ORIGINAL RESEARCH

The Effect of Low-Dose Esketamine on Postoperative Neurocognitive Dysfunction in Elderly Patients Undergoing General Anesthesia for Gastrointestinal Tumors: A Randomized Controlled Trial

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Purpose: This study aims to evaluate the effects of the intraoperative application of low-dose esketamine on postoperative neurocognitive dysfunction (PND) in elderly patients undergoing general anesthesia for gastrointestinal tumors.

Methods: Sixty-eight elderly patients were randomly allocated to two groups: the esketamine group (group Es) (0.25 mg/kg loading, 0.125mg/kg/h infusion) and the control group (group C) (received normal saline). The primary outcome was the incidence of delayed neurocognitive recovery (DNR). The secondary outcomes were intraoperative blood loss, the total amount of fluid given during surgery, propofol and remifentanil consumption, cardiovascular adverse events, use of vasoactive drugs, operating and anesthesia time, the number of cases of sufentanil remedial analgesia, the incidence of postoperative delirium (POD), the intraoperative hemodynamics, bispectral index (BIS) value at 0, 1, 2 h after operation and numeric rating scale (NRS) pain scores within 3 d after surgery.

Results: The incidence of DNR in group Es (16.13%) was lower than in group C (38.71%) ($P < 0.05$). The intraoperative remifentanil dosage and the number of cases of dopamine used in group Es were lower than in group C ($P < 0.05$). Compared with group C, DBP was higher at 3 min after intubation, and MAP was lower at 30 min after extubation in group Es ($P < 0.05$). The incidence of hypotension and tachycardia in group Es was lower than in group C ($P < 0.05$). The NRS pain score at 3 d after surgery in group Es was lower than in group C ($P < 0.05$).

Conclusion: Low-dose esketamine infusion reduced to some extent the incidence of DNR in elderly patients undergoing general anesthesia for gastrointestinal tumors, improved intraoperative hemodynamics and BIS value, decreased the incidence of cardiovascular adverse events and the intraoperative consumption of opioids, and relieved postoperative pain.

Keywords: esketamine, postoperative neurocognitive dysfunction, elderly patients, gastrointestinal surgery

Introduction

After surgical anesthesia, postoperative cognitive dysfunction (POCD) is a common central nervous system complication, with the predominant clinical symptom being a reduction in cognitive function (including learning, memory, mood, emotion, and judgment) in patients.[1] POCD often occurs in patients over the age of about 65 yr and has recently been

recommended as perioperative neurocognitive disorders (PND).[2,3] According to the time of onset, PND includes pre-existing neurocognitive disorders, postoperative delirium (POD) occurring hours to days after surgery, delayed neuro-cognitive recovery (DNR) occurring within 30 days after surgery, and postoperative neurocognitive disorder (POND) occurring weeks to months after surgery.[3] The definition of POCD has changed over the years, and various cognitive assessment tests have been employed in different research, making it difficult to pinpoint the exact incidence of PND.[4,5] As the population ages, the proportion of elderly patients undergoing surgery increases accordingly.

Gastrointestinal tumors mainly include gastric cancer (GC) and colorectal cancer (CRC). GC is the fourth most common malignancy and the second most deadly of all malignancies worldwide.[6,7] CRC is the world's fourth most deadly cancer with nearly 900,000 deaths yearly.[8] The incidence of gastrointestinal tumors is highest in developed countries and has significantly burdened global healthcare finances.[9–11] In senior patients, aging causes increasing levels of pro-inflammatory factors, poorer inflammation inhibition, and a higher prevalence of PND. During gastrointestinal surgery, the trauma and extreme stress cause severe hemodynamic fluctuations and a massive release of inflammatory mediators that affect the central nervous system (CNS), which can result in some postoperative neurological complications (such as cognitive dysfunction and delirium).[12] Therefore, finding practical solutions to avoid PND in elderly patients after gastrointestinal surgery is essential for their prognosis.

Cognitive dysfunction is present in various psychoneurological disorders, such as depressive disorders, Alzheimer's disease (AD), schizophrenia, Parkinson's disease, and others. Many psychiatric disorders may be associated with over-activating the N-methyl-D-aspartic acid receptor (NMDAR).[13] Esketamine is a derivative of ketamine used as a nasal spray for treating depression. Both ketamine and esketamine work by blocking the NMDAR in the brain, however, esketamine has been found to have fewer cognitive side effects compared to ketamine.[14–16] It has been shown that in depressed patients receiving low-dose esketamine, most patients showed a rapid and sustained improvement in their depressive symptoms.[17] Tu et al showed that the induction and maintenance of intraoperative anesthesia with esketamine for the spinal operation had good safety and reliability, facilitated postoperative cognitive recovery, and had relatively mild adverse effects.[18]

There is still a lack of research on esketamine used for the induction and maintenance of anesthesia in elderly patients, especially with gastrointestinal tumors. In conclusion, this study aims to investigate the effect of low-dose esketamine on PND in elderly patients undergoing general anesthesia for gastrointestinal tumors, and to provide a reference for the selection and rational use of clinical anesthetic drugs.

Methods
Study Design
The current study was approved by the Ethics Committee at Union Hospital Tongji Medical College of Huazhong University of Science and Technology (No. UHCT21683) and prospectively registered at the Chinese Clinical Trial Registry (ChiCTR2200059003, date of registration: April 22, 2022). This study is a single-center, double-blind, prospective, randomized controlled clinical trial in Union Hospital Tongji Medical College of Huazhong University of Science and Technology. Patients who would like to participate in this study were selected from May 2022 to August 2022 at Union Hospital Tongji Medical College of Huazhong University of Science and Technology. Written informed consent was obtained from all patients.

Inclusion Criteria
Participants must meet the following inclusive criteria: (1) age ≥65 years; (2) American Society of Anesthesiology (ASA) physical status I–III; (3) body mass index (BMI) 18–30kg/m^2 (4) elective major abdominal surgery under general anesthesia for gastrointestinal tumors; (5) operation time ≥2 hours.

Exclusion Criteria
The exclusion criteria are as follows: (1) preoperative cognitive dysfunction as determined by Mini-Mental State Examination (MMSE) (less than 17 for illiteracy, 20 for primary school education, and 24 for high school education or above); (2) unable to communicate because of aphasia, severely impaired hearing or other difficulties; (3) use of psychotropic drugs (such as clozapine,

risperidone, olanzapine, haloperidol, and chlorpromazine); (4) patients with a history of alcohol abuse or acetylcholine drug use; (5) use of sevoflurane, dexmedetomidine, scopolamine, penehyclidine hydrochloride during the study period; (6) severe circulatory disease (such as severe arrhythmia, hypertension, coronary artery disease, and cardiac insufficiency) and history of cardiac surgery; (7) severe respiratory disease (respiratory failure, severe chronic obstructive pulmonary disease); (8) the history of cerebral hemorrhage; (9) coagulation abnormalities; (10) patients with contraindications to the use of esketamine; (11) patients who experienced severe subcutaneous emphysema, serious adverse events (such as intraoperative hemorrhage and severe hemodynamic fluctuations); (12) emergency surgery; (13) admitted to ICU after surgery; (14) decided to withdraw from the study during the study period; (15) had a second operation within three days after the operation.

Sample Size Calculation

The study was a randomized controlled trial with the intervention group as group Es and the control group as group C. The primary outcome indicator of the study was the incidence of DNR based on the MMSE score on the third day after the operation. According to the literature review and pre-experimental results, the average MMSE score in group C on the third day after the operation was 26.88 ± 1.91. The score on the third day after operation in group Es is estimated to be increased by 1.5, assuming α is 0.05 (bilateral) and the degree of assurance (test efficiency) is 0.9. PASS 15 software was used to calculate that the sample size of group C is 28 and that of group Es is 28. The lost follow-up rate was considered to be 20%, and at least 34 patients were enrolled in each group. Therefore, a total of at least 68 patients are included.

Randomization and Blindness

A double-blind design was used in this study, and patients were divided into group Es and group C using the random number table method. The anesthesia physician was not allowed to observe and record intraoperative patient data during the study; another anesthesiologist recorded intraoperative data. The MMSE scale was used to assess patients' cognitive function 1 day before and 3 days after surgery by a professionally trained anesthetist. POD was assessed using the Richmond Agitation-Sedation Scale (RASS) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) 1 to 3 d after surgery. The incidence of DNR and POD in the 3 d after surgery was recorded. After data collection, the random number table envelope was opened, and analysis was completed to determine the difference between group Es and group C. An overview of this study is presented in Figure 1.

Anesthesia Management

Based on the same other anesthetics in the two groups, esketamine was given at 0.25 mg/kg for induction and 0.125 mg/kg/h for maintenance in group Es, while in group C, 0.9% saline was given in equal volume. Induction of anesthesia after pre-oxygenation with mask ventilation in both groups: intravenous injection of sufentanil (SFDA Approval No.: 11A10331, Yichang Renfu Pharmaceutical Co., Ltd.) 0.25 to 0.5 ug/kg, a bolus injection of etomidate (SFDA Approval No.: YT211016, Jiangsu Enhua Pharmaceutical Co., Ltd.) 0.15 to 0.3 mg/kg and a bolus injection of cisatracurium besilate (SFDA Approval No.: 220227BL, Jiangsu Hengrui Pharmaceutical Co., Ltd.) 0.15 to 0.2 mg/kg after the disappearance of consciousness. Group Es was given esketamine (SFDA Approval No: 211019BL, Jiangsu Hengrui Pharmaceutical Co., Ltd.) 0.25mg/kg, and group C was given an equal volume of 0.9% sodium chloride injection. Five minutes following the start of assisted ventilation, the patient underwent intubation, which was followed by connection to an anesthetic machine and mechanical ventilation. Respiratory parameters were set as follows: tidal volume 6–8 mL/kg, ventilation frequency 12–15 times/min, inspiration-expiration ratio 1:1.5–2, airway pressure <30mmHg, and postapneic end-tidal carbon dioxide pressure (PETCO2) maintained at 35–45mmHg (1 mmHg = 0.133 kPa, considering the effect of pneumoperitoneum, the standard was relaxed appropriately). Anesthesia was maintained by intravenous infusion of propofol (SFDA Approval No.: H20043272, Guangdong Jia Bo Pharmaceutical Co.) 6 to 10 mg/kg/h, remifentanil (SFDA Approval No.: 20A02051, Yichang Renfu Pharmaceutical Co.) 0.2 to 0.3 ug/kg/min and cisatracurium besilate 1 to 2 ug/kg/min. Group Es was given a continuous infusion of esketamine 0.125 mg/kg/h until it was stopped 20 minutes before the end of the operation, and the patients in group C were given an equal volume of 0.9% saline. ECG, HR, SpO2, blood pressure, and BIS were monitored. The BIS depth monitor was used to monitor the depth of sedation, and the pump speed was adjusted to keep the BIS value between 40 and 60 during operation. Under local anesthetic, puncture catheters measured arterial blood pressure through the radial artery. Adapt breathing parameters in accordance with intraoperative arterial blood gas
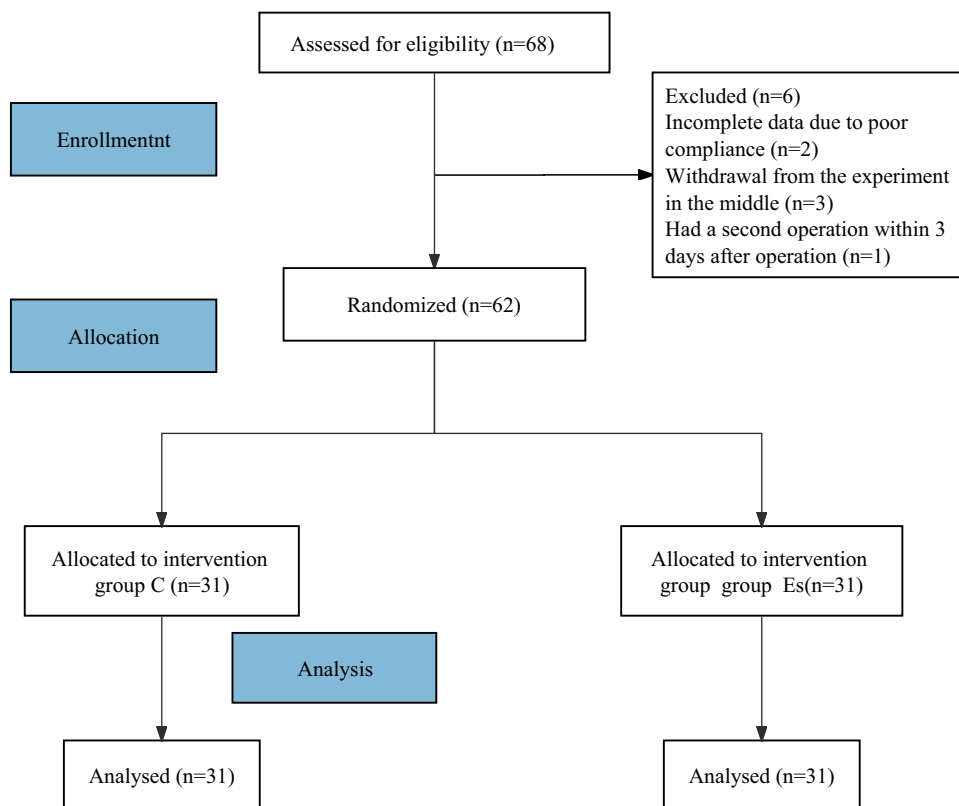
Figure 1 Flowchart of the study design.

measurement to preserve water-electrolyte and acid-base balance. During the operation, hemodynamic stability was maintained. The responsible anesthesiologist injected urapidil 12–25 mg intravenously if hypertension occurred (SBP increased by more than 30% compared to the baseline value or DBP was above 100 mmHg), and continuously nitroglycerin (5 μg/min) if it recurred more than three times. The responsible anesthesiologist administered dopamine 2 mg intravenously and continuously 2–10 μg/kg/min if hypotension frequently occurred more than three times (SBP decreased by more than 30% compared with the baseline value or the absolute value <80 mmHg). The responsible anesthesiologist should administer intravenous atropine 0.5 mg or esmolol 10–20 mg if bradycardia (HR 50<beats/min), tachycardia (HR >100 beats/min), or elevations and drops exceeding 30% of the patient's baseline value for 10 minutes occur. Sufentanil 5 mg, nalbuphine (SFDA Approval No.: 11J12071, Yichang Renfu Pharmaceutical Co., Ltd.) 10mg and tropisetron hydrochloride (SFDA Approval No: 210804 Southwest Pharmaceutical Co., Ltd.) 5mg intravenously 30 minutes prior to the end of the operation. After the operation, the patient was sent to the PACU for observation. All patients were given nalbuphine for patient-controlled intravenous analgesia (PCIA). PCIA configuration includes the following: nalbuphine 50 mg and sufentanil 50 μg diluted to 100 mL, 2 mL/h, bolus 2 mL, lock time 15 min. Once it was determined that the patient was responding promptly to vocal commands and that his or her muscular strength had fully recovered, the tracheal tube was taken out. If the patient is still in pain after awakening, administer sufentanil 5ug for remedial analgesia. After confirming that the patient's reflexes, consciousness, and muscle strength had fully recovered and no serious adverse effects occurred, he was returned to the ward.

Measurement
Data Collection

Patients completed preoperative cognitive status testing using the MMSE scale one day before surgery. Preoperative data collected included patient age, sex, ASA, BMI, education level, co-morbidities, and operative procedure. Intraoperative data were obtained from intraoperative blood pressure, mean arterial pressure (MAP) and heart rate (HR), cardiovascular adverse events, operating time, anesthesia time, the total amount of crystalloids and colloids given during surgery,

intraoperative blood loss, propofol and remifentanil consumption, BIS value, number of cases of dopamine use and sufentanil remedial analgesia. Postoperative information includes the MMSE scale, the frequency of DNR at 3 days after surgery, the incidence of POD from the first to the third day following the operation, and the numerical rating scale (NRS) score three days following the operation.

Assessment of Delayed Neurocognitive Recovery

As most patients in this study had a low level of education, the MMSE scale was chosen to evaluate cognition. The MMSE scale is a reliable clinical test, which is easy to complete and commonly used to measure orientation, memory, attention, calculation, recall, and language skills, with a maximum score of 30.[19] Due to cultural and language differences, we used the Chinese version of the MMSE scale.[20] According to the educational level, the MMSE scale scores of illiterateness < 17, primary school < 20, middle school and above < 24 were defined as cognitive impairment. Patients were assessed for DNR using the MMSE scale when POD was excluded three days after surgery. The score decreased by 2 points after the operation compared with the preoperative score, which is considered DNR.

Assessment of Postoperative Delirium

After the surgery, the patients were observed and engaged in conversation to detect mental status. It is crucial to employ both sedation and agitation methods, such as RASS and a delirium screening tool, because POD is relevant in the postoperative context.[21] CAM-ICU was applied by experienced researchers who were trained in neuropsychological assessment during each 8-h shift, and the patient's mental status was evaluated in terms of the four CAM-ICU characteristics (1) acute changes or fluctuations in mental state, (2) inattentiveness, (3) altered level of consciousness, and (4) disorganized and incoherent thinking.[22] POD was diagnosed if characteristics 1–3, 4 along with 1–2, or 1–4, were present. RASS should first assess the depth of sedation. Patients who are profoundly sedated or unarousable (RASS score ≤ -4) should not be assessed for delirium; if they are arousable (RASS score ≥ -3), they may proceed to assessment by CAM-ICU.

Statistical Analysis

This study is a randomized controlled trial. The primary outcome was the incidence of DNR as determined by MMSE score. The secondary measures were the preoperative, intraoperative, and postoperative variables. Patients were divided into two groups based on a random number table. The experimental group is group Es, and the control group is group C.

All research data were analyzed by IBM SPSS software 26.0. Research data of normal distribution were described as the mean±SD (x ± s), and measures that did not conform to a normal distribution were expressed as the median (interquartile). The two groups were compared by independent sample t-test (normal distribution) or non-parametric test (non-normal distribution). ANOVA with repeated measures design was used for comparison within groups. The chi-squared test performed the comparison of categorical data. $P < 0.05$ was considered to be statistically significant.

Results

Sixty-eight patients were enrolled in this study; six patients (8.8%) dropped out, two had incomplete information due to poor compliance, three withdrew from the trial, and one had a second operation within three days after surgery. The remaining 62 patients completed perioperative information collection, and 31 patients in each group completed statistical analysis (Figure 1).

General Data

There was no significant difference in age, sex ratio, ASA, BMI, education level, preoperative complications (hypertension, diabetes, and coronary heart disease), and operative procedure between the two groups ($P > 0.05$) (Table 1).

Intraoperative Conditions and Drug Use

There was no significant difference in the duration of surgery and anesthesia, the volume of infusion, blood loss, intraoperative propofol consumption, and the cases of postoperative PACU sufentanil remedial analgesia between the two groups ($P > 0.05$). However, compared with group C, the intraoperative remifentanil consumption, the cases of dopamine

Table 1 Patient Demographic and Clinical Parameters

Index	Group C(n=31)	Group Es(n=31)	P
Age (years)	70.55±4.24	69.45±4.35	0.319
Sex (male/female)	24/7	24/7	1.000
ASA (II/III)	24/7	25/6	0.755
BMI (kg/m^2)	23.64±3.36	22.75±2.76	0.261
Education level (years)	9.61±3.17	9.74±2.90	0.868
Preoperative complications			
Hypertension	13 (41.9%)	11 (35.5%)	0.602
Diabetes	2 (6.5%)	3 (9.7%)	1.000
Coronary heart disease	3 (9.7%)	2 (6.5%)	1.000
Operative procedure			
Gastrectomy			
Total	11 (35.5%)	8 (25.8%)	0.409
Distal	3 (9.7%)	6 (19.4%)	0.471
Colectomy			
Extended	11 (35.5%)	7 (22.6%)	0.263
Partial	2 (6.5%)	1 (3.2%)	1.000
Rectum	4 (12.9%)	9 (30.0%)	0.103

Notes: Between-group comparison: p-value reported based on independent sample *t*-test and Wilcoxon rank sum test for quantitative variables and chi-square test for qualitative variables. Data are shown as mean ± standard deviation and number (percent).
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; Group C, control group; Group Es, esketamine group.

use and sufentanil remedial analgesia in group Es were significantly lower (P <0.05). And the BIS value in group Es was significantly higher than that in group C (P <0.001) (Table 2).

Hemodynamic Indexes

Compared with T_0, SBP and MAP at T_1, T_3–T_5, DBP at T_1, T_5 in the two groups, HR at T_2, T_4–T_5 in group C, and HR at T_2–T_5 in group Es were significantly decreased (P <0.05). Compared with group C, DBP at T_1 in group Es was significantly higher (P <0.05), and MAP at T_6 in group Es was significantly lower (P <0.05) (Figure 2). This demonstrated that the anesthetic induction and maintenance of esketamine were more conducive to hemodynamic stability in elderly patients.

Table 2 Intraoperative Data

Index	Group C (n=31)	Group Es (n=31)	P
Duration of surgery (min)	238.39±70.85	268.74±94.56	0.158
Duration of anesthesia (min)	284.32±72.91	316.16±98.76	0.154
Crystalloids infusion (mL)	1754.84±597.27	1888.71±753.18	0.441
Colloids infusion (mL)	738.71±424.01	854.84±264.37	0.202
Blood loss (mL)	235.16±205.26	281.29±236.37	0.415
Propofol consumption (μg)	1781.94±543.00	1766.84±762.04	0.929
Remifentanil consumption (μg)	3908.94±1141.03	3236.16±1399.58	<0.05
BIS value	45±2.92	53±3.61	<0.001
Dopamine use	19 (61.29%)	9 (29.03%)	<0.05
Sufentanil remedial analgesia	8 (25.81%)	6 (19.35%)	0.762

Notes: Between-group comparison: p-value reported based on independent sample *t*-test and Wilcoxon rank sum test for quantitative variables and chi-square test for qualitative variables. Data are shown as mean ± standard deviation and number (percent).
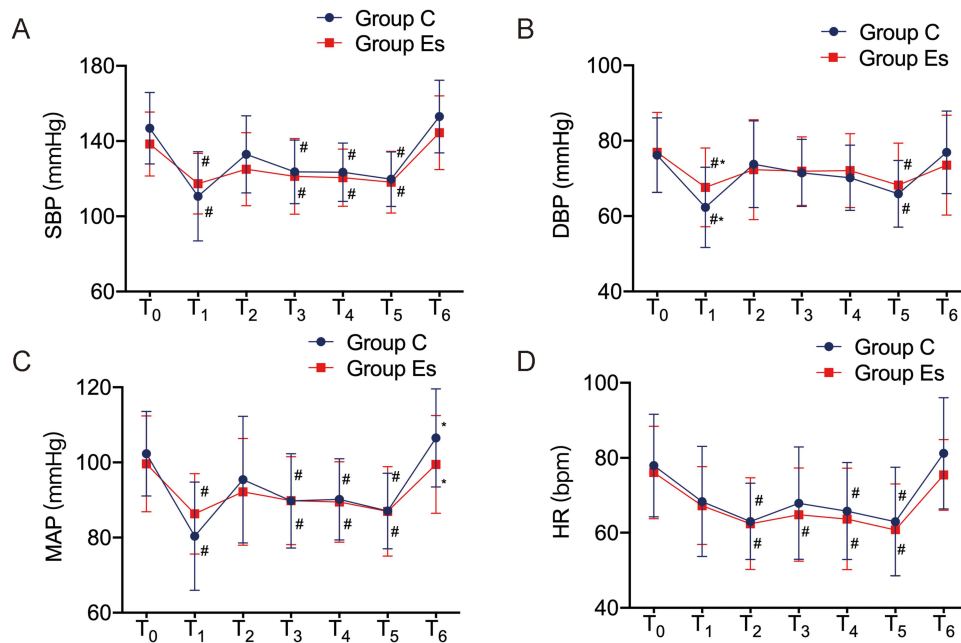**Abbreviations**: BIS, bispectral index; Group C, control group; Group Es, esketamine group.

Figure 2 Comparison of hemodynamic indexes between the two groups. (**A**). SBP; (**B**). DBP; (**C**). MAP; (**D**). HR.
Notes: Compared with T_0 in the same group, $^{\#}P$ <0.05; compared with the control group at the same time point, $^{*}P$ <0.05.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; T_0, before intubation; T_1, 3 min after intubation; T_2, 3 min after surgical skin incision; T_3, 1 h after surgical skin incision; T_4, 2 h after surgical skin incision; T_5, the end of surgery; T_6, 30 min after extubation; Group C, control group; Group Es, esketamine group.

Intraoperative Cardiovascular Adverse Events

Compared with group C, the incidence of hypotension and tachycardia in group Es was significantly lower (P <0.05). There were no significant differences in the incidence of hypertension and bradycardia between the two groups (P >0.05) (Table 3).

MMSE Scores and the Incidence of DNR

The two groups had no significant difference in MMSE scores at D_0 (P >0.05). Three days after surgery (D_3), the MMSE scores decreased in the two groups. Compared with D_0, the MMSE scores at D_3 in group C were significantly lower (P <0.05); there was no significant difference in the MMSE scores at D_3 in group Es (P >0.05). And there was no significant difference in MMSE scores at D_3 between the two groups (P >0.05) (Figure 3). Comparing all patients in the two groups, the incidence of DNR was significantly lower among patients who used esketamine (12 of 31 patients in group C versus 5 of 31 patients in group Es, P = 0.046) (Figure 4). This suggested that the anesthetic induction and maintenance of esketamine were more conducive to promoting the recovery of cognitive function in elderly patients.

NRS Scores and the Incidence of POD

In group C, the incidence of POD was 12.90% (D_1), 9.68% (D_2), and 6.45% (D_3), whereas, in group Es, it was 9.68%, 3.23%, and 0.00%. Although the incidence of POD three days after the operation was lower in group Es than in group C,

Table 3 Intraoperative Cardiovascular Adverse Events

Index	Group C (n=31)	Group Es (n=31)	P
Hypotension	19 (61.29%)	9 (29.03%)	<0.05
Hypertension	4 (12.90%)	4 (12.90%)	1.000
Tachycardia	6 (19.35%)	0 (0%)	<0.05
Bradycardia	6 (19.35%)	12 (38.71%)	0.090

Notes: Between-group comparison: p-value reported based on chi-square test. Data are shown as number (percent).
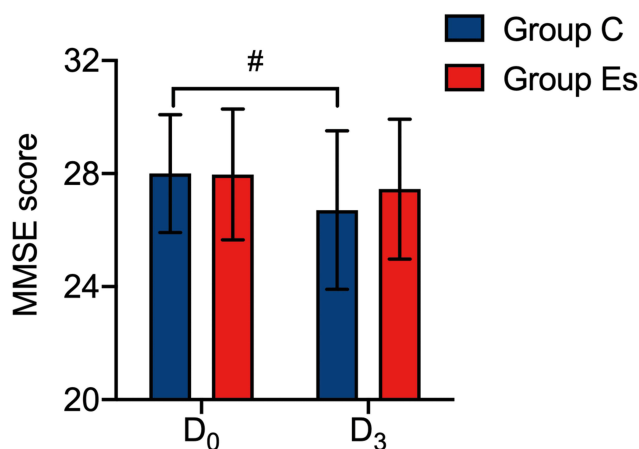**Abbreviations**: Group C, control group; Group Es, esketamine group.

Figure 3 Comparison of MMSE scores between the two groups.
Notes: Compared with T_0 in the same group, [#]P <0.05. An unauthorized version of the Chinese MMSE was used by the study team without permission. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).
Abbreviations: MMSE, Mini-Mental State Examination; D_0, 1 day before surgery; D_3, 3 days after surgery; Group C, control group; Group Es, esketamine group.
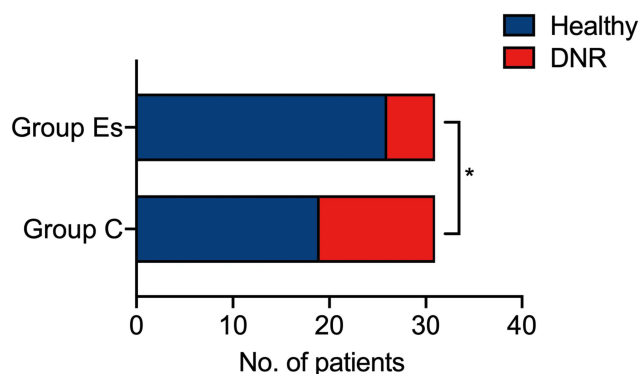

Figure 4 Comparison of the incidence of DNR between the two groups.
Notes: Compared with the control group, *P <0.05.
Abbreviations: DNR, delayed neurocognitive recovery; Group C, control group; Group Es, esketamine group.

there was no significant difference between the two groups (P >0.05) (Table 4). Patients were checked on at the same time in the afternoon at D_1, D_2, and D_3 to measure postoperative pain using the NRS scale. The results showed that the NRS scores were higher in group C than in group Es at D_1 and D_2, and there was no significant difference between the two groups (P >0.05). Compared with group C, the NRS scores at D_3 in group Es was significantly lower (P <0.05) (Table 4).

Table 4 NRS Scores and the Incidence of POD

Index		Group C (n=31)	Group Es (n=31)	P
POD	D_1	4 (12.90%)	3 (9.68%)	0.688
	D_2	3 (9.68%)	1 (3.23%)	0.301
	D_3	2 (6.45%)	0 (0.00%)	0.151
NRS	D_1	3.71±1.37	3.06±1.59	0.092
	D_2	2.81±1.60	2.35±1.43	0.246
	D_3	2.48±1.12	1.81±1.11	<0.05

Notes: Between-group comparison: p-value reported based on independent sample *t*-test and Wilcoxon rank sum test for quantitative variables and chi-square test for qualitative variables. Data are shown as mean ± standard deviation and number (percent).
Abbreviations: POD, postoperative delirium; NRS, numerical rating scale; Group C, control group; Group Es, esketamine group; D_1, 1 day after surgery; D_2, 2 days after surgery; D_3, 3 days after surgery.

Discussion

In this study, we preliminary explored the effect of low-dose esketamine on PND in elderly patients undergoing general anesthesia for gastrointestinal tumors. We referred to the literature when determining the dose of esketamine for anesthesia induction and maintenance.[23] The anesthesia induction dose in the instructions is 0.5mg/kg, but overdose reactions may occur at this dose in elderly patients with gastrointestinal tumors. In our study, we chose 0.25mg/kg esketamine intravenous injection and 0.125 mg/kg/h esketamine continuous infusion; and showed stable hemodynamics in group Es.

As the population ages, the proportion of elderly patients undergoing surgery increases accordingly. POCD is a common central nervous system complication following surgical anesthesia and has lately been recommended as PND.[2,3] PND describes cognitive impairment identified in the preoperative or postoperative period. Depending on the time of onset, PND includes pre-existing neurocognitive disorders before surgery, POD, DNR, and POND. Previously the concept of POCD was distinguished from POD from each other, so this study will follow the POCD concept when discussing PND in addition to POD. POCD often occurs in elderly patients over 65, mainly manifested as memory impairment, mental retardation, language barrier, information processing ability decline, and anxiety.[24] The mechanism of POCD is complex and there are many influencing factors. Previous studies have identified age, low education level, inflammation, postoperative pain, serum 25-OH-D level, and preoperative cognitive impairment as potential risk factors for POCD.[25–29] A prospective longitudinal study of the incidence of POCD in patients of different ages showed that the incidence of POCD at three months after surgery was significantly higher in elderly patients than in young and middle-aged patients and that increasing age, lower education level, previous history of cerebrovascular accident and early POCD were independent risk factors for POCD at three months after surgery.[30] The type and duration of surgery both have an impact on postoperative cognitive function. Due to the high degree of stress, operation time, complex procedure, and postoperative problems, major surgery (such as heart surgery, hip replacement, and gastrointestinal surgery) has varying degrees of influence on patients' cognitive function. A randomized controlled study showed a significantly higher incidence of PND in patients undergoing coronary artery bypass surgery than in non-cardiac surgery.[31]

POD is a form of delirium that occurs in patients after anesthesia and surgery, usually with a high incidence in the first 1–3 days after surgery. Its clinical manifestations are divided into excited delirium, characterized by restlessness, irritability, hallucinations, and delusions, and indifferent delirium, characterized by decreased exercise, sparse speech, and slow reaction. Moreover, mixed delirium in which excited delirium and indifferent delirium coexist. Although most POD patients can recover independently within a few days, severe postoperative accidents (removal of the drainage tube and wound dehiscence caused by emotional excitement) will lead to delayed recovery, prolonged hospitalization, and even life-threatening. European Society of Anesthesiology put forward that POD risk factors include preoperative factors (cardiovascular-related complications, preoperative fasting, dehydration, and hyponatremia or hypernatremia), intraoperative factors (abdominal surgery, cardiothoracic surgery, intraoperative bleeding), and postoperative pain.[21] Additionally, emergency surgery and postoperative complications can increase the incidence POD and the risk of long-term cognitive impairment.[32,33]

Radical operation of gastrointestinal tumor causes trauma and severe stress reaction during the operation, which leads to severe fluctuation of hemodynamics and release of inflammatory mediators thus involving CNS and causing postoperative neurological complications (such as cognitive dysfunction and delirium). According to the latest research results of Yongli, the incidence of early postoperative POCD for gastrointestinal tumors aged 65 and above is 41.0%.[34] In this study, the incidence of POCD in the control group was 38.71% three days after the operation, consistent with the above results. A meta-analysis of risk factors of POD in gastrointestinal surgery showed that the incidence of POD ranged from 8.2% to 54.4%.[35] In this study, the incidence of POD in the control group was 12.9%, 9.68%, and 6.45%, respectively, consistent with the above results.

Esketamine is a chiral cyclohexanone derivative with analgesic and anesthetic effects. It is combined with a sedative anesthetic (propofol) for anesthesia induction and general anesthesia or as a supplement to local anesthesia.[36] Esketamine has high-fat solubility, its plasma concentration reaches its peak within 5 minutes after intramuscular injection, and it is easy to pass through the blood-brain barrier (BBB). Its product is converted into norketamine in vivo. The anesthetic effect of norketamine is 1/5–1/3 as potent as esketamine, and its elimination half-life is long, which can explain why esketamine still has a specific analgesic effect after the patient wakes up from anesthesia.[37] It was found that norketamine mediated the acute and transient cardiovascular, respiratory, and sympathomimetic effects of esketamine by antagonizing the α7 nicotinic acetylcholine receptor.[38,39] Intraoperative hypotension (IOH) hurts tissue perfusion and blood flow.[40] A randomized controlled study performed by Siepe

et al showed that patients undergoing elective or urgent on-pump coronary artery bypass grafting (CABG) had a significantly higher drop in postoperative MMSE scores and developed POD in patients with low MAP (60–70) compared with high MAP (80–90).[41] Therefore, IOH may be related to postoperative neurocognitive impairment due to cerebral hypoperfusion. Tu et al showed that esketamine induction of anesthesia has good safety and reliability, which can improve hemodynamics, reduce surgical stress and inflammatory reaction, shorten the duration of anaesthesia, promote postoperative cognitive recovery, and the adverse effects are relatively mild.[18] Our study showed that intraoperative administration of esketamine reduced the incidence of hypotension and tachycardia and prevented anesthesia-induced blood pressure dips. This phenomenon may be related to the sympathomimetic effect of esketamine and its strong analgesic effect.

Memory is divided into explicit and invisible memory, with explicit memory (declarative memory) involving the hippocampal-middle temporal lobe system and implicit memory (non-declarative memory) including essential associative learning and memory in the cerebellum, amygdala, and other systems.[42] Most cognitive tests in PND relate to postoperative declarative memory, which is formed through lived experience and involves the acquisition of input information and consolidation of memory and output information. Therefore, the relatively clear structures of PND and the brain are hippocampi and related cortical structures, such as the limbic area, parahippocampal area, and hippocampal regions. Long-term potentiation and long-term inhibition, as synaptic plasticity mechanisms, can affect learning and memory.[43] Studies of synaptic pathways associated with long-duration enhancement have found that Schaffer-collateral CA1 synapses in the hippocampus use glutamate to activate NMDA receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which remove Mg^{2+} and then allow Ca^{2+} inward flow to bind to post-emergence neurons, thereby affecting learning and memory.

Studies on synaptic pathways related to long-term potentiation found that the CA1 synapse of Schaffer-collateral in the hippocampus using glutamate to activate the NMDA receptor and AMPA receptor to remove Mg^{2+}, after that, Ca^{2+} inflow is allowed to bind to postsynaptic neurons, thus affecting learning and memory. However, a further increase in cellular Ca^{2+} levels will increase mitochondrial Ca^{2+}, releasing cytochrome c and promoting apoptosis.[44] Most studies suggest that the mechanism of PND after anesthetic surgery is related to the inflammatory response and central Ca^{2+} dysregulation.[45,46] Gill et al showed that visual learning memory improved after intravenous ketamine and that intravenous subanesthetic doses of ketamine did not deteriorate cognitive function.[47] Our study showed that the intraoperative application of esketamine improved the postoperative cognitive function of patients, with a significantly lower incidence of DNR compared to the control group. However, the difference in effect on POD was not significant.

Pain is an essential factor affecting perioperative inflammation. Preoperative pain can cause the release of inflammatory factors, and surgical stimulation further exacerbates the inflammatory response, potentially leading to CNS inflammation and dysfunction. Preoperative pain may also lead to changes in central neurotransmitters such as dopamine, acetylcholine, and 5-hydroxytryptamine, which may be associated with the development of PND. The use of opioid analgesics can relieve intraoperative and postoperative pain. However, excessive or inappropriate use may result in problems such as respiratory depression, pain allergy, drug tolerance, and related side effects (nausea, vomiting, constipation, and dizziness). American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on minimizing perioperative opioid use, including NMDA receptor antagonists in analgesic options for multimodal analgesia to reduce perioperative pain levels and opioid use.[48] A meta-analysis showed that ketamine can reduce the side effects of opioids during operation, but it was not found to be beneficial to POD.[49] A randomized controlled trial by Bornemann-Cimenti et al revealed that perioperative esketamine application decreased opioid use in major laparotomy, but there was no significant difference in postoperative pain levels between the groups. In addition, compared with minimal-dose esketamine (a 0.015 mg/kg/h infusion following a saline bolus) and placebo, there was a significant increase in the low-dose group (a 0.25 mg/kg bolus and 0.125 mg/kg/h infusion for 48 hours) in Intensive Care Delirium Screening Checklist (ICDSC) score (a score of more than three is considered delirium).[23] This study demonstrated that the intraoperative application of low-dose esketamine was significantly associated with a lower incidence of DNR in the three days following surgery compared to the control group, and the intraoperative opioid dose was significantly reduced, which is consistent with the related research results in recent years.[23,37] However, the incidence of POD in the esketamine group was lower than that in the control group three days after the operation, which was inconsistent with the above research results. The different selection of delirium assessment scales and the small sample size may have influenced the study results.

Clinical studies have been conducted to discuss whether using intraoperative electroencephalography (EEG) to control the depth of anesthesia affects PND. Bispectral index (BIS) is a monitoring parameter of EEG, and BIS monitoring is considered one of the crucial tools for potentially preventing PND.[50–54] Farag et al found that according to BIS monitoring, a higher BIS regimen (mean BIS, 50.7) was superior to a lower BIS regimen (median BIS, 38.9) in terms of cognitive recovery (especially in terms of ability to process information) 4–6 weeks after surgery.[55] Studies have shown that ketamine affects EEG activity, increasing the relative power of slow (θ) and fast (γ) waves, thus increasing the BIS value and therefore applying BIS does not objectively reflect the depth of anesthesia.[56,57] However, other studies have found that the effect of low-dose ketamine on BIS values is transient, lasting only a short time after induction of anesthesia, and does not affect the intraoperative BIS-guided monitoring of depth of sedation.[58] In this study, under the condition of keeping blood pressure, HR and MAP stable, BIS monitoring showed that the BIS value of esketamine group (53 ±3.61) was higher than that of the control group (45 ±2.92). Although higher BIS is a pharmacological effect of esketamine, it can also reduce the usage of propofol. A study revealed a greater prevalence of neurological deficits was linked to deep anesthesia with high-dose propofol.[59] The results showed that intraoperative administration of esketamine increased BIS monitoring value, and a higher BIS regimen positively affected postoperative cognitive recovery.

Shortcomings of this study: 1. 68 patients were expected to be included, but 6 patients (8.8%) dropped out due to exclusion criteria. The sample size is relatively insufficient and is a single-center study, so the results are subject to error bias the experimental results. Therefore, conducting a multi-center, large sample study is necessary to explore further the effect of low-dose esketamine on PND in elderly patients; 2. The follow-up period of this study is relatively short, only 3 d postoperative cognitive function assessment was performed, which is not sufficient to explain the effect of esketamine on the long-term cognitive function, and the follow-up period of 7 d, 30 d, and 1 year postoperative should be improved to investigate the long-term effect of esketamine on the cognitive recovery of elderly patients; 3. This study did not collect blood specimens from patients for laboratory analysis. It lacked research on the mechanism of esketamine's effect on patients' cognitive recovery, which requires further improvement of related experiments in follow-up.

Conclusions

Low-dose esketamine infusion reduced to some extent the incidence of DNR in elderly patients undergoing general anesthesia for gastrointestinal tumors, improved intraoperative hemodynamics and BIS value, decreased the incidence of cardiovascular adverse events and the intraoperative consumption of opioids, and relieved postoperative pain.

Data Sharing Statement

An unauthorized version of the Chinese MMSE was used by the study team without permission. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com). All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

Ethics Approval

This study design was approved by the Ethics Committee at Union Hospital Tongji Medical College of Huazhong University of Science and Technology (No. UHCT21683).

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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