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CLINICAL TRIAL REPORT

Effect of Continuous Infusion of Different Doses of Esketamine on the Bispectral Index During Sevoflurane Anesthesia: A Randomized Controlled Trial

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Purpose: To investigate and quantify the effect of continuous esketamine infusion at different doses on the bispectral index (BIS) during sevoflurane anesthesia.

Methods: A total of 120 patients scheduled for elective laparoscopic renal surgery were randomly divided into three groups. Under steady anesthesia and surgical situations, the patient was started on continuous infusion of the study drug: 0.125 mg/kg/h esketamine (group E1), 0.25 mg/kg/h esketamine (group E2), and the same volume of saline (group C). The primary outcome was changes in BIS value after 15 min (T_{15}), 30 min (T_{30}), 45 min (T_{45}), and 60 min (T_{60}) of drug infusion. The secondary outcomes were 95% spectral edge frequency (SEF95), electromyogram (EMG), heart rate (HR), and mean arterial pressure (MAP) from T_0 to T_{60}. Furthermore, postoperative pain, postoperative recovery, and perioperative adverse events were evaluated.

Results: Compared with group C, group E1 exhibited significant BIS elevation at T_{30}–T_{60} and group E2 at T_{15}–T_{60} ($P < 0.001$). Compared with group E1, group E2 showed a more significant BIS elevation at T_{15}–T_{60} ($P < 0.001$). The area under the curve (AUC) of BIS and SEF95 were significantly higher in group E2 than in groups C and E1 ($P < 0.05$). BIS value for any of the three groups was significantly correlated with SEF95 ($P < 0.001$). No significant differences were observed in the AUC of EMG, HR, and MAP among the three groups. Intraoperative remifentanil consumption and postoperative NRS of pain on movement were significantly reduced in group E2 compared with groups C and E1 ($P < 0.05$).

Conclusion: Continuous infusion of both 0.125 and 0.25 mg/kg/h of esketamine increased the BIS value during sevoflurane anesthesia, and the BIS value gradually stabilized with the prolongation of the infusion time.

Keywords: esketamine, bispectral index, 95% spectral edge frequency, sevoflurane

Introduction

The bispectral index (BIS), a derivation of the original electroencephalogram (EEG), is the only FDA-approved index for evaluating anesthesia depth and is a good approach for monitoring the functional state of and changes in the cerebral cortex.[1] BIS-guided anesthesia not only minimizes intraoperative consciousness but also facilitates early postoperative recovery and reduces the risk of neurological complications.[2–5] The BIS correlates well with anesthetics that mainly act via gamma-aminobutyric acid receptors (GABARs), such as propofol, midazolam, and sevoflurane. As these drug concentrations increase, the BIS decreases in a dose-dependent manner.[6–8] However, BIS monitoring does not apply to ketamine anesthesia. Ketamine is an antagonist of the N-methyl-D-aspartate receptor (NMDAR). Previous studies have shown that a bolus of ketamine increases the BIS.[6,9]

Esketamine, the dextro-isomer of ketamine, has approximately twice the affinity for NMDAR as ketamine and is characterized by quicker onset, faster elimination, fewer adverse effects, and better sedative and analgesic potency.[10,11]

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Previous clinical studies have demonstrated that intraoperative esketamine application decreases early pain scores,[12–14] spares opioids,[15,16] reduces hyperalgesia,[17,18] and promotes postoperative recovery in various ways.[19–24]

Quantitative studies on the change in the BIS caused by continuous esketamine infusion during general anesthesia are currently lacking. When the change in the BIS is inconsistent with the real anesthesia depth, an inappropriate anesthetic dose may be administered. Thus, it is important to quantify the change in the BIS to optimize personalized anesthesia. This study aimed to explore and quantify the effect of intravenous continuous infusion of different doses of esketamine on the BIS during sevoflurane anesthesia.

Materials and Methods

Study Design and Ethics

This study was a single-center, prospective, randomized, double-blind, controlled trial. It was approved by the Scientific Research and Clinical Trial Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2023-KY-0511-001) and registered in the Chinese Clinical Trials Registry (ChiCTR2300075902) on September 19, 2023. Written informed consent was obtained from the participants. This trial was conducted in accordance with the ethical standards of the Declaration of Helsinki. The trial report complied with the Consolidated Standards of Reporting Trials (CONSORT) checklist.

Participants

We recruited patients scheduled for elective laparoscopic renal surgery under general anesthesia at the First Affiliated Hospital of Zhengzhou University from September 2023 to November 2023, aged 18 to 65, with American Society of Anesthesiologists (ASA) physical status I or II.

Exclusion Criteria: diagnosed mental illness; history of drug or alcohol abuse; body mass index (BMI) < 18 kg/m^2 or > 30 kg/m^2; severe hepatic or renal dysfunction; known hypersensitivity to esketamine; contraindications to use of esketamine for any of the following conditions: serious risk of elevated blood pressure or intracranial pressure, high intraocular pressure (glaucoma) or penetrating ocular trauma, poorly controlled or untreated hypertension (> 180/110 mmHg at rest), untreated or inadequately treated hyperthyroidism, pregnancy or breastfeeding; communication difficulties.

Withdrawal criteria included less than 1 hour of study drug infusion, intraoperative transfer to open surgery, and postoperative transfer to the ICU.

Randomization and Blinding

Using a computer-generated randomization table, the patients were randomly assigned at a 1:1:1 ratio to 0.125 mg/kg/h esketamine group (group E1), 0.25 mg/kg/h esketamine group (group E2), and control group (group C). The group assignments were secured in sequentially numbered sealed opaque envelopes, which were opened by a nurse before surgery. Both esketamine and saline were prepared in identical 20-mL syringes labeled "study drug" and then placed in opaque envelopes by the same nurse. For group E1, esketamine (2.5 mg/mL), 50 mg, was diluted to 20 mL with saline solution, whereas for group E2, esketamine (5 mg/mL), 100 mg, was diluted to 20 mL with saline solution. An experienced anesthesiologist implemented anesthesia, and another specialized anesthesiologist performed postoperative data collection and follow-up. The patients, nurses, and clinicians were blinded to the group assignments.

Intervention

Under stable anesthesia and surgical conditions, the patient was started on a continuous infusion of the study drug at 0.05 mL/kg/h through a peripheral vein in the upper extremity: 0.125 mg/kg/h esketamine (group E1), 0.25 mg/kg/h esketamine (group E2), and the same volume of saline (group C). Infusion of the study drug was stopped when the deep abdominal wall incision began to be sutured.

Stable anesthesia and surgical conditions consisted of four main aspects: end-expiratory sevoflurane concentration stabilized at 0.8 MAC for at least 10 min; hemodynamic parameters (MAP and HR) were stable; the patient's position was fixed during surgery; pneumoperitoneum had been established and the first stage of surgical excursion had begun.

Outcomes

The primary outcome was the changes in BIS value (Δ-BIS) after 15 min (T_{15}), 30 min (T_{30}), 45 min (T_{45}), and 60 min (T_{60}) of drug infusion.

The secondary outcomes included: the changes in 95% spectral edge frequency (Δ-SEF95) at each of the aforementioned time points; the proportions of BIS value increasing above 20% of the baseline and BIS value above 60 at each of the aforementioned time points; area under the curve (AUC) of BIS value, SEF95, electromyogram (EMG), heart rate (HR), and mean arterial pressure (MAP) from T_0 to T_{60}. Other secondary outcomes were postoperative pain, postoperative recovery, and perioperative adverse events.

Data Collection

During the operation, BIS, SEF95, EMG, MAP, and HR were automatically recorded using a multifunction monitor. At the end of the procedure, data were collected via electronic recording of the same monitor. The selected observation period was from 6 min before to 60 min after the study drug infusion (T_{60}) (data recording every 3 min). The first three values recorded for each patient were averaged to obtain the preinfusion (T_0) baseline values.

We evaluated the numeric rating scale (NRS) of pain at rest and on movement (0 = no pain, 10 = intolerable pain) 30 min after extubation and 24 h postoperatively, the Riker sedation–agitation scale (SAS)[25] and modified Aldrete score[26] 30 min after extubation, incidence of rescue analgesia and emergence agitation (SAS ≥ 5) in the postanesthesia care unit (PACU), NRS of sleep quality (0 = best sleep, 10 = worst sleep) and 15-item quality of recovery (QoR-15)[27] 24 h postoperatively, and incidence of moderate to severe pain (NRS > 3) within 24 h. In addition, intraoperative adverse cardiovascular events (hypotension, hypertension, bradycardia, and tachycardia) and adverse events within 24 h postoperatively, such as dizziness, drowsiness, nausea and vomiting, nightmares, hallucinations, itching, and intraoperative awareness, were also recorded.

Anesthetic and Surgical Management

The patients were routinely fasted for 8 h and abstained from drinking for 2 h. They completed ultrasound-guided T10 level thoracic paravertebral block (0.33% ropivacaine, 20 mL) on the operative side 30 min before operation. After entering the operating room, electrocardiogram (ECG), HR, noninvasive blood pressure (NIBP), and pulse oxygen saturation (SpO_2) were monitored. Invasive arterial blood pressure (NBP) was monitored by radial artery puncture under local anesthesia. The BIS electrode sheet was placed on one side of the forehead and connected to the BIS module configured in the multifunction monitor to record the BIS, SEF95, and EMG. After inducing general anesthesia by alfentanil 40–50 μg/kg, etomidate 0.2 mg/kg, and rocuronium 0.6 mg/kg, an endotracheal tube was introduced, and mechanical ventilation was initiated. Continuous intravenous infusion of remifentanil 0.10–0.25 ug/kg/min and inhalation of sevoflurane 0.8 age-adjusted minimum alveolar concentration (MAC) were adopted to maintain intraoperative anesthesia. The rate of remifentanil infusion was adjusted in response to changes in the patient's vital sign parameters, surgical progress, and stimulation intensity. Intraoperative fluids were infused as needed (crystalloid: colloid = 2:1). If intraoperative hypotension (20% decrease in systolic blood pressure from baseline) occurred, 0.5 mg of metaraminol was injected and maintained at 0.5–1 ug/kg/min; if intraoperative hypertension (20% increase in systolic blood pressure from baseline) occurred, 10–15 mg of urapidil was injected; if intraoperative bradycardia occurred (HR < 50 bpm), 0.3–0.5 mg of atropine was injected; and if intraoperative tachycardia occurred (HR > 100 bpm), 20 mg of esmolol was injected. Intraoperative pumping of rocuronium (3–5 ug/kg/min) was kept to maintain muscle relaxation and was stopped 30 min before the end of the operation.

When suturing the deep abdominal wall incision, hydromorphone 8 ug/kg, flurbiprofen axetil 1 mg/kg and palonosetron 0.25 mg were administered. At the end of the suture, sevoflurane inhalation and remifentanil pumping were terminated. Postoperatively, all patients were transferred to the PACU and administered neostigmine 25 ug/kg and glycopyrrolate 5 ug/kg to reverse residual neuromuscular blockade. The endotracheal tube was removed if the patient regained consciousness, the minute ventilation was greater than 6 L/min, and the respiratory frequency was greater than 12 bpm.

After extubation, patient-controlled intravenous analgesia (PCIA) was initiated, with a protocol of hydromorphone 0.2 mg/kg diluted to 200 mL, a continuous volume of 2 mL/h, a self-controlled dose of 4 mL, and a locking time of 10 min. When the NRS of pain was greater than 3, the patient used self-controlled analgesia; if the NRS of pain remained

greater than 3 after three consecutive compressions of PCIA, flurbiprofen axetil 50 mg was administered for rescue analgesia. When nausea and vomiting occurred, palonosetron 0.25 mg was administered.

Sample Size Calculation and Statistical Analysis

The PASS 15.0 software was used to calculate the sample size. Based on pre-test, the Δ-BIS at T_{15} were 0, 2.5, and 5.0 and the standard deviations were 4.0, 4.0, and 5.0 in groups C, E1, and E2, respectively. Setting α to 0.05 and 1-β to 0.95, the sample size of each group was calculated as 32. Accounting for a 20% dropout rate, 120 patients were finally included.

Statistical analysis and graphing were conducted using SPSS 26.0 and GraphPad Prism 8.0. Normally distributed measures were expressed as mean ± standard deviation (x ± s), and one-way analysis of variance (ANOVA) was employed for intergroup comparison. Non-normally distributed measures were expressed as median (interquartile range) [M (Q1, Q3)], and the Kruskal–Wallis *H*-test was employed for intergroup comparison. Count data were expressed as cases (%), and intergroup comparisons were made using the $\chi 2$ test or Fisher's exact test. Furthermore, inter- and intragroup comparisons of repeated measurement data were made using repeated measures ANOVA. Bonferroni correction was used for multiple comparisons, and $P < 0.05$ was considered to indicate statistical significance.

Results

A total of 150 patients were assessed for eligibility, of whom 30 were excluded before randomization. Consequently, 120 patients were included and randomly divided into three groups: group C (n = 40), group E1 (n = 40), and group E2 (n = 40). Three patients in group C, five in group E1, and four in group E2 were excluded as the study drug infusion was less than 1 hour. Furthermore, two patients in group C, two in group E1, and one in group E2 were excluded due to intraoperative transfer to open surgery. A total of 103 patients (35 in group C, 33 in group E1, and 35 in group E2) were included in the final analysis. The study procedure is presented in Figure 1.

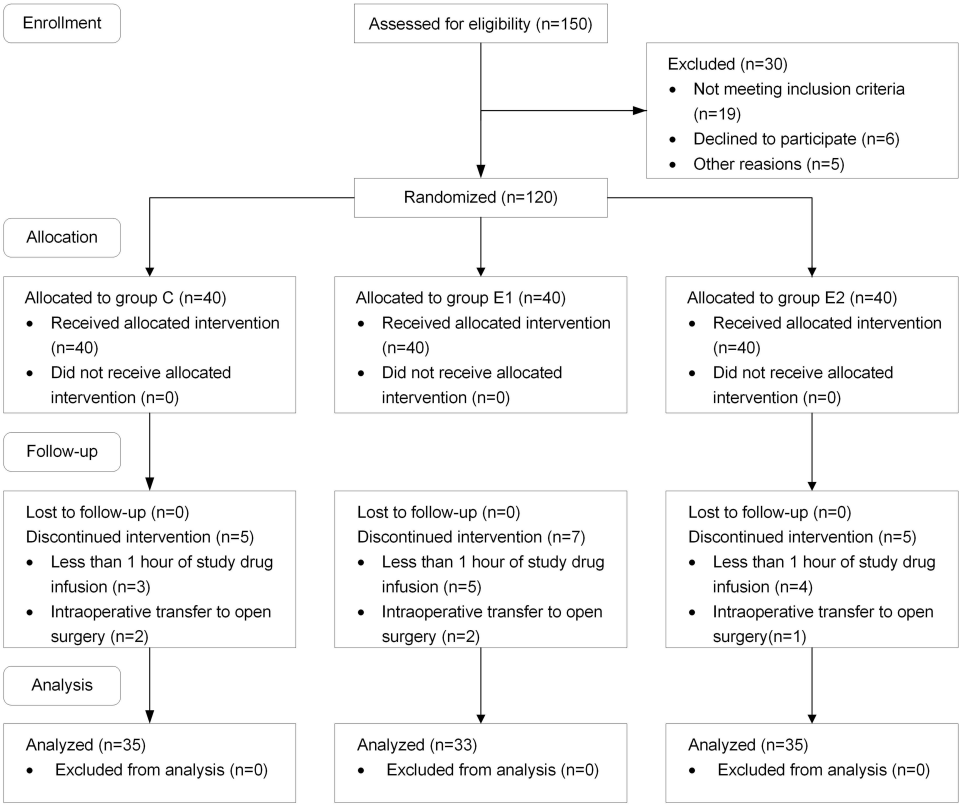

Figure 1 CONSORT flow diagram.
Abbreviations: group C, control group; group E1, 0.125 mg/kg/h esketamine group; group E2, 0.25 mg/kg/h esketamine group.

Baseline and Intraoperative Characteristics

The three groups were well-balanced on baseline characteristics (Table 1). Intraoperative data, including type of surgery, durations of surgery and anesthesia, time from anesthesia induction to begin study drug infusion, time of study drug infusion, fluid balance, and metaraminol dosage, did not differ among the three groups ($P > 0.05$). Remifentanil consumption was significantly reduced in group E2 compared with groups C and E1 ($P = 0.001$, $P = 0.034$) (Table 2).

Primary Outcomes About Δ-BIS and BIS Value

Compared with group C, group E1 exhibited significant BIS elevation at T_{30} (3.6 ± 2.6), T_{45} (5.2 ± 2.9), and T_{60} (6.0 ± 2.6) and group E2 at T_{15} (5.1 ± 2.7), T_{30} (9.1 ± 2.4), T_{45} (10.8 ± 2.2), and T_{60} (12.1 ± 2.0) ($P < 0.001$). Compared with group E1, group E2 showed a more significant BIS elevation at T_{15}–T_{60} ($P < 0.001$). The proportions of BIS values increasing above 20% of baseline were significantly higher in group E2 than in groups C and E1 at T_{30}–T_{60} ($P < 0.05$). Furthermore, the proportions of BIS values above 60 were significantly higher in group E2 than in groups C and E1 at T_{15}–T_{60} ($P < 0.05$) (Table 3).

Table 1 Baseline Characteristics

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
Age, yr	52.0 (45.0–59.0)	54.0 (42.0–61.0)	51.0 (40.0–56.0)	0.212
Male, n (%)	18 (51.4)	21 (63.6)	23 (65.7)	0.421
BMI, kg/m^2	25.4 (23.8–27.4)	24.8 (22.7–26.8)	25.9 (22.9–27.4)	0.455
ASA classification, n (%)				0.216
I	10 (28.6)	14 (42.4)	17 (48.6)	
II	25 (71.4)	19 (57.6)	18 (51.4)	
Smoker, n (%)	7 (20.0)	8 (24.2)	9 (25.7)	0.842
Hypertension, n (%)	10 (28.6)	7 (21.2)	8 (22.9)	0.756
Diabetes, n (%)	2 (5.7)	1 (3.0)	2 (5.7)	1.000
aCCI	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.702
Laboratory test results				
ALT (u/L)	20.0 (13.0–26.0)	17.0 (10.0–26.5)	15.0 (11.0–25.0)	0.566
AST (u/L)	18.0 (14.0–27.0)	18.0 (15.5–25.0)	18.0 (14.0–23.0)	0.865
Creatinine (μmol/L)	74.0 (60.0–92.0)	66.0 (58.5–87.0)	73.0 (61.0–84.0)	0.488
BUN (mmol/L)	5.2 (4.1–6.8)	5.0 (3.7–6.7)	5.2 (4.0–5.8)	0.892
Haemoglobin (g/L)	131.0 ± 18.6	131.8 ± 17.8	135.1 ± 17.1	0.602
Preoperative evaluation				
NRS of pain	0 (0–1.0)	0 (0–0.5)	0 (0–1.0)	0.925
NRS of sleep quality	3.0 (2.0–3.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.228
QoR-15	132.0 (127.0–136.0)	132.0 (124.0–137.5)	130.0 (125.0–138.0)	0.838

Notes: Data are expressed by median (interquartile range), n (%), or mean ± standard deviation.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; BMI, body mass index; ASA, American Society of Anesthesiologists; aCCI, age-adjusted Charlson comorbidity index; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; NRS, numeric rating scale; QoR-15, 15-item quality of recovery.

Table 2 Intraoperative Data

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
Type of surgery, n (%)				0.781
Laparoscopic partial nephrectomy	27 (77.1)	23 (69.7)	26 (74.3)	
Laparoscopic radical nephrectomy	8 (22.9)	10 (30.3)	9 (25.7)	
Duration of surgery (min)	138.0 (112.0–178.0)	147.0 (103.0–181.0)	150.0 (112.0–196.0)	0.735
Duration of anesthesia (min)	165.0 (142.0–206.0)	152.0 (128.0–224.0)	176.0 (141.0–221.0)	0.697
Time from anesthesia induction to begin study drug infusion (min)	51.0 (45.0–68.0)	52.0 (38.0–69.0)	46.0 (41.0–60.0)	0.185
Time of study drug infusion (min)	88.0 (65.0–101.0)	87.0 (63.0–121.0)	95.0 (69.0–130.0)	0.366
Infusion volume (mL)	1300.0 (1000.0–1600.0)	1500.0 (1200.0–2000.0)	1500.0 (1200.0–1800.0)	0.206
Bleeding volume (mL)	50.0 (20.0–100.0)	50.0 (20.0–50.0)	50.0 (20.0–100.0)	0.547
Urine volume (mL)	250.0 (200.0–500.0)	300.0 (200.0–450.0)	250.0 (200.0–500.0)	0.581
Remifentanil dosage (μg/kg/min)	0.184 (0.154–0.215)	0.167 (0.150–0.201)	0.158 (0.142–0.168)[bc]	0.003
Metaraminol dosage (mg)	5.0 (3.2–6.3)	4.2 (2.7–6.5)	4.6 (2.9–6.0)	0.793

Notes: Data are expressed by n (%) or median (interquartile range). [b]*P* < 0.05 vs group C, [c]*P* < 0.05 vs group E1.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group.

Table 3 Changes in BIS Value and SEF95

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
Δ-BIS				
T_{15}	0 ± 3.2	1.4 ± 3.0	5.1 ± 2.7[abc]	<0.001
T_{30}	0.4 ± 2.9	3.6 ± 2.6[ab]	9.1 ± 2.4[abc]	<0.001
T_{45}	0.1 ± 3.0	5.2 ± 2.9[ab]	10.8 ± 2.2[abc]	<0.001
T_{60}	0.2 ± 3.0	6.0 ± 2.6[ab]	12.1 ± 2.0[abc]	<0.001
Δ-SEF95 (Hz)				
T_{15}	0.3 ± 0.6	0.4 ± 0.5	1.6 ± 0.9[abc]	<0.001
T_{30}	0.2 ± 0.7	1.3 ± 0.6[ab]	2.7 ± 1.1[abc]	<0.001
T_{45}	0.1 ± 0.8	1.8 ± 0.9[ab]	3.4 ± 1.1[abc]	<0.001
T_{60}	0.2 ± 0.7	2.1 ± 0.9[ab]	3.7 ± 1.1[abc]	<0.001
BIS value increasing above 20% of baseline, n (%)				
T_{15}	0	0	2 (5.7)	0.327
T_{30}	0	1 (3.0)	15 (42.9)[bc]	<0.001
T_{45}	0	3 (9.1)	26 (74.3)[bc]	<0.001
T_{60}	0	5 (15.2)	32 (91.4)[bc]	<0.001

(*Continued*)

Table 3 (Continued).

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
BIS value above 60, n (%)				
T_{15}	0	0	6 (17.1)[bc]	0.003
T_{30}	0	2 (6.1)	12 (34.3)[bc]	<0.001
T_{45}	0	4 (12.1)	18 (51.4)[bc]	<0.001
T_{60}	0	4 (12.1)	19 (54.3)[bc]	<0.001

Notes: Data are expressed by mean ± standard deviation or n (%). [a]$P < 0.05$ vs 0, [b]$P < 0.05$ vs group C, [c]$P < 0.05$ vs group E1.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; BIS, bispectral index; Δ-BIS, change in BIS value; SEF95, 95% spectral edge frequency; Δ-SEF95, change in SEF95.

Compared with T_0, the BIS values were significantly higher at T_{18}–T_{60} in group E1 and at T_9–T_{60} in group E2 ($P < 0.05$). Compared with T_{60}, significant differences were observed at T_3–T_{36} ($P < 0.05$), whereas there were no significant differences at T_{39}–T_{57} in the BIS values of group E1 ($P > 0.05$). Compared with T_{60}, significant differences were observed at T_3–T_{42} ($P < 0.05$), whereas there were no significant differences at T_{45}–T_{57} in the BIS values of group E2 ($P > 0.05$) (Figure 2A). The AUC of BIS was significantly higher in group E2 (1170 ± 57) than in groups C (721 ± 60) and E1 (863 ± 63) ($P < 0.001$, $P = 0.002$) (Figure 2B).

Secondary Outcomes About Δ-SEF95, SEF95, EMG, HR, and MAP

Compared with group C, group E1 exhibited significant SEF95 elevation at T_{30} (1.3 ± 0.6), T_{45} (1.8 ± 0.9), and T_{60} (2.1 ± 0.9) and group E2 at T_{15} (1.6 ± 0.9), T_{30} (2.7 ± 1.1), T_{45} (3.4 ± 1.1), and T_{60} (3.7 ± 1.1) ($P < 0.001$). Compared with group E1, group E2 showed a more significant SEF95 elevation at T_{15}–T_{60} ($P < 0.001$) (Table 3).

Compared with T_0, SEF95 was significantly higher at T_{18}–T_{60} in group E1 and at T_9–T_{60} in group E2 ($P < 0.05$). Compared with T_{60}, significant differences were observed at T_3–T_{36} ($P < 0.05$), whereas there were no significant differences at T_{39}–T_{57} in the SEF95 of group E1 ($P > 0.05$). Compared with T_{60}, significant differences were observed at

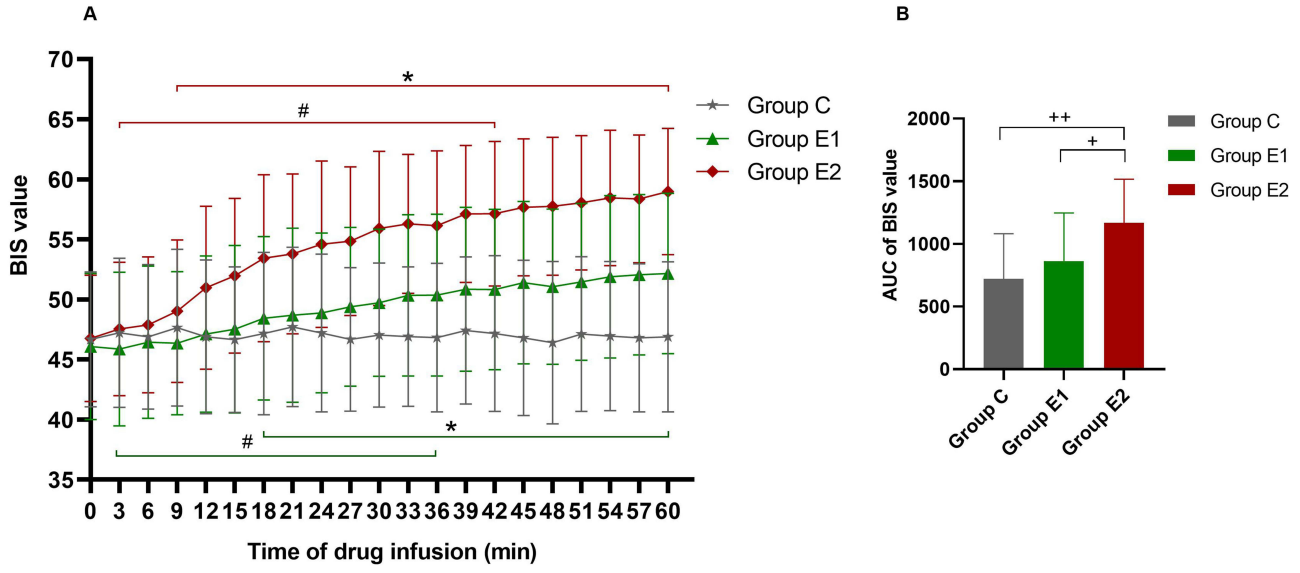

Figure 2 (**A**) BIS value at different time points; (**B**) AUC of BIS value.
Notes: Data are expressed by mean ± standard deviation, *$P < 0.05$ vs T_0, #$P < 0.05$ vs T_{60}, +Means 0.05 level of significance, ++Means 0.001 level of significance.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; BIS, bispectral index; AUC, area under the curve.

T_3–T_{42} ($P < 0.05$), whereas there were no significant differences at T_{45}–T_{57} in the SEF95 of group E2 ($P > 0.05$) (Figure 3A). The AUC of SEF95 was significantly higher in group E2 (304 ± 18) than in groups C (178 ± 18) and E1 (234 ± 19) ($P < 0.001$, $P = 0.029$) (Figure 3B).

Among the three groups, there was no significant difference in the AUC of EMG *(P > 0.05)* (Figure 3C and D), nor were there significant differences in the AUC of HR and MAP *(P > 0.05)* (Figure 4).

Correlation Analysis of the BIS and SEF95

The correlation between BIS and SEF95 during esketamine infusion is unclear, thus, bivariate correlation analysis was conducted, as presented in Figure 5. The BIS value for any of the three groups was significantly correlated with SEF95 ($r_c = 0.75$, $P < 0.001$; $r_{E1} = 0.80$, $P < 0.001$; $r_{E2} = 0.87$, $P < 0.001$; respectively).

Postoperative Pain, Postoperative Recovery, and Perioperative Adverse Events

The NRS of pain on movement 30 min after extubation was significantly lower in group E2 than in groups C and E1 ($P = 0.015$, $P = 0.026$). Furthermore, the NRS of pain on movement 24 h postoperatively was significantly lower in group E2

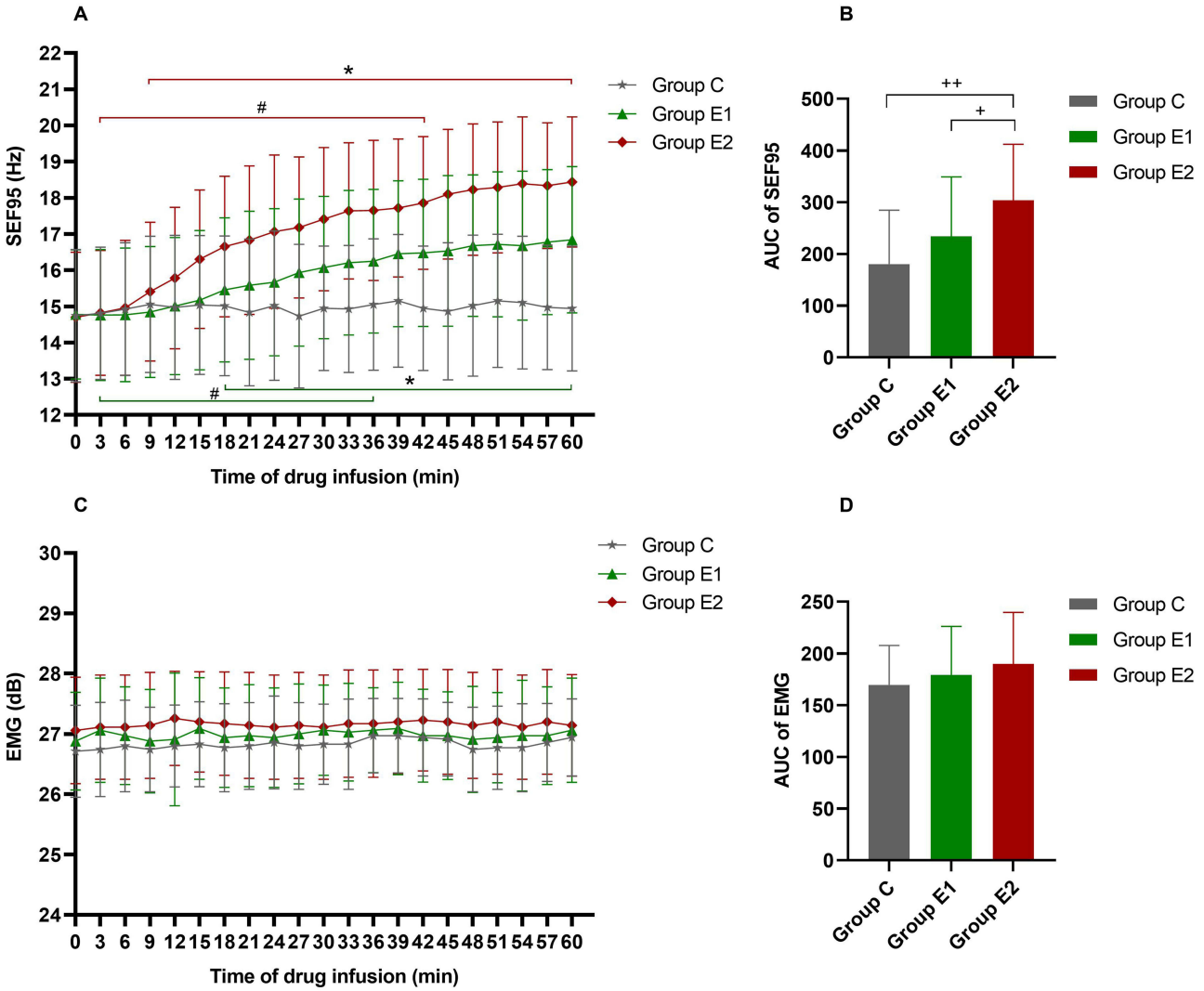

Figure 3 (**A**) SEF95 at different time points; (**B**) AUC of SEF95; (**C**) EMG at different time points; (**D**) AUC of EMG.
Notes: Data are expressed by mean ± standard deviation, $^{*}P < 0.05$ vs T_0, $^{\#}P < 0.05$ vs T_{60}, $^{+}$Means 0.05 level of significance, $^{++}$Means 0.001 level of significance.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; SEF95, 95% spectral edge frequency; EMG, electromyogram; AUC, area under the curve.

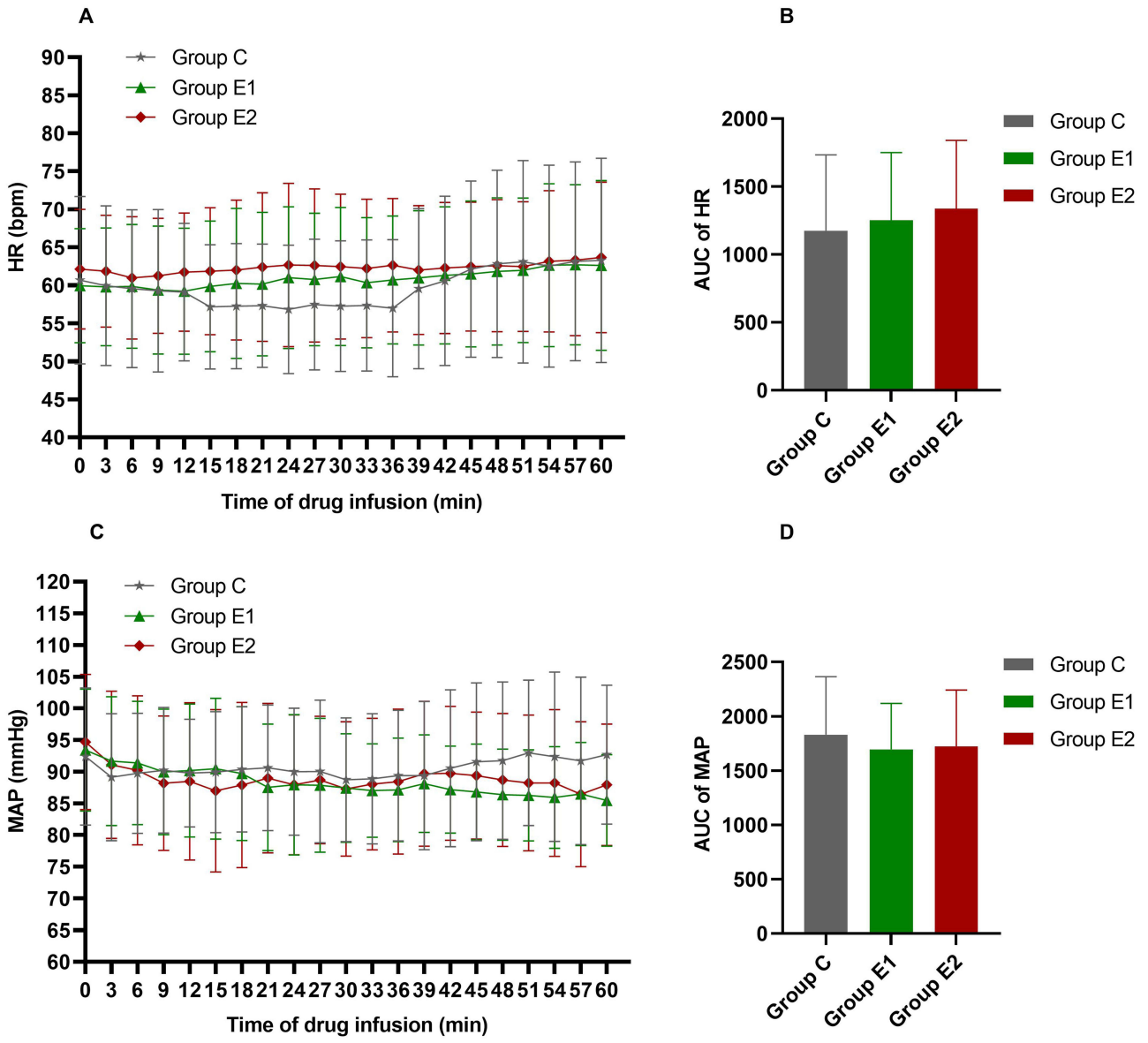

Figure 4 (**A**) HR at different time points; (**B**) AUC of HR; (**C**) MAP at different time points; (**D**) AUC of MAP.
Note: Data are expressed by mean ± standard deviation.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; HR, heart rate; MAP, mean arterial pressure; AUC, area under the curve.

than in groups C and E1 ($P = 0.014$, $P = 0.021$) (Table 4). Other indicators of postoperative recovery and perioperative adverse events did not differ among the three groups ($P < 0.05$) (Tables 4 and 5).

Discussion

In this randomized controlled study of patients undergoing laparoscopic renal surgery, on the background of steady sevoflurane anesthesia, continuous esketamine infusion could increase the BIS value; the higher the dose, the faster and greater the increase. The BIS values gradually stabilized with the prolongation of the infusion time. The changes in SEF95 were similar to those in the BIS, and the two correlated well throughout the esketamine infusion. Moreover, intraoperative esketamine infusion at 0.25 mg/kg/h could save the remifentanil dosage and reduce the early postoperative NRS of pain on movement.

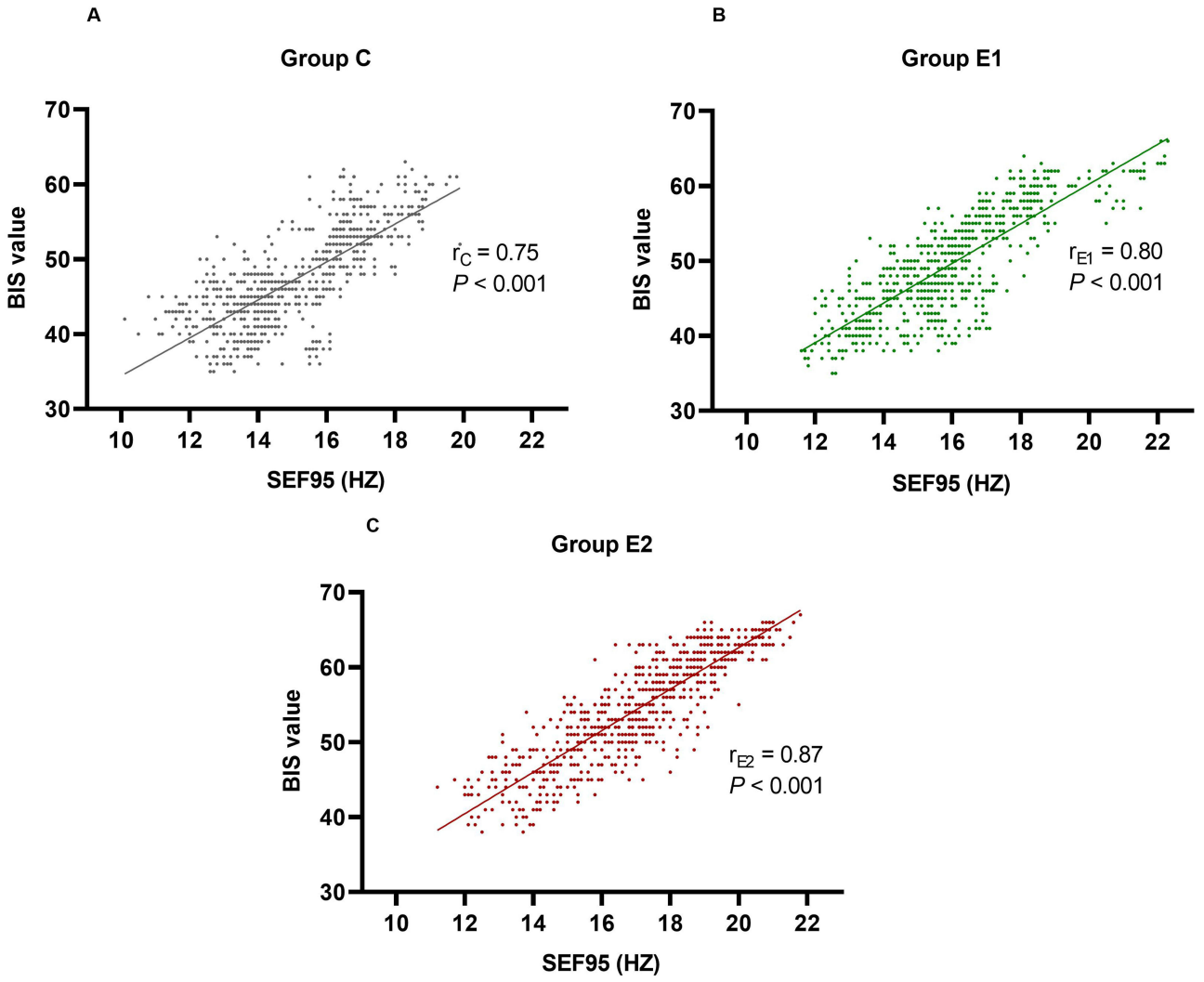

Figure 5 (**A**) Scatter plot of BIS and SEF95 in group C, (**B**) Scatter plot of BIS and SEF95 in group E1, (**C**) Scatter plot of BIS and SEF95 in group E2.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; BIS, bispectral index; SEF95, 95% spectral edge frequency.

Hans et al reported that under stable 2% end-tidal sevoflurane anesthesia, a 0.5 mg/kg bolus of ketamine without continuous infusion significantly increased the BIS values for at least 15 min.[9] Faraoni et al demonstrated that gradual ketamine injection of 0.2 mg/kg over 5 min did not increase the BIS values for the next 15 min during stable target-controlled infusion propofol-remifentanil anesthesia.[28] It was evident that ketamine, delivered in different ways and at different doses, exerted distinct effects on the BIS values. To the best of our knowledge, the present study is the first to explore and quantify the effects of continuous infusion of different doses of esketamine on the BIS values. Our results indicated that infusion of esketamine at 0.125 and 0.25 mg/kg/h resulted in a statistically significant increase in the BIS values. After 18 min of continuous esketamine infusion at 0.125 mg/kg/h, the BIS value started to increase, and gradually stabilized after 39 min. After 45 min of infusion, the BIS value increased by only about 5, and the proportion of BIS values above 60 was about 12%, which was clinically acceptable and had less interference with the judgment of anesthesia depth. This finding is consistent with that of the study by Carrara et al, who found that continuous infusion of an equivalent dose of ketamine (0.25 mg/kg/h) had a negligible effect on the BIS value during desflurane anesthesia.[29] However, with the continuous infusion of esketamine at 0.25 mg/kg/h, the BIS value began to increase after 9 min and gradually stabilized after 45 min, at which time the BIS value increased by approximately 10 and the proportion of BIS

Table 4 Postoperative Pain and Postoperative Recovery

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
Postoperative pain				
NRS of pain at rest 30 min after extubation	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (0–2.0)	0.212
NRS of pain on movement 30 min after extubation	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–2.0)[bc]	0.026
Rescue analgesia in the PACU, n (%)	5 (14.3)	4 (12.1)	2 (5.7)	0.483
NRS of pain at rest 24 h postoperatively	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.256
NRS of pain on movement 24 h postoperatively	3.0 (2.0–3.0)	3.0 (2.0–3.0)	2.0 (2.0–3.0)[bc]	0.022
Moderate to severe pain within 24 h, n (%)	10 (28.6)	9 (27.3)	5 (14.3)	0.297
Postoperative recovery				
Extubation time (min)	22.0 (14.0–35.0)	21.0 (12.0–32.5)	23.0 (15.0–33.0)	0.762
Time in the PACU (min)	54.0 (46.0–69.0)	52.0 (44.5–63.5)	52.0 (46.0–65.0)	0.704
SAS score 30 min after extubation	4.0 (3.0–4.0)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	0.210
Modified Aldrete score 30 min after extubation	9.0 (9.0–10.0)	9.0 (9.0–9.0)	9.0 (9.0–9.0)	0.938
NRS of sleep quality 24 h postoperatively,	4.0 (3.0–6.0)	4.0 (2.0–6.0)	3.0 (2.0–5.0)	0.056
QoR-15 24 h postoperatively	101.0 (87.0–115.0)	103.0 (92.5–115.5)	108.0 (93.0–118.0)	0.244

Notes: Data are expressed by median (interquartile range) or n (%). [b]*P* < 0.05 vs group C, [c]*P* < 0.05 vs group E1.
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; NRS, numeric rating scale; SAS, Ricker sedation-agitation scale; PACU, postanesthesia care unit; QoR-15, 15-item quality of recovery.

Table 5 Perioperative Adverse Events

Variable	Group C (n = 35)	Group E1 (n = 33)	Group E2 (n = 35)	*P* value
Adverse cardiovascular events intraoperatively, n (%)				
Hypotension	16 (45.7)	13 (39.4)	10 (28.6)	0.327
Hypertension	4 (11.4)	2 (6.1)	3 (8.6)	0.907
Bradycardia	4 (11.4)	3 (9.1)	2 (5.7)	0.763
Tachycardia	0	0	0	1.000
Emergence agitation in the PACU, n (%)	5 (14.3)	3 (9.1)	1 (2.9)	0.238
Adverse events within 24h, n (%)				
Dizziness	8 (22.9)	9 (27.3)	11 (31.4)	0.723
Drowsiness	5 (14.3)	5 (15.2)	7 (20.0)	0.787
Nausea and vomiting	7 (20.0)	6 (18.2)	9 (25.7)	0.729
Nightmares	0	0	0	1.000
Hallucinations	0	0	0	1.000
Itching	0	0	1 (2.9)	1.000
Intraoperative awareness	0	0	0	1.000

Notes: Data are expressed by n (%).
Abbreviations: Group C, control group; Group E1, 0.125 mg/kg/h esketamine group; Group E2, 0.25 mg/kg/h esketamine group; PACU, postanesthesia care unit.

value above 60 was approximately 51%, which may obviously interfere with the judgment of anesthesia depth and lead to an overdose of sedative drugs clinically.

Chen et al reported that ketamine significantly reduced the MAC (BAR) of sevoflurane in patients undergoing laparoscopic cholecystectomy compared with sevoflurane alone;[30] similarly, Hamp et al discovered that the use of s-ketamine dose-dependently decreased the MAC of sevoflurane.[31] Therefore, additional administration of esketamine undoubtedly increased the depth of anesthesia, contradicting the increase in BIS values. This phenomenon may be attributed to the characteristic EEG pattern induced by esketamine. As a unique anesthetic agent, the mechanism of ketamine/esketamine is associated with NMDAR inhibition and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels.[32,33] Thus, its EEG features are different from those of GABARs-excited anesthetics, such as sevoflurane. Liu et al reported that on the background of sevoflurane anesthesia, a small dose of esketamine (0.125 mg/kg) induced active EEG spectra with decreased power of slow wave, delta, and alpha and increased power of beta-gamma in the prefrontal lobe.[34] The BIS, as an EEG derivative, is mainly a measure of prefrontal cortical electrical activity rather than the degree of consciousness. Thus, this active EEG pattern may account for the increased BIS values after continuous esketamine infusion in our study. In addition to the increase in the BIS value, it was newly found that under steady sevoflurane anesthesia, the BIS values gradually stabilized as the duration of esketamine infusion grew. This result may be attributed to the gradual stability of the esketamine plasma concentration, and the final stability of the BIS value may reflect a balance between the effects of sevoflurane and esketamine on EEG.

SEF95, which is closely associated with sedation level, represents the frequency threshold below which 95% of the total signal power is contained.[35] Previous studies have shown a significant linear correlation between SEF95 and propofol effect site concentration.[36,37] Under isoflurane anesthesia, SEF95 shows better correlation with the BIS when the BIS values are in the range of 30–80.[38] In the present study, SEF95 significantly increased after continuous infusion of esketamine, and its changes were similar to the BIS. Further analysis revealed that SEF95 correlated well with the BIS during esketamine infusion.

Surgical stimulation, electromyographic activity,[39,40] body position,[41,42] hypothermia,[43] hypoglycemia,[44] and electrical interference from medical instruments can affect the accuracy of BIS readings in the clinical environment.[45] In order to make continuous infusion of esketamine the only variable affecting BIS readings, this study excluded, as much as possible, the interference of other factors on BIS. Therefore, we believe that the results are relatively accurate and credible. First, all patients underwent laparoscopic renal surgery, which is a medium-intensity and relatively stable surgical stimulation that has a low impact on the circulatory system. Moreover, blood pressure and heart rate were intentionally kept stable during the observation period. Second, the EMG signal of 30–40 Hz generated by facial muscle activity overlaps with the spectral range of the signal required to calculate the BIS value;[1] in our investigation, rocuronium was administered as a continuous infusion, and stable EMG signal less than 30 Hz were maintained in all patients intraoperatively. Therefore, the increase in BIS value after esketamine infusion was not caused by a rise in frontal EMG activity. Third, during the observation period, all patients were kept in a fixed position without postural adjustment. Finally, although body temperature and blood glucose were not routinely monitored in this study, all patients were given intraoperative surface warming therapy (warming blankets), and for patients with hyperglycemia complications, changes in blood glucose were closely monitored intraoperatively. Therefore, hypothermia and hypoglycemia events did not occur in this study.

Previous studies have demonstrated that ketamine exerts a direct inhibitory effect on the myocardium but can indirectly excite the cardiovascular system through excitation of the sympathetic nerve center, causing an increase in blood pressure and heart rate in nonanesthetized patients.[46–49] However, no discernible rise in blood pressure or heart rate was observed during esketamine infusion in our study. This could be due to the following reasons: (1) a slow continuous infusion of esketamine has less impact on the circulatory system; (2) during general anesthesia, the direct inhibitory effects of multiple anesthetic drugs on the cardiovascular system may mask the sympathomimetic excitatory effects of esketamine; (3) esketamine was infused as an additional sedative and analgesic drug, resulting in a more complete blockade of injurious stimuli. Therefore, the circulatory effects of esketamine during general anesthesia need to be investigated further.

A systematic review and meta-analysis of perioperative intravenous S-ketamine for acute postoperative pain reported that S-ketamine is effective in reducing early postoperative pain in abdominal surgery.[12] This study found that 0.125 mg/kg/h of esketamine did not significantly alleviate postoperative pain, whereas 0.25 mg/kg/h reduced early postoperative NRS of pain. This may be associated with the analgesic properties of esketamine that are dose-dependent. Studies have shown that, in addition to the NMDAR, part of the analgesic effect of esketamine derives from its agonistic effect on μ-opioid receptor and δ-opioid receptor,[11,50] which may explain lower consumption of intraoperative remifentanil in the group E2. In addition, previous studies by Wang et al and Qiu et al also found that continuous infusion of esketamine could save intraoperative remifentanil consumption.[15,21] However, it is worth noting that all of the above studies lacked objective analgesic monitoring indexes to guide intraoperative remifentanil pumping, and thus the intraoperative opioid-sparing effect of esketamine still needs to be further validated.

This study has several limitations. First, due to the limitation of operation time, only the changes in BIS value within 60 min of esketamine infusion were observed, and no data over a longer period of time was collected for analysis. Second, the plasma concentrations of esketamine were not monitored. Thus, it was impossible to analyze the association between changes in plasma concentration and BIS values. Third, in this study, only the effect of continuous infusion of esketamine on BIS values under sevoflurane anesthesia was observed, and the applicability of our results to other anesthetics, such as propofol and desflurane, is unclear. Finally, although this work quantified the change in BIS values during esketamine infusion, which could provide clinical anesthesiologists with a rough estimate of the original BIS values to prevent overdoses of sedative drugs that can result in hyperanesthesia and hypotensive events, judging the depth of anesthesia under combined esketamine anesthesia is not as simple as a BIS reading minus the BIS increment. This requires us to look for new markers of unconsciousness that are not disturbed by esketamine administration in the future.[51]

Conclusion

In conclusion, this study showed that continuous esketamine infusion increased the BIS value during sevoflurane anesthesia, and the BIS value gradually stabilized with the prolongation of the infusion time. During stabilisation, continuous esketamine infusion at 0.125 mg/kg/h increased the BIS value by about 5, whereas esketamine at 0.25 mg/kg/h increased the BIS value by about 10, twice as much as the lower dose group. In addition, intraoperative esketamine infusion at 0.25 mg/kg/h may be well-recommended for postoperative pain relief.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon request.

Acknowledgments

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Disclosure

The authors declare no conflicts of interest.

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