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CLINICAL TRIAL REPORT

# The Effect of Minimal-Dose S-Ketamine Administration Post-Surgery on Opioids Consumption and Functional Rehabilitation Exercises in Patients Undergoing Minimally Invasive Radical Resection of Esophageal Cancer

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**Study Objective:** To examine the impact of minimal-dose S-ketamine on postoperative analgesia in patients undergoing minimally invasive radical resection for esophageal cancer, with a focus on reducing opioid consumption, enhancing analgesic quality, and facilitating postoperative recovery.

**Methods:** A total of 216 patients undergoing minimally invasive radical resection of esophageal cancer under general anesthesia were randomly assigned into two groups (S-ketamine and control group), receiving intravenous S-ketamine (0.015 mg/kg/h) or an equal volume of saline for 48 h postoperatively. The primary outcome was cumulative oxycodone consumption in the first 48 h post-operatively. Secondary outcomes included functional activity score (FAS) after one bolus administration, numerical rating scale (NRS) pain scores at rest and when coughing, cumulative oxycodone consumption in different time periods, incidence of postoperative nausea and vomiting (PONV), level of sedation (LOS) score, time to first postoperative flatulence, postoperative delirium, activities of daily living assessed by BI (Barthel Index) and so on.

**Main Results:** The postoperative opioid consumption within 48 hours in S-ketamine group was significantly lower than those in placebo group ($P < 0.001$), and the difference between the two groups was 40% (mean: 44.5 mg vs 74.8 mg). FAS after one bolus administration and BI in the S-ketamine group were notably superior to those in the control group ($P < 0.001$). There were Statistical differences between the two groups in the NRS scores at rest at postoperative hour 48 ($P = 0.001$) and the NRS scores when coughing at postoperative hour 12 ($P = 0.011$) with mean differences of −0.3 and 0.4, respectively.

**Conclusion:** Minimal-dose S-ketamine for managing acute postoperative pain in patients undergoing radical resection for esophageal cancer led to a 40% reduction in opioid consumption and promoted rehabilitation.

**Key words:** S-ketamine, minimal dose, esophageal cancer, postoperative analgesia

## Introduction

Thoracic surgery is frequently associated with acute postoperative pain, with a prevalence of moderate-to-severe pain reported to be as high as 62.9%.[1,2] Inadequate perioperative pain management following thoracoscopy can worsen respiratory function, potentially leading to postoperative pulmonary complications, chronic post-thoracotomy pain syndrome (CPTPS), and delayed recovery in patients.[3] Among thoracic surgeries, radical resection of esophageal cancer is known to cause severe acute postoperative pain due to the extensive trauma of the procedure.

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Opioids have traditionally served as the primary treatment for moderate to severe acute postoperative pain.[4] Current recommendations advocate for the implementation of multimodal analgesic regimens and non-opioid interventions to minimize perioperative opioid consumption and mitigate opioid-related adverse effects, such as nausea, vomiting, over sedation, ileus, pruritus, and respiratory depression, enhancing and expediting patients' postoperative recovery.[5]

(*R,S*)-ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist, is a racemic mixture of equal amounts of (*R*)-ketamine (arketamine) and (*S*)-ketamine (S-ketamine).[6,7] S-ketamine is used as an anesthetic in several countries, including China. The 2018 guideline "Intravenous Ketamine for Acute Pain Treatment", jointly issued by the American Society of Regional Anesthesia (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA), advocates for integrating subanesthetic ketamine doses (not exceeding 0.35 mg/kg or 1 mg/kg/h) into postoperative PCIA for surgeries anticipating severe acute postoperative pain in patients. The guidelines suggest that subanesthetic ketamine doses could lead to a 20% reduction in opioid usage for acute postoperative pain management.[8] Nevertheless, the effect of S-ketamine, which exhibits a higher affinity for NMDAR than (R,S)-ketamine and R-ketamine, on opioid consumption for managing acute postoperative pain in patients undergoing radical esophageal cancer resection remains uncertain. The study by Bornemann-Cimenti in 2016 indicated that the dosage of S-ketamine (0.015 mg/kg/h×48h) was similar to that of (R, S)-ketamine (0.25 mg/kg/h×48h) for managing acute postoperative pain.[9] This study aims to investigate the effect of minimal-dose S-ketamine (0.015 mg/kg/h×48h) for acute postoperative pain management on reducing opioid consumption, enhancing analgesic quality, and facilitating postoperative recovery in patients undergoing radical esophageal cancer resection.

# Materials and Methods

## Study Design

This randomized double-blinded controlled trial was conducted at Zhongda Hospital affiliated with Southeast University. The study protocol was approved by the Ethics Committee of Zhongda Hospital affiliated with Southeast University (No. 2022ZDSYLL138-P01) and registered in the Chinese Clinical Trial Register (ChiCTR2100048311, http://www.chictr.org.cn/). Written informed consent was obtained from all participants or their legal representatives before recruitment. This study complies with the Declaration of Helsinki and adhered to the 2010 Consolidated Standards of Reporting Trials (CONSORT).[10]

## Participants

The investigators screened eligible patients the day before surgery (or on Friday if they underwent surgery the following Monday). Patients who met the following criteria were included: aged 18–80 years, ASA status I–III and were scheduled to undergo minimally invasive radical resection of esophageal cancer. Patients who met any of the following criteria were excluded: allergy to S-ketamine or oxycodone, unstable ischemic cardiac disease, increased intracranial or intraocular pressure, untreated or poorly treated hyperthyroidism, psychiatric disease, severe hepatic dysfunction (Child–Pugh grade C), renal failure (requiring renal replacement therapy), severe respiratory dysfunction (respiratory failure type I or type II), previous long-term use of analgesics, previous basic pain (chronic pain), conversion to thoracotomy, transfer to the intensive care unit (ICU), unwillingness or inability to use a PCIA device, and cognitive impairment or inability to communicate.

## Randomization and Blinding

This study included 216 patients who underwent minimally invasive radical resection of esophageal cancer under general anesthesia. Participants were numbered sequentially based on their enrollment order. A nurse used IBM SPSS Statistics 27 to generate random numbers and randomly allocate participants to one of the two groups in a 1:1 ratio. The randomization sequence was generated and placed in sequentially numbered sealed radiopaque envelopes. Once the investigator confirmed eligibility, the envelopes were opened sequentially and participants were assigned to their respective groups by the designated nurse who performed numerical randomization. Intravenous pumps of the drugs were used by the coded PCIA device (with a fixed background infusion rate of 2 mL/h) delivered to the operating rooms by a pharmacist and were started at the end of surgery: Group E, S-ketamine 0.015 mg/kg (diluted to 96 mL with 0.9%

NS); Group C, 96 mL with 0.9% NS. This study was double blinded. The patients, researchers who performed data collection and postoperative follow-up, and clinical staff were blinded to group allocation throughout the study.

## Intervention

### Intraoperative Management

General anesthesia was standardized, and no premedication was administered. Anesthesia was induced intravenously with midazolam (0.03–0.05 mg/kg), propofol (1.5–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and rocuronium (0.6–0.9 mg/kg). Mechanical ventilation was performed after tracheal intubation, and the respiratory rate and tidal volume were adjusted to maintain the PETCO2 at 35–45 mmHg. Intravenous Ketorolac 30 mg was administered to the patients before the surgical procedure. Anesthesia depth was adjusted by target-controlled infusion of propofol and inhalation of a sevoffurane/oxygen/air mix to maintain a bispectral index value between 40 and 60. The remifentanil infusion rate was adjusted based on the mean arterial pressure and heart rate (within 20% of the baseline values).

### Postoperative Management

The coded PCA with a fixed background dose of 2 mL/h were started at the end of surgery: Group E, S-ketamine 0.015 mg/kg (diluted to 96 mL with 0.9% NS); Group C, 96 mL 0.9% NS. All the patients were transferred to the post-anesthesia care unit (PACU) for extubation.

### Postoperative Multimodal Analgesia

After extubation in the PACU, a fixed anesthesiologist performed ultrasound-guided paravertebral nerve block and another PCIA device (oxycodone 50 mg diluted to 100 mL with 0.9% NS) was administered to all patients. An ultrasound-guided paravertebral nerve block was performed by a specialized anesthesiologist with expertise in acute pain management. The ultrasound probe was positioned perpendicularly to the dorsal midline at the spinous processes of the target thoracic vertebrae (T5 and T8), with the inner end of the probe aligned on the dorsal midline. The imaging demonstrated the spinous process of the target thoracic vertebra and the transverse process of the adjacent thoracic vertebra. The probe was then adjusted cephalad to avoid interference with the transverse process of the adjacent thoracic vertebra, ensuring its placement between the two transverse processes and parallel to them. The paravertebral space of the thoracic vertebrae was identified as the region enclosed by the deep portion of the articular process, approximately 1 cm lateral to it, and bounded externally by the pleura. A needle was inserted lateral to the probe, carefully avoiding contact with the pleura, and advanced into the space between the articular process and the pleura. After confirming the absence of blood or cerebrospinal fluid upon aspiration, 10 mL of 0.187% ropivacaine was administered to the paravertebral regions of the target thoracic vertebrae. Oxycodone PCIA was programmed at a background dose of 0–2 mL/h and a single bolus dose of 4 mL, followed by a 10-min interval lockout. All patients received ketorolac (30 mg) intravenously daily. How to use oxycodone PCIA, postoperative follow-up and the adjustment of the PCIA were performed by a fixed nurse and a fixed anesthesiologist: if the NRS pain scores at rest was 0, the background dose would be reduced; otherwise, if the NRS pain scores at rest was > 3, the background dose would be increased until the score was ≤ 3. If the FAS was still grade C after one bolus injection, a bolus dose would be administered again 10 min later and so on until the FAS decreased to grade A/B. The PONV was treated with intravenous tropisetron (2 mg). When the liquid in the pump box of the oxycodone PCIA was exhausted, the original concentration of the medical solution could be added under aseptic conditions. If delirium occurred, dexmedetomidine (0.5 μg/kg) was pumped intravenously within 15 minutes and then infused at a rate of 0.2 to 0.7 μg/kg/h until the symptoms were controlled.

## Outcomes

The primary outcome was cumulative opioid consumption in the first 48 h postoperatively. The main secondary outcomes included FAS scores (after one bolus administration) at postoperative hour 12 ($T_3$), postoperative hour 24 ($T_4$), postoperative hour 48 ($T_5$), postoperative hour 72 ($T_6$), NRS pain scores (at rest and when coughing) at postoperative hour 2 ($T_1$), postoperative hour 6 ($T_2$), $T_3$,$T_4$,$T_5$,$T_6$, and the cumulative opioid consumption in different periods (postoperative 0–24 hours, 24–48 hours, 48–72 hours). Other pre-specified secondary outcomes included LOS scores at $T_2$ - $T_6$, time of first

postoperative flatulation, BI, incidence of PONV, postoperative delirium, pulmonary complications and other complications, duration of chest tube use, length of postoperative hospital stay, and satisfaction of medical workers and patients. Postoperative pain was evaluated using the NRS (11- point scale: 0 [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS < 10 [severe pain], 10 [worst pain imaginable]). Patients regularly used an external vibration expectoration machine (one bolus administration would be given in advance) from postoperative hour 12 and FAS scores (Grade A: no limitation [pain does not limit functional activity at all]; Grade B: mild limitation [pain slightly limits functional activity]; Grade C: Severe limitation [pain severely limits functional activity]) were used to evaluate the effect. Postoperative sedation was assessed using LOS scores (Grade 0: awake and responsive; Grade 1: slightly drowsy, but easy to wake up [Grade 1S: normal sleep state]; Grade 2: frequent drowsiness, easy to wake up, but not continuously awake; Grade 3: difficult to awaken). Activities of daily living were assessed using the Barthel Index (BI), with a total score of 100 points (≥ 60 points, can take care of themselves; 41–59 points, moderate dysfunction, need assistance in daily life; 21–40 points, severe dysfunction, requiring assistance in daily life, and ≤ 20 points requiring assistance in daily life). Postoperative delirium was diagnosed based on the Intensive Care Delirium Screening Checklist (ICDSC) (total scores ≥ 4). Pulmonary complications include pulmonary infection, atelectasis, pulmonary edema and pneumothorax. Other complications include anastomotic leakage and abnormal bleeding. The satisfaction levels of the medical staff and patients were assessed using NRS scores from 0 to 10 points (the higher the score, the better the satisfaction).

## Sample Size Calculation

Oxycodone consumption after minimally invasive radical resection of esophageal cancer in the previous year was calculated for the control group. We calculated the standard deviation (29.6 mg) and mean oxycodone consumption (66.5 mg) (postoperative 0–48 h). The guideline "Intravenous Ketamine for the treatment of Acute Pain" suggested that the addition of subanesthetic doses of ketamine can reduce opioid use by 20%.[8] So the expected reduction in oxycodone consumption would be 13.3 mg (66.5 mg × 20%). With the power set at 90% and a one-sided significance level of 0.05, 172 patients were required to detect differences. Owing to the 20% dropout rate, 216 patients were enrolled in the trial.

## Statistical Analysis

Statistical analyses were performed using a modified intention-to-treat approach, which excluded patients deemed ineligible after enrollment. All data were checked for normal distribution using the Kolmogorov–Smirnov test. Continuous variables are presented as mean (standard deviation, SD) or median (interquartile range, IQR), and Student's *t*-test or Mann–Whitney *U*-test was performed to compare the difference between the two groups according to the Kolmogorov–Smirnov test. Categorical variables are presented as numbers (percentages) and were compared using Pearson's $\chi^2$ test or Fisher's exact test as appropriate.

For the primary outcome, cumulative opioid consumption at postoperative 0–48 hours, Mann–Whitney *U*-tests were performed to compare the difference between the two groups and the median difference and its 95% CI were estimated using the Hodges-Lehmann estimator. Generalized estimating equations (GEEs) with robust standard error estimates were used to account for repeated measures of pain and FAS scores.

Statistical significance was set at $P < 0.05$. Statistical analyses were performed using IBM SPSS version 27 or GraphPad Prism 10.0.

# Results

## Study Population

A total of 325 patients were assessed for eligibility between January 1, 2022, and October 30, 2024. Of these, 216 were eligible and randomized. The final intention-to-treat analysis included 202 patients (Figure 1). Overall, the patient demographics and surgical and anesthetic characteristics were balanced between the groups (Table 1).

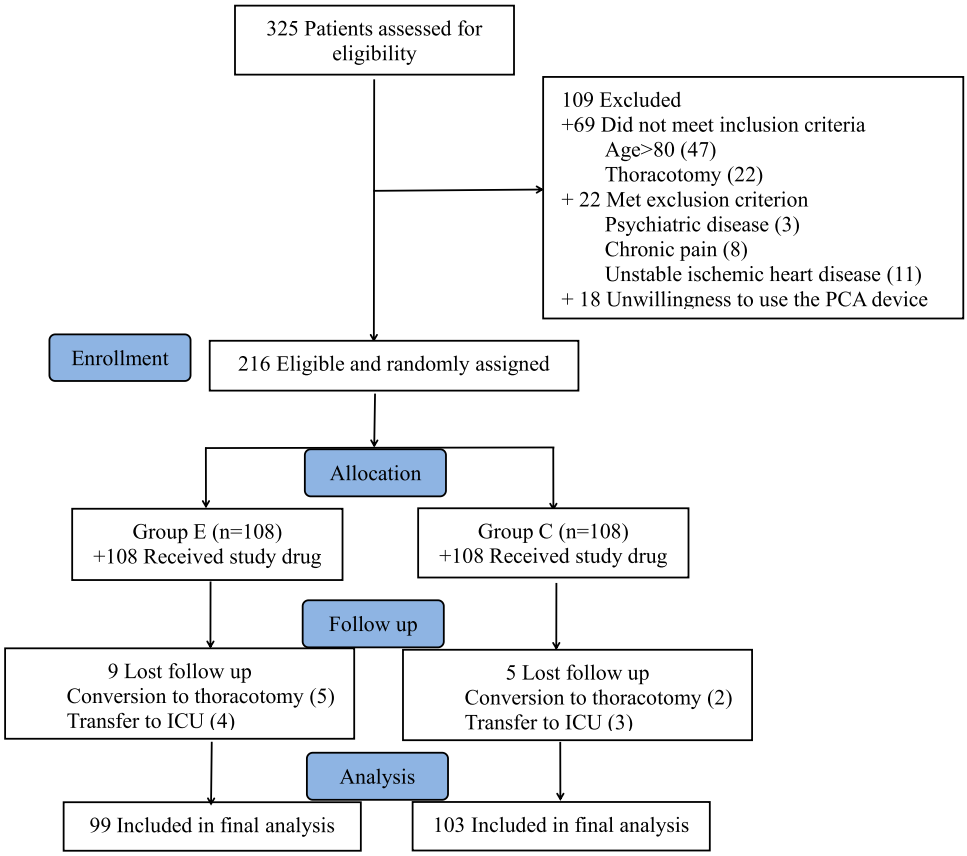


**Figure 1** CONSORT diagram for the study.
**Abbreviations**: ICU, intensive care unit; Group E, S-ketamine group; Group C, control group.

## Primary Outcome Analysis

The postoperative opioid consumption within 48 hours in S-ketamine group was significantly lower than those in placebo group ($P$ <0.001) (Table 2, Figure 2), and the difference between the two groups was 40% (mean: 44.5 mg vs 74.8 mg).

**Table 1** Demographic and Clinical Characteristics at Baseline

| | Group E (n = 99) | Group C (n = 103) | *P* value |
|---|---|---|---|
| Age, mean (SD), y | 65.6 (6.5) | 66.9 (7.2) | 0.202 |
| Gender | | | 0.481 |
| Men, n (%) | 77 (77.8) | 85 (82.5) | |
| Women, n (%) | 22 (22.2) | 18 (17.5) | |
| BMI, mean (SD), kg/m2 | 22.8 (2.7) | 23.5 (3.2) | 0.101 |
| ASA status, n (%) | | | 0.517 |
| I | 22 (22.2) | 27 (26.2) | |
| II | 77 (77.8) | 76 (73.8) | |
| Comorbidity, n (%) | | | |
| Hypertension | 62 (62.6) | 55 (53.4). | 0.202 |
| DM | 13 (13.1) | 19 (18.4) | 0.339 |
| CAD | 8 (8.1) | 5 (4.9) | 0.401 |
| Anemia | 8 (8.1) | 4 (3.9) | 0.244 |

(*Continued*)


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**Table 1** (Continued).

| | Group E (n = 99) | Group C (n = 103) | *P* value |
|---|---|---|---|
| NRS 2002 score ≥ 3 | 21 (21.2) | 20 (19.4) | 0.861 |
| Smoking, n (%) | | | 0.202 |
| Non-smoker | 48 (48.5) | 63 (61.2) | |
| Current smoker | 51 (51.5) | 40 (38.8) | |
| Drinking, n (%) | | | 0.078 |
| Non-drinker | 58 (58.6) | 73 (70.9) | |
| Current drinker | 41 (41.4) | 30 (29.1) | |
| Type of procedure, n (%) | | | 0.382 |
| Ivor-Lewis | 82 (82.8) | 80 (77.7) | |
| McKeown | 17 (17.2) | 23 (22.3) | |
| Duration of anesthesia, median (IQR), min | 370.0 (336.0–445.5) | 356.0 (317.5–416.0) | 0.114 |
| Sufentanil dose, median (IQR), μg | 35.0 (30.0–40.0) | 35.0 (30.0–40.0) | 0.861 |
| Remifentanil dose, median (IQR), mg | 1.0 (1.0–1.3) | 1.0 (1.0–1.4) | 0.884 |

**Notes**: Data are presented as mean (standard deviation), number (percentage), or median (interquartile range).
**Abbreviations**: Group E, S-ketamine group; Group C, control group; BMI: body mass index; ASA: American Society of Anesthesiologists; DM: diabetes mellitus; CAD: coronary artery disease; Anemia: moderate or severe anemia with hemoglobin < 90g/L; NRS 2002 score: the preoperative nutritional risk screening score which was used to assess the risk of malnutrition (≥ 3); Current drinker: patient consumed 4 or more drinks per week. 1 glass is defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of liquor (about 14 grams of alcohol);[11] Ivor-Lewis procedure: two-incision minimally invasive esophagectomy through abdominal and right thoracic incision; McKeown procedure: Three-incision minimally invasive esophagectomy through abdominal, right thoracic and neck incisions; SD: standard deviation; IQR: interquartile range.

**Table 2** Comparison of Oxycodone Consumption (Mg) Between the Two Groups

| Postoperative | Group E (n = 99) | Group C (n =103) | Median Difference (95% CI) | *P* value |
|---|---|---|---|---|
| 0–48 hours | 43.5 (32.3–52.5) | 75.0 (55.0–87.0) | 30.0 (24.0–36.0) | < 0.001 |
| 0–24 hours | 21.0 (15.0–25.0) | 40.0 (29.0–50.0) | 16.0 (12.0–20.0) | < 0.001 |
| 24–48 hours | 21.0 (16.0–25.0) | 34.0 (26.5–40.8) | 13.0 (11.0–16.0) | < 0.001 |
| 48–72 hours | 17.5 (12.0–20.8) | 33.0 (19.0–37.5) | 14.5 (11.5–17.0) | < 0.001 |

**Note**: Data are expressed as median (interquartile range);
**Abbreviations**: Group E, S-ketamine group; Group C, control group; CI: confidence interval;

## Secondary Outcomes Analyses

The NRS pain scores at rest were all ≤ 3, and the FAS (after 1–3 bolus dose administrations) was grade A/B in both groups, which met the requirements for postoperative analgesia. At $T_3$,$T_4$, $T_5$, and $T_6$, the proportion of FAS (after one bolus dose administration) with grade A/B in group E was significantly higher than that in group C ($P < 0.001$, $P= 0.007$, $P < 0.001$, $P < 0.001$, respectively) (Table 3, Figure 2). The NRS pain scores at rest at $T_5$ in group E were lower than those in group C ($P = 0.001$) and the NRS pain scores when coughing at $T_3$ in group E were larger than those in group C ($P = 0.011$) with mean differences of −0.3 and 0.4 respectively (Table 3, Figure 2). The AUC of the NRS pain scores at rest in group E was smaller than that in group C within 72 hours after surgery ($P = 0.027$) (Table 3). Oxycodone consumption in group E was significantly lower than that in group C within 24, 24–48 and 48–72 hours after surgery ($P < 0.001$, $P < 0.001$, $P < 0.001$, respectively) (Table 2, Figure 2), and the differences between the two groups were 40%, 41% and 47% respectively (mean: 23.6 mg vs 39.4 mg, 21.0 mg vs 35.4 mg, 16.9 mg vs 31.8 mg).

## Safety and Other Outcomes Analyses

The proportion of flatulation within 48 h postoperatively in group E was higher than that in group C ($P = 0.029$), the BI at 48 h postoperatively in group E was higher than that in group C ($P = 0.008$) and the postoperative hospital stay in group E was shorter than that in group C ($P = 0.044$) (Table 4). There was no statistically significant difference in postoperative pulmonary complications between the two groups; however, the incidence of postoperative pulmonary complications in

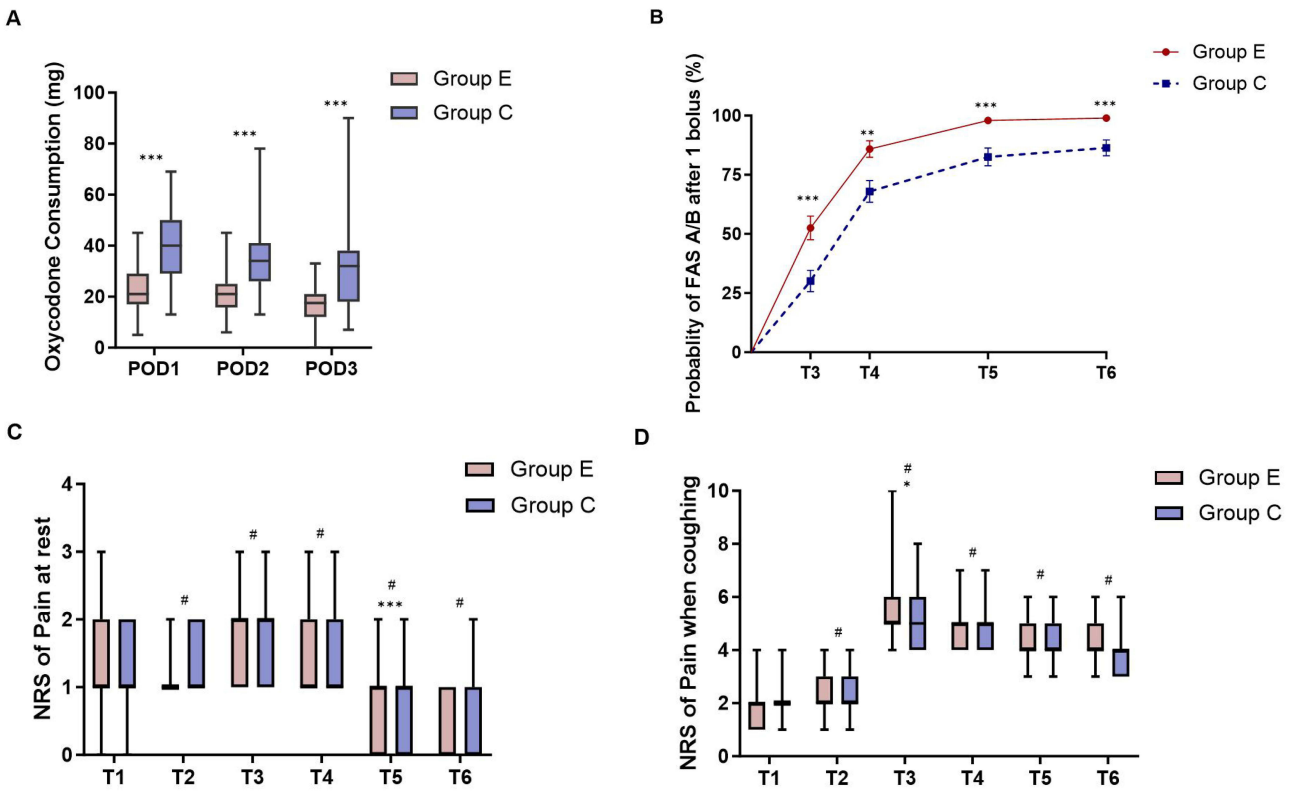


**Figure 2** Comparison of indicators of the analgesic efficacy between the two groups. (**A**). Oxycodone Consumption; (**B**). Probability of FAS A/B after 1 bolus; (**C**). NRS score for pain at Rest; (**D**) NRS of pain when coughing.

**Notes**: Compared with T1 in the same group, #*P* <0.05; compared with Group C at the same time point, **P* <0.05, ***P* <0.01, ****P*<0.001.

**Abbreviations**: Group E, S-ketamine group; Group C, control group; POD 1, postoperative 0–24 h; POD 2; postoperative 24–48 hours; POD 3: postoperative 48–72 hours; T1, postoperative hour 2; T2, postoperative hour 6; T3, postoperative hour 12; T4, postoperative hour 24; T5, postoperative hour 48; T6, postoperative hour 72.

group E (3.7%) was lower than that in group C (10.2%). The LOS scores were all grade 0 or 1 in the two groups, which met the requirements for postoperative analgesia and did not differ significantly between the two groups (Table 4). There were no significant differences in incidence of PONV, other complications, duration of chest tube placement, and satisfaction levels of medical staff and patients between two groups (Table 4).

**Table 3** Comparison of Postoperative Pain Between the Two Groups

| | Group E (n = 99) | Group C (n =103) | Mean Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| FAS scores with grade A/B, n (%) | | | | |
| $T_3$ (at postoperative hour 12) | 55 (55.6) | 32 (31.1) | | < 0.001 |
| $T_4$ (at postoperative hour 24) | 82 (82.8) | 69 (67.0) | | 0.007 |
| $T_5$ (at postoperative hour 48) | 97 (98.0) | 85 (82.5) | | < 0.001 |
| $T_6$ (at postoperative hour 72) | 98 (99.0) | 89 (86.4) | | < 0.001 |
| NRS pain scores at rest, mean (SD) | | | | |
| $T_1$ (at postoperative hour 2) | 1.0 (0.7) | 1.0 (0.7) | 0.0 (−0.2–0.2) | 0.844 |
| $T_2$ (at postoperative hour 6)[a] | 1.2 (0.4)[a] | 1.3 (0.4)[a] | 0.0 (−0.2–0.1) | 0.511 |
| $T_3$ (at postoperative hour 12)[a] | 1.7 (0.7)[a] | 1.8 (0.7)[a] | −0.1 (−0.3–0.1) | 0.279 |
| $T_4$ (at postoperative hour 24)[a] | 1.5 (0.6)[a] | 1.6 (0.7)[a] | −0.1 (−0.3–0.1) | 0.276 |
| $T_5$ (at postoperative hour 48)[a] | 0.8 (0.4)[a] | 0.9 (0.6)[a] | −0.3 (−0.4 – −0.1) | 0.001 |
| $T_6$ (at postoperative hour 72)[a] | 0.7 (0.4)[a] | 0.6 (0.3)[a] | 0.0 (−0.2–0.1) | 0.611 |

(*Continued*)


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**Table 3** (Continued).

| | Group E (n = 99) | Group C (n =103) | Mean Difference (95% CI) | *P* Value |
|---|---|---|---|---|
| NRS pain scores when coughing, mean (SD) | | | | |
| $T_1$ (at postoperative hour 2) | 2.0 (0.7) | 2.0 (0.7) | 0.0 (−0.2–0.2) | 0.694 |
| $T_2$ (at postoperative hour 6) | 2.3 (0.7)[a] | 2.3 (0.6)[a] | 0.0 (−0.2–0.2) | 0.880 |
| $T_3$ (at postoperative hour 12) | 5.5 (1.0)[a] | 5.1 (0.8)[a] | 0.4 (0.1–0.7) | 0.011 |
| $T_4$ (at postoperative hour 24) | 4.9 (0.8)[a] | 4.9 (0.7)[a] | 0.0 (−0.2–0.2) | 0.892 |
| $T_5$ (at postoperative hour 48) | 4.4 (0.7)[a] | 4.2 (0.8)[a] | 0.2 (0.0–0.4) | 0.080 |
| $T_6$ (at postoperative hour 72) | 4.1 (0.7)[a] | 4.0 (0.8)[a] | 0.2 (0.0–0.4) | 0.102 |
| AUC within 72 hours, mean (SD) | | | | |
| NRS pain scores at rest | 71.5 (31.5) | 81.8 (33.9) | −10.3 (−19.4 – −1.2) | 0.027 |
| NRS pain scores when coughing | 308.0 (38.5) | 297.2 (46.6) | 10.7 (−1.2–22.6) | 0.077 |

**Notes**: Data are presented as mean (standard deviation), number (percentage), or median (interquartile range).
**Abbreviations**: Group E, S-ketamine group; Group C, control group; NRS: numerical rating scale; AUC: area under the curve of pain scores and time; FAS (functional activity score): Patients were regularly use the external vibration expectoration machine (a bolus dose would be given in advance) from postoperative hour 12 and FAS scores (Grade A: no limitation [pain does not limit functional activity at all]; Grade B: mild limitation [pain slightly limits functional activity]; Grade C: severe limitation [pain severely limits functional activity]) was used to evaluate the effect; SD: standard difference; CI: confidence interval; [a] $P < 0.05$ compared to TI.

**Table 4** Comparison of Safety and Other Outcomes Between the Two Groups

| | Group E (n = 99) | Group C (n = 103) | *P* value |
|---|---|---|---|
| LOS scores with grade 1 or 1S, n (%) | | | |
| $T_2$ (at postoperative hour 6) | 77 (77.8) | 71 (68.9) | 0.203 |
| $T_3$ (at postoperative hour 12) | 79 (79.8) | 91 (88.3) | 0.070 |
| $T_4$ (at postoperative hour 24) | 6 (6.1) | 8 (7.8) | 0.784 |
| $T_5$ (at postoperative hour 48) | 3 (3.0) | 5 (4.9) | 0.721 |
| $T_6$ (at postoperative hour 72) | 5 (5.1) | 3 (2.9) | 0.492 |
| Flatulating within postoperative 48 hours, n (%) | 44 (44.4) | 30 (29.1) | 0.029 |
| BI at postoperative 48 hours, median (IQR) | 40.0 (40.0–45.0) | 40.0 (35.0–45.0) | 0.008 |
| Duration of chest tube, median (IQR), day | 3.0 (2.0–3.0) | 3.0 (2.0–3.0) | 0.100 |
| Postoperative hospital stay, median (IQR), day | 13.0 (13.0–14.0) | 14.0 (13.0–15.0) | 0.044 |
| Pulmonary complications, n (%) | 4 (4.0) | 12 (11.7) | 0.066 |
| Other complications, n (%) | 8 (8.1) | 5 (4.9) | 0.401 |
| Postoperative delirium, n (%) | 16 (16.2) | 14 (13.6) | 0.694 |
| PONV, n (%) | 18 (18.2) | 13 (12.6) | 0.330 |
| NRS satisfaction scores | | | |
| Patients, median (IQR) | 10.0 (9.0–10.0) | 10.0 (9.0–10.0) | 0.183 |
| Medical workers, median (IQR) | 10.0 (10.0–10.0) | 10.0 (9.0–10.0) | 0.121 |

**Notes**: Data are presented as number (percentage), or median (interquartile range).
**Abbreviations**: Group E, S-ketamine group; Group C, control group; LOS (level of sedation), grade 0 (awake and responsive), grade 1 (a little drowsy, but easy to wake up [grade 1S, Normal sleep state]), grade 2 (frequent drowsiness, easy to wake up, but not continuously awake), grade 3 (difficult to awaken); BI, Barthel Index; PONV, postoperative nausea and vomiting; NRS, Numerical rating scale; IQR, interquartile range.

## Discussion

The main findings of the study are as follows. First, Opioid consumption within the first 48 h postoperatively for acute pain management was significantly lower in the S-ketamine group than in the control group in patients undergoing radical resection for esophageal cancer. Second, the FAS and BI scores were notably higher in the S-ketamine group than in the control group. Moreover, there was a statistically significant difference in the NRS pain scores between the two groups of patients; however, the score differences were less than 1 point. Given that the minimum unit of the NRS score is 1 point and prior studies have demonstrated that a decrease of at least 1.3 points in the NRS pain score relative to

baseline pain intensity is required for clinically meaningful pain relief, the observed differences in this study lacked clinical significance despite being statistically significant.[12–14] Time to first postoperative flatulence and length of postoperative hospital stay were lower in the S-ketamine group than in the control group. There were no significant differences in the incidence of PONV, LOS, postoperative delirium, pulmonary and other complications, duration of chest tube placement, or satisfaction levels of medical staff and patients between the two groups.

## Selection of the Study Population

The addition of subanesthetic doses of ketamine is supported by the guidelines for patients undergoing thoracic surgery expected to cause severe postoperative pain.[8] Postoperative pain following thoracic surgery, particularly radical resection of esophageal cancer, is known to be severe, with incidence rates of moderate to severe pain reaching 62.9%.[2] Given the high demand for analgesia observed in patients undergoing minimally invasive radical resection of esophageal cancer, often necessitating patient-controlled analgesia (PCIA) for over 72 h post-surgery, this study focused on this specific patient population to enhance postoperative pain management.

## Selection of the Primary Outcome and the Secondary Outcome FAS

The perioperative analgesia guidelines aim to achieve postoperative pain tolerance or a pain level of NRS $\leq 3$.[15–17] Our department implemented artificial intelligence patient-controlled analgesia (Ai-PCA) in 2012 and established the Acute Pain Service (APS) in 2017. Due to clinical and ethical considerations, to ensure adherence to the analgesic goal, we strived for homogeneity in pain scores: NRS scores at rest were $\leq 3$ and FAS levels were grade A or B. Therefore, the primary outcome of this study was opioid consumption, which served as an indirect indicator of analgesic efficacy.

In this study, all patients achieved FAS levels of grade A/B following 1–3 bolus administrations and we chose the FAS levels obtained after one bolus administration as the secondary outcome to assess the difference in functional exercise between the two groups. Conventional clinical studies frequently integrate both S-ketamine and opioids into PCIA.[18–20] Moreover, unlike typical clinical studies, we did not incorporate S-ketamine into PCIA because it would result in discrepancies in the bolus between the two groups.

## Selection of S-Ketamine Dosage

S-ketamine, being more potent and less prone to adverse effects than racemic ketamine, is a viable alternative during the perioperative period. A recent meta-analysis by Wang et al[21] indicates that intravenous S-ketamine, when used as an adjunct to general anesthesia, effectively enhanced analgesia, reduced postoperative pain intensity, and minimized opioid requirements in the short term. However, it may also increase the incidence of psychotomimetic adverse events. Notably, the risk of such adverse events is significantly higher in the intra- and postoperative group compared to the intraoperative-only group, possibly due to higher postoperative infusion rates (doses ranged from 0.075 to 0.5 mg/kg for boluses and 1.25 to 10 μg/kg/min for infusions).[21] Studies by Bornemann-Cimenti[9] and Zhang[20] have shown that minimal-dose S-ketamine (0.015 mg/kg/h for 48 hours) yields comparable analgesic effects to conventional low-dose S-ketamine regimens, while also demonstrating similar outcomes to a placebo in terms of postoperative delirium and sedation. Therefore, in light of the literature and the outcomes of preliminary experiments, the minimum dose of S-ketamine (0.015 mg/kg/h for 48 h) was selected for this study to achieve the desired therapeutic effect while minimizing the dosage.

## Exploratory Outcomes Analyses

### Exploratory Primary Outcome Analysis

Our findings indicate that the addition of a minimum dose of S-ketamine to postoperative analgesia reduces the postoperative opioid requirements. Our study showed an approximate 40% decrease in postoperative opioid requirements in the S-ketamine group compared to the control group, consistent with previous research and surpassing the anticipated 20% reduction, confirming the study's statistical power to detect differences between groups.[9,22]

### Exploratory Main Secondary Outcomes Analyses

Multimodal pain management, a key element in Enhanced Recovery After Surgery (ERAS) protocols, often includes the NMDA receptor antagonist ketamine because of its efficacy in reducing opioid consumption and pain levels.[5,21,23,24] The primary aim of analgesia is to enhance postoperative rehabilitation, as indicated by the FAS assessment. Our findings revealed significantly improved FAS scores in the S-ketamine group compared to the control group, highlighting the superior analgesic efficacy of S-ketamine in functional exercises.

### Safety and Other Outcomes

The time to first postoperative flatulence, bowel movements, and length of hospital stay were significantly better in the S-ketamine group than in the control group, possibly because of the reduced postoperative opioid use and enhanced mobilization. No significant differences were observed in LOS scores or postoperative delirium between the groups, consistent with previous studies.[9,20] The incidence of postoperative nausea and vomiting did not differ between the groups, aligning with conflicting findings in the literature.[21,25] Although a decrease in pulmonary complications was noted, it was not statistically significant, nor were other complications. Previous studies suggest that perioperative administration of S-ketamine or ketamine in various surgeries may confer anti-inflammatory and immunoprotective effects with efficacy potentially dose-dependent.[26–29] Inconclusive results may be attributed to inadequate power analysis for this outcome, limiting the study's ability to detect differences.

## Limitations

First, continuous constant-rate intravenous infusion was selected to ensure that the hourly dosage of S-ketamine remained at its minimum level. Nonetheless, incorporating S-ketamine into the PCIA may offer greater clinical convenience. Further studies and design improvements are necessary to build this foundation. Second, this trial was conducted at a single center. Therefore, the generalizability of our findings to other patient populations remains unclear. Third, we did not design multiple dosage groups to determine the optimal dose. The minimal-dose of S-ketamine used in this protocol was based on previous studies. Given the relatively small number of patients undergoing esophageal cancer surgery, it took approximately three years to complete this study. Comparing multiple groups would have further prolonged the research period. Clinically, treatment modalities for various diseases and postoperative analgesia management are continually evolving. A protracted research timeline may introduce potential biases into the results. These limitations could be addressed through multicenter collaboration in future studies. Fourth, no quantitative indicators of hyperalgesia were used in this study. In the pilot study, von fair silk was used to measure the area of pain sensitivity. However, the patients refused because they used a band to fix their chest to relieve pain after surgery, and the process of removing the band was complicated and inconvenient. This limitation should be fully considered in future studies, and alternative methods such as the pressure pain threshold (PPT) assessment are recommended. Fifth, the sample size was calculated based on the primary outcomes. Therefore, it is highly likely that our relatively small sample size underpowered the secondary outcomes (such as the incidence of pulmonary complications and PONV). Large-scale randomized controlled trials should be conducted to address these limitations.

## Conclusion

In conclusion, the minimum dose of S-ketamine for managing acute postoperative pain in patients undergoing radical resection of esophageal cancer leads to a 40% reduction in opioid use and promotes postoperative functional exercise and rehabilitation, which is worthy of clinical promotion.

## Data Sharing Statement

All data generated or analyzed during this study have been included in the published article. Further inquiries regarding the datasets can be directed to the corresponding author upon reasonable request.

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## Disclosure

The authors declare no conflicts of interest in this work.

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