Submitted: 05 November, 2024 Accepted: 06 March, 2025 Published: 08 August, 2025 DOI:10.22514/sv.2025.110

Open Access
Signa Vitae

ORIGINAL RESEARCH

Low dose esketamine for gastrointestinal endoscopy: a double-blinded, randomized controlled trial

Dongsheng Hu[1], Danni Li[1], Honggang Wang[2], Wei Hu[1], Lijun An[1,*]

[1]Department of Anesthesiology, the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, 223301 Huaian, Jiangsu, China
[2]Department of Gastroenterology, the Affiliated Huaian No. 1 People's Hospital of Nanjing Medical University, 223301 Huaian, Jiangsu, China

***Correspondence**
hayyalj@njmu.edu.cn
(Lijun An)

Abstract

Background: Propofol and remifentanil are frequently used together for painless therapeutic gastrointestinal (GI) endoscopy. However, this combination can result in respiratory and cardiovascular depression. The use of esketamine has the potential to counteract these adverse effects. This study evaluates the efficacy and safety of low-dose esketamine combined with a fixed dose of propofol-remifentanil sedation during painless therapeutic GI endoscopy. **Methods**: A total of 400 patients undergoing painless therapeutic GI endoscopy were randomly divided into four groups (n = 100 per group). The control group received propofol and remifentanil, while the other three groups received propofol and remifentanil plus 0.05, 0.10 and 0.15 mg/kg/h esketamine. Throughout the procedure, we recorded hemodynamics, pulse oxygen saturation, somatic responses, adverse event management, emergence delirium and perioperative Mini-Mental State Examination (MMSE) scores. **Results**: Respiratory interventions were significantly higher in the control groupcompared to three esketamine groups (elevated oxygen flow: 15% *vs.* 2%, 2% and 4%; mandibular support: 10% *vs.* 1%, 1% and 3%; mask ventilation: 4% *vs.* 0%, 0% and 0%). Hypotension and bradycardia occurred more frequently in the control group (hypotension: 13% *vs.* 3%, 1% and 1%; bradycardia: 15% *vs.* 5%, 3% and 2%). Although there were no significant differences in gagging among the groups, a reduced response to body movement was documented in patients randomized to esketamine when compared to the control group (1% *vs.* 13%). No significant changes were observed in MMSE scores in any of the groups. **Conclusions**: The continuous infusion of small-dose esketamine in addition to propofol-remifentanil sedation could provide efficient and safe sedation for painless therapeutic GI endoscopic procedures. **Clinical Trial Registration**: The study was registered in the Chinese Clinical Trial Registry (Registration number: ChiCTR2400079866). Date of registration: 15 January 2024.

Keywords

Esketamine; Propofol-remifentanil; Fixed-dose; Sedation; Gastrointestinal endoscopy

1. Introduction

In China, approximately 14 million gastrointestinal (GI) endoscopic procedures are conducted annually, a number anticipated to rise to 51 million by 2030 due to the aging population [1]. Currently, a growing number of patients prefer painless GI endoscopy because it aims to offer greater safety and comfort [2]. However, despite its increasing popularity, no standardized anesthesia protocol is in place to ensure that the anesthesia administered during these procedures is effective, safe, comfortable and satisfactory. Therefore, it is essential to develop methods to provide such anesthesia during GI endoscopic procedures.

The combination of propofol and remifentanil is increasingly preferred over propofol alone for diagnostic and therapeutic GI endoscopy [3–5]. Both agents act rapidly and dissipate quickly after administration, facilitating faster endoscopic procedures and quicker patient recovery. As a result, patients can leave the post-anesthetic care unit (PACU) sooner. When used together, propofol and remifentanil exert a synergistic effect, allowing for the desired outcomes to be achieved with reduced doses of each drug. Nevertheless, the infusion rates and dosages prescribed in the propofol-remifentanil administration protocols may lead to respiratory and cardiovascular depression [6]. These adverse effects can arise with prolonged endoscopic procedures, occasionally necessitating the use of additional drugs. Therefore, this may pose additional risks for patients. Consequently, there is an urgent need for innovative drugs or methods to alleviate these side effects.

Esketamine is the S (+)-isomer of ketamine and a new N-methyl-D-aspartate (NMDA) receptor antagonist. Europe and China have approved esketamine for general anesthesia

as well as perioperative sedation and analgesia, respectively [7]. It is effective in treating both acute and chronic pain at lower dosages, resulting in fewer dose-dependent side effects. The Food and Drug Administration (FDA) has approved intranasal esketamine for treatment-resistant depression, and it is commonly utilized in low-resource settings outside operating rooms and even in patients' homes [8]. Similar to ketamine, esketamine may help mitigate opioid-induced respiratory depression [9–12]. Low-dose esketamine stimulates catecholamine release and activates the sympathetic nervous system, leading to cardiovascular stimulation that can elevate blood pressure and heart rate (HR) [13, 14].

This study aims to evaluate the efficacy and safety of low-dose esketamine administered with fixed-dose propofol-remifentanil for sedation during painless therapeutic GI endoscopy.

2. Materials and methods

2.1 Study design and participants

This study is a prospective, double-blinded, randomized controlled trial aimed at evaluating the efficacy of esketamine in combination with propofol and remifentanil during gastrointestinal polypectomy. The respiratory and circulatory depression, perioperative sedation, and cognitive function of patients were assessed. The study protocol was approved by the Ethics Committee of Huai'an No. 1 People's Hospital affiliated with Nanjing Medical University, China (Ethics approval number: KY-2023-080-02) on 11 July 2023. The study has been registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR2400079866). All participants between 17 July and 15 November 2023 provided a voluntary, written informed consent prior to participation.

2.2 Sample size estimation

We conducted a pre-experiment using two groups: a control group administered with propofol-remifentanil and an experimental group administered with propofol-remifentanil plus 0.10 mg/kg/h of esketamine. Respiratory and cardiovascular adverse events and somatic response rates were recorded for both groups. The significance level was set to $p < 0.05$ with a power of 0.90. The optimal sample size was calculated as 79 patients per group using PASS 19 software (NCSS, Kaysville, UT, USA). Considering a patient dropout rate of 20%, we determined that each group should have at least 99 patients. Therefore, we chose a target sample size of 100 patients per group for ease of calculation and management.

We enrolled 400 patients aged 18–65 years with an American Society of Anesthesiologists physical status of I or II, who were scheduled to undergo gastrointestinal polypectomy under deep sedation/anesthesia without tracheal intubation. The following exclusion criteria were applied: a body mass index (BMI) of >30 kg/m^2, sleep apnea syndrome, contraindications to related drugs, a history of depression, or the use of sedative and analgesic drugs within two weeks prior to the initiation of the study. Additionally, we excluded individuals with neurocognitive or psychiatric disorders, liver or kidney disease or dysfunction, a history of myocardial infarction, poorly controlled hypertension (systolic blood pressure >180 mmHg), cerebrovascular diseases, and language or physical impairments that could hinder completion of the Mini-Mental State Examinations (MMSEs).

2.3 Randomization and blinding

All patients were randomly assigned to one of the four groups—C, E1, E2 and E3—in a 1:1:1:1 ratio based on a computer-generated randomization number using Excel. Specifically, any integral number generated between 1 and 400 divisible by 4 without a remainder was designated as group C, while numbers with remainders of 1, 2 and 3 were assigned as groups E1, E2 and E3, respectively. The computer-generated randomization numbers were recorded and placed in separate opaque envelopes. Prior to each sedation procedure, an assistant responsible for preparing the anesthesia regimens opened the envelopes to determine the appropriate anesthesia protocol to follow.

Induction was conducted using 1.5 mg/kg of propofol. Group C received intravenous anesthesia consisting of 3 mg/kg/h of propofol and 1.8 μg/kg/h of remifentanil. Groups E1, E2 and E3 were administered with 50, 100 and 150 μg/kg/h of esketamine, respectively.An assistant who was not involved in the procedure mixed propofol, remifentanil and esketamine in a 50-mL syringe. The rate of drug administration was uniform across all groups, and the four mixed regimens presented the same appearance. Unaware of the syringe's contents, the anesthesiologist administered the anesthesia based on the instructions in the envelope. Consequently, the anesthesiologists and the patients were blinded to the randomization and group allocation.

2.4 Perioperative management

The patients fasted for 8 h and were deprived of water for 2 h before surgery. MMSEs were performed before surgery as well as one day and three days after the procedure. The patients were administered 10–15 mL/kg of normal saline in the preparation room through a 20 G cannula inserted via the antecubital vein. Upon entering the endoscopy room, patients were positioned in the left lateral position, and a nasal catheter was used for oxygen inhalation (2–3 L/min) and for monitoring end-tidal (ET) CO_2. Routine intraoperative monitoring, which included a bispectral index (BIS), an electrocardiogram (ECG), HR, blood pressure (BP), respiratory rate (RR) and pulse oxygen saturation (SpO_2), was conducted. No pre-induction medications were administered. A mask filled with 100% oxygen (4–6 L/min) was used for at least 3–5 min before induction. Anesthesia was initiated with a slow infusion of a 1.5 mg/kg bolus of propofol over 30 seconds, administered until the eyelash reflex was no longer present. To maintain anesthesia, the Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/SS) was monitored by the same assistant and maintained between 0 and 1 with a BIS target of ≥ 60 but ≤ 72 (60–70 is deep sedation) [15–17]. Hypertension was defined as a mean arterial pressure (MAP) >105 mmHg or an increase of 30% from the baseline. Conversely, hypotension was defined as a MAP <65 mmHg or a decrease of 30% from the baseline. Patients with hypotension and tachycardia

received a bolus dose of 50 μg of phenylephrine, while those with hypotension and bradycardia received a bolus dose of 10 mg of ephedrine. An additional dose of 0.5 mg/kg of propofol was added when the patient showed body movement, eye-opening, hypertension and tachycardia. If the HR was $\leq$50 bpm, 0.25 mg of atropine was injected. When SpO_2 was $\leq$90% for 10 s, chin lift or jaw thrust was used, and the airflow was changed to 5–6 L/min. If SpO_2 continued to fall and become $<$90%, a mask was used to elevate SpO_2 following the withdrawal of the endoscope. If necessary, mask ventilation or tracheal intubation was employed. At the end of the procedure, a follow-up injection of 0.02 mg/kg of nalbuphine was administered, and the patient was transferred to the PACU. Emergence delirium was evaluated using Ricker's sedation-agitation scale. The patient was transported to the ward when the Aldrete score was $\geq$9 [18]. Experienced anesthesiologists and endoscopists performed all procedures.

2.5 Data collection

Baseline data, such as sex, age, height, weight, BMI, American Society of Anesthesiologists (ASA) physical status and operation type, were recorded. BIS (Bispectral Index), $ETCO_2$ (the End-Tidal Carbon Dioxide), HR, MAP (Mean Arterial Pressure), RR (Respiratory Rate) and SpO_2 (Peripheral Oxygen Saturation) were recorded after the patients entered the operating room and during their endoscopic operation.

2.6 Primary and other outcomes

The primary outcome measured was the incidence of cardiovascular and respiratory adverse events, somatic responses, the extent of eye-opening, drug interventions, and hypoxia resulting from respiratory depression and airway maneuvers. Additional outcomes included the time taken to awaken, the quality of awakening, MMSE results, nausea and vomiting.

2.7 Statistical analysis

Sample size calculations were conducted using PASS 17 (NCSS, Kaysville, UT, USA) software. Statistical analysis was performed with GraphPad Prism version 9.5.0 (GraphPad Inc, San Diego, CA, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD), while categorical variables were expressed as N (%) of patients. The normal distribution of all data was assessed by the Kolmogorov-Smirnov test and histograms. To assess differences between groups, the chi-square test or Fisher's exact test was used for categorical variables, while continuous variable comparisons were done using ANOVA (Analysis of Variance) and the Student-Newman-Keuls test for *post hoc* comparisons. The Kruskal-Wallis H rank sum test and Tamhane's T2 method were employed for discrete variables. Repeated measurement data were analyzed using ANOVA with a repeated measurement design. A p-value or corrected p-value of ≤ 0.05 was defined as statistically significant.

3. Results

Fig. 1 shows the study flow chart. A total of 400 patients were enrolled in the trial, with 395 completing the study. Two patients in group C were excluded due to postoperative bleeding and the need for urgent secondary surgery. In group E2, one patient was lost to follow-up, while another opted to discontinue participation. Additionally, one patient in group E3 experienced post-operative hallucinations in the recovery room following surgery. These five patients were excluded, and their corresponding data were removed from the study. No statistically significant differences were observed among the characteristics of patients, including age, sex, height, weight, BMI, duration of surgery and ASA physical status classification (Table 1).

3.1 Incidence of adverse events during the surgery

No significant clinical adverse events were observed during the trial, indicating no serious respiratory complications necessitating pausing the operation, such as the requirement for tracheal intubation. The number of respiratory maneuvers, including basic breathing assistance procedures, such as elevated oxygen flow, mandibular support and mask ventilation, were significantly higher in group C than in the other groups ($p <$ 0.05). In addition, incidents of hypotension and bradycardia requiring medication were more prevalent in group C. No statistically significant difference related to gagging was observed for all groups, although the E1, E2 and E3 groups showed slower body movement responses compared to those in group C (Table 2).

3.2 MMSE and other results

We conducted an MMSE prior to the operation and again on the first and third postoperative days. Sedation did not significantly change MMSE scores among all the groups (Fig. 2). Furthermore, no other side effects, such as emergence delirium, nausea and vomiting, were reported. All patients recovered swiftly in the PACU. Esketamine did not prolong the recovery time (Table 3).

4. Discussion

Our study demonstrated that a low continuous infusion of esketamine , combined with a fixed-dose regimen of propofol-remifentanil for sedation monitored using BIS and MOAA/SS (Modified Observer's Assessment of Alertness/Sedation Scale), leads to stable hemodynamic status, reduced incidence of hypoxemia, and improved perioperative outcomes during therapeutic GI endoscopic procedures.

Multiple studies have focused on identifying the most effective anesthetic in high-volume GI endoscopic procedure centers. Endoscopists typically prefer moderate-to-deep sedation over general anesthesia due to its safety, efficacy and rapid recovery benefits. The combination of propofol and remifentanil has been shown to provide better anesthesia during GI endoscopic procedures [3]. When the dosage of remifentanil is decreased, and the dosage of propofol is increased, there is

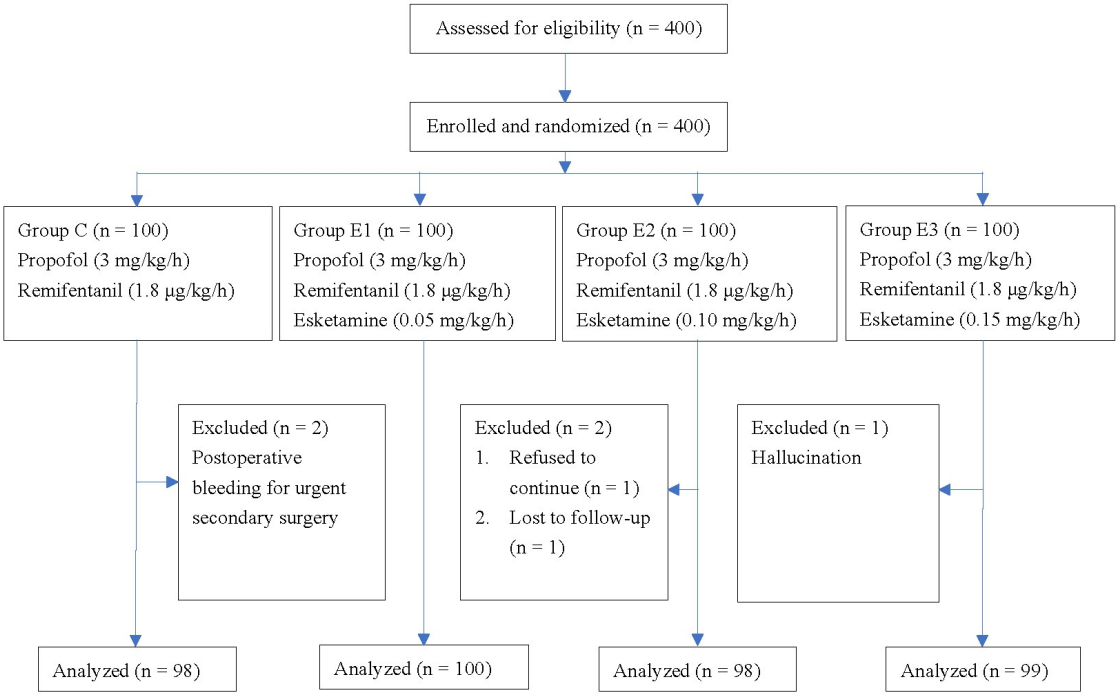

FIGURE 1. Consort flow diagram.

TABLE 1. Demographic characteristics of patients across study groups.

	C	E1	E2	E3	*p*-value
Age (yr)	46.35 ± 9.79	44.23 ± 10.48	44.65 ± 11.12	43.38 ± 12.25	0.7961
Male/Female	62/36	67/33	58/40	64/35	0.7114
BMI (kg/m^2)	23.25 ± 3.23	22.16 ± 2.76	21.94 ± 2.89	23.42 ± 3.17	0.3878
Duration of surgery (min)	45.26 ± 10.35	43.33 ± 11.71	48.80 ± 9.87	47.78 ± 8.86	0.9965
ASA physical status classification (I)	54	57	52	59	0.6968

Data are presented as mean ± SD or number (%).
BMI: body mass index; ASA: American Society of Anesthesiologists.

TABLE 2. Incidence of adverse events among the study groups.

	C	E1	E2	E3	*p*-value
Respiratory adverse events					
Oxygen flow elevated	15 (15%)	2 (2%)	2 (2%)	4 (4%)	0.0002
Mandibular support	10 (10%)	1 (1%)	1 (1%)	3 (3%)	0.0072
Mask ventilation	4 (4%)	0 (0%)	0 (0%)	0 (0%)	0.0072
Tracheal intubation	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Cardiovascular adverse events					
Hypotension	13 (13%)	3 (3%)	1 (1%)	1 (1%)	0.0001
Hypertension	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Bradycardia	15 (15%)	5 (5%)	2 (3%)	2 (2%)	0.0003
Tachycardia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Somatic responses					
Gagging	6 (6%)	2 (2%)	1 (1%)	1 (1%)	0.0921
Body movement	13 (13%)	4 (4%)	1 (1%)	1 (1%)	0.0001

Data are presented as numbers (%).

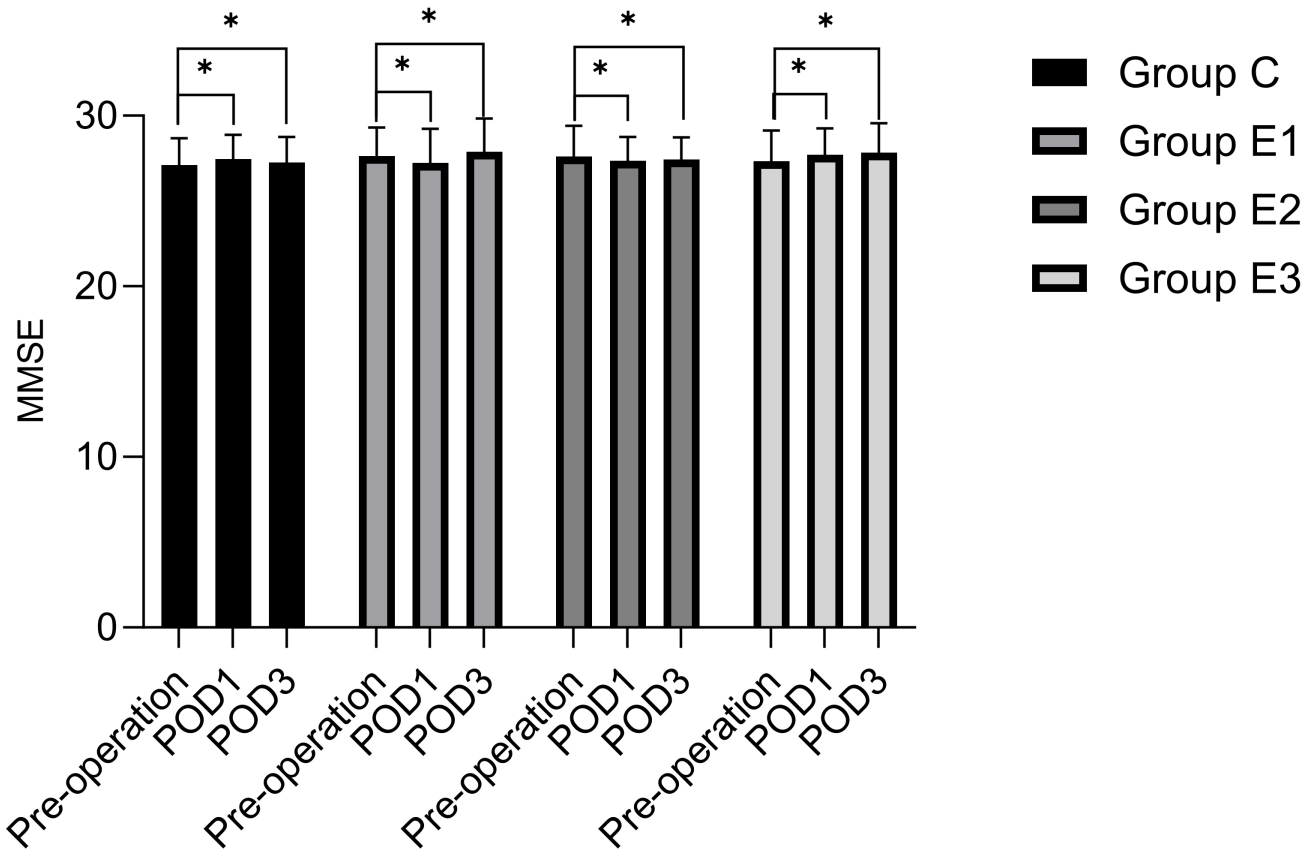

FIGURE 2. MMSE results. MMSE: Mini-Mental State Examination; POD: Post-operative day. *$p > 0.05$.

TABLE 3. Other side effects.

	C	E1	E2	E3	*p*-value
Emergence delirium	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Nausea and vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0000
Recovery time (min)	4.32 ± 1.71	4.50 ± 1.83	4.24 ± 1.56	4.63 ± 1.45	0.3372

Data are presented as number (%) or mean ± SD.

a significant reduction in apnea duration and an extension of recovery time. Conversely, increasing the remifentanil dose while decreasing the propofol dose results in prolonged apnea duration and reduced recovery times. In our current study, we standardized the dosage of propofol and remifentanil to 3 mg/kg/h and 1.8 μg/kg/h, respectively. Additionally, we included esketamine in this study to help induce sedation. Propofol acts on GABA (Gamma-Aminobutyric Acid) receptors to reduce respiratory variability in a dose-dependent manner [8]. However, administering higher doses of 2 mg/kg propofol during deep sedation increases the risk of hypoxemia. In contrast, esketamine helps to maintain respiratory variability, promoting spontaneous breathing while also exhibiting sympathomimetic activities that can relax bronchial smooth muscles and alleviate bronchospasm contraction induced by histamine release, thus effectively reducing airway edema [19]. Therefore, esketamine may help lower the risk of hypoxemia through these mechanisms.

The low dose of propofol we used in our study was associated with relatively high levels of remifentanil and esketamine. This equilibrium was successfully maintained throughout the procedure, even during prolonged operations. No statistically significant difference was observed in gag reflex among all groups, although somatic responses were more frequent in group C. Hence, the gag reflex cannot be considered as a reliable indicator of inadequate sedation during GI endoscopic procedures. Low-dose esketamine can release catecholamines, activating the sympathetic nervous system and leading to an indirect cardiovascular stimulating effect that increases blood pressure and HR. Jonkman *et al.* [11] reported that low-dose esketamine can effectively counteract remifentanil-induced respiratory depression owing to its antagonistic effects on the ventilatory CO_2 chemo-insensitivity associated with remifentanil. Our study demonstrated that the continuous infusion of low-dose esketamine is a safe and is an effective enhancement to a propofol-remifentanil combination.

Esketamine is a novel NMDA receptor antagonist for clinical applications. However, its effectiveness in alleviating

postoperative cognitive decline has not yet been definitively established [20, 21]. Previous studies have shown that a combination of propofol and ketamine can reduce the incidence of the psychotomimetic effect [22]. In their evaluation using the MMSE, Zhan *et al.* [23] noted the presence of psychotomimetic effects but found no significant differences between the groups studied. We evaluated MMSE scores prior to surgery and one and three days after the procedure, and found no notable differences. Intravenous administration of esketamine (0.25–0.5 mg/kg) is widely used for clinical anesthesia. As the dose increases, esketamine-related side effects, such as excessive salivation, hallucinations and delayed postoperative recovery, also tend to increase. Therefore, we initiated a continuous infusion of 0.05–0.15 mg/kg/h of esketamine for maintenance to ensure safety and efficacy.

There is substantial data suggesting that the BIS value may accurately reflect sedation levels during GI endoscopy [24]. However, whether the BIS value obtained with esketamine is more effective for monitoring moderate to deep sedation remains uncertain. Our findings indicate that esketamine has no impact on BIS. According to Carrara *et al.* [25], administering a continuous intravenous infusion of esketamine may be more effective than a bolus for influencing the BIS value. Small-dose esketamine does not affect the BIS value [25].

The results of our study may contribute to reducing the risk of adverse events for high-risk individuals (overweight, accompanied by respiratory disease, *etc.*) who are scheduled to undergo GI endoscopy. However, our study still has several limitations. Firstly, the perioperative follow-up was limited to just four days, with no long-term follow-up conducted. Recent studies have shown that the use of ketamine for procedural sedation is associated with an increased risk of oxygen desaturation and a higher likelihood of patients being discharged to nursing homes [26]. Thus, the long-term safety of esketamine needs to be further studied. Secondly, we utilized a combination of propofol, remifentanil, and esketamine for total intravenous sedation despite ongoing debates regarding the safety profile and effectiveness of this mixture [27, 28]. Additionally, our sample size of 400 cases, determined through a power analysis of preliminary results, is relatively small. The small number of adverse events may suggest underpowered comparisons for rare outcomes. To thoroughly assess the efficacy and safety of low-dose esketamine combined with propofol and remifentanil for painless therapeutic GI endoscopy, a larger, multi-center study with long-term follow-up is necessary. Finally, we acknowledge a lack of data pertaining to cost-effectiveness and patient satisfaction, which could limit the widespread clinical adoption of these findings.

5. Conclusions

The administration of low dose esketamine, combined with propofol-remifentanil, resulted in more stable hemodynamics and a reduced incidence of respiratory adverse events during painless therapeutic GI endoscopy. However, further studies with long follow-up duration are necessary to accurately determine the actual value of esketamine in therapeutic GI endoscopy, especially its long-term impact on cognitive function.

ABBREVIATIONS

GI, gastrointestinal; PACU, postanesthetic care unit; HR, heart rate; BIS, bispectral index; ECG, electrocardiogram; RR, respiratory rate; SpO_2, pulse oxygen saturation; MOAA/SS, Modified Observer's Assessment of Alertness/Sedation Scale; ASA, American Society of Anesthesiologists; SD, standard deviation; MAP, mean arterial pressure; BP, blood pressure; ET, end-tidal; FDA, Food and Drug Administration. MMSEs, Mini-Mental State Examinations; NMDA, N-methyl-D-aspartate; BMI, body mass index; ANOVA, Analysis of Variance; $ETCO_2$, the End-Tidal Carbon Dioxide; GABA, Gamma-Aminobutyric Acid.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

LJA and HGW—designed the study. DSH, DNL and WH—collected data and conducted research; analyzed and interpreted data. DSH and LJA—wrote the initial draft. All authors revised the manuscript, gave intellectual input to the study and approved the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of Huai'an No. 1 People's Hospital affiliated with Nanjing Medical University, China (Ethics approval number: KY-2023-080-02) on 11 July 2023. The study was performed in compliance with the Declaration of Helsinki. All participants provided voluntary, written informed consent.

ACKNOWLEDGMENT

We thank Medjaden Inc. for scientific editing of this manuscript.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Zhou S, Zhu Z, Dai W, Qi S, Tian W, Zhang Y, *et al*. National survey on sedation for gastrointestinal endoscopy in 2758 Chinese hospitals. British Journal of Anaesthesia. 2021; 127: 56–64.

[2] Zhong J, Zhang J, Fan Y, Zhu M, Zhao X, Zuo Z, *et al*. Efficacy and safety of Ciprofol for procedural sedation and anesthesia in non-operating room settings. Journal of Clinical Anesthesia. 2023; 85: 111047.

[3] Wu B, Zhu W, Wang Q, Ren C, Wang L, Xie G. Efficacy and safety of ciprofol-remifentanil versus propofol-remifentanil during fiberoptic bronchoscopy: a prospective, randomized, double-blind, non-inferiority trial. Frontiers in Pharmacology. 2022; 13: 1091579.

[4] Joy PJ, Blanshard HJ. Propofol-remifentanil patient-controlled sedation for endoscopic procedures: a prospective service audit. Canadian Journal of Anesthesia. 2023; 70: 1735–1743.

[5] Wu J, Li N, Zhang J, Tang X, Cao X. Safety and efficacy of remifentanil-propofol combination on "muscle relaxant-free" general anesthesia for therapeutic endoscopic retrograde cholangiopancreatography: a randomized controlled trial. American Journal of Translational Research. 2023; 15: 5292–5303.

[6] De Vico P, Biasucci DG, Aversano L, Polidoro R, Zingaro A, Millarelli FR, *et al*. Feasibility and safety of deep sedation with propofol and remifentanil in spontaneous breathing during endoscopic retrograde cholangiopancreatography: an observational prospective study. BMC Anesthesiology. 2023; 23: 260.

[7] Feeney A, Papakostas GI. Pharmacotherapy: ketamine and esketamine. Psychiatric Clinics of North America. 2023; 46: 277–290.

[8] Wu J, Gu J, Qiu L, Jin X, Zhou Z. Challenges for esketamine nasal spray in China: use and management. Frontiers in Pharmacology. 2024; 15: 1429435.

[9] Mildh L, Taittonen M, Leino K, Kirvelä O. The effect of low-dose ketamine on fentanyl-induced respiratory depression. Anaesthesia. 1998; 53: 965–970.

[10] Algera MH, Kamp J, van der Schrier R, van Velzen M, Niesters M, Aarts L, *et al*. Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal. British Journal of Anaesthesia. 2019; 122: e168–e179.

[11] Jonkman K, van Rijnsoever E, Olofsen E, Aarts L, Sarton E, van Velzen M, *et al*. Esketamine counters opioid-induced respiratory depression. British Journal of Anaesthesia. 2018; 120: 1117–1127.

[12] Jansen SC, van Velzen M, Sarton E, Dahan A, Niesters M, van der Schrier R. Acute effects of esketamine on hypoxic ventilatory response, haemodynamics, and brain function in healthy volunteers. British Journal of Anaesthesia. 2024; 134: 557–563.

[13] Dahan A, van der Schrier R, Smith T, Aarts L, van Velzen M, Niesters M. Averting opioid-induced respiratory depression without affecting analgesia. Anesthesiology. 2018; 128: 1027–1037.

[14] Suleiman A, Wongtangman K, Eikermann M, Stucke AG. Neuroanatomical and pharmaco-physiological effects of hypoxia and esketamine on breathing, the sympathetic nerve system, and cortical function. British Journal of Anaesthesia. 2025; 134: 277–280.

[15] Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, *et al*. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. Journal of Clinical Psychopharmacology. 1990; 10: 244–251.

[16] Bower AL, Ripepi A, Dilger J, Boparai N, Brody FJ, Ponsky JL. Bispectral index monitoring of sedation during endoscopy. Gastrointestinal Endoscopy. 2000; 52: 192–196.

[17] Qadeer MA, Vargo JJ, Patel S, Dumot JA, Lopez AR, Trolli PA, *et al*. Bispectral index monitoring of conscious sedation with the combination of meperidine and midazolam during endoscopy. Clinical Gastroenterology and Hepatology. 2008; 6: 102–108.

[18] Aldrete JA. The post-anesthesia recovery score revisited. Journal of Clinical Anesthesia. 1995; 7: 89–91.

[19] Kamp J, van Velzen M, Aarts L, Niesters M, Dahan A, Olofsen E. Stereoselective ketamine effect on cardiac output: a population pharmacokinetic/pharmacodynamic modelling study in healthy volunteers. British Journal of Anaesthesia. 2021; 127: 23–31.

[20] Li Y, Wu ZY, Zheng WC, Wang JX, Yue X, Song RX, *et al*. Esketamine alleviates postoperative cognitive decline via stimulator of interferon genes/TANK-binding kinase 1 signaling pathway in aged rats. Brain Research Bulletin. 2022; 187: 169–180.

[21] Qiu LL, Pan W, Luo D, Zhang GF, Zhou ZQ, Sun XY, *et al*. Dysregulation of BDNF/TrkB signaling mediated by NMDAR/Ca^{2+}/calpain might contribute to postoperative cognitive dysfunction in aging mice. Journal of Neuroinflammation. 2020; 17: 23.

[22] Yin S, Hong J, Sha T, Chen Z, Guo Y, Li C, *et al*. Efficacy and tolerability of sufentanil, dexmedetomidine, or ketamine added to propofol-based sedation for gastrointestinal endoscopy in elderly patients: a prospective, randomized, controlled trial. Clinical Therapeutics. 2019; 41: 1864–1877.e0.

[23] Zhan Y, Liang S, Yang Z, Luo Q, Li S, Li J, *et al*. Efficacy and safety of subanesthetic doses of esketamine combined with propofol in painless gastrointestinal endoscopy: a prospective, double-blind, randomized controlled trial. BMC Gastroenterology. 2022; 22: 391.

[24] Jang SY, Park HG, Jung MK, Cho CM, Park SY, Jeon SW, *et al*. Bispectral index monitoring as an adjunct to nurse-administered combined sedation during endoscopic retrograde cholangiopancreatography. World Journal of Gastroenterology. 2012; 18: 6284–6289.

[25] Carrara L, Nault M, Morisson L, Godin N, Idrissi M, Fortier A, *et al*. The impact of bolus versus continuous infusion of intravenous ketamine on bispectral index variations and desflurane administration during major surgery: the KETABIS study. European Journal of Anaesthesiology. 2021; 38: 1168–1179.

[26] Salloum E, Lotte Seibold E, Azimaraghi O, Rudolph MI, Beier J, Schaefer MS, *et al*. Association of ketamine use during procedural sedation with oxygen desaturation and healthcare utilisation: a multicentre retrospective hospital registry study. British Journal of Anaesthesia. 2024; 132: 779–788.

[27] Absalom AR, Rigby-Jones AE, Rushton AR, Robert Sneyd J. Demystifying the "Mixifusor". Paediatric Anaesthesia. 2020; 30: 1292–1298.

[28] Malherbe S, Barker N. Mixing of propofol and remifentanil. Paediatric Anaesthesia. 2021; 31: 504–505.

How to cite this article: Dongsheng Hu, Danni Li, Honggang Wang, Wei Hu, Lijun An. Low dose esketamine for gastrointestinal endoscopy: a double-blinded, randomized controlled trial. Signa Vitae. 2025; 21(8): 30-36. doi: 10.22514/sv.2025.110.