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CLINICAL TRIAL REPORT

Effect of Esketamine on Cognitive Recovery After Propofol Sedation for Outpatient Colonoscopy: A Randomized Clinical Trial

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Purpose: While esketamine shows promise as an adjunct in procedural sedation, its impact on postoperative cognitive recovery remains incompletely characterized. This study investigated the effects of esketamine on multiple dimensions of recovery, particularly cognition, in patients undergoing colonoscopy with propofol-based sedation.

Patients and Methods: We conducted this randomized, double-blinded, placebo-controlled trial from January 6, 2023, to May 20, 2024, at two hospitals in China. Patients were randomized in a 1:1 ratio to receive either esketamine 0.2 mg/kg (n = 126) or placebo (n = 126), followed by propofol 1 mg/kg. We administered additional propofol boluses (0.5 mg/kg) to maintain sedation. The study assessed cognitive recovery on postoperative day 3 as the primary outcome, measured by the Postoperative Quality of Recovery Scale (PostopQRS). Secondary outcomes included overall recovery, recovery in other PostopQRS domains, time to discharge, and adverse events.

Results: Esketamine significantly enhanced cognitive recovery compared to placebo on postoperative day 3 (95.2% vs 83.3%, relative risk = 1.14; 95% confidence interval: 1.05–1.25, $P = 0.002$). Discharge times were comparable between groups (odds ratio = 0.70; 95% confidence interval: 0.43–1.16, $P = 0.163$). The esketamine group demonstrated higher satisfaction ($P = 0.003$) and significantly reduced incidences of hypotension (14.3% vs 36.5%, $P < 0.001$), bradycardia (5.6% vs 15.1%, $P = 0.013$), hypoxemia (2.4% vs 8.7%, $P = 0.028$), and injection site pain (21.4% vs 48.4%, $P < 0.001$).

Conclusion: Adding esketamine 0.2 mg/kg to propofol for colonoscopy sedation improved postoperative cognitive recovery, enhanced patient satisfaction, and reduced cardiopulmonary adverse events without prolonging discharge time. These findings establish low-dose esketamine as a beneficial adjunct to propofol in procedural sedation for colonoscopy.

Keywords: cognitive recovery, colonoscopy, esketamine, Propofol, procedural sedation, quality of recovery

Introduction

Colorectal cancer ranks as the third most prevalent malignancy worldwide, with an estimated 1.93 million new cases and 903,859 deaths reported annually.[1] Colonoscopy is the gold standard for screening and diagnosis, offering critical benefits in reducing incidence and mortality through early detection and intervention.[2] The United States Preventive Services Task Force recommends colorectal cancer screening in adults aged 45 to 49 years.[3] However, patient anxiety about procedural discomfort often impedes adherence to these guidelines, significantly contributing to low compliance

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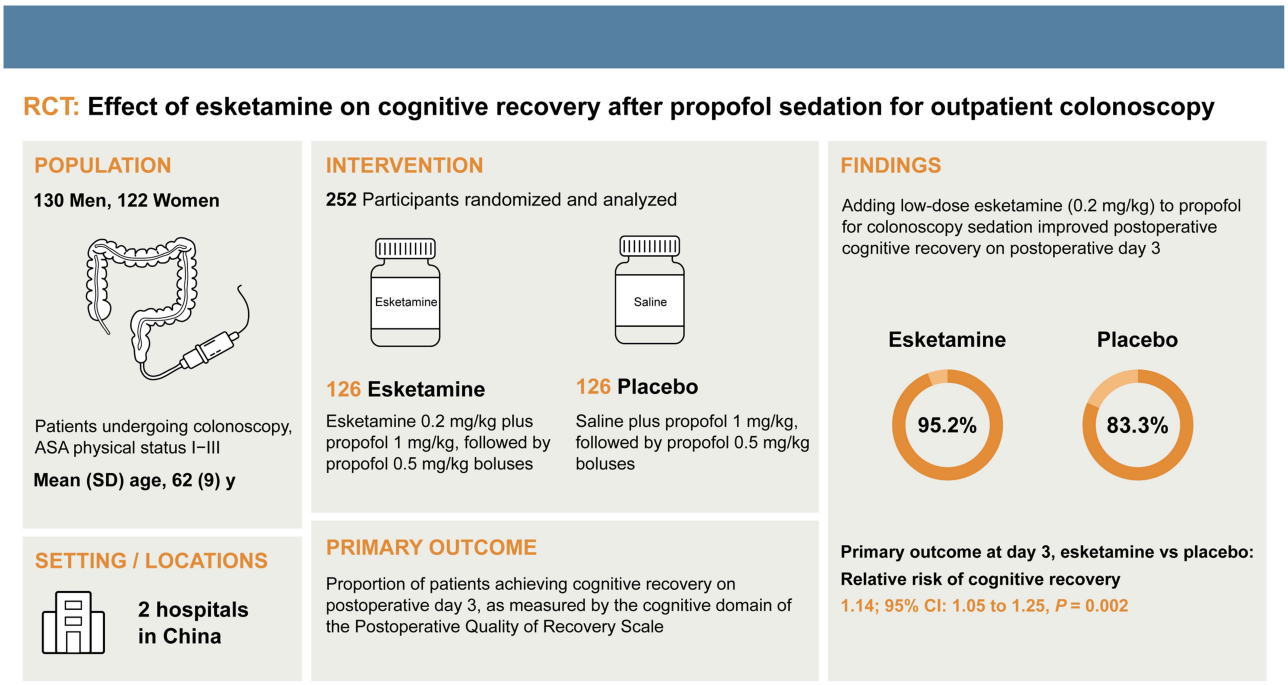
Graphical Abstract



rates.[4] This challenge has led to increased adoption of sedation protocols to enhance patient experience and improve screening adherence.[5]

Propofol, widely used for colonoscopy sedation due to its rapid onset and short duration, can cause hypotension (affecting about 50% of patients) and respiratory depression when administered alone. These effects may lead to organ dysfunction and cardiovascular or neurological complications.[6,7] To mitigate these risks and enhance sedation efficacy, clinicians often combine propofol with adjunctive agents, aiming to improve patient safety and optimize the sedation process.[8–10]

Esketamine, the S-enantiomer of ketamine, has emerged as a promising adjunct in procedural sedation. As an N-methyl-D-aspartate (NMDA) receptor antagonist, esketamine exhibits sympathomimetic and analgesic properties that may counteract propofol's hypotensive and respiratory depressive effects.[11,12] Recent evidence from surgical settings has further supported esketamine's potential benefits. Zhang et al[13] found that incorporating esketamine into general anesthesia enhanced early recovery and cognitive function in patients undergoing modified radical mastectomy, while Zhao et al reported favorable safety and efficacy outcomes with low-dose esketamine during laparoscopic cholecystectomy.[14] Notably, esketamine demonstrates twice the analgesic potency of racemic ketamine while offering fewer psychiatric side effects at equivalent doses.[15]

Despite esketamine's potential advantages, concerns about its impact on cognitive function persist. The NMDA receptor, densely expressed in brain regions crucial for memory and cognition, may trigger schizophrenia-like symptoms and cognitive impairment when antagonized.[16] Previous research has shown that a single preoperative dose of ketamine (1 mg/kg) significantly increased the risk of postoperative cognitive dysfunction compared with placebo.[17] However, the cognitive effects of subanesthetic doses of ketamine or esketamine, particularly when combined with other sedatives, remain insufficiently characterized.

This study evaluated the effect of adding low-dose esketamine (0.2 mg/kg) to propofol sedation on postoperative recovery, particularly cognitive function, in patients undergoing colonoscopy. We hypothesized that patients receiving

esketamine as an adjunct to propofol would improve cognitive recovery, as measured by the Postoperative Quality of Recovery Scale (PostopQRS),[18] compared to those receiving propofol alone. The overall study design and key findings are illustrated in the graphical abstract.

Materials and Methods

Study Design and Ethical Considerations

This prospective, parallel-group, double-blind, randomized clinical trial was conducted at two hospitals in China from January 6, 2023, to May 20, 2024. The study protocol was approved by the Institutional Review Boards of Fujian Provincial Hospital (No. K2022-04-011, approved on April 18, 2022) and Xiapu County Hospital (No. L2022-11, approved on November 21, 2022). All participants provided written informed consent before enrollment. The trial was prospectively registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/showproj.html?proj =186415, ChiCTR2200066353) on December 2, 2022. We conducted the study in adherence to Chinese legal requirements, the World Medical Association Declaration of Helsinki, and Good Clinical Practice guidelines. No protocol changes were made after trial commencement. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[19]

Participants

Eligible participants were adults aged 18 to 75 years with American Society of Anesthesiologists physical status I to III scheduled for elective outpatient colonoscopy. Exclusion criteria encompassed: body mass index greater than 30 (calculated as weight in kilograms divided by height in meters squared), known contraindications or sensitivities to study medications, impaired mobility, need for therapeutic colonoscopy procedures (eg, endoscopic mucosal resection or submucosal dissection), history of psychiatric illness, neurological disease, seizure disorder, substance abuse, preexisting cognitive deficits, pregnancy, and inability to communicate in Mandarin Chinese.

Randomization and Masking

Patients were randomly assigned (1:1) to receive esketamine or placebo using permuted block randomization (block size of 6), stratified by the study center. An independent statistician generated the randomization sequence using R version 4.0.5. Allocation was concealed in sealed, sequentially numbered envelopes and revealed shortly before sedation. Study drugs were prepared in identical 10-mL syringes by research nurses not involved in patient care or assessment. Esketamine was diluted to 2 mg/mL in 0.9% saline to achieve the protocol-specified dose of 0.2 mg/kg (administered as 0.1 mL/kg), while the placebo consisted of an equivalent volume of 0.9% saline. Both solutions were colorless and visually indistinguishable, ensuring proper blinding of all study participants and personnel.

Sedation Procedure

All patients underwent standard bowel preparation before colonoscopy following the local protocol. Standard monitoring was continuously applied in the procedure room, including electrocardiography, pulse oximetry, and noninvasive blood pressure. All patients received nasal cannula oxygen supplementation at 3 L/min per clinical practice. Sedation was induced with intravenous administration of esketamine 0.2 mg/kg or an equivalent volume of 0.9% saline, followed by propofol 1 mg/kg. Throughout the procedure, the attending anesthesiologist maintained the target sedation level, defined as a modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of less than 3,[20] by titrating propofol doses (typically 0.5 mg/kg per bolus).

Outcomes

The primary outcome was the incidence of cognitive recovery on postoperative day 3, assessed using the cognitive domain of the PostopQRS. This time point was selected to minimize the potential confounding effects of propofol sedation, bowel preparation, and procedural stress on neurocognitive recovery assessment. The cognitive domain evaluation comprised five standardized verbal tests measuring memory, attention, and executive function. Following

validated PostopQRS methodology, cognitive recovery was defined quantitatively as achieving scores within 20% of individual baseline measurements across all five tests. This standardized threshold accounts for normal test-retest variability while maintaining clinically meaningful recovery assessment. For instance, in the word recall test, if a patient recalled 5 words at baseline, a postoperative recall of 4 or more words (≥80% of baseline) would indicate recovery for that specific component. Complete cognitive recovery required meeting this threshold across all five cognitive domain tests: word generation, word recall, digits forward, digits back, and word recognition.[21]

Secondary outcomes included overall postoperative recovery, recovery in other PostopQRS domains (physiological, nociceptive, emotive, activities of daily living, and cognitive), emergence time, time to discharge, and endoscopist and patient satisfaction. The PostopQRS was assessed at pre-procedure, 40 minutes after colonoscopy, and then on days 1, 3, and 7. Recovery in each PostopQRS domain was defined as postoperative scores returning to or exceeding individual baseline values, with overall recovery requiring recovery in all five domains. Emergence time was defined as the interval from procedure completion to achieving a MOAA/S score 5. Discharge readiness was determined by Modified Post-Anesthetic Discharge Scoring System scores ≥9.[22] Satisfaction was assessed using 5-point Likert scales (1 = very satisfied, 5 = very dissatisfied) for both endoscopists and patients.[23]

Adverse events were also recorded, including hypotension, bradycardia, hypoxemia, injection site pain, fatigue, dizziness, nausea or vomiting, hallucination, and nightmares. A blinded research assistant at each hospital collected data face-to-face while in the hospital and via telephone after discharge.

Sample Size Estimation

The sample size was calculated using PASS software, version 15.0 (NCSS LLC, UT, USA). Previous research indicated that approximately 80% of patients achieve cognitive recovery according to PostopQRS criteria on postoperative day 3.[24] With an anticipated baseline recovery rate of 80% in the control group, we calculated that 101 patients per group would provide 90% power to detect a difference of 15 percentage points (from 80% to 95%) using a two-sided test at a significance level of 0.05. Anticipating a 20% attrition rate due to potential dropouts or incomplete follow-up, we established a target enrollment of 126 participants per group.

Statistical Analysis

We assessed the distribution of continuous variables for normality with the Shapiro–Wilk test and Q-Q plot. Data are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), or number (percentage). We used independent t-tests, Mann-Whitney *U*-tests, and chi-square or Fisher's exact test, as appropriate.

We compared the primary outcome (cognitive recovery rate on postoperative day 3) between groups using the chi-square test, calculating relative risk (RR) with 95% confidence intervals (CIs). We fitted a generalized linear mixed model with a binomial distribution and logit link function to analyze changes in recovery rates over time. The model included fixed effects for treatment (esketamine vs placebo), time, and their interaction, with random intercepts for subjects to account for within-subject correlations in the repeated measurements. Results are presented as odds ratios (ORs) with 95% CIs. We analyzed time to discharge readiness using Kaplan-Meier survival analysis and Log-rank test and calculated hazard ratios with 95% CIs using a Cox proportional hazards model.

Primary analyses followed the intention-to-treat principle, including all 252 randomized participants (126 per group). Multiple imputation was used to handle missing data from participants who did not complete the study protocol, with sensitivity analyses performed on the per-protocol population (121 esketamine, 118 placebo). Statistical significance was set at 2-sided $P < 0.05$. Analyses were performed using R version 4.3.3 and IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Between January 6, 2023, and May 20, 2024, we screened 266 eligible patients and randomized 252 to receive either esketamine or placebo (Figure 1). All participants received their allocated treatment except one in the placebo group, who withdrew consent. Twelve participants (five esketamine, seven placebo) were lost to follow-up, resulting in a final per-

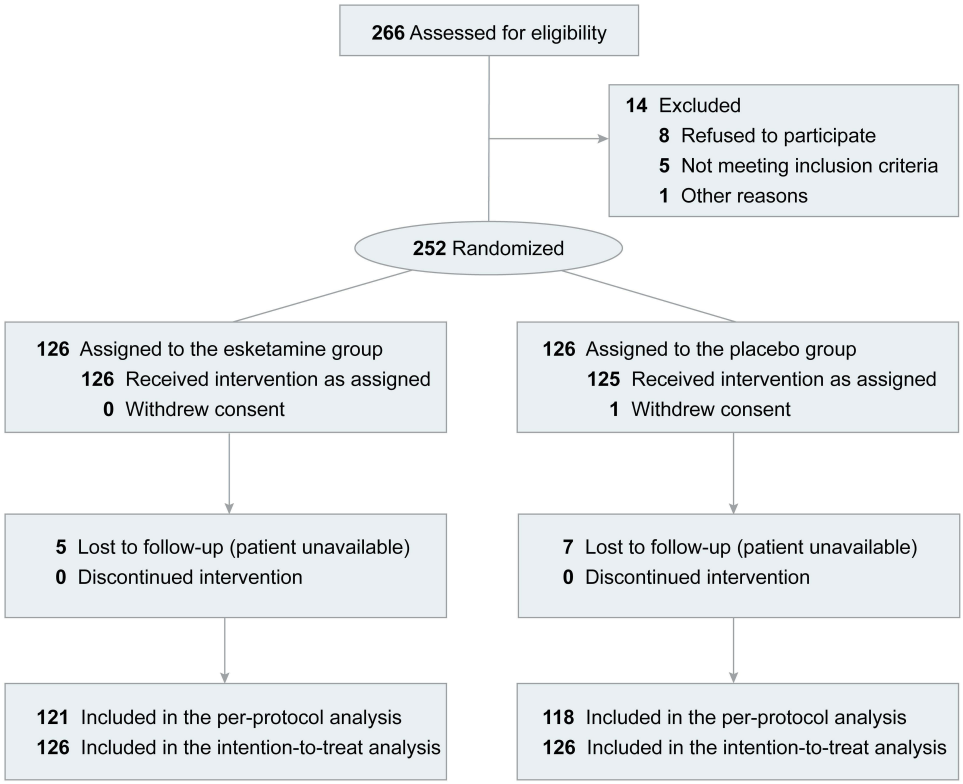


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study.

protocol population 239. Baseline characteristics were well-balanced between the esketamine and placebo groups, with no statistically significant differences observed in age, sex, BMI, ASA physical status, or comorbidities (Table 1).

The proportion of patients achieving cognitive recovery on postoperative day 3 was significantly higher in the esketamine group compared with the placebo group (95.2% vs 83.3%, RR = 1.14; 95% CI: 1.05–1.25, $P = 0.002$), with similar findings in per-protocol analysis (RR = 1.11; 95% CI: 1.04–1.19; $P < 0.001$). A significant treatment-by-time

Table 1 Patient Characteristics

Characteristic	Esketamine (n = 126)	Placebo (n = 126)	*P* value
Age, median (IQR), y	64.5 (54.0–69.0)	65.0 (55.0–69.0)	0.308
Sex, n (%)			0.313
Male	69 (54.8)	61 (48.4)	
Female	57 (45.2)	65 (51.6)	
Height, mean (SD), cm	165.6 (5.9)	166.3 (6.1)	0.332
Weight, median (IQR), kg	63.0 (58.0–68.0)	65.0 (60.0–68.0)	0.092
BMI, median (IQR), kg/m^2	22.7 (21.5–24.4)	23.0 (21.8–24.3)	0.256
ASA physical status, n (%)			0.581
I	28 (22.2)	35 (27.8)	
II	84 (66.7)	79 (62.7)	
III	14 (11.1)	12 (9.5)	

(*Continued*)

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Table 1 (Continued).

Characteristic	Esketamine (n = 126)	Placebo (n = 126)	*P* value
Education, median (IQR), y	10.5 (6.0–12.0)	9.0 (6.0–12.0)	0.645
Comorbidities, n (%)			
Coronary artery disease	19 (15.1)	24 (19.0)	0.402
Chronic obstructive pulmonary disease	16 (12.7)	13 (10.3)	0.554
Diabetes mellitus	14 (11.1)	18 (14.3)	0.449
Hypertension	38 (30.2)	33 (26.2)	0.435

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; SD, standard deviation.

interaction ($P = 0.015$, Figure 2A) revealed that while the cognitive recovery was similar between groups at 40 minutes (OR = 0.70; 95% CI: 0.43–1.16, $P = 0.163$), the esketamine group showed significantly higher recovery rates at day 3 (OR = 4.00; 95% CI: 1.56–10.28, $P = 0.004$). By postoperative day 7, failure to recover occurred in 2.4% of esketamine versus 9.5% of placebo patients ($P = 0.026$, Table 2).

Figure 2B-F illustrate recovery trajectories for overall recovery and recovery in other domains of the PostopQRS (nociceptive, emotive, activities of daily living, and physiological). The model revealed a significant treatment-by-time interaction for overall recovery ($P < 0.001$). At postoperative day 3, the odds of overall recovery in the esketamine group were significantly higher than in the control group (OR = 3.80; 95% CI: 1.56–9.21; $P = 0.003$). No statistically significant differences were observed between the groups in the nociceptive, emotive, activities-of-daily-living, and physiological domains (all $P > 0.05$, Table 2). Emergence time was similar between the esketamine and placebo groups (15 [11–17] vs 15 [12–19] min; median difference, −1 min; 95% CI: −2 to 0; $P = 0.127$). Median (IQR) discharge time was 20 (18–25) minutes for esketamine and 22 (18–25) minutes for placebo (difference, −1 min; 95% CI: −2 to 0 min; HR, 1.19; 95% CI: 0.93–1.53; $P = 0.121$; Figure 3). Patients receiving esketamine reported higher satisfaction scores ($P = 0.003$) and required significantly less propofol ($P < 0.001$) compared to the placebo group. Endoscopist satisfaction scores and procedure time did not differ significantly between groups (both $P > 0.05$; Table 3).

Esketamine was associated with significantly lower incidences of hypotension (14.3% vs 36.5%, $P < 0.001$), bradycardia (5.6% vs 15.1%, $P = 0.013$), and hypoxemia (2.4% vs 8.7%, $P = 0.028$) compared to placebo. Injection site pain also occurred less frequently in the esketamine group (21.4% vs 48.4%, RR = 0.44; 95% CI: 0.30–0.65, $P < 0.001$). No significant differences were observed in other adverse events, including fatigue, dizziness, nausea or vomiting, hallucination, and nightmares (all $P > 0.05$, Figure 4).

Discussion

Our study demonstrated that esketamine 0.2 mg/kg as an adjunct to propofol for colonoscopy sedation provides multiple significant benefits. As the first investigation of esketamine specifically in propofol-based sedation for colonoscopy, our findings represent an important advancement in procedural sedation protocols, distinguishing it from previous research in general anesthesia settings. Cognitive recovery rates were significantly higher in the esketamine group compared to placebo on postoperative day 3. The esketamine group exhibited lower incidences of hypotension, bradycardia, hypoxemia, and injection site pain. Importantly, these benefits were achieved without prolonging emergence or discharge times, or increasing the occurrence of psychotomimetic adverse effects. Moreover, patients receiving esketamine reported higher satisfaction scores. These consistently favorable results, spanning cognitive function and physiological parameters, suggest that low-dose esketamine offers a valuable optimization of current sedation protocols for colonoscopy procedures.

Supporting our initial hypothesis, esketamine significantly enhanced cognitive recovery on postoperative day 3. Our findings align with emerging evidence from recent clinical trials, where subanesthetic doses of esketamine administered

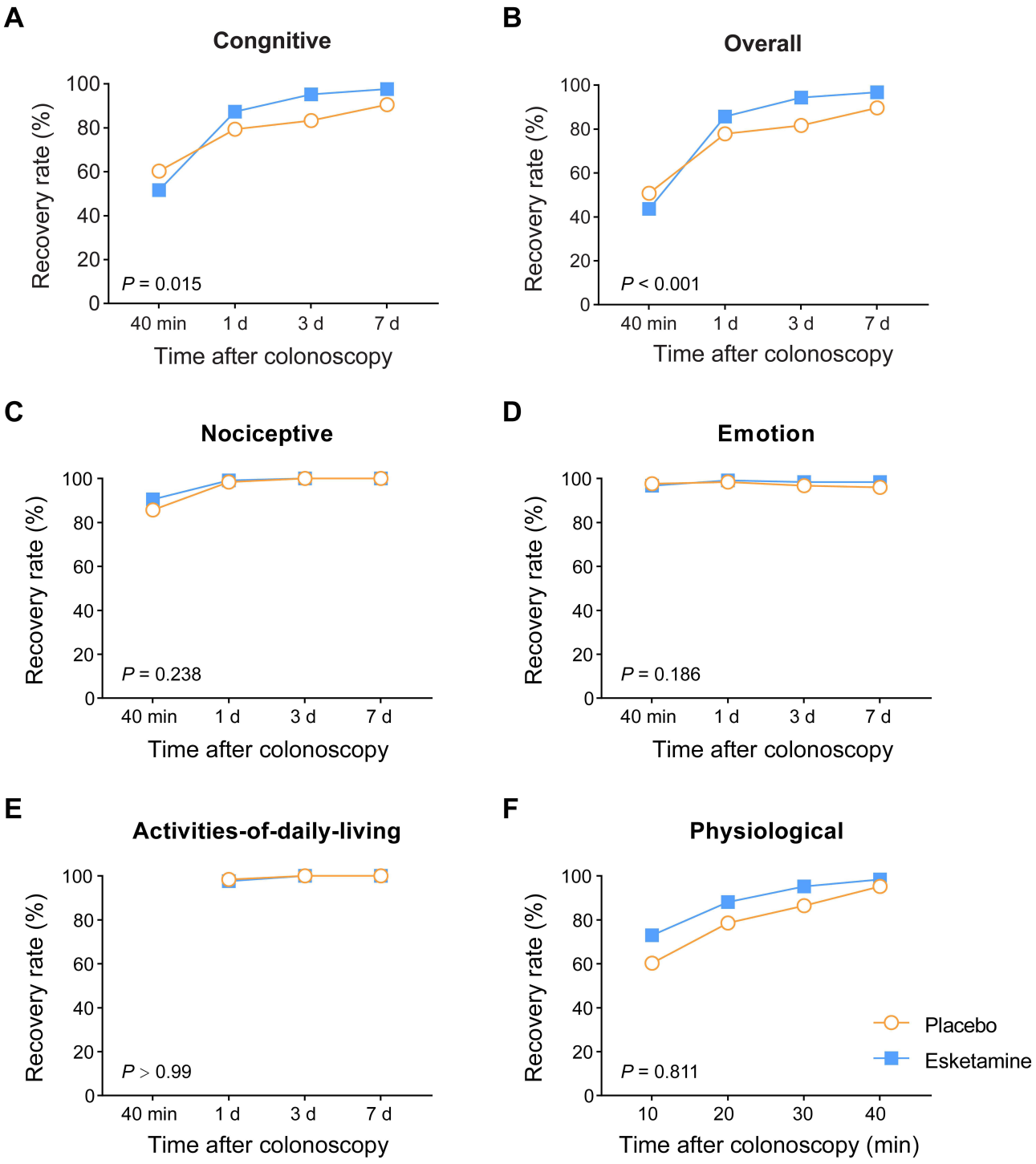

Figure 2 Recovery rates overall and by individual domains measured using the Postoperative Quality of Recovery Scale (PostopQRS) following colonoscopy.
Note: (**A**) Proportion of patients recovered in the cognition domain. (**B**) Overall recovery across all PostopQRS domains. (**C**) Nociceptive recovery (pain and nausea). (**D**) Emotive recovery (anxiety and depression) (**E**) Recovery of activities of daily living. (**F**) Physiologic recovery. Data points represent the proportion of patients recovered in each domain at specified time intervals. *P* values for group differences over time were derived from generalized linear mixed models, reflecting time-by-treatment interactions.

intraoperatively were associated with enhanced early cognitive function.[24,25] The observed cognitive benefit was substantial, with a recovery rate of 95.2% in the esketamine group compared to 83.3% in the placebo group (RR = 1.14; 95% CI: 1.05–1.25, $P = 0.002$). The mechanistic basis for this improvement likely lies in esketamine's complex

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Table 2 Recovery Rates Overall and by Individual Domains for Patients Undergoing Colonoscopy

	n (%)		Estimated Difference (95% CI)	Odd ratio (95% CI)	*P* value
	Esketamine (n = 126)	Placebo (n = 126)			
Cognitive					
40 min	65 (51.6)	76 (60.3)	−0.09 (−0.21 to 0.03)	0.70 (0.43 to 1.16)	0.163
1 day	110 (87.3)	100 (79.4)	0.08 (−0.01 to 0.17)	1.79 (0.91 to 3.53)	0.094
3 day	120 (95.2)	105 (83.3)	0.12 (0.04 to 0.19)	4.00 (1.56 to 10.28)	0.004
7 day	123 (97.6)	114 (90.5)	0.07 (0.01 to 0.13)	4.32 (1.19 to 15.69)	0.026
Overall					
40 min	55 (43.7)	64 (50.8)	−0.07 (−0.19 to 0.05)	0.75 (0.46 to 1.23)	0.257
1 day	108 (85.7)	98 (77.8)	0.08 (−0.02 to 0.17)	1.71 (0.89 to 3.29)	0.105
3 day	119 (94.4)	103 (81.7)	0.13 (0.05 to 0.21)	3.80 (1.56 to 9.21)	0.003
7 day	122 (96.8)	112 (88.9)	0.08 (0.02 to 0.14)	3.81 (1.22 to 11.93)	0.021
Nociceptive					
40 min	114 (90.5)	108 (85.7)	0.05 (−0.03 to 0.13)	1.58 (0.73 to 3.44)	0.246
1 day	125 (99.2)	124 (98.4)	0.01 (−0.02 to 0.03)	2.02 (0.18 to 22.52)	0.569
3 day	126 (100.0)	126 (100.0)	0.00 (0.00 to 0.00)	1.00 (0.00 to ∞)	>0.99
7 day	126 (100.0)	126 (100.0)	0.00 (0.00 to 0.00)	1.00 (0.00 to ∞)	>0.99
Emotion					
40 min	122 (96.8)	123 (97.6)	−0.01 (−0.05 to 0.03)	0.74 (0.16 to 3.39)	0.702
1 day	125 (99.2)	124 (98.4)	0.01 (−0.02 to 0.03)	2.02 (0.18 to 22.52)	0.569
3 day	124 (98.4)	122 (96.8)	0.02 (−0.02 to 0.05)	2.03 (0.37 to 11.30)	0.418
7 day	124 (98.4)	121 (96.0)	0.02 (−0.02 to 0.06)	2.56 (0.49 to 13.46)	0.266
Activities of daily living					
1 day	123 (97.6)	124 (98.4)	0.00 (−0.04 to 0.03)	0.66 (0.11 to 4.03)	0.654
3 day	126 (100.0)	126 (100.0)	0.00 (0.00 to 0.00)	1.00 (0.00 to ∞)	>0.99
7 day	126 (100.0)	126 (100.0)	0.00 (0.00 to 0.00)	1.00 (0.00 to ∞)	>0.99
Physiological					
10 min	92 (73.0)	76 (60.3)	0.13 (0.01 to 0.24)	1.78 (1.05 to 3.03)	0.033
20 min	111 (88.1)	99 (78.6)	0.10 (0.00 to 0.19)	2.02 (1.02 to 4.01)	0.045
30 min	120 (95.2)	109 (86.5)	0.09 (0.02 to 0.16)	3.12 (1.19 to 8.20)	0.021
40 min	124 (98.4)	120 (95.2)	0.03 (−0.01 to 0.07)	3.10 (0.61 to 15.66)	0.171

Note: We fitted a generalized linear mixed model with a binomial distribution and logit link function to analyze changes in recovery rates over time.

Abbreviation: CI, confidence interval.

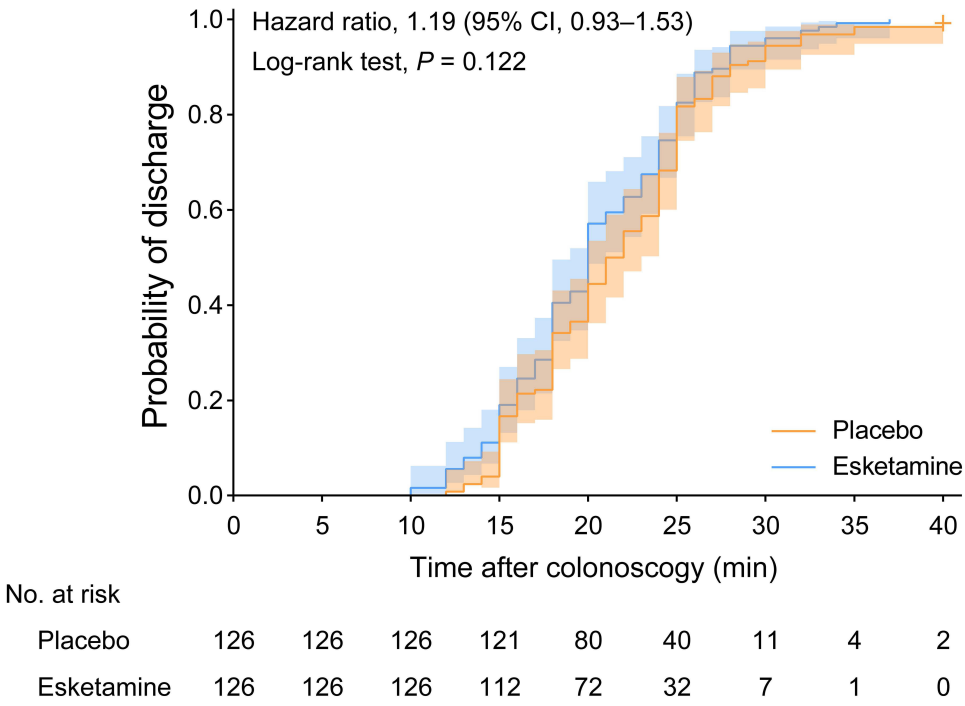

Figure 3 Discharge probability during 40 min after colonoscopy.
Note: Discharge time was based on a Modified Post Anesthesia Discharge Scoring System (PADSS) score of 9 or greater. Time-to-event distributions between groups were compared using the Log rank test. Hazard ratios with 95% CIs were calculated using a Cox proportional hazards model. No significant differences were observed between the esketamine and placebo groups.
Abbreviation: CI, confidence interval.

pharmacological profile as an NMDA receptor antagonist, which modulates glutamatergic neurotransmission and initiates downstream signaling cascades promoting synaptic plasticity.[26–29] Such molecular processes, including activation of brain-derived neurotrophic factor and mammalian target of rapamycin pathways, may contribute to enhanced cognitive

Table 3 Secondary Outcomes

Characteristic	Esketamine (n = 126)	Placebo (n = 126)	*P* value
Induction time, median (IQR), sec	86 (76–95)	89 (78–102)	0.042
Colonoscopy duration, median (IQR), min	23 (20–27)	24 (20–28)	0.440
Propofol consumption, median (IQR), mg	140 (120–280)	200 (180–240)	<0.001
Emergence time, median (IQR), min	15 (11–17)	15 (12–19)	0.127
Discharge time, median (IQR), min	20 (18–25)	22 (18–25)	0.121
Patient satisfaction, n (%)			0.003
Very satisfied	69 (54.8)	58 (46.0)	
Satisfied	49 (38.9)	38 (30.2)	
Neutral	6 (4.8)	17 (13.5)	
Dissatisfied	2 (1.6)	11 (8.7)	
Very dissatisfied	0 (0.0)	2 (1.6)	

(*Continued*)

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Table 3 (Continued).

Characteristic	Esketamine (n = 126)	Placebo (n = 126)	*P* value
Endoscopist satisfaction, n (%)			0.478
Very satisfied	66 (52.4)	58 (46.0)	
Satisfied	58 (46.3)	64 (50.8)	
Neutral	2 (1.6)	4 (3.2)	
Dissatisfied	0 (0.0)	0 (0.0)	
Very dissatisfied	0 (0.0)	0 (0.0)	

Abbreviation: IQR, interquartile range.

performance during the postoperative period. This promising finding represents a novel application of esketamine in colonoscopy sedation, suggesting potential neuroprotective benefits beyond its established role in procedural sedation and analgesia.

Our study demonstrated a significantly lower incidence of cardiopulmonary adverse events in the esketamine group, specifically hypotension (14.3% vs 36.5%), bradycardia (5.6% vs 15.1%), and hypoxemia (2.4% vs 8.7%), consistent with previous research findings.[12,30] This enhanced hemodynamic stability can be attributed to two key factors: the significant reduction in propofol consumption (5.8 mg/kg/h vs 7.7 mg/kg/h, representing a 25% decrease) and esketamine's inherent sympathomimetic properties. The combination of these effects appears to effectively counteract propofol-induced circulatory and respiratory depression.[31] Notably, we observed no significant differences in psychotomimetic adverse effects between groups, likely due to propofol's potential attenuation of esketamine-related psychotomimetic effects and the relatively low subanesthetic dosage employed.[32] These findings suggest that combining low-dose esketamine with propofol may provide a safer sedation profile for colonoscopy procedures, particularly in patients at elevated risk for cardiopulmonary complications, while maintaining a favorable side effect profile.

Our trial revealed no significant differences in emergence or discharge times between the esketamine and placebo groups, aligning with previous studies.[33,34] This finding further supports esketamine's role as an optimal adjunct in

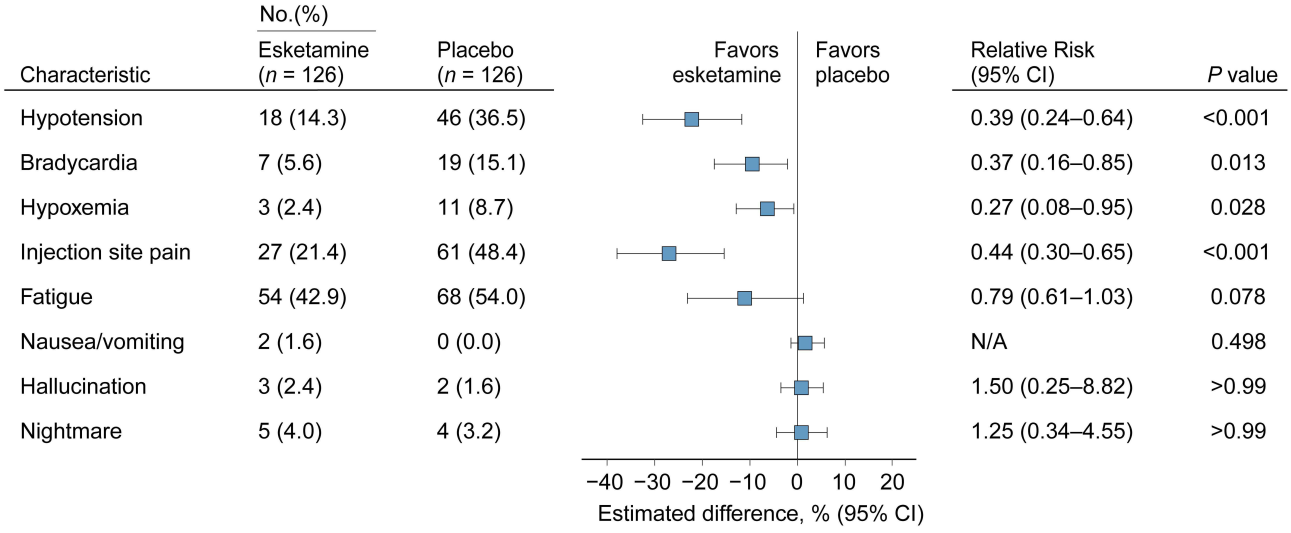

Figure 4 Adverse events comparison between esketamine and placebo groups.
Note: Adverse event rates were compared between groups using chi-square or Fisher's exact tests with calculated rate differences and 95% confidence intervals. The esketamine group was associated with lower incidences of hypotension, bradycardia, hypoxemia, and injection site pain compared with the placebo group.
Abbreviations: CI, confidence interval; N/A, not applicable.

propofol-based sedation, as it maintains clinical efficiency without compromising discharge readiness—a crucial factor for optimizing patient turnover and resource allocation in ambulatory endoscopy centers. The ability to improve recovery and reduce adverse events without prolonging procedural times represents a significant advantage in the high-volume setting of outpatient colonoscopy.

Patients receiving esketamine reported higher satisfaction scores (P = 0.003) and experienced significantly less propofol injection pain (21.4% vs 48.4%, RR = 0.44; 95% CI: 0.30–0.65, $P < 0.001$). This finding aligns with previous research demonstrating that coadministration of esketamine and propofol mitigated propofol injection pain in patients undergoing general anesthesia.[35] Notably, propofol injection pain is ranked as the seventh most important low-morbidity clinical anesthesia problem and significantly impacts patient satisfaction.[36] The enhanced patient satisfaction observed in our study reflects a comprehensive improvement in the patient experience, attributable to reduced propofol injection pain and esketamine's overall beneficial effects on the sedation process.

A key strength of our study is the use of the PostopQRS, which offers distinct advantages in evaluating cognitive function. The PostopQRS assesses recovery over time at both group and individual levels, with demonstrated feasibility in face-to-face and telephone interviews. Importantly, it evaluates recovery relative to individual preoperative baselines, allowing for a more nuanced and personalized evaluation of cognitive recovery compared to absolute score assessments.[18] This approach enhances our cognitive function measurements' sensitivity and clinical relevance.

However, this study has several limitations. First, we evaluated only one subanesthetic dose of esketamine (0.2 mg/kg), which precludes a comprehensive dose-response analysis and limits our ability to determine the optimal dosage for balancing efficacy and safety. Second, our sample size may have been insufficient to detect statistically significant differences in rare esketamine-related psychotomimetic adverse effects between groups, potentially underestimating these risks. Finally, the stringent eligibility criteria, while ensuring internal validity, limit the generalizability of our findings to the broader colonoscopy patient population with diverse comorbidities and risk factors.

Conclusion

The addition of low-dose esketamine (0.2 mg/kg) to propofol for colonoscopy sedation yielded significant improvements in multiple domains: enhanced cognitive recovery on postoperative day 3, reduced cardiopulmonary complications (hypotension, bradycardia, and hypoxemia), decreased injection site pain, and increased patient satisfaction—all achieved without prolonging discharge times. While these findings demonstrate promising clinical benefits, implementation in routine practice requires careful consideration. Healthcare providers should carefully select patients, particularly those at higher risk of propofol-related adverse events, adhere to the studied dose, and monitor patients closely. Future research priorities should include large-scale, multi-center trials to validate these findings, establish optimal dosing strategies, evaluate outcomes in specific patient subgroups, assess long-term safety and economic implications, and elucidate the underlying mechanisms of improved recovery. Such comprehensive investigation will be essential for optimizing esketamine's role in procedural sedation protocols.

Data Sharing Statement

The deidentified participant data, study protocol, and statistical analysis plan can be accessed from the corresponding author upon reasonable request.

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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 all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author reports no conflicts of interest in this work.

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