Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Effects of Esketamine on Postoperative Delirium and Postoperative Cognitive Function in Elderly Gastrointestinal Tumor Patients with Preoperative Anxiety

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Purpose: The aim of this study is to investigate the effects of administering low-dose esketamine during anesthesia induction on the occurrence of postoperative delirium (POD) and postoperative cognitive function in elderly patients with preoperative anxiety.

Patients and Methods: Elderly patients aged 60–80 years and with preoperative anxiety who were undergoing surgery for gastrointestinal tumors were enrolled. The patients were randomly divided into an esketamine group or a placebo group. Upon intravenous induction of general anesthesia, the placebo group received normal saline, while the esketamine group received a subanesthetic dose (0.25 mg/kg) of esketamine. The primary outcome was the incidence of POD and the Mini-Mental State Examination (MMSE) score within 7 days after the operation (d1 to d7). Secondary outcomes included perioperative hemodynamic adverse events, postoperative anxiety, postoperative pain score, and analgesic consumption.

Results: 118 patients were screened for eligibility, and 100 were recruited and analyzed. The incidence of POD within 7 days after surgery in the esketamine group was significantly lower than the placebo group (24.00% vs 48.00%, $P < 0.05$). The MMSE scores at postoperative day1 (d1) were significantly higher in the esketamine group than placebo group (29.00 [28.00–30.00] vs 27.25 [25.00–29.00], Bonferroni-adjusted $P = 0.0014$). The esketamine group had a lower cumulative incidence of delayed neurocognitive recovery (dNCR) within 7 days after surgery (26.00% vs 54.00%, $P < 0.05$). When compared to the placebo group, esketamine group had lower incidence of bradycardia and hypotension events during anesthesia induction period ($P < 0.05$), and the visual analogue anxiety (VAS-A) score on d1 was lower (Bonferroni-adjusted $P < 0.05$). Moreover, the esketamine group had significantly lower plasma concentrations of serum levels of Interleukin-6 (IL-6) and S100 calcium-binding protein β (S100β) on d1 (Bonferroni-adjusted $P < 0.05$).

Conclusion: In elderly patients with preoperative anxiety who undergo gastrointestinal tumor surgery, administering a low-dose intravenous esketamine injection (0.25 mg/kg) during anesthesia induction can decrease the incidence of POD and improve early postoperative cognitive function.

Keywords: esketamine, preoperative anxiety, postoperative delirium, postoperative cognitive function, elderly patients

Introduction

Postoperative delirium (POD), an acute neuropsychiatric syndrome, is a common and serious complication in elderly patients after general anesthesia.[1] Classified under postoperative neurocognitive disorders (PND), postoperative delirium (POD) is clinically identified by its hallmark features: acutely fluctuating consciousness, diminished attentional capacity, and disordered thought processes.[2] Based on the timing of symptom onset, postoperative neurocognitive disorders (PND)

Received: 18 March 2025
Accepted: 30 September 2025
Published: 17 October 2025

encompass several distinct phases: pre-existing neurocognitive disorders, postoperative delirium (POD) manifesting within hours to days after surgery, delayed neurocognitive recovery (dNCR) observed within the first 30 postoperative days, and postoperative neurocognitive disorder (POND) emerging weeks to months later.[3] The incidence of POD in elderly surgical patients is reported to be almost 20% - 45%. POD is affected by multiple factors such as advanced ages, type of operation and preoperative affective disorder.[4] POD is associated with many adverse effects such as delaying function recovery, an increase in morbidity, mortality and health care cost. It also increases the risk of dementia for elderly patients.[5]

Preoperative anxiety is a common phenomenon in patients undergoing selective surgery. Preoperative anxiety has been shown to correlate to postoperative pain as well as POD. Previous studies demonstrated that preoperative anxiety is a significant risk factor for POD and postoperative cognitive dysfunction.[6] Gastrointestinal tumors rank in the top three of the incidence of global cancer. Surgical resection is the main method for treating gastrointestinal tumors. The proportion of elderly people with gastrointestinal tumor is more than 60%.[7] Due to the prolonged course, recurrent disease, long operational duration, poor prognosis, and high treatment cost, patients with gastrointestinal tumors are likely to experience serious preoperative anxiety, which further elevate their risk of POD.

Current interventions for POD include both non-pharmacological and pharmacological strategies. Non-pharmacological approaches, such as the Hospital Elder Life Program (HELP), emphasize reorientation, sleep hygiene, early mobilization, and nutritional support.[8] Pharmacological interventions include dexmedetomidine, an α2-adrenergic agonist with anti-inflammatory properties, and melatonin receptor agonists like ramelteon, though evidence for their efficacy remains inconclusive.[9,10] However, no gold-standard treatment has been established for POD, highlighting the need for further research.

Ketamine was introduced into clinical practice by 1970 and used extensively for anesthesia, analgesia and sedation.[11] Moreover, interest regarding its potential utilization for the treatment of major depressive disorder has increased.[12] Esketamine is a right-handed monomer of ketamine that has strong analgesic effects. The mechanism of esketamine is the same as ketamine, which works via non-competitive antagonism of N-methyl-D-aspartate (NMDA) receptors to inhibit the opening of its receptor channels. Esketamine has a high affinity for NMDA receptors, as much as four times that of ketamine.[13] The NMDA receptors are closely associated with cognitive function, and studies have shown that esketamine can modulates glutamatergic signaling by inhibiting NMDA receptor overactivation, thereby attenuating excitotoxicity while enhancing synaptic plasticity.[14] Additionally, recent studies have shown that esketamine not only inhibits pro-inflammatory cytokines (such as IL-6), but also enhances neurotrophic support by upregulating the brain-derived neurotrophic factor (BDNF) signaling pathway, which is critical for the survival of neurons and the protection of cognitive functions.[15,16] Esketamine also demonstrates rapid anxiolytic effects, likely mediated through the mammalian target of rapamycin (mTOR) pathway and AMPA receptor activation.[17,18] Due to its higher clearance rate in vivo and lower incidence of adverse events, esketamine is usually combined with sedative anesthetics and widely used in general anesthesia.[19] Collectively, esketamine demonstrates both anxiolytic and neuroprotective properties, indicating its potential to mitigate POD and protect postoperative cognitive function in elderly patients with preoperative anxiety. Currently, no studies have specifically examined the effects of esketamine on POD and cognitive function in elderly patients with preoperative anxiety.

In this study, we conducted a randomized controlled study in elderly patients undergoing gastrointestinal cancer surgery and with preoperative anxiety to explore the effects of a subanesthetic dose of esketamine on the incidence of POD and early cognitive function.

Methods

Trial Participants

Patients between the ages of 60 and 80 who were diagnosed with gastrointestinal malignancies based on imaging, pathology, and other relevant examinations at the Second Affiliated Hospital of Guangzhou Medical University were included in the trial if they met the surgical indications, had American Society of Anesthesiologists (ASA) physical status II to III, and had an Amsterdam preoperative anxiety and information scale (APAIS) score of 12 or higher.[20]

Exclusion criteria for the study included the following: (1) Mini-Mental State Examination (MMSE) score ≤ 26;[21] (2) deafness or language communication disorder; (3) severe risk of elevated intracranial pressure; (4) renal insufficiency (serum creatinine > 177 μmol/L); (5) liver dysfunction; (6) body mass index (BMI) ≥ 30 kg/m^2; (7) poorly controlled or untreated hypertension (resting systolic/diastolic blood pressure exceeding 180/100 mmHg); (8) mental illness or use of sedatives, antidepressants, or other drugs that affect drug metabolism; (9) sinus bradycardia or severe atrioventricular block; (10) untreated or insufficiently treated hyperthyroidism; (11) acute angle closure glaucoma; (12) allergies to the ingredient or excipients of esketamine.

Sample Size

PASS 15 software was used to calculate the sample size. Since all the subjects were divided into the esketamine group and placebo group, with the incidence of POD as the primary outcome, based on our pilot study results, the incidence rate of POD in the esketamine group was 8%, that in the placebo group was 36%. With a significance level (α) of 0.05, a power of 80%, the calculated total sample size for the two groups using PASS 15 software is 61 patients. Considering a dropout rate of 10%, at least 68 subjects were planned to be included in the study. Finally, we included 118 patients in the actual research process.

Randomization and Blinding

The study included 118 patients who were assigned randomly to the following two groups: esketamine (group E) and placebo (group P). Participant allocation was performed using a free Internet service (www.randomization.com). A computer-generated random list was created, following the principle of complete randomization with a 1:1 ratio. The group assignments were then sealed in opaque envelopes by the nurse anesthetist.

The dispensing and labeling of the study drug was checked by the pharmacist and the anesthesia nurse. Neither individual participated in the follow-up study, but both signed a confidentiality agreement to ensure the safety of the experimental protocol. On the day of the operation, a nurse not involved in the patient's care opened the envelope containing the data assigned by the study group. The nurse then prepared the indicated drug with 50 mL syringe in the operating room and labeled the syringe as the "study drug" along with the patient number. The anesthesiologists, patients, researchers in charge of follow-up, and statisticians were not aware of the random allocation until the final statistical analysis was complete. In cases of medical emergencies, such as patients' condition deteriorating during surgery or adverse events (AEs), the primary investigator documented the drug distribution. The specific "study medicine", either esketamine or saline, was recorded in the surgical anesthesia record sheet after the final statistical analysis was complete.

Research Procedure

All patients were interviewed 1 day before surgery (d0) to assess their preoperative anxiety using the Amsterdam preoperative anxiety and information scale (APAIS) and visual analogue simulation scale (VAS-A). Additionally, preoperative cognitive function was assessed using the MMSE. Once the patients were screened to validate they met the inclusion criteria, they and their relatives were informed about the research protocol and signed the informed consent form.

On the day of surgery, the patients were routinely connected to the monitoring equipment upon entering the operating room. At the same time, they received verbal education and comfort. Vital signs, including blood pressure (BP), electrocardiogram (ECG), respiratory rate (RR), pulse oxygen saturation (SpO2), and bispectral index (BIS), were monitored and recorded regularly. Prior to anesthesia induction, the patient received 100% oxygen via a mask for 10 minutes. To prevent excessive secretion, an intravenous injection of penehyclidine hydrochloride (0.5 mg) was administered. For intravenous induction, etomidate (0.3 mg/kg) and sufentanil (0.3 μg/kg) were used, and the 'study drug' (0.25 mL/kg) was administered based on the randomization protocol. The 'study drug' was a standardized 50 mL syringe containing either esketamine (1 mg/mL) or 0.9% normal saline for injection. Both of the saline and study drug are colorless transparent liquid. Subsequently, patients received cisatracurium (0.15 mg/kg) after entering a coma-like state. After 5 minutes of positive pressure ventilation, endotracheal intubation was performed using a visual laryngoscope, and a gastric tube was inserted. Subsequently, central venous catheterization and arterial catheterization were

performed. A sustained micro-pump of general anesthesia maintenance drugs was used for all patients, and a combination of intravenous and inhalation anesthesia was used to maintain the desired depth of anesthesia. Sevoflurane (1%-2%) was inhaled, and propofol (2–4 mg/kg*h) and remifentanil (0.05–0.15 μg/kg*min) were administered to maintain a BIS value between 40 and 60. The aim was to keep the mean arterial pressure (MAP) and heart rate (HR) fluctuation within 30% of the baseline levels. Cisatracurium was administered at a dosage of 4–6 mg every 40–60 minutes. 0.5 mg Tropisetron was administered at the 10min before the end of surgery. The body temperature was preserved at 36°C during the operation and post-anesthesia care unit (PACU). All the enrolled patients were given postoperative patient-controlled analgesia (PCA) pumps. The formula of the PCA pump was sufentanil 100 ug + tropisetron 10 mg, mixed to 100 mL, with a pump rate of 2 mL/h, and a PCA volume of 2 mL, with a lockout time of 20 minutes. After the patients regained consciousness after extubation, the PCA pumps were turned on.

Outcome Measures

The primary outcome of this study was to determine the incidence of POD and cognitive function within 7 days after the operation (d1 to d7). POD was evaluated using the Chinese version of the 3-Minute Diagnostic Confusion Assessment Method (3D-CAM), which has a sensitivity of 84%–99% and a specificity of 90%-97%.[22,23] The severity of POD was assessed using the CAM Severity Profile Scale (CAM-S). Mild to moderate delirium was defined as a CAM-S score of 3–5, while severe delirium was defined as a CAM-S score of 6–7.[24] The postoperative cognitive function of patients was assessed using MMSE, a validated screening test for cognitive impairment. This test evaluates language skills, direction, memory and recall, numerical skills, and attention and provides a numerical value.[25] The patients' baseline MMSE scores were determined during preoperative visits. Using preoperative MMSE (Mini-Mental State Examination) baseline scores as reference, we calculated postoperative deviations from baseline. Patients demonstrating deviations exceeding twice the standard deviation with concurrent impairment across multiple cognitive domains were diagnosed with dNCR.[26,27]

The following were evaluated as secondary outcomes. Anxiety levels within 7 days after the operation were measured using the VAS-A. The incidence rate of restlessness during the awakening period in PACU was recorded. Various vital signs were recorded at multiple time points: 5 minutes after entering the operating room (T0), completion of intubation (T1), five minutes after intubation (T2), beginning of surgery (T3), 10 minutes after the start of surgery (T4), end of surgery (T5), and time of leaving the PACU (T6). The levels of serum S100β, IL-6, and NSE were also measured at three different time points (T0, T5, d1). Hemodynamic adverse events during anesthesia induction (T1 to T3) and anesthesia maintenance (T3 to T5) were recorded; these included hypotension events, bradycardia events, hypertension events, and tachycardia events. The numeric rating scale (NRS) score was used to assess the patients' resting pain and activity pain upon discharge from the PACU, as well as within 7 days after the operation, and their analgesia pump use. The intraoperative intravenous maintenance dosage and the time it took for patients to experience bowel movements and pass gas after the operation were also recorded.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics for Windows, version 27.0 (IBMCorp., Armonk, N.Y., USA). For continuous variables, the data distribution was assessed using the Shapiro–Wilk test for normality. Homogeneity of variance was confirmed via Levene's test. Normally distributed data are expressed as mean (standard deviation, SD) and analyzed with either the independent samples *t*-test or repeated-measures ANOVA. Non-normally distributed data are presented as median (interquartile range, IQR) and analyzed using the Mann–Whitney *U*-test or Friedman test. The Bonferroni correction was applied after significant results were obtained in either repeated-measures ANOVA or Friedman tests. For post-hoc pairwise tests following a significant Friedman test, Bonferroni-adjusted Wilcoxon signed-rank tests were performed. Counting data, such as the incidence of POD, are expressed as the number of cases (percentage), and the chi-square/Fisher's exact test was used. Missing data due to participant dropouts were managed by listwise deletion (complete-case analysis), excluding patients with incomplete datasets from the analysis. Statistical charts were created using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com. P-values less than 0.05 were considered statistically significant.

Results

After exclusion (Figure 1), 181 patients have been assessed for eligibility from September 2022 to September 2023, 63 patients declined to participate in study. Therefore, 118 enrolled patients were assigned randomly to the esketamine or placebo group. In the esketamine group, 5 patients failed to cooperate with postoperative evaluation and 4 patients failed to cooperate with the postoperative blood drawing. In the placebo group, 4 patients failed to cooperate with postoperative evaluation and 5 patients failed to cooperate with the postoperative blood drawing. 100 patients were finally included in the statistics, including 50 patients in the esketamine group and 50 patients in the placebo group. Baseline characteristics and perioperative data for the patients such as age, BMI, ASA, smoking, anemia and preoperative anxiety were collected for each enrolled patient. There was no significant difference between esketamine group and control group (Table 1).

Compared to the placebo group, the esketamine group had a significantly lower incidence of POD (12/50 [24.00%] vs 24/50 [48.00%], P = 0.0211) (Table 2). There was no significant difference in the incidence of severe postoperative delirium between the two groups among the patients with POD. On d1, the median MMSE score (IQR) of the esketamine group was significantly higher than that of the placebo group (29.0 [28.0 to 30.0] vs 27.25 [25.0 to 29.0]; Bonferroni-adjusted P = 0.0014) (Figure 2A). The cumulative incidence of dNCR within 7 days after surgery was significantly lower in the esketamine group than in the placebo group (13/50 [26.0%] vs 27/50 [54.0%], P = 0.0043) (Figure 2B) (Supplementary Table 1).

On d1, the VAS-A score was lower for the esketamine group than the placebo group (3.00 [2.00 to 4.00] vs 4.00 [2.75 to 5.00]; Bonferroni-adjusted P = 0.0126) (Figure 3) (Supplementary Table 2). Additionally, there were no significant differences in the resting or active state pain scores (NRS) from d1 to d7 (P > 0.05). The PCA press times at the time of leaving the PACU and on d1 and d2 were also not significantly different between the two groups (P > 0.05). Furthermore, there were no significant differences in the postoperative exhaust time points between the two groups (P > 0.05) (Supplementary Table 3).

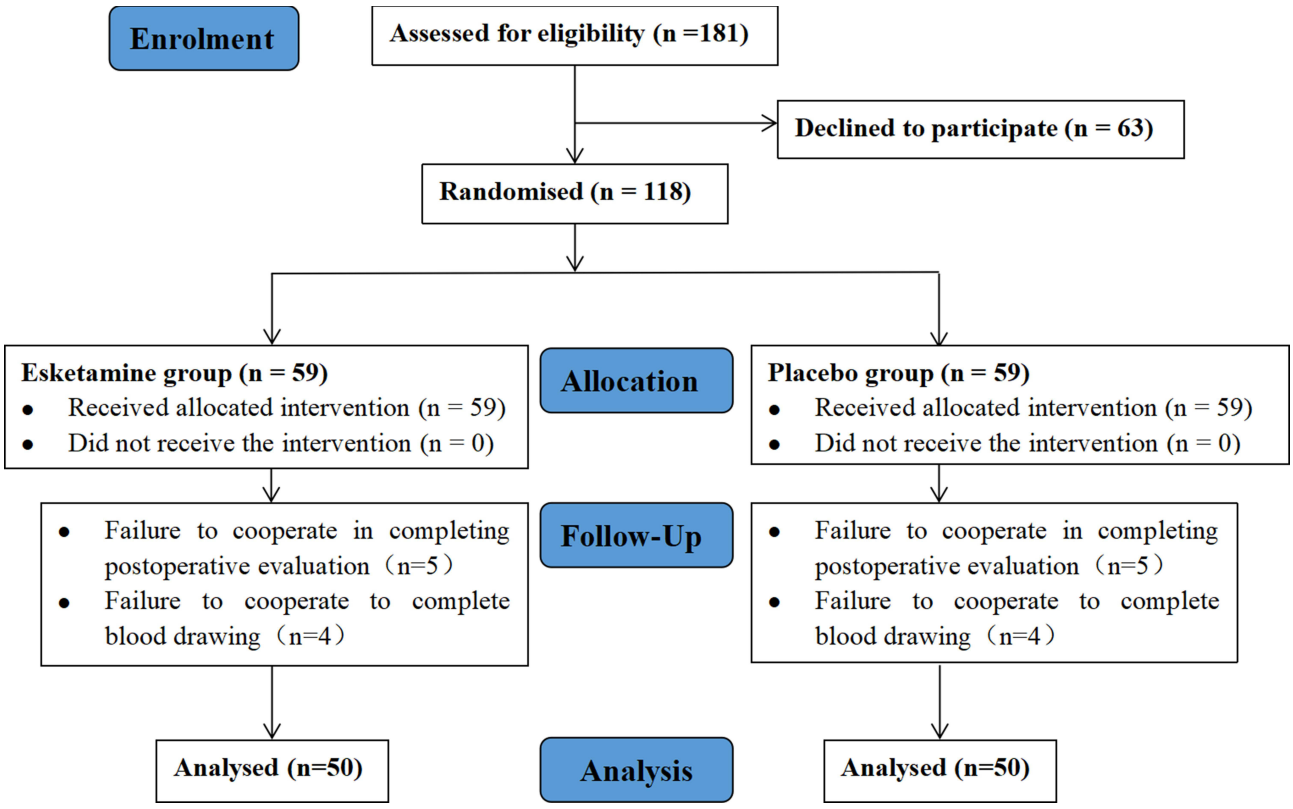

Figure 1 CONSORT flow diagram illustrating the study design and participant progression.

https://doi.org/10.2147/DDDT.S528902

Table 1 Demographic and Baseline Data in Patients

	Esketamine n = 50	Placebo n = 50	*P*
Age (years)	67.38 (4.11)	68.26 (4.74)	0.3239
Females	18 (36.00%)	25 (50.00%)	0.1574
BMI (body mass index; kg/m^2)	22.60 (2.47)	21.95 (2.36)	0.1844
ASA physical status			
1-2	44 (88.00%)	44 (88.00%)	> 0.999
3	6 (12.00%)	6 (12.00%)	
Preoperative MMSE score (d0)	29.00 [29.00 to 30.00]	29.00 [28.00 to 30.00]	0.2196
Amsterdam preoperative anxiety scale score (APAIS) (d0)	18.80 (3.84)	17.94 (3.32)	0.2346
Visual anxiety simulation scale (VAS-A) score (d0)	5.0 [3.0 to 7.0]	5.0 [4.0 to 6.0]	0.7781
Preoperative complications			
Hypertension	18 (36.00%)	21 (42.00%)	0.3783
Diabetes	5 (10.00%)	5 (10.00%)	>0.999
Coronary heart disease	2 (4.00%)	1 (2.00%)	>0.999
Tumor location			
Stomach	9 (18.00%)	8 (16.00%)	0.9518
Colon	29 (58.00%)	29 (58.00%)	
Rectum	12 (24.00%)	13 (26.00%)	
Duration of anesthesia (min)	278.9 (70.9)	272.6 (64.23)	0.6433

Notes: d0: 1 day before surgery. The data are presented as mean (standard deviation), median (25th percentile, 75th percentile), or number (percent).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; MMSE, mini-mental state examination; VAS-A, Visual anxiety simulation scale.

Table 2 The Outcome of Postoperative Delirium (POD)

	Esketamine (n = 50)	Placebo (n = 50)	OR (95% CI)	*P*
POD within 7 days after surgery	12 (24.00%)	24 (48.00%)	0.371 (0.164 to 0.840)	0.0211 *
d1	9 (75.00%)	18 (75.00%)		
d2	2 (16.67%)	6 (25.00%)		
d3	0	0		
d4	1 (8.33%)	0		
d5 to d7	0	0		
Cumulative severe POD (CAM-S > 5)	3 (25.00%)	7 (26.17%)	0.810 (0.192 to 3.542)	> 0.999

Notes: POD: postoperative delirium; the data of POD within 7 days after surgery are presented as number (percent). CAM-S: CAM Severity Profile Scale, mild to moderate delirium was defined as a CAM-S score of 3–5, while severe delirium was defined as a CAMS-S score > 5. d1: postoperative day 1; d2: postoperative day 2; d3: postoperative day 3; d4: postoperative day 4; d5: postoperative day 5; d6: postoperative day 6; d7: postoperative day 7. *p < 0.05.

No significant differences were observed between the esketamine and placebo groups in intraoperative doses of remifentanil or propofol (P > 0.05). The incidence of restlessness in the PACU was not significantly different between the esketamine group and the placebo group (P > 0.05). At T0, T1, T2, T3, T4, T5, and T6, there were no significant differences between the two groups for the main vital signs (P > 0.05 for HR, MAP, and BIS) (Figure 4). The incidence of hypotensive events from T1 to T3 was significantly lower in esketamine group than placebo group (24.00% vs 44.00%, P = 0.0095) (Table 3). Additionally, the incidence of bradycardia events at T1-T3 was lower in esketamine group than placebo group (12.00% vs 28.00%, P = 0.0455). The incidence of hypertension and tachycardia events at T1-

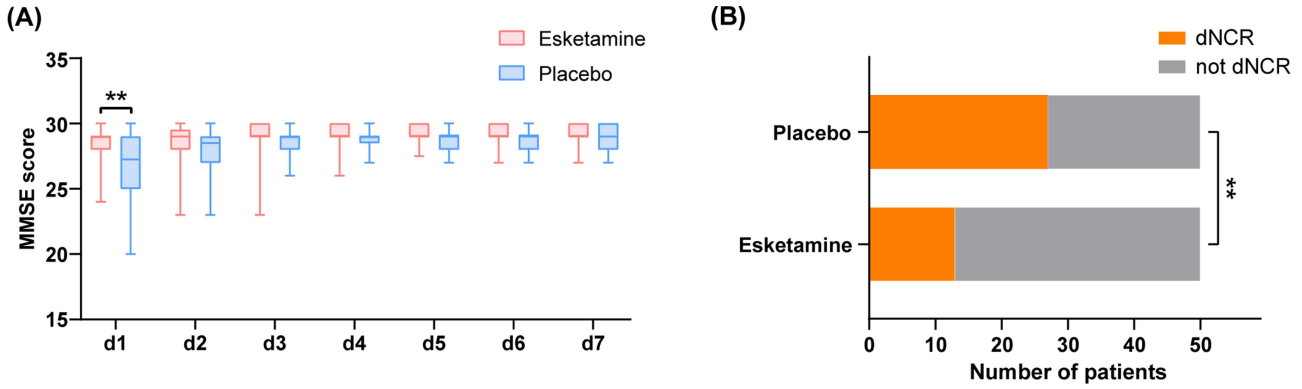

Figure 2 (**A**) Comparison of MMSE scores between the esketamine and placebo groups. $^{**}P < 0.01$ after Bonferroni-adjusted Wilcoxon signed-rank test. (**B**) Comparison of the incidence of dNCR between the esketamine and placebo groups. $^{**}P < 0.01$ from Chi-square test.
Abbreviations: MMSE, Mini-Mental State Examination; dNCR, delayed neurocognitive recovery.

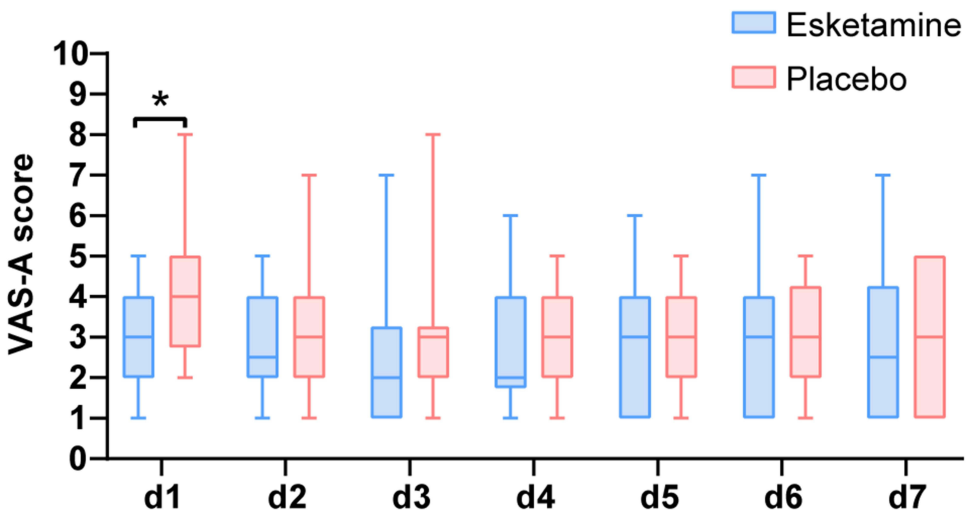

Figure 3 Comparison of VAS-A scores between the esketamine and placebo groups.$^{*}P < 0.05$ after Bonferroni-adjusted Wilcoxon signed-rank test.
Abbreviation: VAS-A, Visual anxiety simulation scale.

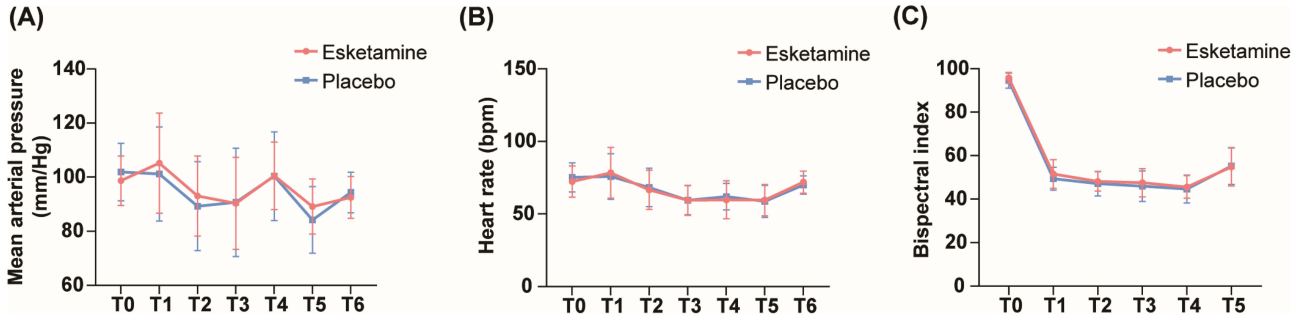

Figure 4 Mean arterial pressure (MAP), heart rate (HR), and bispectral index (BIS) for all patients. (**A**) Comparison of MAP at different time points between the esketamine and placebo groups; (**B**) Comparison of HR at different time points between the esketamine and placebo groups; (**C**) Comparison of BIS at different time points between the esketamine and placebo groups. There were no significant differences between the esketamine and placebo groups.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; BIS, bispectral index.

https://doi.org/10.2147/DDDT.S528902

Table 3 Secondary Outcomes During Operation

	Esketamine (n = 50)	Placebo (n = 50)	OR (95% CI)	*P*
Cumulative dose of remifentanil (μg/kg/min)	0.061 (0.018)	0.058 (0.012)		0.441
Cumulative dose of propofol (mg/kg/h)	2.322 (0.558)	2.326 (0.500)		0.970
Restlessness in the PACU	11 (22.00%)	13 (26.00%)	0.803 (0.316 to 1.946)	0.6396
Hypotension events				
T1 to T3	12 (24.00%)	22 (44.00%)	0.402 (0.178 to 0.915)	0.0095**
T3 to T5	16 (32.00%)	19 (38.00%)	0.768 (0.339 to 1.695)	0.5294
Bradycardia events				
T1 to T3	6 (12.00%)	14 (28.00%)	0.351 (0.121 to 1.000)	0.0455*
T3 to T5	11 (22.00%)	10 (20.00%)	1.128 (0.417 to 2.837)	0.8061
Hypertension events				
T1 to T3	4 (8.00%)	3 (6.00%)	1.362 (0.349 to 5.625)	> 0.999
T3 to T5	10 (20.00%)	9 (18.00%)	1.139 (0.450 to 2.989)	0.7988
Tachycardia events				
T1 to T3	3 (6.00%)	2 (4.00%)	1.532 (0.301 to 8.897)	> 0.999
T3 to T5	3 (6.00%)	4 (8.00%)	0.734 (0.178 to 2.867)	> 0.999

Notes: Hypotension event: blood pressure fluctuation is 20% lower than baseline or SBP is less than 90 mmHg; Hypertension event: blood pressure fluctuation is 20% higher than SBP baseline or SBP is greater than 160 mmHg; Bradycardia event: heart rate is less than 50 beats/min; Tachycardia event: heart rate is higher than 100 bpm. T1: completion of intubation; T2: five minutes after intubation; T3: beginning of surgery; T5: end of surgery. The data are presented as mean (standard deviation) or median (25th percentile, 75th percentile). $^{**}P < 0.01$, $^{*}P < 0.05$.

T3 was not significantly different between the two groups (P > 0.05). From T3 to T5, the incidence of hypotension, bradycardia, tachycardia, and hypertension did not differ significantly between groups (P > 0.05) (Table 3). No other clinically significant adverse effects were reported in either group.

At 5 minutes after entering the operating room (T1) and at the end of surgery (T5), the serum concentrations of IL-6, S100β, and NSE were not significantly different between the esketamine and placebo groups (Bonferroni-adjusted P > 0.05). At 24 hours after surgery (d1), the serum IL-6 concentrations were significantly lower in the esketamine group compared to the placebo group (Bonferroni-adjusted P < 0.0001) (Figure 5A). Additionally, the serum S100β protein concentration was lower in the esketamine group at d1 (Bonferroni-adjusted P = 0.0082) (Figure 5B). There was no significant difference in the serum NSE concentration between the two groups on d1 (Bonferroni-adjusted P > 0.05) (Figure 5C) (Supplementary Table 4).

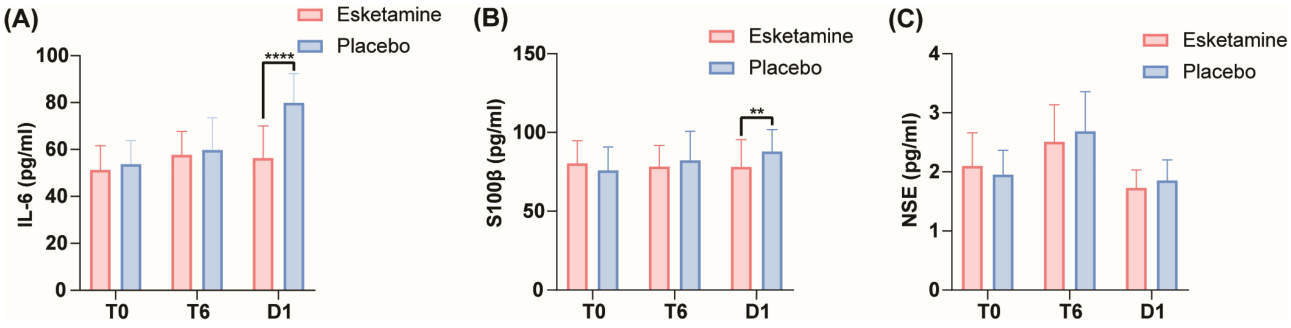

Figure 5 Serum IL-6, S100β, and NSE levels of the subjects in the two groups. (**A**) Comparison of serum IL-6 concentrations in the esketamine and placebo groups at T0, T6, and d1; (**B**) Comparison of serum S100β protein concentrations between the two groups at three time points; (**C**) Comparison of serum NSE concentrations at different time points between the two groups. **** $P < 0.0001$, ** $P < 0.01$ after Bonferroni correction.
Abbreviations: IL-6, interleukin-6; NSE, neuron-specific enolase.

Discussion

Esketamine, an FDA-approved drug for the treatment of depression, has been demonstrated to exert rapid, powerful, and long-lasting antidepressant effects. It can also rapidly alleviate preoperative anxiety, especially the acute anxiety induced by surgical events.[28] In this randomized, double-blind, placebo-controlled study, we investigated the safety and efficacy of a low dose of esketamine (0.25 mg/kg) administered during anesthetic induction. Our findings indicate that a low dose of esketamine can reduce the occurrence of POD and improve postoperative cognitive function in elderly patients with gastrointestinal tumors who also experience preoperative anxiety.

The incidence of preoperative anxiety is reported to be as high as 60–80%.[29] Anxiety has been identified as a significant risk factor for PND in the elderly, with higher anxiety levels associated with a greater risk of cognitive impairment.[30] In this study, we evaluated the anxiety levels of patients before and after surgery. The results indicated that elderly patients with gastrointestinal tumors and preoperative anxiety experienced a decrease in anxiety levels after a successful surgery. Furthermore, the anxiety levels on postoperative day 1 were significantly lower in the esketamine group than the placebo group, suggesting that a low dose of esketamine during anesthesia induction can effectively alleviate postoperative anxiety. Previous research has demonstrated that a single dose of ketamine (0.25 to 1 mg/kg) to anxious patients has anxiolytic effects; these effects occur within 1 hour of dosing and last for approximately one week.[31] Additionally, a recent retrospective study indicated that a single dose of esketamine can rapidly and significantly reduce patient anxiety, and the effect seems to last for 1 day.[32] In our study, we also found that the use of a small dose of esketamine during the induction period can effectively relieve anxiety in patients in the early postoperative period. It is worth noting that esketamine has a relatively short half-life (287.5 ± 110.2 min). However, to date, pharmacokinetic data in humans is limited. Esketamine is thought to share similar pharmacodynamics and pharmacokinetic properties with ketamine. Metabolic studies have shown that ketamine and esketamine, as well as its metabolites norketamine, dehydronorketamine, and hydroxynorketamine, may have long half-life times and thus exert analgesic and anti-anxiety actions even at low plasma concentrations.[33] Similarly, the subanesthetic dose of esketamine had postoperative anti-anxiety effects in this study, likely due to its blockade of other neuronal receptors such as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or mTOR (mammalian target of rapamycin).[34,35]

It is well-established that PND is closely related to neuroinflammation.[36] Researchers have confirmed that the higher the levels of pro-inflammatory cytokines are, the worse cognitive function is.[37] IL-6, a pro-inflammatory cytokine, plays a crucial role in hippocampal injury and contributes to inflammation-related learning and memory impairment.[38] One meta-analysis has shown that the occurrence of postoperative cognitive dysfunction is associated with serum IL-6 concentrations, indicating that IL-6 could serve as an indicator for evaluating postoperative cognitive dysfunction.[39] Previous in vitro investigations have also indicated that esketamine could alleviate LPS-induced neuroinflammation by reducing autophagy in neuronal cells in hippocampal tissues and decreasing the levels of proinflammatory cytokines such as IL-1β, IL-6, and TNF-α.[40] Similar to our study, a recent randomized controlled trial demonstrated that a subanesthetic dose (0.15 mg/kg) of esketamine significantly reduced plasma levels of IL-6 and S100β.[41] Our study has further validated that anesthesia induction with a low dose of esketamine reduces serum IL-6 levels in elderly patients with anxiety, suggesting esketamine may reduce the incidence of POD and cognitive impairment due to its anti-inflammatory effects.

Serum S100β is a calcium-binding protein found mainly in astrocytes and oligodendrocytes.[42] When brain injury occurs, the blood-brain barrier is damaged, and glial cells are activated to release S100β into the CSF and blood.[43] For these reasons, S100β is considered a biomarker for brain injury and is reportedly correlated with postoperative cognitive dysfunction and delirium. Our study revealed a significant decrease in the serum S100β protein concentration in the esketamine group compared to the placebo group 24 hours after the operation, indicating that the low-dose esketamine intervention during anesthesia induction may reduce perioperative brain injury and protect brain tissue.

NSE is a highly specific marker of neurons and neuroendocrine cells. This protein can provide quantitative measures of brain damage and improve the diagnosis and outcome evaluation in traumatic brain injury, ischemic stroke, intracerebral hemorrhage, and seizures. Several observational studies have shown a close association between serum NSE levels and postoperative cognitive function with 24 h and at 2d and 9d.[44] However, a RCT study showed significantly higher NSE levels in the POCD patients compared to the patients without POCD at 2 days, but not within 24 h.[45] In our study, serum levels of

NSE were measured only at T0, T5, and d1 time points, with no significant differences observed between the esketamine and control groups at any of these intervals. This outcome may be attributed to the restriction of our measurements to the initial 24-hour postoperative period, whereas NSE detection likely requires extended monitoring time points.

Elderly patients often experience issues such as decreased cardiac function, reduced cardiac output, and poor vascular elasticity.[46] Additionally, long-term fasting and gastrointestinal symptoms prior to surgery cause elderly patients undergoing elective surgery for gastrointestinal tumors to be more susceptible to hypotension and adverse cardiovascular events during general anesthesia.[47] In our study, patients in the esketamine group exhibited significantly lower rates of hypotension and bradycardia from the completion of intubation to the start of surgery. Esketamine does exhibit sympathetic activity, which can increase blood pressure levels by enhancing cardiac output.[48] The use of low-dose esketamine may thus effectively counteract the hemodynamic inhibition caused by other anesthetic drugs without increasing the incidence of hypertension and tachycardia events.

In this study, the total amount of remifentanil administered to the esketamine group was not different from that administered to the placebo group. Moreover, there were no significant differences between the two groups regarding pain scores (NRS) and the number of analgesic pump compressions. This specific finding suggests that a single low-dose esketamine may not have significant effects on the analgesic drug demand during operation or early postoperative pain control. In our study, each patient used a postoperative analgesic pump with sufentanil as the main analgesic drug. Sufentanil pumped continuously at a background speed can produce strong analgesic effects. This finding agrees with data from Jaksch, who indicated that when adequate opioid analgesia was administered routinely during the perioperative period, low-dose esketamine did not contribute to postoperative pain relief; additionally, it did not reduce the demand for postoperative analgesia.[49] A possible explanation for this finding is that the continuous intraoperative and postoperative administration of opioids appears to inhibit the release of primary afferent transmitters at the presynaptic opioid receptors at the end of the C fiber. As a result, the effectiveness of NMDA receptor antagonist administration does not seem obvious. In addition, our results showed that the total amount of propofol administered during anesthesia maintenance was not different between the esketamine and placebo groups. This is different from another study in which esketamine was given as a single injection plus intravenous maintenance for an Encoscopic RetrogradCholangio-Pancreatography (ERCP) operation,[50] showing that low-dose esketamine reduced the total amount of propofol required for sedation. It should be noted that the operation time of gastrointestinal tumor resection surgery in the present study was much longer than the ERCP surgery. Although esketamine has sedative and analgesic effects, a smaller single dose during anesthesia induction seems to have no effect on intraoperative sedation and analgesic requirements.

There were several limits to this study. Firstly, this study is a single-centred randomized study, the sample size is relatively small. Further research with a larger sample size and multiple clinical research centers is needed to validate the neuroprotection effect of esketamine on elderly patient. Secondly, anxiety and depression are often comorbid and may jointly influence cognitive outcomes. We evaluated the anxiety state in this study for postoperative patients, but we do not have an assessment depression status for the patient. Thirdly, in this study, the serum level of IL-6 and S100β is used to reflect the neuroinflammation and brain injury. Although the content determination in the cerebrospinal fluid is more appropriate, the ethic and the feasibility of actual operation limit the application of cerebrospinal fluid specimen in this study. Also, we assessed neurocognitive function only at 7 days postoperatively and did not evaluate long-term outcomes at 30 days or 6 months after surgery We will take into consideration the possibility of extending the follow-up period in our future related research. Moreover, further research exploring the specific mechanisms by which esketamine improves cognitive function is a worthy pursuit in the future.

Given that preoperative anxiety has become common, the potential neurological benefits of esketamine on patients with preoperative anxiety would have important clinical significance. Importantly, low-dose esketamine leads to more stable hemodynamics during induction stage, indicating it can be used as a promising induction anesthetic for the elderly patients.

Conclusion

In this study, we found that a low dose of 0.25 mg/kg esketamine during anesthesia induction reduces the incidence of POD and improve early postoperative cognitive function in elderly patients with preoperative anxiety who undergo

gastrointestinal tumor surgery. Moreover, the elderly patients administered with esketamine showed more stable hemodynamics during induction. Esketamine administration relieve post-opereative anxiety, but had no effect on post-operative pain and analgesics consumption.

Data Sharing Statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics Approval and Consent to Participate

The study was conducted following the Consolidated Standards of Reporting Trials statement and the Declaration of Helsinki. This study was approved by the Clinical Research and Application Ethics Committee of the Second Affiliated Hospital of Guangzhou Medical University (Reference: 2022-hs-25-02) and registered at the Chinese Clinical Trial Registry (registration no. ChiCTR2200064031). Prior to participation, all patients were fully informed of the research proposal and provided written informed consent.

Acknowledgments

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Funding

This Funding was supported by the Guangdong Basic and Applied Basic Research Foundation (No. 2022A1515010810 and No. 2020A1515010070), Guangzhou City and College Joint Project (20220102153), and Chen Xiao-ping Foundation for the Development of Science and Technology of Hubei Province (CXPJJH125022-09).

Disclosure

The authors declare no competing interests in this work.

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