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CLINICAL TRIAL REPORT

Effect of Esketamine on Perioperative Inflammatory Factors and Postoperative Analgesic Outcomes in Patients with Obstructive Sleep Apnea Syndrome: A Randomized Controlled Trial

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Purpose: The effect of esketamine on perioperative inflammatory factors and postoperative analgesic outcomes in patients with Obstructive sleep apnea syndrome (OSAS) remains unclear. This trial assesses whether 0.25 mg · kg^{-} esketamine during general anesthesia can reduce the inflammatory level and relieve postoperative pain in OSAS patients.

Patients and Methods: 96 adult patients with OSAS underwent palatopharyngoplasty under general anesthesia was included in our research. Following anesthetic introduction, subjects were randomized to either 0.25 mg · kg^{-} esketamine (in 20mL solution; esketamine group) or an equivalent volume of saline (Control group). The primary result was the level of IL-6 and TNF-α before the infusion of esketamine, 40min, 4h, and 24h after the esketamine infusion. Secondary outcomes was NRS scores immediately after tracheal extubation, 4h after the infusion, postoperative day 1 (POD1), postoperative day 2 (POD 2) and postoperative day 7 (POD 7).

Results: The esketamine group demonstrated significantly reduced IL-6 and TNF-α levels at 40 minutes post-infusion (P<0.001) and showed lower the numerical rating scale(NRS)scores with less rescue analgesia immediately after extubation (P<0.001) compared to the control group, despite prolonged extubation and post-anesthesia care unit (PACU) stay (P<0.001). Across POD1-2, the esketamine group maintained reduced NRS scores (P<0.001) and analgesic doses (P=0.021), higher quality of recovery-15 (QoR-15) scores and patient satisfaction scores (P<0.001) relative to control group. It is important to note that the significant differences in inflammatory markers and pain scores between groups were not sustained at the 24-hour assessment and on postoperative day 7, respectively, indicating transient effects.

Conclusion: Intraoperative infusion of 0.25 mg·kg^{-} esketamine provided transient suppression of inflammatory responses and reduced early postoperative pain in OSAS patients. However, these benefits were exploratory and time-limited, and must be weighed against prolonged extubation and PACU stay.

Keywords: esketamine, OSAS, IL-6, TNF-α, NRS

Introduction

OSAS represents the most prevalent respiratory sleep disorder, affecting 9% to 39% of adults with disproportionately higher rates among men and elderly populations.[1] This condition manifests through recurrent complete or partial airway collapse, leading to episodic hypopnea and apnea events. The resultant inadequate ventilation produces elevated arterial carbon dioxide levels and chronic intermittent hypoxia (CIH).[2,3] Patients with OSAS have a high incidence of postoperative

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acute pain, because its unique pathophysiological changes, such as hypoxia, oxidative stress, systemic inflammation, and sleep fragmentation, may aggravate acute pain and affect the anti-pain mechanism.[2,4–6] Therefore, the demand for perioperative analgesia in OSAS patients is increasing, but due to these patients' high sensitivity to the analgesics especially opioids,[7,8] the apply of opioids in OSAS patients has more problems when compared to other patients, the increased incidence of respiratory depression and hypoxia significantly increases their perioperative risks.[9,10] Therefore, it is particularly important to find new anesthetics or analgesics that can effectively relieve pain and have low side effects.

Current evidence suggests that hyperalgesia observed in OSAS patients stems from sleep fragmentation, which heightens pain sensitivity while concurrently promoting inflammatory responses and spontaneous nociception.[4,11,12] Hypoxemic episodes further contribute to this pathophysiology by triggering reactive oxygen species formation, substantially upregulating pro-inflammatory cytokine expression, and sensitizing nociceptors.[2] Among these mediators, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) serve as the most extensively characterized and clinically relevant biomarkers.[13,14]

Esketamine, being the S-isomer of ketamine, primarily exerts its anesthetic and analgesic properties by blocking the N-methyl-D-aspartic acid (NMDA) receptors.[15] Experimental evidence from both cellular and animal models demonstrates ketamine's anti-inflammatory properties via microglial suppression.[16–19] Clinical observations in treatment-resistant depression (TRD) further reveal that low-dose ketamine administration attenuates systemic inflammation through downregulation of pro-inflammatory mediators, notably TNF-α and IL-6.[20] Relative to ketamine, esketamine provides effective analgesia with markedly reduced respiratory compromise due to its unique pharmacological profile. The agent elevates circulating catecholamine concentrations, promoting bronchodilation.[21,22] Simultaneously, esketamine enhances CO_2 sensitivity within respiratory control centers, mitigating opioid-associated ventilatory suppression.[23] This advantageous respiratory safety profile renders esketamine particularly suitable for postoperative pain management in OSAS populations.

The purpose of this study is to investigate whether esketamine infusion during general anesthesia can reduce the inflammatory level and relieve postoperative pain in OSAS patients. Although the analgesic properties of esketamine are well-established in general surgery, and prior studies have examined its effect on inflammatory factors in patients undergoing coronary artery bypass grafting and non-cardiac surgeries, its specific impact on the perioperative inflammatory response and its risk-benefit profile in the high-risk, understudied OSAS population remain elusive.[24,25] This study assumes that esketamine can diminishes plasma inflammation and alleviates pain in individuals with OSAS. The main results are the IL-6 and TNF-α plasma concentrations of OSAS patients undergoing general anesthesia, those inflammatory factors were measured before, 40min after, 4h after and 24h after the infusion of esketamine, all the patients were under the same anesthesia scheme. The secondary results included the scores of NRS immediately after tracheal extubation, 4h after the infusion, and POD1, POD2 and POD7. To our knowledge, this is the first randomized controlled trial to evaluate the anti-inflammatory effect and comprehensively assess the trade-offs between analgesic benefits and recovery times of esketamine in this specific surgical population.

In this study, we chose to administer a 0.25 $mg \cdot kg^{-1}$ esketamine dose via infusion within 40 minutes. This decision was based on the fact that most patients with OSAS have a larger body weight. To avoid overdosing, we selected a subanesthetic dose of esketamine.[26] The 40-minute infusion duration was selected to minimize the side effects of esketamine, as previously demonstrated in prior studies.[27] Previous research has shown that the maximum plasma concentration of esketamine can be achieved within 1 to 2 minutes after intravenous injection, with an average decay half-life of roughly 4 hours. Therefore, we chose to measure plasma inflammatory factor levels at 40 minutes, 4 hours, and 24 hours after the infusion, which is consistent with some earlier studies.[20,28] It is worth noting that firstly, the single low-dose (0.25 $mg \cdot kg^{-1}$) and short intraoperative infusion regimen was chosen based on preliminary safety data in a high-risk OSAS population, prioritizing hemodynamic stability and minimizing psychomimetic side effects. However, this design inherently limits our ability to assess the impact of different dosing strategies or prolonged exposure on the durability of the anti-inflammatory and analgesic effects. Consequently, the transient nature of the benefits observed was an anticipated outcome of this specific intervention. Secondly, our study was not powered to detect differences in long-term outcomes beyond the immediate postoperative period (eg, POD7 and beyond), as the primary focus was on the early inflammatory and pain responses. Therefore, the lack of persistent benefit at later time points is a recognized limitation of the current study design.

Materials and Methods

Ethical Considerations

This single-center, double-blind, randomized controlled trial occurred at the First Affiliated Hospital of Zhengzhou University following institutional ethics committee approval (2024-KY-0219-002) and prospective registration (ChiCTR2400091876, https://www.chictr.org.cn/bin/project/edit?pid=242552, principal investigator: Jing Liu, registered November 5, 2024). The trial protocol is provided in Supplement Material 1. The research followed CONSORT standards, and the trial was conducted in accordance with the ethical standards of the Declaration of Helsinki. Signed consent was secured from each participant a minimum of 24 hours before data gathering and the procedure.

Study Design and Participants

Adults aged 18 to 70 years with OSAS undergoing palatopharyngoplasty and ASA physical status I–III were eligible. Exclusions comprised active infection, severe cardiopulmonary disease, significant neuropsychiatric disorders or cognitive impairment, recent steroid or NSAID use (within 30 days), esketamine contraindications or allergy, and poorly managed high blood pressure (SBP >180 mmHg or DBP >110 mmHg).

Randomization and Blinding

Randomization employed 1:1 block allocation (block size=4) using the R package "blockrand," performed by an independent investigator. Sealed opaque envelopes were opened preoperatively by anesthesia personnel blinded to enrollment, management, and assessment procedures. Subjects were administered esketamine 0.25 mg · kg^{-1} (Jiangsu Hengrui Pharmaceutical Co Ltd) or matching saline placebo in identical 20-mL syringes, with weight-based dosing calculations. A study nurse prepared syringes for anesthesiologist administration, with blinding maintained for all participants, assessors, and clinical personnel throughout the trial.

Anesthesia Protocol

All patients received standardized perioperative management without pharmacological premedication. Intraoperative monitoring included standard ASA parameters (electrocardiography, noninvasive blood pressure monitoring, capnography, pulse oximetry measurement, and bispectral index). Arterial cannulation under local anesthesia enabled continuous arterial blood pressure and mean arterial pressure assessment. Anesthetic induction was achieved using etomidate (0.2 mg · kg^{-1}), alfentanil (40–50 μg · kg^{-1}), and rocuronium (0.7–1.0 mg · kg^{-1}) to enable endotracheal intubation. Mechanical ventilation was initiated using 8–10 mL·kg-1 tidal volumes and 10–12 breaths·min-1 respiratory frequency. Following induction, participants received either esketamine 0.25 mg · kg^{-1} or equivalent volumes of normal saline (both diluted to 20 mL) via continuous infusion over 40 minutes. Maintenance anesthesia comprised remifentanil 0.1–0.2 μg · kg^{-1} · min^{-1}, propofol 4–12 mg · kg^{-1} · h^{-1}, desflurane 3% in oxygen 50% at 2 L · min^{-1}, with intermittent rocuronium administration. Drug infusions were titrated to maintain hemodynamics within 20% of baseline values and BIS 40–60. Hemodynamic management included atropine 0.5 mg for bradycardia below 50 beats · min^{-1} and ephedrine or phenylephrine for blood pressure decreases exceeding 20% from baseline. Prophylaxis included 2 g propacetamol and 0.25 mg palonosetron given 30 minutes before case completion.

Postoperatively, anesthetic agents were discontinued and patients were transferred to the PACU while intubated. Neuromuscular reversal with neostigmine 0.3 mg · kg^{-1} and atropine was administered based on clinical assessment. Extubation occurred following complete recovery of consciousness and muscle strength. Following extubation, patients with NRS pain scores or agitation scores ≥4 were administered intravenous oxycodone 0.1 mg · kg^{-1}. PACU monitoring continued until Steward recovery scores reached ≥4, at which point ward transfer was permitted. Subsequent pain management in the ward involved propacetamol 2 g for NRS scores ≥4.

Outcome Measurements, Blood Samples Collection and Testing

Blood samples were collected from the arterial puncture catheter at four time points (before the infusion of esketamine, 40min after the infusion, 4h after the infusion and 24h after the infusion), and all blood samples were collected by 10 mL

EDTA vacuum extractor. Samples underwent immediate centrifugation at 3000 rpm for 10 minutes at a temperature of 4°C. Plasma samples were kept at −80°C prior to measuring IL-6 and TNF-α levels via ELISA.

The primary outcome was the patients' serum levels of IL-6 and TNF-α at the four time points mentioned above. Additional assessments included:

- Pain assessment using the NRS scores immediately after tracheal extubation, 4h after the infusion, and on POD1, POD2 and POD7. QoR-15 scores, the Hospital Anxiety and Depression Scale (HADS) scores and the Epworth Sleepiness Scale (ESS) scores on the day before surgery, POD1, POD2 and POD7.
- Extubation time, PACU length of stay, and RASS scores assessed at 15-minute intervals for one hour following extubation.
- Rescue analgesia and antiemetics were provided when clinically indicated.
- Postoperative nausea and vomiting were assessed during PACU recovery.
- MAP and heart rate were continuously monitored using an anesthesia information system (Docare V5.0, Suzhou Medicalsystem Technology, Suzhou, China) at one-minute intervals, with data recorded at predetermined time-points: pre-induction (T1), immediate tracheal intubation (T2), anesthesia completion (T3), and post-extubation period (T4).Patient satisfaction scores.
- Esketamine-related adverse events were documented, including gastrointestinal effects (nausea, vomiting), neurological symptoms (hallucinations, nightmares, disorientation, dizziness, blurred vision), and cardiopulmonary complications (excessive sedation, respiratory depression).
- Intraoperative hemodynamic complications were monitored, including hypotension, hypertension, bradycardia, and tachycardia.

Sample Size Calculation

In this study, PASS 15.0 was employed to determine the projected sample size, utilizing data from our preliminary study (unpublished data, n = 12). The mean difference in IL-6 levels between 40 min after infusion and baseline was −0.63 pg · mL^{-1} in the esketamine group (group E: 0.25 mg · kg^{-1} within 40 minutes) and 0.14 pg · mL^{-1} in the control group (group C: the same amount of normal saline within 40 minutes), and the standard deviation (sd) was 1.04 and 1.42 respectively. Assuming that α is 0.05, β is 0.2, and the withdrawal rate is 10%, each group needs 48 patients. Finally, this study needs to recruit 96 patients.

Statistical Analysis

Statistical normality was evaluated through the Shapiro–Wilk method. Continuous data are displayed in terms of mean (SD) or median (IQR), while categorical data are shown as number (%), based on distribution. A linear mixed-effects model was fitted to the repeated measures data. The model specified an unstructured covariance structure, included subject identification as a random intercept, and treated time, group, and their interaction as fixed effects. Significant interactions underwent post-hoc pairwise comparisons with Bonferroni adjustment for multiple testing. Missing data were accommodated within the mixed-effects framework. Between-group comparisons used Student's *t*-test or Mann–Whitney *U*-test for parametric and nonparametric data, respectively. Confidence intervals (95%) were estimated using the Hodges-Lehmann method. Categorical data employed χ^2 or Fisher's exact tests for comparison; ordinal variables utilized Wilcoxon rank-sum analysis. Primary findings are presented along with 95% confidence ranges. An observed P-value under 0.05 signals statistical significance. The statistical computations were executed on RStudio 4.3.1 (RStudio, located in Boston, Massachusetts).

Results

Between November 5, 2024, and April 1, 2025, 120 individuals were screened; 12 met exclusion criteria and 12 declined participation. The remaining 96 participants underwent randomization to esketamine or control groups (48 per group). Two subjects were subsequently withdrawn due to consent revocation or incomplete follow-up, yielding a final cohort of 94 participants (47 esketamine, 47 control; Figure 1).

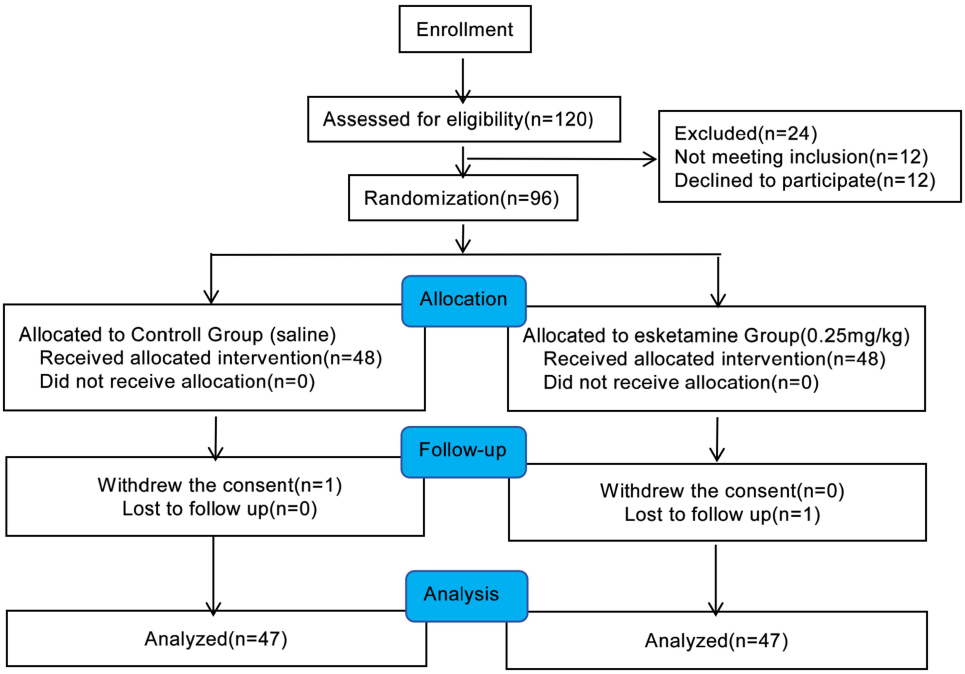

Figure 1 CONSORT flow diagram.
Abbreviations: CONSORT, Consolidated Standards of Reporting Trials.

Patient Demographics and Clinical Characteristics

Baseline characteristics including demographics (age, height, weight, BMI, sex, ethnicity), ASA status, educational level, smoking history, and comorbidities (coronary artery disease, hypertension, stroke) were comparable between groups (Table 1). It is worth mentioning that although 2 patients in the control group had a history of stroke, the patients are not in the acute or subacute stages of the stroke.

Table 1 Patient Demographic Characteristics Among the Two Groups

	Esketamine (n =47)	Control (n =47)	*P-value*
Age (yr), mean (SD)	41.1 (10.0)	41.1 (13.7)	0.980
Height (cm), mean (SD)	172.0 (7.7)	171.7 (7.4)	0.828
Weight (kg), Median [IQR]	88.0 [76.0, 95.0]	80.0 [75.0, 97.5]	0.535
BMI (kg · m $^{-2}$), Median [IQR]	29.1 [26.3, 31.9]	28.3 [26.6, 31.2]	0.623
Sex, n (%), male	42 (89.4)	42 (89.4)	>0.999
Nation, n (%), Han Chinese	47 (100.0)	46 (97.9)	>0.999
ASA physical status, n (%)			0.401
I	0	0	
II	26 (55.3)	30 (63.8)	
III	21 (44.7)	17 (36.2)	
Education, n (%)			0.582
Illiteracy	6 (12.8)	6 (12.8)	
Primary school	15 (31.9)	21 (44.7)	
High school	14 (29.8)	12 (25.5)	
College education and above	12 (25.5)	8 (17.0)	
Smoking, n (%), yes	17 (36.2)	18 (38.3)	0.831
Coronary artery disease, n (%), yes	0 (0.0)	3 (6.4)	0.241
Hypertension, n (%), yes	20 (42.6)	15 (31.9)	0.286
Stroke history, n (%), yes	0 (0.0)	2 (4.3)	0.475

Note: Data are presented as mean ±SD, median with IQR, or number (percentage).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

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Clinical Characteristics and Outcomes

Perioperative characteristics and clinical outcomes were analyzed between groups, including intraoperative anesthetic dosage, anesthesia duration, operation duration, fluids infusion, blood loss, use of intraoperative vasoactive drugs, incidence of PONV, incidence of postoperative agitation, and incidence of antiemesis. No significant differences were found between the two groups in these parameters (all $P>0.05$; Table 2). However, the esketamine group demonstrated significantly longer extubation time (48.0 [43.0, 53.0] vs 32.0 [29.0, 35.0], $P<0.001$) and PACU stay compared to the control group (70.0 [65.0, 77.0] vs 64.0 [60.0, 69.0], $P<0.001$). Conversely, the esketamine group showed relatively lower NRS scores immediately after the extubation (3.0 [3.0, 3.0] vs 4.0 [4.0, 4.0], $P<0.001$), reduced rescue analgesic doses in PACU (0.0 [0.0, 0.0] vs 3.0 [3.0, 3.0], $P<0.001$), and reduced analgesic administration rates in the ward compared to the control group (29.8% vs 53.2%, $P=0.021$) (Table 2).

Hemodynamic measurements, including MAP and HR, at four time points (T1: before induction, T2: immediately after tracheal intubation, T3: at the end of anesthesia, T4: immediately after extubation) showed no statistically significant differences between the two groups ($P>0.05$ at each time; Supplemental Figure 1).

The Primary Outcome Measures: Plasma Levels of IL-6 and TNF-α

Following the initiation of surgery and subsequent infusion, plasma concentration levels of IL-6 and TNF-α were elevated from baseline in both groups. However, as the primary outcome of this study, we observed that compared with the control group, the increase of IL-6 (7.89 [6.43, 11.15] vs 11.36 [8.52, 12.75], $P<0.001$) and TNF-α (10.32 [8.47, 13.83] vs 12.83 [10.85, 15.68], $P<0.001$) in the ketamine group was significantly reduced 40 minutes after infusion (Figure 2). This differential inflammatory response suggests that esketamine may exert modulatory effects on surgery-induced proinflammatory cytokine production in the acute perioperative period.

Patients' Postoperative Pain, the Quality of Recovery, Anxiety, Depression and Sleep Comparison

NRS and QoR-15 scores for both groups are showed in Figure 3. The esketamine group demonstrated relatively lower NRS scores immediately after extubation, on POD1 (6.0 [5.0, 7.0] vs 7.0 [7.0, 7.0], $P<0.001$) and POD2 (3.0 [2.0, 3.0] vs 4.0 [3.0, 5.0], $P<0.001$) compared with the control group, while no significant differences were observed at POD7

Table 2 Intraoperative, PACU and General Ward Data

	Esketamine (n =47)	Control (n =47)	*P-value*
Intraoperative data			
Propofol dosage (mg), Median [IQR]	168.0 [124.0, 220.0]	170.0 [120.0, 204.0]	0.722
Remifentanil dosage (ug), Median [IQR]	840.0 [600.0, 1000.0]	860.0 [620.0, 1100.0]	0.498
Anesthesia duration (min), Median [IQR]	86.0 [62.0, 103.0]	80.0 [59.0, 101.0]	0.513
Operation duration (min), Median [IQR]	72.0 [55.0, 92.0]	68.0 [49.0, 90.0]	0.283
Fluids infusion (mL), Median [IQR]	600.0 [500.0, 800.0]	500.0 [400.0, 650.0]	0.099
Blood loss (mL), Median [IQR]	5.0 [5.0, 10.0]	5.0 [5.0, 10.0]	0.731
Vasoactive drugs used, n (%), yes	12 (25.5)	17 (36.2)	0.264
PACU			
Extubation time (min), median [IQR]	48.0 [43.0, 53.0]	32.0 [29.0, 35.0]	<0.001
PACU length of stay (min), median [IQR]	70.0 [65.0, 77.0]	64.0 [60.0, 69.0]	<0.001
NRS immediately after tracheal extubation, median [IQR]	3.0 [3.0, 3.0]	4.0 [4.0, 4.0]	<0.001
PONV (%), Yes	2 (4.3)	2 (4.3)	>0.999
Agitation (%),Yes	3 (6.4)	2 (4.3)	>0.999
Remedial analgesia in PACU (mg), median [IQR]	0.0 [0.0, 0.0]	3.0 [3.0, 3.0]	<0.001
Antiemesis (%), No	2 (4.3)	2 (4.3)	>0.999
Remedial analgesia in ward, n (%), yes	14 (29.8)	25 (53.2)	0.021

Note: Data are presented as mean ±SD, median with IQR, or number (percentage).
Abbreviations: PACU, post-anesthesia care unit; NRS, numerical rating scale; PONV, postoperative nausea and vomiting.

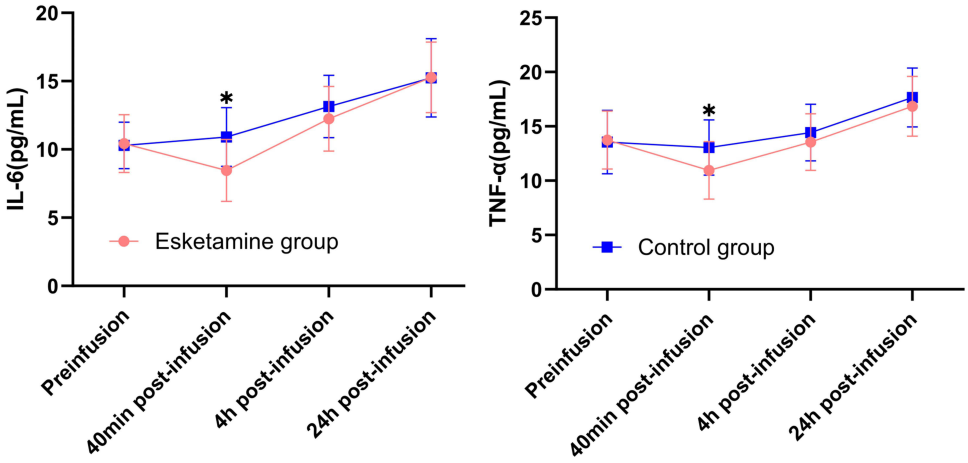

Figure 2 Comparison of inflammatory factors (IL-6, TNF-α). Values represent the estimated means with standard error; analyses were conducted with the use of a mixed-effects mo time, group*time as fixed effects. *P < 0.001.

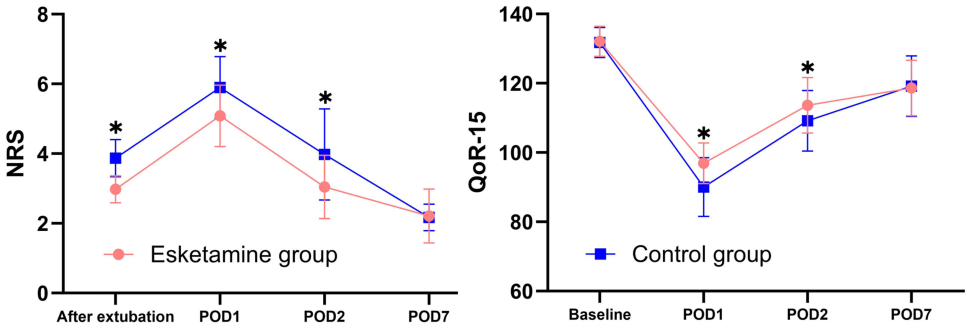

Figure 3 Postoperative pain and quality of recovery. NRS and QoR-15 values represent the estimated means with standard error; analyses were conducted with the use of a mixed-effects mo time, group*time as fixed effects. *P < 0.001.
Abbreviations: NRS, numerical rating scale; QoR-15, quality of recovery-15; POD1, postoperative day 1; POD2, postoperative day 2; POD7, postoperative day 7.

(P=0.718). The QoR-15 scores were notably higher in the esketamine group on POD1 (98.0 [96.0, 100.0] vs 91.0 [88.0, 95.0], P<0.001) and POD2 (115.0 [110.0, 120.0] vs 109.0 [103.0, 111.0], P<0.001) compared with the control group, with no significant differences observed at POD7 (P=0.718). These findings suggest that esketamine reduces early postoperative pain and improves early postoperative recovery quality in patients with OSAS. HADS-A, HADS-D, and ESS scores for both groups are presented in Supplemental Table 1. Postoperative HADS-A, HADS-D, and ESS scores were reduced from baseline in both groups. No significant differences were found between the groups for any of these measures (all P>0.05).

Adverse Events

There were no significant differences in PONV or postoperative agitation occurrence between the two groups (all P > 0.05) (Table 2). Furthermore, there were no significant differences in the incidence of hallucinations, nightmares, dizziness, blurred vision, disorientation, postoperative sleepiness and respiratory depression between the two groups (all P > 0.05) (Table 3), and no notable elevation in blood pressure or heart rate were seen in the esketamine group. (Supplemental Figure 1).

Subgroups Analyses

Figures 4 and 5 display variations in primary outcomes by age, BMI, sex, ASA scale, and smoking status. Cytokine (IL-6, TNF-α) levels within subgroups of each cohort remained stable throughout the study, showing no notable changes.

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Table 3 Adverse Events of Esketamine

	Esketamine (n =47)	Control (n =47)	*P-value*
Hallucinations, n (%)	3 (6.4)	2 (4.3)	>0.999
Nightmares, n (%)	1 (2.1)	1 (2.1)	>0.999
Dizziness, n (%)	4 (8.5)	3 (6.4)	>0.999
Blurred vision, n (%)	3 (6.4)	3 (6.4)	>0.999
Orientation disorder, n (%)	2 (4.3)	1 (2.1)	>0.999
Postoperative sleepiness, n (%)	0	0	1.000
Respiratory depression, n (%)	0	0	1.000

Note: Data are presented as number (percentage). The Pearson chi-squared test or Fisher's exact probability method was used for comparisons between groups.

Discussion

In the present study, we demonstrated that intraoperative esketamine infusion (0.25 mg · kg^{-1} in 40 minutes) significantly reduced inflammatory marker levels, including IL-6 and TNF-α, at 40 minutes post-infusion. However, this anti-inflammatory effect was not sustained at 4 and 24 hours post-infusion, as evidenced by unchanged levels of IL-6 and TNF-α. Esketamine resulted in early improvements in analgesia and recovery quality, while also being associated with an extended duration of stay in the recovery room (Figure 3 and Table 2).

To date, limited trials have explored esketamine's influence on perioperative inflammatory markers in OSAS patients. Esketamine's anti-inflammatory properties may result from NF-κB inhibition, thereby reducing cytokine gene transcription.[29] In addition, esketamine affects the kynurenine pathway and inhibits the deterioration of proinflammatory cytokines.[30,31] In a study by Welters et al,[24] intravenous esketamine administration 1–3 mg · kg^{-1} during cardiac surgery anesthesia induction, followed by continuous infusion 2–3 mg · kg^{-1} · h^{-1} throughout surgery, demonstrated significantly attenuated increases in pro-inflammatory cytokine IL-6 at 6 hours post-aortic cross-clamping compared to the sufentanil group. Additionally, several studies h explored ketamine's impact on inflammatory markers. In Chen et al's research, patients with treatment-resistant depression (TRD) received ketamine 0.5 mg · kg^{-1}, ketamine 0.25 mg · kg^{-1}, or saline infusion within 40min respectively after general anesthesia induction. The results showed that compared with saline group, 0.5 mg · kg^{-1} ketamine group had a lower level of IL-6 at 40 minutes after infusion, and a lower level of TNF-α at 40 and 240 minutes after infusion.[20] However, Cho et al[32] administered intravenous ketamine (0.5 mg·kg^{-1}) to off-pump CABG patients. The results revealed no significant intergroup differences in serum IL-6 and TNF-α concentrations compared to the saline group. To sum up, the anti-inflammatory effect of esketamine is affected by the dosage and infusion time.

In the present study, our study focused specifically on OSAS patients. Although our findings demonstrated significantly attenuated increases in IL-6 and TNF-α at 40 minutes following esketamine infusion (0.25 mg · kg^{-1}) compared to the saline group, this effect was not sustained at 4 and 24 hours post-infusion. This lack of sustained anti-inflammatory action might be attributed to either the absence of continuous esketamine infusion during the perioperative period or the relatively low dosage administered. While the anti-inflammatory effects in our trial were transient, esketamine administration was associated with prolonged extubation time and PACU stay. This suggests that pursuing enhanced anti-inflammatory effects through increased dosage and infusion duration might potentially improve anti-inflammatory outcomes but could lead to prolonged recovery time. Furthermore, it might elevate the likelihood of esketamine-specific negative effects, like unfavorable hemodynamic changes.[33] Therefore, we recommend that larger-scale studies are advised to fully elucidate the clinical significance of the observed cytokine alterations following esketamine application, including outcome variables and complication rates.

Although the anti-inflammatory effect was transient and continuous intraoperative esketamine infusion prolonged the recovery and length of stay in PACU, it is worth noting that our study demonstrated that intraoperative esketamine infusion reduced NRS pain scores immediately after the extubation and on POD1 and POD2, and increased QoR-15 scores on POD1 and POD2, without increasing the incidence of adverse events. However, no significant improvements in pain control and recovery quality were observed on POD7. Esketamine exerts its effects through multiple molecular targets, with its primary mechanism of anesthetic and analgesic actions being non-competitive antagonism of NMDA

	No.of Patients		IL-6 levels, Mean (95% CI)		Between-Group Difference (95% CI)	$P_{interaction}$
	Esketamine	Control	Esketamine	Control		
pre-surgical IL-6						
Age(yr)						0.347
<60	45	44	10.4(6.4-14.5)	10.4(7.1-13.7)	0.0(-0.8-0.8)	
⩾60	2	3	10.2(2.4-18.0)	8.5(6.8-10.2)	1.7(-3.9-7.3)	
BMI(kg m^{-2})						0.114
<28	19	23	9.9(5.7-14.1)	10.5(7.0-14.0)	-0.6(-1.8-0.6)	
⩾28	28	24	10.8(6.8-14.8)	10.1(6.9-13.3)	0.7(-0.3-1.7)	
Sex						0.095
Female	5	5	11.2(8.1-14.3)	9.1(5.8-12.5)	2.1(-0.0-4.1)	
Man	42	42	10.3(6.1-14.6)	10.4(7.1-13.7)	-0.1(-0.9-0.7)	
ASA						0.069
II	26	30	10.3(6.0-14.5)	10.7(7.3-14.1)	-0.4(-1.5-0.6)	
III	21	17	10.6(6.5-14.7)	9.6(6.8-12.3)	1.0(-0.1-2.2)	
Smoking						0.347
No	30	29	10.6(6.4-14.7)	10.1(6.7-13.5)	0.4(-0.6-1.4)	
Yes	17	18	10.2(6.0-14.4)	10.5(7.2-13.9)	-0.4(-1.6-0.9)	
40-min post-ind IL-6 levels						
Age(yr)						0.794
<60	45	44	8.4(4.1-12.8)	10.9(6.7-15.1)	-2.5(-3.4--1.6)	
⩾60	2	3	9.1(1.0-17.3)	11.1(5.6-16.6)	-1.9(-8.5-4.6)	
BMI(kg m^{-2})						0.674
<28	19	23	8.4(3.6-13.2)	10.6(6.3-15.0)	-2.3(-3.7--0.8)	
⩾28	28	24	8.5(4.2-12.8)	11.2(7.1-15.3)	-2.6(-3.8--1.5)	
Sex						0.744
Female	5	5	8.8(4.0-13.7)	10.8(5.4-16.3)	-2.0(-5.3-1.2)	
Man	42	42	8.4(4.0-12.9)	10.9(6.8-15.1)	-2.5(-3.4--1.6)	
ASA						0.176
II	26	30	8.3(4.0-12.5)	11.2(6.8-15.7)	-2.9(-4.1--1.8)	
III	21	17	8.7(4.0-13.4)	10.4(6.7-14.1)	-1.7(-3.0--0.3)	
Smoking						0.804
No	30	29	8.5(3.8-13.1)	10.9(6.6-15.1)	-2.4(-3.5--1.2)	
Yes	17	18	8.4(4.2-12.6)	11.0(6.7-15.3)	-2.6(-4.0--1.2)	
4-h post-ind IL-6 levels						
Age(yr)						0.388
<60	45	44	12.3(7.6-16.9)	13.3(8.8-17.8)	-1.0(-2.0--0.1)	
⩾60	2	3	11.9(5.1-18.7)	11.0(9.5-12.6)	0.9(-4.0-5.7)	
BMI(kg m^{-2})						0.206
<28	19	23	11.7(7.0-16.5)	13.3(8.6-18.1)	-1.6(-3.1--0.1)	
⩾28	28	24	12.6(8.1-17.1)	13.0(8.7-17.3)	-0.4(-1.6-0.9)	
Sex						0.708
Female	5	5	12.2(3.3-21.0)	12.5(8.0-17.1)	-0.4(-4.8-4.1)	
Man	42	42	12.3(8.2-16.3)	13.2(8.7-17.7)	-1.0(-1.9--0.0)	
ASA						0.033
II	26	30	11.8(8.2-15.3)	13.5(8.9-18.2)	-1.7(-2.8--0.7)	
III	21	17	12.8(7.2-18.4)	12.5(8.4-16.5)	0.3(-1.2-1.9)	
Smoking						0.725
No	30	29	12.0(6.5-17.6)	13.0(8.5-17.6)	-1.0(-2.3-0.3)	
Yes	17	18	12.6(10.3-15.0)	13.3(8.8-17.9)	-0.7(-1.9-0.5)	
24-h post-ind IL-6 levels						
Age(yr)						0.882
<60	45	44	15.1(10.2-20.1)	15.0(9.5-20.6)	0.1(-1.0-1.2)	
⩾60	2	3	18.7(16.5-20.9)	18.2(13.8-22.6)	0.5(-2.5-3.5)	
BMI(kg m^{-2})						0.372
<28	19	23	14.6(9.2-19.9)	15.2(9.4-20.9)	-0.6(-2.3-1.1)	
⩾28	28	24	15.8(11.0-20.5)	15.3(9.6-21.0)	0.4(-1.0-1.9)	
Sex						0.702
Female	5	5	15.7(11.5-19.8)	16.3(10.7-21.9)	-0.6(-3.7-2.5)	
Man	42	42	15.2(10.0-20.4)	15.1(9.5-20.8)	0.1(-1.1-1.3)	
ASA						0.106
II	26	30	14.3(9.5-19.2)	15.2(9.5-20.8)	-0.8(-2.2-0.6)	
III	21	17	16.4(12.0-20.8)	15.4(9.6-21.2)	1.0(-0.7-2.7)	
Smoking						0.292
No	30	29	15.2(10.0-20.4)	15.6(9.8-21.4)	-0.4(-1.9-1.0)	
Yes	17	18	15.4(10.6-20.3)	14.6(9.3-20.0)	0.8(-0.9-2.5)	

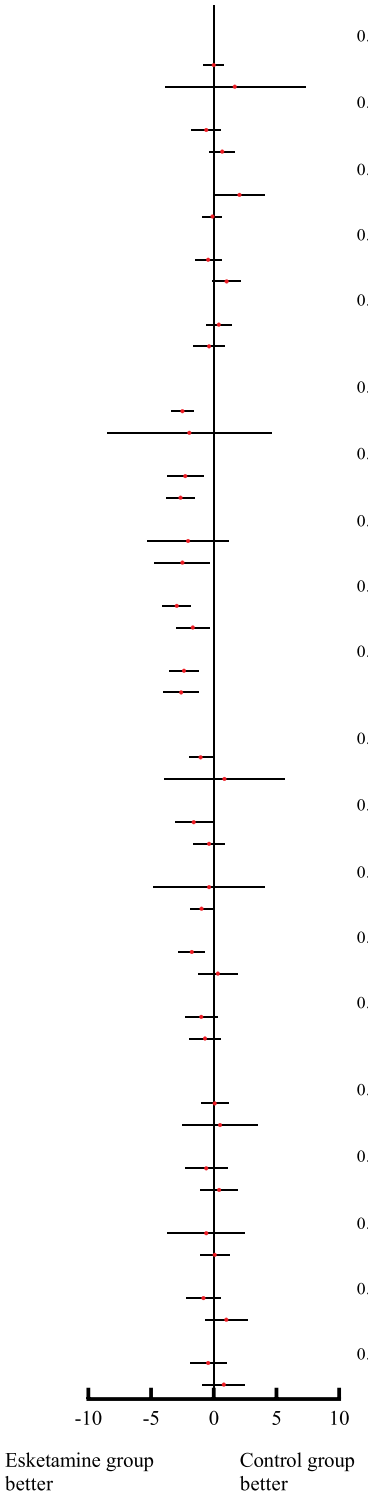

Figure 4 Changes in the IL-6 levels by subgroups of age, BMI, sex, ASA, smoking. Analyses are conducted with the use of a mixed-effects model, with group, group*time as fixed effects.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

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	No.of Patients		TNF-α levels, Mean (95% CI)		Between-Group Difference (95% CI)	$P_{interaction}$
	Esketamine	Control	Esketamine	Control		
pre-surgical TNF-α						
Age(yr)						
<60	45	44	13.8(8.4-19.1)	13.5(7.6-19.3)	0.3(-0.9-1.5)	0.481
⩾60	2	3	13.1(12.4-13.8)	14.7(10.6-18.8)	-1.6(-4.0-0.9)	
BMI(kg m^{-2})						
<28	19	23	12.7(8.0-17.4)	13.5(7.5-19.5)	-0.8(-2.4-0.9)	0.174
⩾28	28	24	14.4(9.2-19.6)	13.6(8.0-19.2)	0.8(-0.7-2.3)	
Sex						
Female	5	5	13.5(10.6-16.5)	12.3(5.3-19.3)	1.2(-2.2-4.6)	0.541
Man	42	42	13.8(8.3-19.2)	13.7(8.1-19.3)	0.1(-1.1-1.3)	
ASA						
II	26	30	13.3(7.6-19.0)	13.8(8.1-19.4)	-0.5(-2.0-1.0)	0.172
III	21	17	14.3(9.9-18.7)	13.2(7.2-19.1)	1.1(-0.6-2.9)	
Smoking						
No	30	29	13.3(8.1-18.6)	12.8(7.0-18.6)	0.5(-0.9-1.9)	0.54
Yes	17	18	14.5(9.5-19.5)	14.7(9.7-19.7)	-0.2(-1.9-1.5)	
40-min post-ind TNF-α levels						
Age(yr)						
<60	45	44	11.1(5.9-16.2)	13.0(8.0-18.0)	-1.9(-3.0--0.9)	0.15
⩾60	2	3	8.4(7.5-9.4)	13.9(8.1-19.7)	-5.5(-8.8--2.1)	
BMI(kg m^{-2})						
<28	19	23	10.4(5.7-15.1)	13.0(7.5-18.6)	-2.6(-4.2--1.0)	0.456
⩾28	28	24	11.3(5.8-16.7)	13.1(8.6-17.6)	-1.8(-3.2--0.4)	
Sex						
Female	5	5	11.8(5.4-18.3)	13.0(6.9-19.1)	-1.2(-5.1-2.8)	0.559
Man	42	42	10.8(5.8-15.9)	13.0(8.1-18.0)	-2.2(-3.3--1.1)	
ASA						
II	26	30	10.8(5.6-16.0)	13.1(7.7-18.5)	-2.3(-3.7--0.9)	0.655
III	21	17	11.1(5.9-16.3)	12.9(8.7-17.2)	-1.8(-3.4--0.3)	
Smoking						
No	30	29	10.8(5.4-16.1)	12.4(7.5-17.3)	-1.6(-3.0--0.3)	0.29
Yes	17	18	11.2(6.3-16.2)	14.1(9.4-18.7)	-2.8(-4.4--1.2)	
4-h post-ind TNF-α levels						
Age(yr)						
<60	45	44	13.6(8.5-18.8)	14.3(9.2-19.5)	-0.7(-1.8-0.4)	0.173
⩾60	2	3	11.6(10.7-12.4)	15.6(11.5-19.7)	-4.1(-6.5--1.6)	
BMI(kg m^{-2})						
<28	19	23	13.2(8.5-18.0)	14.1(8.7-19.6)	-0.9(-2.5-0.7)	0.992
⩾28	28	24	13.8(8.4-19.2)	14.7(9.9-19.5)	-0.9(-2.3-0.5)	
Sex						
Female	5	5	14.4(8.9-19.8)	13.6(6.7-20.5)	0.8(-3.2-4.7)	0.302
Man	42	42	13.4(8.3-18.6)	14.5(9.6-19.5)	-1.1(-2.2-0.0)	
ASA						
II	26	30	13.4(8.3-18.5)	14.4(9.2-19.6)	-1.0(-2.4-0.4)	0.763
III	21	17	13.7(8.5-19.0)	14.4(9.3-19.6)	-0.7(-2.4-1.0)	
Smoking						
No	30	29	13.3(8.1-18.5)	13.7(8.5-18.9)	-0.4(-1.8-0.9)	0.286
Yes	17	18	14.0(8.9-19.0)	15.6(11.3-19.8)	-1.6(-3.2--0.0)	
24-h post-ind TNF-α levels						
Age(yr)						
<60	45	44	16.9(11.5-22.4)	17.5(12.3-22.8)	-0.6(-1.7-0.5)	0.135
⩾60	2	3	14.8(13.9-15.8)	19.3(13.5-25.1)	-4.5(-7.8--1.1)	
BMI(kg m^{-2})						
<28	19	23	16.4(11.2-21.6)	17.5(12.0-22.9)	-1.0(-2.7-0.6)	0.792
⩾28	28	24	17.1(11.6-22.6)	17.9(12.6-23.1)	-0.7(-2.2-0.8)	
Sex						
Female	5	5	17.6(11.2-24.1)	16.8(10.7-23.0)	0.8(-3.2-4.8)	0.324
Man	42	42	16.8(11.5-22.1)	17.8(12.5-23.0)	-1.0(-2.2-0.1)	
ASA						
II	26	30	16.6(11.4-21.7)	17.8(12.3-23.2)	-1.2(-2.6-0.2)	0.395
III	21	17	17.2(11.5-22.9)	17.4(12.3-22.6)	-0.2(-2.0-1.5)	
Smoking						
No	30	29	16.6(11.3-21.9)	17.0(11.7-22.2)	-0.4(-1.7-1.0)	0.324
Yes	17	18	17.3(11.7-22.9)	18.8(14.0-23.5)	-1.5(-3.2-0.3)	

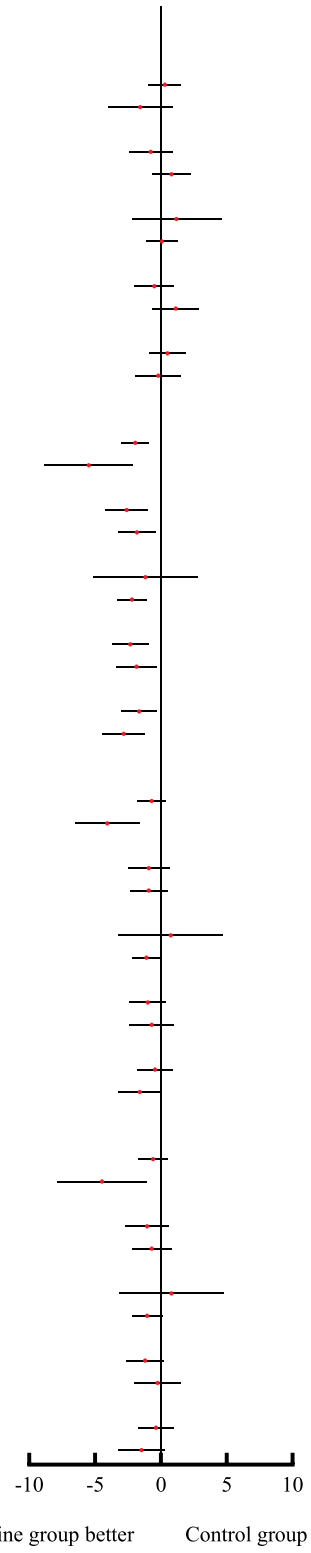

Figure 5 Changes in the TNF-α levels by subgroups of age, BMI, sex, ASA, smoking. Analyses are conducted with the use of a mixed-effects model, with group, group*time as fixed effects.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

receptors. Additionally, esketamine interacts with opioid receptors, including kappa and mu receptors,[34] and exhibits inhibitory effects on central sensitization,[35] all of which contribute to its analgesic properties. And the improvement in recovery quality can be linked to the reduction in pain. Several earlier studies support these findings. Xiang Cheng et al[36] found that perioperative esketamine improved postoperative analgesia at 24 and 48 hours, as well as recovery quality at 48 hours in patients undergoing thoracoscopic surgery. Min Zhu et al[37] discovered that esketamine improved QoR-15 scores on POD1 and POD3, and NRS pain scores within 24 hours postoperatively in patients receiving modified radical mastectomy. Collectively, these results suggest that the use of esketamine during surgery has a beneficial effect on improving postoperative pain and recovery quality.

Sleep fragmentation in OSAS patients may induce preoperative hyperalgesia,[11] potentially affecting baseline pain sensitivity between groups. One limitation of our study design was the absence of preoperative baseline pain threshold assessment. Nevertheless, through rigorous randomization protocols, we can reasonably assume that this potential confounder was statistically balanced between the groups. Improved postoperative pain relief contributes to enhanced recovery quality. Notably, patients receiving esketamine treatment showed no increase in postoperative respiratory adverse events compared to the control group, indicating the safe application of esketaminet in perioperative pain management in this patient population.

To quantitatively assess the clinical trade-off, we calculated the number needed to treat (NNT) for an early improvement in recovery quality and the number needed to harm (NNH) for a prolonged PACU stay (Supplemental Table 2). The analysis yielded an NNT of 7.874 and an NNH of 5.882, resulting in a benefit-to-risk ratio (NNT/NNH) of 1.339. This ratio, which is greater than 1, indicates that the likelihood of achieving a clinically meaningful improvement in recovery quality with esketamine outweighs the risk of prolonged PACU stay by 33.9%. Therefore, despite the observed delay in recovery room discharge, the net clinical benefit of intraoperative esketamine in enhancing early recovery quality appears to be positive.

This study has several limitations that require recognition. Firstly, the single-center design and limited sample size (n=96) may restrict generalizability. Secondly, our analysis is limited to the levels of IL-6 and TNF-α within 24 hours. Further research is also warranted on other cytokines, including IL-1β and IL-8, as well as the factor levels between 48 to 72 hours post-surgery. Finally, the optimal effective dosage and regimen of esketamine administration remain controversial. Future studies should focus on the following directions. First, esketamine may enhance multimodal analgesia in OSAS patients. Second, continuous infusion or combination therapy regimens of esketamine should be explored to prolong the anti-inflammatory effects. Furthermore, further studies with extended follow-up periods (>7 days) are required to examine its effects on pain chronification and sleep quality. In line with the current findings, future research should also incorporate more frequent biomarker assessments extending to at least 72 hours to precisely map the time course of esketamine's biological effects.

Conclusions

This study provides preliminary evidence that intraoperative infusion of esketamine (0.25 $mg \cdot kg^{-1}$) is associated with short-lived suppression of inflammatory cytokine levels and a reduction in early postoperative pain in OSAS patients. These potential benefits, however, were accompanied by operational downsides, namely prolonged extubation time and PACU length of stay. The results suggest that esketamine could be further investigated as a component of multimodal analgesia for OSAS patients, but its clinical utility requires confirmation through future, multi-center trials with extended follow-up and optimized dosing regimens to better define the risk-benefit profile.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

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Disclosure

The authors declare no conflict of interest.

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