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Original Article

Effect of continuous subanesthetic esketamine infusion on postoperative fatigue in patients undergoing laparoscopic radical resection for colorectal cancer: a randomized controlled study

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Abstract: This study aimed to examine the effect of subanesthetic esketamine on postoperative fatigue in patients who underwent laparoscopic colorectal surgery. A total of 62 patients, including 32 in the esketamine group and 30 in the control group, were analysed in this study. Compared with the control group, the patients in the esketamine group had reduced Identity-Consequence Fatigue Scale (ICFS) on the 3rd and 7th days after surgery ($P<0.05$). There were also significant differences in the Positive and Negative Affect Schedule (PANAS) scale between the two groups. The positive affect scale was higher on postoperative day 3 (POD3), while the negative affect scale was lower on POD3 and postoperative day 7 (POD7) in the esketamine group than in the control group. However, the scores of postoperative hand grip strength, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Numeric Rating Scale (NRS) and Athens Insomnia Scale (AIS) were not significantly different between the two groups. Furthermore, mediation analysis showed that esketamine played an anti-fatigue role through improving emotional heath. Importantly, no adverse reactions occurred at this dosage of esketamine. Finally, our study suggested that subanesthetic esketamine improved postoperative fatigue, stabilized postoperative mood, reduced intraoperative remifentanil consumption, and promoted postoperative intestinal function recovery without increasing adverse reactions.

Keywords: Esketamine, postoperative fatigue, emotional functioning, laparoscopic colorectal surgery

Introduction

Postoperative fatigue (POF) is one of the most common complications after colorectal cancer surgery, manifested as exhaustion, sleepiness or insomnia, low mood, inability to concentrate, and lack of initiative, which tends to be overlooked. Its pathophysiological mechanism has not been fully elucidated, and few intervention measures have been shown to reduce POF [1-3]. A previous study reported that negative emotion, positive emotion, dysfunction and pain were latent variables; nevertheless, the covariance structure model showed that negative and positive emotions markedly influence POF, while dysfunction and physical pain had no obvious effect on POF [4]. Moreover, the author argued that psychological therapies or drugs might be more effective in reducing the fatigue of patients undergone surgery. However, recent animal and clinical studies have found that POF is associated with abnormal glutamate metabolism in the brain, which may be related to the dysregulation of emotion, suggesting that modulating glutamate delivery may have a potential therapeutic effect on POF [5-7].

Esketamine is the S-enantiomer of ketamine, a mixture of R-ketamine and S-ketamine, with satisfying sedative, analgesic, anti-inflammatory and mood-improving effects. In recent years, a growing number of studies have shown that both subanesthetic doses of ketamine and

esketamine have rapid but sustained antidepression effects [8]. Accumulating evidence suggests that esketamine has a higher binding affinity to NMDA receptors than ketamine does, with fewer side effects [9, 10]. In terms of the anti-depression effect, Liu et al. found that pretreatment with S-ketamine can reduce postoperative depression in breast cancer patients more effectively than pretreatment with R-ketamine [11]; therefore, we focused our study on esketamine. As to the anti-fatigue effect, Saligan et al. first described the rapid and sustained anti-fatigue effect of ketamine in patients with treatment-resistant depression, and suggested that the mechanism by which ketamine improves fatigue is related to its anti-depression effects [12]. Another study explored the correlation of ketamine with fatigue as well as depression and found that ketamine improved fatigue in patients with treatment-resistant depression by boosting motivation and mood [13]. Regarding fatigue after surgery, Zhao et al. reported that a subanesthetic dose of ketamine could act as an antifatigue agent due to its anti-inflammatory and neuroprotective effects [14]. However, few studies have explored the effect of esketamine on POF and its functional mechanism. Therefore, this study aimed to assess the effect of the continuous infusion of subanesthetic dose of esketamine on POF in patients undergoing colorectal cancer surgery and explore its effects from both positive and negative emotional aspects as well.

Materials and methods

Study design and patient enrollment

This study was a prospective, double-blind, randomized controlled trial, which was approved by the Ethics Committee of Affiliated Hospital of Xuzhou Medical University (XYFY2022-KL209-01) and was registered in the Chinese Clinical Trial Registry Center (ChiCTR2200056278). The study was performed at the Affiliated Hospital of Xuzhou Medical University from July 2022 to October 2022, and written informed consent was obtained from all participants. The patien inclusion criteria were as follows: (1) scheduled for laparoscopic radical resection for colorectal cancer; (2) 18 to 79 years of age; (3) with BMI between 18.5-28 kg/m^2; and (4) with ASA physical status between I-III. The exclusion criteria were as follows: (1) declined to participate in the study; (2) with preoperative fatigue; (3) with history of preoperative radiotherapy and chemotherapy; (4) with severe liver or renal dysfunction; (5) allergic to esketamine; (6) with serious risk of elevated blood pressure or intracranial pressure; (7) with untreated or undertreated hyperthyroidism; and (8) with drug and alcohol dependence.

Randomization and blinding

Stratified block randomization was performed according to sex (male or female) and surgical method (anus retention or not). Every stratum was randomized at a ratio of 1:1 to the esketamine group or control group, in blocks of 4. The randomization scheme was stored in a light-tight sealed envelope that was opened successively according to the inclusion order. The eligible patients were assigned according to the allocation list in the envelope. Identical packaging of Esketamine and saline was prepared by a person who was not involved in the subsequent anesthetic administration or data collection. All investigators as well as participants, data collectors and assessors were unaware of grouping.

Intervention

After patients entered the operating room, intravenous access was established, and ECG, invasive arterial blood pressure and pulse oxygen saturation were monitored. Anesthesia induction was as follows: midazolam (0.03 mg/kg), etomidate (0.3 mg/kg), sufentanil (0.6 μg/kg) and rocuronium (0.6 mg/kg). Before tracheal intubation, esketamine (0.1 mg/kg) was intravenously injected into the patients in the esketamine group at the rate of 0.1 mg/kg·h until the end of surgery. In the control group, the same volume of normal saline was used. Endotracheal intubation was performed after complete muscle relaxation, and then bilateral ultrasound-guided transversus abdominis plane block and internal jugular central veinous catheterization were performed. For anesthesia maintenance, combined inhalation, and intravenous anesthesia with remifentanil 4-18 μg/kg/h, Propofol 2-6 mg/kg/h and 1% sevoflurane was used in each group. Cisatracurium was given intravenously as needed. The bispectral index (BIS) was maintained at 40-60, $P_{ET}CO_2$ at 35-45 mmHg, heart rate (HR) and MAP fluctuated within 20% of the baseline, and

vasoactive drugs were used when necessary. Remifentanil and propofol intravenous infusions were stopped at the end of the surgery, while sevoflurane was halted 30 minutes earlier. When extubation was ready, the tracheal tube was removed from patients, and the patient-controlled intravenous analgesia, with sufentanil (2 μg/kg) and tropisetron (6 mg) in 100 ml of saline, was performed with an electronic analgesia pump, in which the background infusion rate was 2 ml/h, while the PCA dose was 0.5 ml/time, and the locking time was 15 minutes.

Outcomes

The primary outcome was the Identity-Consequence Fatigue Scale (ICFS) score on postoperative days (POD) 1, 3 and 7, while the secondary outcomes were the Positive and Negative Affect Schedule (PANAS) scale, hand grip strength, Athens Insomnia Scale (AIS) score on POD1, 3, 7. The Numeric Rating Scale (NRS) score on POD1, 2, 3, 7 as well as the levels of serum platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) on POD1 were also monitored as the secondary outcomes. The dosages of propofol and remifentanil, time from intravenous medication withdrawal to extubation, Ramsay score at extubation, length of hospital stay, and adverse reactions were also recorded. The ICFS is a self-report questionnaire that provides a comprehensive evaluation on patient's POF from five different dimensions, such as fatigue, vigorousness, concentration, energy and daily activity [15]. Each entry is scored on a scale of 1 to 6, with a higher score indicating more fatigue. Due to the limited daily activity of the patients during hospitalization, the activity data were uniformly excluded. Grip strength was used to measure skeletal muscle function. For the PANAS score, 10 positive and 10 negative emotional adjectives were tested, while each adjective has five choices representing a score of 1 to 5. A higher score indicates a higher level of emotional expression.

Sample size

The sample size was calculated based on our pilot study which showed that the estimated effect size was 0.75. With a level of α=0.05, β=0.10, and effect size =0.75, we calculated that 58 patients (29 participants per group) were required by G-power software. Considering a 10% dropout rate, we recruited 64 patients in total.

Statistical analysis

SPSS 26.0 and GraphPad Prism 9.0 were used for all analyses. The data were analyzed with the per protocol principle. In continuous data, normality was tested by the Kolmogorov-Smirnov test. The normally distributed data were represented as the mean ± SD and were examined by two-sample independent t-tests between groups, while the non-normally distributed data were represented by the median and interquartile range (M (IQR)) and were analyzed with the Mann-Whiney U test. The qualitative data were expressed as the frequency. The chi-square test or Fisher's precision probability test was performed. The analysis of the mediation effect was performed with PROCESS Marco using the Bootstrap method to explore the association among esketamine, emotional functioning, and POF. A repeated-measures ANOVA followed by Bonferroni's post hoc test was used to determine if the repeated outcomes at each time point differed between the two groups. The significance level was P<0.05 for two-sided tests.

Results

Demographics and baseline characteristics

A total of 64 participants were randomized to either the control or esketamine group, with 32 patients in each group. In the control group, 2 patients were transferred to open surgery due to severe intraperitoneal adhesions. Ultimately, 62 patients including 30 in the control group and 32 in the esketamine group, were analyzed with the per-protocol principle (**Figure 1**). According to the baseline characteristics (**Table 1**), there were no statistically significant differences in age, sex, BMI, ASA physical status, educational status, operation history, preoperative hemoglobin and albumin, and TNM stage or pathological type between the two groups (P>0.05).

POF

When we examined the ICFS score, we noticed a significant difference in the group interaction and time (F=10.66, P<0.001); hence, a simple

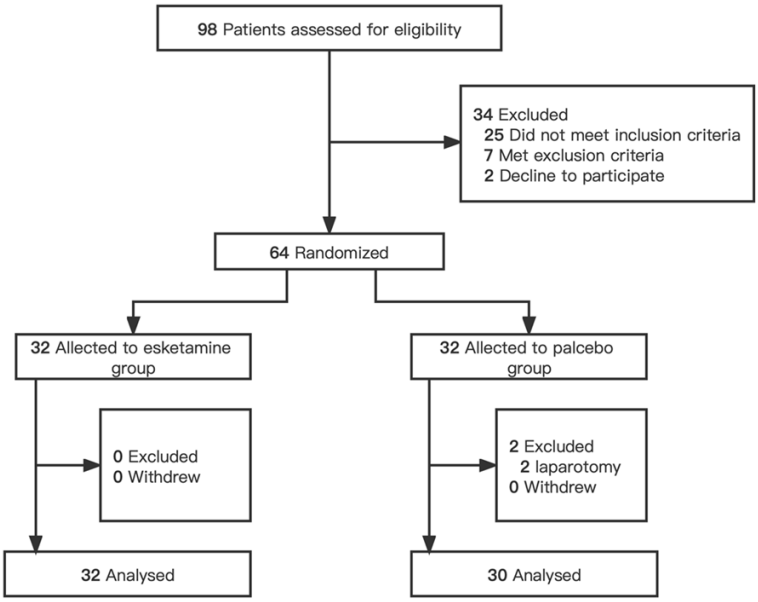

Figure 1. Study Flowchart. Sixty-four participants were randomized. Two patients were excluded from the placebo group, and none were excluded from the esketamine group.

effect was tested. There was no significant difference in ICFS before surgery (F=0.689, *P*=0.410) or on POD1 (F=2.235, *P*=0.140) between the two groups. However, the ICFS score of the esketamine group (83.63±9.62) was lower than that of the control group (91.27±8.71) on POD3 (F=10.706, *P*=0.002) and also on POD7 (esketamine group: 71.56± 9.79; control group: 78.27±9.69; F=7.329, *P*=0.009) (**Table 2**). Overall, the ICFS scores were increased in both groups after the surgery. As shown in **Figure 2**, the score peaked on the first day after surgery and then gradually decreased.

Hand grip strength

As summarized in **Table 3**, esketamine had no statistically significant effect on hand grip strength on the day before surgery (F=0.023, *P*=0.879), POD1 (F=0.877, *P*=0.353), POD3 (F=0.015, *P*=0.904), and POD7 (F=0.265, *P*=0.609).

Positive and negative emotion scores

We also found that there was no statistical difference in emotional state between the two groups one day before (positive affect: *P*= 0.985; negative affect: *P*=0.630) or after surgery (positive affect: *P*=0.266; negative affect: *P*=0.543). Nevertheless, compared with the control group, the esketamine group showed increased positive emotion score (F=4.685, *P*=0.034) but decreased negative emotion score (F=6.391, *P*=0.014) on POD3. The negative emotion was also significantly ameliorated on POD7 (F=8.006, *P*=0.006) in the esketamine group, while the positive emotion score presented a trend of improvement but was not significantly different (F= 3.203, *P*=0.079) (**Table 4**).

NLR, PLR, AIS and NRS scores

Our results showed that esketamine had no effect on the scores of postoperative NRS ($F_{group*time}$=2.475, P= 0.067; F_{group}=0.064, P=0.801; F_{time}=325.758, *P*<0.001) and AIS ($F_{group*time}$=2.199, P=0.115; F_{group}=0.950, P=0.334; F_{time}=2225.180, *P*< 0.001). There was also no significant difference on the scores of NLR (*P*=0.176) and PLR (*P*=0.346) between the two groups on POD1 (**Table 5**).

Adverse events and other indicators

We also assessed the effect of esketamine on other parameters. For example, we found that the esketamine group consumed less remifentanil (*P*=0.048) and had a significantly shorter first flatus time (*P*=0.044). However, there were no differences in propofol dosage, extubation time, Ramsay score at extubation, length of postoperative hospital stay, or adverse effects such as nausea, vomiting, fever, dizziness, headache, agitation, nightmare and hallucination (*P*>0.05) between the two groups (**Table 6**).

Mediation analysis on POD3

To further investigate the correlation of esketamine with emotional state, and POF, we performed mediation analyses, which determined the importance of the direct, indirect, and overall impacts. A bootstrapped 95% confidence interval (CI) revealed that positive and negative emotions acted as mediators of POF, resulting

Table 1. Demographics and baseline characteristics

	Esketamine group (n=32)	Control group (n=30)	*P* value
Age (years)	60.16±7.97	62.87±8.37	0.196
Sex (n)			0.829
Male	19	17	
Female	13	13	
BMI (kg/m^2)	23.18±3.35	23.30±2.30	0.871
ASA (n)			0.591
I	13	14	
II	17	16	
III	2	0	
Educational status (n)			0.832
Primary school or below	12	13	
Junior high school	13	10	
Senior high school or above	7	7	
Operation history (n)	10	11	0.652
Hemoglobin (g/L)	116.59±24.17	121.53±23.28	0.416
Albumin (g/L)	40.60±4.19	40.67±3.56	0.947
PSQI score	4.00 (3.00 to 5.00)	4.00 (3.00 to 5.00)	0.258
TNM stage (n)			0.543
I	3	2	
II	18	13	
III	11	15	
Pathological type (n)			0.492
Adenocarcinoma	30	30	
Other	2	0	

Data are presented as the mean ± SD, median (Q1 to Q3), number; BMI, body mass index; ASA, American Society of Anesthesiologists; PSQI, Pittsburgh Sleep Quality Index.

Table 2. Comparison of ICFS scores

	Esketamine group (n=32)	Control group (n=30)	*P* value
Preoperative 1 d	50.47±3.80	51.13±3.22	0.410
Postoperative 1 d	97.69±5.18[a]	99.60±4.88[a]	0.140
Postoperative 3 d	83.63±9.62[a,b]	91.27±8.71[a,b]	0.002
Postoperative 7 d	71.56±9.79[a,b,c]	78.27±9.69[a,b,c]	0.009

Data are presented as the mean ± SD. ICFS, Identity-Consequence Fatigue Scale. Compared with Preoperative 1 d, [a]*P*<0.05; compared with Postoperative 1 d, [b]*P*<0.05; compared with Postoperative 3 d, [c]*P*<0.05.

in the indirect effects of 2.947 and 1.622, respectively. Sixty percent of the total variance in POF was accounted for by the indirect effect of emotional state (**Table 7**).

Discussion

In this study, we analyzed the effect of the intraoperative use of esketamine in patients undergoing colorectal laparoscopic surgery to relieve POF. We found that a subanesthetic dose of esketamine could improve the ICFS score, reduce the dosage of remifentanil, upregulate positive emotions and downregulate negative emotions. Importantly, no adverse effects were noticed in patients with esketamine administration.

We observed that the ICFS scores were significantly lower in the esketamine group than in the control group on POD3 and POD7, although there was no difference on POD1. One possible explanation is that the POF degree on POD1 in patients with colorectal cancer is so severer that additional interventions, such as esketamine, only added minimal benefits. However, esketamine significantly improved fatigue at days 3 and 7 after surgery, which was consistent with a recent study on colorectal cancer patients with radical laparoscopic surgery, in which patients who received

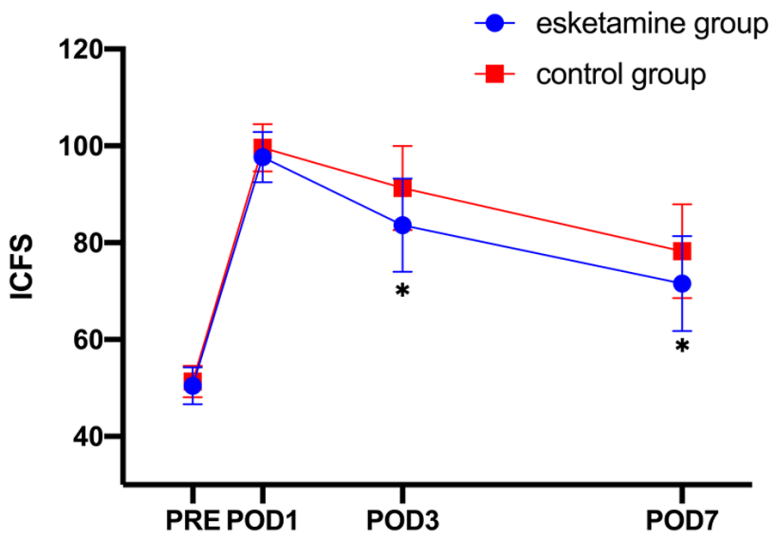

Figure 2. ICFS score at different time points. ICFS, Identity-Consequence Fatigue Scale; PRE, Preoperative; POD, Postoperative Day. A repeated-measures ANOVA followed by Bonferroni's post hoc test was used. The horizontal axis is the time, and the vertical axis is the ICFS score. The data are expressed as the mean ± SD. *Compared with the control group, $P<0.05$.

Table 3. Comparison of hand grip strength

	Esketamine group (n=32)	Control group (n=30)	*P* value
Preoperative 1 d	27.05±7.76	27.34±6.81	0.879
Postoperative 1 d	19.50±5.91	18.17±5.70	0.353
Postoperative 3 d	22.99±7.45	23.20±6.56	0.904
Postoperative 7 d	25.20±7.22	26.11±6.62	0.609

Data are presented as the mean ± SD.

Table 4. Comparison of PANAS scores

	Time	Esketamine group (n=32)	Control group (n=30)	*P* value
Positive Affect	Preoperative 1 d	24.88±5.06	24.90±5.20	0.985
	Postoperative 1 d	11.53±1.02[a]	11.23±1.08[a]	0.266
	Postoperative 3 d	21.56±4.56[a,b]	19.20±4.00[a,b]	0.034
	Postoperative 7 d	24.81±5.56[b,c]	22.40±5.02[a,b,c]	0.079
Negative Affect	Preoperative 1 d	26.84±3.92	26.3±4.90	0.630
	Postoperative 1 d	34.34±3.08[a]	34.83±3.23[a]	0.543
	Postoperative 3 d	30.28±2.90[a,b]	32.67±4.42[a]	0.014
	Postoperative 7 d	28.31±4.00[a,b,c]	31.27±4.22[a,b,c]	0.006

Data are presented as the mean ± SD. The interaction between group and time had statistical significance on positive affect ($F=4.391$, $P=0.026$), and a simple effect was tested. Compared with preoperative 1 d, [a]$P<0.05$; compared with postoperative 1 d, [b]$P<0.05$; compared with Postoperative 3 d, [c]$P<0.05$.

a single dose of intravenous ketamine 0.3 mg/kg before skin incision had reduced POF on POD3, POD5 and POD7 [14]. Nevertheless, Zhao et al. reported that in patients undergoing breast cancer surgery, a low dose of ketamine infusion (bolus of 0.5 mg/kg followed by 0.25 mg/kg/h until the end of surgery) had no effect on the ICFS score at 3 and 7 days after surgery [16], in contrast to our findings. A possible explanation is that the abdominal surgery we evaluated takes longer time as well as involves far more tissue injury and physiological stress than breast cancer surgery does.

POF can also manifest as varying degrees of muscle weakness caused by skeletal muscle oxidative stress and mitochondrial dysfunction after surgery. Hence, grip strength was used to reflect the postoperative skeletal muscle dysfunction. However, we did not observe a significant difference in hand grip strength between the two groups at 1, 3 and 7 days after surgery, suggesting that the low dosage of esketamine might not have a significant effect on muscle fatigue.

In our study, the ICFS scale combined with the grip strength assessment was used to evaluate the mental and peripheral fatigue. Our data showed that esketamine could improve the self-assessment mental fatigue but not the peripheral fatigue. Since the mechanism of POF remains unclear and POF is affected by perioperative factors such as pain, sleep, and mood [17], how esketamine works to improve fatigue after surgery is unknown, despite a report that ketamine exerts its anti-fatigue effect by altering glutamate metabolism, which may be associated with emotion regulation [13, 18].

Emotional disorder after colorectal cancer surgery is not only caused by surgical stress but

Table 5. Comparison of AIS score, NRS score, NLR and PLR

	Time	Esketamine group (n=32)	Control group (n=30)	*P* value
AIS score	Postoperative 1 d	10.97±1.66	11.13±1.22	0.660
	Postoperative 3 d	8.22±1.39	8.77±1.14	0.095
	Postoperative 7 d	5.84±1.35	6.07±1.17	0.491
NRS score	Postoperative 1 d	3.91±0.59	3.90±0.54	0.966
	Postoperative 2 d	3.16±0.45	3.30±0.60	0.258
	Postoperative 3 d	2.56±0.62	2.73±0.58	0.269
	Postoperative 7 d	1.81±0.74	1.63±0.71	0.337
NLR	Preoprative	2.12 (1.58 to 2.62)	2.21 (1.66 to 2.95)	0.464
	Postoperative 1 d	10.91 (8.28 to 14.69)	9.34 (6.40 to 13.00)	0.176
PLR	Preoprative	153.86 (120.28 to 178.88)	156.18 (124.94 to 182.21)	0.602
	Postoperative 1 d	274.72±88.83	252.40±96.06	0.346

Data are presented as the mean ± SD, median (Q1 to Q3); AIS, Athens Insomnia Scale; NRS, Numeric Rating Scale; PLR, platelet to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio. NRS score: $F_{group*time}$=2.475, *P*=0.067; F_{group}=0.064, *P*=0.801; F_{time}=325.758, *P*<0.001. AIS score: $F_{group*time}$=2.199, *P*=0.115; F_{group}=0.950, *P*=0.334; F_{time}=2225.180, *P*<0.001.

Table 6. Adverse events and other indicators

	Esketamine group (n=32)	Control group (n=30)	*P* value
Propofol dosage (mg)	479.72±134.68	462.47±129.05	0.609
Remifentanil dosage (mg)	1.96±0.68	2.28±0.55	0.048
BIS	47.06±2.33	47.63±2.79	0.384
Blood loss	80.00 (70.00 to 80.00)	80.00 (77.50 to 80.00)	0.231
Operation time (min)	200.06±45.07	198.8±48.00	0.915
Awakening time (min)	11.30±1.89	10.93±1.65	0.423
Extubation time (min)	12.38±2.15	12.57±2.06	0.722
Ramsay score at extubation	3.00 (2.25 to 3.00)	3.00 (2.00 to 3.00)	0.474
Length of postoperative hospital stay (d)	8.00 (8.00 to 10.00)	8.0 (7.00 to 10.00)	0.615
Time to first flatus	2.00 (2.00 to 3.00)	3.00 (2.00 to 3.25)	0.044
Nausea (n)	18	20	0.400
Vomiting (n)	7	8	0.660
Fever (n)	1	2	0.607
Dizziness (n)	1	1	>0.999
Headache (n)	0	1	0.484
Agitation (n)	2	1	>0.999
Nightmares (n)	0	0	>0.999
Hallucinations (n)	0	0	>0.999

Data are presented as the mean ± SD, median (Q1 to Q3), number; BIS, bispectral index.

Table 7. Mediating model examination by bootstrap on POD3

	Esketamine→POF		
	Effect	SE	95% CI
Direct effect	3.072	1.486	(0.097, 6.048)
Indirect effect	4.569	1.919	(0.926, 8.468)
Positive Affect	2.947	1.568	(0.199, 6.298)
Negative Affect	1.622	0.945	(0.164, 3.776)

POF, postoperative fatigue; SE, standard error; CI, confidence interval.

also by concerns about the disease and the treatment efficacy. Esketamine has rapid antidepression effects in patients with mood disorders, but the perioperative effect of adjuncts used as general anesthetics on postoperative mood remains to be determined. A previous study compared the effects of propofol alone or in combination with low-dose ketamine on postoperative mood and found that the combination therapy could significantly improve postoperative mood [19]. Furthermore, this study

suggested that the effect might be related to the antagonizing activity of ketamine against NMDA receptors and its anti-anxiety activity [19]. In our study, the positive emotion score on POD3 was higher in the intervention groups than in the control group, while the negative emotion scores were lower at days 3 and 7 after surgery. Previous studies have suggested that the mechanism by which esketamine regulates mood may be related to the reduction in the activation of negative emotional stimuli in the relevant brain regions that regulates the reward circuits in the limbic system and promotes the release of monoamine neurotransmitters such as dopamine [20, 21]. In addition, the long-term effects of ketamine and esketamine have also been investigated [22, 23]. For example, Zhao et al. found that the intraoperative administration of ketamine in neurosurgery patients improved the depression symptoms both on the third day after surgery and at the time of discharge [22]. Another study reported that, in cesarean section, the administration of 0.5 mg/kg esketamine after the delivery significantly reduced the incidence of postpartum depression on the 3rd and 30th days after surgery [23]. Nevertheless, how Esketamine improves the long-term mood health remains to be elucidated, although it was suggested that ketamine might cause long-term synaptic changes in the mesolimbic dopamine system [24].

Further mediation analysis on the data of POD3 showed that esketamine played an anti-fatigue role, which was related to the improvement of emotional functioning. Consistent with our findings, Salmon et al. have reported that postoperative emotional disorder is an important factor not only attributing to POF but also aggravating the degree of POF [4, 25]. In addition, psychological factors can cause neuroendocrine disorders, including the dysfunction of the HPA axis and SAM system, which is one of the mechanisms of POF [26, 17]. Furthermore, postoperative emotional distress will make patients inactive, manifested as a reduction in physical activity, which is one of the measurement dimensions of POF and negatively impacts the quality of recovery [27]. Hence, the improvement in postoperative mood would promote patients to actively cope with surgical trauma and encourage patients to feel energetic again, thereby reducing POF and helping postoperative recovery. Moreover, POF can also aggravate mood disorders, which form a vicious cycle of emotion and fatigue. Hence, Esketamine will help create a positive cycle and have a long-term effect by improving emotional health.

In this study, although subanesthetic esketamine had effects on postoperative emotion and fatigue, no effect was observed on postoperative pain scores, NLR, PLR and AIS score. However, Zhao et al. used a single dose of subanesthetic ketamine in colorectal cancer surgery and found that it had a lasting effect on POF after surgery [14]. The authors proposed that the mechanism was related to the anti-inflammatory action of ketamine, which is different from our observations in this study. One possible explanation is that our study only measured PLR and NLR on POD1 and did not continuously monitor the postoperative inflammation level, which was insufficient to reflect the postoperative inflammatory changes in patients. Alternatively, the effect of esketamine on inflammatory markers may be dose-dependent [28]. Indeed, it has been reported in modified radical mammary surgeries that NLRs were reduced by different doses of S-ketamine (0.25, 0.5, or 0.75 mg/kg/h) in a dose dependent manner [28]. In addition, S-ketamine had no effect on PLR, consistent with our results.

In terms of perioperative analgesia, our study found that esketamine could reduce the intraoperative remifentanil dosage but had no significant effect on the postoperative NRS pain score. The analgesic effect of esketamine is believed to result from blocking NMDA receptors and its binding to μ-opioid receptors, with a relatively short half-life, which could explain the reduction of remifentanil in the esketamine group [29]. However, NRS scores at 1, 2, 3 and 7 days after surgery showed no significant differences between the two groups. In fact, a similar result was also found in a previous study, in which the affective component of pain was significantly improved in the ketamine group after laparoscopic bariatric surgery, and the improvement was relatively durable [30]. The difference in the duration of the effects on emotion and pain by esketamine may be the results of different mechanisms involved. It is also possible that the NRS scale is too general to recognize subtle differences in postoperative pain, and esketamine may improve the emotional component of pain at higher degree.

Few studies have investigated the impact of esketamine on postoperative sleep disorders and the mechanism. Previous studies have shown that Ketamine influences circadian rhythms by controlling clock genes. In addition, a recent study found that 0.3 mg/kg/h perioperative esketamine infusion could reduce the incidence of postoperative sleep disturbance [31-33]. Nevertheless, this study did not find an effect of esketamine on postoperative sleep improvement, which may be due to the different dosages and administration times of esketamine tested in this study. It is worth noting that the time of surgery also affects circadian rhythms and may be a factor attributing to sleep disorders.

There are several limitations in this study. First, since there are many factors affecting POF, the sample size of this study is relatively small, which may affect the reliability of the study results to some extent. However, this study conducted stratified block randomization based on sex and surgical methods, and there was no significant difference in baseline data between the two groups, which somewhat balanced the major influencing factors. Second, in our study, only the per protocol analysis was used, which may partly exaggerate the effect of esketamine. Third, the neurocognitive function of the patients was not assessed in this study, although the assessment of attention dimension in the ICFS reflected the cognitive fatigue of the patients. Lastly, this study did not explore the specific molecular or neural circuit mechanisms of postoperative fatigue, which should be further clarified by neuroimaging and metabolomics in future studies.

Conclusions

In conclusion, we found that the perioperative use of esketamine could reduce POF in patients with colorectal cancer through improving the mental health of the patients.

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Disclosure of conflict of interest

None.

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