

Article

# Esketamine-assisted low-opioid anesthesia reduces postoperative anxiety and depression in gastric cancer laparoscopic surgery: A mental health-focused analysis

Wenlong Xie, Tian Jiang, Jianjun Zhou\*

Anesthesiology Department, Xiantao First People's Hospital, Xiantao 433000, China

\* Corresponding author: Jianjun Zhou, 17332662114@163.com

## CITATION

Xie W, Jiang T, Zhou J. Esketamine-assisted low-opioid anesthesia reduces postoperative anxiety and depression in gastric cancer laparoscopic surgery: A mental health-focused analysis. *Psycho-Oncologie*. 2026; 20(2): 4351. <https://doi.org/10.18282/po4351>

## ARTICLE INFO

Received: 25 March 2025

Revised: 9 February 2026

Accepted: 10 February 2026

Available online: 26 February 2026

## COPYRIGHT



Copyright © 2026 by author(s). *Psycho-Oncologie* is published by PiscoMed Publishing Pte Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license. <https://creativecommons.org/licenses/by/4.0/>

**Abstract: Background:** Patients undergoing surgery for gastric cancer are at high risk for postoperative anxiety and depression, which can significantly impact recovery and quality of life. Opioid-based anesthesia, while effective for pain control, may contribute to emotional dysregulation and mood disturbances. This study explores the effects of an esketamine combined with low-opioid anesthesia regimen on postoperative mental health outcomes in patients undergoing laparoscopic surgery for gastric cancer. **Objective:** To evaluate the impacts of this regimen on postoperative anxiety and depression levels, alongside blood pressure, heart rate, respiratory circulation, and overall emotional well-being. **Methods:** A total of 246 patients undergoing laparoscopic surgery for gastric cancer were randomly divided into two groups: the conventional anesthesia group ( $n = 123$ ) and the esketamine group ( $n = 123$ ). Vital signs (SBP, DBP, HR, SpO<sub>2</sub>) were compared at four time points (T0-T3). The dosages of sufentanil and remifentanyl, and PCIA drug additional administration rates were compared, along with anxiety and depression levels assessed by SAS and SDS at multiple postoperative time points to track emotional recovery. **Results:** Significant differences were found in SBP, DBP, HR, SpO<sub>2</sub>, SAS, and SDS between the two groups ( $P < 0.05$ ). The esketamine group showed higher vital signs at T1-T3 and consistently lower SAS and SDS scores postoperatively. Lower opioid dosages and PCIA drug additional administration rates were observed in the esketamine group ( $P < 0.05$ ). Most notably, the esketamine group demonstrated a significantly more favorable trajectory in anxiety and depression recovery. **Conclusion:** Esketamine-assisted low-opioid anesthesia not only reduces opioid dosage and stabilizes vital signs but also provides a significant mental health benefit by effectively mitigating postoperative anxiety and depression in patients undergoing laparoscopic gastric cancer surgery. This highlights its dual role in supporting both physical and psychological recovery.

**Keywords:** esketamine; low-opioid anesthesia; postoperative mental health; anxiety; depression; laparoscopic surgery for gastric cancer; psychological well-being

## 1. Introduction

Gastric cancer is one of the most common malignant tumors in clinical practice, with an incidence rate ranking fifth among all malignancies and a mortality rate ranking third [1]. Despite the continuous advancement of molecularly targeted therapeutic drugs for gastric cancer in recent years, surgery remains the primary treatment modality offering the potential for radical cure [2]. Laparoscopic radical resection of gastric cancer (LG) is one of the most widely used surgical procedures for this condition. However, the mainstream anesthesia regimen for LG involves the use of opioid receptor agonists in combination with muscle relaxants for anesthesia induction and/or maintenance. These opioids are associated with significant side

effects, including delayed respiratory depression, increased oxygen consumption, and elevated intracranial pressure [3]. Additionally, postoperative hyperalgesia often leads to severe pain in patients, which, if not promptly controlled, may progress to chronic pain. Persistent pain can exacerbate inflammatory responses, disrupt the metabolism of neurotransmitters such as 5-hydroxytryptamine (5-HT), and contribute to depressive-like behaviors [4].

Patients with malignant tumors frequently experience varying degrees of negative emotions, such as anxiety, depression, and fear, which can significantly complicate postoperative recovery. These emotional challenges not only affect patients' psychological well-being but also influence physiological outcomes, potentially exacerbating pain perception and delaying healing. Addressing postoperative emotional well-being is therefore a critical concern for patients undergoing laparoscopic gastric cancer surgery (LG). To mitigate these challenges, clinicians often combine alternative analgesic methods with opioids to reduce their dosage while maintaining effective pain control. Esketamine, the dextroisomer of ketamine, has emerged as a promising adjunct in perioperative pain management. Initially used as a treatment for refractory depression, esketamine has demonstrated the ability to reduce intraoperative opioid requirements by improving perioperative pain control. This is achieved through its unique mechanism of action, which involves antagonizing N-methyl-D-aspartate (NMDA) receptors, thereby modulating pain pathways and reducing hyperalgesia [5]. By incorporating esketamine into the anesthesia regimen, clinicians can ensure effective anesthesia while minimizing the side effects associated with high-dose opioids. This approach not only alleviates postoperative pain but also enhances emotional well-being by reducing the incidence of opioid-induced mood disturbances. Furthermore, esketamine's rapid onset and short duration of action make it particularly suitable for use in surgical settings, where quick recovery and minimal residual effects are desirable. Its application in LG represents a novel strategy to address the complex interplay between pain and emotions, offering the potential to improve both physical and psychological outcomes for patients. Future research should continue to explore the optimal dosing and administration protocols for esketamine in this context, as well as its long-term effects on patient quality of life.

In these patients, the use of esketamine is particularly beneficial due to its dual role in providing effective analgesia and improving emotional state. Given the high incidence of anxiety and depression in gastric cancer patients, and the limitations of conventional anesthesia in addressing these issues, esketamine offers a promising solution. Its mechanism of antagonizing NMDA receptors not only reduces postoperative pain but also mitigates tumor-related inflammation and associated emotional disturbances. This makes it a valuable adjunct in the anesthesia regimen for LG, enhancing both the physiological and psychological well-being of patients.

## **2. Materials and methods**

### **2.1. General Information**

A total of 246 patients with gastric cancer who underwent LG in XX Hospital from January 2021 to December 2024 were selected as the research subjects. They

were divided into the conventional anesthesia group and the esketamine group by the random number table method, with 123 cases in each group. In the conventional anesthesia group, there were 67 males and 56 females; the age ranged from 49 to 65 years old, with an average age of ( $56.37 \pm 5.43$ ) years old; according to the Tumor-Node-Metastasis (TNM) staging: 16 cases were in stage I, 72 cases were in stage II, and 35 cases were in stage III; according to the American Society of Anesthesiologists (ASA) classification: 48 cases were in grade I, 52 cases were in grade II, and 23 cases were in grade III. In the esketamine group, there were 72 males and 51 females; the age ranged from 50 to 65 years old, with an average age of ( $55.10 \pm 5.93$ ) years old; TNM staging: 13 cases were in stage I, 78 cases were in stage II, and 32 cases were in stage III; ASA classification: 45 cases were in grade I, 50 cases were in grade II, and 28 cases were in grade III. There was no significant difference in the baseline data between the two groups of patients ( $P > 0.05$ ).

Inclusion Criteria: 1) Meeting the diagnostic criteria for gastric cancer [6], and all patients were diagnosed pathologically by gastroscopy. 2) Having surgical indications and all receiving LG treatment. 3) Aged between 30 and 80 years old. 4) Having no contraindications to anesthesia. 5) The patients gave informed consent and signed the informed consent form.

Exclusion Criteria: 1) ASA classification  $>$  grade III. 2) Having non-cancerous chronic pain, anxiety disorder, or depression before the operation. 3) Having a history of drug abuse in the past. 4) Taking opioid analgesics for a long time. 5) Being allergic to the drugs involved in this study. 6) Having other combined malignant tumors.

## 2.2. Methods

Both groups of patients received LG. The conventional anesthesia group was given conventional-dose opioid anesthesia, and the esketamine group was given esketamine combined with low-dose opioid anesthesia.

Intraoperative anesthetic drug dosing was guided by the target Bispectral Index (BIS) range of 40–60. Propofol and remifentanyl were titrated based on BIS values and clinical signs (e.g., blood pressure, heart rate) to maintain stable anesthesia.

Both groups of patients were fasted for 8 hours and prohibited from drinking for 6 hours as routine. After entering the operating room, they were placed in a supine position, a venous access was established, blood volume was replenished, and the patients were given low-flow oxygen inhalation (3 L/min). All vital signs of the patients were closely monitored, such as electrocardiogram, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), bispectral index (BIS), partial pressure of arterial oxygen (PaO<sub>2</sub>), partial pressure of arterial carbon dioxide (PaCO<sub>2</sub>), and oxygen saturation (SpO<sub>2</sub>).

Anesthesia Induction: Both groups of patients were intravenously injected with propofol injection (Jiabo Pharmaceutical Co., Ltd., National Medicine Approval No. H20051842, specification: 20 mL: 200 mg) at a dose of 2 mg/kg, sufentanil hydrochloride (Yichang Humanwell Pharmaceutical Co., Ltd., National Medicine Approval No. H20054172, specification: 2 mL: 100 µg) at a dose of 2 µg/kg, and atracurium besilate for injection (Huanglong Pharmaceutical Co., Ltd., National Medicine Approval No. H20183355, specification: 20 mg) at a dose of 0.2 mg/kg.

On the basis of the conventional induction regimen, the esketamine group was intravenously injected with esketamine hydrochloride injection (Hengrui Medicine Co., Ltd., National Medicine Approval No. H20193336, specification: 2 mL:50 mg) at a dose of 0.1 mg/kg. The conventional anesthesia group was intravenously injected with an equal volume of normal saline on the basis of the conventional induction regimen. Tracheal intubation and mechanical ventilation were performed 3 minutes after the injection of the anesthesia induction drugs. The respiratory rate was maintained at 12 to 15 breaths/min, the tidal volume was maintained at 6 to 10 mL, and the inspiratory-expiratory ratio was 1:2.

**Anesthesia Maintenance:** Both groups were pumped with propofol at a rate of 4 to 10 mg/(kg·h) and remifentanyl hydrochloride (Enhua Pharmaceutical Co., Ltd., National Medicine Approval No. H20143315, specification: 2 mg) at a rate of 0.1 to 0.3 µg/(kg·min). Rocuronium bromide (North China Pharmaceutical Co., Ltd., National Medicine Approval No. H20103495, specification: 2.5 mL:25 mg) was used as a muscle relaxant during the operation in both groups.

On the basis of the conventional maintenance regimen, the esketamine group was intravenously pumped with esketamine at a rate of 4 µg/(kg·min), and the conventional anesthesia group was pumped with an equal volume of normal saline on the basis of the conventional maintenance regimen. During the operation, it was ensured that the patient's BIS index was between 40 and 60, the end-tidal partial pressure of CO<sub>2</sub> was between 35 and 45 mmHg, and the blood pressure fluctuation was within ±25% of the baseline value. If the patient had body movement during the operation, an additional 0.1 µg/kg of sufentanil was given. The muscle relaxant and esketamine were stopped 30 minutes before the end of the operation, and all anesthetics were stopped 5 minutes before the end of the operation.

If the patient's muscle relaxation recovery was poor, neostigmine methylsulfate at a dose of 0.03 mg/kg, glycopyrronium bromide at a dose of 0.2 mg, etc. were given to reverse the muscle relaxation. After the patient recovered spontaneous respiration and the oxygen saturation was >95%, the tracheal intubation was removed, and the patient was transferred to the Post Anesthesia Care Unit (PACU). All patients received a conventional postoperative analgesia regimen: patient-controlled intravenous analgesia (PCIA) was used. The analgesic drugs were sufentanil at a dose of 2 µg/kg + ketorolac tromethamine (Red Sun Pharmaceutical Co., Ltd., National Medicine Approval No. H20183297, specification: 1 mL:30 mg) at a dose of 120 mg + 0.9% normal saline at a volume of 100 mL, and the drug was pumped at a rate of 2 mL/h. Each time the patient self-administered an additional analgesic dose of 2 mL, and the interval time for self-controlled additional analgesia was ≥ 15 min.

## **2.3. Observation indicators**

### **2.3.1. Blood pressure, heart rate, and respiratory circulation indicators**

The intraoperative vital sign indicators of the two groups of patients were meticulously recorded to evaluate the physiological effects of the anesthesia regimens. Specifically, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SpO<sub>2</sub>) were measured at four critical time points: immediately after anesthesia induction (T<sub>0</sub>), during tracheal intubation (T<sub>1</sub>), at the

start of the operation (T2), and at the end of the operation (T3). These time points were selected to capture the dynamic physiological responses to anesthesia induction, airway management, surgical stimulation, and recovery from anesthesia. The data were collected using standardized monitoring equipment to ensure accuracy and consistency. Statistical analysis was performed using repeated measures analysis of variance (ANOVA) to assess differences in vital signs between the two groups across the time points. This approach allowed for a comprehensive evaluation of the hemodynamic and respiratory stability provided by each anesthesia regimen, highlighting the potential advantages of the esketamine-based low-opioid approach in maintaining intraoperative physiological stability. The findings contribute to understanding how different anesthesia strategies impact patient physiology during laparoscopic gastric cancer surgery, offering insights for optimizing perioperative care.

### **2.3.2. Dosage of opioid drugs**

The dosages of sufentanil and remifentanyl administered during the operation were meticulously recorded for both groups of patients. These opioids are commonly used for their potent analgesic effects; however, their usage can be associated with side effects such as respiratory depression and hemodynamic instability. By comparing the dosages between the conventional anesthesia group and the esketamine group, we aimed to evaluate the potential of esketamine to reduce opioid requirements while maintaining effective pain control. The data were collected by the anesthesiology team throughout the surgical procedure, ensuring accurate and consistent documentation. Statistical analysis was performed to compare the mean dosages between groups, with significance set at  $P < 0.05$ . This comparison provides insights into the efficacy of the esketamine-based low-opioid anesthesia regimen in minimizing opioid use, which is crucial for reducing postoperative complications and enhancing patient recovery. The findings suggest that the integration of esketamine into the anesthesia protocol may offer a promising approach to optimizing perioperative care in patients undergoing laparoscopic gastric cancer surgery.

### **2.3.3. Postoperative pain situation**

The additional administration of patient-controlled intravenous analgesia (PCIA) analgesic drugs within 24 and 48 hours postoperatively was carefully documented and compared between the two groups. PCIA is a critical component of postoperative pain management, allowing patients to self-administer analgesics as needed for optimal pain relief. By quantifying the frequency of additional drug administration, we aimed to assess the adequacy of intraoperative analgesia and its impact on postoperative recovery. Data were collected by nursing staff during routine postoperative care, ensuring accurate and timely recording of each PCIA activation. Statistical analysis was performed to compare the mean additional doses between groups, with significance set at  $P < 0.05$ . This comparison provided insights into the effectiveness of the anesthesia regimens in reducing postoperative pain and the need for supplementary analgesics. The findings indicated that the esketamine group required fewer additional doses of PCIA drugs, suggesting better pain control and highlighting the potential of esketamine-based low-opioid anesthesia to enhance postoperative recovery and reduce opioid-related side effects.

#### **2.3.4. Changes in emotional state**

One day before the operation, 1 day, 3 days, and 7 days after the operation, the Self-Rating Anxiety Scale (SAS) [7] and the Self-Rating Depression Scale (SDS) [8] were used to evaluate the changes in the anxiety and depression emotions of the two groups of patients, so as to reflect the changes in the overall emotional state of the patients. The SAS contains 20 items and uses a 4-level scoring method (1 to 4 points, including positive and negative scoring). After adding all the scores, the raw score is obtained. After multiplying the raw score by 1.25 and rounding it off, the integer part is the standard score. According to the results of the Chinese norm,  $SAS \geq 50$  points indicates anxiety, and the score is positively correlated with the anxiety state. The SDS contains 20 items, and the scoring method and score conversion method are the same as those of the SAS. In China, an SDS score  $\geq 53$  points indicates that the patient has a depressive state, and the score is positively correlated with the patient's depressive symptoms.

The SAS and SDS were used to assess patients' emotional states. Measurements were taken 1 day before the operation, and 1, 3, and 7 days after the operation. Although the postoperative follow-up period was relatively short, this timeframe was selected to focus on the acute recovery phase. Future studies could extend the follow-up to 14 or 30 days to further evaluate long-term emotional recovery.

#### **2.4. Statistical methods**

The data of this study were processed using SPSS 20.0 statistical software. All quantitative data in this study conform to the normal distribution and are expressed as mean  $\pm$  standard deviation ( $x \pm s$ ). The t-test was selected for between-group comparisons, and the F-test was used for repeated measures ANOVA. Categorical data are presented as frequency and percentage ( $n$ , %), and the  $X^2$  test was used. The significance level was set at  $\alpha = 0.05$ .

#### **2.5. Missing data handling**

No significant missing data were encountered. For the few missing data points, the last observation carried forward (LOCF) method was used.

#### **2.6. Multiple comparison adjustments**

The Bonferroni correction was applied to adjust for multiple comparisons, with the significance level adjusted to  $\alpha = 0.05/\text{number of comparisons}$ .

### **3. Results**

#### **3.1. Blood pressure, heart rate, and respiratory circulation indicators**

##### **3.1.1. HR**

There were statistically significant differences in the interaction, time, and between-group comparisons of HR between the two groups of patients ( $P < 0.05$ ). Starting from T1, the HR of the patients in both groups gradually decreased, and at T3, the HR increased, and there were statistically significant differences compared with the previous time points ( $P < 0.05$ ). The HR levels of the esketamine group at T1,

T2, and T3 were consistently higher than those of the conventional anesthesia group ( $P < 0.05$ ), as shown in **Table 1**.

**Table 1.** Comparison of HR levels in different periods between the two groups (times/min,  $\bar{x} \pm s$ ).

| Group                 | Case | T <sub>0</sub>    | T <sub>1</sub>    | T <sub>2</sub>    | T <sub>3</sub>             |
|-----------------------|------|-------------------|-------------------|-------------------|----------------------------|
| Routine anesthesia    | 123  | 75.75 $\pm$ 10.92 | 70.11 $\pm$ 6.40* | 66.24 $\pm$ 4.45* | 70.23 $\pm$ 8.27* $\Delta$ |
| Esketamine            | 123  | 76.92 $\pm$ 10.83 | 74.63 $\pm$ 8.52  | 71.34 $\pm$ 5.61* | 73.60 $\pm$ 8.55* $\Delta$ |
| <i>F mutual/P</i>     |      | 30.309/<0.001     |                   |                   |                            |
| <i>F interblock/P</i> |      | 15.670/<0.001     |                   |                   |                            |
| <i>F times/P</i>      |      | 8.966/<0.001      |                   |                   |                            |

Note: \*, indicates vs. T<sub>0</sub>,  $P < 0.05$ ;  $P < 0.05$ ;  $\Delta$ ,  $P < 0.05$  vs. T<sub>2</sub>.

### 3.1.2. Blood pressure

Comparing the SBP and DBP levels between the two groups, interaction, time, and group were significant ( $P < 0.05$ ); SBP and DBP decreased after the T<sub>1</sub> ( $P < 0.05$ ), SBP and DBP in Sketamine were higher in T<sub>1</sub>, T<sub>2</sub> and T<sub>3</sub> than the conventional anesthesia group ( $P < 0.05$ ), see **Tables 2** and **3**.

**Table 2.** Changes in SBP levels during different periods in the two groups (mmHg,  $\bar{x} \pm s$ ).

| Group                 | Case | T <sub>0</sub>     | T <sub>1</sub>     | T <sub>2</sub>     | T <sub>3</sub>               |
|-----------------------|------|--------------------|--------------------|--------------------|------------------------------|
| Routine anesthesia    | 123  | 135.61 $\pm$ 15.77 | 129.27 $\pm$ 6.64* | 124.21 $\pm$ 5.29* | 129.59 $\pm$ 10.94* $\Delta$ |
| Esketamine            | 123  | 135.98 $\pm$ 15.76 | 132.69 $\pm$ 8.73* | 128.28 $\pm$ 6.70* | 131.64 $\pm$ 10.66* $\Delta$ |
| <i>F mutual/P</i>     |      | 24.300/<0.001      |                    |                    |                              |
| <i>F interblock/P</i> |      | 18.633/<0.001      |                    |                    |                              |
| <i>F times/P</i>      |      | 10.251/<0.001      |                    |                    |                              |

Note: \*, indicates vs. T<sub>0</sub>,  $P < 0.05$ ;  $P < 0.05$ ;  $\Delta$ ,  $P < 0.05$  vs. T<sub>2</sub>. 1mmHg = 0.133Kpa.

**Table 3.** Changes in DBP levels during different periods in the two groups (mmHg,  $\bar{x} \pm s$ ).

| Group                 | Case | T <sub>0</sub>   | T <sub>1</sub>    | T <sub>2</sub>    | T <sub>3</sub>             |
|-----------------------|------|------------------|-------------------|-------------------|----------------------------|
| Routine anesthesia    | 123  | 89.99 $\pm$ 8.33 | 84.40 $\pm$ 6.62* | 80.42 $\pm$ 5.33* | 84.50 $\pm$ 7.91* $\Delta$ |
| Esketamine            | 123  | 89.67 $\pm$ 8.35 | 86.86 $\pm$ 6.59* | 83.12 $\pm$ 5.66* | 85.92 $\pm$ 8.29* $\Delta$ |
| <i>F mutual/P</i>     |      | 37.241/<0.001    |                   |                   |                            |
| <i>F interblock/P</i> |      | 25.262/<0.001    |                   |                   |                            |
| <i>F times/P</i>      |      | 16.785/<0.001    |                   |                   |                            |

Note: \* T<sub>0</sub>,  $P < 0.05$ ;  $P < 0.05$ , T<sub>0</sub>;  $\Delta$ ,  $P < 0.05$ . 1mmHg = 0.133Kpa.

### 3.1.3. SpO<sub>2</sub>

The interaction, time, and comparison of SpO<sub>2</sub> in both groups ( $P < 0.05$ ); after entering the T<sub>1</sub>, SpO<sub>2</sub> increased, and the difference increased in T<sub>3</sub> ( $P < 0.05$ ); and SpO<sub>2</sub> in esketamine group was higher than T<sub>1</sub>, T<sub>2</sub>, and T<sub>3</sub> than that of conventional anesthesia ( $P < 0.05$ ), as shown in **Table 4**.

**Table 4** Changes in SpO<sub>2</sub> levels during different periods in the two groups  $P < 0.05$ .

**Table 4.** Changes in SpO<sub>2</sub> levels during different periods in the two groups ( $\bar{x} \pm s$ ).

| Group                 | Case | T <sub>0</sub> | T <sub>1</sub> | T <sub>2</sub> | T <sub>3</sub>             |
|-----------------------|------|----------------|----------------|----------------|----------------------------|
| Routine anesthesia    | 123  | 98.43 ± 1.21   | 95.25 ± 1.05*  | 93.01 ± 1.27*  | 97.66 ± 1.62* <sup>Δ</sup> |
| Esketamine            | 123  | 98.21 ± 1.39   | 96.83 ± 0.87*  | 94.92 ± 0.85*  | 97.99 ± 1.63 <sup>Δ</sup>  |
| <i>F mutual/P</i>     |      | 437.062/<0.001 |                |                |                            |
| <i>F interblock/P</i> |      | 366.363/<0.001 |                |                |                            |
| <i>F times/P</i>      |      | 183.741/<0.001 |                |                |                            |

### 3.2. Amount of opioid drugs

The dosage of sufentanil and remifentanil for esketamine was lower than those in the conventional anesthesia group ( $P < 0.05$ ), as shown in **Table 5**.

**Table 5.** Comparison of opioid use in the two groups ( $\bar{x} \pm s$ ).

| Group              | Case | Sulfentanil (μg) | Remifentanil (mg) |
|--------------------|------|------------------|-------------------|
| Routine anesthesia | 123  | 40.22 ± 10.66    | 2.03 ± 0.11       |
| Esketamine         | 123  | 20.32 ± 8.56     | 1.76 ± 0.12       |
| <i>t</i>           |      | 16.143           | 18.395            |
| <i>P</i>           |      | <0.001           | <0.001            |

### 3.3. Postoperative pain status

The incidence of PCIA analgesia in the 24 h and 48 h postoperative periods of the esketamine group was lower than that in the conventional anesthesia group ( $P < 0.05$ ), as shown in **Table 6**.

**Table 6.** Comparison of postoperative pain between the two groups ( $n, \%$ ).

| Group              | Case | Postoperative 24 h | Postoperative 48 h |
|--------------------|------|--------------------|--------------------|
| Routine anesthesia | 123  | 16(13.01)          | 23(18.69)          |
| Esketamine         | 123  | 6(4.88)            | 11(8.94)           |
| $\chi^2$           |      | 4.992              | 4.915              |
| <i>P</i>           |      | 0.025              | 0.027              |

### 3.4. Changes in emotional state

Comparing SAS and SDS, interaction, time, and group significance ( $P < 0.05$ ); SADS and SDS scores increased after 1d and SDS and SDS scores decreased compared with the previous time ( $P < 0.05$ ), from 1 d to 7d were always lower than those of the conventional anesthesia group ( $P < 0.05$ ), see **Tables 7 and 8**.

**Table 7.** Comparison of SAS scores between the two groups at different time points (score,  $\bar{x} \pm s$ ).

| Group                                                                                                                                     | Case | Preoperative 1d  | Preoperative 1d   | Preoperative 3d   | Preoperative 7d            |
|-------------------------------------------------------------------------------------------------------------------------------------------|------|------------------|-------------------|-------------------|----------------------------|
| Routine anesthesia                                                                                                                        | 123  | 48.15 $\pm$ 4.41 | 57.21 $\pm$ 5.52* | 60.17 $\pm$ 5.63* | 57.26 $\pm$ 3.44* $\Delta$ |
| Esketamine                                                                                                                                | 123  | 48.39 $\pm$ 4.20 | 53.81 $\pm$ 4.13* | 57.29 $\pm$ 4.20* | 54.13 $\pm$ 3.23* $\Delta$ |
| <i>F mutual/P</i>                                                                                                                         |      | 143.376/<0.001   |                   |                   |                            |
| <i>F interblock/P</i>                                                                                                                     |      | 125.226/<0.001   |                   |                   |                            |
| <i>F times/P</i>                                                                                                                          |      | 106.947/<0.001   |                   |                   |                            |
| Note: * compared to 1d, $P < 0.05$ ; compared to 1d, $P < 0.05$ ; $\Delta$ Represents and is compared with 3d after surgery, $P < 0.05$ . |      |                  |                   |                   |                            |

**Table 8.** Comparison of SDS scores between two groups at different time points (score,  $\bar{x} \pm s$ ).

| Group                                                                                                                                             | case | Preoperative 1d  | Preoperative 1d   | Preoperative 3d   | Preoperative 7d            |
|---------------------------------------------------------------------------------------------------------------------------------------------------|------|------------------|-------------------|-------------------|----------------------------|
| Routine anesthesia                                                                                                                                | 123  | 46.26 $\pm$ 4.24 | 52.29 $\pm$ 4.07* | 55.15 $\pm$ 3.27* | 51.52 $\pm$ 3.66* $\Delta$ |
| Esketamine                                                                                                                                        | 123  | 46.78 $\pm$ 4.21 | 48.36 $\pm$ 3.53* | 52.10 $\pm$ 2.29* | 48.20 $\pm$ 2.67* $\Delta$ |
| <i>F mutual/P</i>                                                                                                                                 |      | 115.390/<0.001   |                   |                   |                            |
| <i>F interblock/P</i>                                                                                                                             |      | 80.161/<0.001    |                   |                   |                            |
| <i>F times/P</i>                                                                                                                                  |      | 59.767/<0.001    |                   |                   |                            |
| Note: * compared to 1d, $P < 0.05$ ; compared to 1d, $P < 0.05$ ; $\Delta$ Representation and comparison with 3d after surgery, with $P < 0.05$ . |      |                  |                   |                   |                            |

## 4. Discussion

General anesthesia consists of three essential elements: hypnosis, analgesia, and muscle relaxation. Opioid anesthetic drugs are the most commonly used analgesics. Although their analgesic effect is clear, due to factors such as addiction and significant adverse reactions, they are contrary to the concept of comfortable medical care and the requirements of fast-track surgery advocated in clinical practice at present. Therefore, opioid-free anesthesia has been a research hotspot in recent years. Salomé et al. [9] found in a Meta-analysis that opioid-free anesthesia can provide good analgesic effects during general anesthesia and reduce the use of postoperative opioids and related adverse events. Analgesic drugs such as lidocaine and dexmedetomidine have been recommended to replace opioids alone or in combination [10]. As a new analgesic and sedative drug, esketamine has obvious analgesic effects and also has antidepressant effects. Theoretically, it can also be used as an opioid substitute in general anesthesia for LG.

The results of this study showed that the intraoperative dosages of sufentanil and remifentanil in the esketamine group were significantly lower than those in the conventional anesthesia group, and the additional analgesic frequencies of PCIA in the esketamine group at 24 h and 48 h after surgery were lower than those in the conventional anesthesia group ( $P < 0.05$ ). This indicates that adding esketamine to the conventional anesthesia regimen for LG can effectively reduce the infusion volume of opioids during the anesthesia maintenance stage, achieve the goal of low - opioid anesthesia, and can further reduce postoperative pain compared with the opioid anesthesia regimen. The reasons are as follows: As a lipophilic drug, ketamine can block the connection between the thalamus - neocortex transmission system, inhibit

this pain - conducting pathway, and it can activate opioid receptors to play an analgesic role. Moreover, ketamine can produce analgesic effects at a relatively low blood drug concentration, and the pain threshold can be increased after intravenous injection of a sub-dose. After ketamine is split into two optical isomers, the dextrorotatory isomer is esketamine [11]. Esketamine not only retains most of the advantages of ketamine but also significantly improves sedation and analgesia effects. Only 1/2 of the dose of esketamine can obtain an anesthetic effect similar to that of ketamine [12]. Thus, it can be seen that the excellent analgesic mechanism of esketamine can effectively reduce the use of intraoperative opioids. The key mechanism of postoperative pain caused by opioids is hyperalgesia, which may be related to the enhanced activity of the central glutamatergic system involving N-methyl-D-aspartate (NMDA) receptors, resulting in neuronal sensitization. Esketamine can reduce the binding of amino acids to NMDA receptors, inhibit the generation of pain-sensing neurons, prevent central sensitization, and improve postoperative pain.

The results of this study showed that the fluctuations in blood pressure, heart rate, and SpO<sub>2</sub> during esketamine anesthesia were all smaller than those in the conventional anesthesia group ( $P < 0.05$ ), suggesting that esketamine-combined low-opioid anesthesia has less impact on the patient's respiratory and blood circulation than conventional opioid anesthesia. The reasons are as follows: Sufentanil can directly dilate peripheral blood vessels and can induce an increase in vagus nerve tension, resulting in circulatory depression. Although vasopressors can be used synergistically during the operation to ensure perfusion pressure, improper handling can cause excessive blood pressure fluctuations, leading to sinus tachycardia and large fluctuations in heart rate. Esketamine - combined low - opioid anesthesia can reduce the use of drugs such as sufentanil and relieve circulatory depression. On the other hand, esketamine itself can stimulate the sympathetic nerve, release endogenous catecholamines, increase the patient's blood pressure and cardiac output, and improve the heart rate. One of the typical side effects of opioids is respiratory depression. An animal experiment [13] confirmed that seven different opioids can all cause respiratory depression in rats, which may be related to the fact that these drugs can inhibit medullary respiratory motor neurons. One of the major advantages of esketamine is that it has a slight impact on the patient's respiratory system. Occasionally, transient and self-recoverable short-term respiratory depression may occur, so it can effectively ensure the patency of the patient's respiratory circulation.

The results showed that the SAS and SDS scores of the two groups of patients increased after surgery and declined to a certain extent until 7 days after surgery, and the scores of the esketamine group were continuously lower than those of the conventional anesthesia group ( $P < 0.05$ ), suggesting that the application of esketamine can effectively improve the postoperative anxiety and depression states of patients. Negative emotions almost run through the entire course of the onset of patients with malignant tumors. Zabora et al. [14] found in a large-scale study involving 4996 patients with 14 types of malignant tumors that the incidence of depression exceeded 30%. Age, income, discomfort, and uncertainty about treatment outcomes are all factors contributing to the occurrence of depression. In addition, postoperative gastric cancer patients experience the loss of physiological organ function and integrity, changes in diet, etc. These factors can all increase the risk of

anxiety and depression [15]. Past studies [16] have confirmed that anxiety and depression can reduce the treatment compliance of cancer patients, increase the risk of suicide and additional health expenditures, and are an independent risk factor for the increase in patient mortality. Since malignant tumors cannot be completely cured, and maintenance treatment is difficult and has significant side effects, the effects of conventional psychological nursing and psychotherapy are generally limited. Esketamine was clinically approved for the treatment of adult refractory depression in 2019. However, its specific antidepressant mechanism is not yet fully clear, and it may be related to the fact that this drug can promote the release of glutamate, resulting in the acute activation of postsynaptic AMPA receptors. In addition, there are multiple comorbid factors between pain and depression, including the activation of inflammatory factors, abnormal neurotransmitter secretion, changes in neurotrophic factors, and hyperalgesia. Severe acute pain caused by opioids is also one of the reasons for the deterioration of patients' emotions, while esketamine can effectively reduce postoperative pain and also play a role in improving anxiety and depression.

The results of this study are consistent with previous research, which has shown that esketamine can effectively reduce the use of opioid drugs and improve patients' postoperative emotional state [9,10]. However, our study further demonstrates that esketamine can also enhance the stability of intraoperative vital signs and improve postoperative pain control, which has not been fully documented in previous studies. The unique mechanism of esketamine, which involves NMDA receptor modulation and the reduction of tumor - related inflammation, may play a key role in these outcomes. By inhibiting the release of pro - inflammatory cytokines and reducing the activity of the central glutamatergic system, esketamine not only alleviates postoperative pain but also positively impacts the patients' emotional well - being.

## **5. Conclusion**

In conclusion, compared with conventional opioid anesthesia, the application of esketamine - combined low - opioid anesthesia in laparoscopic gastric cancer (LG) patients offers several significant advantages, with pronounced benefits for postoperative mental health. First, it effectively reduces the intraoperative use of opioids such as sufentanil and remifentanil, minimizing the risk of opioid-related side effects such as respiratory depression and hemodynamic instability. Second, this regimen helps stabilize vital signs, including blood pressure, heart rate, and respiratory circulation, reducing fluctuations that could otherwise complicate perioperative management. Third, postoperative pain control is significantly improved, with reduced requirements for additional analgesic drugs within 24 and 48 h postoperatively. This translates to better patient comfort and faster recovery. Most importantly, this regimen confers a distinct mental health advantage. The emotional well-being of patients is markedly enhanced, with significantly lower levels of anxiety and depression observed up to seven days postoperatively, indicating a positive and proactive impact on psychological recovery during a critical phase. These findings highlight the clinical value of esketamine-based low-opioid anesthesia in optimizing holistic perioperative care for LG patients, offering a safer, more effective, and psychologically supportive alternative to traditional opioid-dominated regimens. Future research should further

explore the long-term mental health benefits and broader applicability of this approach in enhancing patient psychological resilience and overall outcomes.

**Author contributions:** Conceptualization, WX and TJ; methodology, WX; software, WX; validation, WX, WX and TJ; formal analysis, TJ; investigation, TJ; resources, TJ; data curation, TJ; writing—original draft preparation, TJ; writing—review and editing, WX; visualization, WX; supervision, WX; project administration, JZ; funding acquisition, JZ. All authors have read and agreed to the published version of the manuscript.

**Funding:** None.

**Ethical approval:** The procedures for both T1 and T2 surveys adhered to the (i) Declaration of Helsinki, and (ii) ethical principles for medical, psychological, and sociological research involving human participants. Xiantao first people's Hospital Research Ethics Committee approved the study protocol (Lunshen [2021-001-01] No). All participants signed the informed consent in this study.

**Informed consent statement:** Informed consent was obtained from all subjects involved in the study.

**Conflict of interest:** The authors declare no conflict of interest.

## References

1. Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. *Lancet*. 2020; 396(10251): 635–648. doi: 10.1016/s1040-8428(97)10023-3
2. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA: A Cancer Journal for Clinicians*. 2021; 71(3): 264–279. doi: 10.3322/caac.21657
3. Song X, Wang F, Dong R, et al. Efficacy and safety of remimazolam tosylate combined with esketamine for analgesic sedation in mechanically ventilated ICU patients: A single-arm clinical study protocol. *Frontiers in Medicine*. 2022; 9: 832105. doi: 10.3389/fmed.2022.832105
4. Zhao X, Cao F, Liu Q, et al. Behavioral, inflammatory and neurochemical disturbances in LPS and UCMS-induced mouse models of depression. *Behavioural Brain Research*. 2019; 364: 494–502. doi: 10.1016/j.bbr.2017.05.064
5. Nielsen RV, Fomsgaard JS, Nikolajsen L, et al. Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. *European Journal of Pain*. 2019; 23(3): 455–460. doi: 10.1002/ejp.1317
6. Ajani JA, D'Amico TA, Almhanna K, et al. Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. *Journal Of the National Comprehensive Cancer Network*. 2016; 14(10): 1286–1312.
7. Li H, Jin D, Qiao F, et al. Relationship between the Self-Rating Anxiety Scale score and the success rate of 64-slice computed tomography coronary angiography. *The International Journal of Psychiatry in Medicine*. 2015; 51(1): 47–55. doi: 10.1177/0091217415621265
8. Yue T, Li Q, Wang R, et al. Comparison of hospital anxiety and depression scale (HADS) and Zung self-rating anxiety/depression scale (SAS/SDS) in evaluating anxiety and depression in patients with psoriatic arthritis. *Dermatology*. 2019; 236(2): 170–178. doi: 10.1159/000498848
9. Salomé A, Harkouk H, Fletcher D, et al. Opioid-Free Anesthesia Benefit–Risk Balance: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Journal of Clinical Medicine*. 2021; 10(10): 2069. doi: 10.3390/jcm10102069
10. Beloeil H. Opioid-free anesthesia. *Best Practice & Research Clinical Anaesthesiology*. 2019; 33(3): 353–360. doi: 10.1016/j.bpa.2019.09.002
11. Weber F, Wulf H, Fau-Gruber M, Gruber M, et al. Sketamine and s-norketamine plasma concentrations after nasal and iv administration in anesthetized children. *Paediatr Anaesth*. 2004; 14(12): 983–988. doi: 10.1111/j.1460-9592.2004.01358.x

12. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. *Journal of Pharmacology and Experimental Therapeutics*. 1992; 260(3): 1209–1213. doi: 10.1016/s0022-3565(25)11430-4
13. Kuo A, Wyse BD, Meurermans W, et al. In vivo profiling of seven common opioids for antinociception, constipation and respiratory depression: no two opioids have the same profile. *British Journal of Pharmacology*. 2015; 172(2): 532–548. doi: 10.1111/bph.12696
14. Zabora J, BrintzenhofeSzoc K, Curbow B, et al. The prevalence of psychological distress by cancer site. *Psychooncology*. 2001; 10(1): 19–28. doi: 10.1002/1099-1611(200101/02)10:1<19::aid-pon501>3.0.co;2-6
15. Brintzenhofe-Szoc KM, Levin TT, Li Y, et al. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. *Psychosomatics*. 2009; 50(4): 383–391. doi: 10.1176/appi.psy.50.4.383
16. Satin JR, Linden W, Phillips MJ. Depression as a predictor of disease progression and mortality in cancer patients: a metaanalysis. *Cancer*. 2009; 115(22): 5349–5361. doi: 10.1002/cncr.24561