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Review Article

Cardiorespiratory complications of neuraxial opioids in patients with obstructive sleep apnea: a systematic review☆,☆☆

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Abstract We sought to determine the rate of cardiorespiratory complications following neuraxial opioid administration in the setting of obstructive sleep apnea (OSA). This systematic review of the leading biomedical databases originated from a university-affiliated, tertiary-care teaching hospital. A systematic search of Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the International Pharmaceutical Abstracts Database (1970 - September 2011) was undertaken. Cardiorespiratory complications were stratified into minor and major based on existing OSA literature. Five studies, including a total of 121 patients, were selected for analysis. All studies comprised low-quality evidence. Six major cardiorespiratory complications were reported among 5 (4.1%) patients and included three deaths, one cardiorespiratory arrest, and two episodes of severe respiratory depression. Five of these complications occurred during continuous fentanyl-containing epidural infusions and without concurrent positive airway pressure treatment. The rate of cardiorespiratory complications following the administration of neuraxial opioids to surgical patients with OSA is difficult to determine.

1. Introduction

Neuraxial opioids may improve the quality and duration of neuraxial anesthesia and produce excellent analgesia [1–5]. However, these important perioperative benefits may be offset by the risks of neuraxial opioids, including pruritis, nausea and vomiting, urinary retention, and most important, respiratory depression [1,2,6,7]. The latter complication is dose-dependent [8–16], with a reported frequency that approaches 3% following the administration of 0.8 mg of intrathecal morphine [11]. Rostral spread within the cerebrospinal fluid to the chemosensitive respiratory centers in the brainstem is thought to be the basis for this occurrence [2].

Patients with obstructive sleep apnea (OSA) are especially sensitive to the potent respiratory depressant effects of opioid

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medications [17], which result in suppression of pharyngeal muscle activity, airway obstruction, hypoxemia, and even death [18–20]. One proposed mechanism for this phenomenon involves the upregulation of opioid receptors induced by recurrent episodes of hypoxemia [21,22]. It has therefore been suggested that patients with OSA are at greater risk of neuraxial opioid-induced respiratory depression as compared with the general population [19]. Anesthesia providers may question the role of neuraxial opioids for perioperative analgesia in the setting of OSA.

Some patients with OSA who receive neuraxial opioids may inadvertently sustain undue risk while others who do not receive neuraxial opioids may needlessly forfeit the very real benefits of this technique. To explore the effect of OSA on the incidence of cardiorespiratory complications relative to the general surgical population receiving neuraxial opioids, the rate of such adverse events first must be determined, hence the purpose of this systematic review.

2. Materials and methods

The authors performed a literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines using the Medline (1948 - September 2011), Embase (1974 - September 2011), Cochrane Central Register of Controlled Trials (3rd quarter 2011), Cochrane Database of Systematic Reviews (2005 - September 2011), and the International Pharmaceutical Abstracts (1970 - September 2011) databases. A reference librarian familiar with literature search protocols of the Cochrane Collaboration conducted the electronic search strategy with input from the authors.

The search strategy included the following free-text and index terms: “epidural”, “intrathecal”, “spinal”, “neuraxial”, “opioids”, “obstructive sleep apnea (or apnoea),” “analgesia”, and “anesthesia”. The primary medical subject heading (MeSH) index terms in Medline were “obstructive sleep apnea,” “opioids,” “intrathecal”, and “epidural”. Additional relevant search terms included “obesity hypoventilation syndrome”, “sleep apnea syndromes”, “hypopnea” or “hypopnoea”, and “sleep disordered breathing”. Search results were cross-referenced with each of the MeSH terms “respiratory insufficiency”, “respiratory system abnormalities”, “cardiovascular abnormalities”, and “postoperative complications”.

To supplement our database searches, we hand searched the reference lists of all retrieved articles. We also reviewed the abstract archives from the following professional meetings to capture any additional relevant material: Canadian Anesthesiologists’ Society (2000–2010), American Society of Anesthesiologists (2000–2010), American Society of Sleep Medicine (2000–2010), and the International Anesthesia Research Society (2000–2010). Articles were limited to English studies conducted in human adults. Only those studies that were designed to report cardiorespiratory complications following neuraxial opioid administration in OSA patients were included in the present review. Studies investigating neuraxial anesthesia without opioids in non-OSA and OSA patients were excluded. Two reviewers (DO and SA) independently assessed all material for possible inclusion. In the initial phase of the review, irrelevant articles were excluded based on the title of the article. In the second phase, the abstract and/or full-text articles were evaluated to determine suitability for inclusion. The number of excluded articles and the rationale for exclusion were recorded.

Cardiorespiratory complications were defined and stratified into minor and major based on relevant literature evaluating this construct in patients with OSA [23,24]. Minor complications included: documented desaturation (oxygen saturation [SaO_2] < 90% and/or 4% reduction from the last recorded value either in association with witnessed apneic episodes or not explained by other conditions such as atelectasis, pneumonia, or thromboembolic disease), bradypnea (respiratory rate < 8 breaths/min), hypertension or hypotension (systolic blood pressure > 160 mmHg or < 90 mmHg, respectively), and bradycardia (heart rate < 55 bpm). Major complications included death, respiratory distress, symptomatic arrhythmia, myocardial ischemia or infarction, cardiorespiratory arrest, or any minor complication necessitating intervention with atropine, epinephrine, naloxone, supplemental oxygen, positive airway pressure (PAP) treatment, intubation or reintubation, unplanned hospital admission, or transfer to the intensive care unit.

Using the ASA OSA guidelines’ perioperative risk score [18] as a guide, the following data were extracted from each study: type of investigation, level of evidence (see below), number of patients with OSA who received neuraxial opioid therapy, average body mass index (BMI) and percentage of obese (BMI > 30 kg/m^2) patients in the cohort, method of preoperative diagnosis of OSA, severity of OSA (as defined by the ASA guidelines), baseline arterial carbon dioxide tension ($PaCO_2$), administration of perioperative PAP treatment, nature of postoperative respiratory monitoring, type of surgery, type of anesthesia, opioid details (type, route, and dose(s) administered), and occurrence of any minor or major complications. When required, the corresponding author of the source study was contacted to provide additional information. All included studies were graded for strength of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence classification system [25]. The methodological quality of each study was independently evaluated by the first author (DO). In case of doubt, the second author (SA) was consulted.

3. Results

The PRISMA guideline [26] was followed for the description of the main search strategy (Fig. 1). The initial search strategy yielded 149 articles, of which 45 were excluded

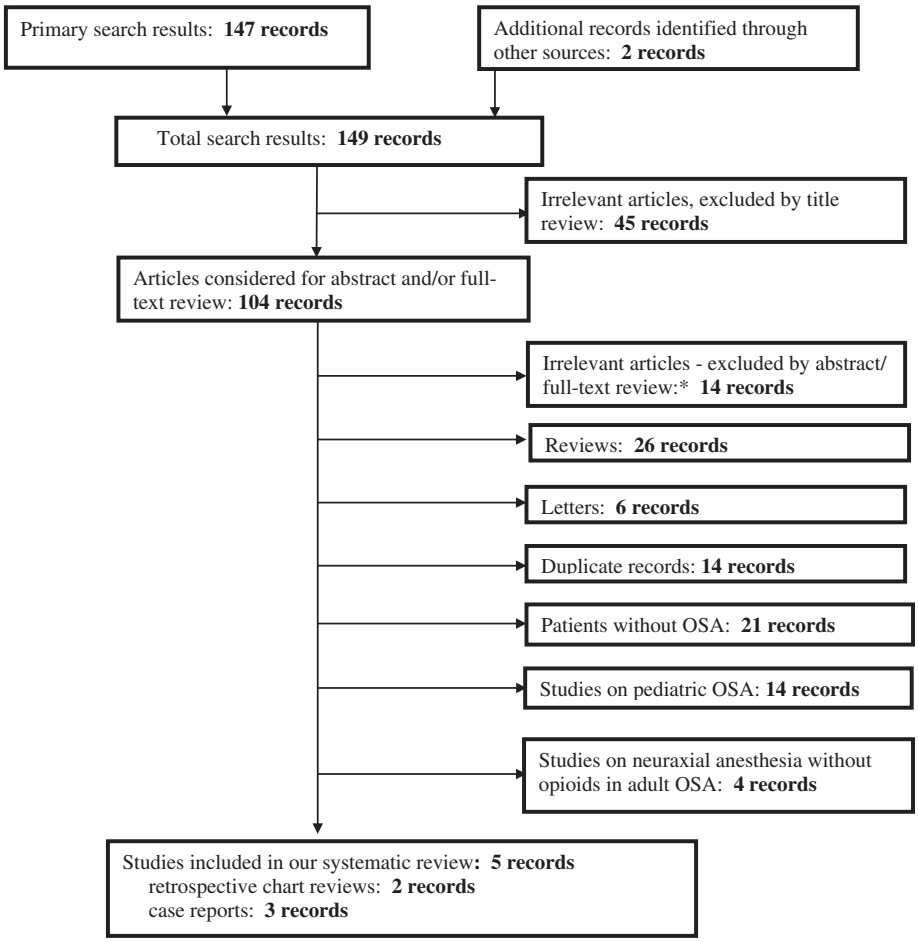

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram [26]. *One study reported three major complications (including two deaths) out of 3,866 patients receiving neuraxial analgesia with opioids. However, the actual number of minor and major complications specifically in patients with obstructive sleep apnea (OSA) could not be obtained from the source study or corresponding author [27].

based on the study title. Of the remaining 104 articles, 6 studies were considered for inclusion. One of these studies reported three major complications (including two deaths) out of 3,866 patients receiving neuraxial opioids, although the actual number of minor and major complications specifically in patients with OSA could not be obtained from the source study or corresponding author; this study was thus excluded [27] from analysis. In the end, 5 studies met our inclusion criteria. Two were retrospective chart reviews [28,29] and the others were case reports [30–32]. We identified a total of 121 patients with OSA who received neuraxial opioids over a 24-year period (1987–2011). One hundred one (90.1%) of the patients identified originated from a single study [28].

4.1. Patient characteristics

The presence of OSA was identified preoperatively (known OSA) in all but one of the 121 patients (Table 1). Preoperative diagnosis of OSA was based on a nonvalidated, department-specific preoperative screening questionnaire in the majority of cases (90.8%) [28], with the remainder based on formal polysomnography (6.7%) [29,30] or past medical history with no diagnostic tool reported (2.5%) [31,32]. Among the 8 patients who had undergone polysomnography preoperatively [29,30], the apnea-hypopnea index [33] was between 25 and 45 for five of these patients [29], and greater than 45 for three others [29,30]. The presence of OSA was identified postoperatively in retrospect (unknown OSA) for one patient (0.08%), postmortem, through family correspondence [31].

Only two-thirds of the patients with known OSA were utilizing some form of PAP therapy at home prior to their scheduled surgery [28–30]. Types of therapy included continuous positive airway pressure (93.9%), bilevel positive airway pressure (4.9%), or C-Flex™ (Respironics; Murrysville PA, USA) (1.2%). For all patients undergoing preoperative PAP therapy, PAP was continued postoperatively. For one patient with known but untreated OSA, PAP was initiated following an intraoperative cardiorespiratory arrest [29]. The extent of preoperative compliance with PAP therapy was not explicitly reported in any of the studies.

Table 1 Characteristics of patients with obstructive sleep apnea (OSA) receiving neuraxial opioids

Authors/citation	Design/ LOE [26]	n	Gender (M:F)	Age (yrs)	BMI (% of n with BMI > 30 kg/m^2)	Preop OSA dx method	OSA severity	Baseline $PaCO_2$ (mmHg)	Preop PAP (n)	Postop PAP (n)	Postop respir monit (n)
Berend et al [28] 2010	R / 2c	109	59:50	63	38.4 (54.5%) *	Q	ND	ND	CPAP (73) BiPAP (2) C-Flex (1) None (33)	CPAP (73) BiPAP (2) C-Flex (1) None (33)	CPO (109)
Kapala et al [30] 2009	CR / 4	1	1:0	63	26.8 (0%) *	PSG	Sev	52	BiPAP	BiPAP	ND
Parikh et al [29] 2002	R / 2c	7	4:3	64	34 (71.4%) *	PSG	Mod or Sev	ND	CPAP (4) BiPAP (1) None (2)	CPAP (5) BiPAP (1) None (1)	IPO (7)
Ostermeier et al [31] 1997	CR / 4	3	1:2	51	33.6 (66.7%) *	H (2) None (1) †	ND	ND	None	None	IPO (3)
Pellechia et al [32] 1987	CR / 4	1	1:0	68	ND (ND)	H	ND	45	None	None	ND

LOE=level of evidence, BMI=body mass index, preop=preoperative, dx=diagnosis, postop=postoperative, PAP=positive airway pressure therapy, respir=respiratory, monit=monitoring, R=retrospective chart review, Q=clinical questionnaire, ND=no data, CPAP=continuous positive airway pressure, CPO=continuous pulse oximetry, BiPAP=bilevel positive airway pressure, C-Flex™=PAP device (Respironics; Murrysville PA, USA), CR=case report, PSG=polysomnography, Sev=severe, Mod=moderate, IPO=intermittent pulse oximetry, H=clinical history.

* Percentage of patients with a BMI > 35 kg/m^2.

† Diagnosis of OSA was made postoperatively.

The overwhelming majority of patients (97.5%) underwent total joint arthroplasty [28–30] while the remainder underwent general surgical and urologic procedures [30–32]. Neuraxial anesthesia (with or without sedation) was the sole surgical anesthetic for most patients (96.7%) [28–31], while general anesthesia (3.3%) [29,31,32] was used for the few remaining patients.

4.2. Neuraxial opioids

The most frequently administered type of neuraxial opioid was morphine (96.7%) [28–32]. Fentanyl (3.3%) was administered far less often [29,31]. Most patients received only a single bolus of neuraxial opioid intraoperatively via the intrathecal route (93.4%) [28–30]. Intrathecal opioid was comprised exclusively of morphine, ranging between 100 and 300 μg for orthopedic [28,29] and general surgical procedures [30], with the majority of patients receiving 200 μg to 250 μg in a single bolus (79.6%) [28,30] (Table 2A). Eight patients (6.6%) received neuraxial opioids via the epidural route [29,31,32]; in all but one patient these opioids were initiated postoperatively [31]. Fentanyl was administered only via the epidural route by continuous infusion [29,31].

4.3. Cardiorespiratory complications after neuraxial opioid administration

For most patients, cardiorespiratory complications were either minor (12.3%) [28] or absent (83.5%) (Table 2B) [28–30,32]. Six major complications, including three deaths, were reported among 5 (4.1%) patients [29,31]. Four of these major complications involved patients with known but untreated OSA receiving continuous epidural fentanyl-containing infusions for postoperative analgesia. One of the 5 patients who suffered a major complication had undergone general anesthesia for surgery [31]. Of note, all 6 major complications occurred prior to the year 2000.

In their retrospective review of 7 patients with known OSA receiving neuraxial opioids, Parikh and colleagues [29] described one patient who became asystolic and unresponsive, with jerky, respiratory movements following the administration of spinal anesthesia with 150 μg of morphine. The elapsed time between administration of intrathecal morphine and onset of the cardiorespiratory arrest was not documented. However, the cardiorespiratory arrest occurred 5 minutes following initiation of propofol sedation (30 μg/kg/min) and the patient was successfully resuscitated. It seems unlikely that intrathecal morphine was the precipitating factor in this patient's cardiorespiratory arrest; the subarachnoid local anesthetic and/or propofol sedation are more probable causes in this context. Another patient was dyspneic and cyanotic on postoperative day (POD) 2 after total knee arthroplasty with a continuous epidural bupivacaine-fentanyl infusion, and required supplemental oxygen, naloxone therapy, and intubation. This patient had received intravenous fentanyl 200 μg intraoperatively with no other systemic opioids administered at any time thereafter. It, too, seems unlikely that this patient's respiratory distress was directly related to neuraxial fentanyl, as dyspnea is more suggestive of a primary pulmonary event than opioid-related respiratory depression.

Ostermeier and colleagues [31] described sudden and fatal postoperative respiratory arrests in three patients with OSA receiving fixed-rate, continuous postoperative bupivacaine-

Table 2A Perioperative anesthetic management of patients with obstructive sleep apnea (OSA) receiving neuraxial opioids

Author/citation	Type of surgery (n)	Surg anesthetic (n)	Anesthetic agent	Systemic opioid	Neuraxial opioid				Neuraxial local anesthetic
					route	type	dose (n)	mode	
Berend et al [28] 2010	TJA (109)	S (109)	None	None	I	M	100 μg (6) 200–250 μg (89) 300 μg (14)	SB	B 7.5 - 10.5mg
Kapala et al [30] 2009	Bowel (1)	CSE (1)	Midaz 4 mg Keta 160 mg	F 125 μg	I	M	200 μg	SB	L 100 mg B 77.5 mg
Parikh et al [29] 2002	TJA (7)	GA (2)	ND	ND	E *	M	ND	ND	ND
		S (1)	Midaz 0.5 mg PPF 30 μg/kg/min	None	I	M	150 μg	SB	B 16 mg
		E (1)	None	F 200 μg	E *	F	10 μg/mL	CI	B 0.5%
		S (2)	ND	ND	I	M	ND	ND	ND
		E (1)	ND	ND	E	M	ND	ND	ND
Ostermeier et al [31] 1997	TJA (1)	GA (1)	ND	ND	E *	F	70 μg/hr	CI	B 0.06 - 0.5%
	TJA (1)	E (1)	Midaz 2 mg	None	E *	F	70 μg/hr	CI	B 0.06%
	Bowel (1)	E (1)	None	ND	E	F	80 μg/hr	CI	B 0.1%
Pellechia et al [32] 1987	Bladder (1)	GA (1)	Thiam 400 mg N_2O - O_2 (60%) Enflur 0.6 - 2.0%	None	E *	M	4 mg	Bolus q18h x 4	None

Medication data are presented as the total perioperative dose administered, where available.
n=number of patients, Surg=surgical, TJA=total joint arthroplasty, S=spinal, I=intrathecal, M=morphine, SB=single bolus, B=bupivacaine, CSE=continuous spinal-epidural, Midaz=midazolam, F=fentanyl, L=lidocaine, Keta=ketamine, GA=general anesthesia, ND=no data, E=epidural, PPF=propofol, CI=continuous infusion, Thiam=thiamylal, N_2O - O_2,= nitrous oxide - oxygen, q18h x 4=every 18 hrs for 4 doses, Enflur=enflurane.
* Neuraxial opioid administration was initiated postoperatively for analgesia.

fentanyl infusions for analgesia. In two of the three patients, OSA was known but untreated. In the remaining case, the diagnosis was made retrospectively through family correspondence. Two of these fatal events occurred on POD 3 and POD 2. For one patient, who died on POD 3, transient desaturation to a SaO_2 of 86% occurred on POD 2 and required supplemental oxygen therapy. The rate of epidural infusion had not been reduced following this event on POD2, at the discretion of the attending physicians. No systemic opioid had been coadministered to this patient at any time. No data were provided relating to the coadministration of systemic opioids to the other two patients who suffered fatal respiratory arrests.

5. Discussion

Our systematic review of the literature identified 5 patients (4.1%) among a published aggregate of 121 surgical patients with OSA who suffered at least one major cardiorespiratory complication following the administration of neuraxial opioids. Nevertheless, due to the limited number and quality of studies reviewed herein, we were unable reliably to determine the rate of cardiorespiratory complications following the administration of neuraxial opioids to surgical patients with OSA. While the majority of major cardiorespiratory events in OSA patients were delayed and associated with both continuous fentanyl-containing epidural infusions and the absence of PAP therapy, a causative relationship could not be ascertained definitively due to the nature and design of the source studies. Indeed, the association of adverse outcomes and the lack of perioperative PAP therapy has been elucidated elsewhere [34,35], though these findings have not been consistent [36,37]. It is noteworthy that 5 of the 6 major complications occurred on POD2 or later, which may at least be partially explained by rapid eye movement (REM) rebound, a phenomenon believed to contribute to delayed respiratory depression in OSA patients following surgery [38–41]. Unfortunately, the heterogeneity of the data collectively examined herein did not allow for any quantitative or qualitative description of risk with respect to the severity of OSA, type and dose of neuraxial opioid administered, or the use of PAP therapy. Finally, the present data are necessarily subject to many potential and undisclosed confounders, most notably the concomitant administration of systemic opioids or other sedative medications, which alone may cause or significantly contribute to the occurrence of adverse cardiorespiratory events.

In spite of recent initiatives to brand opioid-induced respiratory depression a "national patient safety priority" [42], our knowledge of the safety of neuraxial opioids in the setting of OSA remains inadequate. This knowledge gap is underscored by various practice guidelines that have been published at least in part to assist anesthesia providers

Table 2B Complications following neuraxial opioid administration in patients with obstructive sleep apnea (OSA)

Author/Citation	Neuraxial route (n)	Opioid type	Opioid dose (n)	Minor Complic	Major Complic	Remarks
Berend et al [28] 2010	I (109)	M	100 μg (6) 200–250 μg (89) 300 μg (14)	Yes *	None	All pts were treated with PAP and monitored with continuous pulse oximetry postop. Hospital LOS significantly longer for pts with OSA vs nonOSA controls (2.3 vs 1.8 days) †.
Kapala et al [30] 2009	I (1)	M	200 μg	None	None	PAP was used intraop and postop.
Parikh et al [29] 2002	E (2)	M	ND	None	None	
	I (1)	M	150 μg	None	Intraop cardiorespir arrest	OSA known but untreated. PAP initiated following the major complication.
	E (1)	F	10 μg/mL	None	Cyanotic episode on ward on POD 2	OSA known but untreated.
	I (2)	M	ND	None	None	
	E (1)	M	ND	None	None	
Ostermeier et al [31] 1997	E (1)	F	70 μg/hr	None	Fatal respir arrest on POD 3	OSA known but untreated.
	E (1)	F	70 μg/hr	None	Transient desaturn to 86% req supplement O_2 therapy on POD 2 Fatal respir arrest on POD 3	OSA known but untreated. Rate of epidural infusion not reduced following initial major complic, at discretion of attending MD.
	E (1)	F	80 μg/hr	None	Fatal respir arrest on POD 2	OSA unknown and diagnosed retrospectively, postmortem, through family correspondence.
Pellechia et al [32] 1987	E (1)	M	4 mg	None	None	OSA known but untreated preop and postop.

Complic=complication(s), I=intrathecal, M=morphine, pts=patients, PAP=positive airway pressure therapy, LOS=length of stay, intraop=intraoperative, postop=postoperatively, E=epidural, ND=no data, F=fentanyl, cardiorespir=cardiorespiratory, POD=postoperative day, respir=respiratory, desaturn=desaturation, req=required, supplement=supplemental, MD=medical doctor.

* Transient hypoxemia (SpO_2 < 92%) was significantly more common in OSA patients than nonOSA controls (11.2% vs 2.9%; $P = 0.0063$).

† $P < 0.001$.

administering or considering the use of neuraxial opioids in this challenging patient population. A thorough search of the literature identified 5 American [18,19,43–45], two Canadian [46,47], and two European [48,49] practice guidelines related to the use of neuraxial opioids in OSA patients, all of which were published between 2003 and 2010 and are summarized in Table 3. For the majority of guideline recommendations identified, the strength of evidence was either based on the consensus of expert opinion [18,43,47,49] or not documented [43,44,48]. The remainder of the recommendations cited noncomparative observational studies [19], scant systematic empirical evidence [45], and cohort studies at risk of bias [46]. With the exception of the ASA OSA guidelines [18], most recommendations were nonspecific, stating that perioperative opioid therapy should be used with caution [43,44,49] or avoided altogether [45,47,48] in OSA patients. While the use of systemic opioids may pose a greater risk than neuraxial opioids in combination with local anesthetics, none of the guidelines explicitly commented on intrathecal opioid administration; and only three sets of guidelines concluded that epidural opioid administration was either controversial [43] or should be avoided [45,47] in OSA patients. No guidelines made specific recommendations regarding the type or dose of neuraxial opioid administration in OSA patients in the perioperative period.

The foremost limitation of the present review was the inability to estimate the true frequency of severe cardiorespiratory complications, a situation that underscores the challenges associated with calculating the incidence of uncommon events in medicine. As a matter of fact, any estimation of the true incidence of cardiorespiratory complications necessarily requires a reliable denominator, which, in the present case, was the total number of patients with OSA who received neuraxial opioids over a given time period. The challenge of calculating a denominator is reflected by the limited utility of the otherwise insightful ASA Closed Claims database project for estimating the likelihood of risk [50]. Reliable quantification of the denominator should be achieved through concerted and collaborative large-scale prospective investigation, as evidenced by the recent successful Royal College of Anaesthetists' national initiative to determine the incidence of major complications of neuraxial anesthesia in the United Kingdom

Table 3 Practice guidelines for neuraxial opioid administration in patients with obstructive sleep apnea (OSA)

Authors/ citation	Society	Title	Route	Strength of evidence	Authors' conclusions
American sources					
Adesanya et al [44] 2010	ACCP	Periop mgmt of OSA	E & I	ND *	Postop opioid tx should be individualized and titrated with extreme caution in OSA pts.
Haeck et al [45] 2009	ASPS	Evidence-based pt advisory: pt assessmt & prevention of pulmonary side effects in surgery Part 1: OSA & obstructive lung disease	E	Little systematic empirical evidence	It may be advisable to avoid E opioids unless other options (eg, NSAIDs or reg anesthesia with local anesthetics alone) are inappropriate or unavailable.
Horlocker et al [19] 2009	ASA	Practice guidelines for prevention, detection, & mgmt of respir depression assocd w/neuraxial opioid administrn	E & I	Suggestive literature w/noncomparative observatl studies	OSA pts may have associated respir depression when neuraxial opioids used. During history-taking, anesthesiologist should pay particular attention to signs and symptoms of OSA.
Gross et al [18] 2006	ASA	Practice guidelines for periop mgmt of OSA pts	E	Equivocal †	Evidence is equivocal for use of E opioids vs IM/IV opioids in reducing respir depression.
			E & I	Insufficient / consultants agree	Exclusion of neuraxial opioids for analgesia reduces risk vs techniques that include opioids. If neuraxial analgesia is planned, benefits of neuraxial opioid inclusion must be compared w/risks.
			E & I	Insufficient / consultants agree ‡	Reg analgesic techniques w/out opioids reduce likelihood of adverse events vs systemic opioids. Reg analgesic techniques should be considered to reduce or eliminate need for systemic opioids.
Meoli et al [43] 2003	AASM	Upper airway mgmt of adult pt w/OSA in periop period: avoiding complics	E & I	Expert opinion	Analgesic dosing must be carefully titrated to ensure adequate pain relief w/out compromising upper airway muscle tone. More research req to define magnitude of risk & optimal periop care in OSA pts having surgery.
			E	ND *	Controversy exists over use of E opioids in OSA pts.
Canadian sources					
Seet & Chung [47] 2010	CAS	Mgmt of sleep apnea in adults: functional algorithms for periop period: continuing professl developmt	E & I	Expert opinion	Multimodal techniques should be used to minimize postop opioid administrn, inc. neuraxial catheters dispensing local anesthetics (without opioids) & opioid-sparing analgesics.
Fleetham et al [46] 2006	CTS	Dxs & treatment of sleep disordered breathing in adults	E & I	Case–control studies or cohort studies w/ risk of bias	Medications given during anesthesia & postop period may increase severity of OSA-hypopnea syndrome.
European sources					
Chambers & Beckwith [48] 2007	AAGBI	Periop mgmt of the morbidly obese pt	E & I	ND *	Avoidance of opioid medication avoids many potential difficulties.
Mackay et al [49] 2003	SIGN	Mgmt of OSA/hypopnoea syndrome in adults	E & I	Expert opinion	Postop opioid analgesia should be titrated carefully to avoid increasing frequency of apneic episodes & precipitating O_2 desaturation.

ACCP=American College of Chest Physicians, periop=perioperative, mgmt=management, E=epidural, I=intrathecal, ND=no data, postop=postoperative, tx=therapy, ASPS=American Society of Plastic Surgeons, pt(s)=patient(s), assessmt=assessment, NSAIDs=nonsteroidal anti-inflammatory drugs, reg=regional, ASA=American Society of Anesthesiologists, respir=respiratory, assocd=associated, administrn=administration, observatl=observational, IM=intramuscular, IV=intravenous, AASM=American Academy of Sleep Medicine, periop=perioperative, complic(s)=complication(s), req=required, CAS=Canadian Anesthesiologists Society, professl=professional, developmt=development, inc=including, CTS=Canadian Thoracic Society, Dxs=diagnoses, AAGBI=Association of Anaesthetists of Great Britain and Ireland, SIGN=Scottish Intercollegiate Guidelines Network.

* The strength of evidence was not documented.

† Evidence-based data are present but inadequate to permit inference of a relationship between an intervention and an outcome.

‡ There are too few published studies to investigate the relationship between an intervention and an outcome, but consultants agree.

[51]. Furthermore, in order reliably to quantify the true incidence of cardiorespiratory complications, the sample of OSA patients examined must be a faithful representation of the OSA population as a whole. Unfortunately, the diagnostic tools used to identify OSA were highly variable among the source studies reviewed, and did not reflect the ease and availability of multiple screening questionnaires that have been validated for rapid identification of patients at risk for OSA [52–55].

In addition, reliable estimation of the numerator – number of cardiorespiratory complications – was undermined by the general tendency for underreporting of adverse outcomes in the medical literature [56–58]. Despite best efforts, capturing cardiorespiratory complications may be challenging, as evidenced by the heterogeneous outcome measures used in the source studies. Transient oxygen desaturations [28], hypercapnia [31], and multiple clinical features [29,31] (cyanosis, apneic spells, and unresponsiveness) were some of the surrogate measures used for detection of opioid-induced complications. However, each of these measures was subject to its own limitations, thus hindering inter-study comparison. For example, pulse oximetry has poor sensitivity in detecting hypercapnia and hypoventilation with supplemental oxygen administration [59–61]. Conversely, without supplemental oxygen, a decrease in SaO_2 may be seen with even mild hypoventilation, thereby contributing to false alarms [60]. Serial assessment of hypercarbia via arterial blood gas analysis is impractical, especially in patients without indwelling arterial catheters. End-tidal carbon dioxide monitoring in nonintubated patients tends to underestimate $PaCO_2$ and is not universally available [60]. Finally, clinical features of opioid-induced respiratory depression can be misleading. For example, the frequency of apneic episodes in OSA patients may be underestimated even by a skilled observer, given the possibility of chest movement despite airway obstruction and inadequate ventilation [60], while a normal respiratory rate may be observed with hypercapnia [62,63].

In summary, the rate of cardiorespiratory complications following neuraxial opioid administration in surgical patients with OSA cannot be determined based on the existing literature. Practitioners should be mindful of the absence of evidence regarding the safety of neuraxial opioids in this patient population. Our findings underscore the need for large, prospective, observational studies that incorporate validated screening tools, reliable diagnostic tests, homogeneous sample populations, standardized monitoring for operationally defined complications, and faithful recording of adverse events in order to reliably quantify risk. In so doing, the relationship between safety and analgesic efficacy of neuraxial opioids in the setting of OSA will be borne of evidence rather than expert opinion.

References

[1] Cole PJ, Craske DA, Wheatley RG. Efficacy and respiratory effects of low-dose spinal morphine for postoperative analgesia following knee arthroplasty. Br J Anaesth 2000;85:233-7.
[2] Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276-310.
[3] Murphy PM, Stack D, Kinirons B, Laffey JG. Optimizing the dose of intrathecal morphine in older patients undergoing hip arthroplasty. Anesth Analg 2003;97:1709-15.
[4] Rathmell JP, Pino CA, Taylor R, Patrin T, Viani BA. Intrathecal morphine for postoperative analgesia: a randomized, controlled, dose-ranging study after hip and knee arthroplasty. Anesth Analg 2003;97:1452-7.
[5] Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979;50:149-51.
[6] Bailey PL, Rhondeau S, Schafer PG, et al. Dose–response pharmacology of intrathecal morphine in human volunteers. Anesthesiology 1993;79:49-59.
[7] Glass PS. Respiratory depression following only 0.4 mg of intrathecal morphine. Anesthesiology 1984;60:256-7.
[8] Abouleish E, Rawal N, Rashad MN. The addition of 0.2 mg subarachnoid morphine to hyperbaric bupivacaine for cesarean delivery: a prospective study of 856 cases. Reg Anesth 1991;16:137-40.
[9] Flisberg P, Rudin A, Linnér R, Lundberg CJ. Pain relief and safety after major surgery. A prospective study of epidural and intravenous analgesia in 2696 patients. Acta Anaesthesiol Scand 2003;47:457-65.
[10] Fuller JG, McMorland GH, Douglas MJ, Palmer L. Epidural morphine for analgesia after caesarean section: a report of 4880 patients. Can J Anaesth 1990;37:636-40.
[11] Gwirtz KH, Young JV, Byers RS, et al. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain: seven years' experience with 5969 surgical patients at Indiana University Hospital. Anesth Analg 1999;88:599-604.
[12] Kato R, Shimamoto H, Terui K, Yokota K, Miyao H. Delayed respiratory depression associated with 0.15 mg intrathecal morphine for cesarean section: a review of 1915 cases. J Anesth 2008;22:112-6.
[13] Kotelko DM, Dailey PA, Shnider SM, Rosen MA, Hughes SC, Brizgys RV. Epidural morphine analgesia after cesarean delivery. Obstet Gynecol 1984;63:409-13.
[14] Rygnestad T, Borchgrevink PC, Eide E. Postoperative epidural infusion of morphine and bupivacaine is safe on surgical wards. Organisation of the treatment, effects and side-effects in 2000 consecutive patients. Acta Anaesthesiol Scand 1997;41:868-76.
[15] Shapiro A, Zohar E, Zaslansky R, Hoppenstein D, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. J Clin Anesth 2005;17:537-42.
[16] Tsui SL, Irwin MG, Wong CM, et al. An audit of the safety of an acute pain service. Anaesthesia 1997;52:1042-7.
[17] Brown KA, Laferrière A, Lakheeram I, Moss IR. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. Anesthesiology 2006;105:665-9.
[18] Gross JB, Bachenberg KL, Benumof JL, et al; American Society of Anesthesiologists Task Force on Perioperative Management. Practice Guidelines for the Perioperative Management of Patients with Obstructive Sleep Apnea: a Report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Anesthesiology 2006;104:1081-93.
[19] American Society of Anesthesiologists Task Force on Neuraxial Opioids, Horlocker TT, Burton AW, Connis RT, et al. Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration. Anesthesiology 2009;110:218–30.
[20] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230-5.
[21] Brown KA, Laferrière A, Moss IR. Recurrent hypoxemia in young children with obstructive sleep apnea is associated with reduced opioid requirement for analgesia. Anesthesiology 2004;100:806-10.

[22] Moss IR, Laferrière A. Central neuropeptide systems and respiratory control during development. Respir Physiol Neurobiol 2002;131:15-27.
[23] Gupta RM, Parvizi J, Hanssen AD, Gay PC. Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: a case–control study. Mayo Clin Proc 2001;76:897-905.
[24] Mador MJ, Abo Khamis M, Nag N, Mreyoud A, Jallu S, Mehboob S. Does sleep apnea increase the risk of cardiorespiratory complications during endoscopy procedures? Sleep Breath 2011;15:393-401.
[25] OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford, UK: Oxford Centre for Evidence-Based Medicine. Available at: http://www.cebm.net/index.aspx?o=1025. Accessed September 15, 2011.
[26] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[27] Ramachandran SK, Haider N, Saran KA, et al. Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy. J Clin Anesth 2011;23:207-13.
[28] Berend KR, Ajluni AF, Núñez-García LA, Lombardi AV, Adams JB. Prevalence and management of obstructive sleep apnea in patients undergoing total joint arthroplasty. J Arthroplasty 2010;25(6 Suppl):54-7.
[29] Parikh SN, Stuchin SA, Maca C, Fallar E, Steiger D. Sleep apnea syndrome in patients undergoing total joint arthroplasty. J Arthroplasty 2002;17:635-42.
[30] Kapala M, Meterissian S, Schricker T. Neuraxial anesthesia and intraoperative bilevel positive airway pressure in a patient with severe chronic obstructive pulmonary disease and obstructive sleep apnea undergoing elective sigmoid resection. Reg Anesth Pain Med 2009;34:69-71.
[31] Ostermeier AM, Roizen MF, Hautkappe M, Klock PA, Klafta JM. Three sudden postoperative respiratory arrests associated with epidural opioids in patients with sleep apnea. Anesth Analg 1997;85:452-60.
[32] Pellecchia DJ, Bretz KA, Barnette RE. Postoperative pain control by means of epidural narcotics in a patient with obstructive sleep apnea. Anesth Analg 1987;66:280-2.
[33] Iber C, Ancoli-Israel S, Chesson A, and Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. 1st ed. Westchester (IL): American Academy of Sleep Medicine, 2007. p.17,45-46.
[34] Rennotte MT, Baele P, Aubert G, Rodenstein DO. Nasal continuous positive airway pressure in the perioperative management of patients with obstructive sleep apnea submitted to surgery. Chest 1995;107:367-74.
[35] Squadrone V, Coha M, Cerutti E, et al; Piedmont Intensive Care Units Network (PICUN). Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. JAMA 2005;293:589-95.
[36] Drummond GB, Stedul K, Kingshott R, et al. Automatic CPAP compared with conventional treatment for episodic hypoxemia and sleep disturbance after major abdominal surgery. Anesthesiology 2002;96:817-26.
[37] Liao P, Yegneswaran B, Vairavanathan S, Zilberman P, Chung F. Postoperative complications in patients with obstructive sleep apnea: a retrospective matched cohort study. Can J Anaesth 2009;56:819-28.
[38] Eastwood PR, Szollosi I, Platt PR, Hillman DR. Comparison of upper airway collapse during general anaesthesia and sleep. Lancet 2002;359(9313):1207-9.
[39] Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest 2006;129:198-205.
[40] Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. Anesthesiology 1990;73:52-61.
[41] Rosenberg J, Wildschiødtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. Br J Anaesth 1994;72:145-50.
[42] Weinger M, Lee L.A. "No patient shall be harmed by opioid-induced respiratory depression". Park Ridge (IL): Anesthesia Patient Safety Foundation Newsletter 2011; 26:21-28.
[43] Meoli AL, Rosen CL, Kristo D, et al; Clinical Practice Review Committee; American Academy of Sleep Medicine. Upper airway management of the adult patient with obstructive sleep apnea in the perioperative period–avoiding complications. Sleep 2003;26:1060-5
[44] Adesanya AO, Lee W, Greilich NB, Joshi GP. Perioperative management of obstructive sleep apnea. Chest 2010;138:1489-98.
[45] Haeck PC, Swanson JA, Iverson RE, Lynch DJ; ASPS Patient Safety Committee. Evidence-based patient safety advisory: patient assessment and prevention of pulmonary side effects in surgery. Part 1. Obstructive sleep apnea and obstructive lung disease. Plast Reconstr Surg 2009;124(4 Suppl):45S-56S.
[46] Fleetham J, Ayas N, Bradley D, et al; CTS Sleep Disordered Breathing Committee. Canadian Thoracic Society guidelines: diagnosis and treatment of sleep disordered breathing in adults. Can Respir J 2006;13:387-92.
[47] Seet E, Chung F. Management of sleep apnea in adults - functional algorithms for the perioperative period: Continuing Professional Development. Can J Anaesth 2010;57:849-64.
[48] Chambers W, Beckwith P. Perioperative management of the morbidly obese patient. The Association of Anesthetists of Great Britain and Ireland. London, England; 2007:1-13. Available at: http://www.aagbi.org/sites/default/files/Obesity07.pdf. Accessed October 15, 2011.
[49] Mackay T, Banham S. Management of Obstructive Sleep Apnoea/-Hypopnoea Syndrome in Adults. Scottish Intercollegiate Guidelines Network. Edinburgh, Scotland; 2003:1-35. Available at: http://www.sign.ac.uk/pdf/sign73.pdf. Accessed October 15, 2011.
[50] Lee LA, Posner KL, Domino KB, Caplan RA, Cheney FW. Injuries associated with regional anesthesia in the 1980s and 1990s: a closed claims analysis. Anesthesiology 2004;101:143-52.
[51] Cook TM, Counsell D, Wildsmith JA; Royal College of Anaesthetists Third National Audit Project. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth 2009;102:179-90.
[52] Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. Can J Anaesth 2010;57:423-38.
[53] Chung F, Yegneswaran B, Liao P, et al. Validation of the Berlin questionnaire and American Society of Anesthesiologists checklist as screening tools for obstructive sleep apnea in surgical patients. Anesthesiology 2008;108:822-30.
[54] Chung F, Yegneswaran B, Liao P, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008;108:812-21.
[55] Ramachandran SK, Josephs LA. A meta-analysis of clinical screening tests for obstructive sleep apnea. Anesthesiology 2009;110:928-39.
[56] Leape LL. Reporting of adverse events. N Engl J Med 2002;347:1633-8.
[57] Kaldjian LC, Jones EW, Rosenthal GE. Facilitating and impeding factors for physicians' error disclosure: a structured literature review. Jt Comm J Qual Patient Saf 2006;32:188-98.
[58] Kaldjian LC, Jones EW, Rosenthal GE, Tripp-Reimer T, Hillis SL. An empirically derived taxonomy of factors affecting physicians' willingness to disclose medical errors. J Gen Intern Med 2006;21:942-8.
[59] Carvalho B. Respiratory depression after neuraxial opioids in the obstetric setting. Anesth Analg 2008;107:956-61.
[60] Weinger M. Dangers of postoperative opioids. Park Ridge (IL): Anesthesia Patient Safety Foundation Newsletter 2007;21:61-8.
[61] Macintyre PE, Loadsman JA, Scott DA. Opioids, ventilation and acute pain management. Anaesth Intensive Care 2011;39:545-58.
[62] Kopka A, Wallace E, Reilly G, Binning A. Observational study of perioperative PtcCO2 and SpO2 in non-ventilated patients receiving epidural infusion or patient-controlled analgesia using a single earlobe monitor (TOSCA). Br J Anaesth 2007;99:567-71.
[63] Ready LB, Oden R, Chadwick HS, et al. Development of an anesthesiology-based postoperative pain management service. Anesthesiology 1988;68:100-6.