Effect of esketamine on opioid consumption and postoperative pain in thyroidectomy: a randomized controlled trial

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Abstract

Aim: Thyroidectomy is frequently associated with substantial postoperative pain. Esketamine, an N-methyl-D-aspartate receptor antagonist, has been demonstrated to be effective in multiple analgesia. We hypothesized that intraoperative administration of esketamine may reduce perioperative opioid consumption and postoperative pain in patients undergoing thyroidectomy. Methods: Sixty patients undergoing thyroidectomy were randomly assigned to two groups. Patients in the saline group received a pre-incisional intravenous bolus of 0.9% NaCl followed by an intraoperative infusion of 0.9% NaCl; patients in the esketamine group received a pre-incisional intravenous bolus of esketamine (0.5 mg kg-1) followed by an intraoperative infusion of esketamine (0.24 mg kg-1 h-1). The primary outcome was perioperative sufentanil consumption. The postoperative pain, sleep quality, and adverse events during the first postoperative 24 h were also evaluated. Results: Patients in the esketamine group consumed significantly less sufentanil than those in the saline group (24.6 ± 3.1 μg vs. 33.7 ± 5.1 μg, mean difference, 9.1; 95% confidence interval, 6.9–11.3, P <0.001). Postoperative pain scores were significantly lower in the esketamine group than those in the saline group during the first 24 h postoperatively (P <0.05). Patients receiving esketamine experienced higher sleep quality than those in the saline group during surgical night (P = 0.043). There were no significant differences in adverse events between the two groups. Conclusion: Intraoperative administration of esketamine reduces perioperative sufentanil consumption and postoperative pain without increasing adverse events in patients undergoing thyroidectomy. The development of combined anesthesia regimens, including esketamine, may foster strategies for pain management during thyroidectomy.

Title page

Title

Effect of esketamine on opioid consumption and postoperative pain in thyroidectomy: a randomized controlled trial

Running Head :

Esketamine for analgesia in thyroidectomy

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The authors declare that there is no conflict of interest.

Ethics approval statement:

This prospective randomized controlled trial was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (approval no.: YX2021-106).

Patient consent statement:

Written consent was obtained from all patients.

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Clinical trial registration

The study was prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2100053459) on November 21, 2021.

Principal Investigator statement:

The authors confirm that the Principal Investigator for this paper is Yun Wu and that she had direct clinical responsibility for patients.

Key words

S-ketamine, thyroidectomy, opioid, postoperative pain, multimodal analgesia

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What is already known about this subject:

1. Thyroidectomy is frequently associated with substantial postoperative pain.
2. Esketamine has been demonstrated to be effective in multiple analgesia.
3. Co-administration of anesthetics could improve the efficacy of analgesia and reduce the incidences of adverse events caused by a single drug.

What this study adds:

1. Intraoperative administration of esketamine reduced the perioperative opioid consumption in patients undergoing thyroidectomy.
2. Intraoperative administration of esketamine reduced pain intensity after thyroidectomy.
3. Intraoperative administration of esketamine improved sleep quality in patients undergoing thyroidectomy.

Abstract

Aim: Thyroidectomy is frequently associated with substantial postoperative pain. Esketamine, an N-methyl-D-aspartate receptor antagonist, has been demonstrated to be effective in multiple analgesia. We hypothesized that intraoperative administration of esketamine may reduce perioperative opioid consumption and postoperative pain in patients undergoing thyroidectomy.

Methods: Sixty patients undergoing thyroidectomy were randomly assigned to two groups. Patients in the saline group received a pre-incisional intravenous bolus of 0.9% NaCl followed by an intraoperative infusion of 0.9% NaCl; patients in the esketamine group received a pre-incisional intravenous bolus of esketamine (0.5 mg kg^{-1}) followed by an intraoperative infusion of esketamine (0.24 mg kg^{-1} h^{-1}). The primary outcome was perioperative sufentanil consumption. The postoperative pain, sleep quality, and adverse events during the first postoperative 24 h were also evaluated.

Results: Patients in the esketamine group consumed significantly less sufentanil than those in the saline group (24.6 ± 3.1 μg vs. 33.7 ± 5.1 μg, mean difference, 9.1; 95% confidence interval, 6.9–11.3, $P<0.001$). Postoperative pain scores were significantly lower in the esketamine group than those in the saline group during the first 24 h postoperatively (P <0.05). Patients receiving esketamine experienced higher sleep quality than those in the saline group during surgical night ($P = 0.043$). There were no significant differences in adverse events between the two groups.

Conclusion: Intraoperative administration of esketamine reduces perioperative sufentanil consumption and postoperative pain without increasing adverse events in patients undergoing thyroidectomy. The development of combined anesthesia regimens, including esketamine, may foster strategies for pain management during thyroidectomy.

Introduction

Thyroid surgeries have evolved into safe procedures with low morbidity and mortality.[1] Concerns with surgery are most commonly associated with postoperative pain, which results from extensive tissue dissection and tension. Opioids are the most potent analgesics in clinical anesthesia; however, prescription opioids are a substantial contributor to drug-related adverse effects and the risk of dependence and abuse.[2] Thus, reducing postsurgical pain using opioid-sparing techniques can have long-term benefits.[3] Multimodal analgesia is useful in reducing opioid consumption following myriad surgeries, including orthopedic, gynecologic, colorectal, and bariatric surgery. Nonetheless, the adoption of multimodal analgesia in head and neck surgeries has lagged.

Ketamine inhibits N-methyl-d-aspartate (NMDA) receptor activation and attenuates the wind-up and central sensitization associated with hyperalgesia, opioid tolerance, and chronic pain.[4]Numerous publications have stated that adjuvant ketamine reduces postoperative pain and opioid consumption postoperatively.[5-8]

However, the psychotomimetic effects of ketamine, such as visual disturbances and dizziness, can compromise patient satisfaction. Esketamine, the left-handed optical isomer of racemic ketamine, is purported to have higher potency and a lower incidence of adverse events than racemic ketamine.[9] In this randomized controlled trial, we evaluated the opioid-sparing effect of esketamine during thyroid surgery. The primary outcome was perioperative sufentanil consumption. Pain and sleep quality during the first 24 h postoperatively were recorded as secondary outcomes. We hypothesized that the administration of esketamine would reduce perioperative sufentanil consumption, along with better pain control and sleep quality 24 h after surgery.

Methods

Study Design

This prospective randomized controlled trial was approved by the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (approval no.: YX2021-106) and was prospectively registered in the Chinese Clinical Trial Registry (ChiCTR2100053459) on November 21, 2021. The study was conducted from December 2021 to May 2022 in the Department of Anesthesiology and Perioperative Medicine at the Second Affiliated Hospital of Anhui Medical University. This study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) criteria[10] and in compliance with the Helsinki Declaration. Written informed consent was obtained from all the patients.

Patients scheduled to undergo elective thyroidectomy were enrolled in this study. The inclusion criteria were age between 18 and 65 years and American Society of Anesthesiologists physical (ASA) status of I–II. The exclusion criteria were body mass index (BMI) >30 kg m^{-2}, preoperative analgesic and sedative medication, unstable ischemic cardiac disease, severe pulmonary hypertension, uncontrolled hypertension, increased intracranial or intraocular pressure, liver and kidney dysfunction, history of chronic pain, psychiatric disorders or alcohol abuse, allergy to medication used in the study, pregnancy, and lactation.

The enrolled patients were randomly assigned to either the control group (Group CON) or the esketamine group (Group KET) using software at a 1:1 ratio. An assistant who was not associated with the study performed random allocation by preparing coded and sealed opaque envelopes for allocation concealment. A nurse unaffiliated with patient care opened the envelopes shortly before induction and prepared the study medication outside the operating room. The agent used for this study was diluted with NaCl (0.9%) to yield two study drug syringes: a 10-mL syringe containing either 5 mg/mL esketamine or NaCl (0.9%) and a 50-mL syringe containing either 1 mg/mL esketamine or NaCl (0.9%), which were identical in appearance and were labeled as "study medication" with patient number. Thereafter, patients, anesthesiologists, nurses providing postoperative care, surgeons, investigators, and outcome assessors were blinded to the patients' group allocation and did not have access to randomization until the data analysis was complete.

Based on the assigned group, patients in Group CON received a bolus of 0.1 mL kg^{-1} intravenous NaCl (0.9%) immediately before incision, followed by NaCl (0.9%) infusion of 0.24 mL kg^{-1} h^{-1}, which continued until the beginning of wound closure. Patients in Group KET received a bolus of intravenous esketamine (0.5 mg kg^{-1}) immediately before incision, followed by esketamine infusion of 0.24 mL kg^{-1} h^{-1} (corresponding to an esketamine dose of 0.24 mg kg^{-1} h^{-1}) that continued until the beginning of wound closure. An anesthesiologist injected the bolus dose from a 5-mL syringe before incision and initiated infusion from the 50-mL syringe.

After arrival in the operating room, intravenous access was established and vital parameters, including heart rate (HR), electrocardiogram, blood pressure, and pulse oximetry, were monitored throughout the surgery. Intravenous dexamethasone (8–10 mg) was administered to prevent postoperative nausea and vomiting (PONV). General anesthesia induction and tracheal intubation were performed using midazolam (0.05 mg kg^{-1}), sufentanil (0.4 μg kg^{-1}), etomidate (0.3 mg kg^{-1}), and rocuronium (0.9 mg kg^{-1}). Parecoxib sodium (40 mg) was administered after induction for pre-emptive analgesia. Maintenance of anesthesia was achieved by continuous infusion with propofol (4–6 mg kg^{-1} h^{-1}) and remifentanil (0.15–0.25 μg kg^{-1} min^{-1}). Muscle relaxation was achieved by weight-adjusted atracurium dosing by the attending anesthesiologist. The assessment of the depth of anesthesia was based on clinical evaluation by the anesthesiologist, and a bolus of

sufentanil (5–10 μg) was administered when the patient's HR or blood pressure increased by >20% from basal measurements. At an appropriate depth of anesthesia, an intermittent bolus of urapidil was administered if the mean arterial pressure (MAP) was >90 mmHg or evaluated by >20% of baseline values. Esmolol was administered if HR was >120 bpm. In case of hypotension, defined as MAP <60 mmHg or reduction by >20% of baseline values, additional fluid and an intermittent bolus of ephedrine were administered. Atropine was administered to patients with severe bradycardia (HR <50 bpm). The dosage of vasoactive agent was at the discretion of the anesthesiologist.

All patients were transferred to the post-anesthesia care unit (PACU) for recovery after extubation. A nurse blinded to the protocols evaluated the pain intensity at rest and coughing using an 11-point numeric rating scale (NRS), which ranged from "0" (meaning no pain) to "10" (meaning worst pain imaginable). When the NRS score was [?]4 or patients verbalized the need for additional pain relief, the attending anesthesiologist reviewed and provided intravenous boluses of sufentanil at 0.1 μg kg^{-1} for rescue analgesia. The level of alertness/sedation was assessed using the Richmond Agitation Sedation Scale (RASS) 30 min postoperatively. The RASS is a 10-point scale ranging from -5 to +4. A score of -5 denotes a patient who does not respond to voice or physical stimulation, 0 characterizes a calm and alert patient, and +4 denotes a combative and violent patient who poses danger to the staff.[11] MAP and HR were recorded perioperatively. Once the PACU discharge criteria were met, patients were transferred to the ward and non-steroidal anti-inflammatory drugs were provided to the patients as needed for pain relief, as reviewed and decided by the attending surgeons.

The opioid-related side effects of PONV and psychotomimetic side effects of nightmares, hallucinations, dizziness, and diplopia were assessed postoperatively. Rescue droperidol was administered for PONV, and psychotomimetic side effects were treated and monitored until discharge according to hospital service guidelines. Patients were interviewed 24 h postoperatively by the attending anesthesiologist using the following questionnaire: 1. What is the last thing you remember before going to sleep? 2. What is the first thing you remember waking up? 3. Do you remember anything between going to sleep and waking up? 4. Did you dream of the procedure? 5. What was the worst thing about your operation?[12]

The primary outcome was perioperative sufentanil consumption. Secondary outcomes included the NRS pain scores at rest and coughing, evaluated at 0.5, 2, 4, 6, 12, and 24 h postoperatively; quality of sleep in the night following surgery, evaluated using a 4-point scale (1, slept well; 2, disturbed sleep; 3, nightmares; 4, sleepless); time to extubation, defined as time from the end of surgery to extubation; incidences of PONV and psychotomimetic side effects; incidences of hemodynamic instability events; and chronic pain scores in 3 month postoperatively.

Statistical Analysis

The sample size of the study was calculated using PASS V.15.0 (NCSS, Kaysville, UT) for Windows. According to a previous study showing that patients receiving ketamine required 24% less intraoperative opiate medications,[13] we accepted that at least a 20% reduction in perioperative sufentanil consumption was clinically significant. Based on the results of our pilot study with five patients in each group (mean sufentanil consumption was 32.0 μg and 25.5 μg for Groups CON and KET, respectively, using a pooled standard deviation [SD] of 5.7), two simple t-tests were performed and the group allocation ratio was 1:1. Considering a power of 0.90, an alpha error of 0.01, and a loss to follow-up rate of 20%, the required sample size for each group was calculated as 30. Therefore, 60 patients were included in the study.

All statistical analyses were performed using SPSS (version 24.0; IBM, Armonk, NY). Statistical significance was set at $P<0.05$. Kolmogorov–Smirnov tests were used to test the normality of the data distribution. Continuous variables are expressed as mean (SD) or median (interquartile range [interquartile range]). Student's t-test was used to compare parametric variables with a normal distribution between the two groups. The Mann–Whitney comparison was used to compare parametric variables without a normal distribution. Categorical variables were expressed as numbers (percentages) and intergroup differences were assessed using chi-squared or Fisher's exact tests, as appropriate.

Repeated measurements of intraoperative hemodynamic parameters and postoperative pain scores were

analyzed using a linear mixed model[14,15] to evaluate the association between dependent variables over time and esketamine infusion. The Wilcoxon matched-pairs signed-rank test was used for binary comparisons of sleep quality within groups.

Results

The CONSORT flow diagram of this trial is shown in Figure 1. Patients were recruited between December 10, 2021 and May 25, 2022. Of the 67 patients who underwent thyroid surgery and were screened for suitability, 7 were excluded, of whom 2 had uncontrolled hypertension and 5 declined to participate. Ultimately, 60 patients were enrolled and randomized, all of whom were followed up until the end of the study.

Table 1 shows patient and surgical characteristics. There were no significant differences between groups in age, sex distribution, BMI, ASA physical status, type of surgery, or duration of surgery (Table 1).

Compared with the Group CON, perioperative sufentanil consumption was significantly reduced in Group KET (33. 7 ± 5.1 μg vs. 24.6 ± 3.1 μg, mean difference, 9.1; 95% confidence interval, 6.9–11.3, $P<0.001$). There were no significant differences between the two groups in regards of intraoperative remifentanil consumption (1118.5 ± 294.9 μg vs. 1045.8 ± 302.0 mg, $P = 0.349$) or propofol consumption (513.50 ± 210.0 mg vs. 476.2 ± 170.1 μg, $P = 0.453$) (Table 2).

Postoperatively, five patients in Group CON and no patients in Group KET reported NRS scores >3; however, this did not reach significance. None of the patients received rescue analgesia in the PACU. In the ward, one patient in Group CON required analgesic therapy, and diclofenac lidocaine was administered by the attending surgeon. There were no significant differences between groups with regard to the time to extubation or RASS score 30 min postoperatively. The incidence of postoperative nausea was 3.3% in Group CON and 13.3% in Group KET, whereas the incidence of postoperative vomiting was 6.7% in Group CON and 10.0% in Group KET; however, these differences were not statistically significant. Psychotomimetic side effects were not significantly different between groups. The most common side effect was dizziness (CON: 30.0% vs. KET: 27%, $P = 0.774$). One patient in Group KET experienced transient diplopia, which resolved spontaneously over time. None of the patients experienced hallucinations or nightmares, and none reported intra-operative awareness after surgery (Table 3).

Patients in Group KET experienced lower NRS pain scores at rest and coughing than those in Group CON at all timepoints in the first 24 h postoperatively (Figure 2). . Pain scores in 3 months postoperatively were equally low and comparable between the two groups (Table 3).

Preoperative sleep quality scores were comparable between the two groups. During the night of surgery, patients in Group KET experienced higher sleep quality (2 [1, 2]) than those in Group CON (3 [1, 4]) ($P = 0.043$). When we compared the intragroup values using the Wilcoxon matched-pairs test, patients in Group CON reported significantly poorer sleep quality when compared with the preoperative value (preoperative value, 1 [1, 2] vs. postoperative value, 3 [1,4], $P = 0.004$); however, there was no significant difference between the preoperative and postoperative values in Group KET in terms of sleep quality (preoperative quality, 2 [1,4] vs. postoperative quality, 2 [1,2], $P = 0.347$, Table 3).

There were no significant differences in MAP between groups at any timepoints. Patients in Group KET exhibited a higher HR 10 min after injection of esketamine, while HR values were similar at other timepoints between groups (Figure 3). The incidences of hypotension and bradycardia in Group CON (13.3% and 10.0%, respectively) were both comparable with those in Group KET (13.3% and 0%, respectively), and none of the patients exhibited hypertension or tachycardia.

Discussion

Our data revealed that bolus injection followed by continuous infusion of esketamine reduced sufentanil consumption during thyroidectomy. Moreover, patients receiving esketamine reported lower pain scores during the first postoperative 24 h and experienced higher sleep quality on the night of surgery than those in Group CON. We observed no between-group differences in psychotomimetic side effects.

Patients undergoing thyroid surgery experience mild to moderate pain levels after the first week postoperatively,[16] while specialty and procedure-specific guidelines for pain management do not presently exist within otorhinolaryngology–head and neck surgery.[17] Thus, our randomized controlled trial helped develop an evidence-based approach for perioperative pain management in patients undergoing thyroidectomy.

Multimodal analgesia involves the use of several different analgesic medications to target multiple receptors within nociceptive and neuropathic pathways to provide opioid-reduced anesthesia, thus reducing acute postoperative pain.[18,19] Activation of C-fiber nociceptors evokes an NMDA receptor-mediated state of central hyperexcitability in spinal cord neurons, which accounts for post-injury pain and hyperalgesia.[20,21] This has led to interest in the pain-relieving properties of clinically available NMDA receptor antagonists such as ketamine.[6,22,23] Studies have consistently reported the promising effect of ketamine in reducing postoperative pain and opioid consumption,[13,24,25] and the analgesic effect can be achieved by far smaller doses than are required in anesthesia.[26] However, the most common form of ketamine in clinical practice is a racemic mixture of two optical isomers: levo-ketamine (R-ketamine) and extro-ketamine (esketamine). The reported psychotropic side effects have reduced the clinical use of racemic ketamine.[27,28]

Esketamine is a left-handed optical isomer of racemic ketamine. The S-enantiomer has been postulated to be approximately twice as effective than the racemic mixture of ketamine in preventing the central summation of pain.[9,29,30] The use of esketamine is increasing worldwide and may be an attractive alternative to racemate for perioperative use. Low-dose racemic ketamine is defined as an intravenous bolus of less than 1 mg/kg and/or continuous intravenous infusion at rates below 20 μg $kg^{-1}min^{-1}$.[31] Thus, we chose a dose with 0.5 mg/kg bolus pre-incisional injection followed by 2.4 mg kg^{-1} h^{-1} until the beginning of wound closure. As hypothesized, patients receiving a low dose of esketamine required 27% less intraoperative sufentanil and experienced less pain intensity after thyroidectomy.

Our results are consistent with those reported by Argiriadou et al., who showed that pre-incisional and repeated intraoperative esketamine added to a combined anesthetic regimen improved pain relief after visceral surgery.[32] They also found that patients receiving esketamine required a lower rate of additional analgesia than those receiving placebo. However, we found no significant intergroup differences in the incidence of rescue analgesia requirement. Compared with major abdominal surgery in the study by Argiriadou et al., thyroidectomy might caused relatively less tissue trauma, which may have led to lower postoperative pain. All patients were treated using multimodal analgesia in our clinical practice. We chose sufentanil because it is the most potent opioid in clinical anesthesia.[33,34] Additionally, we used parecoxib sodium for pre-emptive analgesia, and dexamethasone could also serve as an adjunctive analgesic.[35] Moreover, good manipulation abilities and skills of surgeons might have helped minimize the pain experienced by patients, thus explaining the low number of patients complaining of moderate-to-severe postoperative pain (NRS >3) in both groups, and only one patient in Group CON required rescue analgesia. Even then, infusion of esketamine helped reduce postoperative pain scores, which may translate to better patient experience.

Conversely, some studies have reported negative results for the opioid-sparing effect of esketamine. In an opioid-naïve adult population, injection of 0.5 mg kg^{-1} bolus of esketamine followed by 0.12 or 0.6 mg $kg^{-1}h^{-1}$ infusion was not shown to be superior to placebo in reducing opioid consumption after lumbar fusion surgery.[36] Similar conclusions also showed that patients receiving a 0.5 mg kg^{-1} bolus of esketamine before skin incision followed by a continuous infusion of 2 μg $kg^{-1}min^{-1}$ until 2 h after emergence did not consume less morphine or report less pain during the first 5 days after knee arthroscopy.[37] Different findings between studies may be related to patient populations and surgical procedures. Additionally, the opioid-sparing effects of esketamine have been reported to be age, dosage, and infusion time associated.[22] Thus, further research is required to evaluate the efficacy of esketamine in reducing opioid consumption and pain intensity during different surgeries.

Patients in Group CON experienced reduced sleep quality after thyroidectomy, which may be due to surgical trauma and postoperative pain.[38,39] However, intraoperative infusion of esketamine maintained a sleep quality comparable to that preoperatively. Meanwhile, patients receiving esketamine experienced higher sleep quality than those receiving placebo postoperatively. Since ketamine has been demonstrated to prolong the

average duration of deep sleep and modulate circadian rhythms by regulating clock genes,[40,41] our findings further suggest that esketamine may be a favorable anesthetic regimen for its analgesic and dormant effects.

Because of its higher affinity for NMDA receptors, low doses of esketamine preferentially bind to postsynaptic NMDA receptors in the dorsal horn of the spinal cord rather than in the brain. Hence, analgesia may be achieved with a lower risk of psychotomimetic side effects.[42-45] We did not find increased psychotomimetic adverse events in patients receiving esketamine, which is consistent with previous studies.[32] In addition, ketamine increases blood pressure and HR via sympathetic activation.[9] With a low dose of esketamine, we obtained stable hemodynamics during surgery without any uncontrollable hypertension or tachycardia. Esketamine may compromise the monitoring of anesthesia depth. In a previous study, patients randomized to the esketamine group exhibited a higher perioperative bispectral index and required higher doses of propofol during ambulatory hemorrhoidectomy, which was speculated to be the reason for the delayed recovery time.[46] Therefore, the depth of anesthesia was assessed based only on the clinical evaluation by the attending anesthesiologist in our study. Extubation time was not delayed in Group KET and no patients reported intraoperative awareness.

Our study has some limitations. First, we tested only a single dose of esketamine. Further investigations employing a quantitative dosage of esketamine on postoperative pain and opioid consumption in patients undergoing thyroidectomy, are needed. Second, the NRS and sleep quality scale are not objective indicators; therefore, they may affect the efficacy of the evaluation. Third, while we found no differences in the incidence of PONV or psychomimetic side effects, a larger-scale study is needed to assess this properly.

Conclusion

Bolus injection of 0.5 mg kg^{-1} of esketamine followed by infusion at 0.24 mg kg^{-1} h^{-1}reduced the perioperative sufentanil consumption and postoperative pain intensity in patients undergoing thyroidectomy. The development of combined anesthesia regimens, including esketamine, may foster strategies for pain management during thyroidectomy.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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Data availability statement:

Data are available by sending email to wuyunanyi@163.com.

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Table 1. Patient Demographic Characteristics and Surgical Parameters.

	Group CON (n = 30)	Group KET (n = 30)	*P* value
Age, y	42.4 (12.0)	45.1 (11.0)	0.373
Sex, male, n (%)	5 (16.7)	4 (13.3)	1.000
Body mass index, kg/m^2	23.4 (2.6)	23.4 (2.5)	0.942
ASA physical status, n (%)			1.000
I	28 (93.3)	28 (93.3)	
II	2 (6.7)	2 (6.7)	
Type of surgery,n (%)			0.667
Thyroidectomy	4 (13.3)	2 (6.7)	
Thyroidectomy+ lymph node dissection	26 (86.7)	28 (93.3)	
Duration of surgery, min	102.6 (25.1)	97.5 (27.3)	0.457

Data are presented as mean (standard deviation) or n (%). *P*values are from independent samples *t* tests, chi-squared or Fisher's exact tests, as appropriate. CON, control; KET, esketamine; ASA, American Society of Anesthesiologists.

Table 2. Intraoperative Anesthetics Consumptions.

Anesthetics	Group CON (n = 30)	Group KET (n = 30)	Median difference (95% CI)	*P* value
Sufentanil, μg	33.7 (5.1)	24.6 (3.1) *	9.1 (6.9 to 11.3)	<.001
Remifentanil, μg	1118.5 (294.9)	1045.8 (302.0)	72.8 (-81.5 to 227.0)	0.349
Propofol, mg	513.5 (210.0)	476.2 (170.1)	37.3 (-61.5 to 136.1)	0.453

Data are presented as mean (standard deviation). *P* values are from independent samples *t* tests. *$P<0.05$ indicates statistically significant differences between groups. CON, control; KET, esketamine; CI, confidence interval.

Table 3. Postoperative Parameters.

	Group CON (n = 30)	Group KET (n = 30)	*P* value
Patients with NRS scores > 3, n (%)	5 (16.7)	0 (0)	0.052
Patients receiving rescue analgesia, n (%)			
In the PACU	0 (0)	0 (0)	1.000
In the ward	1 (3.3)	0 (0)	1.000
Time to extubation, min	8.3 (4.2)	10.3 (4.3)	0.084
RASS scores at 30 min postoperatively	0 (0, 0)	0 (0, 0)	1.000
PONV, n (%)			
Nausea	1 (3.3)	4 (13.3)	0.350

Vomiting	2 (6.7)	3 (10.0)	1.000
Psychotomimetic side effects, n (%)			
Dizziness	9 (30.0)	8 (26.7)	0.774
Diplopia	0 (0)	1 (3.3)	1.000
Hallucinations	0 (0)	0 (0)	1.000
Nightmares	0 (0)	0 (0)	1.000
Quality of sleep			
Preoperative	1 (1, 2)	2 (1, 4)	0.083
Postoperative	3 (1, 4)	2 (1, 2)	0.043*
P [a]	0.004	0.347	
Pain scores in 3 months postoperatively	0 (0, 2)	0 (0, 1)	0.518

Data are presented as mean (standard deviation), median (interquartile range) or n (%). P values are from independent samples $t$tests, Mann–Whitney comparison, chi-squared or Fisher's exact tests, as appropriate. $^{*}P$ <0.05 indicates statistically significant differences between groups.P [a] values are from Wilcoxon matched-pairs signed-rank test for intragroup comparisons.P <0.05 indicates statistically significant differences compared with preoperative values. CON, control; KET, esketamine; NRS, numeric rating scale; PACU, post-anesthesia care unit; RASS, Richmond Agitation Sedation Scale; PONV, postoperative nausea and vomiting.

Figure legends

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of patient enrollment, allocation, follow-up, and analysis. CON, control; KET, esketamine.

Figure 2. Postoperative pain scores at rest (A) and at coughing (B) during the first 24 h postoperatively. $^{*}P$<0.05 indicates statistically significant differences between groups. NRS, numeric rating scale; CON, control; KET, esketamine.

Figure 3. Perioperative MAP and HR values. $^{*}P$<0.05 indicates statistically significant differences between groups. CON, control; KET, esketamine; MAP, mean arterial pressure; HR, heart rate.