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Effects of Intraoperative Low-Dose Esketamine on Postoperative Inflammatory Response and Clinical Recovery in Elderly Patients Undergoing Colorectal Cancer Resection: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract: Surgical trauma in elderly patients undergoing colorectal cancer resection often triggers a robust systemic inflammatory response leading to delayed recovery. Esketamine, a noncompetitive NMDA receptor antagonist, may possess anti-inflammatory properties. This study aimed to evaluate the effects of intraoperative low-dose esketamine on serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) levels, and clinical recovery outcomes in this population. This was a single-center, prospective, randomized, double-blind, placebo-controlled trial. Sixty elderly patients (60–85 years, ASA grade I–II) scheduled for elective laparoscopic radical resection of colorectal cancer were randomized (1:1) to receive either low-dose esketamine (0.2 mg/kg/h) or normal saline (control) during anesthesia maintenance. The primary outcome was the concentration of serum TNF-α at preoperative, 0.5h, and 16h postoperative time points. Secondary outcomes included IL-6 levels, intraoperative propofol consumption, anesthesia recovery and extubation times, postoperative Visual Analogue Scale scores, the frequency of patient-controlled analgesia compressions, and the incidence of adverse events. Forty-six patients (n=26 in the esketamine group; n=20 in the control group) were finally included in the statistical analysis. Compared to the control group, the esketamine group exhibited significantly lower TNF-α concentrations at 0.5h and 16h postoperatively ($P < 0.05$). After adjusting for baseline imbalance, no statistically significant differences were observed in postoperative IL-6 levels between the two groups ($P > 0.05$). The esketamine group showed significantly lower intraoperative propofol consumption ($P < 0.001$), shorter anesthesia recovery and extubation times ($P < 0.05$), and reduced VAS scores at 6h-48h post-surgery ($P < 0.05$). Furthermore, hospitalization duration was shorter in the esketamine group ($P < 0.001$). There was no significant increase in adverse events such as hallucinations or nausea. Intraoperative low-dose esketamine (0.2 mg/kg/h) effectively suppresses the postoperative release of TNF-α, reduces propofol requirements, and enhances postoperative analgesia and clinical recovery in elderly patients undergoing colorectal surgery.

Trial Registration: The study was retrospectively registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2500101206) on April 22, 2025.

Keywords: Esketamine; TNF-α ; IL-6; colorectal cancer; elderly patients; postoperative inflammation; enhanced recovery after surgery

1 Background

Epidemiological statistics indicate that by 2040, the annual incidence of new colorectal cancer cases worldwide is projected to reach 3.2 million, with deaths expected to rise to 1.1 million [1]. Colorectal cancer is the third most prevalent cancer and has the highest mortality rate among malignant tumors of the digestive system, posing a significant threat to public health [2-4]. In China, colorectal cancer currently has the highest prevalence among digestive diseases [5,6].

Laparoscopic surgery is frequently performed in patients with colorectal cancer. However, trauma, postoperative pain, and other stimuli can elicit significant stress responses and hemodynamic fluctuations during the procedure. This response results in the release of numerous inflammatory mediators, including tumor necrosis factor-α, C-reactive protein (CRP), and interleukin-6 [7,8]. Additionally, various opioids are required for perioperative analgesia. Excessive opioid use often increases the risk of adverse reactions, such as nausea, vomiting, pruritus, constipation, and respiratory depression, which may subsequently delay patient discharge and recovery and lead to a range of postoperative complications [9,10].

Currently, the necessity of low-opioid anesthesia is explicitly recognized within the framework of enhanced recovery after surgery (ERAS) protocols [11]. Esketamine is an intravenous anesthetic agent that provides both sedation and analgesia. It is a dextroisomer of high-purity ketamine which is obtained through a specialized separation and purification process. Although its site of action is similar to that of ketamine, esketamine exhibits higher receptor affinity, and its pharmacokinetics are more controllable [12]. Research has demonstrated that esketamine can inhibit inflammation while concurrently reducing opioid requirements [13-16]. However, few studies have investigated the perioperative anti-inflammatory effects of esketamine in patients with colorectal cancer . Therefore, this study aims to examine the impact of intraoperative low-dose esketamine on the levels of intraoperative and postoperative inflammatory markers TNF-α and IL-6 in these patients. This study aimed to develop improved anesthesia protocols and clinical medication strategies for patients undergoing colorectal cancer treatment.

2 Methods

2.1 Design and Study Subjects

This study is a prospective, randomized, double-blind clinical trial conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethics Committee of the First People's Hospital of Jintang County (Approval No. 2021-017) on July 20, 2021. The trial was retrospectively registered with the Chinese Clinical Trial Registry (registration number: ChiCTR2500101206) on April 22, 2025 prior to manuscript submission. All study procedures were conducted in accordance with the Declaration of Helsinki, and complete original medical records of all participants are available for traceability.This study was reported in strict accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2025 Statement guidelines.

This prospective clinical trial was conducted from September 2021 to December 2023 at the First People's Hospital of Jintang County. All patients were followed up until hospital discharge.

2.2 Eligibility Criteria

Inclusion criteria: (1) Participants aged 60 to 85 years with a Body Mass Index ranging from 18.5 to 25; (2) Individuals undergoing elective laparoscopic-assisted radical resection for colon or rectal cancer; (3) American Society of Anesthesiologists classification of I to II, with NYHA cardiac function class I–II.

Exclusion criteria: (1) individuals with mental health disorders; (2) a history of esketamine use, known allergies, use of sedative medications, or substance dependence; (3) individuals with infectious diseases; (4) patients currently enrolled in other clinical trials; (5) patients with scoliosis or other conditions that preclude the performance of epidural puncture; and (6) patients who declined to sign informed consent forms.

Withdrawal criteria: (1) patients with blood loss exceeding 500 ml during surgery, along with cardiovascular events such as severe hypotension and arrhythmia; (2) patients for whom laparoscopic surgery is challenging, necessitating a transition to open surgery; (3) patients requiring postoperative

transfer to the ICU; (4) instances of withdrawal or death; and (5) unsuccessful or ineffective epidural puncture.

2.3 Patient Population

The sample size was calculated based on the primary outcome of serum TNF-α concentration at 16 hours postoperatively. According to pre-experimental data, with α=0.05, β=0.1, test power=0.9, bilateral test, and a 10% dropout rate, at least 30 patients were required in each group. Therefore, 60 patients were planned to be randomly assigned in a 1:1 ratio.

From September 2021 to December 2023, a total of 89 patients scheduled for laparoscopic colorectal cancer resection were consecutively screened. Among them, 29 patients were excluded before randomization (25 did not meet the inclusion criteria, 4 declined to participate). Finally, 60 eligible patients were enrolled and randomized into the esketamine group (n=30) and the control group (n=30). After randomization, 14 patients were excluded according to the withdrawal criteria, and 46 patients were finally included in the statistical analysis (26 in the esketamine group, 20 in the control group).

2.4 Randomization and Blinding

Participants were randomly assigned to the two groups in a 1:1 ratio using a computer-generated random number sequence. Group allocation was concealed using sequentially numbered, opaque sealed envelopes, which were opened by a dedicated anesthesiology nurse immediately before anesthesia induction.

The dedicated nurse prepared study medications in identical 50 mL syringes: the esketamine group received esketamine diluted with 0.9% sodium chloride, and the control group received an equal volume of 0.9% sodium chloride placebo at the same infusion rate. All attending anesthesiologists, postoperative outcome assessors and patients were blinded to group allocation throughout the study.

2.5 Treatment Protocols

Preoperative fasting was standardized to 8–10 hours for solid foods and 2 hours for clear fluids in accordance with ERAS protocols. Upon arrival in the operating room, multiparameter monitoring was initiated, which included invasive arterial pressure measurement through radial artery cannulation, continuous 5-lead electrocardiography with ST-segment analysis, and end-tidal carbon dioxide ($EtCO_2$) monitoring.

Ultrasound-guided thoracic epidural catheterization was conducted in the T11–T12 interspace using a 6–13 MHz linear transducer. A test dose of 3 mL of 1% lidocaine was administered to rule out intravascular or intrathecal placement, followed by intermittent boluses of 0.75% ropivacaine (5 mL every 60 minutes). Central venous access was established via ultrasound-guided catheterization of the right internal jugular vein after intubation.

General anesthesia induction involved pre-oxygenation with 100% oxygen at a flow rate of 6 L/min for 3 minutes, followed by the sequential administration of propofol via target-controlled infusion (TCI) using the Schnider model, achieving an effect-site concentration (Ce) of 4.0 μg/mL. This was accompanied by rocuronium bromide at a dosage of 0.8 mg/kg and sufentanil at 0.3 μg/kg. Tracheal intubation was performed using 7.0 mm–7.5 mm internal diameter tubes, with cuff pressures maintained below 25 cmH_2O.

Intraoperative maintenance for the esketamine group consisted of sevoflurane at an end-tidal concentration of 1.5%, combined with propofol TCI at a Ce of 2.0 μg/mL–3.0 μg/mL and esketamine at a

rate of 0.2 mg/kg/h. The control group received identical sevoflurane and propofol regimens with saline placebo infused at matching rates. Hemodynamic targets were set to maintain a Bispectral Index of 40–60, a heart rate of 50–80 bpm, and mean arterial pressure within ±20% of baseline.

Esketamine and saline infusions were discontinued 40 minutes prior to fascial closure, whereas sevoflurane was terminated 20 minutes before extubation. Propofol administration continued until 5 minutes before extubation, with a final 5 mL bolus of 0.75% ropivacaine administered epidurally 20 minutes prior to the completion of the procedure. The core temperature was maintained at or above 36.5°C using forced-air warming.

2.6 Data Collection and Assessment

Primary Outcome: The concentration of TNF-α (pg/mL) in venous blood was compared between the two groups one day before surgery (D0), 0.5 hours after surgery (D1), and 16 hours after surgery (D2).

Secondary Outcome:

1) The concentration of IL-6 in the venous blood (pg/mL) was compared between the two groups at D0, D1, and D2.

2) The time from propofol cessation to recovery and extubation time (min) was recorded, along with the intraoperative dosages of propofol (mg) and ropivacaine (mg).

3) VAS scores were recorded at five time points: 6 hours, 12 hours, 24 hours, 48 hours, and 72 hours after surgery.

4) The number of patients who experienced adverse reactions within 72 hours was documented in detail to calculate the incidence of such reactions.

5) Time to first flatus and length of hospital stay for patients were recorded.

6) The total number of PCA compressions was counted.

2.7 Statistical Analysis

Statistical analysis of the experimental data was conducted using SPSS version 25.0. Quantitative data were compared between the two groups using the t-test or rank-sum test. Repeated-measures ANOVA was used to analyze quantitative index data collected at multiple time points. Sphericity was tested by Mauchly's test, and the Greenhouse-Geisser correction was applied when sphericity was violated.Categorical variables were analyzed using the chi-squared test or Fisher's exact test. Statistical significance was set at $p < 0.05$.

3 Results

3.1 Patient Characteristics

The CONSORT flow diagram of patient enrollment and allocation is shown in Figure 1. No statistically significant differences were found between the two groups in age, sex, body weight, tumor site, or tumor differentiation degree (all $P > 0.05$), indicating comparable baseline characteristics (Table 1).

Post-randomization exclusions were more frequent in the control group (9/30, 30.0%) than in the esketamine group (3/30, 10.0%; $\chi^2 = 3.75$, $P = 0.053$), mainly due to conversion to open surgery, intraoperative blood loss > 500 mL and postoperative ICU admission.

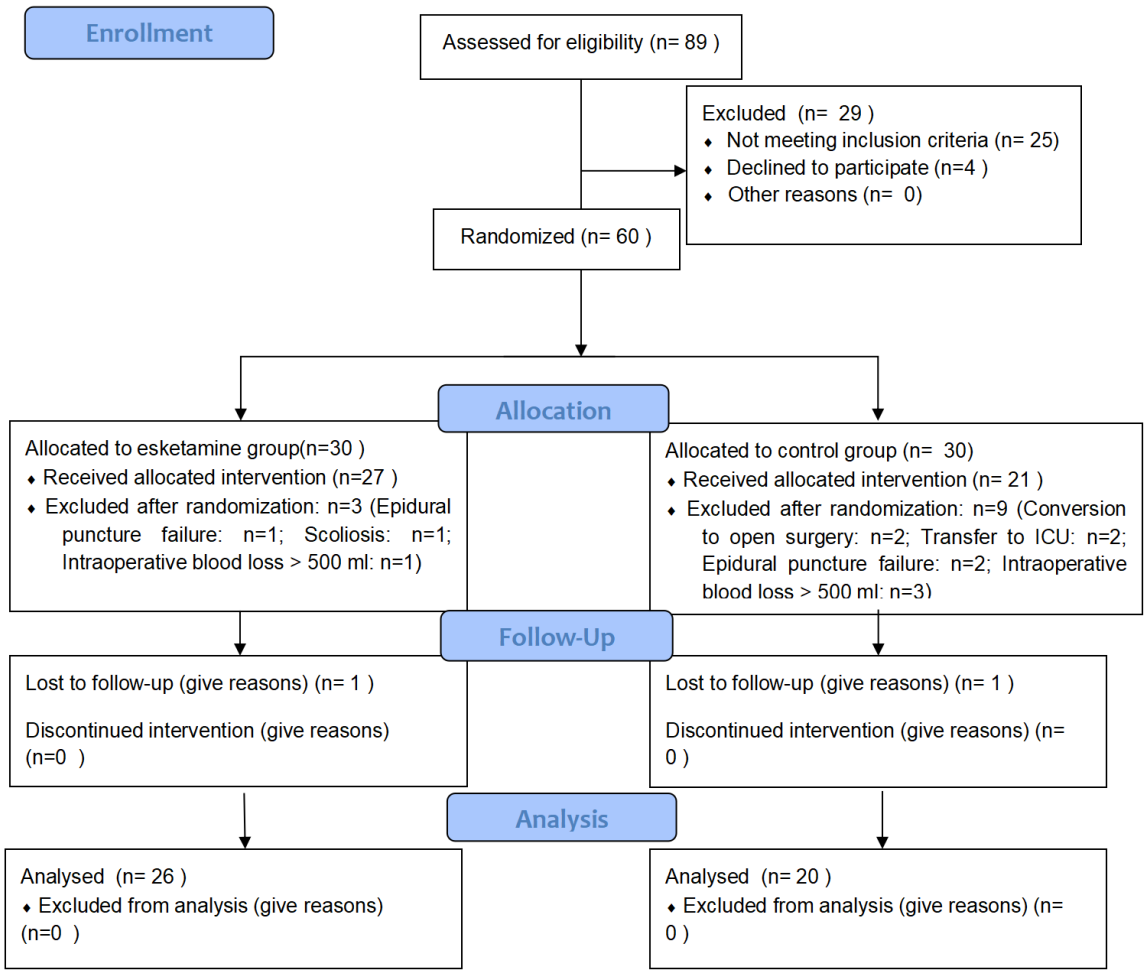


Figure 1. CONSORT flow diagram of patient enrollment, randomization and follow-up

Table 1: Baseline clinical characteristics of patients

Variables	Esketamine group（n = 26）	Control group （n = 20）	T, Z, or chi-square values	Difference (95% confidence interval)	*P*-value

Age (years)	66（63，74.5）	69（61.25，72）	0.63	-1（-5，4）	0.532
Sex, n (%)			2.56	/	0.114
Male	15（57.7%）	16（80%）		/	
Female	11（42.3%）	4（20%）		/	
Weight(kg)	55.23 ± 5.83	55.45 ± 7.25	0.11	-0.22（-4.11，3.67）	0.910
Tumor site，n (%)			0.011	/	0.916
Rectum	16（61.5%）	12（60%）		/	
Colon	10（38.5%）	8（40%）		/	
Tumor differentiation, n (%)			0.086	/	0.958
High	12（46.2%）	10（50%）		/	
Moderate	8（30.8%）	6（30%）		/	
Low	6（23.1%）	4（20%）		/	

Notes: Data are presented as mean ± standard deviation, median (IQR), or n (%).

3.2 Primary Outcome: Serum TNF-α Levels

Repeated-measures ANOVA indicated a significant group×time interaction (F=7.32, P=0.002). The esketamine group demonstrated a 50.4% reduction in TNF-α levels at 16 hours compared to the control group (Δ=11.71 pg/mL, 95% CI 8.93-14.49) (Table 2).

Table 2: Comparison of serum TNF-α levels at different time points (pg/mL)

Parameter	Control group (pg/mL)	Esketamine group (pg/mL)	Difference (95% confidence interval)	*P*-value
D0	7.51 ± 2.00	7.95 ± 3.84	0.44 (-1.21, 2.09)	0.601

D1	13.48 ± 9.64 ※	8.01 ± 3.13 #	-5.47 (-7.12, -3.82)	<0.001
D2	23.17 ± 5.56 ※	11.46 ± 4.99 ※#	-11.71 (-14.49, -8.93)	<0.001

Notes: Data are presented as mean ± standard deviation. 1 day before surgery (D0), 0.5 hours after surgery (D1), 16 hours after surgery (D2). ※ vs. D0, *P*<0.05; # vs. the control group, *P*<0.05.

3.3 Secondary Outcome: Serum IL-6 Levels

Baseline IL-6 levels were significantly lower in the esketamine group than in the control group (P = 0.025). Repeated-measures ANOVA showed a significant time effect for IL-6 (F = 289.4, P < 0.001), indicating that IL-6 levels increased significantly postoperatively in both groups in response to surgical stress. The group×time interaction effect did not reach statistical significance after adjusting for baseline (F = 2.14, P = 0.125).

After adjusting for baseline IL-6 levels using ANCOVA, there was no statistically significant difference in IL-6 levels at 0.5 hours (adjusted P = 0.142) or 16 hours (adjusted P = 0.079) postoperatively between the two groups. A downward trend in IL-6 was observed in the esketamine group, but did not reach statistical significance (Table 3).

Table 3: Comparison of serum IL-6 levels at different time points (pg/mL)

Parameter	Control group (pg/mL)	Esketamine group (pg/mL)	Difference (95% confidence interval)	*P*-value	Adjusted P-value*
D0	5.76 ± 2.44	4.04 ± 2.72	-1.72 (-3.21, -0.23)	0.025	-
D1	64.16 ± 10.45 ※	58.42 ± 10.75 ※	-5.74 (-12.03, -0.55)	0.073	0.142
D2	116.61 ± 24.22 ※	81.79 ± 21.95 ※	-34.82 (-50.11, -19.53)	＜0.001	0.079

Notes: Data are presented as mean ± standard deviation. 1 day before surgery (D0), 0.5 hours after surgery (D1), 16 hours after surgery (D2). ※ vs. D0, *P*<0.05.Adjusted for baseline IL-6 level using ANCOVA.

3.4 Intraoperative Drug Consumption

Intraoperative propofol consumption was 66.3% lower in the esketamine group than in the control group (P < 0.001). No significant difference was found in ropivacaine dosage between the two groups (P = 0.211) (Table 4).

Table 4: Comparison of intraoperative drug dosages

Parameter	Control group （n = 20）	Esketamine group （n = 26）	Z-value	Difference (95% confidence interval)	*P* value
Dosage of ropivacaine(mg)	10（10，11.5）	10（10，10）	1.25	0（0，0）	0.211
Dosage of propofol (mg)	445（400, 495）	150（120，200）#	4.89	-295.0 (-340.0, -250.0)	< 0.001

Note: Data are presented as medians (interquartile ranges). #vs. the control group, *P*<0.05.

3.5 Anesthesia Recovery and Clinical Recovery

The esketamine group had significantly shorter anesthesia recovery time and extubation time than the control group (both P < 0.05). Postoperative hospital stay was 3.11 days shorter in the esketamine group (P < 0.001). Time to first flatus showed a decreasing trend in the esketamine group but did not reach statistical significance (P = 0.063) (Table 5).

Table 5: Comparison of anesthesia and clinical recovery indicators

Parameter	Control group （n=20）	Esketamine group （n=26）	Z/T value	Difference (95% confidence interval)	*P* value
Recovery time (min)	10.5 (7.0, 16.0)	7.0 (5.0, 11.0)#	2.28（z-value）	-3.0 (-6.0, 0.0)	0.022
Extubation time (min)	17.0 (12.0, 22.0)	10.0 (7.0, 17.0)#	2.83（z-value）	-7.0 (-11.0, -2.0)	0.005
Hospital stay (days)	23.80 ± 1.82	20.69 ± 2.06#	5.34(T value）	-3.11（-4.28，-1.93）	< 0.001

Time to first flatus (days)	4（3.25，4）	3（2，3）	1.86（z-value）	-1.0 (-2.0, 0.0)	0.063

Note: Data are presented as mean ± standard deviation or median (interquartile range). #vs. the control group, *P*<0.05

3.6 Postoperative Pain and Analgesic Consumption

VAS pain scores were significantly lower in the esketamine group at 6 h to 48 h postoperatively. No significant difference was observed at 72 hours (P = 0.079) (Table 6, Fig. 2).

The total number of PCA compressions was significantly lower in the esketamine group than in the control group (P < 0.001), indicating reduced demand for rescue analgesia (Table7).

Table 6: Comparison of VAS pain scores at different postoperative time points

Parameter	Control group	Esketamine group	Difference (95% confidence interval)	*P*-value
6 h (T1)	4（3，4）	2（2，3）#	-2.0 (-2.5, -1.5)	<0.001
12 h (T2)	3（3，4）	2（2，3）#	-1.0 (-1.5, -0.5)	0.003
24 h (T3)	3（2，3）	2（2，2）#	-1.0 (-1.0, -0.5)	0.008
48 h (T4)	2（2，2）	2（1.75，2）#	-0.25 (-0.5, 0.0)	0.042
72 h (T5)	1（1，2）	1（1，1）	-0.5 (-1.0, 0.0)	0.079

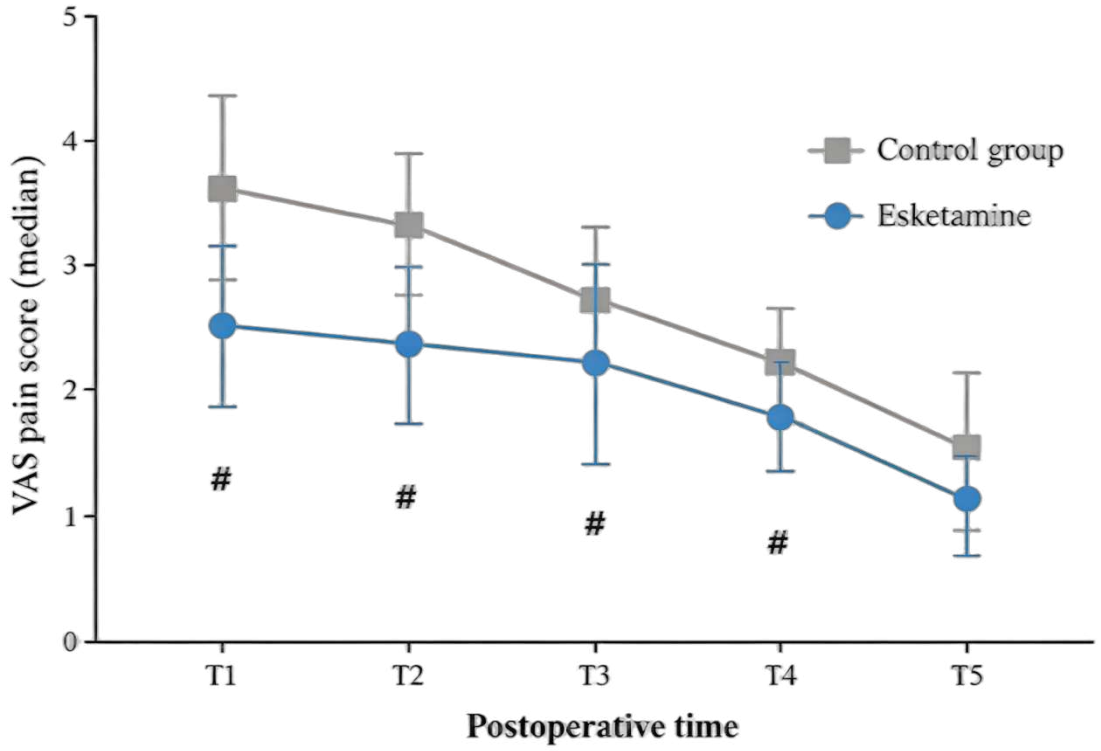


Figure 2: Line chart of VAS score changes over time

Notes: Data are presented as medians (interquartile ranges). T1:6 hours after surgery; T2:12 hours after surgery; T3:24 hours after surgery; T4:48 hours after surgery; T5:72 hours after surgery. #vs. the control group, $P<0.05$

Abbreviations: VAS, visual analogue scale.

Table 7: Comparison of total PCA compressions

Parameter	Control group （n=20）	Esketamine group （n=26）	z-value	Difference (95% confidence interval)	*P*- value
PCA compressions (times)	4.0 [3.0, 5.0]	2.0 [1.0, 2.0]	4.12	-2.0 (-3.0, -1.0)	< 0.001

Notes: Data are presented as median (interquartile range). Abbreviations: PCA, Patient-Controlled Analgesia.

3.7 Safety Outcomes

No statistically significant differences were found in the incidence of nausea and vomiting, or dizziness between the two groups (all $P > 0.05$). No cases of respiratory depression or hallucinations/nightmares were reported in either group (Table 8).

Table 8: Comparison of adverse event incidence between groups [n (%)]

Parameter	Nausea and vomiting	Dizziness	Respiratory depression	Hallucinations/nightmares
Control group (n = 20), n (%)	5（25%）	7（35%）	0	0
Esketamine group (n = 26), n (%)	1（3.85%）	3（11.54%）	0	0
Total	6（13.04%）	10（21.74%）	0	0
P-value (Fisher's exact test)	0.072	0.077	-	-

Note: Data are presented as n (%).

4 Discussion

Surgical trauma activates the sympathetic nervous system and triggers an immune response. This process leads to the release of numerous inflammatory factors, including IL-6 and TNF-α, which promote the growth, survival, and immune evasion of cancer cells [17-18]. There is a correlation between tumor occurrence, progression, and inflammation [19]. TNF-α, one of the earliest identified inflammatory cytokines with high sensitivity, induces the production of additional inflammatory factors. Notably, it promotes the release of IL-6, thereby activating the cytokine network and promoting the inflammatory response [20-21]. IL-6 is a reliable and significant indicator of inflammation in the context of tissue injury or severe disease [22], and it plays a critical role in tumor initiation and progression.

This study examined the effects of low-dose esketamine on intraoperative inflammatory factors in patients with colorectal cancer. In the control group, postoperative serum levels of TNF-α (13.48 ± 9.64 pg/mL at 0.5 h, 23.17 ± 5.56 pg/mL at 16 h) and IL-6 (64.16 ± 10.45 pg/mL at 0.5 h, 116.61 ± 24.22 pg/mL at 16 h) were significantly elevated compared with preoperative baseline levels (TNF-α: 7.51 ± 2.00 pg/mL; IL-6: 5.76 ± 2.44 pg/mL).In the esketamine group, TNF-α levels were significantly lower at

0.5 h and 16 h postoperatively [(8.01 ± 3.13) pg/mL, (11.46 ± 4.99) pg/mL] compared with the control group.This suggests that esketamine significantly inhibits the release of the inflammatory factor TNF-α. Relevant studies conducted by domestic and international scholars support the conclusions of this research [23-28]. Mechanistically, esketamine has been shown to inhibit the phosphorylation and nuclear translocation of NF-κB p65 in both cellular and animal models, thereby suppressing the transcription of downstream pro-inflammatory cytokines including TNF-α [29,30]. Multiple NF-κB binding sites have been identified in the promoter regions of TNF-α-regulated inflammatory genes, forming a positive feedback loop that amplifies the inflammatory cascade [31,32].

For IL-6, we observed a downward trend in the esketamine group, but the difference did not reach statistical significance after adjusting for baseline imbalance. Several factors may explain this result. First, the pro-inflammatory mechanisms of IL-6 differ from those of TNF-α; IL-6 can also exert a pro-inflammatory effect through the activation of gp130 [33,34]. Second, the influence of other anesthetic agents used during the procedure may have contributed to the observed discrepancies in the test results. Another factor to be considered is the inhibitory effect of propofol on IL-6. Both domestic and international studies have demonstrated that propofol can suppress the inflammatory response induced by surgical stimulation, primarily by inhibiting IL-6, TNF-α, and other inflammatory mediators in a dose-dependent manner [35-37].In our study, propofol consumption was markedly lower in the esketamine group; theoretically, reduced propofol exposure would weaken anti-inflammatory effects. However, IL-6 levels still trended lower in the esketamine group, suggesting that esketamine's anti-inflammatory effect offset the reduction caused by lower propofol dosage, resulting in a net neutral to beneficial effect. Third, the relatively small sample size and higher-than-expected dropout rate reduced the statistical power for detecting differences in IL-6, which is a secondary outcome. The observed downward trend still suggests potential anti-inflammatory value, which warrants verification in larger studies.

In this experiment, VAS pain scores were significantly lower in the esketamine group from 6 h to 48 h postoperatively, which was consistent with the reduced PCA compression frequency. This finding suggests that the administration of small doses of esketamine during the procedure not only provided effective analgesic and sedative effects, but also sustained these effects for an extended period postoperatively, without increasing the incidence of adverse reactions. A meta-analysis of 28 randomized controlled trials confirmed that perioperative esketamine significantly reduces postoperative pain intensity and decreases rescue analgesia requirements by approximately 49%, with an overall opioid-sparing effect ranging from 30% to 50% in laparoscopic surgery populations [38] . Numerous studies have reported that intraoperative use of low-dose esketamine can reduce opioid requirements [15,39-40]. Following the administration of small doses of esketamine, the N-methyl-D-aspartic acid receptor can be noncompetitively blocked, contributing to antihyperalgesia, reducing abnormal pain, and enhancing pain tolerance, thereby facilitating analgesia.

Notably, the esketamine group also showed reduced propofol consumption, faster anesthesia recovery, and shorter hospital stay. These benefits align with the goals of ERAS protocols, and support the use of low-dose esketamine as a multifunctional adjuvant in geriatric oncologic surgery.

5 Conclusion

Low-dose esketamine (0.2 mg/kg/h) serves as a multifaceted adjunct in the perioperative setting. It exhibits anti-inflammatory properties, evidenced by a 50.4% reduction in TNF-α levels at 16 hours postoperatively. Additionally, it demonstrates a propofol-sparing effect, resulting in a 66.3% decrease in propofol demand ($P<0.001$). Furthermore, this regimen is associated with a reduction in hospitalization duration by 3.11 days ($P<0.001$).Given these findings, the incorporation of this regimen into ERAS protocols for geriatric oncological surgery is warranted.In clinical practice, this regimen provides a

reference for optimizing perioperative anesthesia protocols under the ERAS framework, and warrants further validation in multicenter, large-sample prospective clinical trials.

6 Limitations

This study has several limitations. First, it is a single-center study with a relatively small sample size, and the final sample size was lower than planned, which may result in insufficient statistical power for some secondary outcomes, particularly IL-6. Second, baseline IL-6 levels were imbalanced between groups; although ANCOVA was used for adjustment, residual confounding cannot be fully excluded. Third, the trial was retrospectively registered, which may introduce potential reporting bias. Fourth, the dropout rate in the control group (30%) was higher than the pre-specified 10%, with uneven dropout distribution between groups, which may introduce selection bias. Finally, only short-term postoperative outcomes were observed, and long-term oncologic prognosis was not evaluated. Multicenter, large-sample prospective studies are needed to further verify these findings.

Availability of Data and Materials

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

Ethics approval and consent to participate

Written informed consent was obtained from all individual participants prior to enrollment in this study. All participants were fully informed of the study purpose, procedures, potential risks and benefits, and their right to withdraw at any time without penalty. The informed consent procedure was performed in full compliance with the principles of the Declaration of Helsinki, and both the study protocol and consent form were reviewed and approved by the Medical Ethics Committee of the First People's Hospital of Jintang County (Approval No. 2021-017).

No waiver of informed consent was applied in this study, and all enrolled participants provided voluntary written consent.

Author Contributions

QY, TXX and TL contributed equally to this work.
QY: Conceptualization, Data curation, Writing – original draft, Writing – review and editing, Formal Analysis, Visualization.
TXX: Data curation, Investigation, Methodology validation.
TL: Data curation, Formal analysis.
LSJ: Investigation, Project administration.
LDY: Project administration, Supervision, Writing – review and editing.
All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Conflicts of Interest

The authors declare no conflicts of interest to report regarding the present study.

References

[1] BRAY F, LAVERSANNE M, SUNG H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [J]. *CA Cancer J Clin*, 2024, 74(3): 229-63.doi:10.3322/caac.21834

[2] ZHU Z, QIN J N, CHEN R X, et al. Effects of different aspirin doses on improving prognosis in patients with advanced colorectal cancer after chemotherapy [J]. *China Med. Her*, 2019, 16(8): 104-7.

[3] ZHAO Y. Clinical efficacy and safety of raltitrexed combined with oxaliplatin after failure of first-line treatment in colorectal cancer [J]. Contemp. Med., 2019, 25(6): 26-7.doi:10.3969/j.issn.1009-4393.2019.06.010

[4] 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 [J]. *CA Cancer J Clin*, 2018, 68(6): 394-424.doi:10.3322/caac.21492

[5] ZHENG R S, SUN K X, ZHANG S W, et al. Analysis of the epidemic status of malignant tumors in C hina, 2015 [J]. Chin. J. Oncol. 2019, 41(1):19-28.doi:10.3760/cma.j.issn.0253-3766.2019.01.005

[6] DU C X. Dynamic changes of ghrelin during the stress response phase after rectal cancer surgery with two surgical procedures and their clinical significance [J]. *Chin. J. Gen. Surg*. 2014, (10): 1440-3.doi:10.7659/j.issn.1005-6947.2014.10.028

[7] ALKHAYYAT M, ABUREESH M, GILL A, et al. Lower Rates of Colorectal Cancer in Patients With Inflammatory Bowel Disease Using Anti-TNF Therapy [J]. *Inflamm Bowel Dis*, 2021, 27(7): 1052-60.doi:10.1093/ibd/izaa252

[8] RUIZ J I, LEI X, GIORDANO S H, et al. Survival in patients with rheumatoid arthritis and recently di agnosed early-stage colorectal, lung, or prostate cancer receiving tumour necrosis factor inhibitors: a r etrospective cohort study [J]. *Lancet Rheumatol*, 2025.doi:10.1016/s2665-9913(24)00379-5

[9] SHAFI S, COLLINSWORTH A W, COPELAND L A, et al. Association of Opioid-Related Adverse Drug Events With Clinical and Cost Outcomes Among Surgical Patients in a Large Integrated Health Care Delivery System [J]. *JAMA Surg*, 2018, 153(8): 757-63.doi:10.1001/jamasurg.2018.1039

[10] PAUL A K, SMITH C M, RAHMATULLAH M, et al. Opioid Analgesia and Opioid-Induced Advers e Effects: A Review [J]. Pharmaceuticals (Basel), 2021, 14 (11): 1091.doi:10.3390/ph14111091

[11] RONG L Q, KAMEL M K, RAHOUMA M, et al. High-dose versus low-dose opioid anesthesia in adu lt cardiac surgery: A meta-analysis [J]. *J Clin Anesth*, 2019, 57: 57-62.doi:10.1016/j.jclinane.2019.03.009

[12] JIN B, YANG H, LUO H. Pharmacological characteristics of esketamine and advances in its clinical a pplication [J]. *Huaihai Med*. J.2024, 42(1): 104-6.doi:10.14126/j.cnki.1008-7044.2024.01.027

[13] ALI H M, MOKHTAR A M. Effect of Single Compared to Repeated Doses of Intravenous S(+) Keta mine on the Release of Pro-inflammatory Cytokines in Patients Undergoing Radical Prostatectomy [J] . *Anesth Essays Res*, 2017, 11(2): 282-6.doi:10.4103/aer.AER_28_17

[14] CUI Y M, LI X F, XIE L X, et al. Effects of low-dose esketamine on postoperative delirium and infla mmatory factors in geriatric frail patients undergoing hip replacement surgery [J]. *Pract. Geriatr*, 202 4, 38(12): 1205-9,14.doi:10.3969/j.issn.1003-9198.2024.12.004

[15] BRINCK E C V, 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 [J]. *Anesth Analg*, 2021, 132(1): 69-79.doi:10.1213/ane.0000000000004729

[16] FALK E, SCHLIEPER D, VAN CASTER P, et al. A rapid positive influence of S-ketamine on the anxiety of patients in palliative care: a retrospective pilot study [J]. *BMC Palliat Care*, 2020, 19(1): 1.doi:10.1186/s12904-019-0499-1

[17] REN X D, YUAN J J, LI L L, et al. Lung protective effects of subanesthetic dose esketamine in patien ts undergoing one-lung ventilation for radical esophagectomy [J]. *J. Zhengzhou Univ*. (Med. Sci.), 202 3, 58(3): 382-7.doi:10.13705/j.issn.1671-6825.2022.07.048

[18] MARGRAF A, LUDWIG N, ZARBOCK A, et al. Systemic Inflammatory Response Syndrome After Surgery: Mechanisms and Protection [J]. Anesth Analg, 2020, 131(6): 1693-707.doi:10.1213/ane.00 00000000005175

[19] HOU N G, AI D B, SUN L X, et al. Effects of ketamine on perioperative inflammatory cytokines and free radicals in patients undergoing one-lung ventilation [J]. J. Clin. Anesthesiol, 2007, 23(9): 720-2.doi:10.3969/j.issn.1004-5805.2007.09.005

[20] WEI P Y, XIA B J, SHEN Q R, et al. Effect of TNF-α intradiscal injection on the expression of β-catenin and Adamts-5 in cartilage endplate [J]. *Chin. Mod. Doctor*, 2018, 56(17): 24-7, [Front 3].

[21] YI W W, WEN Y F, LIU X, et al. Effect of NF-κB inhibitor on the expression of inflammatory factor s in lipopolysaccharide-stimulated degenerative human nucleus pulposus cells [J]. J. Third Mil. Med. Univ, 2017, 39(8): 755-9.doi:10.16016/j.1000-5404.201610083

[22] PROCHáZKA V, LACINA L, SMETANA K, JR., et al. Serum concentrations of proinflammatory biomarker interleukin-6 (IL-6) as a predictor of postoperative complications after elective colorectal surgery [J]. World J Surg Oncol, 2023, 21(1): 384.doi: 10.1186/s12957-023-03270-9

[23] XING X H, ZHAO J, YU S S, et al. Effects of esketamine versus sufentanil on the induction and recovery quality of general anesthesia [J]. *Chin. J. Clin. Physicians*, 2023, 51(12): 1424-7.doi:10.3969/j.issn.2095-8552.2023.12.011

[24] YANG J W, ZHANG D, ZHOU P. Effects of different doses of esketamine combined with sufentanil on pain, inflammatory factors, and stress response in cesarean section parturients [J]. *Chin. Med. Innov*, 2024, 21(35): 65-9.doi:10.3969/j.issn.1674-4985.2024.35.015

[25] JIN D L, LI J F, LIU H L. Effects of esketamine combined anesthesia on intraoperative hemodynamics in patients undergoing thoracoscopic lobectomy [J]. *Clin. Res., 2024*, 32(9): 69-72.doi:10.12385/j.issn.2096-1278(2024)09-0069-04

[26] WANG T, WENG H, ZHOU H, et al. Esketamine alleviates postoperative depression-like behavior through anti-inflammatory actions in mouse prefrontal cortex [J]. *J Affect Disord*, 2022, 307: 97-107.doi:10.1016/j.jad.2022.03.072

[27] JIANG M, LI Q, MAO M, et al. Evaluation of clinical effects of Esketamine on depression in patients with missed miscarriage: A randomized, controlled, double-blind trial [J]. *J Affect Disord*, 2023, 329: 525-30.doi:10.1016/j.jad.2023.02.127

[28] HOU N N, ZHANG M Y, ZHANG Y W, et al. Safety and efficacy of low-dose esketamine weakly opioidized anesthesia in elderly patients with lumbar spinal stenosis undergoing surgery: a prospective, double-blind randomized controlled trial [J]. *BMC Anesthesiol*, 2025, 25(1): 57.doi:10.1186/s12871-025-02908-3

[29] HAN B, JIN F, ZHONG Y, et al. Esketamine ameliorates postoperative cognitive dysfunction aggravated by preoperative acute sleep deprivation in aged mice via the TLR4/NF-κB pathway [J]. Front Aging Neurosci, 2026, 18: 1798915.doi: 10.3389/fnagi.2026.1798915

[30] WANG Y, CAO M, ZHANG Y, et al. The CB2-PKC pathway is involved in esketamine-induced anti-inflammation in BV-2 microglial cells exposed to lipopolysaccharides [J]. Am J Transl Res, 2024, 16(9): 4466-78.doi: 10.62347/RRZF5229

[31] XIE P, LI C, LYU K. Curcumin reduces liver injury in non-alcoholic fatty liver disease rats by regulating TNF-α/NF-κB signaling pathway via miR-155 [J]. *Mod. Immunol*, 2025, 45(1): 27-36.

[32] CHEN Y, MALLEM K, ASBELL P A, et al. A latent profile analysis of tear cytokines and their assoc iation with severity of dry eye disease in the Dry Eye Assessment and Management (DREAM) study [J]. *Sci Rep*, 2024, 14(1): 526.doi:10.1038/s41598-024-51241-1

[33] HALL C, NGUYEN D T, MENDOZA K, et al. Inhibition of IL-6 trans-signaling promotes post-strok e functional recovery in a sex and dose-dependent manner [J]. *J Neuroinflammation*, 2025, 22(1): 52.d oi:10.1186/s12974-025-03365-y

[34] ZORC R, REDMOND C, SYLVESTER M, et al. A coding single nucleotide polymorphism in the inte rleukin-6 receptor enhances IL-6 signalling in CD4 T cells and predicts treatment response to tocilizu mab in giant cell arteritis [J]. Ann Rheum Dis, 2025.doi:10.1016/j.ard.2025.01.049

[35] LIAN F, CAO C, DENG F, et al. Propofol alleviates postoperative cognitive dysfunction by inhibiting inflammation via up-regulating miR-223-3p in aged rats [J]. *Cytokine*, 2022, 150: 155783.doi:10.1016/j.cyto.2021.155783.

[36] NIE Y, LI S, YAN T, et al. Propofol Attenuates Isoflurane-Induced Neurotoxicity and Cognitive Impairment in Fetal and Offspring Mice [J]. *Anesth Analg*, 2020, 131(5): 1616-25.doi:10.1213/ANE.0000000000004955.

[37] ZHAO N, QIN R, LIU B, et al. Sevoflurane versus propofol on immediate postoperative cognitive dys function in patients undergoing cardiac surgery under cardiopulmonary bypass: a comparative analysis [J]. J Cardiothorac Surg, 2025, 20(1): 54.doi:10.1186/s13019-024-03327-0

[38] Li JZ, Wang XQ. Esketamine for Postoperative Multimodal Analgesia in Laparoscopic Surgery: A Systematic Review and Meta-Analysis [J]. J Pain Res, 2026, 19: 597557. doi:10.2147/JPR.S597557

[39] RIDDELL J M, TRUMMEL J M, ONAKPOYA I J. Low-dose ketamine in painful orthopaedic surgery: a systematic review and meta-analysis [J]. *Br J Anaesth*, 2019, 123(3): 325-34.doi:10.1016/j.bja.2019.05.043

[40] 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]. *J Clin Anesth*, 2021, 68: 110071.doi:10.1016/j.jclinane.2020.110071

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