REVIEW

Timing of postoperative respiratory emergencies: when do they really occur?

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Purpose of review
Opioid-induced postoperative respiratory depression has garnered attention and calls for vigilance. However, a higher level of monitoring equates to increased use of hospital resources and is impractical to apply for all postoperative patients. Understanding the temporal pattern of postoperative respiratory emergency occurrences would allow for improved triage of monitoring resources for high-risk patients. Our objective is to describe the temporal pattern of risk of postoperative opioid-induced respiratory failure.

Recent findings
The literature suggests that postoperative opioid-induced respiratory depression is more frequent and severe than previously believed. In response, national patient advocacy groups have proposed improved postoperative monitoring of high-risk patients, especially those with sleep-disordered breathing. Published series of patients who have had adverse respiratory events suggest that the first 24 postsurgical hours comprise the period of highest risk, with most events occurring within the first 12 h. Further, study findings have suggested that adverse respiratory events often occur shortly after administration of opioid analgesics.

Summary
Emerging evidence indicates that the first postsurgical day carries the highest risk of adverse respiratory events, and this risk is often associated with opioid administration. Resources for increased monitoring should be directed to these high-risk times.

Keywords
hypercapnic respiratory failure, obstructive sleep apnea, opioid analgesics

INTRODUCTION

Postoperative hypercapnic respiratory failure is a serious adverse event that can lead to severe permanent morbidity, such as anoxic brain injury, or death [1▪▪]. Obstructive sleep apnea (OSA) and opioid analgesia are recognized as important risk factors for hypercarbic respiratory failure. OSA is common and often undiagnosed [2]. It has been associated with increased rates of postoperative respiratory complications [3]. Opioid analgesia is the primary treatment of moderate-to-severe postoperative pain, and perioperative opioid administration has increased in response to the Joint Commission's standards of assessing and managing pain [4]. Previous reports of opioid-induced respiratory depression have suggested an incidence of less than 1% [5,6], but recent evidence suggests that more than 20% of postsurgical patients have prolonged episodes of hypoxemia, many of which are unrecognized by healthcare staff [7▪]. In acknowledgment of this problem, calls for more vigilant postoperative monitoring have been made for high-risk surgical patients administered opioid analgesics [8–10]. Although emerging technology may accurately monitor patients for postoperative respiratory depression, many of these modalities are still impractical for widespread use [11]. Therefore, the ability to triage surgical patients at high risk for respiratory complications is attractive. Unfortunately, an estimated 20% of adult surgical patients are at high risk for OSA [2], thus the reliance of a positive OSA screen (e.g., STOP-BANG [12], Flemons criteria [13]) is not sufficiently specific for use as a triage mechanism to identify patients at high risk for postoperative respiratory complications. Some studies have reported that patients with untreated OSA or a positive OSA screen who have observed episodes

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KEY POINTS

- Surgical patients are at highest risk for adverse respiratory events in the first few postsurgical hours, especially following discharge from the PACU.
- The daily pattern of patient admissions to postsurgical wards may be the primary factor of the circadian patterns of postoperative respiratory arrests.
- Events can still occur shortly after a reassuring nursing assessment of patient vital signs, but of note, patient somnolence may be an underappreciated warning sign of pending respiratory arrest.
- The pattern of postoperative respiratory depression after neuraxial administration of opioids is complex; monitoring should follow the published guidelines of the American Society of Anesthesiologists Task Force on Neuraxial Opioids.
- Pediatric patients undergoing tonsillectomy typically have respiratory arrests on the first postoperative day, but unlike for adult patients, these events often occur after hospital discharge.

of respiratory depression during phase I anesthesia recovery are at risk for respiratory complications [14] and warrant increased monitoring levels [15]. Improved understanding of when patients are at increased risk for hypercapnic respiratory arrests would further help to tailor postoperative monitoring requirements. Our main objective is to describe the temporal relationship of periods of increased risk of postoperative hypercarbic respiratory failure or arrest.

TEMPORAL RELATIONSHIP OF CRITICAL RESPIRATORY EVENTS AND DISCHARGE FROM THE POSTANESTHESIA CARE UNIT

In 2015, our Mayo Clinic team published an audit of naloxone administrations to treat respiratory depression in postsurgical patients within the first 48 h following dismissal from the postanesthesia care unit (PACU) [16▪▪]. The majority (58%) of naloxone administrations occurred within 12 h of PACU dismissal and 88% occurred within 24 h. When analyzing the frequency of naloxone administrations in 2-h increments, we noted that the first and second 2-h periods were notable for 19% of administrations each, with subsequent leveling off of administration frequency (Fig. 1) [16▪▪]. The same year, Lee *et al.* [1▪▪] published an audit of postoperative opioid-induced respiratory depression from the Anesthesia Closed Claims Project database. The reported temporal pattern of failure events was similar, with 88% of events occurring within the first 24 postoperative hours and 12% within the first 2 postoperative hours.

Although these are contemporary reports of the timing of postoperative critical respiratory events, previous reports have made similar observations. Ramachandran *et al.* [17] observed 32 postoperative critical respiratory events, of which 34% occurred within the first 6 h and 81% within the first day. In 2005, Taylor *et al.* [18] similarly reported that 56.5 and 77.4% of postoperative critical respiratory events occurred within the first 12 and 24 postsurgical hours, respectively.

The consistency of these reports suggests that the period immediately following discharge from the phase I postanesthesia period represents the highest risk of hypercarbic respiratory failure. Theoretically, prolonging the PACU duration for high-risk patients could reduce the incidence of respiratory events in a less-controlled environment, such as the postsurgical ward. However, our institution has a robust clinical pathway to identify patients at risk and delay their PACU discharge until signs of respiratory depression subside [14,19]. Nevertheless, our pattern of emergent naloxone administration was similar to other institutions not following this practice [16▪▪].

After the immediate high-risk period of the first few postsurgical hours, events rate declines dramatically and is relatively stable. This temporal distribution points to possible different causes of respiratory arrests occurring in the early period compared with later. However, etiologic associations between these two phases have not been studied. Taylor *et al.* [18] speculated that residual anesthetic drugs, muscle relaxants, and opioid analgesics could contribute to early respiratory arrests, whereas primarily buildup of opioid metabolites could contribute to later respiratory arrests. To further explore the differences between early and late postoperative respiratory arrests, we subsequently explored the timing of these events during phase I recovery and the day–night distribution of these events after PACU discharge.

RESPIRATORY EVENTS IN THE POSTANESTHESIA CARE UNIT

Recognition that patients are prone to complications related to anesthesia and surgery in the early postoperative period resulted in development of the PACU, a ward notable for intensive monitoring, low nurse to patient ratios, and immediate access to anesthesia providers. During this period, respiratory problems are frequent, and the most commonly used criteria for PACU discharge specifically assesses whether the patient can maintain the airway

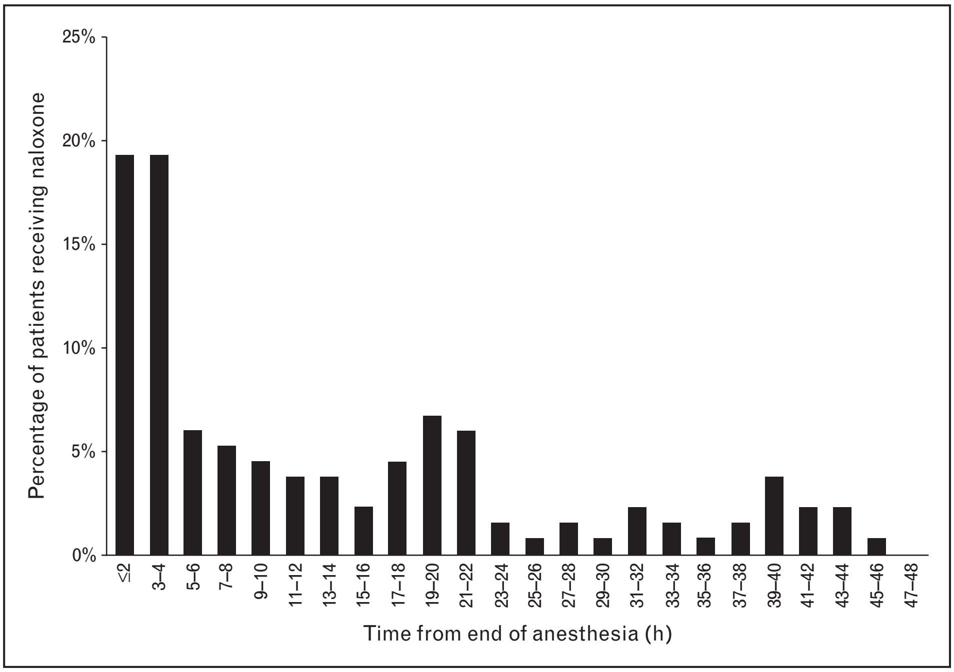

FIGURE 1. Frequency of naloxone administration following discharge from the postanesthesia care unit. Data represent all 134 naloxone administrations to postsurgical patients on the regular ward within 48 h of surgery. Adapted with permission from [16▪▪].

without support or coughs on command and can maintain acceptable oxyhemoglobin saturations [20]. Our institution also has incorporated a protocol to delay PACU discharge when patients are witnessed to have apneic or hypopneic events or episodes or hypoxemia or patients who are moderately to heavily sedated report severe pain [14,19].

Broadly, two pharmacologic classes can contribute to early postoperative respiratory problems: the neuromuscular blocking drugs [21] and the analgesic and sedative medications resulting in depressed respiratory drive [22]. Understanding when respiratory depression occurs during the PACU stay would be useful in understanding the relative contributions of residual neuromuscular blockade and decreased respiratory drive. Epstein *et al.* [23▪] have proposed that if the majority of cases occurred early during the PACU stay, neuromuscular blockade would more likely be the contributing factor. Analysis of hypoxemic episode among 137 757 PACU patients found that peak occurrence was on arrival, yet approximately 70% of episodes occurred after the first 30 min in the PACU (Fig. 2). The analysis found that required tracheal reintubations occurred after the first 30 min for 63% of patients. Although the mechanism of respiratory depression was not assessed specifically, Epstein *et al.* [23▪] hypothesized that residual neuromuscular blockade is more important in episodes of hypoxia that develop within 30 min of PACU admission. The finding that the majority of episodes occurred after 30 min suggests other factors (e.g., opioid use) were also paramount.

DISTRIBUTION OF RESPIRATORY EVENTS BY HOUR

The day–night pattern of respiratory arrests in postsurgical patients has been previously described only by Ramachandran *et al.* [17]. They noted a peak occurrence between the time of 12:00 and 17:59. This single observation mirrors similar diurnal patterns observed in medical emergency team activations where peak activation frequency occurs during weekday and daylight hours [24,25]. This pattern seems a function of the time of day when peak hospital admissions occur [25]. The reason for this pattern is not clear. However, a recent study of patients admitted to a surgical ICU provides a plausible mechanism [26▪]. In that study, patients admitted to the ICU had the data of their vital signs analyzed for abnormalities that would trigger an emergency team activation (e.g., bradypnea, tachypnea, oxyhemoglobin desaturations). The investigators observed that the pattern of trigger occurrences (50% related to respiratory rate and 30% to oxyhemoglobin desaturation) was associated with patient admissions (i.e., more triggers occur in the hours closest to admission) rather than a circadian pattern.

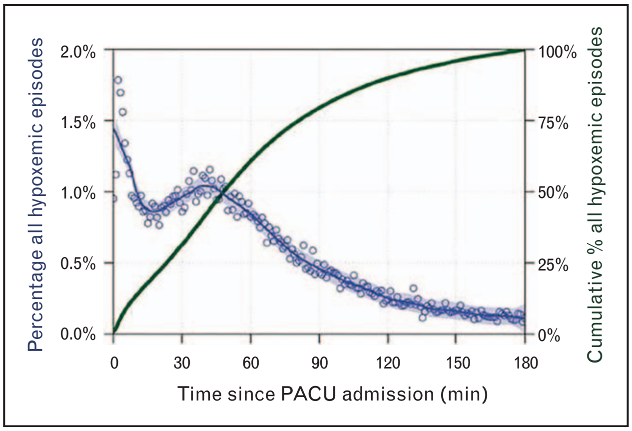

FIGURE 2. Frequency of hypoxic episodes in postoperative patients admitted to the PACU. PACU, postanesthesia care unit. Adapted with permission from [23■].

Whether a similar pattern exists for postsurgical patients admitted to the regular ward is not known. However, risk of naloxone administration increases during the 4 h following PACU discharge. In 2015, we audited naloxone administrations [16■■]. A clock hour depiction from the data of naloxone administrations in the first 4 h showed a circadian pattern of peak administrations during afternoon and evening, coinciding with peak PACU discharges of patients (Fig. 3, top panel). In consideration of naloxone administrations occurring more than 4 h from PACU discharge, the pattern was randomly distributed (Fig. 3, bottom panel). The lack of a circadian pattern for respiratory arrests was unexpected because it is in contrast to knowledge regarding changes in sleep architecture and in breathing during sleep following anesthesia.

Chung *et al.* [27] conducted sleep studies on postoperative nights 1, 3, 5, and 7. They found that sleep architecture (e.g., rapid eye movement sleep) was most affected the first night, whereas disturbances of breathing during sleep — primarily because of increases in hypopnea — peaked the third night. Clear association between moderate-to-severe sleep-disordered breathing and postoperative respiratory arrests has not been firmly established [28], which may explain the disconnect between the timing of highest risk of respiratory failure and the night of greatest sleep breathing disturbances. In addition, opioid analgesic requirements decrease with time after surgery, and patients typically are exposed to fewer opioids by the third night.

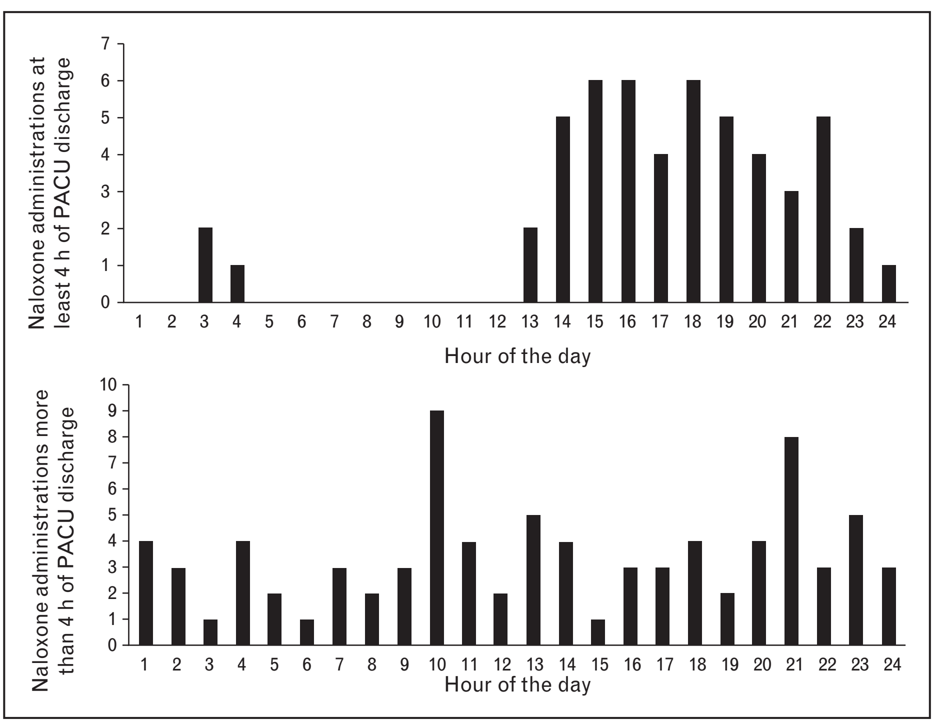

FIGURE 3. The hour of the day of naloxone administration following discharge from the PACU. Upper panel, naloxone administrations within 4 h of PACU discharge. Administrations are more likely to occur in the afternoon and early evening hours (Rayleigh test, $P < .01$). Lower panel, naloxone administrations more than 4 h after PACU discharge and uniformly distributed over the course of the day (Raleigh test, $P = .70$). Data represent all 134 administrations of naloxone to postsurgical patients on the regular ward within 48 h of surgery. PACU, postanesthesia care unit.

PATIENT ASSESSMENT AND SUBSEQUENT RESPIRATORY EVENTS

Nurses are the most important members of the healthcare team in monitoring hospitalized patients and are crucial in early identification of patients whose health is deteriorating acutely. Better nurse staffing models improve patient survival following in-hospital cardiac arrests [29]. When nursing staff are equipped with the means to continuously monitor oxyhemoglobin saturation postoperatively, the numbers of rescue events and ICU transfers decreased [30]. However, in many contemporary practices, patients hospitalized in standard wards undergo intermittent nursing evaluations of vital signs and clinical status [30]. This mode of patient assessment has been found problematic for hypoxemia detection. Sun *et al.* [7▪] found that intermittent nursing checks identified only 5% of hypoxemic episodes lasting greater than 60 min and as detected by continuous pulse oximetry. Further, investigators have shown that oxyhemoglobin saturation averaged 6.5% greater with manual measurements than with automated ones [31▪]. That observation suggests that the physical act of patient assessment may increase patient arousal and mask opioid-induced sedation.

The closed claim analysis of postoperative opioid-induced respiratory depression provides insight into the timing between nursing checks and severe respiratory events [1▪▪]. In the analysis, the majority (78%) of claims had a nursing check within 2 h, with 12 (24%) of 50 claims occurring within 15 min of the event (Fig. 4) [1▪▪]. This observation demonstrates that patients can still have decompensation shortly after a nursing evaluation and suggests that continuous monitors of respiratory status may be superior to intermittent checks. However, the investigators also found that 62% of nursing evaluations noted that patients were somnolent, and they speculate that increased appreciation that somnolence may indicate pending respiratory arrest might improve the predictive power of nursing assessments.

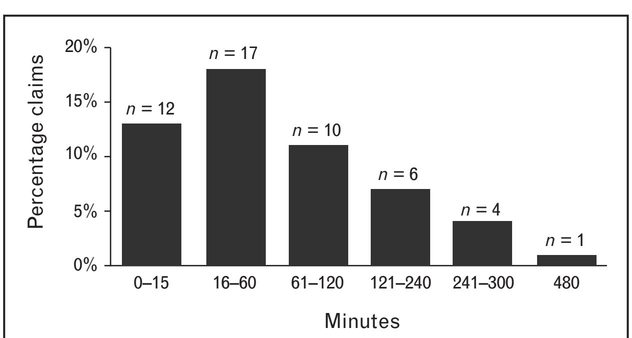

FIGURE 4. Time between last nursing check and discovery of opioid-induced respiratory depression. Adapted with permission from [1▪▪].

NEURAXIAL OPIOID ADMINISTRATION AND POSTOPERATIVE RESPIRATORY DEPRESSION

Shortly after the adoption of neuraxial administration of opioids for perioperative analgesia, clinicians observed that patients could have respiratory depression hours after intrathecal injection of hydrophilic opioid morphine [32,33]. Respiratory depression following intrathecal morphine administration has a typical onset of 2–4 h; peak effect, 5–10 h; and resolution by 20 h [34]. After epidural morphine administration, respiratory depression shows a biphasic pattern with an initial period of respiratory depression 2 h following injection, representing systemic absorption of morphine by the epidural veins, and a later period at approximately 8 h, representing cephalad spread of morphine in the cerebral spinal fluid [35]. However, the timing of respiratory depression has been described as almost 24 h from administration of neuraxial morphine [36].

Unlike hydrophilic opioids, lipophilic opioids rapidly diffuse from the neuraxial space and undergo systemic absorption. Plasma fentanyl levels following intravenous or epidural administration are known to be similar [37]. Compared with hydrophilic opioids, the lipophilic opioids administered into the neuraxial space produced earlier respiratory depression, with peak effect at approximately 2 h after administration and complete resolution by 8 h typically [38]. The differences in the temporal relationship between the development of respiratory depression and the timing of neuraxial administration of an opioid is reflected by the 2009 guidelines of the American Society of Anesthesiologists Task Force on Neuraxial Opioids [39].

NALOXONE ADMINISTRATION TO PEDIATRIC PATIENTS

To our knowledge, only one study reports the timing of naloxone administered to postoperative pediatric patients. Chidambaran *et al.* [40▪▪] reported findings in children similar to in adults. Among 38 hospitalized children, 74.1% of 27 postsurgical naloxone administration events occurred within 24 h of the procedure and 59.3% on the day of surgery. Information regarding the rates of postoperative respiratory depression in children primarily comes from studies of adenotonsillectomy, where the most frequent complication is postoperative respiratory compromise (approximately 9%) [41]. This complication is more frequent in children with OSA than children without OSA (odds ratio 4.90, 95% confidence interval 2.38-10.00) [41].

A study of children who had neurologic injury or death after tonsillectomy, identified by a survey of Society of Pediatric Anesthesia members and the American Society of Anesthesiologists closed claims, found that 77% of cases occurred within 24 h of surgery (when the timing was known), but 69% occurred following hospital discharge [42]. Interestingly, OSA did not influence the timing of events. Analysis of 242 malpractice claims after tonsillectomy identified from the LexisNexis claims database of 1984–2012 found 26 cases related to opioid use, of which 15 were fatal events in the postoperative period [43]. Of these 15 cases, seven reported location and timing of death. On the surgery day, three patients died in the hospital and two at home; on the day after surgery, one patient died in the hospital and one at home. However, a survey conducted by the American Academic of Otolaryngology identified 46 deaths or brain injuries linked to apnea or medication-related deaths, of which 29 events (63.0%) occurred over the first 3 postoperative days without the typical spike on the first day [44].

Although these reports do not provide a granularity of data for assessing risk by postoperative hour, many events occurred after hospital discharge —which argues that pediatric surgical patients are at highest risk several hours later than their adult counterparts. Nixon *et al.* [45] have shown that on the first postoperative night, children with OSA continue to have disrupted sleep from upper airway obstruction despite removal of obstructing lymphoid tissue. Further, children who have OSA and undergo tonsillectomy in the morning have less postoperative oxyhemoglobin desaturation than those who have surgery in the afternoon [46].

CONCLUSION

The first few hours following PACU discharge are high risk for postoperative respiratory emergencies. Many of these events occur in the late afternoon, reflecting peak PACU discharge rates. Triage of additional monitoring resources to selected patients during this time may reduce morbidity and mortality rates. Important exceptions include the complex patterns of respiratory depression following neuraxial analgesia and among pediatric tonsillectomy patients where the highest risk appears to occur several hours later than for adult patients, with many events happening after hospital discharge.

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Conflicts of interest

There are no conflicts of interest.

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■■ of outstanding interest

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