivery analgesia:

   a. An analgesic dose–response ceiling exists for neuraxial morphine for postcesarean analgesia (level A [intrathecal] and B-R [epidural]).

   b. Increasing doses of neuraxial morphine can increase the duration of analgesia (level A).

   c. Increasing doses of neuraxial morphine increase the risk of opioid-related side effects (eg, pruritus, nausea, vomiting) (level A).

d. Higher neuraxial morphine doses increase the risk of respiratory depression (level C-LD).
e. Nonopioid multimodal analgesic regimens allow for both reduction in neuraxial dosing and systemic opioid use in the perioperative setting (level A).

2. Recommendations:

a. The Task Force members strongly agree that low-dose intrathecal morphine and epidural morphine should be used to minimize opioid-related side effects (class 2A).
b. The Task Force members agree that a multimodal nonopioid analgesic approach is beneficial to use in addition to neuraxial morphine (class 2A).

Surveys of SOAP Membership and International Experts on Respiratory Monitoring Following Neuraxial Morphine in the Obstetric Population

SOAP members (Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C802) and an international group of experts (Supplemental Digital Content 3, Appendix 2, http://links.lww.com/AA/C803) were surveyed to understand current practices nationally and internationally for neuraxial morphine administration and respiratory monitoring practices.

Survey of SOAP Members. A SOAP member survey was designed to determine membership opinions regarding current ASA/ASRA guideline recommendations for monitoring following neuraxial morphine as applied to the obstetric population (Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C802).[3] In addition, members were queried on a first draft proposal of these consensus statement recommendations so their feedback could be used for consideration in the final consensus statement. A nonvalidated nested structure survey designed by this consensus group was sent via an emailed link in February 2017 to all SOAP members with 2 subsequent reminders sent 1 week apart to complete the survey. The response rate to the SOAP member survey was 59%, with 339 of 571 members responding. This SOAP member survey demonstrated that almost all responding members (91%) routinely use intrathecal morphine for postcesarean delivery analgesia. This rate of use of intrathecal morphine is higher than the previously reported survey from 2009, where 77% of SOAP members used intrathecal morphine.[16] The majority of SOAP members (67%) use low-dose (stated as ≤0.15 mg in the survey) intrathecal morphine in their practice. Almost two-thirds of respondents (64%) follow current ASA/ASRA guidelines (ie, respiratory rate [RR] and sedation monitoring every 1 hour for the first 12 hours and 2 hours for the next 12 hours) for healthy obstetric patients.[3] Thirty-seven percent felt the ASA/ASRA guidelines are too strict for low-risk parturients, though 55% of member felt the guidelines were just right. The majority (60%) agreed or were neutral with the first draft recommendations from this consensus statement that healthy women receiving low-dose morphine (>0.05 to ≤0.15 mg) should be monitored with sedation scores and RRs every 3 hours for 12 hours. Of those who disagreed, the majority (81%) felt our initial recommendations of every 3 hours were too long an interval between respiratory monitoring. In response to the SOAP member survey and the SOAP comment period, the Task Force writing group voted to change the initial recommendation of respiratory monitoring every 3 hours for 12 hours to every 2 hours for 12 hours. Two-thirds of respondents also agreed or were neutral that ultra–low-dose intrathecal morphine (≤0.05 mg) should require no additional monitoring. In their current practice, the majority (64%) of respondents increased the frequency and/or intensity of respiratory monitoring in women with risk factors for respiratory depression such as obesity and sleep apnea.

Survey of International Experts. An international experts' survey was designed to assess their opinions on the recommendations presented in this consensus statement and determine potential implications on postcesarean analgesic practices in their respective countries (Supplemental Digital Content 3, Appendix 2, http://links.lww.com/AA/C803). International experts were selected based on their leadership involvement in international societies in obstetric anesthesia and their research publications in obstetric anesthesia. Diversity in country representation was considered in selection of these experts. International experts were sent a nonvalidated nested structure survey, designed by this consensus group that was sent via email link in September 2017. Thirty experts from outside the United States were surveyed, with a 93% response rate (28/30). Over 90% of experts reported using neuraxial techniques for cesarean delivery but only 43% used neuraxial morphine routinely. The majority of international practitioners (54%) felt that current ASA/ASRA guidelines were overly conservative with respiratory monitoring in healthy women receiving low-dose neuraxial morphine. Seventy-three percent agreed that no additional respiratory monitoring beyond routine postoperative care should be required with ultra–low-dose intrathecal (≤0.05 mg) or epidural (≤1 mg) morphine. Most respondents (63%) agreed or were neutral with our initial recommendations from this consensus statement that healthy women receiving low-dose morphine (>0.05 to ≤0.15 mg) should be monitored with sedation scores and RRs every 3 hours for 12 hours. The majority (89%) also agreed that respiratory monitoring frequency intervals should be performed at a minimum according to ASA/ASRA recommendations in women with comorbidities and risk factors for development of respiratory depression.[3] Barriers to using neuraxial morphine in respondents' practice included hospital policy, inability to monitor postoperatively, and lack of drug availability. The majority (69%) felt the SOAP consensus statement recommendations had the potential to increase utilization of neuraxial morphine for postcesarean delivery analgesia in their respective countries.

LITERATURE BACKGROUND SUPPORTING SOAP TASK FORCE RECOMMENDATIONS

Mechanism of Respiratory Depression

Neuraxial opioids can cause respiratory depression by both direct and indirect mechanisms, and the timing of respiratory depression onset can be biphasic, early, and late.[17–20] Early-onset respiratory depression, specifically, reduced brainstem ventilatory response to hypoxia, could occur between 30 and 90 minutes after injection due to rapid vascular uptake of the opioid, but this is unlikely with low doses of neuraxial morphine used in modern practice.[21] Delayed depression of the ventilatory drive, 6 to 18 hours after neuraxial morphine injection,[22] may occur due to rostral spread through the cerebrospinal fluid (CSF) and penetration of the brainstem, with maximum depression occurring 6.5–7.5 hours after morphine administration.[23,24] Although uptake into the CSF is slower when morphine is administered epidurally rather than intrathecally approximately 60–90 minutes, rostral spread also occurs with epidural administration that can lead to delayed respiratory depression.[25–27] The clinical data on timing of respiratory depression after neuraxial morphine administration were conducted in a small sample of male subjects (N = 10 per group) who did not undergo surgical procedures and who received higher doses of neuraxial morphine (0.3 mg intrathecal morphine and 10 mg epidural morphine) than are used clinically in obstetrics.[22,23] Hydrophilic opioids (eg, morphine) are associated with delayed respiratory depression after epidural or intrathecal injection. Due to the hydrophilic nature of morphine, the opioid remains in the aqueous CSF much longer than other, more hydrophobic opioids (eg, fentanyl). This feature of morphine greatly improves its bioavailability, thus producing the desired prolonged analgesia after lumbar neuraxial morphine administration.[17]

Safety of Neuraxial Morphine for Postcesarean Analgesia

The 2015 US National Vital Statistics Report noted 3,977,745 births nationally, of which 32% of births were via cesarean delivery.[28] The majority of anesthesiologists who specialize in obstetric anesthesiology, for at least the past decade, have been using neuraxial morphine for analgesia following cesarean delivery[16] (Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C802). There are no studies that report the precise number of cesarean deliveries performed using neuraxial morphine, but data obtained from 2009 indicated the majority of women in academic centers in the United States likely received neuraxial morphine for postcesarean analgesia.[16]

The safety profile of modern low-dose intrathecal and epidural morphine to treat pain postcesarean delivery has been demonstrated both through research and clinical use over an extended time. The widespread use of neuraxial morphine in the United States suggests that cases of death and disability would be anticipated and reported if respiratory depression was a significant clinical problem in the setting of cesarean delivery. The Serious Complication Repository (SCORE) systematically tracked complications related to obstetric anesthesia in academic centers over a 5-year period.[29] There were 90,795 neuraxial anesthetics for cesarean delivery reported between 2004 and 2009 among these institutions, and the vast majority of women received neuraxial morphine. There were no reported cases of respiratory arrest secondary to neuraxial opioid administration. The American Society of Anesthesiologists Closed Claims Project database that analyzed claims related to anesthesia administration between 1990 and 2009 found only 1 case of respiratory depression after cesarean delivery.[30] The patient received a continuous epidural infusion (CEI) of bupivacaine and fentanyl for analgesia, not neuraxial morphine. Additionally, there is no evidence that the ASA/ASRA Practice Guidelines for the Prevention, Detection, and Management of Respiratory Depression Associated with Neuraxial Opioid Administration, first published in 2009, have reduced the incidence of respiratory depression or improved safety.

A 2009 survey evaluated intrathecal opioid use for elective cesarean delivery in the United Kingdom.[31] At that time, 90% (183/203) of units in the United Kingdom administered neuraxial diamorphine and the other 10% used neuraxial morphine. Diamorphine is a lipid-soluble drug, but its active metabolite is morphine. One hundred fourteen (56%) units had departmental guidelines for postoperative monitoring of patients, but only 34 (30%) were compliant with the National Institute for Health and Care Excellence (NICE) recommendations (hourly RR, sedation, and pain scores for 12 hours after neuraxial diamorphine and for 24 hours after neuraxial morphine).[31,32] Only a minority of units were aware of the existence of the NICE guidelines. As a testament to the safety profile of these 2 intrathecal opioids, none of the units surveyed and led by consultants reported any documented cases of respiratory depression following neuraxial opioids in obstetrics, despite its frequent use.[31] In the latest 2015 Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries (MBRACE-UK) report of 2,305,920 pregnancies (national collaborative to monitor maternal deaths) and previous triennial Confidential Enquiry into Maternal and Child Health/Center for Maternal and Child Enquires (CEMACH/CEMACE) reports, none of the reported maternal deaths were attributable to maternal neuraxial opioid administration.[33] There were also no reported intensive care unit (ICU) admissions attributed to neuraxial opioid-induced respiratory depression in the summary of Intensive Care National Audit and Research Center (ICNARC) data from 2007[34,35] to 2009 to 2012 admissions.[36,37]

Incidence of Respiratory Depression After Neuraxial Morphine for Postcesarean Analgesia

The true incidence of respiratory depression following neuraxial morphine administration for cesarean delivery is unknown, due in part to the lack of a standard definition for respiratory depression.[38] RR, pulse oximetry oxygen saturation (Spo_2), and hypercarbia have each been used at various numerical "cutoffs" as indicators of respiratory depression in obstetric studies, along with consciousness levels or sedation scores, depressed ventilatory response to hypoxia or hypercarbia, and clinical interventions (eg, naloxone requirement, oxygen administration, bag-mask ventilation).[38] Retrospective, observational studies likely underestimate the true incidence of respiratory depression, while prospective research studies that utilize continuous monitoring techniques (eg, transcutaneous carbon dioxide (CO_2) measurements, capnography, Spo_2) likely overestimate the incidence, as events that meet the definitions of respiratory depression are not associated with clinically relevant events.[39–41] Finally, the heterogeneity of administered neuraxial morphine doses hampers efforts to obtain a true incidence of respiratory depression.

In the obstetric population, the incidence of respiratory depression following neuraxial morphine has been reported to range between 0% and 1.3% when using bradypnea as a clinical measure of respiratory depression.[42–46] One large retrospective study (N = 5036) in women who received intrathecal (0.05–0.25 mg) or epidural (1–5 mg) morphine for cesarean delivery aimed to capture clinically relevant episodes of respiratory depression (defined as either requiring naloxone administration or a rapid response team call) found no instances of respiratory depression.[47] A systematic literature review performed by a subset of authors from this consensus statement aimed to determine the incidence of “clinically significant” respiratory depression after cesarean delivery in women receiving neuraxial morphine or diamorphine.[1] The systematic review included 78 articles (randomized controlled trials, prospective observational, retrospective studies, and case reports), with a total of 18,455 women who received neuraxial morphine or diamorphine for postoperative analgesia after elective and emergency cesarean delivery. Clinically significant respiratory depression was defined as requirement for (1) airway intervention, (2) oxygen therapy for hypoxia ($Spo_2 < 90\%$) or bradypnea (RR < 8/min), (3) pharmacological therapy to reverse opioid narcosis, or (4) documented excessive sedation requiring more than verbal stimulation. Sixteen cases of clinically significant respiratory depression were identified among 18,452 patients. Three cases were considered by authors to be definitely/probably/possibly due to the morphine (administered in low doses: intrathecal morphine ≤150 μg and epidural morphine ≤3 mg) after cesarean delivery. The incidence of clinically significant respiratory depression from published studies in this systematic review was estimated to be 1.63 per 10,000 (95% confidence interval [CI], 00.62–8.77) women. There were 2 cases considered by the authors to be definitely caused by low-dose neuraxial morphine resulting in clinically significant respiratory depression, indicating an incidence of 1.08 per 10,000 (95% CI, 00.24–7.22).[1] Thus, the risk of morbidity or mortality in a healthy obstetric patient following administration of low-dose of neuraxial morphine appears extremely low. Among nonobstetric patients receiving neuraxial opioids, underlying comorbidities are associated with increased likelihood of respiratory depression.[48]

Mixed Obstetric and Nonobstetric Study Populations. Retrospective and prospective database analyses of mixed populations (including a total of 8927 obstetric and 12,434 nonobstetric patients) indicate a wide range of incidences for respiratory depression: between 0.26% and 3% for intrathecal morphine (dose ranges from 0.15 to 0.8 mg) and between 0% and 2.8% for epidural morphine (dose ranges from 2 to 5 mg).[49] Differences in the incidence of respiratory depression among the studies likely reflect heterogeneity in definitions, monitoring techniques for respiratory depression, dosing regimens, and surgical populations.[49,50] Importantly, higher morphine doses, above 0.25 mg, may be associated with frequencies of respiratory depression that do not necessarily reflect current risks using ultra–low-dose (≤0.05 mg) or low-dose (0.05 to ≤0.15 mg) neuraxial morphine.

RESPIRATORY MONITORING TECHNIQUES AFTER CESAREAN DELIVERY

Respiratory monitoring techniques for patients should ideally be noninvasive, reliable, and inexpensive. Continuous monitoring should capture intermittent and delayed respiratory events.[23,39,40,49,51] Hypercapnia and desaturation occur concurrently in the healthy lung, with desaturation occurring soon after hypercapnia ensues.[15] Oxygen supplementation can modify this relationship, normalizing RRs and oxygen saturation in the presence of significant hypercapnia.[39,52–54] Hypoxemia induced by intrathecal morphine may not manifest as decreased RR,[55] rather as an irregular breathing pattern before opioid-induced apnea.[56,57] Somnolence is often observed before clinically important respiratory depression occurs.[30] RR may be less important than depth of respiration, presence of upper airway obstruction, work of breathing, and other qualitative measures of breathing.[58] The ASA and ASRA guidelines[3] propose hourly respiratory monitoring through nurse assessments of RR and sedation for 24 hours in postcesarean patients following single-shot neuraxial morphine administration. There are no studies or any evidence demonstrating that the ASA and ASRA guidelines[3] have reduced morbidity or mortality associated with respiratory depression in the obstetric population. As previously reported, the incidence of respiratory depression is low, and studies reporting respiratory depression in the obstetric population are presented in Table 2.

NURSING ASSESSMENTS

Intermittent RR counting, usually by clinical staff, is the most commonly utilized respiratory assessment after cesarean delivery.[16] As this requires physical presence of staff, it is not performed continuously. It is unclear how intermittent rate counts compare to electronic monitoring in terms of staff workload and cost burden, in preventing the rare occurrence of respiratory depression following neuraxial morphine administration.[59] Nursing assessment of RR is challenging and time-consuming to perform leading to inconsistent measurement. Nursing assessment of RR has not been shown to correlate with hypercapnic events or apnea alert events measured by transcutaneous CO_2 measurements and capnography.[5,39,41,60] In addition, nurses may elevate the importance of RR over somnolence to identify pending respiratory depression.[30,36] Multiple studies assessing nurse compliance with respiratory monitoring report that assessment of level of sedation is the parameter with the lowest likelihood of accurate measurement and documentation.[5,58]

CONTINUOUS RESPIRATION MONITORS

Pulse Oximetry

A 2009 Cochrane review by Pedersen et al[61] included 5 randomized controlled trials with 22,992 postoperative patients, monitored with or without continuous pulse oximetry. Pulse oximetry improved early detection and

Table 2. Obstetric Studies With Incidence Data for Respiratory Depression Secondary to Neuraxial Morphine

Author, Year	Cohort Size	Retrospective/ Prospective	Definition of Respiratory Depression	IT Dose (mg)	EPI Dose (mg)	Other Opioids	Incidence (%)
Kato et al,[43] 2008	1915	Retrospective	Bradypnea = RR < 10/min Severe RD = Naloxone	0.15		Y	Bradypnea: 0.26 Severe RD: 0.052
Abouleish et al,[44] 1991	856	Prospective	Spo_2 ≤ 85% or RR ≤ 10/min	0.2		Y	0.9
Fuller et al, [45] 1990	4880	Retrospective	RR < 10/min		2–5	Y	0.25
Kotelko et al,[46] 1984	276	Prospective	RR < 10/min		5	Y	0
Crowgey et al,[47] 2013	5036	Retrospective	Need for naloxone or rapid response team for respiratory events	0.15	3	Y	0
Bauchat et al,[39] 2017	120	Prospective	Hypercapnic episode > 50 mm Hg for 2 min	0.15		Y	32
Ladha et al,[40] 2017	721	Prospective	Hypoxemia Mild Spo_2 < 90% Severe Spo_2 < 85% for 30 s	0.15		N	Mild RD: 23 Severe RD: 4
Weiniger et al,[41] 2018	74	Prospective	"Apnea alert event" ($Etco_2$ < 5 mm Hg for 30–120 s)	0.15		Y	53% had apnea alert event

Abbreviations: $Etco_2$, end-tidal carbon dioxide, using capnography; EPI, epidural; IT, intrathecal; N, no; RD, respiratory depression; RR, respiratory rate; Spo_2, oxygen saturation; Y, yes.

treatment of hypoventilation and hypoxemia. Monitoring changed patient management more frequently and reduced unplanned respiratory admissions to the ICU, decreased the length of ICU readmission or both, however, did not reduce overall morbidity and mortality in the perioperative period. One significant concern was the false alarms that likely inflated the reported incidence of postoperative desaturation.[62] In addition, false alarms may lead to alarm fatigue as demonstrated by the American Society of Anesthesiologists Closed Claims Project database for opioid-related respiratory depression, where 33% of patients who experienced morbidity were being monitored via continuous pulse oximetry.[30] Two studies in the obstetric population utilizing continuous pulse oximetry demonstrated low rates of desaturation events (Spo_2 < 85%) of 0.1% and 4%, but patients who desaturated were more likely to be obese or have a positive Berlin questionnaire (sleep apnea screening questionnaire).[40,44] False alarms also led to decreased patient satisfaction and continuous monitoring restricted mobility,[44] and alarms may be particularly problematic in postpartum sleep-deprived patients and their newborns.

CO_2 Monitors

Hypercapnia may be an early sign of respiratory depression, which can be detected using arterial CO_2 measurements, transcutaneous CO_2 measurements, and capnography. Arterial blood gas measurements of oxygen and CO_2 are considered the gold standard for measurements of arterial oxygenation and hypercapnia, however, are invasive, intermittently measured, and not routinely used. Transcutaneous CO_2 measurements are continuous, more accurate than end-tidal CO_2 measurements, and within 0–6 mm Hg of arterial blood gas CO_2 measurements. However, RR and depth of breathing are not measured,[63–66] and transcutaneous CO_2 monitoring is a newer technology that is expensive and not widely available. Capnography is a continuous monitor providing a RR and quantitative measure of CO_2; however, its accuracy is dependent on tidal volumes and nasal breathing and the monitor is bothersome to postpartum women.[41]

Studies utilizing transcutaneous CO_2 and capnography show significant increases in arterial CO_2 levels and potential apneic events following intrathecal morphine administration in the obstetric population.[39,41,67] One prospective study of 120 women receiving 0.15 mg intrathecal morphine for cesarean delivery used continuous transcutaneous CO_2 measurements and demonstrated a 32% incidence of hypercapnia, defined by sustained hypercapnia >50 mm Hg for 2 minutes. Patients with higher baseline CO_2 levels were at higher risk of hypercapnic episodes.[39] Another prospective study of postcesarean delivery women receiving 0.15 mg intrathecal morphine utilized continuous capnography and found a 53% incidence of apnea alert events.[41] However, despite sustained hypercapnia and apnea alert events, no obstetric patients in either of these trials required naloxone administration or experienced clinically significant sedation or an adverse respiratory event.[39,41] Additionally, in both studies, all nurse assessments of hourly RRs were recorded ≥14 breaths per minute and no sedation assessment parameters correlated with the transcutaneous CO_2 or capnography measures indicative of respiratory depression. Thus, although 0.15 mg intrathecal morphine after cesarean delivery affects the peripartum ventilatory drive as reflected by episodes of hypercapnia or hypoxemia, it does not appear to cause clinically significant respiratory depression. The relationship between subclinical hypercapnia and clinically relevant respiratory events requires further study.

Additional Monitors

Thoracic impedance, acoustic plethysmography, and photoplethysmography have been described as continuous methods of RR monitoring. Thoracic impedance monitoring can only occur with the use of electrocardiography monitoring. Acoustic plethysmography and photoplethysmography are newer and more expensive than thoracic impedance monitoring.[68–70] Acoustic monitoring is more accurate than thoracic impedance and well tolerated by patients in the PACU.[68–70] Photoplethysmography overestimates RR when airway obstruction is present. With this technique, oxygen saturation is monitored simultaneously via digit pulse oximetry, which is prone to inaccuracies during finger movement. A respiratory volume monitor utilizing a sensor that detects impedance to calculate minute ventilation, tidal volume, and RR is a potentially useful continuous monitoring technology. It is more sensitive at detecting respiratory changes than capnometry alone and has been shown to predict respiratory depression in patients using patient-controlled analgesia (PCA) with intravenous morphine in the PACU.[71–73] None of these technologies have been studied in the obstetric population.

In conclusion, the ideal modality and frequency of respiratory monitoring to prevent adverse respiratory outcomes is unknown. The incidence of bradypnea when RRs are monitored intermittently (eg, hourly) by clinical staff is exceedingly rare following administration of low doses of intrathecal morphine for cesarean delivery. Continuous monitoring technology is the only way to identify adverse respiratory parameters that occur intermittently and unpredictably. Noninvasive continuous respiratory monitoring such as pulse oximetry, capnography, and transcutaneous CO_2 measurements are not widely applied following cesarean delivery.[16] The routine use of continuous monitors to detect respiratory depression for all women undergoing cesarean delivery seems excessively conservative, and intensive respiratory monitoring may be better accepted when only applied to higher-risk patients.

DURATION OF RESPIRATORY MONITORING FOLLOWING NEURAXIAL MORPHINE ADMINISTRATION

Recommendations for duration of respiratory monitoring are frequently based on studies of the pharmacological properties of neuraxial opioids. One small study measured ventilatory response to CO_2 in women undergoing cesarean delivery receiving placebo, 0.1 or 0.25 mg of intrathecal morphine. The ventilatory response to progressive hypercapnia was measured intermittently (baseline, 3 hours, 6 hours, 12 hours,16 hours, and 24 hours) using a modified Read rebreathing technique that extrapolated CO_2 response curves with a computer-controlled data acquisition system.[74] Intermittent ventilatory responses to CO_2 did not differ from baseline CO_2 values at 2.5–3 hours or at any other measured time point, after administration of intrathecal morphine. Although the authors concluded that intrathecal morphine did not cause depression of the ventilatory variables, CO_2 response was measured intermittently with patient stimulation and only 10–12 women were recruited per study group. In a small sample of volunteer male subjects who received high doses of neuraxial morphine (0.3 mg intrathecal morphine and 10 mg epidural morphine),[22–24] maximum depression occurred 6.5–7.5 hours after neuraxial morphine administration.[23,24] The duration of analgesia and side effects after neuraxial morphine are dose dependent.[75] Based on limited studies, early-onset respiratory depression should be evident during the immediate period following neuraxial opioid administration, and late-onset respiratory depression, if it were to occur, would likely be at 6.5–7.5 hours after administration.[23,24] There have been no reported cases of respiratory depression beyond 12 hours after neuraxial morphine administration in the obstetric patient population at clinically relevant doses without confounding clinical factors, such as concomitant systemic opioid administration, wrong route administration, or patient risk factors.[1] Duration of monitoring for respiratory depression should reflect the expected duration of respiratory depression after neuraxial morphine. At contemporary doses, respiratory depression is extremely unlikely to occur after 12 hours.

PATIENT AND PERIOPERATIVE RISK FACTORS INCREASING THE LIKELIHOOD TO DEVELOP RESPIRATORY DEPRESSION FOLLOWING NEURAXIAL MORPHINE

The majority of the SOAP members (65%) and international experts (89%) in the field of obstetric anesthesia agree that monitoring should be increased in women with risk factors for respiratory depression (Supplemental Digital Content 2–3, Appendix 1, http://links.lww.com/AA/C802, Appendix 2, http://links.lww.com/AA/C803). In general surgical populations, reported risk factors for respiratory depression after systemic and neuraxial opioid administration include respiratory, cardiac, and renal comorbidities (ASA physical status ≥III), OSA, obesity, chronic opioid use, concomitant systemic opioid administration, concurrent sedating medication administration, and hypoxemia, hypoventilation, or apnea observed in the PACU (Box 2).[30,51,76–79] In addition, the ASA Closed Claims Project database confirms that the majority of cases of respiratory depression were associated with patient risk factors such as obesity, OSA, and increased age.[30]

There is a paucity of data on risk factors for respiratory depression related to neuraxial morphine administration specific to the obstetric population. The prospective studies to determine the incidence of respiratory depression often exclude obstetric patients with additional risk factors for respiratory depression. Reports from studies are mixed as to whether obesity itself increases the risk of respiratory depression. One retrospective study with 856 patients only demonstrated respiratory depression (pulse oximetry <85% or RR < 10/min) in obese women (N = 8).[44] Another large retrospective study including 5036 patients identified no cases of respiratory depression (naloxone administration or rapid response team activation) after administration of spinal morphine 0.15 mg or epidural morphine 3 mg. Sixty-three percent of women in this study were obese (mean body mass index [BMI] = 34 kg/m^2) and 18% had a BMI ≥40 kg/m^2.[47]

Many of the risk factors for respiratory depression in the general surgical population can be extrapolated to the obstetric population, but there are also unique risk factors in the obstetric population. These include magnesium sulfate administration for preeclampsia and pregnancy-related hypertension. In a systematic review of the literature to evaluate the side effects of magnesium sulfate for seizure prophylaxis in preeclampsia, the incidence of respiratory depression ranged from 0% to 8.2%.[80] In the largest prospective randomized control trial studying magnesium sulfate for seizure prophylaxis in women with preeclampsia, the Eclampsia Trial Collaborative, the incidence of respiratory depression related to magnesium administration was 8.2% using an unspecified definition of respiratory depression.[81] Although the existing research poorly defines respiratory depression in this subgroup of patients with preeclampsia, the consensus group believes administration of magnesium concomitantly with neuraxial opioid warrants closer respiratory monitoring.

Physiological and hormonal changes during pregnancy alter sleep architecture and predispose to development and/or worsening of OSA.[82,83] A recent meta-analysis[84] demonstrated that sleep apnea screening tools used in the general population (Berlin questionnaire, STOP-BANG, Epworth Sleepiness Scale) have shown modest predictive abilities and frequently overestimate sleep apnea in pregnancy. A model incorporating frequent snoring (yes/no), chronic hypertension (yes/no), age, and BMI (continuous) performed significantly better than the Berlin or Epworth assessment tools in pregnancy for predicting OSA.[13] Other investigators found BMI >35 kg/m^2, falling asleep while talking with someone, and history of treatment for hypertension highly predictive of OSA in pregnancy.[14] Obesity has been shown to predispose women to desaturation events postcesarean delivery following 0.15 and 0.2 mg intrathecal morphine.[43,44] While the literature is sparse, the consensus group does not consider obesity a contraindication to neuraxial morphine but associated comorbidities must be assessed; thus, the consensus group chose the World Health Organization definition of class III obesity (BMI ≥40 kg/m^2) to consider increased intensity of respiratory monitoring.[85] Due to the association of OSA with obesity and hypertension, the consensus group agreed it is best practice to screen for OSA in women with class I obesity (BMI ≥30 kg/m^2) and women with existing or pregnancy-induced hypertension. There are no validated screening tools for OSA in the pregnant population, so practitioners are encouraged to use a combination of aforementioned risk factors, clinical judgment, and available general surgical population OSA screening tools when determining appropriate respiratory monitoring following neuraxial opioid administration in pregnant women.[86] Obstetric patients undergoing cesarean delivery are surgical patients who may require opioid analgesia via any route during the perioperative period, and the writing group agreed that all women who present for cesarean delivery, irrespective of whether intrathecal morphine will be administered, should be assessed and screened for risk factors for respiratory depression. Patients' underlying risk factors for respiratory depression should determine respiratory monitoring in the postoperative setting in accordance with institutional guidelines, with neuraxial morphine dose being an additional consideration to maintain or adjust these respiratory monitoring requirements. A suggested "clinical decision tool" and checklist for clinicians to use or modify for patient risk stratification and sleep apnea screening in women undergoing cesarean delivery to determine appropriate postoperative respiratory monitoring parameters or order sets are provided in Table 1 and Supplemental Digital Content 4–5, Appendix 3, http://links.lww.com/AA/C804, Appendix 4, http://links.lww.com/AA/C805, respectively.

PATIENT-CENTERED MODEL FOR POSTCESAREAN DELIVERY ANALGESIA MANAGEMENT

The SOAP task force recommends adjusting monitoring practices based on the likelihood of women experiencing respiratory depression. Women who receive neuraxial morphine for postcesarean analgesia in institutions that follow the ASA/ASRA Practice Guidelines for respiratory monitoring receive postoperative nursing assessments as often as hourly for first 12 hours and every 2 hours for the next 12 hours.[3] This may contribute to numerous disturbances and associated sleep deprivation.[15,87] Women undergoing cesarean delivery report higher levels of exhaustion and average 2 hours less of sleep per night with more broken sleep than women who deliver vaginally.[88,89] Sleep deprivation after cesarean delivery has adverse associations including postpartum depression, perineal pain, backache, headache, incisional pain, altered pain perception, mastitis, and difficulty with breastfeeding.[90–93] A best practice suggestion for nursing respiratory assessments states that sleeping patients who have normal respiratory patterns should not be woken for sedation assessments.[94]

Effective analgesia, such as that provided by neuraxial morphine, could encourage healthy sleep.[95–97] Nonetheless, overly frequent monitoring for respiratory depression may inadvertently interfere with healthy women's ability to sleep, with potential untoward negative effects. In the healthy, obstetric population, minimizing unnecessary respiratory monitoring as appropriate will help promote patient-centered care.

BENEFITS OF NEURAXIAL MORPHINE FOR CESAREAN DELIVERY

Neuraxial morphine provides superior analgesia following cesarean delivery compared to intravenous opioid PCA.[95,97] Numerous meta-analyses and systematic reviews in the obstetric population[95,97–99] confirm that local anesthetic and opioid delivered by patient-controlled epidural analgesia (PCEA) or CEI provide superior postoperative pain relief to that provided by intravenous PCA, but single-shot neuraxial morphine provides independence from infusion pumps, more uniform analgesia and less work for the patient and nursing staff than any of these patient-controlled techniques. Neuraxial morphine also provides better analgesia than local anesthetic regional blocks (eg, transversus abdominis plane block).[100,101] Most studies demonstrate that epidural morphine administration provides better analgesia than local anesthetic wound infiltration techniques.[102,103] Local anesthetics administered via transversus abdominis plane block or wound infiltration techniques have decreased systemic opioid requirements when provided as analgesic adjuvants when neuraxial opioids are not administered.[104]

Neuraxial hydromorphone was utilized when preservative-free morphine was unavailable in the United States and is a reasonable alternative with similar analgesic benefit and side effect profile.[105] The dosing equivalence of neuraxial hydromorphone to neuraxial morphine has not been studied extensively. One study by Sviggum et al[106] explored the 90% effective dose (ED90), defined as numeric rating scale pain scores ≤3 up to 12 hours, using up-down sequential allocation with a biased-coin design and found a dosing ratio of 2:1 for intrathecal morphine (150 µg) to intrathecal hydromorphone (75 µg) administration. However, neuraxial morphine's physicochemical properties suggest a longer duration of action than hydromorphone, hydromorphone has not been studied as thoroughly and lacks the track record of safety that neuraxial morphine has, and therefore if available, intrathecal morphine is the preferred single-shot intrathecal opioid in this setting.

In summary, the literature supports the use of neuraxial morphine for postcesarean delivery analgesia as this method provides the most efficacious analgesia and is the easiest to administer when utilizing neuraxial anesthesia for cesarean delivery.

Respiratory Depression Following Neuraxial Versus Patient-Controlled Intravenous Morphine

Studies overall demonstrate equivalence in the rates of respiratory depression when comparing neuraxial and patient-controlled intravenous opioids in any given postoperative patient population. Several comparative observational studies in the nonobstetric, general surgical population have documented the incidence of respiratory depression with intravenous PCA ranging from 0% to 11.5% depending on respiratory monitoring modality and monitoring frequency and are equivalent to those reported for neuraxial opioids which range from 0.1% to 15%.[53,65,107–112] The American Society of Anesthesiologists Closed Claims Project database reports similar frequencies of patient injury due to neuraxial and intravenous PCA opioid administration.[30] Dalchow et al[67] demonstrated no difference in hypercapnia rates in women receiving intravenous opioid via PCA versus a single 0.3 mg intrathecal diamorphine (0.1 mg intrathecal morphine equivalence) following cesarean delivery, but used 2 separate hospital populations for comparison. Most of the comparative observational studies in the general surgical population utilize continuous or patient-controlled epidural opioid dosing in a different and older patient population. Due to the paucity of data comparing intravenous PCA to single-shot neuraxial morphine in the obstetric population, we should be cautious to extrapolate equivalent risk of respiratory depression with these techniques using the general surgery population data.

Multimodal Analgesia to Reduce Opioid Consumption

Multimodal analgesic strategies should be used to improve the analgesic efficacy of neuraxial morphine for postcesarean analgesia while minimizing the use of systemic opioids for breakthrough pain.[113] Nonopioid multimodal analgesic regimens that include medications such as acetaminophen, NSAIDs, cyclooxygenase (COX)-2 inhibitors, dexamethasone, gabapentinoids, and local anesthetic techniques may reduce opioid consumption and improve postoperative pain management in both nonobstetric and obstetric patient populations.[113–118] Meta-analyses and recent studies demonstrate that the majority of women require <30 mg of morphine equivalents in 24 hours following administration of low-dose intrathecal or epidural morphine with or without nonopioid analgesic medications.[39,41,75,96] Many of the dose-finding studies for both intrathecal and epidural morphine utilized a variety of multimodal analgesic regimens, making studies difficult to compare directly. However, studies in the setting of low-dose intrathecal morphine after cesarean delivery almost universally show that NSAIDs and acetaminophen reduce pain and need for opioid analgesics, with a range of 0–15 mg of morphine equivalence consumed for breakthrough pain in the first 24 hours.[95,119,120] Although acetaminophen, NSAIDs, and local anesthetic techniques have demonstrated analgesic benefit in the setting of neuraxial morphine, the relative efficacy of each analgesic medication and the role of COX-2 inhibitors, dexamethasone, and gabapentinoids for postcesarean delivery analgesia is uncertain. Utilizing multimodal analgesia postcesarean delivery may allow for reduction in neuraxial morphine dosing without compromising analgesia.[95,119–122] When choosing a multimodal analgesic regimen in the postpartum period, it is important to consider the drug safety in this setting with particular emphasis on compatibility with lactation and breastfeeding.[123] Assessment of underlying patient comorbidities and potential side effects of these adjuvant medications must be made to select the ideal nonopioid multimodal regimen for patients receiving neuraxial opioids.[114,124,125]

The consensus group recognizes that neuraxial morphine in conjunction with nonopioid multimodal analgesia does not completely mitigate the need for opioid analgesia, and the majority of women still require analgesics for breakthrough pain. Median opioid consumption does not capture the individual patient's analgesic medication needs, and most of the studies find a non-normal distribution of opioid utilization, with the majority of women requiring little to no opioid for breakthrough pain with neuraxial morphine and multimodal analgesic regimens, and only a small percentage (10%–20%) of women with high analgesic needs.[126] If opioid pain medications are required, oral opioid medications have been shown to have similar efficacy to intravenous opioids, less side effects, and potential advantages (eg, lower cost, enhanced mobility) and are therefore preferable to intravenous opioids in both the perioperative and postcesarean delivery settings.[127] Intravenous opioids should be reserved for severe pain not responsive to oral opioids or patients not tolerating oral medications. Increased respiratory monitoring should be considered if intravenous opioids are deemed necessary in addition to neuraxial morphine and a nonopioid multimodal analgesic regimen.

OPTIMAL DOSING OF NEURAXIAL MORPHINE TO MAXIMIZE ANALGESIA WHILE MINIMIZING SIDE EFFECTS

Neuraxial Morphine Dosing and the Risk of Respiratory Depression

Reducing the dose of neuraxial morphine reduces its respiratory depressant effect.[23,128,129] A meta-analysis conducted by Gehling et al[50] of mixed nonobstetric and obstetric populations (28 studies; n = 790) sought to determine adverse effects of intrathecal morphine in patients undergoing surgery with spinal anesthesia. They found that higher doses (≥0.3 mg) of intrathecal morphine were associated with high frequency of respiratory depression, 9% (7/80) compared to lower doses 1% (2/247), albeit not a statistically significant difference.[50]

A meta-analysis by Sultan et al[75] evaluated the respiratory depressant effects of the most commonly clinically utilized intrathecal morphine doses used in current obstetric anesthesia practice. The investigators evaluated the effects of 0.05–0.1 mg versus higher doses >0.1–0.25 mg of intrathecal morphine on the RR following elective cesarean delivery.[75] A total of 8 randomized controlled studies investigated the incidence (using a variety of definitions) of maternal respiratory depression up to 24 hours after intrathecal morphine administration.[50,74,130–135] There were no reported episodes of respiratory depression in this meta-analysis; however, inclusion of only 480 women, relative to other larger studies presented in Table 2, suggests it was likely underpowered.[75]

Studies investigating neuraxial morphine at low doses have thus far been underpowered to detect differences in the rare complication of respiratory depression. Nonetheless, neuraxial dosing regimens should aim to administer the lowest effective dose of morphine to minimize side effects and possibly the risk of respiratory depression.

Intrathecal Morphine Dosing: Analgesic Duration and Side Effects

Multiple dose–response studies have been conducted to elucidate the optimal dosing for intrathecal morphine for cesarean analgesia.[134,136,137] Most studies demonstrate minimal or no additional benefit in pain scores or opioid use for breakthrough pain using analgesic doses above 0.075 to 0.1 mg intrathecal morphine.[119,132,134,136–138] Two studies also demonstrate that in combination with intravenous NSAIDs, ultra low doses such as 0.025 or 0.05 mg can have comparable analgesic benefit but of shorter duration than 0.1 or 0.15 mg intrathecal morphine, respectively.[119,135] Although some studies demonstrate additional analgesic benefit of dosing above 0.1 mg,[139] side effects such as pruritus, nausea, and vomiting increase with dosing and mitigate the additional analgesic benefits.

Dahl et al[132] performed a meta-analysis comparing intrathecal morphine (doses 0.05–0.2 mg) versus systemic opioids after cesarean delivery. This systematic review found median time to first analgesic requirement in the intrathecal morphine group to be 27 hours (range, 11–29). Palmer et al[137] found increased pruritus but no differences in nausea or vomiting with increasing dose of intrathecal morphine (0.025–0.5 mg). Antiemetic use increased in an impact study from 24% when utilizing 0.1 mg intrathecal morphine to 52% when using 0.2 mg for cesarean delivery.[140] Berger et al[119] compared 0.05, 0.1, and 0.15 mg intrathecal morphine among 144 women and found pruritus was more severe in the 0.1 and 0.15 mg groups when compared with the lowest dose group, but nausea and pruritus treatment were not different among the 3 groups. No respiratory depression or significant sedation occurred in any patients.

The meta-analysis by Sultan et al[75] also evaluated the analgesic duration and side effects of the commonly used intrathecal morphine doses for cesarean delivery (0.05–0.1 mg versus >0.1–0.25 mg). The mean time to first analgesic request (primary outcome) was longer (mean difference, 4.49 hours; 95% CI, 1.85–7.13; P = .0008) in the high-dose group compared to the low-dose group. The range of mean times to first analgesic request in the high-dose group was between 13.8 and 39.5 hours compared to 9.7 and 26.6 hours in the low-dose group. Heterogeneity in the duration of analgesia may reflect differences in NSAID administration intraoperatively and/or postoperatively. Pain scores at 12 hours as well as morphine consumption at 24 hours were not significantly different. The incidence of nausea or vomiting and pruritus was lower in the low-dose group.[75]

In summary, the duration of analgesia of intrathecal morphine can be prolonged by increasing the dose, without reducing pain scores or rescue opioid use at the potential expense of increasing maternal opioid-related side effects of pruritus, nausea or vomiting, and respiratory depression. The 2017 SOAP member survey demonstrates that intrathecal morphine dosing has decreased since 2009,[16] currently 68% use ≤0.15 mg and 89% use ≤0.2 mg (Supplemental Digital Content 2, Appendix 1, http://links.lww.com/AA/C802). The majority (71.5%) of international experts in obstetric anesthesia whose countries use intrathecal morphine utilize ≤0.15 mg with 0.1 mg (53.6%) being the most commonly administered dose (Supplemental Digital Content 3, Appendix 2, http://links.lww.com/AA/C803). For the purpose of this consensus statement, the definition of "low-dose" morphine (>0.05 to ≤0.15 mg intrathecal and >1 to ≤3 mg epidural morphine) and the accompanying respiratory monitoring parameters were based on evidence from the literature balancing the effects of increasing dose on both analgesia and side effects with the most common practices of SOAP members and international experts.

Epidural Morphine Dosing: Analgesic Duration and Side Effects

The optimal dose for postcesarean epidural morphine is unclear, and dosing has been based on intrathecal morphine equivalency studies and dose-finding studies. Equipotent dosing requires use of a conversion ratio of 20:1 to 30:1 between epidural and intrathecal administration. Multiple studies confirm that intrathecal morphine doses of 0.075, 0.1, and 0.2 mg are the analgesic and side effect equivalent to epidural morphine doses of 2, 3, and 4 mg, respectively.[42,141] Several studies have compared the postcesarean analgesic efficacy of epidural and intrathecal morphine.[42,141,142] One meta-analysis demonstrated equivalence for analgesic efficacy, but recommended intrathecal administration as this causes less fetal drug exposure than epidural morphine.[142]

Similar postcesarean analgesia and adverse effects were found with 2.5, 3, and 4 mg doses of epidural morphine[143]; however, Rosen et al[144] found that 2 mg did not provide postcesarean analgesia comparable to 5 and 7.5 mg of epidural morphine. The optimal dose was found to be 3 mg in a large retrospective study, and 3.75 mg in a dose–response study.[45,121]

A systematic review by Bonnet et al[96] of various epidural morphine doses after cesarean delivery reported median time until first request for analgesia of 19.0 hours (range, 5.4–29.2 hours). A longer duration of analgesia was found with larger epidural morphine doses (8.9 hours with 2 mg vs 26.8 hours with 6 mg).[96] In this systematic review, they were unable to demonstrate a correlation between epidural morphine dose and incidence of pruritus or nausea.[96] The largest randomized controlled study to date exploring epidural morphine dose and analgesic duration demonstrated no significant difference between 1.5 and 3 mg.[121] However, the study included a multimodal regimen with scheduled NSAIDs that may have mitigated analgesic differences between lower and higher epidural morphine dose groups.

In summary, increasing doses of epidural morphine prolong analgesia following cesarean delivery, while the ideal analgesic dose to maximize analgesia and minimize side effects is between 1.5 and 3 mg of epidural morphine in combination with a multimodal analgesic postoperative regimen.

ACKNOWLEDGMENTS

A list of International Obstetric Anesthesiology Experts is as follows: Australia: Dr Michael Paech, Dr Surbhi Malhotra; Austria: Dr Clemens Ortner; Belgium: Dr Marc Van de Velde, Dr Patricia Lavand'homme; Brazil: Dr Monica Siaulys, Dr Carlos Othon Bastos; Canada: Dr Philippe Richebe, Dr Jose Carvalho; China: Dr Mingjun Xu; Chile: Dr Hector Lacassie; Columbia: Dr Mauriscio Vasco; Egypt: Dr Mohamed Mohamed Tawfik; France: Dr Frederic Mercier, Dr Dominique Chassard; Germany: Dr Peter Kranke; Iceland: Dr Olof Viktorsdottir; Indonesia: Dr Susilo Chandra; Israel: Dr Sharon Einav; Panama: Dr Luis Eduardo de la Ossa, Dr Rita Tello; Singapore: Dr Alex Sia; South Africa: Dr Sean Chetty, Dr Robert Dyer; Spain: Dr Emilia Guasch; Switzerland: Dr Thierry Girard, Dr Christian Kern; and United Kingdom: Dr Nuala Lucas.

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