Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Effect of Low-Dose Esketamine Combined with Propofol on Postoperative Fatigue in Colonoscopy: A Randomized Clinical Trial

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Purpose: Postoperative fatigue (POF) is a common occurrence following colonoscopy, primarily attributed to bowel preparation and endoscopic probe stimulation, and is associated with worse postoperative outcomes. Esketamine, an antidepressant anesthetic, has shown the potential to enhance postoperative recovery through various mechanisms. We hypothesized that the low-dose esketamine could alleviate POF in outpatients undergoing colonoscopy.

Methods: 200 participants scheduled for painless colonoscopy were enrolled, with 151 patients included in the primary endpoint analysis. Patients were randomly received 0.15 mg/kg esketamine or 0.1 μg/kg sufentanil before anesthesia induction. The primary outcome was the incidence of POF, assessed using the Identity-Consequence Fatigue Scale-10 (ICFS-10) scores at 30 min after colonoscopy. Secondary outcomes included ICFS-10 scores at baseline and 1 day post-colonoscopy, time to discharge and patients' satisfaction.

Results: The incidence of POF was significantly lower in the esketamine group (Group E) compared to the sufentanil group (Group S) (28% vs 44%, $P = 0.036$). There were no significant differences in ICFS-10 scores between the two groups at baseline and 1 day post-colonoscopy. However, discharge time was significantly shorter in Group E than in Group S (25 min vs 30 min, $P = 0.001$). In Group E, there was improved hemodynamic stability and greater patients' satisfaction.

Conclusion: The administration of esketamine significantly reduced the incidence of POF and shortened discharge time in patients undergoing colonoscopy. A regimen of 0.15 mg/kg esketamine combined with propofol proved to be an effective anesthesia strategy for painless colonoscopy.

Keywords: esketamine, postoperative fatigue, colonoscopy

Introduction

Postoperative fatigue (POF) is a group of physiological and psychological symptoms that hinder patients resuming normal activities after surgery. It is mainly manifested as insomnia, inattention, low mood, and lack of initiative. POF is a major cause of interference in the functional recovery of patients after surgery, with a longer duration.[1] Approximately 90% of patients undergoing laparoscopic radical gastrectomy experienced POF,[2] and up to 65% of patients with esophagectomy had persistent fatigue five years post-surgery.[3] A retrospective study indicated that up to 37.5% of patients undergoing gastrointestinal endoscopy developed postoperative fatigue syndrome one day after the procedure.[4]

At present, interventions for relieving POF focus on mitigating pain, enhancing sleep, and promoting psychological relaxation.[5] Esketamine is a new type of anesthetic drug with comprehensive effects, including analgesia, antidepressants, and enhanced sleep quality.[6,7] A small sample clinical study showed that continuous subanesthetic esketamine infusion improved POF and stabilized postoperative mood in patients undergoing laparoscopic colorectal surgery.[8] Therefore, esketamine may be an ideal medication for improving POF in patients.

Received: 27 February 2025
Accepted: 19 May 2025
Published: 29 May 2025

Colorectal cancer is one of the most commonly diagnosed cancers worldwide. Colonoscopy is an invasive and complex procedure with a highly effective screening tool in the diagnosis and treatment of colorectal diseases.[9] A multicenter observational study indicated that up to one-third of patients had impaired work productivity after colonoscopy.[10] Patients undergoing colonoscopy often experience anxiety, poor sleep, and POF due to bowel preparation and endoscopic probe stimulation.[11] These factors may decrease patients' satisfaction and willingness to participate in repeated screening. Consequently, POF in outpatients is increasingly recognized by anesthesiologists. It is crucial to develop a higher-quality anesthesia program for outpatient care.

Currently, research on POF primarily focuses on patients undergoing major surgeries.[12,13] Thus, in this randomized clinical trial, we examined the effect of low-dose esketamine on POF in outpatients undergoing painless colonoscopy.

Methods

Study Design

This study was a single-center, prospective, randomized, double-blind clinical trial. It was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ2023-08-24) and registered in the Chinese Clinical Trial Registry (ChiCTR2300073838, Principal Investigator: Xuesheng Liu, Date of Registration, July 24, 2023) before patient enrollment. Written informed consent was obtained from the participants. The study procedure was conducted in the First Affiliated Hospital of Anhui Medical University and was in line with the Declaration of Helsinki.

Study Participants

We recruited patients scheduled for elective painless colonoscopy at the First Affiliated Hospital of Anhui Medical University from August 2023 to July 2024, aged 18 to 65, with American Society of Anesthesiologists (ASA) physical status I or II, undergoing routine colonoscopy diagnosis or treatment, the expected colonoscopy time was not more than 30 minutes, clearly understand and voluntarily participate in the study. Exclusion Criteria: severe liver or renal dysfunction; known neuropsychiatric disorders (Parkinson's disease, epilepsy, or schizophrenia); contraindications or allergies to esketamine; a history of psychiatric disorders; preoperative use of relevant anxiolytic sedative medications; severe uncontrolled hypertension (> 180/110 mmHg at rest); body mass index (calculated as weight in kilograms divided by height in meters squared) higher than 30 kg/m^2; inability to communicate.

Study Procedure

In our study, randomization was performed using a computer-generated sequence in a 1:1 ratio, with allocation concealed in consecutively numbered, sealed, opaque envelopes. These envelopes were opened only after patient enrollment. A designated research anesthetist, who was not involved in intraoperative care, outcome assessment, or data analysis, was responsible solely for preparing the study medication. Although this anesthetist was not blinded, he was not informed of the study hypothesis, group definitions, or outcome measures. His role was strictly limited to preparing the investigational drug (esketamine or sufentanil) based on the group code in the envelope. All study drugs were diluted in 0.9% saline to a total volume of 20 mL, and syringes were indistinguishable in appearance. All other personnel, including the attending anesthesiologists, endoscopists, patients, and investigators responsible for perioperative care and data collection, were fully blinded to group allocation. The randomization code remained concealed until after completion of statistical analysis.

In the preparation room, all enrolled patients were assessed using the ICFS-10, the Hospital Anxiety and Depression Scale (HADS), and the Athens Insomnia Scale (AIS). Then, patients were established intravenous access and monitored by Electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), and respiratory rate. Oxygen at a rate of 2 to 4 L/ min was administered by the mask to all patients in the whole process. Anesthesia induction was initiated by esketamine (0.15 mg/kg, Jiangsu Hengrui Medical Co., Ltd., China) or sufentanil (0.1 μg/kg, Yichang Human Well Pharmaceutical Co., Ltd., China), followed by propofol (1.5–2.0 mg/kg, Beijing Fessen Yusca by Pharmaceutical Co., Ltd. China). The level of the sedation was

accessed using the Modified Observer's Assessment of Alertness/Sedation (MOAA/S). 0.5 mg/kg of propofol was administered as a rescue sedative if MOAA/S was above 1 after induction. The colonoscopy could be initiated when the patients achieved sufficient sedation (MOAA/S ≤ 1). During the colonoscopy procedure, the target sedation level was set at a score of 2 (only responding to prodding or shaking stimuli). The maintenance dose of sedation was by bolus top-ups (0.3–0.5 mg/kg propofol) in case of signs of motor or verbal reaction, which affected the operation of endoscopist.

During the procedure, if SpO_2 was < 95%, the anesthesiologist took steps to make a jaw thrust maneuver or further positive pressure ventilation. If non-invasive mean blood pressure (MBP) was < 60 mmHg, 2.0 mg dopamine was administered intravenously. If the HR was below 50 bpm, 0.5 mg (Anhui Changjiang Pharmaceutical Co., Ltd., China) atropine was injected intravenously. Other adverse events were recorded and treated according to clinical operation standards.

After the colonoscopy, all patients were transferred to the Post Anesthesia Care Unit (PACU). When patients responded immediately to the name spoken in a normal tone (MOAA/S ≥ 5), they recovered to full alertness. When the post-anesthesia discharge scoring system (PADSS) scores was at least 9 points, the patient was allowed to leave the endoscopy center. In PACU, adverse indicators such as injection pain, postoperative pain were defined as NRS scores ≥ 1 (range, 0–10, with 0 indicating no pain and 10 indicating the most severe pain experienced by the patient), postoperative nausea and vomiting (PONV), hypoxemia (SpO2 < 90% for ≥ 10s), dizziness, hallucination, nightmare and emergence agitation were evaluated. Intraoperative variables were recorded as follows: colonoscopy time (the time from the insertion of colonoscopy to the withdrawal of colonoscopy); sedation recovery time (the time from the MOAA/S ≤ 1 to the moment of MOAA/S = 5); hemodynamic parameters at different time points (T1: arrival at the examination room, T2: immediately after the start of the colonoscopy, T3: endoscope reached the cecum; T4: at the end of the colonoscopy, T5: hospital discharge or 30 min after colonoscopy); the satisfaction degree of endoscopists and patients (measured using a 100-mm visual analog scale: 0 = completely dissatisfied and 100 = completely satisfied). The endoscopists' satisfaction was assessed at the conclusion of the colonoscopy, while patients' satisfaction was measured 30 min after colonoscopy or before discharge.

Study Outcomes

The primary outcome was the incidence of POF at 30 min after colonoscopy or before discharge. POF was defined as ICFS-10 (Identity-Consequence Fatigue Scale-10) scores ≥ 24 with clinical significance.

A researcher blinded to the grouping, conducted an interview using the ICFS-10, which comprises a concise set of 10 questions. The total score of the ICFS-10 ranged from 10 to 57, with higher scores indicating more fatigue.

Secondary outcomes were as follows: ICFS-10 scores at baseline and 1 day post- colonoscopy, total propofol dosage, time to discharge (the time from the end of colonoscopy to the PADSS scores ≥ 9), and patients' satisfaction.

Statistical Analysis

Sample size was based on our pilot study with PASS 15.0, in which the incidence of POF at 30 min after the procedure was 42% in Group S. We hypothesized that low-dose of esketamine could reduce the incidence of POF from 42% to 21%. To achieve a statistical power of 80% with an $\alpha = 0.05$, we calculated that each group would require 76 patients.

Statistical analysis was performed using SPSS for Windows version 25.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of the variables was examined using the Kolmogorov–Smirnov test. Continuous variables in a normal distribution were presented as mean ± standard deviation (SD), while non-normal data were presented as median and interquartile range. Between-group comparisons of quantitative data were analyzed using either the Student's independent *t*-test or the Mann–Whitney *U*-test. Hemodynamic parameters were compared using repeated measures analysis of variance (ANOVA). Categorical variables were presented as number and frequency, compared using the $\chi 2$ test or Fisher's exact test. A logistic regression model was assessed the potential risk factors associated with POF. $P < 0.05$ was considered statistically significant.

Results

A total of 200 patients were assessed for eligibility, and 48 patients were excluded based on the exclusion criteria. 152 patients were randomized into two groups. In Group S, one patient whose colonoscopy was more than 30 minutes was excluded (Figure 1). In total, 151 patients were enrolled in the primary endpoint analysis. Demographic and baseline characteristics were listed in Table 1. There were no significant differences between the two groups in terms of age, AIS scores, HADS-A scores, HADS-D scores, or underlying disease. Colonoscopy time and recovery time were no differences between the two groups ($P > 0.05$).

The incidence of POF was significantly lower in Group E than in Group S (28% vs 44%, $P = 0.036$). There were no statistical differences in ICFS-10 scores at baseline and 1 day after colonoscopy between the two groups, however, the postoperative ICFS-10 scores declined in all patients compared with baseline. The propofol dosage was not different between Group S (0.231 ± 0.085 mg/kg/min) and Group E (0.234 ± 0.087 mg/kg/min). The discharge time in Group E was 25 (25, 25) min, significantly shorter than in Group S (30 [25, 35] min, $P = 0.001$). Patients' satisfaction in Group E was significantly higher than in Group S ($P = 0.010$); however, there was no significant difference in endoscopists' satisfaction between the two groups ($P = 0.450$) (Table 2).

Multivariable logistic regression was used to explore the risk factors associated with POF, and these were found to include preoperative ICFS-10 scores (Odds ratio [OR], 1.227; 95% CI, 1.072–1.404), preoperative AIS scores (OR, 1.42; 95% CI, 1.053–1.916), preoperative depression scores (HADS-D: OR, 1.424; 95% CI, 1.040–1.949), and postoperative pain scores (OR, 2.652; 95% CI, 1.050–6.701) (Figure 2).

There was no significant difference in perioperative MBP between the two groups ($P = 0.051$), while perioperative HR was a significant difference between groups ($P = 0.015$). Our data showed that MBP and HR decreased significantly

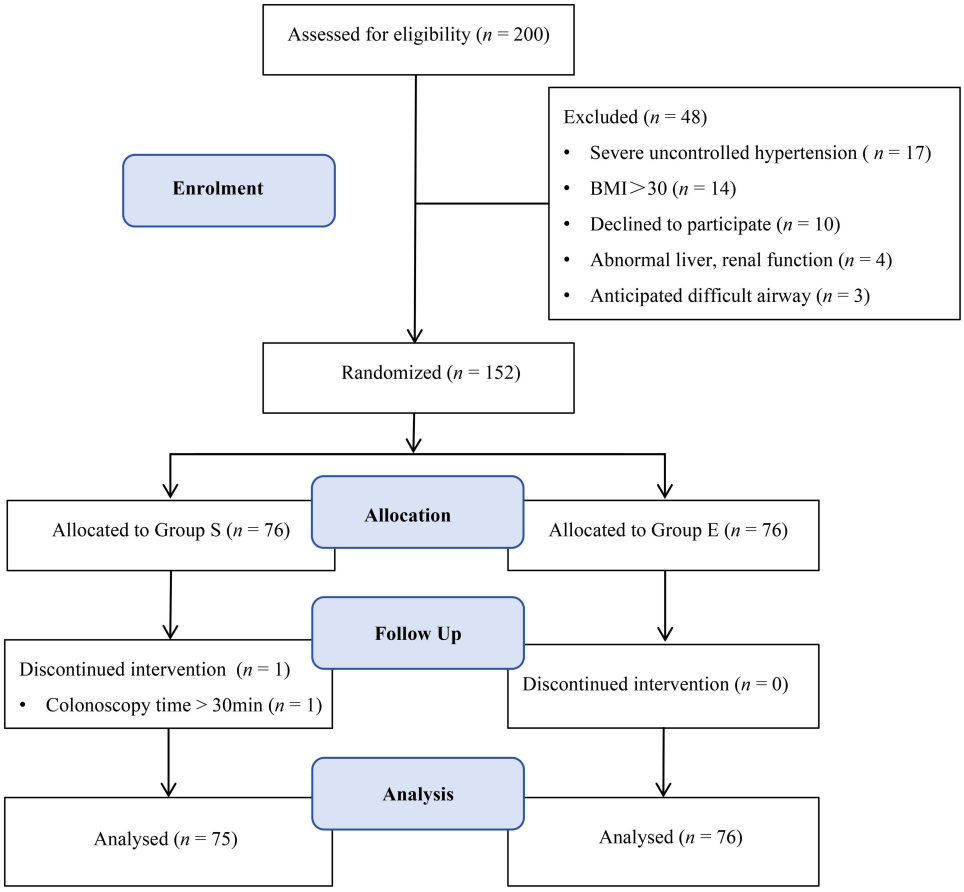

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flowchart of patients.
Abbreviations: Group S, 0.1 μg/kg sufentanil before anesthesia induction; Group E, 0.15 mg/kg esketamine before anesthesia induction.

Table 1 Demographic Characteristics and Perioperative Data

	Group S (n= 75)	Group E (n = 76)	*P* value
Age (years)	46.03 ± 12.91	44.46 ± 11.92	0.440
Male, n (%)	36 (48%)	35 (46%)	0.811
BMI (kg/m^2)	23.63 ± 2.75	23.24 ± 2.84	0.401
ASA, n (%)			0.790
I	46 (61%)	45 (59%)	
II	29 (39%)	31 (41%)	
Hypertension, n (%)	13 (17%)	11 (14%)	0.631
Diabetes, n (%)	3 (4%)	2 (3%)	0.681
Smoker, n (%)	10 (13%)	8 (11%)	0.595
AIS scores baseline (IQR)	3 (2, 4)	3 (3, 4)	0.248
HADS-A scores, median (IQR)	5 (4, 7)	6 (4, 7)	0.138
HADS-D scores, median (IQR)	4 (3, 6)	4 (3, 5)	0.334
Colonoscopy time (min)	10.791 ± 2.385	11.046 ± 2.655	0.535
Sedation recovery time (min)	12.581 ± 4.445	12.367 ± 4.431	0.767

Note: Data are presented as mean ± SD, median [IQR] or numbers (%).
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ASA, American Society of Anesthesiologists; AIS, Athens Insomnia Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression.

Table 2 Outcomes of the Patients Among the Two Groups

	Group S (n = 75)	Group E (n = 76)	*P* value
ICFS-10 scores ≥ 24, n (%)	33 (44%)	21 (28%)	0.036*
ICFS-10 scores			
Baseline	16 (14, 19)	16.5 (14, 19)	0.598
30 min later	23 (22, 27)	22 (21, 25.75)	0.002*
1 day later	15 (12, 18)	14 (12, 18)	0.466
Propofol (mg/kg/min)	0.231± 0.085	0.234 ± 0.087	0.853
Discharge time	30 (25, 35)	25 (25, 25)	0.001*
Patients' satisfaction	90 (90,100)	100 (90,100)	0.010*
Endoscopists' satisfaction	90 (90,100)	95 (90,100)	0.450

Note: Data are presented as numbers (%), median [IQR] and mean ± SD. *: P < 0.05, Group S vs Group E.
Abbreviation: ICFS-10, Identity Consequence Fatigue Scale-10.

after anesthesia in each group. However, MBP and HR were significantly higher in Group E than in Group S at the procedure. It presented the fluctuations of MBP and HR were more stable in Group E (Figure 3).

In this study, the incidences of injection pain, postoperative pain, PONV, and dizziness was not significantly different between groups. No patient experienced nightmares and emergence agitation during the study. One patient in Group S had hypoxemia during colonoscopy. Only one patient in Group E experienced hallucinations, which resolved spontaneously after a few minutes (Table 3).

Discussion

In this prospective randomized study, low-dose esketamine combined with propofol effectively reduced the incidence of POF and alleviated fatigue symptoms in patients undergoing colonoscopy. These findings align with previous studies. For instance, preoperative and postoperative analgesia with esketamine has been shown to decrease the incidence of POF from 53% to 34% on postoperative day 3 following laparoscopic radical gastrectomy.[2] Similarly, in patients undergoing

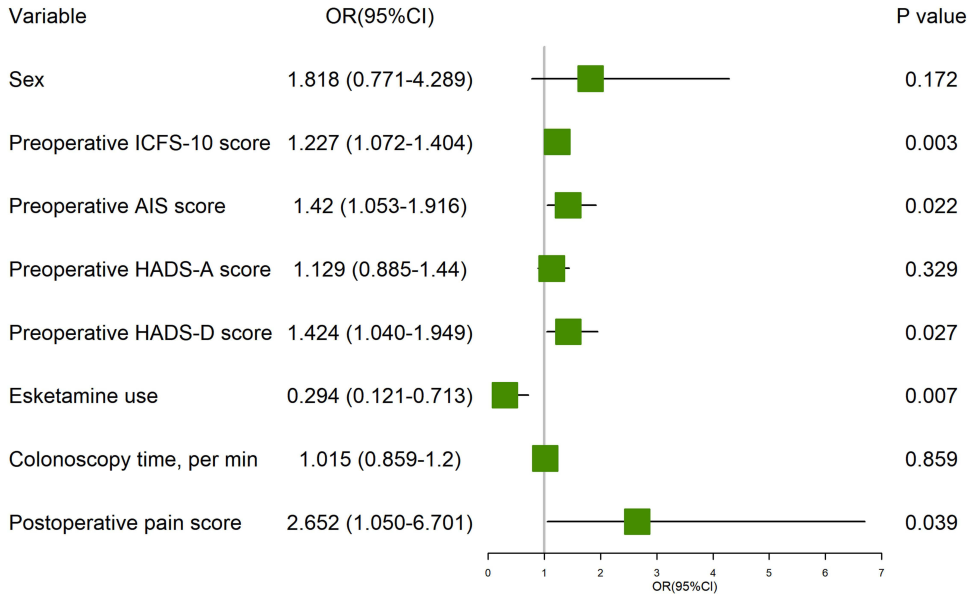

Figure 2 Forest plot analyzing factors association with incidence of POF in multivariable logistic regression.
Abbreviations: ICFS-10, Identity-Consequence Fatigue Scale-10; AIS, Athens Insomnia Scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; OR, odds ratio; 95% CI, 95% confidence interval.

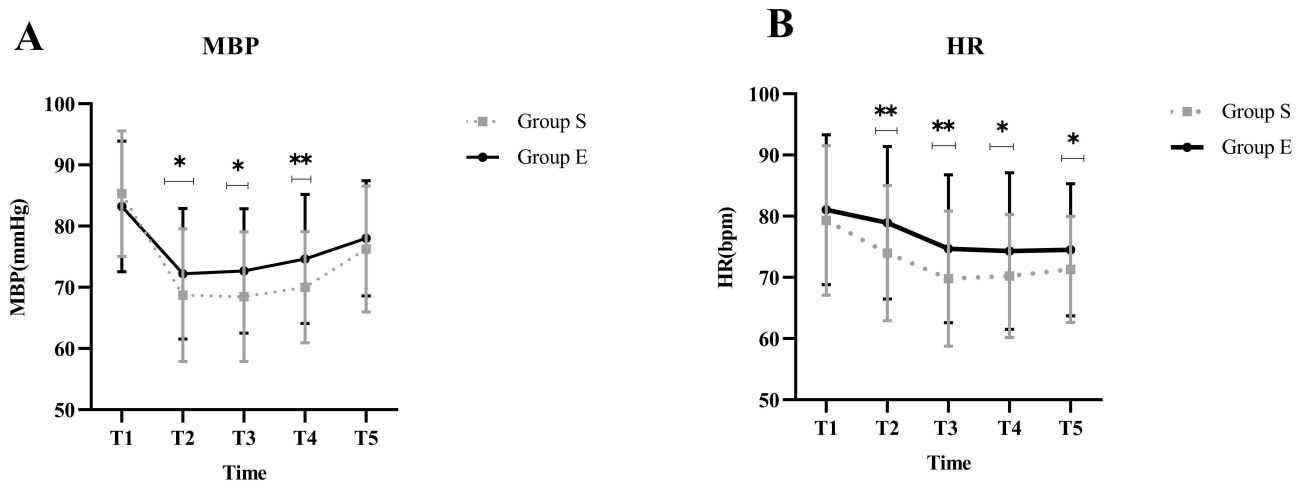

Figure 3 Comparison of the perioperative MBP (**A**) and HR (**B**) among the two groups.
Notes: Group S=0.1μg/kg sufentanil, Group E=0.15 mg/kg esketamine. *: *P*<0.05, **: *P*<0.001, Group S vs Group E.
Abbreviations: MBP, non-invasive mean blood pressure; HR, heart rate; T1, arrival at the examination room; T2, immediately after the start of the colonoscopy; T3, endoscope reached the cecum; T4, at the end of the colonoscopy; T5, hospital discharge or 30 min after the colonoscopy.

colorectal cancer radical resection, continuous subanesthetic esketamine infusion improved self-reported mental fatigue on postoperative days 3 and 7, although it did not significantly affect peripheral fatigue, and facilitated recovery of postoperative intestinal function.[8] Recently, a retrospective study showed that a single dose of 0.2 mg/kg esketamine combined with propofol reduced the incidence of postoperative fatigue syndrome in patients undergoing gastroenterological endoscopy.[4]

Esketamine, the S-enantiomer of ketamine, exhibits a higher affinity for noncompetitive N-methyl-D-aspartate (NMDA) receptor and fewer adverse effects compared to ketamine in clinical practice.[14] Emerging evidence suggests that a low-dose of esketamine (0.15 mg/kg) combined with propofol is both safe and effective for patients undergoing endoscopy.[15] Based on these findings, a 0.15 mg/kg dose of esketamine was selected in this study to minimize side effects. At our study center, the combination of low-dose sufentanil and propofol for sedation is the standard practice,

Table 3 Adverse Events Among the Two Groups

Variable, n (%)	Group S (n = 75)	Group E (n = 76)	*P* value
Injection pain	13 (17%)	12 (16%)	0.799
Postoperative pain	7 (9%)	8 (11%)	0.806
PONV	6 (8%)	5 (7%)	0.737
Dizziness	10 (13%)	9 (12%)	0.782
Dopamine	21 (28%)	11 (14%)	0.042*
Atropine	2 (3%)	0 (0%)	0.245
Hypoxemia	1 (1%)	0 (0%)	0.497
Hallucinations	0 (0%)	1 (1%)	1.000
Nightmare	0 (0%)	0 (0%)	1.000
Emergence agitation	0 (0%)	0 (0%)	1.000

Note: Data are presented as numbers (%).
Abbreviation: PONV, postoperative nausea and vomiting.

aligning with a recent national survey conducted in China.[16] In this study, there were no significant differences between groups in propofol dosage or postoperative pain, indicating that 0.15 mg/kg esketamine is comparable to 0.1 μg/kg sufentanil as an adjuvant analgesic.

POF is inherently subjective and challenging to quantify, with no established gold standard for diagnosis. The Christensen's Fatigue Scale (ChrFs) is a single-item measure, that lacks the ability to distinguish between the mental and behavioral components of POF.[17] Paddison et al[18] developed the Identity Consequence Fatigue Scale (ICFS) to evaluate perioperative fatigue, but its comprehensive nature makes it time-intensive for clinical use. The Identity-Consequence Fatigue Scale-10 (ICFS-10), a shortened version of the ICFS-31, is adapted for surgical patients in the Chinese population and offers greater clinical applicability.[19] In this study, the ICFS-10 was utilized to more accurately assess POF. There were no significant intergroup differences in ICFS-10 scores at baseline and 1 day after colonoscopy. However, within each group, ICFS-10 scores decreased 1 day after the procedure compared to baseline, likely reflecting the effects of pre-procedure preparation.[10] Furthermore, the minimal tissue trauma associated with colonoscopy, in contrast to major surgeries, may contribute to a quicker recovery and reduced fatigue levels.

The mechanism underlying POF is multifaceted, influenced by both physiological and psychological factors. Animal experiments have suggested a potential relationship between POF and NMDA. NMDA receptor antagonists have been shown to alleviate central fatigue in patients.[20] Previous research has demonstrated that NMDA receptor antagonists may reduce POF through various mechanisms, including minimizing tissue damage, attenuating inflammatory responses, promoting the clearance of brain metabolites, and providing analgesic benefit.[21] Ketamine might alleviate central fatigue by reducing postoperative serum tumor necrosis factor (TNF)-α and interleukin (IL)-6 to mitigate the inflammatory response, by decreasing S100β protein and neuron-specific enolase (NSE) concentrations to counteract potential brain injury.[22] Additionally, ketamine's efficacy in treating resistant depression may stem from its ability to improve fatigue by enhancing motivation and mood.[23] Among mothers with prenatal depression, a single dose of 0.2 mg/kg esketamine administered after delivery reduced the incidence of depression episodes within 42 days to approximately 25%.[24] In this present study, esketamine significantly improved ICFS-10 scores at 30 minutes after colonoscopy, potentially due to its perioperative antidepressant properties and its ability to stabilize postoperative mood.

The rapid discharge time is a key indicator of the quality of procedural sedation, directly contributing to reduced consumption of medical resources. This is particularly critical for ambulatory endoscopy centers, which often face high turnover and limited capacities of the PACU. In this study, esketamine significantly shortened the discharge time, suggesting its potential to enhance postoperative recovery and increase ambulatory endoscopy centers turnover rates. Supporting this, a recent propensity score-matched cohort study also demonstrated that the use of esketamine significantly improved the discharge rates within 3 days following knee arthroscopic surgery.[25] The patients' satisfaction is a vital indicator of healthcare quality. Esketamine has been shown to significantly enhanced patients' satisfaction,

aligning with findings of previous work.[26] This improvement might be due to its overall positive effects on the sedation process and better postoperative cognitive recovery.

Hemodynamic fluctuations are the most common intraoperative adverse events during painless endoscopy. Research has demonstrated that hypotension can be directly harmful for postoperative organ function, particularly in high-risk patients. A high-quality multicenter clinical trial provided strong evidence that adding 0.15 mg/kg esketamine to propofol sedation significantly reduces the incidence of composite hypotension and desaturation events during gastrointestinal endoscopy.[27] In this study, the use of vasoactive drugs was significantly lower in Group E compared to Group S, while no atropine was required in Group E. These findings indicated that esketamine combined with propofol provide superior hemodynamic stability, likely due to esketamine's ability to activate the sympathetic nervous system and counteract the circulatory inhibition caused by propofol.[28,29] The incidence of hypoxemia in this study was relatively low, attributed to the use of mask oxygen inhalation and preoxygenation before anesthesia. Additionally, obese patients, who are at higher-risk for hypoxemia, were excluded from the study population.

Multivariable logistic regression analysis revealed that preoperative ICFS-10 scores, preoperative AIS scores, preoperative depression scores, and postoperative pain scores were significantly associated with the occurrence of POF, consistent with findings from previous studies.[30,31] Prior research has demonstrated that esketamine can enhance the quality of postoperative recovery through multiple mechanisms,[32] alleviate postoperative sleep disturbances,[7] and relieve postoperative depression and pain symptoms[24] in patients undergoing non-cardiac major surgeries. By addressing these key risk factors, esketamine emerges as a promising preventive agent for POF.

This study has several limitations that should be acknowledged. First, we exclusively recruited young patients with ASA physical status I–II, as these individuals typically have higher requirements for postoperative comfort and an urgent need to resume normal activities. Second, while a higher dose of esketamine may enhance its fatigue-reducing effects and further reduce propofol consumption, it could also increase the risk of adverse effects. Thus, the optimum dosage of esketamine remains to be determined. Finally, this was a single-center study, which may limit the generalizability of the findings. Further high-quality, large-scale, multi-center prospective studies are necessary to confirm and extend these results.

Conclusion

In summary, this prospective randomized clinical trial demonstrated that administration of 0.15 mg/kg esketamine significantly reduced the incidence of POF and shortened discharge time for patients undergoing colonoscopy. The combination of esketamine and propofol proved to be an effective and beneficial anesthesia regimen for painless colonoscopy.

Abbreviations

POF, postoperative fatigue; ICFS-10, Identity-Consequence Fatigue Scale-10; HADS, Hospital Anxiety and Depression Scale; AIS, Athens Insomnia Scale; MOAA/S, Modified Observer's Assessment of Alertness/Sedation; PACU, Post Anesthesia Care Unit; PONV, Postoperative nausea and vomiting; NMDA, N-methyl-D-aspartate.

Data Sharing Statement

The datasets used during this study are available from corresponding authors on reasonable request.

Acknowledgment

The study was registered in the Chinese Clinical Trial Registry (ChiCTR2300073838, Principal Investigator: Xuesheng Liu, Date of Registration, July 24, 2023).

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 research was supported by the Joint Project of Anesthesiology and Pharmacology of 2021 Peak Discipline Construction Project in the First Affiliated Hospital of Anhui Medical University (9001001813) and Anhui Medical University (2022xkj150).

Disclosure

The authors report no potential conflicts of interest in this work.

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