Heliyon 10 (2024) e27593

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Effect of subanesthetic dose of esketamine on postoperative pain in elderly patients undergoing laparoscopic gastrointestinal tumor Surgery:A prospective, double-blind, randomized controlled trial

Zhaojun Jing, Yu Han, Yi Li, Rui Zeng, Jin Wu, Yiting Wang, Peng Jiang *

Department of Anesthesiology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China

ARTICLE INFO

Keywords:
Esketamine
Pain
Analgesia
Elderly
Delirium

ABSTRACT

Purpose: Postoperative pain is prevalent and severe complication in elderly surgical patients. Multiple studies propose that a small dose of esketamine administered intraoperatively can alleviate postoperative pain and curtail opioid usage. We aimed to evaluate the impact of esketamine on postoperative acute pain among elderly patients with gastrointestinal tumors.

Patients and methods: This is a prospective, parallel-group, randomized controlled trial. Ninety patients aged 60 and above, undergoing resection of gastrointestinal tumors, were randomly assigned to two groups: esketamine group (Group S, a single dose of 0.25 mg/kg and 0.1 mg/kg/h infusion) and control group (Group C, saline). Visual Analogue Scale (VAS) pain scores were the primary outcome. Remifentanil consumption, instances of rescue analgesia, delirium, sleep quality, postoperative recovery quality, serum levels of inflammatory cytokines, and adverse events within 72 h post-surgery were secondary outcomes, respectively.

Results: Data of 87 of 99 eligible patients were analyzed. VAS scores at rest in Group S were lower than those in Group C at 6 h [1.2 (0.6, 1.6) vs 1.6 (1.0, 2.0), $P = 0.003$], 12 h [1.4 (1.0, 2.0) vs 2.0 (1.5, 2.0), $P < 0.001$], and 24 h [1.8 (1.3, 2.0) vs 2.2 (1.6, 2.6), $P < 0.001$] postoperatively. At 6 h post-surgery, VAS score during coughing was lower in Group S than Group C [2.0 (2.0, 2.3) vs 2.0 (2.0, 3.0), $P = 0.009$]. The instances of rescue analgesia were fewer in group S compared to group C ($P = 0.007$). Furthermore, the esketamine group showed improved sleep quality and QoR-15 score ($P < 0.05$) postoperatively.

Conclusion: Intravenous administration of esketamine as an adjunct to general anesthesia can decrease the intensity of pain for 24 h without additional adverse effects after laparoscopic gastrointestinal tumor surgery.

1. Introduction

Gastrointestinal tumors are notably prevalent among the elderly population [1]. The primary approach for addressing early-stage gastrointestinal tumors is surgical resection. However, poor postoperative pain management is frequently encountered and is of significant concern.

The intricate interplay of multiple drugs, diseases, and age-associated pharmacokinetic and pharmacodynamic modifications,

* Corresponding author. Department of Anesthesiology, Affiliated Hospital of Jiangsu University, 438 Jie Fang Road, Zhenjiang, Jiangsu, 212001, China.

E-mail address: doctorjp@163.com (P. Jiang).

https://doi.org/10.1016/j.heliyon.2024.e27593
Received 30 January 2024; Received in revised form 2 March 2024; Accepted 4 March 2024
Available online 5 March 2024

coupled with the decline in physiological function, complicates pain management for elderly patients [2]. Disturbingly, the rate of inadequate control over acute postoperative pain in the elderly can be as substantial as 50%–75% [3]. The incidence of postoperative delirium (POD) among elderly individuals undergoing gastrointestinal surgery has been documented to reach 8%–54% [4]. This susceptibility is potentially linked to pain, opioid-based analgesia, and inflammatory response to injuries [5]. Furthermore, apart from its correlation with POD, unaddressed postoperative acute pain hampers early mobility, retards functional recuperation, elongates hospitalization, inflates medical costs, and may even culminate in chronic pain [6]. Given these implications, effective perioperative pain management has emerged as a pivotal concern for both anesthesiologists and surgeons.

Given the escalating numbers of elderly patients undergoing surgery and the expanding adoption of enhanced recovery after surgery (ERAS) principles, the adoption of multimodal analgesia for perioperative pain management in elderly patients has become indispensable. The N-methyl-D-aspartate (NMDA) receptor blocker, ketamine, is an intravenous general anesthetic that exerts analgesic effects, constituting a vital element of multimodal analgesia [7]. The current ketamine used clinically is a racemic mixture of two optical isomers, levo-ketamine (R-ketamine) and right-ketamine (S-ketamine). S-ketamine, also known as esketamine, demonstrates heightened affinity for NMDA receptors and boasts doubly robust sedative and analgesic attributes compared to ketamine [8–10]. We posit that esketamine could ameliorate acute postoperative pain, mitigate intraoperative opioid consumption, and potentially diminish the incidence of postoperative delirium. Thus, this study endeavors to assess the effectiveness and safety of intravenous esketamine to improve postoperative pain among elderly patients with gastric colorectal tumors.

2. Materials and methods

2.1. Ethics approval and study design

This study received ethical approval from the Medical Ethics Committee of the Affiliated Hospital of Jiangsu University (KY2022H0507-10) and was registered in the Chinese Clinical Trials Registry (NO.ChiCTR2200061276).

The trial followed a prospective, randomized double-blind controlled design and was conducted within the Department of Anesthesia at the Affiliated Hospital of Jiangsu University from June 20, 2022 to June 30, 2023. The trial adheres to the guidelines outlined in the Consolidated Standards of Reporting Trials (CONSORT) checklist.

2.2. Participants

Written informed consent was obtained from all participants involved in the trial.

Inclusion Criteria: Age $\geq$ 60 years; American Society of Anesthesiologists (ASA) grades I–III; Body mass index (BMI) within the range of 18.0–30.0 kg/m^2; Undergoing laparoscopic gastrointestinal tumor surgery (e.g., Gastric and colorectal tumor resection) under general anesthesia; Consent to postoperative patient-controlled intravenous analgesia (PCIA); Competent to provide informed consent.

Exclusion Criteria: A history of preoperative opioid or alcohol abuse; History of chronic pain; Individuals with cognitive impairment, as assessed through the Mini-Mental State Examination (MMSE) (illiteracy $<$17, primary school level $<$20, junior high school or above $<$24); Presence of neurological disorders; Severe cardiopulmonary, liver, and kidney dysfunction; Severe visual impairment; Patients with elevated intraocular pressure or heightened intracranial pressure; Untreated or inadequately treated hyperthyroidism; Lack of cooperation or communication skills; Allergic reaction to any drug utilized in the study.

2.3. Randomization and blinding

A computer-generated randomization sequence was employed to allocate participants to two groups at a 1:1 ratio. The allocation of groups and study numbers was concealed within sealed opaque envelopes, handled by an anesthesia nurse who was not involved in the study. This nurse prepared the experimental drugs based on the randomization sequence prior to anesthesia induction, delivering them to the anesthesiologist overseeing perioperative anesthesia management. The study drugs were diluted with 0.9% NaCl using a 50-ml syringe. In the Esketamine group, the syringe contained 1 mg/ml of esketamine, while in the Control group, it contained 50 ml of normal saline. An anesthesiologist administered a bolus dose from the 50-ml syringe after anesthesia induction and prior to incision. Subsequently, the remaining drug within the 50-ml syringe was employed for intraoperative infusion. Throughout this process, the participants, anesthetists, surgeons, and outcome-assessing nurses remained unaware of the group assignments.

2.4. Interventions

Following the induction of anesthesia and prior to the incision of surgery, a dose of 0.25 mg/kg of esketamine or an equivalent volume of normal saline was administered. This was followed by a continuous intravenous infusion of 0.1 mg/kg/h, continuing until 30 min before the conclusion of the surgical procedure. All patients were preoperatively educated on the utilization of the patient-controlled analgesia (PCA) device and the 10-step visual analog scale (VAS), which rates pain from 0 (no pain) to 10 (most intense imaginable pain).

2.5. Anesthesia procedure

After entering the operating room, patients underwent standard monitoring, encompassing non-invasive and invasive arterial

blood pressure, pulse oxygen saturation, electrocardiogram, and bispectral index. A bilateral transversus abdominis plane block (TAPB) was performed using 20 ml of 0.375% ropivacaine for two groups of participants. Before anesthesia, dexamethasone (8 mg), penehyclidine hydrochloride (0.4 mg) were administered.

Anesthesia was induced with 0.04 mg/kg midazolam, 1.5 mg/kg propofol, 0.5 μg/kg sufentanil and 0.9 mg/kg rocuronium. All patients in both groups underwent total intravenous anesthesia. General anesthesia was maintained with propofol and remifentanil. The target controlled infusion rate of propofol was adjusted to maintain the bispectral index within the range of 40–60. The infusion rate of remifentanil (0.05–0.25 μg/kg/min) was adjusted by the attending anesthesiologist in response to changes in surgical stimulation intensity and patient's vital sign parameters. The goal was to sustain heart rate and blood pressure fluctuations within 20% of their baseline values. Neuromuscular blockade was maintained through periodic rocuronium injections as necessary. To prevent postoperative nausea and vomiting, 0.075 mg of palonosetron was administered to all patients. All anesthetics were ceased at the end of surgery. Patients were transferred to the postanesthesia care unit (PACU) with the patient-controlled intravenous analgesia pump in place and running until the third postoperative day.

2.6. Postoperative management

In the PACU, standard monitoring of patient vital signs was upheld. The anesthesia nurse assessed the patient's consciousness every 5 min by either calling the patient's name or tapping slightly the patient's shoulder. Tracheal extubation occurred when the patient demonstrated full wakefulness and met the criteria for extubation. The time from discontinuation of anesthetic drugs to removal of the tracheal tube was recorded. Discharge from the PACU to the ward was determined based on Aldrete score criteria (score ≥ 9), length of PACU stay was defined as the time from entry to meeting the criteria.

The postoperative analgesia protocol included patient-controlled intravenous analgesia and rescue analgesia. The PCIA pump was set up with hydromorphone 0.15 mg/kg and normal saline to 150 ml. The initial dose of PCIA pump was set at 2 ml, with a background infusion rate of 2 ml/h, a PCIA dose of 0.5 ml, and a locking time of 15 min. If VAS score exceeded 3 points or if adequate analgesia was not achieved after three PCIA button presses, an additional intravenous injection of 40 mg parecoxib sodium was administered as rescue analgesia.

2.7. Outcome assessment

The primary outcome measures included VAS pain scores at rest and during coughing, assessed at the PACU and at specific postoperative intervals: 6 h, 12 h, 24 h, 48 h, and 72 h.

Secondary Outcomes: (1) Remifentanil consumption. (2) Number of times the patient pressed the PCIA device and instances of rescue analgesia. (3) Delirium assessment utilizing the Confusion Assessment Method (CAM) [11] performed twice daily from the first to the third postoperative day, with at least a 6-h interval between assessments. Patients were also assessed on the day of surgery at least 2 h after surgery end time. (4) Sleep quality evaluated using the Athens Insomnia Scale [12] (AIS) during the first to third postoperative days. (5) Quality of Recovery (QoR)-15 score [13] measured at 48 h postoperatively. (6) Serum levels of inflammatory cytokines interleukin-6 (IL-6) and interleukin-1β (IL-1β) were assessed through venous blood samples collected preoperatively and 1 day, 3 days after surgery. (7) Recorded parameters encompassed operating time, extubation time, PACU duration, and adverse events within 72 h postoperatively.

2.8. Sample size calculation

The sample size was determined based on previous published studies. A meta-analysis [14] indicated that intravenous esketamine significantly decreased pain within a 24-h timeframe. A study showed that perioperative administration of esketamine was associated with a 0.8 reduction in pain scores, therefore, we hypothesized a 0.8-point reduction in the resting VAS score at 24 h in comparison to the control group [15]. The sample size was calculated using PASS 15 software, with a 1:1 parallel control design, two-sided test, $\alpha = 0.05$, and accounting for a 15% dropout rate, a total of 90 patients (45 per group) were recruited to provide 80% power to detect the difference.

2.9. Statistical analysis

Statistical analyses were performed utilizing SPSS 22.0 software. The distribution of data was assessed through the Shapiro-Wilk test. Data were summarized as mean (standard deviation [SD]), median (interquartile range [IQR]), or number (%). For normally distributed data, two-independent samples *t*-test or repeated measures variance analysis were used. For non-normally distributed data, Mann-Whitney *U* test or generalized estimation equation were applied. Categorical data were analyzed using X^2 test or Fisher's exact test. A significance level of $P < 0.05$ was deemed statistically significant.

3. Results

A total of 99 patients were initially screened for eligibility between June 20, 2022 to June 30, 2023. Among them, 6 were excluded due to not meeting inclusion criteria, and 3 declined to participate. The remaining 90 patients were randomly assigned to two groups. Ultimately, 87 participants completed the study, with 1 patient from the S group and 1 patient from the C group excluded due to

surgery conversion to laparotomy, and 1 patient from the C group was removed due to severe postoperative hypotension and clamp analgesia pump. Hence, the final analysis included 87 patients, with 44 in the esketamine group and 43 in the control group (Fig. 1).

3.1. Clinical baseline characteristics

The ASA grade, age, sex, BMI, type of surgery, and MMSE score demonstrated balance between the two groups. The operation duration, extubation time, and PACU stay time showed no significant differences between the two groups ($p > 0.05$). These results are summarized in Table 1.

3.2. Postoperative pain

Comparing group C, group S exhibited reduced VAS scores at rest at 6 h, 12 h, and 24 h postoperatively ($P < 0.05$). No statistically significant differences were detected at PACU and 48 h, 72 h postoperatively. Additionally, VAS scores during coughing at 6 h postoperatively were lower in group S compared to group C ($P < 0.05$). No significant differences in VAS scores during coughing were observed at other time points (Table 2). The instances of PCIA device pressing and rescue analgesia were fewer in group S compared to group C ($P < 0.05$, Table 3). Intraoperative remifentanil consumption did not significantly differ between the two groups (1.00 [0.80, 1.45] vs 1.36 [0.89, 1.8], $P = 0.064$, Table 1).

3.3. Postoperative delirium

Within 3 days postoperatively, 1 patient in the S-ketamine group and 5 patients in the Control group developed delirium. The incidence of delirium over postoperative days 1–3 was 2.27% in group S and 11.63% in group C, with no significant difference ($P = 0.194$). These results are outlined in Table 3.

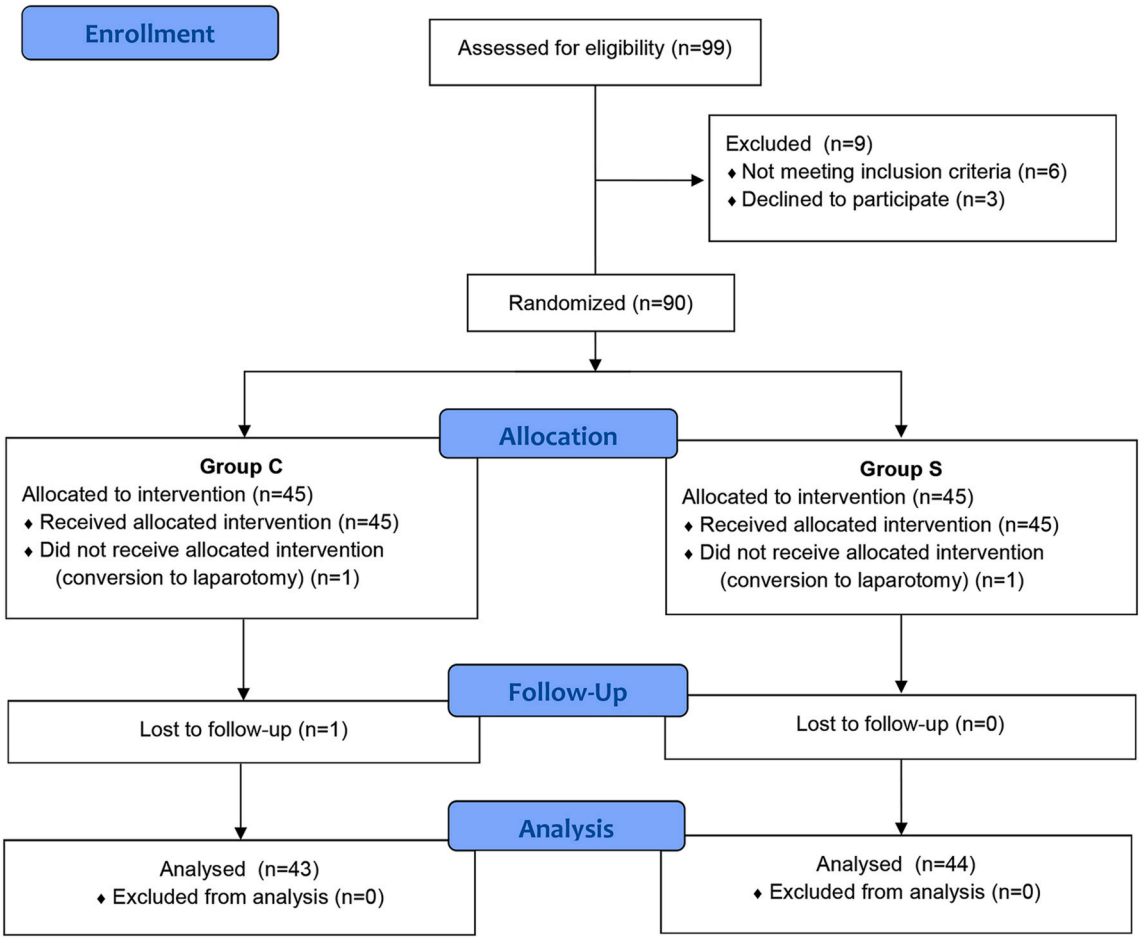

Fig. 1. Patients enrollment diagram.

Table 1
Baseline patient characteristics and perioperative data for all patient, data are summarized by number (%), median (interquartile range) or mean (standard deviation).

	Esketamine group (44)	Control group (43)	*p*-Value
Age (years)	69.20 ± 6.22	71.47 ± 6.18	0.093
Sex (male)	30 (68.2%)	26 (60.5%)	0.452
BMI (kg/m^2)	23.02 ± 2.19	23.54 ± 2.58	0.316
ASA score			
II	35 (79.5%)	34 (79.1%)	0.956
III	9 (20.5%)	9 (20.9%)	
MMSE score	26 (25, 27)	26 (25, 27)	0.653
Surgical procedure			
Laparoscopic radical gastrectomy	21 (47.7%)	20 (46.5%)	0.946
Laparoscopic radical colectomy	16 (36.4%)	15 (34.9%)	
Laparoscopic radical rectectomy	7 (15.9%)	8 (18.6%)	
Operation duration (min)	182.5 (152, 211.5)	200 (170, 227.5)	0.165
Extubation time (min)	34.41 ± 18.84	31.14 ± 19.93	0.434
PACU stay time (min)	64.18 ± 24.05	59.40 ± 21.75	0.333
Remifentanil consumptiom (mg)	1.00 (0.80, 1.45)	1.36 (0.89, 1.8)	0.064

Table 2
Visual analog scale pain scores at rest and during coughing in patients postoperatively.

Time		Esketamine group	Control group	*p*-Value
T1	Rest	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	0.918
	Cough	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.771
T2	Rest	1.2 (0.6, 1.6)[a]	1.6 (1.0, 2.0)	0.003
	Cough	2.0 (2.0, 2.3)[a]	2.0 (2.0, 3.0)	0.009
T3	Rest	1.4 (1.0, 2.0)[a]	2.0 (1.5, 2.0)	0.000
	Cough	3.0 (2.0, 3.0)	3.0 (2.6, 3.0)	0.089
T4	Rest	1.8 (1.3, 2.0)[a]	2.2 (1.6, 2.6)	0.000
	Cough	3.0 (2.5, 3.5)	3.2 (3.0, 4.0)	0.119
T5	Rest	1.1 (1.0, 1.8)	1.0 (1.0, 1.8)	0.849
	Cough	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	0.247
T6	Rest	0.5 (0.0, 1.0)	0.5 (0.0, 1.0)	0.869
	Cough	2.0 (1.2, 2.0)	2.0 (1.0, 2.0)	0.246

NOTE. Data are presented as median (interquartile range); [a]Compared with Control group, $P < 0.05$; T1: when exiting from PACU; T2: 6 h postoperatively; T3: 12 h postoperatively; T4: 24 h postoperatively; T5: 48 h postoperatively; T6: 72 h postoperatively.

Table 3
Secondary outcomes during the study period.

Secondary Outcomes	Esketamine group	Control group	*p*-Value
Incidence of delirium	1 (2.27%)	5 (11.63%)	0.194
Times of PCIA device pressing	2 (1, 5.75)[a]	4 (1, 9)	0.049
Times of rescue analgesia	0 (0, 0)[a]	0 (0, 1)	0.007

NOTE. Data are presented as median (interquartile range) or number (percentage); [a]Compared with Control group, $P < 0.05$.

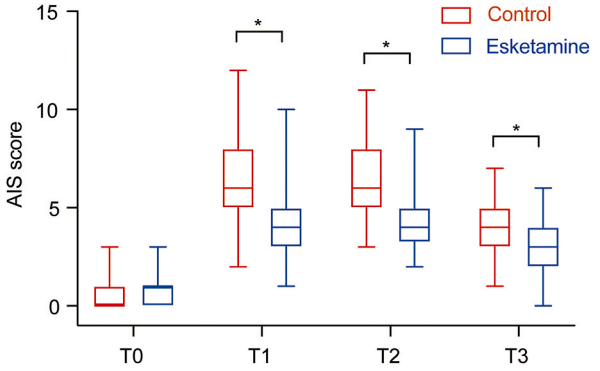

Fig. 2. Sleep Quality Scores. *$P < 0.05$. T0: pre-operation; T1: 1 d after operation; T2: 2 d after operation; T3: 3 d after operation.

3.4. Quality of sleep and quality of postoperative recovery

Preoperatively, there were no differences in Athens Insomnia Scale scores between the two groups. However, the Esketamine group showed improvement compared to the Control group from the first to the third postoperative day ($P < 0.001$, < 0.001, $= 0.006$, respectively; Fig. 2). At 48 h postoperatively, QoR-15 scores were significantly higher in the Esketamine group than the Control group (120.0 [116.0, 123.0] vs 112.0 [106.0, 116.0], $P < 0.05$, Fig. 3).

3.5. Inflammation indicators

Comparisons between the two groups revealed no statistically significant differences in serum levels of the inflammatory cytokines interleukin-1β (IL-1β) and interleukin-6 (IL-6) prior to surgery and at 1 day and 3 days postoperatively (Fig. 4 A.B).

3.6. Adverse events

No significant variations were observed in the incidence of adverse events between the two groups within the initial 72 h following surgery. These adverse events encompassed nausea and vomiting, hallucination, dizziness, nightmare, and excessive oral secretion ($P < 0.05$, Table 4).

4. Discussion

This study revealed that the administration of intravenous subanesthetic esketamine during laparoscopic resection of gastrointestinal cancer in elderly patients can effectively alleviate postoperative pain within a limited timeframe, not exceeding 24 h post-surgery. However, it did not demonstrate a reduction in the incidence of postoperative delirium.

Ketamine is the only clinical anesthetic that can provide both analgesic and sedative effect. However, its application is limited due to the side effects such as hallucinations and nightmares. Esketamine, a S-isomer of ketamine, which has stronger analgesic and hypnotic effects and a lower incidence of adverse reactions [16]. The main mechanism of analgesia is to block NMDA receptors noncompetitively, it also can bind to the μ and δ receptors in opioid receptors. Esketamine can be a good substitute for the use of racemic ketamine during the perioperative period. A recent published meta-analysis [14] indicated that intravenous esketamine as an adjunct to general anesthesia is effective for decreasing the intensity of pain and opioid requirements in a short time after surgery, our findings are consistent with theirs. Although the pain relief effect appeared transient, its significance during the early postoperative period, especially within the first 24 h, is noteworthy for promoting early mobilization and enhancing patient comfort [17]. However, our study found no difference in pain scores between the two groups at PACU. This discrepancy may be attributed to a initial analgesic dose was set in the PCIA device.

Consistent with our study, Miziara et al. [18] executed continuous intraoperative infusion of esketamine (0.3 mg/kg/h) in patients under intravenous anesthesia with target-controlled infusion of remifentanil and propofol. Their study highlighted superior postoperative pain control over the initial 12 h following laparoscopic cholecystectomy when compared to a placebo. It has been posited that investigations into substances with analgesic or antihyperalgesic effects should establish their efficacy postoperatively in tandem with clinically relevant anesthesia, including perioperative opioids [19,20]. Remifentanil's continuous infusion during surgery is associated with opioid-induced hyperalgesia. Although a short-acting opioid, remifentanil's rapid efficacy regression and absence of postoperative respiratory depression render it widely employed. Esketamine, besides its analgesic properties, also demonstrates anti-hyperalgesic effects. Studies have shown that the occurrence of hyperalgesia is related to the activation of NMDA receptor pathway in the spinal cord [21]. Combining remifentanil infusion with intraoperative esketamine might represent a more suitable analgesic approach. A similar study by Argiriadou et al. [22] demonstrated improved postoperative pain after abdominal surgery with intravenous esketamine administration. Their findings align with ours, as fewer patients in the esketamine group necessitated additional postoperative analgesics, with reduced rescue analgesic consumption. Furthermore, they noted enhanced mood in the

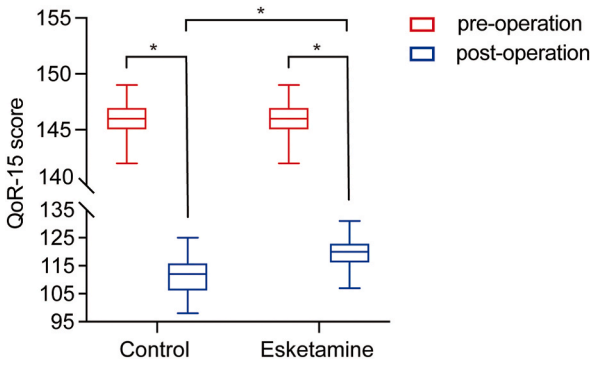

Fig. 3. 15-Item quality of recovery questionnaire scores. *P < 0.05.

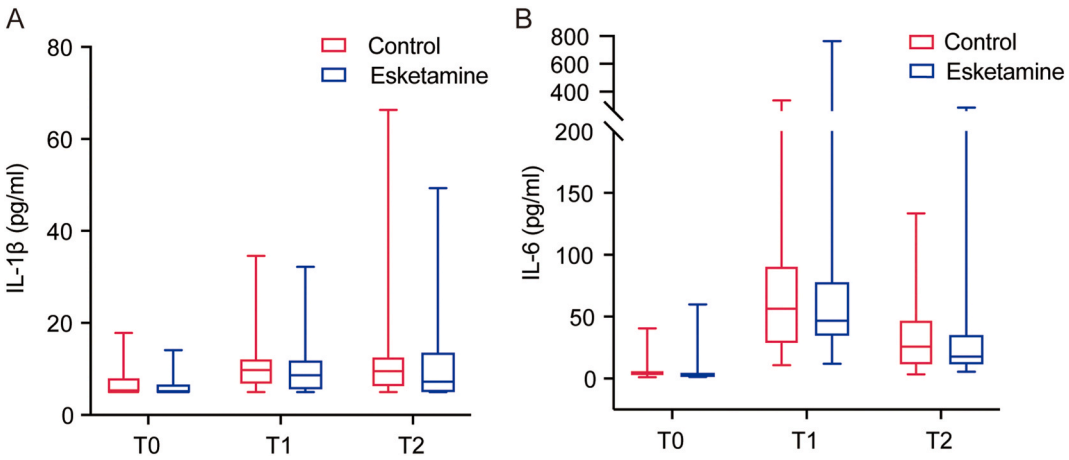

Fig. 4. Serum Inflammatory Indicators. (A) Serum IL-1β levels. (B) Serum IL-6 levels. T0: pre-operation; T1: 1 d after operation; T2: 3 d after operation.

Table 4
Incidence and frequency of postoperative adverse events.

group	Nausea and vomiting	Hallucination	Dizziness	Nightmare	Excessive oral secretion	total
C	6 (13.95%)	0 (0)	3 (6.98%)	0 (0)	0 (0)	9 (20.93%)
S	3 (6.82%)	0 (0)	2 (4.55%)	0 (0)	2 (4.55%)	7 (15.91%)

esketamine group, potentially attributed to ameliorated postoperative pain.

Jaksch W et al. [23] concluded that perioperative small-dose esketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. In the same manner as our administration, a single dose before incision and followed by a continuing infusion intraoperatively, but the results were contrary to ours. We found that aimed to effect a reduction in the patients' VAS score < 3 as quickly as possible, they made a repetitive administration of morphine in the early postoperative period, resulting in an increased consumption of morphine at 24 h and 48 h after surgery in both groups compared with other studies, and lower VAS scores in both groups.

The effect of esketamine on perioperative cognitive function in older adults is currently controversial [24]. It has been reported in a study [25] that subanesthetic esketamine may reduce the incidence of perioperative neurocognitive disorders and improve early postoperative cognitive function in elderly patients undergoing gastrointestinal surgery. This could potentially be related to the anti-inflammatory effect of esketamine. In addition, pain, use of opioid, sleep disturbances are also risk factors for delirium. Confusion Assessment Method (CAM) is a widely used delirium assessment tool, compiled by Inouye et al. [11] in 1990 in the United States and suitable for non-psychiatrists, including Acute Onset and Fluctuating Course, Inattention, Disorganized Thinking and Altered Level of Consciousness. CAM has good sensitivity (94%–100%) and specificity (90%–95%) for diagnosing delirium. In our study, the incidence of delirium in esketamine group was lower than that in control group, but the difference was insignificant between the two groups; The pathogenesis of postoperative delirium (POD) remains enigmatic. Emerging evidence [26] suggests a pivotal role of inflammation in the process of postoperative cognitive dysfunction. Pro-inflammatory cytokines such as IL-1β and IL-6 influence essential neuronal functions for learning and memory [27]. Some studies [28,29] demonstrate the anti-inflammatory potential of esketamine. Although esketamine did not reduce inflammatory factor levels in our study, this may partly explain the absence of difference in the incidence of postoperative delirium between the two groups. A possible explanation could be that the dose of esketamine used in our study was small. What's more, the sample size of our study was calculated based on the 24 h resting VAS score, the primary outcome of the study, which might have led to the trial being underpowered to detect any difference in delirium. It has been reported that the incidence of delirium after gastrointestinal surgery is about 8%–54% [4]. In our study, the incidence of postoperative delirium was 11.63% in the control group and 2.27% in the esketamine group. Although there was no statistical significance in the incidence of delirium between the two groups, the incidence of delirium in the esketamine group was lower than that in the conventional gastrointestinal surgery. This may be related to the improvement of pain and sleep in the early postoperative period, after all, the peak period of delirium is the first 24 h after surgery. Sleep disturbance could interfere with the function of neuronal pathways [30], thereby affecting the occurrence of delirium.

Di Qiu et al. [31] suggested that esketemine can prevent poor postoperative sleep and postoperative sleep disturbance (PSD) in patients who underwent gynecological laparoscopic surgery, which is consistent with our results. Pain is a leading cause of post-operative sleep disturbance [32]. The improvement of sleep quality by esketamine may be achieved through the mediating effect of pain relief. Otherwise, PSD is often seen alongside depression in patients after surgery [33,34]. Esketamine has been demonstrated to have rapid and robust antidepressant effect [35,36]. Besides, it has been proposed that esketamine may be an independent factor for

improving sleep quality and is not solely a result of postoperative pain and mood improvement [37]. Accumulating evidence [38,39] suggests that esketamine can modulate circadian rhythm system, but the exact mechanism remains unclear.

QoR-15 score in group S was significantly higher than that in the control group. Several studies [40,41] also confirm this. The improvement in pain scores at rest and sleep quality in the esketamine group likely contributes to the higher postoperative QoR-15 score in group S compared with group C. A systematic review [42] reported that the minimum clinically important difference in the QoR-15 score was 6.0 points, suggesting that an intervention during the perioperative period resulting in such a change would have a meaningful impact on improving the patient's health status. Our findings indicate a meaningful difference of 8.0 points in the QoR-15 score between the two groups.

However, our study has several limitations. First, the sample size was determined primarily based on the primary outcome, leading to relatively low statistical power for certain outcomes due to the modest sample size. Second, we only recorded whether delirium occurred and did not assess the severity of postoperative cognitive decline. Third, the application of local regional nerve block technique with analgesia could intersect with the analgesic effect of esketamine. Finally, although a subanesthetic dose of esketamine was used in our study, its infusion could affect Bispectral index during general anesthesia, potentially causing changes in the required dosage of sedatives and analgesics.

5. Conclusion

The administration of intravenous esketamine can effectively reduce the intensity of pain during the first 24 h after surgery without additional adverse effects in older adults undergoing laparoscopic resection for gastrointestinal cancer.

Ethics statement

This study was reviewed and approved by the Medical Ethics Committee of the Affiliated Hospital of Jiangsu University with the approval number: [KY2022H0507-10]. All participants/patients (or their proxies/legal guardians) provided informed consent to participate in the study.

Funding

The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author, upon reasonable request.

CRediT authorship contribution statement

Zhaojun Jing: Writing – original draft, Software, Methodology, Investigation, Data curation. **Yu Han:** Writing – review & editing, Software. **Yi Li:** Software, Formal analysis. **Rui Zeng:** Methodology, Formal analysis. **Jin Wu:** Writing – review & editing, Methodology. **Yiting Wang:** Investigation, Data curation. **Peng Jiang:** Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27593.

References

[1] P.C. Enzinger, R.J. Mayer, Gastrointestinal cancer in older patients, Semin. Oncol. WB Saunders 31 (2) (2004) 206–219.
[2] J.L. McKeown, Pain management issues for the geriatric surgical patient, Anesthesiol. Clin. 33 (3) (2015) 563–576.
[3] R. Karani, D.E. Meier, Systemic pharmacologic postoperative pain management in the geriatric orthopaedic patient, Clin. Orthop. Relat. Res. 425 (2004) 26–34.

[4] A.F.M. Scholz, C. Oldroyd, K. McCarthy, et al., Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery, J. Br. Surg. 103 (2) (2016) e21–e28.
[5] S.K. Inouye, R.G.J. Westendorp, J.S. Saczynski, Delirium in elderly people, Lancet 383 (9920) (2014) 911–922.
[6] A. Prabhakar, K.F. Mancuso, C.P. Owen, et al., Perioperative analgesia outcomes and strategies, Best Pract. Res. Clin. Anaesthesiol. 28 (2) (2014) 105–115.
[7] E.S. Schwenk, E.R. Viscusi, A. Buvanendran, et al., Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American society of regional anesthesia and pain medicine, the American academy of pain medicine, and the American society of anesthesiologists, Reg. Anesth. Pain Med. 43 (5) (2018) 456–466.
[8] P.F. White, J. Schüttler, A. Shafer, et al., Comparative pharmacology of the ketamine isomers: studies in volunteers, Br. J. Addiction: Br. J. Anaesth. 57 (2) (1985) 197–203.
[9] F. Weber, H. Wulf, M. Gruber, et al., S-ketamine and s-norketamine plasma concentrations after nasal and iv administration in anesthetized children, Pediatr. Anesth. 14 (12) (2004) 983–988.
[10] S. Fanta, M. Kinnunen, J. Backman, et al., Population pharmacokinetics of S-ketamine and norketamine in healthy volunteers after intravenous and oral dosing, Eur. J. Clin. Pharmacol. 71 (4) (2015).
[11] S.K. Inouye, C.H. van Dyck, C.A. Alessi, et al., Clarifying confusion: the confusion assessment method: a new method for detection of delirium, Ann. Intern. Med. 113 (12) (1990) 941–948.
[12] C.R. Soldatos, D.G. Dikeos, T.J. Paparrigopoulos, The diagnostic validity of the Athens Insomnia scale, J. Psychosom. Res. 55 (3) (2003) 263–267.
[13] P.A. Stark, P.S. Myles, J.A. Burke, Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15, Anesthesiology 118 (6) (2013) 1332–1340.
[14] X. Wang, C. Lin, L. Lan, et al., Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis, J. Clin. Anesth. 68 (2021) 110071.
[15] D.G. Snijdelaar, H.B. Cornelisse, R.L. Schmid, et al., A randomised, controlled study of perioperative low dose s (+)-ketamine in combination with postoperative patient-controlled s (+)-ketamine and morphine after radical prostatectomy, Anaesthesia 59 (3) (2004) 222–228.
[16] S. Mikkelsen, S. Ilkjaer, J. Brennum, et al., The effect of naloxone on ketamine-induced effects on hyperalgesia and ketamine-induced side effects in humans, J. Am. Soc. Anesthesiol. 90 (6) (1999) 1539–1545.
[17] E.C.V. Brinck, K. Maisniemi, J. Kankare, et al., Analgesic effect of intraoperative intravenous S-ketamine in opioid-naïve patients after major lumbar fusion surgery is temporary and not dose-dependent: a randomized, double-blind, placebo-controlled clinical trial, Anesth. Analg. 132 (1) (2020) 69–79.
[18] L.E.P.G. Miziara, R.F. Simoni, L.O. Esteves, et al., Efficacy of continuous S (+)-ketamine infusion for postoperative pain control: a randomized placebo-controlled trial, Anesthesiol. Res. Pract. (2016).
[19] J. Katz, C.J.L. McCartney, Current status of pre-emptive analgesia, Curr. Opin. Anesthesiol. 15 (4) (2002) 435–441.
[20] A.K. Mishra, M. Afzal, S.S. Mookerjee, et al., Pre-emptive analgesia: recent trends and evidences, Ind. J. Pain 27 (3) (2013) 114–120.
[21] M. Ma, Z. Wang, J. Wang, et al., Endomorphin analog exhibited superiority in alleviating neuropathic hyperalgesia via weak activation of NMDA receptors, J. Neurochem. 155 (6) (2020) 662–678.
[22] H. Argiriadou, S. Himmelseher, P. Papagiannopoulou, et al., Improvement of pain treatment after major abdominal surgery by intravenous S+-ketamine, Anesth. Analg. 98 (5) (2004) 1413–1418.
[23] W. Jaksch, S. Lang, R. Reichhalter, et al., Perioperative small-dose S (+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used, Anesth. Analg. 94 (4) (2002) 981–986.
[24] M S H.R. Maybrier, A.B. Abdallah, et al., Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial, Lancet 390 (10091) (2017) 267–275.
[25] C. Han, H. Ji, Y. Guo, et al., Effect of subanesthetic dose of esketamine on perioperative neurocognitive disorders in elderly undergoing gastrointestinal surgery: a randomized controlled trial, Drug Des. Dev. Ther. (2023) 863–873.
[26] X. Lin, Y. Chen, P. Zhang, et al., The potential mechanism of postoperative cognitive dysfunction in older people, Exp. Gerontol. 130 (2020) 110791.
[27] I.B. Hovens, R.G. Schoemaker, E.A. van der Zee, et al., Postoperative cognitive dysfunction: involvement of neuroinflammation and neuronal functioning, Brain Behav. Immun. 38 (2014) 202–210.
[28] W. Tu, H. Yuan, S. Zhang, 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. Tourism Res. 13 (3) (2021) 1701.
[29] I.D. Welters, M.K. Feurer, V. Preiss, et al., Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass, Br. J. Anaesth. 106 (2) (2011) 172–179.
[30] B. Song, J. Zhu, A novel application of ketamine for improving perioperative sleep disturbances, Nat. Sci. Sleep (2021) 2251–2266.
[31] D. Qiu, X.M. Wang, J.J. Yang, et al., Effect of intraoperative esketamine infusion on postoperative sleep disturbance after gynecological laparoscopy: a randomized clinical trial, JAMA Netw. Open 5 (12) (2022) e2244514.
[32] M. Luo, B. Song, J. Zhu, Sleep disturbances after general anesthesia: current perspectives, Front. Neurol. 11 (2020) 629.
[33] A. Steiger, M. Pawlowski, Depression and sleep, Int. J. Mol. Sci. 20 (3) (2019) 607.
[34] A. Wichniak, A. Wierzbicka, W. Jernajczyk, Sleep as a biomarker for depression, Int. Rev. Psychiatr. 25 (5) (2013) 632–645.
[35] R. Bahr, A. Lopez, J.A. Rey, Intranasal esketamine (SpravatoTM) for use in treatment-resistant depression in conjunction with an oral antidepressant, Pharm. Therap. 44 (6) (2019) 340.
[36] M.S. Salahudeen, C.M. Wright, G.M. Peterson, Esketamine: new hope for the treatment of treatment-resistant depression? A narrative review, Therap. Adv. Drug Saf. 11 (2020) 2042098620937899.
[37] Ke yao Zhang, Bao Yuan, Min Wang, et al., Effect of Perioperative Continuous Infusion of S-Ketamine on the Quality of Postoperative Recovery of Patients Undergoing Modified Radical Mastectomy: a Randomized Controlled Trial, PREPRINT (Version 1) available at: Research Square, 2022, https://doi.org/10.21203/rs.3.rs-1697135/v1.
[38] S. Koncz, N. Papp, D. Pothorszki, et al., (S)-Ketamine but not (R)-Ketamine shows acute effects on depression-like behavior and sleep-wake architecture in rats, Int. J. Neuropsychopharmacol. 26 (9) (2023) 618–626.
[39] S. Sato, B. Bunney, L. Mendoza-Viveros, et al., Rapid-acting antidepressants and the circadian clock, Neuropsychopharmacology 47 (4) (2022) 805–816.
[40] M. Zhu, S. Xu, X. Ju, et al., Effects of the different doses of esketamine on postoperative quality of recovery in patients undergoing modified radical mastectomy: a randomized, double-blind, controlled trial, Drug Des. Dev. Ther. (2022) 4291–4299.
[41] X. Cheng, H. Wang, M. Diao, et al., Effect of S-ketamine on postoperative quality of recovery in patients undergoing video-assisted thoracic surgery, J. Cardiothorac. Vasc. Anesth. 36 (8) (2022) 3049–3056.
[42] P.S. Myles, M.A. Shulman, J. Reilly, et al., Measurement of quality of recovery after surgery using the 15-item quality of recovery scale: a systematic review and meta-analysis, Br. J. Anaesth. 128 (6) (2022) 1029–1039.