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# Intravenous Infusion of Lidocaine Can Accelerate Postoperative Early Recovery in Patients Undergoing Surgery for Obstructive Sleep Apnea

Authors' Contribution:

Study Design A  
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Funds Collection G

ABCDEFG 1 **Chenglan Xie**

BF 1 **Qiao Wang**

ABCDEFG 2 **De Huai**

1 Department of Anesthesiology, The Affiliated Huaian Hospital of Xuzhou Medical University and Huaian Second People's Hospital, Huaian, Jiangsu, P.R. China

2 Department of Ear, Nose and Throat, The Affiliated Huaian Hospital of Xuzhou Medical University and Huaian Second People's Hospital, Huaian, Jiangsu, P.R. China

**Corresponding Authors:**

Chenglan Xie, e-mail: xiechenglan@163.com, De Huai, e-mail: 18305236699@126.com

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Obstructive sleep apnea (OSA) is defined by intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep. Intermittent and recurrent hypoxia/reoxygenation is the main pathophysiological mechanism of OSA. Its consequences include systemic inflammation, activation of the sympathetic nervous system, and release of oxygen free radicals.

Infusion of intravenous (IV) lidocaine has anti-inflammatory, antihyperalgesic, and analgesic properties, supporting its use as an anesthetic adjuvant. Lidocaine can reduce nociception and/or cardiovascular responses to surgical stress, as well as postoperative pain and/or analgesic requirements. Because of the high prevalence of OSA in obese patients, the use of opioids to manage postoperative pain in that population is often accompanied by the development of adverse respiratory events, such as hypoventilation and hypoxemia. IV infusion of lidocaine has been shown to enhance the quality of early recovery after laparoscopic bariatric and upper airway surgery. However, limited evidence exists regarding its use in patients undergoing surgery for OSA. In addition, whether IV infusion of lidocaine can improve postoperative early recovery in patients undergoing surgery for OSA remains unknown. Therefore, we hypothesized that IV infusion of lidocaine can improve postoperative early recovery in patients undergoing surgery for OSA. Perioperative infusion also may be a promising analgesic adjunct to enhanced recovery after surgery (ERAS) protocols.

**Keywords:** **Infusions, Intravenous • Lidocaine • Sleep Apnea, Obstructive**

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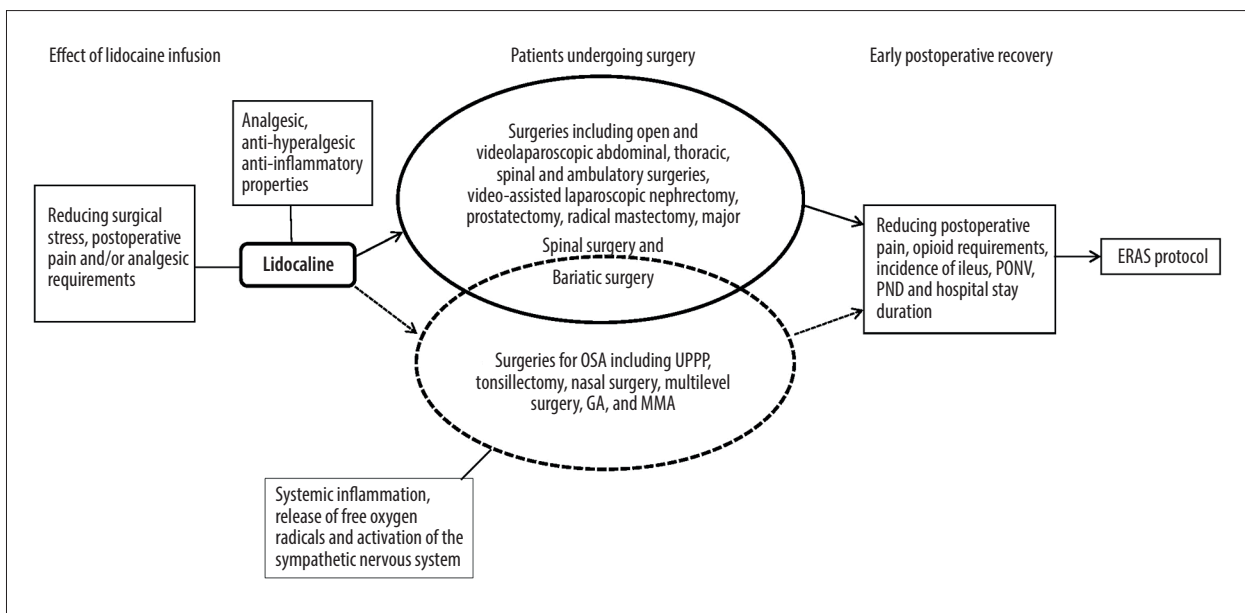
**Background**

The incidence of obstructive sleep apnea (OSA), defined as intermittent and recurrent episodes of partial or complete obstruction of the upper airway during sleep, has been rising throughout the world [1,2]. Untreated OSA is associated with decreased quality of life, increased risk of cardiovascular disease and all-cause mortality, and impaired cognitive function [3]. Continuous positive airway pressure (CPAP) is the first-line therapy for OSA, but it is not always tolerated. Surgeries indicated for OSA have varying degrees of efficacy. Uvulopalatopharyngoplasty (UPPP) is the most common surgical treatment for OSA. Adenotonsillectomy is the first-line surgical therapy for children with OSA. Aside from tracheostomy, maxillomandibular advancement is the most successful surgical intervention for OSA, with outcomes similar to those with CPAP [4].

Pain after surgical procedures for OSA is classified as moderate to severe. Postoperative pain is a noxious stimulus produced by tissue damage caused by surgery, which can result in problems such as sleep disturbance, respiratory adverse effects, cardiovascular adverse effects, impaired gastrointestinal motility, and poor wound healing. In addition to affecting patient recovery, postoperative pain can reduce patient satisfaction and quality of life after surgery. Appropriate control of pain can reduce morbidity, improve surgical results, and decrease hospital costs. Opioids are the mainstay analgesics for moderate as well as severe acute pain. However, use of these drugs can increase incidence of postoperative complications,

including vomiting, respiratory depression, excessive sedation, pruritus, and slowing of gastrointestinal function, as well as urinary retention. Recent data also suggest that extensive use of opioids is associated with hyperalgesia [5]. These opioid-related adverse events (AEs) prevent smooth postoperative early recovery and prolong hospital stays.

Patients with OSA are very sensitive to the respiratory depression caused by opioids [6]. An alternative to opioids is intravenous (IV) infusion of lidocaine, which has antihyperalgesic, anti-inflammatory, and analgesic characteristics that reduce nociception and/or cardiovascular responses to surgical stress, as well as postoperative pain and/or analgesic requirements (Figure 1). Perioperative infusion of lidocaine may be a useful adjunct to enhanced recovery after surgery (ERAS) protocols [7-10]. Although perioperative infusion of the drug also has a significant impact on reducing intraoperative hemodynamic instability and anesthetic requirements, our major focus here is perioperative recovery, including reduction in postoperative pain, opioid-related AEs, and postoperative neurocognitive dysfunction (PND), and shortening of hospital stays. Few studies have examined the effect of IV infusion of lidocaine for OSA surgery. There are only 3 studies available on the topic [11-13]. The first study showed no benefit in adults undergoing tonsillectomy. Another study, despite clearly being underpowered, showed that IV infusion of lidocaine can improve the quality of postoperative early recovery after upper airway surgery, including UPPP. The third study showed that IV infusion of lidocaine decreased postoperative vomiting in children undergoing tonsillectomy. However, it remains unknown



**Figure 1.** Schematic representation of lidocaine infusion in patients undergoing surgery for obstructive sleep apnea. OSA – obstructive sleep apnea, PONV – postoperative nausea and vomiting, PND – postoperative neurocognitive dysfunction, UPPP – uvulopalatopharyngoplasty, MMA – maxillomandibular advancement, GA – genioglossal advancement.

whether IV infusion of lidocaine also can enhance postoperative early recovery in patients undergoing surgery for OSA.

## Hypothesis

Clinical applications of perioperative infusion of lidocaine have been studied in many trials in patients undergoing abdominal procedures, ambulatory procedures, and other types of surgery [12-41]. In these surgical procedures, lidocaine infusion has been shown to reduce postoperative pain, opioid requirements, ileus duration, and incidence of postoperative nausea and vomiting (PONV) and PND, and shorten hospital stays. IV infusion of lidocaine has been shown to enhance the quality of early recovery after laparoscopic bariatric and upper airway surgery [13,17,42,43]. However, a single study showed that IV lidocaine significantly decreased postoperative opioid consumption, but when used after bariatric surgery, it was clinically irrelevant [44]. Continuous ketamine and remifentanyl infusion plus nefopam, paracetamol, and parecoxib before wound closure may partly explain those results. Because of the high incidence of OSA in patients who are obese, the use of opioids in this population is often accompanied by the development of adverse respiratory events such as hypoventilation and hypoxemia. Perioperative infusion of lidocaine may result in a postoperative benefit to patients with OSA, which may be useful for ERAS protocols. Based on the studies described above, we hypothesized that IV infusion of lidocaine can improve postoperative early recovery in patients undergoing surgery for OSA (Figure 1).

## Hypothesis Evaluation

### Clinical Applications

Meta-analyses and systematic reviews have shown that perioperative infusion of lidocaine is effective in reducing postoperative pain, opioid requirements, and duration of ileus, and shortening hospital stays [45-56]. However, an updated review by the Cochrane Collaboration, based on new analysis techniques, resulted in a substantial downgrade in conclusions about perioperative use of IV lidocaine [57]. The quality of evidence on which to base a conclusion about the benefit of the drug's use in this setting was limited, given the heterogeneity of the studies included in the analysis [58].

Infusion of lidocaine has been shown to be of benefit in open and video-assisted laparoscopic abdominal, thoracic, spinal, and ambulatory surgeries [14-21,33,36,38-42,59-64]. Therefore, it can be used in postsurgical recovery protocols, specifically ERAS protocols. Other studies have found evidence of benefit for infusion of lidocaine for conditions involving acute and chronic pain,

including radical prostatectomy, open nephrectomy, major spinal surgery, and radical mastectomy [22,30,31,37,52,59,65-67]. In bariatric surgery and upper airway surgery, infusion of lidocaine reduced opioid consumption, which was associated with improved recovery scores [13,17,42]. Furthermore, OSA is more prevalent in individuals who are morbidly obese than in the general population. Perioperative infusion of lidocaine could be beneficial as an alternative for patients with obesity and OSA because they are fairly sensitive to the respiratory-depressant effects of opioids.

Besides improving analgesia, perioperative infusion of lidocaine decreases the incidence of PONV [12,28,35,39,46,48,50]. This effect has been attributed to an increase in intestinal motility and/or a reduction in postoperative pain and opioid use. Other studies suggest that the reduction is not related to an opioid-sparing effect [12]. Moreover, intraoperative administration of lidocaine decreases the occurrence of early PND in patients undergoing coronary artery bypass and spinal surgery, perhaps because of its neuroprotective effects [21,25,68].

Adenotonsillectomy is the first-line surgical therapy for children with OSA who do not have craniofacial anomalies, and tonsillectomy is one of the surgical therapies for adults with OSA. However, IV infusion of lidocaine had no beneficial effect on postoperative pain in adults undergoing tonsillectomy. The lack of a statistically significant analgesic effect in the abovementioned study might have been due to its small sample size [11]. The study of children undergoing tonsillectomy with and without adenoidectomy showed no difference in terms of opioid consumption during the intraoperative and postoperative periods. The absence of a difference, however, could be explained by the inadequate power of the study to find differences in terms of pain outcomes, because the sample size calculation was based on postoperative vomiting [12]. Our study showed that IV infusion of lidocaine can improve the quality of early postoperative recovery from upper airway surgery, including UPPP [13]. Even if the sample size was calculated based on postoperative recovery quality, the number of patients with OSA was clearly underpowered to show statistical differences.

### Safety and Protocol for Administration

Toxicity from perioperative lidocaine infusion is extremely uncommon. Perioral paresthesia, metallic taste, slurred speech, diplopia, light-headedness, tinnitus, confusion, agitation, muscular spasms, and seizures have been reported with plasma concentrations of lidocaine higher than 5 to 8 µg/mL [7,8,69]. A 55-year-old man with well-controlled HIV who was on highly active antiretroviral therapy was given 1 mg/kg/h of IV lidocaine for postoperative pain. He experienced tachycardia, hypertension, and oxygen desaturation on postoperative Day 2

because of a significant pharmacokinetic interaction between the lidocaine and his HIV medications [69]. Carabona et al measured serum concentrations of lidocaine in patients undergoing bariatric surgery. Lidocaine dosage was based on adjusted body weight (ideal body weight+0.4×[current bodyweight–ideal body weight]). Patients received a 1.5 mg/kg IV bolus of lidocaine over 10 minutes (with a maximal dose of 100 mg) after anesthesia induction, followed by continuous infusion of 2 mg/kg/h throughout the operation. The rate of lidocaine infusion was reduced to 1 mg/kg/h until discharge from the recovery room. The study showed that serum concentrations of lidocaine never exceeded 5 µg/mL and the median serum concentration was 1.45 µg/mL (range, 0.98–1.88 µg/mL) during bariatric surgery [70]. In addition, no ideal protocol has been established for administration of systemic lidocaine. When lidocaine is administered as a 1 mg/kg bolus following continuous infusion of 2 mg/kg/h, plasma concentrations are well below the toxic level (5 µg/mL) even after 1 day [9]. Thus, recommended lidocaine doses in the perioperative period are 1 to 2 mg/kg as an initial bolus, followed by continuous infusion of 1 to 2 mg/kg/h and infusion termination at the end of the post-anesthesia care unit (PACU) stay because of the lack of clear benefit of prolonged infusion beyond that [7,9,46,71]. Monitoring of lidocaine levels also can be considered in patients who are at increased risk of lidocaine toxicity, have abnormal kidney or liver functions, or who cannot communicate about symptoms of lidocaine toxicity. Treatment of systemic lidocaine toxicity has been described and involves combining measures for symptom control, such as oxygen and benzodiazepines, with lipid emulsion injection [72].

### Mechanisms of Action

Lidocaine is an amide-based local anesthetic with antihyperalgesic, analgesic, and anti-inflammatory characteristics. The drug's analgesic effects are considered to be mediated via suppressing spontaneous impulses generated from injured nerve fibers as well as the proximal dorsal root ganglion. This happens through inhibiting sodium channels and G-protein-coupled and N-methyl-D-aspartate receptors [7,8,73,74]. Many studies have demonstrated that perioperative lidocaine infusion is very efficient while underscoring that its clinical efficiency may differ, based on the surgical process. Nevertheless, no apparent mechanistic rationale exists for why lidocaine efficiency would vary from what has been observed in, for example, gastrointestinal surgery. Blood levels of inflammatory

mediators have been shown to be higher after gastrointestinal surgery than after less invasive procedures. Therefore, perioperative infusion of lidocaine would be less efficient for processes, including abdominal hysterectomy, total hip arthroplasty, and laparoscopic renal surgery, which are probably less invasive because they are associated with a relatively low degree of inflammation [9,75–77]. Therefore, the difference in effectiveness of lidocaine may be due, in part, to the drug's anti-inflammatory properties. Systemic lidocaine significantly attenuates plasma levels of complement and proinflammatory cytokines such as interleukin (IL)-6, IL-8, and IL-1 receptor antagonist (IL-1RA) at the end of surgery and up to 72 hours after the procedure [62,78]. The anti-inflammatory effects of lidocaine are attributable to neural transmission blockade with tissue injury, which leads to neurogenic inflammation attenuation and activation of the intrinsic anti-inflammatory pathway. Lidocaine inhibits migration and release of lysosomal enzymes and granulocytes, which leads to reduced release of anti-inflammatory and proinflammatory cytokines, thereby promoting peripheral and central sensitization suppression and resulting in the hypothetical antihyperalgesic effect [45].

Besides its anti-inflammatory properties, lidocaine is a scavenger of reactive oxygen species and can inhibit the sympathetic response to surgery [73,79,80]. The pathophysiological consequences of intermittent hypoxia in OSA are systemic inflammation, release of oxygen free radicals, and activation of the sympathetic nervous system [6]. Therefore, perioperative infusion of lidocaine may be effective in improving postoperative early recovery in patients with OSA.

### Conclusions

Perioperative infusion of lidocaine can improve postoperative early recovery by reducing postoperative pain and complications, shortening hospital stays, and enhancing patient satisfaction without compromising safety. Thus, it can be considered in ERAS protocols for patients undergoing OSA surgery. More studies are necessary to establish the optimum dose, timing, and duration of lidocaine infusion in this setting.

### Conflicts of Interest

None.



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