Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

CLINICAL TRIAL REPORT

Effect of Perioperative Subanesthetic Dose of Esketamine on Postoperative Recovery Quality in Patients Undergoing Laparoscopic Gastrointestinal Surgery: A Randomised, Double-Blind, Controlled Trial

Ye Zhang[1,2], Shuqin Li[1,2], Cheng Wu[1,2], Liuyi Song[1,2], Li Hu[1,2], Jian Lu[1,2]

[1]Department of Anesthesiology, The Second Hospital of Jiaxing, The Second Affiliated Hospital of Jiaxing University, Jiaxing City, People's Republic of China; [2]Jiaxing Key Laboratory of Basic Research and Clinical Transformation of Perioperative Precision Anesthesia, Jiaxing City, People's Republic of China

Correspondence: Jian Lu, Email ljp200681@163.com

Background: To evaluate the effect of perioperative subanesthetic dose of esketamine on the postoperative recovery quality in patients undergoing laparoscopic gastrointestinal surgery.

Methods: A total of 144 patients undergoing elective surgery for gastrointestinal tumors were selected and randomly assigned to either the esketamine group or the control group, with 72 patients in each group. Based on the standardized general anesthesia protocols, the esketamine group received an intravenous injection of esketamine at a dose of 0.2 mg/kg during the induction of anesthesia and an additional 0.2 mg/kg 30 minutes before the end of the surgery. Patient-controlled intravenous analgesia (PCIA) was administered for 48 hours, the esketamine group was treated with sufentanil (0.04 μg/kg/h) combined with esketamine (0.02 mg/kg/h) and sufentanil (0.04 μg/kg/h) was used as the control group. The scores of 40-items Quality of Recovery Scale (QoR-40) were recorded one day before surgery, one day after surgery, three days after surgery, and five days after surgery. Numerical Rating Scale (NRS) pain scores were recorded at postoperative intervals of 6 hours, 24 hours, 36 hours, and 48 hours. Levels of interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and brain-derived neurotrophic factor (BDNF) in venous blood were analyzed prior to entering the operating room, upon arrival at the recovery room, and on the second postoperative day.

Results: A total of 140 patients completed this study. Compared to the control group, the QoR-40 scores in the esketamine group were significantly higher at 1, 3, and 5 days post-surgery ($Z = -10.080$, $Z = -8.178$, $Z = -4.139$, $P < 0.05$). In addition, the resting NRS scores were significantly lower at 6 hours, 24 hours, 36 hours, and 48 hours post-surgery in the esketamine group ($Z=-6.322$, $Z=-5.736$, $Z=-6.563$, $Z=-5.920$, $P < 0.05$).

Conclusion: This study found that the perioperative use of subanesthetic esketamine improved early postoperative recovery quality and reduced postoperative pain levels in patients undergoing laparoscopic gastrointestinal surgery.

Keywords: esketamine, recovery quality, laparoscopic gastrointestinal surgery, pain, anesthesia

Introduction

Gastrointestinal tumor is a common clinical malignant tumor of the digestive system, with an increasing incidence in recent years.[1] Patients with gastrointestinal tumors are accompanied by anxiety, depression, sleep disorders, pain, and other symptoms during the perioperative period, which can trigger a stress response.[2] This stress reaction increases the occurrence of postoperative adverse events and affects postoperative rehabilitation. In addition, due to preoperative bowel preparation and fasting, most patients have suffered insufficient effective blood volume. These concomitant conditions are frequently linked to the quality of postoperative recovery.[3] As anesthesiologists, we are responsible for ameliorating the postoperative experience

Received: 24 November 2024
Accepted: 17 July 2025
Published: 1 August 2025

of patients by reducing the incidence of postoperative adverse reactions and shortening the recovery time for daily activities. Our goal is to improve the overall quality of postoperative recovery of patients.[4]

The choice of perioperative anesthesia drugs has an important influence on the postoperative recovery of patients.[5] Esketamine is a right-handed isomer of ketamine and n-methyl-D-aspartate (NMDA) receptor antagonist. It is twice as potent as ketamine and produces a stronger analgesic effect.[6,7] Due to the dose-dependent side effects of ketamine, esketamine has a low incidence of adverse reactions.[8] In addition, esketamine has a high clearance rate and rapid metabolism, which enhances the controllability of anesthesia, allowing patients to wake up more quickly and safely.[9] Recent studies on esketamine in patients with gastrointestinal tumors have focused on conventional indicators of recovery, such as fatigue syndrome, emotional response, tumor growth, pain, and subanesthetic doses of ketamine have been shown to reduce the production of inflammatory factors and diminish the inflammatory response.[10–13] Data to assess overall recovery outcomes from the perspective of patients with gastrointestinal tumors is insufficient. The 40-items Quality of Recovery Scale (QoR-40) score is a patient-centered measure designed to assess the health status of patients following surgery and anesthesia. QoR40 is reliable, effective, and demonstrates high clinical acceptability.[14,15]

Therefore, this study was designed to investigate the effects of perioperative intravenous administration of low-dose esketamine on early recovery quality in patients undergoing laparoscopic gastrointestinal surgery, as well as its impact on postoperative inflammatory responses and pain. To establish a patient-centered perioperative anesthesia management program for patients with laparoscopic gastrointestinal surgery, with the goals of enhancing the quality of postoperative recovery and promoting the recovery process for patients.

Materials and Methods

Study Design and Participants

This prospective, randomized controlled trial has been approved by the Ethics Committee of the Second Hospital of Jiaxing (JXEY-2022ZFYJ178). This study complied with the 1964 Helsinki Declaration and its later amendments. The study was registered at chictr.org (ChiCTR2300070160). All patients in this study were initiated after the completion of clinical trial enrollment, and written informed consent was obtained from all enrolled patients or their guardians for participation in this study.

Patients undergoing elective laparoscopic gastrointestinal surgery were selected as the study subjects. Inclusion criteria: patients aged from 18 to 75 years, the median age between the two groups is 69.0 vs 69.5, the male/female between the two groups was, respectively, 44/26 and 40/30, ASA I–III, gastrointestinal malignancy surgery, no history of mental disorders, dementia, or cognitive impairment before surgery, all scores could be completed. Exclusion criteria: patients who are unwilling to participate in the study, those with a history of drug contraindications, and individuals who are unable to cooperate with the study.

Randomization and Blinding

Using SPSS software (version 21.0, SPSS, Chicago, United States), random numbers were generated in a 1:1 ratio to randomize patients into esketamine and control groups. During the study period, patients received either esketamine or placebo (0.9% saline) administered by nurses, in accordance with the random number assignment. Patients, clinicians (including surgeons and anesthesiologists), as well as all researchers who performed preoperative and postoperative assessments and data collection were unaware of the group assignments.

Study Interventions

Esketamine was administered intravenously at a dosage of 0.2 mg/kg during the induction of anesthesia, and again at 0.2 mg/kg 30 minutes prior to the end of the surgery. PCIA was analgesia for 48 hours, the esketamine group was treated with sufentanil (0.04 μg/kg/h) combined with esketamine (0.02 mg/kg/h) and sufentanil (0.04 μg/kg/h) was used for the control group.

Anesthesia Management

After arriving at the operating room, all patients were monitored using noninvasive blood pressure (NIBP), pulse oximetry (SpO_2), 5-lead electrocardiography (ECG), partial pressure of end-tidal CO_2 ($PetCO_2$), and temperature. Additionally, the bispectral index (BIS, Aspect, USA) was utilized to measure the depth of sedation. Anesthesia was induced through the intravenous administration of esketamine (Jiangsu Hengrui Pharmaceutical Co., LTD., batch number: 230520BL) 0.2 mg/kg, sufentanil (Yichang Renfu Pharmaceutical Co., LTD., batch number: 31A101612) 0.4–0.5 μg/kg, Propofol (Beijing Fresenius Kabi Medical Co., LTD., batch number: 16SI8685) 1–2 mg/kg, etomidate (Jiangsu Hengrui Pharmaceutical Co., LTD., batch number: TYT23J18) 0.2 mg/kg and cisatracurium (Jiangsu Hengrui Pharmaceutical Co., LTD., batch number: 20071411) 0.2 mg/kg, Endotracheal intubation was performed under using a laryngoscope, and the patient was connected to a ventilator with a tidal volume of 6–8 mL/kg. Adjust the breathing rate to maintain the end-expiratory PCO_2 at 35–45 mmHg. After intubation, 1–2% sevoflurane (Hangzhou MSD Pharmaceutical Co., LTD., batch number: 20101531) was inhaled, propofol 4–6 mg/kg/h and remifentanil (Yichang Renfu Pharmaceutical Co., LTD., batch number: 30A00401) 0.1–0.3 μg/kg/min were injected intravenously to maintain the depth of anesthesia. BIS values were maintained at 40–55. The heart rate and arterial blood pressure were maintained within 20% of baseline levels. Nasopharyngeal temperature was maintained ≥36°C. Postoperative analgesics were administered for PCIA.

Study Outcomes

The main outcome of this study was the recovery quality scores measured one day before surgery and one, three, and five days post-surgery, which were evaluated using the QoR-40 scale. The QoR-40 assesses the overall recovery of patients through 40 items across five dimensions; including physical comfort (12 items), physical independence (5 items), pain (7 items), emotional state (9 items), and psychological support (7 items).[16] The higher the score, the better the quality of postoperative recovery. The secondary outcome measures were resting NRS pain scores assessed at 6, 24, 36, and 48 hours post-surgery. The NRS scale utilizes an 11-point system, where "0" indicates no pain and "10" represents the worst possible pain. NRS scores are categorized as mild (1–3), moderate (4–6), or severe (7–10).[17,18] Rescue analgesia was performed when the NRS score was greater than 4. Additionally, changes in perioperative plasma levels of IL-1β, IL-6, and BDNF were detected by enzyme-linked immunosorbent assay (ELISA).[19]

Sample Size Calculation

The sample size was calculated based on the QoR-40 score for the main outcome measure. The small clinically important difference (MCID) in the QoR-40 scale was 6.3.[16] The sample size was calculated by G*Power 3.1. Based on the preliminary study data, the effect size is 0.6. Given a significance set at the level of 0.05, with a 2-sided, power at 90%, 120 patients were needed, a dropout rate of 15%, the final sample size was determined to be 69 patients each group.

Statistical Analysis

Data were analyzed with the SPSS 21.0 (IBM, SPSS, Inc., Chicago, IL). The normality and homogeneity of data variance were confirmed by Shapiro–Wilk and Levene tests, respectively. The levels of plasma IL-6 and TNF-α were analyzed by two-way repeated measures ANOVA, with "group" as the between-subject factor and "time" as the within-subject factor, and by Mauchly's Sphericity test. When the assumption of sphericity was violated, the Greenhouse–Geisser correction was applied to the repeated measures ANOVA. Bonferroni correction was then used for post hoc pairwise comparisons to control for multiple testing. The levels of plasma BDNF were presented as median (interquartile range), and the Friedman test was used for comparison at different time points within the group, the Nemenyi test was used for post hoc, and the Mann–Whitney test was used for comparison between groups at different time points and Bonferroni correction was used for multiple comparisons. Continuous data were expressed as the mean±SD and were analyzed by the unpaired, two-tailed *t*-test for normally distributed data. The recovery quality score and resting NRS score were indicated as median (interquartile range) and analyzed using the Mann–Whitney test. Categorical variables were reported as number (%) and were analyzed with Pearson's chi-square test or Fisher's exact test, as appropriate. $P < 0.05$ was considered statistically significant.

Results

General Information

From April to August 2023, a total of 144 participants were enrolled and randomized. All of these patients provided informed consent, and only 140 were included in the data analysis (Figure 1). The baseline characteristics of patients in the two groups were comparable (Table 1). There were no significant differences in age, height, body weight, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, type of surgery, duration of surgery, urine volume, fluid volume, and blood loss volume ($P > 0.05$, Table 1).

Occurrence of Adverse Reactions Within 48 Hours After Surgery

The adverse reactions observed within 48 hours after surgery included nightmares/dreaminess, hallucinations, dizziness, lethargy, postoperative nausea, and vomiting (PONV). There were no statistically significant differences between the two groups ($P > 0.05$) (Table 2).

Changes in Recovery Quality Score

There were no significant differences in recovery quality scores between the esketamine group and control group one day before surgery ($Z = -4.270$, $P > 0.05$). The quality of recovery scores were significantly higher in the esketamine group compared to the control group on day 1 after surgery ($Z = -10.080$, $P < 0.05$), on day 3 after surgery ($Z = -8.178$, $P < 0.05$), and on day 5 after surgery ($Z = -4.139$, $P < 0.05$) (Figure 2). The difference of QoR-40 on POD 5 was statistically significant, but not clinically significant.

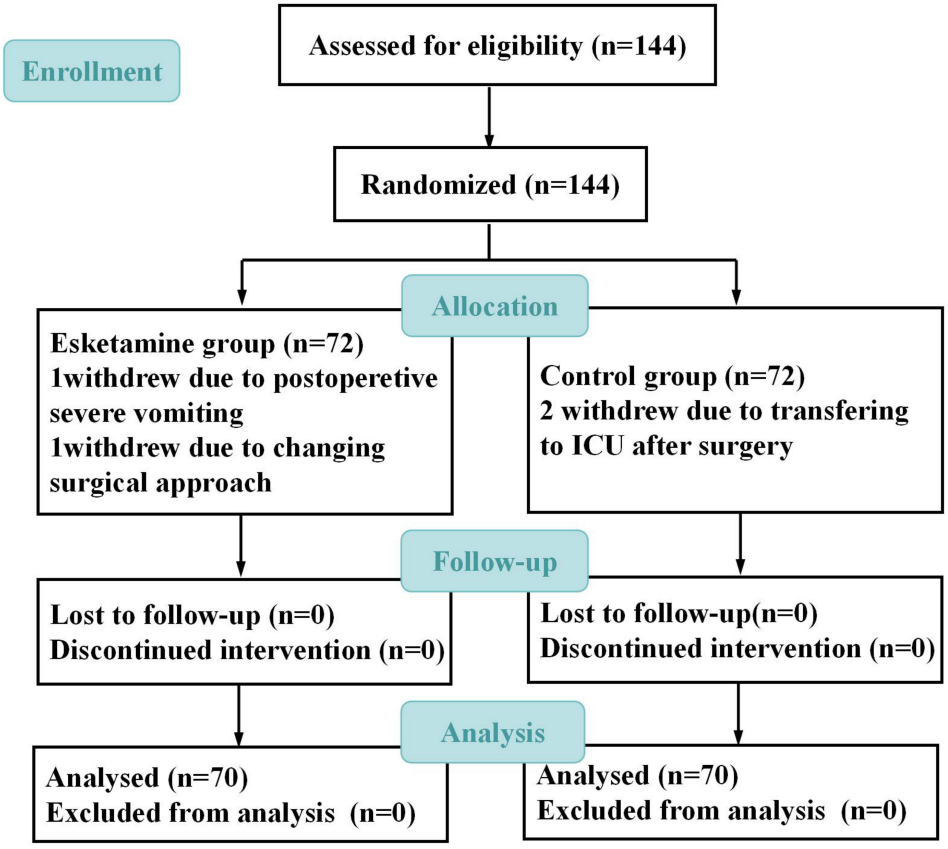

Figure 1 Patient flowchart.

Table 1 Patient Demographic and Baseline Characteristics

	Esketamine (n=70)	Control (n=70)	*t*/χ2/Z-value	*P*-value
Age (y)	69.0 (59.75–73.25)	69.5 (61.75–75)	−0.586	0.558
Sex, n (%)			0.476	0.49
Male	44 (62.9)	40 (57.1)		
Female	26 (37.1)	30 (42.9)		
Height (cm)	163.3±8.1	162.6±8.0	−0.447	0.655
Weight (kg)	61.6±10.9	62.1±13.8	−0.396	0.692
BMI (kg/m2)	22.9±2.8	3.0±5.1	−0.021	0.983
ASA class, n (%)			1.704	0.192
II	63 (90)	60 (85.7)		
III	7 (10)	10 (14.3)		
Type of disease, n (%)			0.991	0.319
Gastric cancer	14 (20)	19 (27)		
Colorectal cancer	56 (80)	51 (73)		
Surgical duration (min)	239.71±72.306	213.56±67.861	−2.669	0.108
Urine volume (mL)	600 (500–800)	500 (400–625)	−2.302	0.221
Blood loss (mL)	30 (20–50)	30 (20–50)	−1.047	0.295
Fluid volume (mL)	2500 (2000–2725)	235 (2000–2500)	−1.327	0.185

Note: All data are expressed as mean ± SD, frequency (%), and median (first quartile - third quartile).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 Comparison of the Occurrence of Adverse Reactions Within 48 h After Surgery Between the Two Groups (n=70)

	Esketamine	Control	x2	P
Nightmares	0 (0)	0 (0)	–	–
Hallucinations	0 (0)	0 (0)	–	–
Dizziness	2 (2.8)	3 (4.2)	0.000	1.000
Lethargy	4 (5.7)	5 (7.1)	0.000	1.000
PONV	8 (11.4)	7 (10)	0.075	0.785
Total	14 (20.0)	15 (21.4)	0.043	0.835

Note: The data are presented as the number (%).

Changes in Postoperative Pain Intensity

The resting NRS scores of the esketamine group were significantly lower than those of the control group at 6 hours post-surgery (Z=−6.322, $P < 0.05$), at 24 hours post-surgery (Z=−5.736, $P < 0.05$), at 36 hours post-surgery (Z=−6.563, $P < 0.05$), at 48 hours post-surgery (Z=−5.920, $P < 0.05$) (Figure 3).

Changes in Plasma IL-6, TNF-α, and BDNF During Perioperative Period

Compared to T0, plasma levels of IL-6 and TNF-α in two groups showed an increasing trend at T1 and T2; however, there were no significant differences between the two groups at the various time points ($P > 0.05$) (Figure 4A and B). Compared to T0, plasma BDNF levels showed a downward trend at T1; however, there were no significant differences in plasma BDNF levels between the two groups at different time points ($P > 0.05$) (Figure 4C).

Discussion

With advancements in anesthesia safety and surgical techniques, the evaluation of postoperative recovery quality has emerged as a major research finding. In this prospective randomized clinical trial, we found that intravenous injection of esketamine at a dose of 0.2 mg/kg at the time of anesthesia induction, followed by an additional 0.2 mg/kg administered 30 minutes before

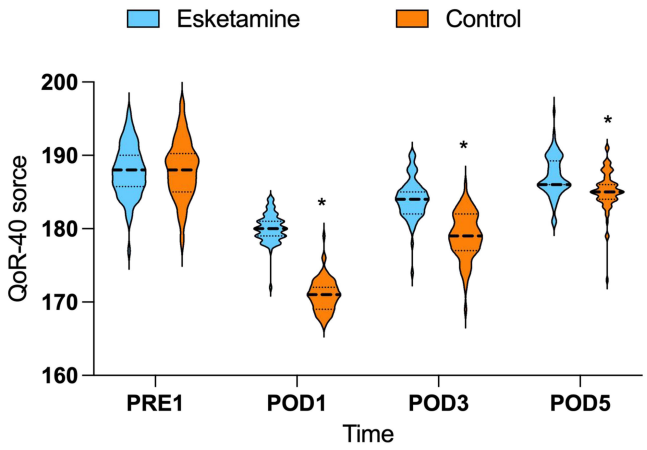

Figure 2 Violin chart of the distribution of perioperative QoR40 scores. PRE1, POD1, POD3, and POD5 respectively represented on the first day before surgery, the first day, the third day, and the fifth day after surgery. Data were represented by quartile range, maximum value, and minimum value. *$P < 0.05$ VS Control group.

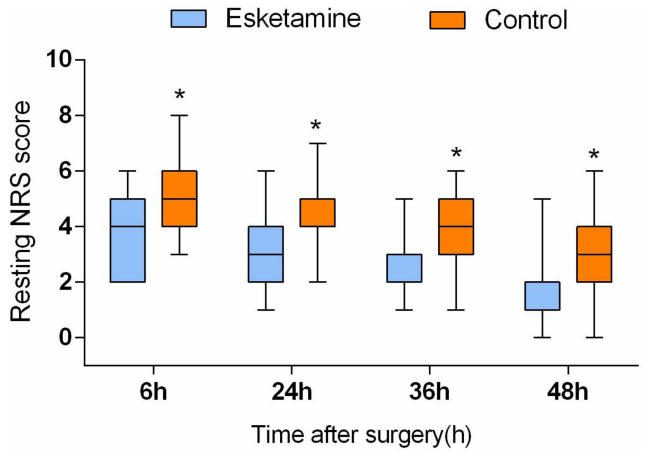

Figure 3 Box plots of the distribution of resting NRS pain scores at 6, 24, 36, and 48 hours post-surgery. The data are median, quartile range, and adjacent values. *$P < 0.05$ VS Control group.

the end of surgery, along with an infusion of a combination of esketamine (0.02 mg/kg/h) combined with sufentanil (0.04 μg/kg/h) as PCA during the initial 48 hours after surgery, improved early postoperative quality scores (on POD 1 and 3) in patients undergoing laparoscopic gastrointestinal surgery. This finding has important guiding significance for the selection of anesthesia methods and drugs in patients undergoing laparoscopic gastrointestinal surgery.

Esketamine, the S (+) isomer of ketamine, has a titer that is twice that of ketamine. Esketamine is an NMDA receptor antagonist that primarily exerts its effects through the NMDA receptor, producing both sedative and analgesic effect.[20,21] The esketamine dose chosen for this study was determined based on existing references and the potential adverse effects associated with esketamine.[22,23]

This study found that there were significant differences in postoperative recovery quality scores between the esketamine group and the control group, suggesting that the perioperative injection of esketamine could promote early postoperative recovery in patients undergoing laparoscopic radical resection of gastrointestinal tumors. Esketamine improves postoperative recovery for several reasons. First of all, esketamine has the potential to reduce the intensity of acute postoperative pain.[24] Ketamine with sub-anesthetic doses improved the quality of recovery after surgery in patients with colorectal cancer by providing analgesic effects.[11] In addition, Zeng et al revealed that intravenous esketamine may lower postoperative pain scores and reduce opioid consumption.[25] The results of our study indicated that esketamine significantly decreased postoperative resting NRS pain scores at 6, 24, 36, and 48 hours. Second,

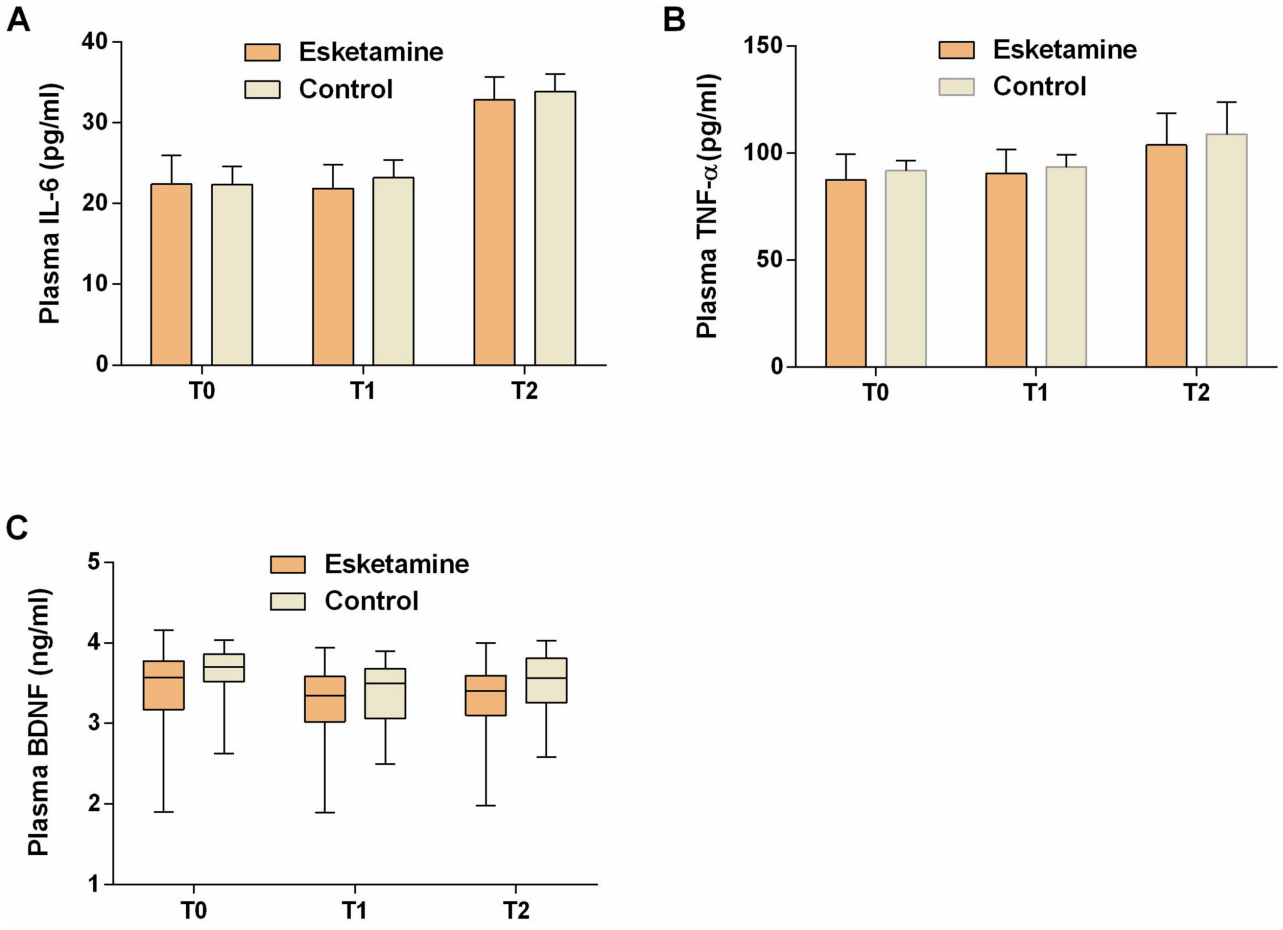

Figure 4 Perioperative Changes in Plasma IL-6 (**A**), TNF-a (**B**) and BDNF (**C**). T0, T1 and T2 represented the time points before anesthesia induction, before leaving the post-anesthesia care unit, and the second day after surgery, respectively. The line represents the median, the boxes represent the interquartile range (IQR), whiskers represent the range.

esketamine elevates the levels of neurotransmitters, such as dopamine, in the ventral striatum and caudate nucleus. This increase stimulates limbic structures, leading to a heightened sense of emotional comfort for patients.[26] Jiang et al revealed that esketamine can increase the serum concentrations of 5-hydroxytryptamine, dopamine, thereby improving postpartum depressive symptoms.[27] The change of emotion after operation can significantly impact the rapid recovery speed of patients. Myles et al found that the minimum clinically important difference (MCID) in the QoR-40 scale is 6.3.[28] In this study, the intravenous administration of esketamine resulted in an increase of more than 6.3 points in the total QoR-40 scores on both day 1 and day 3, suggesting that the intravenous injection of esketamine significantly improved early postoperative recovery of patients with laparoscopic radical resection of gastrointestinal tumors, and demonstrating its clinical value.

Liu et al revealed that postoperative pain is an important factor affecting patients' ability to recover quickly after surgery.[29] In this study, the resting NRS scores decreased at various time points post surgery in the esketamine group, indicating that perioperative intravenous esketamine may offer effective postoperative analgesia. This is consistent with previous research results.[30,31] This is likely due to esketamine's role, as a non-competitive antagonist of the NMDA receptor, which induces a sustained blocking effect by shortening the opening time of ion receptor channels, additionally, by decreasing the rate of separation from the receptor.[32] Furthermore, tissue injury activates NMDA receptors, leading to the production of NO. Esketamine reduces the production of NO by inhibiting NO synthase, thereby alleviating inflammatory pain.[33]

Previous studies have demonstrated that peripheral inflammatory factors increase in tumor patients after surgery, and that inhibiting the perioperative peripheral inflammatory response can promote early recovery in these patients.[34,35] Wang et al revealed that pro-inflammatory cytokines, such as TNF-α and IL-6 are involved in the regeneration of neurons.[36] In

https://doi.org/10.2147/DDDT.S502718

elderly individuals, the impact of inflammation is more pronounced due to a decline in cellular regenerative capacity. Zhang et al showed that serum levels of TNF-α and IL-6 were significantly elevated in patients after the surgery.[37] Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family. BDNF is important in neuronal development, survival, and the maintenance of the nervous system, and is mainly expressed in the hippocampus and cortex. Liu et al[38] found that surgical incisions induced learning disorders in mice by inhibiting the BDNF signaling pathway in the hippocampus and amygdala. Vignoli et al[39] found that the learning consolidation ability of mice decreased with the decrease of BDNF level, because BDNF produced by the central nervous system can rapidly pass the blood–brain barrier. Therefore, the level of BDNF in plasma can reflect the level of BDNF in brain tissue.[40] The present study also revealed that there was no statistically significant difference in serum TNF-α, IL-6 and BDNF levels between the two groups at different time points after surgery. This is different from previous studies; however, it does not mean that esketamine lacks anti-inflammatory effects. It is possible that the inflammatory response induced by the surgery far outweighs the anti-inflammatory effects of esketamine. Therefore, further research is needed.

The rational anesthesia program is not only associated with efficacy, but also with occurrence and severity of adverse reactions. Many recent studies have found that low-dose ketamine can reduce the incidence of adverse responses.[41,42] In this study, no significant differences were observed in the occurrence of postoperative dizziness, sleepiness, nausea, vomiting, hallucinations, and nightmares between the two groups within 48 hours after surgery. Avidan et al[43] have also confirmed that the administration of low-dose ketamine does not increase the incidence of postoperative ketamine-related adverse events.

There are several limitations in this study. First, we only observed the effects of esketamine on the quality of recovery during the perioperative period, and the postoperative follow-up duration for of patients was relatively short. A previous study found a correlation between the quality of recovery and the quality of life three months post-surgery.[44] Therefore, the findings of this study have certain significance for the long-term health of patients. Secondly, future clinical trials involving other types of surgery are necessary to investigate the long-term effects of esketamine on patient recovery. Finally, as a single-center study, while this accurately reflects the clinical situation, it may somewhat limit the generalizability of the findings. Therefore, future multi-center studies involving various anesthesia protocols are necessary to further validate our findings.

Conclusion

Perioperative subanesthetic doses of esketamine can improve the quality of early postoperative recovery in patients undergoing laparoscopic gastrointestinal surgery, reduce postoperative pain scores, and do not increase adverse reactions. It is evident that perioperative subanesthetic doses of esketamine can provide a novel, patient-centered approach to perioperative anesthesia management.

Data Sharing Statement

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

Acknowledgments

The authors gratefully acknowledge all the people that have made this study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported Medical Health Science and Technology Project of Zhejiang Province (2024KY1683), Jiaxing City science and technology project (2023AD31010).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
2. Iglseder B, Frühwald T, Jagsch C. [Delirium in geriatric patients]. Delir bei geriatrischen Patienten. *Wien Med Wochenschr*. 2022;172(5–6):114–-121. doi:10.1007/s10354-021-00904-z
3. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911–922. doi:10.1016/S0140-6736(13)60688-1
4. Moorthy A, Ní Eochagáin A, Dempsey E, et al. Postoperative recovery with continuous erector spinae plane block or video-assisted paravertebral block after minimally invasive thoracic surgery: a prospective, randomised controlled trial. *Br J Anaesth*. 2023;130(1):e137–e147. doi:10.1016/j.bja.2022.07.051
5. Coppens M, Van Caelenberg E, De Regge M. Postoperative innovative technology for ambulatory anesthesia and surgery. *Curr Opin Anaesthesiol*. 2021;34(6):709–713. doi:10.1097/ACO.0000000000001036
6. Xu Y, He L, Liu S, et al. Intraoperative intravenous low-dose esketamine improves quality of early recovery after laparoscopic radical resection of colorectal cancer: a prospective, randomized controlled trial. *PLoS One*. 2023;18(6):e0286590. doi:10.1371/journal.pone.0286590
7. Xu C, Wei X, Zhang C, et al. Esketamine prevents propofol-induced injection pain: randomized controlled trial. *Front Pharmacol*. 2022;13:991559. doi:10.3389/fphar.2022.991559
8. Al Mukhaizeem S, Nasa A, Waldron D, et al. Investigating the effectiveness of oral ketamine on pain, mood and quality of life in treatment resistant chronic pain. *Front Pain Res*. 2023;4:1268985. doi:10.3389/fpain.2023.1268985
9. Wang J, Huang J, Yang S, et al. Pharmacokinetics and safety of esketamine in Chinese patients undergoing painless gastroscopy in comparison with ketamine: a randomized, open-label clinical study. *Drug Des Devel Ther*. 2019;13:4135–4144. doi:10.2147/DDDT.S224553
10. Zhao L, Zhang H, Cheng H. Effect of a single sub-dose of ketamine on postoperative fatigue syndrome in colorectal cancer patients undergoing radical laparoscopic surgery: a double-blind, pilot study. *J Affect Disord*. 2022;312:146–151. doi:10.1016/j.jad.2022.06.029
11. Ren Q, Hua L, Zhou X, et al. Effects of a single sub-anesthetic dose of ketamine on postoperative emotional responses and inflammatory factors in colorectal cancer patients. *Front Pharmacol*. 2022;13:818822. doi:10.3389/fphar.2022.818822
12. Grass F, Cachemaille M, Martin D, et al. Pain perception after colorectal surgery: a propensity score matched prospective cohort study. *Biosci Trends*. 2018;12(1):47–53. doi:10.5582/bst.2017.01312
13. Blaj C, Bringmann A, Schmidt EM, et al. ADNP is a therapeutically inducible repressor of WNT signaling in colorectal cancer. *Clin Cancer Res*. 2017;23(11):2769–2780. doi:10.1158/1078-0432.CCR-16-1604
14. Myles PS, Richards T, Klein A, et al. Postoperative anaemia and patient-centred outcomes after major abdominal surgery: a retrospective cohort study. *Br J Anaesth*. 2022;129(3):346–354. doi:10.1016/j.bja.2022.06.014
15. Myles PS, Shulman MA, Reilly J, et al. Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis. *Br J Anaesth*. 2022;128(6):1029–1039. doi:10.1016/j.bja.2022.03.009
16. Myles PS, Weitkamp B, Jones K, et al. Validity and reliability of a postoperative quality of recovery score: the QoR-40. *Br J Anaesth*. 2000;84 (1):11–15. doi:10.1093/oxfordjournals.bja.a013366
17. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med*. 2007;22 (10):1453–1458. doi:10.1007/s11606-007-0321-2
18. Atisook R, Euasobhon P, Saengsanon A, Jensen MP. Validity and utility of four pain intensity measures for use in international research. *J Pain Res*. 2021;14:1129–1139. doi:10.2147/JPR.S303305
19. Abdallah MS, Mosalam EM, Zidan AA, et al. The antidiabetic metformin as an adjunct to antidepressants in patients with major depressive disorder: a proof-of-concept, randomized, double-blind, placebo-controlled trial. *Neurotherapeutics*. 2020;17(4):1897–1906. doi:10.1007/s13311-020-00878-7
20. Trimmel H, Helbok R, Staudinger T, et al. S(+)-ketamine: current trends in emergency and intensive care medicine. *Wien Klin Wochenschr*. 2018;130(9–10):356–366. doi:10.1007/s00508-017-1299-3
21. Zhang C, He J, Shi Q, et al. Subanaesthetic dose of esketamine during induction delays anaesthesia recovery a randomized, double-blind clinical trial. *BMC Anesthesiol*. 2022;22(1):138. doi:10.1186/s12871-022-01662-0
22. Li J, Wang Z, Wang A, et al. Clinical effects of low-dose esketamine for anaesthesia induction in the elderly: a randomized controlled trial. *J Clin Pharm Ther*. 2022;47(6):759–766. doi:10.1111/jcpt.13604
23. Huang Z, Liu N, Hu S, et al. Effect of dexmedetomidine and two different doses of esketamine combined infusion on the quality of recovery in patients undergoing modified radical mastectomy for breast cancer - a randomised controlled study. *Drug Des Devel Ther*. 2023;17:2613–2621. doi:10.2147/DDDT.S422896
24. Wang X, Lin C, Lan L, et al. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth*. 2021;68:110071. doi:10.1016/j.jclinane.2020.110071
25. Zeng X, Zhang X, Jiang W, et al. Efficacy of intravenous administration of esketamine in preventing and treating rebound pain after thoracic paravertebral nerve block: a prospective randomized, double-blind, placebo-controlled trial. *Drug Des Devel Ther*. 2024;18:463–473. doi:10.2147/DDDT.S448336
26. Bozymski KM, Crouse EL, Titus-Lay EN, et al. Esketamine: a novel option for treatment-resistant depression. *Ann Pharmacother*. 2020;54 (6):567–576. doi:10.1177/1060028019892644
27. Jiang Q, Qi Y, Zhou M, et al. Effect of esketamine on serum neurotransmitters in patients with postpartum depression: a randomized controlled trial. *BMC Anesthesiol*. 2024;24(1):293. doi:10.1186/s12871-024-02681-9
28. Myles PS, Myles DB, Galagher W, et al. Minimal clinically important difference for three quality of recovery scales. *Anesthesiology*. 2016;125 (1):39–45. doi:10.1097/ALN.0000000000001158
29. Liu Q, Lin JY, Zhang YF, et al. Effects of epidural combined with general anesthesia versus general anesthesia on quality of recovery of elderly patients undergoing laparoscopic radical resection of colorectal cancer: a prospective randomized trial. *J Clin Anesth*. 2020;62:109742. doi:10.1016/j.jclinane.2020.109742

30. Jing Z, Han Y, Li Y, et al. Effect of subanesthetic dose of esketamine on postoperative pain in elderly patients undergoing laparoscopic gastrointestinal tumor Surgery: A prospective, double-blind, randomized controlled trial. *Heliyon*. 2024;10(5):e27593. doi:10.1016/j.heliyon.2024.e27593
31. Brinck ECV, Maisniemi K, Kankare J, et al. Analgesic effect of intraoperative intravenous s-ketamine in opioid-naïve patients after major lumbar fusion surgery is temporary and not dose-dependent: a randomized, double-blind, placebo-controlled clinical trial. *Anesth Analg*. 2021;132 (1):69–79. doi:10.1213/ANE.0000000000004729
32. Holter KM, Lekander AD, Pierce BE, et al. Use of quantitative electroencephalography to inform age- and sex-related differences in NMDA receptor function following MK-801 administration. *Pharmaceuticals*. 2024;17(2):237. doi:10.3390/ph17020237
33. Fan W, Liu Q, Zhu X, et al. Regulatory effects of anesthetics on nitric oxide. *Life Sci*. 2016;151:76–85. doi:10.1016/j.lfs.2016.02.094
34. Chen J, Liu S, Wang X, et al. HDAC6 inhibition alleviates anesthesia and surgery-induced less medial prefrontal-dorsal hippocampus connectivity and cognitive impairment in aged rats. *Mol Neurobiol*. 2022;59(10):6158–6169. doi:10.1007/s12035-022-02959-4
35. Zhu Y, Zhou M, Jia X, et al. Inflammation disrupts the brain network of executive function after cardiac surgery. *Ann Surg*. 2023;277(3):e689–e698. doi:10.1097/SLA.0000000000005041
36. Wang X, Zhou J, Zhang G. Effects of conventional nursing in the operating room combined with transcutaneous electrical acupoint stimulation on postoperative cognitive dysfunction after total knee arthroplasty in elderly patients. *J Orthop Surg Res*. 2024;18(1):906. doi:10.1186/s13018-023-04348-6
37. Zhang S, Liu C, Sun J, et al. Bridging the gap: investigating the link between inflammasomes and postoperative cognitive dysfunction. *Aging Dis*. 2023;14(6):1981–2002. doi:10.14336/AD.2023.0501
38. Liu Z, Liu F, Liu X, et al. Surgical incision induces learning impairment in mice partially through inhibition of the brain-derived neurotrophic factor signaling pathway in the hippocampus and amygdala. *Mol Pain*. 2018;14:1744806918805902. doi:10.1177/1744806918805902
39. Vignoli B, Battistini G, Melani R, et al. Peri-synaptic glia recycles brain-derived neurotrophic factor for LTP stabilization and memory retention. *Neuron*. 2016;92(4):873–887. doi:10.1016/j.neuron.2016.09.031
40. Williams RA, Johnson KW, Lee FS, et al. A common human brain-derived neurotrophic factor polymorphism leads to prolonged depression of excitatory synaptic transmission by isoflurane in hippocampal cultures. *Front Mol Neurosci*. 2022;15:927149. doi:10.3389/fnmol.2022.927149
41. Hambrecht-Wiedbusch VS, Li D, Mashour GA. Paradoxical emergence: administration of subanesthetic ketamine during isoflurane anesthesia induces burst suppression but accelerates recovery. *Anesthesiology*. 2017;126(3):482–494. doi:10.1097/ALN.0000000000001512
42. Chen MH, Cheng CM, Gueorguieva R, et al. Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: a double-blind randomized placebo-control study. *Neuropsychopharmacology*. 2019;44(12):2112–2118. doi:10.1038/s41386-019-0480-y
43. Avidan MS, Maybrier HR, Abdallah AB, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet*. 2017;390(10091):230. doi:10.1016/S0140-6736(17)31467-8
44. Gornall BF, Myles PS, Smith CL, et al. Measurement of quality of recovery using the QoR-40: a quantitative systematic review. *Br J Anaesth*. 2013;111(2):161–169. doi:10.1093/bja/aet014