ORIGINAL RESEARCH

Effect of Subanesthetic Dose of Esketamine on Perioperative Neurocognitive Disorders in Elderly Undergoing Gastrointestinal Surgery: A Randomized Controlled Trial

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Background: Perioperative neurocognitive disorders (PND), including delayed neurocognitive recovery (dNCR) and postoperative cognitive dysfunction (POCD), are common postoperative complications in elderly patients and adversely affect their prognosis. The study was designed to explore the effects of esketamine on postoperative cognitive function in elderly patients who underwent gastrointestinal surgery under general anesthesia and its potential mechanism.

Methods: Eighty-four patients aged 65 and above undergoing gastrointestinal surgery were randomly divided into 2 groups: the esketamine group (group S) and the control group (group C). Group S received intravenous sub-anesthetic doses of esketamine (0.15 mg/kg) 5 minutes before the initiation of surgery, while group C received the same volume of saline. A battery of neuropsychological tests was used to assess cognitive function before surgery, 7 days, and 3 months after surgery. The primary outcome was the incidence of dNCR at 7 days postoperatively and POCD at 3 months postoperatively in both groups. The secondary outcome measures included changes in the levels of serum interleukin-6 (IL-6) and calcium-binding protein β (S100β) before and 1 day after surgery.

Results: The incidence of dNCR in group S was lower than that of group C (18.15% vs 38.24% P=0.033). Contrarily, there was no difference in both groups regarding POCD 3 months postoperatively (6.06% vs 14.37% P=0.247). Plasma IL-6 and S100β levels were significantly elevated in both groups on postoperative day 1 (p<0.05), but esketamine pretreatment reduced these levels to some extent compared with group C (p<0.05).

Conclusion: Sub-anesthetic doses of esketamine might reduce the incidence of dNCR and improve early postoperative cognitive function in elderly patients undergoing gastrointestinal surgery, which might be related to the anti-neuroinflammation effects of esketamine.

Keywords: esketamine, perioperative neurocognitive disorders, gastrointestinal surgery, elderly, neuroinflammatory

Introduction

Cognitive impairment following anesthesia and surgery is a common complication in elderly individuals, mainly manifested falls in memory, attention, information processing, and cognitive flexibility.[1] In 2018, new recommendations for the nomenclature of cognitive change associated with anesthesia and surgery recommended perioperative neurocognitive disorders (PND) as an overarching term for cognitive decline identified in the perioperative period, including acute postoperative delirium (POD), delayed neurocognitive recovery (within the 30 days recovery period, dNCR), and postoperative neurocognitive dysfunction (from expected recovery 30 days to 12 months, POCD).[2,3] Previous studies have shown that patients aged 65 and above who underwent non-cardiac surgery had a 26% prevalence of POCD 1 week after surgery which decreased to 10% 3 months postoperatively.[4] PND is associated with delayed recovery, prolonged

hospital stays, additional healthcare expenditures, and even increased probability for 1-year postoperative mortality.[5] However, up to date, limited treatment options for PND are available and the exact mechanism remains unclear.

Several studies have suggested that neuro-inflammation induced by surgery and anesthesia is a major contributor to the development of POCD.[6,7] It is well known that aseptic surgical trauma causes inflammation at the surgical site, which is amplified via peripheral pro-inflammatory cytokines, and this leads to disruption of the blood–brain barrier (BBB), allowing pro-inflammatory cytokines to enter the central nervous system (CNS) and activate microglia. Once activated, microglia continue to up-regulate the expression of pro-inflammatory cytokines, thus amplifying neuro-inflammation could lead to neuronal apoptosis and contribute to the development of POCD.[8,9]

Ketamine, formerly referred to as a "dissociative anesthetic", has reemerged as a useful anesthetic/analgesic agent. The unique properties of ketamine and its large versatility make it suitable to be used in anesthesia, procedural sedation, and pain management.[10,11] As a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, the binding of ketamine to NMDA receptors leads to decreased frequency and duration of Ca^{2+} channel opening and thus inhibits glutaminergic transmission. This mechanism has proven to be neuro-protective in several neurological conditions.[12] A meta-analysis has demonstrated that ketamine administration could reduce IL-6 production in patients undergoing surgery,[13] which was the major pro-inflammatory cytokine and used as a biomarker of the inflammatory reaction. Furthermore, a bolus of 0.5 mg/kg ketamine at induction of anesthesia improved recent verbal and nonverbal memories and executive functions 1 week after surgery in patients undergoing cardiac procedures.[14] Inflammatory regulatory properties of ketamine are increasingly the focus of attention.

Esketamine is the S-enantiomer of ketamine which displays an approximately fourfold greater affinity for the glutamate NMDA receptor[15] and has been FDA-approved in the United States in 2019 for treating depression that has failed to respond to trials of two or more antidepressants. A majority of esketamine studies focused on the treatment of resistant depression.[16–18] Recent years have witnessed a growing interest and enthusiasm of anesthesiologists for the application of esketamine in gastrointestinal endoscopy,[19] endoscopic retrograde cholangiopancreatography,[20] abortion surgery,[21] etc. Intravenous esketamine as an adjunct to general anesthesia has demonstrated its clinical superiority to ketamine in double analgesic potencies, spared opioid requirements, improved recovery, and few adverse effects.[22] Furthermore, recent studies have shown that sub-anesthetic doses of esketamine could maintain the stability of hemodynamics during anesthesia induction[23] and reduce postoperative pain in the PACU in the elderly, without affecting postoperative nausea and vomiting, and postoperative agitation.[24] However, there are currently rare data on the impact of sub-anesthetic doses of esketamine on postoperative cognitive function in elderly patients.

Here, we investigated the effect of the sub-anesthetic doses of esketamine on postoperative cognitive function in elderly patients undergoing gastrointestinal surgery and also explored the potential mechanisms of PND.

Methods
Ethical Considerations
The randomized, prospective, controlled, double-blind study was approved by the Ethics Committee of Affiliated Yixing Hospital of Jiangsu University (approval number: LS2022K080-1) and performed consistent with the principles of the Helsinki Declaration on Human Experimentation. This trial was registered at the Chinese Clinical Trial Registry http://www.chictr.org.cn/showproj.aspx?proj=169798 (ChiCTR2200062421). All participants provided written informed consent.

Study Design and Participants
Patients aged 65 and above who received gastrointestinal surgery under general anesthesia, MMSE scores >24,[25,26] right-handed, and ASA I–III were included in the study from August 11 to November 10, 2022. Exclusion criteria were as follows: 1) history of neurodegenerative diseases (Alzheimer's disease and Parkinson's disease)[27,28]; 2) intracranial hypertension; 3) severe uncontrolled hypertension; 4) communication disorders; 5) glaucoma; 6) serious postoperative complications and admitted to the ICU; 7) reoperation; and 8) loss of follow-up. As repeated neuropsychological testing

could produce a practice effect and result in misinterpretation of outcomes,[29] 15 age- and sex-matched volunteers were recruited from the friends and family members of patients in the trial group using the same exclusion criteria.

Randomization and Blind

A computer random number sequence was generated by an independent statistician before the initiation of the study. The allocations were printed and placed in separate sealed envelopes, and the patients were randomly divided into 2 groups in a 1:1 ratio: the esketamine group (group S) was intravenously instilled with 0.15mg/kg esketamine (Drug batch number: 211222BL; 2mL/50mg, Jiangsu Hengrui Pharmaceutical, Co Lianyungang, China) 5min before the beginning of the surgery, while the control group (group C) was administered the same volume of normal saline similarly.

Anesthesia Protocol

Anesthesia protocols were standardized, and no anticholinergic agents were used as premedication. All patients received standard monitoring on admission to the operating theatre, including oxygen saturation (SpO_2), ECG, noninvasive blood pressure, invasive arterial blood pressure, and the Bispectral Index (BIS).[30]

Anesthesia induction was performed by sequential administration of midazolam [(0.04 mg/kg), 1mL/5mg, Jiangsu Enhua Pharmaceutical Co, Xuzhou, China], sufentanil [(0.3μg/kg), 1mL/μg, Yichang Renfu Pharmaceutical Co, Yichang, China], propofol [(1–2 mg/kg), 20mL/0.2g, Sichuan Guorui Pharmaceutical Co, Leshan, China] and cisatracurium [(0.15 mg/kg), 5mL/10mg, Jiangsu Hengrui Pharmaceutical Co, Lianyungang, China)]. All patients were intubated 3 minutes afterward and then mechanically ventilated with 100% oxygen, VT 8–10mL/kg, frequency 10–14/min, keeping an end-tidal CO_2 of 30–40 mmHg during the surgery procedure. Sufentanil 0.1μg/kg was administrated before the skin incision. The anesthesia was maintained with a continuous intravenous infusion of propofol 4–12 mg/kg/h and remifentanil 15-40 μg/kg/h (1mg, Jiangsu Enhua Pharmaceutical Co, Xuzhou, China), with intermittent injections of cisatracurium to maintain muscle relaxation and concentration titration to maintain hemodynamic stability and adequate depth of anesthesia (BIS values 40–60). Ketorolac 30mg (1mL/30mg, sdnewtimes pharmaceutical Co, Xinyi, China) was given intravenously 5 minutes before sewing and the intravenous administration of anesthetics was stopped 5min before the end of the operation. Reversal of residual neuromuscular blockade was done with a mixture of neostigmine [(0.02 mg/kg), 1mL/0.5mg, Henan Runhong Pharmaceutical Co, Zhengzhou, China] and atropine[(0.01 mg/kg), 1mL/0.5mg, Tianjin Jinyao Pharmaceutical Co, Tianjin, China] and the patient was extubated. Patients were subsequently transferred to the ward after 15min monitoring without a continuous postoperative analgesia program proposed by the anesthesiologist. Rescue analgesia was provided with ketorolac 30mg IV injection whenever the patient complained of a Visual Analogue Scale. (VAS) score equal to or more than 4, and the maximum total daily was not allowed to exceed 120mg.

Demographic data were self-reported by participants, and other medical data were obtained from hospital medical records.

Neuropsychological Testing and Diagnosis of PND

All patients received a standard battery of neuropsychological tests before surgery, at 7 days and 3 months after surgery, while the health volunteers underwent testing in a corresponding time interval. According to a 1995 consensus statement (CS)[31] and recommendations from the International Study on Postoperative Cognitive Dysfunction, this series of neuropsychological tests was chosen (ISPOCD).[4,32] It consisted of the Trail Making Test (Part A), the RAVLT Memory Test, the Verbal Fluency Test, the Finger Tapping Test, the Digit Symbol subtest of the Wechsler Adult Intelligence Scale (Chinese version), the Digit Span (forward and backward) subtest of the Wechsler Memory Scale (Chinese version), the Grooved Pegboard Test, and the Block Test 9 tests. The neuropsychological testing battery used here was designed to measure short- and intermediate-term memory, attention and concentration, executive function, and psychomotor skills. All neuropsychological tests were conducted by an independent experienced psychiatrist blinded to the trial.

According to the International Study of PND definition,[4] PND was diagnosed by calculating the "Z-score". In each test, the Z value was obtained by subtracting the mean change in healthy controls from the difference

between the postoperative score and the preoperative baseline score and then dividing it by the standard deviation of the health volunteers' change score. The cognitive decline was defined as those with a Z-score ≤ -1.96 on at least 2 different tests.

Plasma Samples

There has been a good supply of evidence confirming that patients who develop POCD show increases in serum and cerebrospinal fluid (CSF) pro-inflammatory cytokines,[33,34] particularly interleukin 6 (IL-6) and S100β.[35,36] Therefore, we investigated whether esketamine could alleviate postoperative cognitive deficits by detecting the levels of S100β and IL-6 in serum.

The plasma samples were collected to detect the levels of S100β and IL-6 before surgery and 1 day after the surgery. A peripheral blood sample of 5 mL was taken and put into EDTA anticoagulant tubes. The samples were immediately centrifuged at 3000×g for 10 min at 4 °C and stored at −80°C for subsequent analysis. Serum IL-6 and S100β were measured by using commercially available ELISA kits (Boster Biological Technology Co, Wuhan, China, and Signalway Antibody Co, Nanjing, China), according to the manufacturer's instructions.

Statistical Analysis
Sample Size Calculation

PASS 15.0 software was used to calculate the sample size. According to previous reports, the incidence of POCD in geriatric patients with gastrointestinal tumors is 40%.[37] The pilot study showed that esketamine administration could reduce the incidence of PND by 30%. Given a power of 85% and a significance level of 5%, the sample size was determined to be 66, with 33 subjects in each arm using a 1:1 ratio for the groups. We added 20% for missing data or attritions, so a final sample size of 84 patients (42 patients per group) was recruited.

Data Analysis

We used IBM SPSS version 25 (IBM SPSS, Armonk, NY) for all analyses. Continuous variables were presented as a mean or median (interquartile range) and processed with Student's t-test. Categorical variables were presented as the number of patients and processed with the Chi-squared test or Fisher's exact probability test. The levels of plasma S-100β and IL-6 were analyzed by one-way repeated measures ANOVA. $P<0.05$ was considered statistically significant.

Result
Enrolled Patients

A study flow diagram is shown in Figure 1. A total of 84 patients were scheduled to undergo gastrointestinal surgery under general anesthesia and 15 volunteers were recruited for this study. Seventeen patients were excluded due to Parkinson's (n=1), low education (n=3), poorly controlled hypertension (n=1), admission to the ICU after surgery (n=1), refusal to participate in the study (n=7), serious complications after surgery (n=1), and missing follow-up at 3 months after surgery (n=3). Ultimately, 67 patients were included in the analysis, 34 in group C and 33 in group S. The demographic data of surgical patients and healthy volunteers were comparable (Table 1).

Demographic, Clinical, and Surgical Characteristics

Demographic and clinical and surgical variables were similar between group C and group S (P>0.05), except for the higher dose of remifentanil (P=0.003), an increased postoperative VAS scores (P=0.032), an elevated ketorolac consumption (P=0.043) in group C (Table 2).

Cognitive Outcomes

Table 3 summarizes the neuropsychological test results. According to the above diagnostic criteria, 5 patients in group S (18.75%) and 13 patients in group C (38.24%) were diagnosed with dNCR at 7 days after surgery, while 2 patients in

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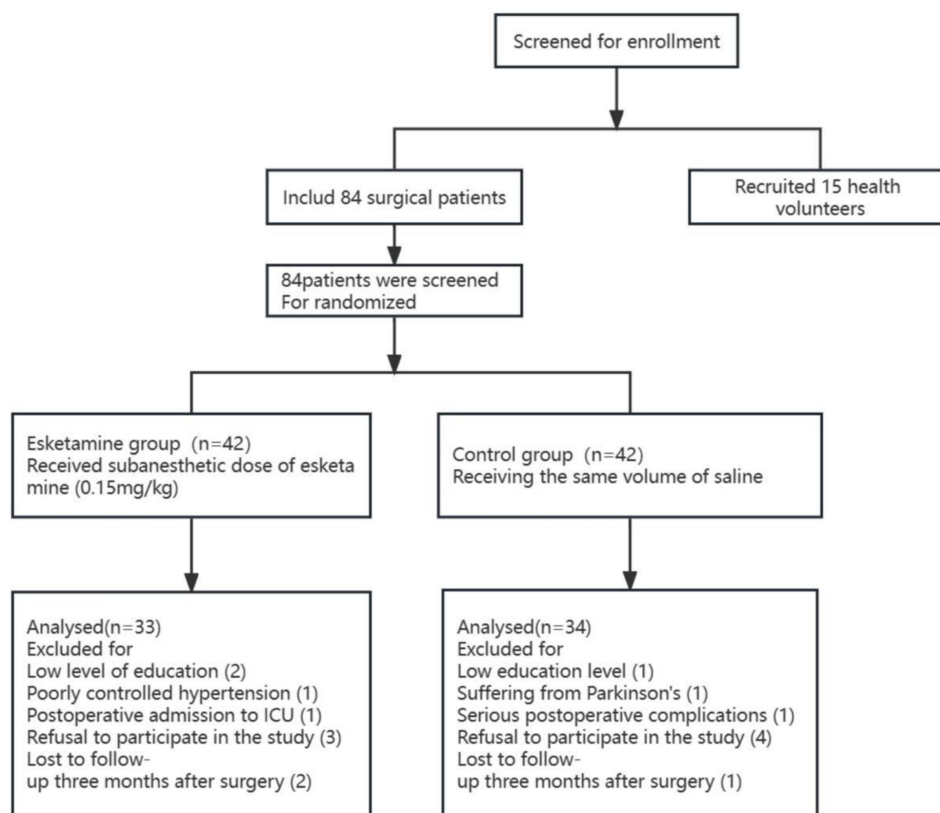
Figure 1 Enrollment flowchart.

group S (6.06%) and 5 patients in group C (14.71%) were diagnosed with POCD at 3 months after surgery. The incidence of dNCR at 7 days after surgery was lower in group S, compared with patients in group C (P<0.05); however, the incidence of POCD 3 months after surgery was similar in both groups (P>0.05) (Table 4).

Patient scores on the different tasks are presented in Table 5. Compared with Group S, patients in group C performed worse primarily in the delayed memory panel of the RAVLT memory test (P<0.05), the Grooved Pegboard Test (P<0.05), and the Finger Tapping Test (P<0.05) 7 days after surgery (Table 5).

Table 1 Baseline Characteristics of Surgical Patients and Volunteers

Variables	Surgical Patients (n=67)	Health Volunteers (n=15)	P value
Age [years, mean (SD)]	70.30(6.92)	72.00(4.64)	0.386
Male [sex, n(%)]	37(55.22)	7(46.67)	0.548
Height [cm, mean (SD)]	165.04(8.60)	164.40(6.33)	0.785
Weight [kg, mean (SD)]	63.62(9.73)	62.07(6.87)	0.560
Body mass index [kg/m^2, mean (SD)]	23.17(2.92)	22.92(1.66)	0.657
MMSE score [point, mean (SD)]	28.24(1.44)	27.87(1.06)	0.347
Smoking [n(%)]	18(26.87)	4(26.67)	1.000
Alcoholism [n(%)]	19(28.36)	5(33.33)	0.702
Education level> 9[n(%)]	17(25.37)	5(33.33)	0.529

Notes: Data are expressed as mean (SD), except for categorical data which are expressed as n(%).
Abbreviation: MMSE, mini-mental state examination.

Table 2 Demographic, Clinical, and Surgical Characteristics in Both Groups

Variables	Group S (n=33)	Group C (n=34)	P value
Age [years, mean (SD)]	70.60(7.63)	70.00(6.25)	0.723
Male [sex, n(%)]	18(54.55)	19(55.89)	0.912
Height [cm, mean (SD)]	164.91(9.05)	165.18(8.26)	0.900
Weight [kg, mean (SD)]	63.32(10.04)	63.91(9.56)	0.805
Body mass index [kg/m^2, mean (SD)]	23.13(3.42)	23.21(2.40)	0.907
MMSE score[point, mean (SD)]	28.58(1.15)	27.91(1.62)	0.058
Smoking [n(%)]	10(30.30)	8(23.53)	0.532
Alcoholism [n(%)]	9(27.27)	10(29.41)	0.846
Education level > 9 [years, n(%)]	7(21.21)	10(29.41)	0.484
Propofol [mg, mean (SD)]	1064.15(433.72)	1003.26(229.02)	0.473
Remifentanil [mg, mean (SD)]	0.82(0.32)	1.04(0.27)	0.003[a]
Anesthesia duration [min, mean (SD)]	201.97(70.92)	182.41(41.64)	0.172
Surgical duration [min, mean (SD)]	164.79(64.68)	151.21(38.55)	0.299
Recovery time [min, mean (SD)]	10.6(6.20)	8.63(4.08)	0.125
Extubation time [min, mean (SD)]	14.67(6.12)	12.44(3.83)	0.081
Postoperative nausea and vomiting [min, mean (SD)]	8(24.24)	12(35.29)	0.323
Rescue ketorolac dose [mg, mean (SD)]	12.73(16.82)	22.06(19.97)	0.043[a]
VAS score [point, mean (SD)]	2.12(0.74)	2.53(0.79)	0.032[a]

Notes: Data are expressed as mean (SD), except for categorical data which are expressed as n (%). [a]P<0.05, Student's *t*-test, Chi-squared test or Fisher's exact probability test.
Abbreviations: MMSE, mini-mental state examination; VAS, visual analogue scale.

Table 3 Neuropsychological Test Results

Test	7 Days After Surgery		3 Months After Surgery	
	Group S	Group C	Group S	Group C
Rey Auditory Verbal Learning (Immediate)	3	4	1	1
Rey Auditory Verbal Learning (Delayed)	8	13	3	5
Digit Symbol Subtest	3	4	1	2
Grooved Pegboard Test	9	15	4	4
Digit Span Subtests	3	2	1	2
Verbal Fluency Test	2	2	1	2
Finger-tapping Task	6	9	2	1
Trail Making Test	3	2	1	0
Block Test	1	1	0	1
PND	5	13	2	5

Abbreviation: PND, perioperative neurocognitive disorders.

Table 4 Incidence of PND in Both Groups

	Group S	Group C	P value
dNCR [n(%)]	5/33(18.15%)	13/34(38.24%)	P=0.033[a]
POCD [n(%)]	2/33(6.06%)	5/34(14.71%)	P=0.247

**Notes**: [a]P<0.05, Chi-squared test or Fisher's exact probability test.

Serum IL-6 and S100B Levels

The plasma levels of S-100β and IL-6 presented similar varying trends in both groups increasing significantly (Figures 2 and 3, P<0.05) at 1-day post-surgery compared to preoperative, and plasma levels at 1 day after surgery in the S group were dramatically lower than those of the C group (Figures 2 and 3, P<0.05).

Table 5 Performance in Neuropsychological Test

Test	Domain	Baseline, Mean (SD)			7 Days After Surgery, Mean (SD)			3 Months After Surgery, Mean (SD)		
		Group S	Group C	P value	Group S	Group C	P value	Group S	Group C	P value
Rey Auditory Verbal Learning (Score)	Immediate recall	36.75 (2.73)	36.82 (3.07)	0.926	34.33 (4.11)	33.47 (3.15)	0.338	34.15 (2.46)	34.12 (3.20)	0.962
Rey Auditory Verbal Learning (Score)	Delayed recall	7.03 (0.88)	6.91(0.83)	0.573	6.27(1.42)	5.26 (1.24)	0.003[a]	6.12 (1.32)	5.91(1.46)	0.541
Digit Symbol Subtest (Score)	Information processing speed and attention	18.42 (1.70)	18.76 (1.46)	0.381	16.97 (1.63)	16.85 (2.09)	0.800	17.55 (1.91)	17.15 (2.32)	0.446
Grooved Pegboard Test (Dominant hand, Time, s)	Flexibility and coordination	97.30 (10.44)	98.47 (8.70)	0.620	106.06 (11.94)	118.50 (9.96)	<0.001[a]	106.21 (9.89)	105.26 (9.07)	0.684
Digit Span Subtests (forward and backward, Total score)	Attention, concentration and immediate memory	9.18 (1.10)	9.00(1.23)	0.527	7.67(1.45)	7.18 (1.29)	0.148	7.85 (1.87)	7.76(1.28)	0.831
Verbal Fluency Test (score)	Flow of thought organization and ideation	36.79 (2.26)	37.53 (2.86)	0.245	35.61 (1.64)	36.21 (2.20)	0.211	35.39 (3.08)	35.03 (3.37)	0.646
Finger-tapping Task (Score)	Fine motor skills	44.79 (3.09)	43.97 (3.09)	0.283	43.21 (2.80)	41.71 (3.22)	0.046[a]	42.48 (3.42)	41.24 (2.36)	0.086
Trail Making Test A (Time, s)	Attention and psychomotor speed	56.48 (9.80)	56.18 (8.84)	0.893	65.39 (9.49)	63.09 (11.08)	0.364	60.39 (9.51)	59.76 (11.00)	0.803
Block Test (Score)	Visual Analysis and Spatial Recognition	5.39 (0.19)	5.24(0.85)	0.433	4.48(0.76)	4.32 (1.15)	0.500	5.21 (0.89)	4.91(1.08)	0.221

Notes: The standard deviation of each test is calculated from all scores of pre-operative, post-operative and healthy volunteers. [a]$P<0.05$, Student's *t*-test.

IL-6
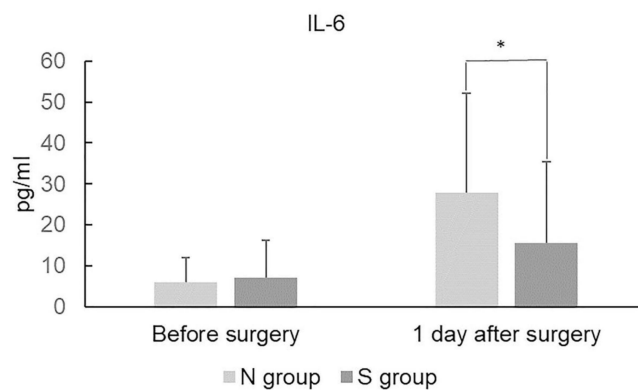
Figure 2 Plasma IL-6 concentrations (pg/mL) at different time points.*P<0.05.
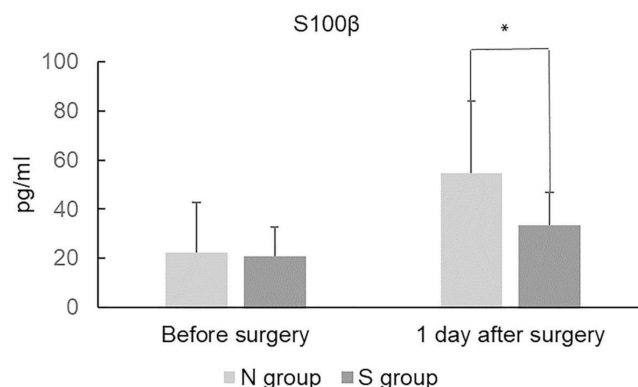
S100β

Figure 3 Plasma S100β concentrations (pg/mL) at different time points. *P<0.05.

Discussion

A systematic review and meta-analysis including six RCTs have suggested that ketamine intraoperative administration may offer some protection towards POCD; however, the grade quality of evidence was very low.[38] The effect of ketamine on postoperative cognitive function remains controversial,[39,40] confusing the research on esketamine. In the present study, we found that the esketamine group performed better than the control group on the delayed memory panel of the RAVLT memory test, grooved pegboard test, and finger tapping test at 7 days postoperatively. The observed results indicated that a single dose of 0.15mg/kg esketamine could reduce the incidence of dNCR 7 days following surgery and improve early postoperative cognitive function in elderly patients undergoing gastrointestinal surgery but without any impact on long-term neuro-cognitive prognosis. Our result was consistent with the study by Tu et al[41] and highlighted the neuroprotective property of esketamine.

To date, there is no defined dose range of sub-anesthetic dose esketamine available. It has been documented that the sub-anesthetic dose of ketamine is in the range between 0.3 and 0.5mg/kg.[42] As esketamine has twofold higher potency compared with racemic ketamine,[19] it is generally accepted that the range of sub-anesthetic dose of esketamine is 0.15–0.25 mg/kg. A sub-anesthetic dose of 0.2mg/kg esketamine was applied in a majority of research.[43] However, it has also been reported that patients exhibited post-operative mental symptoms even at a sub-anesthetic dose of 0.25mg/kg esketamine.[44] Considering subjects of this study were elderly who underwent gastrointestinal surgeries, we selected the smaller dose of 0.15mg/kg of esketamine.

A previous study[39] compared the effect of esketamine to remifentanil on the neurocognitive outcome after open-heart surgery in 106 patients has concluded that esketamine offers no greater neuroprotection. Considering the anti-inflammatory[45] and neuroprotective[46] effects of remifentanil used in the control group, we do not think the neuro-protective effect of esketamine could be ignored.

Our study also found that the plasma level of IL-6 and S100β protein in group S was significantly lower than that in group C, confirming the anti-inflammatory and neuroprotective properties of esketamine. IL-6 increases after surgery and is positively correlated with the severity of surgical trauma, thereby regarded as an inflammatory biomarker presenting surgery-related injury.[47] S100β is a class of calcium-binding proteins found mainly in central glial cells such as astrocytes and microglia. When central neurons and the BBB are damaged, S100β release and increase its level in the peripheral blood.[48] Therefore, an increase in peripheral S100β is considered a specific marker of brain injury.[49] We speculated that esketamine administration might inhibit the release of surgery-induced peripheral inflammatory cytokines and then suppress neuro-inflammation in CNS and neuronal apoptosis. Esketamine has been demonstrated to be effective in suppressing neuro-inflammation in rodent models,[50,51] which supported our perspective to some extent.

Early-stage research in cardiac surgery under extracorporeal circulation has shown that the administration of a single IV low dose of ketamine (0.25 mg/kg) at induction of anesthesia steadily reduced the production of IL-6 until the seventh postoperative day, a long time after ketamine has disappeared from patients' blood.[52] Likewise, we proposed that esketamine might also have a similar mode of action; thus, a single dose of esketamine could improve cognitive decline 7 days after surgery but not 3 months post-operatively.

Aside from the neuroprotective activity mentioned above, this study presented the advantage of sub-anesthetic doses of esketamine as an adjuvant of general anesthesia. Esketamine exerted less opioid consumption and relatively mild adverse responses. We did not find a delayed recovery time in group S, which seemed inconsistent with the study by Zhang et al[24] 0.2mg/kg esketamine used in their study, higher than 0.15 mg/kg in the present study, might explain the difference in recovery following surgery.

This study has some limitations. First, the relatively small number of patients we recruited provides evidence for the effect of esketamine on reducing the incidence of PND in patients undergoing gastrointestinal surgery, but further studies would require some multicenter, large-sample clinical trials to validate it. Second, we only examined the changes in serum inflammatory factor levels in patients 1 day before and after surgery and did not examine their long-term postoperative levels, which is not sufficient to reflect the dynamic changes in serum inflammatory factors. Finally, the concentration of S100β and IL-6 in the cerebrospinal fluid may be more appropriate for assessing central neuro-inflammation. However, ethical issues limit the collection of cerebrospinal fluid in the current study.

Conclusions

In summary, the administration of subanesthetic doses of esketamine before the initiation of surgery could attenuate early postoperative cognitive impairment. The underlying mechanism might be related to the anti-neuro-inflammatory and neuroprotective effects of esketamine.

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). The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors on reasonable requests.

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; have 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 authors declare that they have no competing interests in this work.

References

1. Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, Van Leeuwen BL. Thinking through postoperative cognitive dysfunction: how to bridge the gap between clinical and pre-clinical perspectives. *Brain Behav Immun*. 2012;26(7):1169–1179. doi:10.1016/j.bbi.2012.06.004

2. Evered L, Silbert B, Knopman DS, et al. Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Anesthesiology*. 2018;129(5):872–879. doi:10.1097/ALN.0000000000002334

3. Fan W, Mai L, Zhu X, Huang F, He H. The role of microglia in perioperative neurocognitive disorders. *Front Cell Neurosci*. 2020;14:261. doi:10.3389/fncel.2020.00261

4. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. *Lancet*. 1998;351(9106):857–861. doi:10.1016/s0140-6736(97)07382-0

5. Lin X, Chen Y, Zhang P, Chen G, Zhou Y, Yu X. The potential mechanism of postoperative cognitive dysfunction in older people. *Exp Gerontol*. 2020;130:110791. doi:10.1016/j.exger.2019.110791

6. Subramaniyan S, Terrando N. Neuroinflammation and perioperative neurocognitive disorders. *Anesth Analg*. 2019;128(4):781–788. doi:10.1213/ANE.0000000000004053

7. Vacas S, Degos V, Feng X, Maze M. The neuroinflammatory response of postoperative cognitive decline. *Br Med Bull*. 2013;106(1):161–178. doi:10.1093/bmb/ldt006

8. Alam A, Hana Z, Jin Z, Suen KC, Ma D. Surgery, neuroinflammation and cognitive impairment. *EBioMedicine*. 2018;37:547–556. doi:10.1016/j.ebiom.2018.10.021

9. Safavynia SA, Goldstein PA. The role of neuroinflammation in postoperative cognitive dysfunction: moving from hypothesis to treatment. *Front Psychiatry*. 2019;9:752. doi:10.3389/fpsyt.2018.00752

10. Ghojazadeh M, Sanaie S, Paknezhad SP, Faghih SS, Soleimanpour H. Using ketamine and propofol for procedural sedation of adults in the emergency department: a systematic review and meta-analysis. *Adv Pharm Bull*. 2019;9(1):5–11. doi:10.15171/apb.2019.002

11. Pouraghaei M, Moharamzadeh P, Paknezhad SP, Rajabpour ZV, Soleimanpour H. Intranasal ketamine versus intravenous morphine for pain management in patients with renal colic: a double-blind, randomized, controlled trial. *World J Urol*. 2021;39(4):1263–1267. doi:10.1007/s00345-020-03319-4

12. Rueda Carrillo L, Garcia KA, Yalcin N, Shah M. Ketamine and its emergence in the field of neurology. *Cureus*. 2022;14(7):e27389. doi:10.7759/cureus.27389

13. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg*. 2012;115(4):934–943. doi:10.1213/ANE.0b013e3182662e30

14. Hudetz JA, Iqbal Z, Gandhi SD, et al. Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. *Acta Anaesthesiol Scand*. 2009;53(7):864–872. doi:10.1111/j.1399-6576.2009.01978.x

15. Bahji A, Vazquez GH, Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *J Affect Disord*. 2021;278:542–555. doi:10.1016/j.jad.2020.09.071

16. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*. 2018;75(2):139–148. doi:10.1001/jamapsychiatry.2017.3739

17. Hudgens S, Floden L, Blackowicz M, et al. Meaningful change in depression symptoms assessed with the Patient Health Questionnaire (PHQ-9) and Montgomery-Åsberg Depression Rating Scale (MADRS) among patients with treatment resistant depression in two, randomized, double-blind, active-controlled trials of esketamine nasal spray combined with a new oral antidepressant. *J Affect Disord*. 2021;281:767–775. doi:10.1016/j.jad.2020.11.066

18. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;178(5):383–399. doi:10.1176/appi.ajp.2020.20081251

19. Wang J, Huang J, Yang S, et al. Pharmacokinetics and safety of esketamine in Chinese patients undergoing painless gastroscopy in comparison with ketamine: a randomized, open-label clinical study. *Drug Des Devel Ther*. 2019;13:4135–4144. doi:10.2147/DDDT.S224553

20. Yang H, Zhao Q, Chen HY, et al. The median effective concentration of propofol with different doses of esketamine during gastrointestinal endoscopy in elderly patients: a randomized controlled trial. *Br J Clin Pharmacol*. 2022;88(3):1279–1287. doi:10.1111/bcp.15072

21. Chen J, Zou X, Hu B, et al. Effect of different doses of esketamine compared with fentanyl combined with propofol on hypotension in patients undergoing painless abortion surgery: a prospective, randomized, double-blind controlled clinical trial. *BMC Anesthesiol*. 2022;22(1):305. doi:10.1186/s12871-022-01848-6

22. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth*. 2021;68:110071. doi:10.1016/j.jclinane.2020.110071

23. Li J, Wang Z, Wang A, Wang Z. Clinical effects of low-dose esketamine for anaesthesia induction in the elderly: a randomized controlled trial. *J Clin Pharm Ther*. 2022;47(6):759–766. doi:10.1111/jcpt.13604

24. Zhang C, He J, Shi Q, Bao F, Xu J. Subanaesthetic dose of esketamine during induction delays anaesthesia recovery a randomized, double-blind clinical trial. *BMC Anesthesiol*. 2022;22(1):138. doi:10.1186/s12871-022-01662-0

25. Rossi A, Burkhart C, Dell-Kuster S, et al. Serum anticholinergic activity and postoperative cognitive dysfunction in elderly patients. *Anesth Analg*. 2014;119(4):947–955. doi:10.1213/ANE.0000000000000390

26. Holmgaard F, Vedel AG, Rasmussen LS, Paulson OB, Nilsson JC, Ravn HB. The association between postoperative cognitive dysfunction and cerebral oximetry during cardiac surgery: a secondary analysis of a randomised trial. *Br J Anaesth*. 2019;123(2):196–205. doi:10.1016/j.bja.2019.03.045

27. Han Y, Han L, Dong MM, et al. Preoperative salivary cortisol AM/PM ratio predicts early postoperative cognitive dysfunction after noncardiac surgery in elderly patients. *Anesth Analg*. 2019;128(2):349–357. doi:10.1213/ANE.0000000000003740

28. Liu T, Yin C, Li Y, et al. Effects of transcutaneous electrical acupoint stimulation on postoperative cognitive decline in elderly patients: a pilot study. *Clin Interv Aging*. 2021;16:757–765. doi:10.2147/CIA.S309082

29. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol*. 1991;59(1):12–19. doi:10.1037//0022-006x.59.1.12

30. McCarrey AC, Pacheco J, Carlson OD, et al. Interleukin-6 is linked to longitudinal rates of cortical thinning in aging. *Transl Neurosci*. 2014;5 (1):1–7. doi:10.2478/s13380-014-0203-0

31. Borchers F, Spies CD, Feinkohl I, et al. Methodology of measuring postoperative cognitive dysfunction: a systematic review. *Br J Anaesth*. 2021;126(6):1119–1127. doi:10.1016/j.bja.2021.01.035

32. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT; ISPOCD group. The international study of postoperative cognitive dysfunction. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand*. 2001;45(3):275–289. doi:10.1034/j.1399-6576.2001.045003275.x

33. Buvanendran A, Kroin JS, Berger RA, et al. Upregulation of prostaglandin E2 and interleukins in the central nervous system and peripheral tissue during and after surgery in humans. *Anesthesiology*. 2006;104(3):403–410. doi:10.1097/00000542-200603000-00005

34. Hirsch J, Vacas S, Terrando N, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J Neuroinflammation*. 2016;13(1):211. doi:10.1186/s12974-016-0681-9

35. Peng L, Xu L, Ouyang W. Role of peripheral inflammatory markers in postoperative cognitive dysfunction (POCD): a meta-analysis. *PLoS One*. 2013;8(11):e79624. doi:10.1371/journal.pone.0079624

36. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): a meta-analysis of observational studies. *PLoS One*. 2018;13(4):e0195659. doi:10.1371/journal.pone.0195659

37. Xi L, Fang F, Yuan H, Wang D. Transcutaneous electrical acupoint stimulation for postoperative cognitive dysfunction in geriatric patients with gastrointestinal tumor: a randomized controlled trial. *Trials*. 2021;22(1):563. doi:10.1186/s13063-021-05534-9

38. Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: a systematic review and meta-analysis. *Acta Anaesthesiol Scand*. 2018;62(9):1182–1193. doi:10.1111/aas.13168

39. Nagels W, Demeyere R, Van Hemelrijck J, Vandenbussche E, Gijbels K, Vandermeersch E. Evaluation of the neuroprotective effects of S (+)-ketamine during open-heart surgery. *Anesth Analg*. 2004;98(6):1595–1603. doi:10.1213/01.ANE.0000117227.00820.0C

40. Bateman RM, Sharpe MD, Jagger JE. 36th international symposium on intensive care and emergency medicine: Brussels, Belgium. 15–18 March 2016. *Crit Care*. 2016;20(Suppl 2):94. doi:10.1186/s13054-016-1208-6

41. Tu W, Yuan H, Zhang S, et al. Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients. *Am J Transl Res*. 2021;13(3):1701–1709.

42. Lahti AC, Koffel B, LaPorte D, Tamminga CA. Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. *Neuropsychopharmacology*. 1995;13(1):9–19. doi:10.1016/0893-133X(94)00131-I

43. Zhan Y, Liang S, Yang Z, 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 Gastroenterol*. 2022;22(1):391. doi:10.1186/s12876-022-02467-8

44. Yuan JJ, Chen SH, Xie YL, et al. Effects of subanesthetic dose of esketamine on opioid consumption after thoracoscopic surgery. *Zhonghua Yi Xue Za Zhi*. 2022;102(15):1108–1113. doi:10.3760/cma.j.cn112137-20211116-02559

45. Kim CH, Jeong SS, Park SJ, Choi EJ, Kim YH, Ahn JH. Anti-inflammatory effect of remifentanil in lipopolysaccharide-stimulated amniotic epithelial cells. *J Dent Anesth Pain Med*. 2019;19(5):253–260. doi:10.17245/jdapm.2019.19.5.253

46. Jeong S, Kim SJ, Jeong C, et al. Neuroprotective effects of remifentanil against transient focal cerebral ischemia in rats. *J Neurosurg Anesthesiol*. 2012;24(1):51–57. doi:10.1097/ANA.0b013e3182368d70

47. Tang JX, Baranov D, Hammond M, Shaw LM, Eckenhoff MF, Eckenhoff RG. Human Alzheimer and inflammation biomarkers after anesthesia and surgery. *Anesthesiology*. 2011;115(4):727–732. doi:10.1097/ALN.0b013e31822e9306

48. Linstedt U, Meyer O, Kropp P, Berkau A, Tapp E, Zenz M. Serum concentration of S-100 protein in assessment of cognitive dysfunction after general anesthesia in different types of surgery. *Acta Anaesthesiol Scand*. 2002;46(4):384–389. doi:10.1034/j.1399-6576.2002.460409.x

49. Michetti F, Corvino V, Geloso MC, et al. S100B protein in biological fluids: more than a lifelong biomarker of brain distress. *J Neurochem*. 2012;120(5):644–659. doi:10.1111/j.1471-4159.2011.07612.x

50. Wang T, Weng H, Zhou H, et al. Esketamine alleviates postoperative depression-like behavior through anti-inflammatory actions in mouse prefrontal cortex. *J Affect Disord*. 2022;307:97–107. doi:10.1016/j.jad.2022.03.072

51. Zhang J, Ma L, Wan X, Shan J, Qu Y, Hashimoto K. (R)-Ketamine attenuates LPS-induced endotoxin-derived delirium through inhibition of neuroinflammation. *Psychopharmacology*. 2021;238(10):2743–2753. doi:10.1007/s00213-021-05889-6

52. Roytblat L, Talmor D, Rachinsky M, et al. Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. *Anesth Analg*. 1998;87 (2):266–271. doi:10.1097/00000539-199808000-00006