Perioperative opioids aggravate obstructive breathing in sleep apnea syndrome: mechanisms and alternative anesthesia strategies

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Purpose of review
Opioids induce and increase the severity of most sleep-disordered breathing in all patients, but especially in morbidly obese patients. Discussed herein are the direct impact and mechanisms of opioids on inducing and exacerbating obstructive sleep apnea syndrome in normal and morbidly obese patients.

Recent findings
Respiratory depression is a larger problem than obstructive sleep apnea syndrome during the first night after an opioid anesthesia because of the reduced amount of deep sleep and rapid-eye-movement sleep. Acute tolerance to the analgesic effects of opioids can be observed after one anesthetic opioid dose, although tolerance to the side-effects of opioids develops more slowly. Therefore, it makes sense to avoid all opioids intraoperatively. A recently developed multimodal nonopioid anesthesia method may prevent development of acute tolerance and facilitate postoperative pain management with less opioids and sleep-disordered breathing.

Summary
A multimodal nonopioid anesthesia method avoids the necessity for intraoperative opioids, reduces the need for postoperative opioid use, and improves analgesia with less narcotic.

Keywords
analgesia, anesthesia, obstructive sleep apnea syndrome, opioids

INTRODUCTION
Nausea, vomiting, dizziness, and constipation represent the most common side-effects of opioid use, with a prevalence of around 30%. Sleep-disordered breathing (SDB), such as obstructive sleep apnea syndrome (OSAS), associated with opioids are reported to occur frequently [1], but accurate prevalence data are missing. Is opioid-induced sleep apnea a real clinical problem? Walker et al. [2] described a broad spectrum of SDB under opioids, including obstructive disturbances, central apnea/hypopnea, hypoventilation, irregular respiration, and respiratory drive impairment. If opioids induce or exaggerate OSAS, it is important to understand why this occurs and how to avoid the use of opioids perioperatively while maintaining analgesia.

OPIOIDS AGGRAVATE RESPIRATORY DEPRESSION IN DIFFERENT PATIENT POPULATIONS
Morbidly obese patients, with or without OSAS, experience frequent oxygen desaturation episodes postoperatively after total intravenous anesthesia followed by patient-controlled intravenous analgesia (PCIA) with morphine [3]. These desaturation episodes can indicate obstructive breathing or respiratory depression because of opioids.

Waters et al. [4] found that children with OSAS have respiratory depression compared with age-matched control study participants, when breathing spontaneously under inhalation anesthesia with the upper airway secured.

A small dose of opioids caused additional respiratory depression in children with OSAS, leading to an increased need for respiratory support. This finding shows that children with OSAS have an increased sensitivity to the effect of opioids.

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KEY POINTS

- Opioids induce OSAS and increase its severity.
- Opioid tolerance to analgesia can occur after a single dose.
- Total intravenous opioid-free anesthesia is possible without increased stress reactions.
- Multimodal analgesia and multimodal anesthesia reduce the occurrence of postoperative OSAS.

Most studies have revealed that opioids administered by epidural or intravenous routes depress respiration frequency and depth; however, respiratory depression was more frequent in PCA than in patient-controlled epidural anesthesia [5].

In undisturbed study participants receiving morphine via PCIA after surgery, Drummond et al. [6] found that all patients had abnormal breathing patterns, and 50% of patients had cyclical airway obstruction as measured by changes in chest wall movement. The increase in obstructive breathing occurred in both OSAS and non-OSAS patients; however, the extent and differences between these groups of patients were less documented.

MECHANISMS OF OPIOID-INDUCED SLEEP-DISORDERED BREATHING

Opioid receptors are found on mechanosensory receptors in the airways. Opioids activate laryngeal adductor motor neurons and depress laryngeal abductor and pharyngeal constrictor motor neurons, thereby decreasing upper airway diameter [7**].

In a review of 10 studies, Ehsan et al. [7**] found that opioids increased upper airway obstruction in all studies, but resulted in clinical airway obstruction in only half of the studies. Other anesthetics, like propofol and midazolam, induced and aggravated upper airway obstruction, when combined with opioids. Only ketamine and dexmedetomidine seemed to have minimal effects on upper airway diameter.

Bernards et al. [8] found that oxygen saturation was significantly lower in OSAS patients receiving remifentanil. However, study participants with moderate OSAS had a decrease in obstructive apnea after remifentanil anesthesia during the first night, but experienced increased central apnea. This observation was explained by the fact that remifentanil increased stage 1 sleep, decreased rapid-eye-movement sleep, increased arousal from sleep, and decreased sleep efficiency. The amount of deep sleep and rapid-eye-movement sleep might compensate for the following nights increasing the risk of OSAS, when most patients left already a close observation at the intensive care or hospital.

Although the studies cited in this Cochrane Review were limited, Mason et al. [9**] concluded that significant clinical and statistical decreases in minimum overnight blood oxygen level were observed with remifentanil, zolpidem, and triazolam. Other opioids were not investigated; therefore, the use of any opioid to anesthetize patients with OSAS should be approached with caution and a first night observation might not be sufficient.

Pediatric SDB is often caused by hypertrophy of the tonsils, and is commonly managed by tonsillectomy. In a recent randomized trial, Kelly et al. [10] concluded that post-tonsillectomy morphine use should be limited in all children because it may be unsafe in certain children. Sometimes, fatal or life-threatening events occurred in children with genetic alterations who underwent adenotonsillectomy for obstructive sleep apnea [11].

OPIOID TOLERANCE AND ITS IMPACT ON OBSTRUCTIVE SLEEP APNEA SYNDROME

Long-term use of opioids can be problematic because of the rapid development of profound tolerance to the analgesic effects coupled with the slow development of tolerance to many of the untoward side-effects including SDB. It was already known that short-term opioid infusions with Remifentanil, such as those used for anesthesia, could induce acute tolerance within 90 min, whereas the tolerance to its nonanalgesic effects (e.g., respiratory depression) has not yet developed [12].

Acute tolerance is mediated predominantly by pharmacodynamic mechanisms, manifested as a decreased response following a single administration of the agent. Acute pharmacodynamic tolerance occurs when the response of the receptor diminishes over time [13]. Rivat et al. [14] demonstrated acute tolerance in rats after fentanyl administration at doses used for anesthesia. After recovery from an anesthetic dose of fentanyl, rats had a reduced nociceptive threshold that required more analgesics or opioids, which remained active for more than 1 week. If anesthesia was combined with inflammation (such as after surgery), the hyperalgesia became even stronger for a longer period. However, the tolerance for side-effects developed more slowly. When higher opioid doses were required to maintain analgesia, the incidence of obstructive breathing increases.

Ultra-low dose (0.05 µg/kg) fentanyl administration for up to 2 weeks postoperative anesthesia-induced hyperalgesia, but not analgesia, in rats
This finding indicated that low levels of opioids after opioid anesthesia induced the opposite effect. Therefore, any ability to reduce opioid use postoperatively without avoiding intraoperative opioids will fail. Crivits and Mulier reported in an observational study on 400 patients after laparoscopic gastric bypass, significant less nausea, less cold or shivering, and less pain occurred in the patients receiving total opioid-free anesthesia, when compared with those getting sufentanil anesthesia. There was a significant lower use of piritramide (dipidolor) in the patients receiving opioid-free anesthesia (6 ± 9 mg) compared with the patients receiving sufentanil (16 ± 10 mg) [1].

Opioid reinforcement of central sensitization in inflammatory pain states could be partially prevented by small amounts of N-methyl-D-aspartate receptor blockers like ketamine [15]. Therefore, ketamine at doses of 0.25 mg/kg might be clinically useful in OSAS patients if opioids cannot be excluded perioperatively. At this dose, ketamine has some analgesic properties and limited hallucination effects [15].

Chronic tolerance can be mediated through either pharmacokinetic or pharmacodynamic mechanisms, resulting in a long-term decrease in drug response in the face of constant systemic exposure. Pharmacokinetic tolerance occurs when drug metabolism is altered as a function of time, often because of the drug being an inducer of a metabolic enzyme. In cases where chronic tolerance develops, cross-tolerance within the pharmacologic class also may occur [13]. The third class of acquired tolerance is attributed to learning, either behavioral or conditioned. Behavioral tolerance occurs when an individual learns to function despite repeat exposure to a drug. Alcohol abusers, for example, may not show motor impairment during intoxication because of learned adaptations and awareness of their impairment [13]. When this adaptation fails, as during sleep, the effects and side-effects of intoxication increase in intensity. This could explain why respiratory depression is more frequently seen in patients during sleep.

**METHODS TO AVOID PERIOPERATIVE USE OF OPIOIDS**

Opioids induce or aggravate obstructive breathing in all patients, including patients with OSAS. During anesthesia, an artificial airway or close observation by an anesthesiologist can prevent or treat this problem. Therefore, it was thought that short-acting opioids like remifentanil would be ideal for OSAS patients [16]. However, the increased postoperative pain because of central sensitization by remifentanil requires additional opioid treatment, which increases the risk for SDB. Therefore, it is important to identify methods to reduce the need for intraoperative opioid use first, which then will facilitate the reduction of postoperative opioid use with recently developed methods [17].

An initial approach is to use loco-regional anesthesia alone or in combination with general anesthesia [18**]. In this approach, it is important to avoid any opioid use for general anesthesia. If the loco-regional block works properly, only hypnotics with or without neuromuscular blockers are needed. We have learned to use balanced anesthesia by including opioids to reduce the dose of hypnotic agents, and in cases where the loco-regional block does not work well. In addition, low-dose opioids are frequently added in combination with the loco-regional agent to enhance its effect, although this opioid is absorbed systemic and might induce SDB as well [5]. In addition, nonopioid additives are available, like clonidine, which prolong and intensify the effect of local anesthetics [19].

A second approach is to avoid all opioids during general anesthesia by relying on hypnotics to induce sleep and use drugs that block the autonomic nervous system reaction to pain stimuli. This method was first demonstrated with high doses of α-2 agonists like clonidine [20] and dexmedetomidine [21]. α-2 agonists have direct sedative effects [22], direct analgesic effects [23], and autonomic blocking effects [24]. The autonomic blocking effects are especially required during anesthesia and can be achieved easily with high doses of opioids. High doses of α-2 agonists, like those used in veterinary anesthesia, allow monotherapy without the use of opioids [25]. Veterinary anesthesiologists can use atipamezole to reverse the anesthetic’s effect and prevent long-term sedation postoperatively [26]. Sedation should be avoided in OSAS patients, but this antidote is not available for human clinical use. Therefore, multimodal methods are required during anesthesia to reduce the postoperative sedative effects. Local anesthetics like lidocaine 1.5 mg/kg/h [27], low-dose ketamine 0.1 mg/kg/h [28], and magnesium 10 mg/kg/h [29] can be used intraoperatively to improve the autonomic block and postoperative analgesia, while reducing the need for opioids. Each of these drugs has been shown to reduce the opioid requirement peri and postoperatively. Hofer et al. [21] showed the possibility of opioid-free anesthesia by using only dexmedetomidine; Marc de Kock was the first to combine some of these agents to avoid all opioids perioperatively.

Combining nonopioid drugs improves anesthesia. The minimum alveolar concentration of
sevoflurane was lowest when dexmedetomidine was combined with lidocaine versus each drug alone in an opioid-free anesthesia dog model [30*].

The use of nonopioid analgesics after opioid-free anesthesia is frequently sufficient to deal with postoperative pain. If surgical trauma can be reduced by minimally invasive procedures and anti-inflammatory drug administration, further reduction of analgesics and improved quality of recovery are possible [31]. Local wound infiltration with long-acting local anesthetics is also helpful [32].

Apart from classical nonopioid analgesics like NSAID and paracetamol, low-dose dexmedetomidine at 0.3 μg/kg/h [33] or clonidine 150 μg/day can be given [34]. Lidocaine at 1 mg/kg/h, which is below the sedative threshold, might also be useful. Recently, a large review on the use of peroperative intravenous lidocaine found evidence of early reduction of postoperative pain but not nausea or other recovery parameters. Most patients, however, did not receive opioid-free anesthesia in those studies [35*].

Low-dose ketamine and magnesium provide multimodal analgesia in the postanesthesia care unit and negates the need for opioids or reduces the need to a single low dose of morphine in the early postoperative period [28].

The approach of using opioid-free anesthesia combined with multimodal postoperative analgesia, reduces the need for more additional therapy postoperatively in OSAS patients [36*]. Screening for OSAS and implementing the optimal preoperative treatment independent of surgery is still required. The need to follow OSAS patients with intensive or medium-level care and the use of continuous positive airway pressure masks for several days postoperative in patients who do not need home continuous positive airway pressure masks before anesthesia is now a question if total opioid-free anesthesia and analgesia has been given.

CONCLUSION

Opioids induce and increase the severity of OSAS and other SDB in all patients. After the first opioid dose, acute tolerance to its analgesic effects can occur, whereas tolerance to its side-effects develops more slowly, which can explain the increased obstructive breathing postoperatively in these patients. Screening and treating these at-risk patients with intensive care is difficult and expensive. The use of multimodal anesthesia to avoid intraoperative opioid anesthesia reduces the postoperative necessity for opioids, and improves analgesia.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: ■ of special interest ■■ of outstanding interest


The study is a good overview of the effect of all types of anesthetics, including opioids on pharyngeal airway patency, as seen from the sleep endoscopy viewpoint.

9. Mason M, Gates CJ, Smith I. Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea. Cochrane Database Syst Rev 2015; 14:7. Cochrane overview of all publications regarding the impact of opioids on OSAS. However, the useful papers are very limited, which makes it difficult to draw any conclusions regarding the different opioids.

The paper is an overview of classical postoperative analgesia that avoids opioids, but without any focus on reducing perioperative opioids.


Lidocaine use alone to reduce postoperative opioids was shown to be insufficient or even questionable. The study highlighted the importance of reducing perioperative opioids and combining them with other nonopioids.


The study showed that opioid-free total intravenous anesthesia was possible. This and comparable methods are used today in many centers. The basics are a combination of dexmedetomidine and lidocaine, but many other additives can be used as well to achieve a multimodal regimen, where each drug can be used at a lower dose.