

## ORIGINAL RESEARCH

# Effects of different doses of esketamine on hemodynamic indexes, pain stress indexes, and VAS scores in patients with benign ovarian tumors undergoing laparoscopic resection induced by remifentanyl

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**Abstract**

This study aimed to investigate the effects of different doses of esketamine on hemodynamic indicators, pain stress indicators and Visual Analog Scale (VAS) scores in patients undergoing laparoscopic resection for benign ovarian tumors induced by remifentanyl. A total of 110 patients with benign ovarian tumors scheduled for laparoscopic resection between June and December 2023 were included in the study and divided into three groups: Group A (35 cases), Group B (37 cases), and Group C (38 cases), based on their anesthesia regimen. Anesthesia induction for all groups included propofol, remifentanyl, and cisatracurium. Group A received an intravenous dose of 0.8 mg/kg esketamine, Group B received 0.6 mg/kg esketamine and Group C did not receive esketamine. The results revealed statistically significant differences in average arterial pressure and heart rate at various time points within each group ( $p < 0.05$ ), and significant differences were observed in Substance P (SP) and Prostaglandin E2 (PEG2) at three different time points within each group ( $p < 0.05$ ). VAS scores during and after surgery at 6 and 12 hours significantly differed among the three groups ( $p < 0.05$ ). There was a significant difference in awakening time among the three groups ( $p < 0.05$ ). However, there were no statistically significant differences in the incidence of adverse reactions among the three groups ( $p > 0.05$ ). In conclusion, both 0.6 mg/kg and 0.8 mg/kg doses of esketamine effectively prevented remifentanyl-induced hyperalgesia in patients undergoing laparoscopic resection for benign ovarian tumors, significantly reducing patient pain. Notably, the 0.6 mg/kg dose of esketamine demonstrated better hemodynamic stability, promoted patient recovery, and showed superior clinical utility compared to the 0.8 mg/kg dose.

**Keywords**

Different doses; Esketamine; Remifentanyl; Laparoscopic resection of benign ovarian tumors; Hemodynamics; VAS score

## 1. Introduction

Benign ovarian tumor is a common clinical gynecological disease with a high incidence rate, ranking second only to uterine fibroids among female genital tumors [1]. Its onset can severely impact both the physical and psychological well-being of patients, necessitating timely intervention to alleviate clinical symptoms and improve overall outcomes. Surgical resection is currently the primary treatment approach for benign ovarian tumors, with laparoscopic surgery emerging as the preferred modality due to its minimally invasive nature, reduced postoperative discomfort, and quicker recovery. Preoperative anesthesia plays a pivotal role in laparoscopic surgery for benign ovarian tumor removal [2], requiring attributes such

as rapid onset, effective analgesia, and swift emergence to minimize patient discomfort, ensure surgical precision, and optimize procedural outcomes. Remifentanyl, a short-acting intravenous anesthetic agent, offers the advantages of a rapid onset of action and prompt recovery. However, it is essential to acknowledge that the analgesic effects of remifentanyl may fade rapidly upon discontinuation of the infusion, predisposing patients to nociceptive hypersensitivity and adversely affecting surgical treatment and outcomes [3–5]. Therefore, there is a compelling need to explore more suitable, safe, and pragmatic approaches to mitigate nociceptive hypersensitivity in patients undergoing laparoscopic resection. Esketamine, a novel N-methyl-D-aspartate (NMDA) receptor antagonist, has garnered attention as an anesthetic with exceptional analgesic

properties due to its rapid onset and elimination, preservation of spontaneous breathing, control of circulatory excitation, increased analgesic efficacy compared to ketamine, and a reduced risk of adverse effects [6, 7]. Presently, there is no definitive consensus on the utilization of esketamine in the context of laparoscopic resection for benign ovarian tumors, nor is there a consensus on the optimal dosage for achieving maximal efficacy [8, 9]. This study aims to evaluate and analyze the differential effects and effectiveness of varying esketamine doses in patients diagnosed with benign ovarian tumors scheduled for laparoscopic resection at our institution.

## 2. Material and methods

### 2.1 Clinical data

A total of 110 patients with benign ovarian tumors admitted to our hospital between June and December 2023 were selected and divided into 3 groups by random number table method. No significant differences ( $p > 0.05$ ) were found between them regarding baseline characteristics (Table 1).

The study inclusion criteria were: (1) patients meeting the diagnostic criteria for ovarian tumors as outlined in the Modern Clinical Oncology Series, (2) classified as American Society of Anesthesiologists (ASA) grade I–II, (3) aged 18 years or older, and (4) satisfying surgical indications and undergoing retrograde laparoscopic resection.

Exclusion criteria were defined as follows: (1) recent use of immunosuppressive drugs within the preceding 3 months, (2) presence of psychiatric disorders or cognitive impairments, (3) pregnancy or lactation status, (4) concomitant diagnosis of other malignancies (such as lung cancer or liver cancer), and (5) coexisting immune, circulatory, or hematologic disorders. The CONSORT flowchart of this paper is shown in Fig. 1.

### 2.2 Experimental procedures

Before surgery, all patients in the three groups adhered to an 8-hour fasting and drinking regimen. Upon entering the operating room, various vital signs of the patients were monitored using a multifunctional vital sign monitor (Model YT58-HY2850, Beijing Hefuda Technology Co., Ltd., Beijing, China), including arterial pressure, heart rate, body temperature, and pulse oxygen saturation. Anesthesia induction involved intravenous administration of propofol (1.5 mg/kg), remifentanyl (1  $\mu$ g/kg), and cis-atracurium (0.15 mg/kg). For patients in Groups A and B, anesthesia induction was supplemented with intravenous infusion of esketamine at dosages of 0.8 mg/kg and 0.6 mg/kg, respectively. Esketamine infusions were administered at regular 15-minute intervals. In contrast, Group C did not receive esketamine. Maintenance of anesthesia across all three groups consisted of intravenous infusion of remifentanyl at a rate of 0.3  $\mu$ g/(kg·min) combined with propofol at 6 mg/(kg·h). Intraoperative blood pressure fluctuations were controlled to maintain them at approximately 20% of the baseline values. Additionally, electroencephalogram (EEG) dual frequency index levels were regulated to remain within the range of 40–50. At the end of the operation, the infusion of propofol and remifentanyl was stopped immediately.

Subsequently, the endotracheal tube was removed once the patient exhibited restored spontaneous breathing and was transferred to the recovery room for continuous observation over a 90-minute period. Patients were eligible for transfer to the ward if no abnormalities were detected during this period.

### 2.3 Observed indicators

Various parameters were meticulously examined and compared among the three patient groups, encompassing surgical-related indicators, hemodynamic indexes, pain stress indicators, pain scores, and the incidence of adverse effects.

(1) Surgical-related indicators included the duration of the surgical procedure, time to awakening, extubation time, and cumulative morphine dosage over 24 hours.

(2) Hemodynamic indexes, comprising mean arterial pressure and heart rate, were measured at three-time points: 15 minutes before surgery, 30 minutes into the surgical procedure, and 1 hour following surgery. These measurements were obtained using a vital sign monitor (VS900, Myriad, Shenzhen, China).

(3) Pain stress indicators involved the collection of 3 mL of venous blood from each group before surgery, during surgery, and 1-hour post-surgery. The blood samples were then centrifuged (with an 8 cm radius, 3200 revolutions per minute, for 10 minutes) according to the manufacturer's instructions.

(4) Pain scores were assessed at 2, 6, and 12 hours following the surgical procedure using the Visual Analog Scale (VAS). The VAS score ranged from 0, indicating an absence of pain, to 10, indicating severe pain. Higher scores were indicative of more intense pain.

(5) Adverse reactions, including symptoms such as nausea, vomiting, dizziness and chills, were also monitored and documented.

### 2.4 Statistical processing

The SPSS v25.0 software (International Business Machines Corporation, Armonk, NY, USA) was used for data analysis, and  $t$  and chi-squared tests ( $\chi^2$ ) were used to test the measurement and count data, respectively, with  $p < 0.05$  representing a significant difference between groups.

## 3. Results

### 3.1 Comparison of clinical data of the three groups

The results showed no statistically significant difference between the clinical data of the three groups (Table 1).

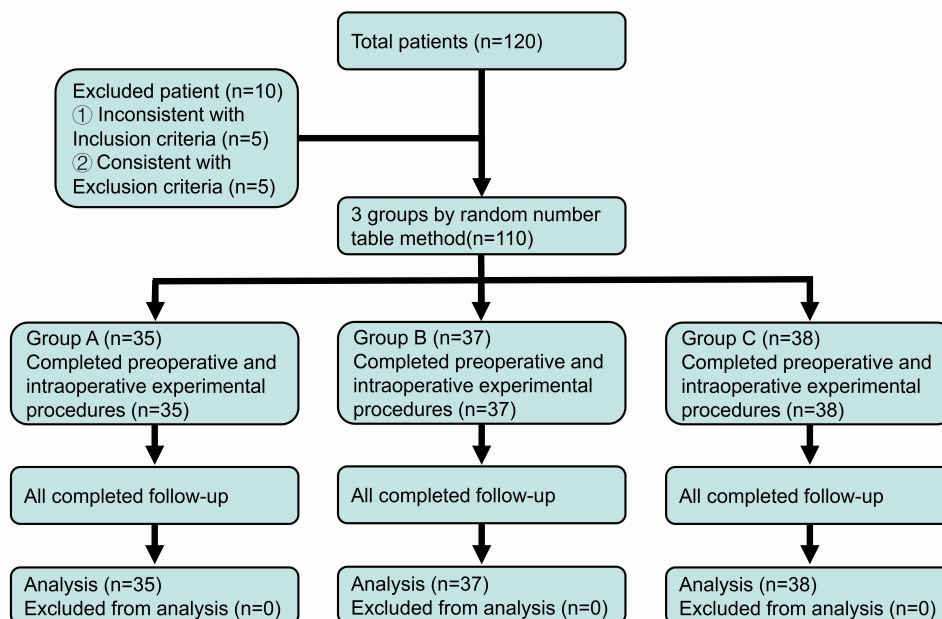
### 3.2 Comparison of hemodynamic indexes in the three groups

The comparative analysis of mean arterial pressure and heart rate among the three groups, conducted at three distinct time intervals (15 minutes preoperatively, 30 minutes intraoperatively, and 1 hour postoperatively) using Analysis of Variance (ANOVA) design, yielded significant findings that are summarized as follows:

**TABLE 1. Comparison of clinical data in the three groups.**

Indicator	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	$F/\chi^2$	$P$
Age (yr)	40.21 ± 3.22	40.19 ± 3.20	40.14 ± 3.16	0.005	0.995
BMI (kg/m <sup>2</sup> )	22.51 ± 1.02	22.49 ± 1.04	22.45 ± 1.01	0.025	0.975
Duration of disease (mon)	7.83 ± 0.75	7.81 ± 0.78	7.79 ± 0.78	0.024	0.976
ASA Classification					
Grade I	20	21	20	0.139	0.932
Grade II	15	16	18		
Academic qualifications					
High School and below	17	18	18	0.011	0.994
College and above	18	19	20		
Marital Status					
Married	20	20	22	0.191	0.908
Unmarried	10	11	12		
Widowed	5	6	4		
Career					
Workers	14	15	17	0.059	0.970
Farmers	12	13	12		
Teacher	7	5	4		
Others	2	4	5		
Symptoms					
Hidden pain in the abdomen	22	24	23	0.151	0.927
Difficulty in urination	13	13	15		

ASA: American Society of Anesthesiologists; BMI: Body Mass Index.

**FIGURE 1. CONSORT flow chart.**

(1) Statistically significant differences ( $p < 0.05$ ) were observed between the three groups concerning mean arterial pressure and heart rate at both the 30-minute intraoperative and 1-hour postoperative time points. Additionally, within-group comparisons demonstrated statistical significance ( $p < 0.05$ ) for mean arterial pressure and heart rate at various time points.

(2) Comparisons within each group showed that mean arterial pressure and heart rate at 30 minutes intraoperatively and 1 hour postoperatively were significantly higher ( $p < 0.05$ ) than those recorded at 15 minutes preoperatively. Furthermore, at the 1-hour postoperative mark, both mean arterial pressure and heart rate were significantly lower ( $p < 0.05$ ) compared to the 30-minute intraoperative measurements.

Notably, Group B exhibited lower mean arterial pressure and heart rate values than Groups A and C at the 30-minute and 1-hour postoperative intervals, with statistically significant differences ( $p < 0.05$ ) evident. Further details can be found in Table 2.

### 3.3 Comparison of pain stress indicators in the three groups

The comparative analysis of mean arterial pressure and heart rate among the three groups, conducted at three distinct time intervals (15 minutes preoperatively, 30 minutes intraoperatively, and 1 hour postoperatively) using a repeated measures ANOVA design, which yielded significant findings and can be summarized as follows:

(1) Statistically significant differences ( $p < 0.05$ ) were observed between the three groups for mean arterial pressure and heart rate at both the 30-minute intraoperative and 1-hour postoperative time points. Additionally, within-group comparisons demonstrated statistical significance ( $p < 0.05$ ) for mean arterial pressure and heart rate at various time points.

(2) Comparisons within each group showed that mean arterial pressure and heart rate at 30 minutes intraoperatively and 1 hour postoperatively were significantly higher ( $p < 0.05$ ) than those recorded at 15 minutes preoperatively. Furthermore, at the 1-hour postoperative mark, both mean arterial pressure and heart rate were significantly lower ( $p < 0.05$ ) compared to the 30-minute intraoperative measurements.

Notably, Group B exhibited lower mean arterial pressure and heart rate values than Groups A and C at the 30-minute and 1-hour postoperative intervals, with statistically significant differences ( $p < 0.05$ ) evident. Further details are shown in Table 3.

### 3.4 Comparison of pain scores in the three groups

Comparing the VAS scores of the three groups at 2, 6 and 12 h postoperatively and conducting ANOVA (repeated measures design) showed the following results:

(1) Statistically significant differences ( $p < 0.05$ ) were observed in the VAS scores between the three groups at the intraoperative phase and 6 and 12 hours postoperatively, indicating notable distinctions in pain perception between the groups. Furthermore, statistically significant differences ( $p < 0.05$ ) in VAS scores were identified within each group at different time points post-surgery.

(2) The VAS scores at 6 h and 12 h postoperatively in all three groups were significantly lower than those at 2 h postoperatively ( $p < 0.05$ ). In addition, the VAS scores at 12 h postoperatively in all three groups were significantly lower than those at 6 h postoperatively ( $p < 0.05$ ), and the VAS scores at 6 h and 12 h postoperatively in Group C were significantly higher than those in Groups A and B ( $p < 0.05$ ). Further details are shown in Table 4.

### 3.5 Comparison of surgery-related indexes among the three groups

As shown in Table 5, analysis of the cumulative 24-hour morphine dosage, extubation time and operation time did not reveal any statistically significant differences among the three groups through ANOVA ( $p > 0.05$ ), while a significant difference in awakening time was observed among the groups, as indicated by ANOVA ( $p < 0.05$ ). Specifically, Group B exhibited a shorter awakening time compared to Groups A and C, and there was no statistically significant difference in the awakening time between Groups A and C ( $p > 0.05$ ).

### 3.6 Comparison of the incidence of adverse reactions in the three groups

Further analysis showed that during hospitalization, there were no significant differences between the incidence of adverse events among the three examined groups ( $p > 0.05$ ), as shown in Table 6.

## 4. Discussion

Benign ovarian tumors often present insidiously, with early symptoms lacking specificity, including subtle abdominal discomfort, urinary issues, and abdominal distension. As these tumors progress, they manifest a wider array of symptoms. Currently, the primary clinical approach for treating benign ovarian tumors involves surgical methods, with laparoscopic surgery being the most effective option [10]. However, the use of remifentanyl, an ultra-short-acting opioid analgesic commonly used in clinical practice, has raised concerns. Some studies have suggested that continuous infusion of remifentanyl during surgery may lead to postoperative pain hypersensitivity, potentially reducing the overall effectiveness of opioid-based analgesia. Additionally, it may contribute to agitation during the postoperative awakening phase, negatively affecting patient recovery [11–13]. In contrast, esketamine, a novel anesthetic analgesic, has demonstrated superior and more pronounced analgesic effects than ketamine. Nevertheless, there is currently no standardized clinical dosing protocol for esketamine [14, 15]. Therefore, this study aimed to determine the optimal esketamine dose for anesthesia in patients undergoing laparoscopic resection for benign ovarian tumors to provide a reference for anesthetic procedures in the clinical management of this condition.

The results of this study highlight an important finding—Group B, administered with a lower dose of 0.6 mg/kg esketamine for anesthesia, exhibited a significantly shorter awakening time compared to both Groups A and C. This finding suggests that opting for the 0.6 mg/kg esketamine dosage in

**TABLE 2. Comparison of hemodynamic indices in the three examined groups ( $\bar{x} \pm s$ ).**

Indicator	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	F	p
Heart rate (beats/min)					
Preoperative 15 min	89.42 ± 8.75	88.13 ± 9.16	90.42 ± 9.02	0.612	0.544
Intraoperative 30 min	108.20 ± 9.85*	94.71 ± 9.15*▲	112.42 ± 9.74*	34.676	<0.001
Postoperative 1 h	103.44 ± 8.62*#	92.80 ± 8.24*#▲	101.73 ± 8.13*#	17.223	<0.001
F	40.374	5.400	56.939		
p	<0.001	0.006	<0.001		
Mean arterial pressure (mmHg)					
Preoperative 15 min	75.07 ± 7.23	76.17 ± 8.02	74.31 ± 7.67	0.558	0.574
Intraoperative 30 min	104.25 ± 7.93*	93.20 ± 8.42*▲	102.82 ± 7.64*	20.659	<0.001
Postoperative 1 h	92.34 ± 6.71*#	80.35 ± 6.94*#▲	91.07 ± 7.83*#	30.755	<0.001
F	141.105	47.679	131.108		
p	<0.001	<0.001	<0.001		

Notes: \*The difference is statistically significant at  $p < 0.05$  compared with the preoperative 15 min in this group; #The difference is statistically significant at  $p < 0.05$  compared with the intraoperative 30 min in this group; ▲The difference is statistically significant at  $p < 0.05$  compared with Groups A and C at the same time point.

**TABLE 3. Comparisons of pain stress indicators in the three examined groups ( $\bar{x} \pm s$ ).**

Indicator	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	F	p
PEG2 (pg/mL)					
Preoperative	108.42 ± 10.05	106.83 ± 8.72	105.61 ± 9.46	0.814	0.446
Intraoperative	121.47 ± 11.42*	124.38 ± 9.20*	138.64 ± 12.01*▲	26.142	<0.001
Postoperative 1 h	138.74 ± 13.20*#	142.75 ± 10.42*#	165.05 ± 14.12*#▲	46.367	<0.001
F	59.872	132.999	233.453		
p	<0.001	<0.001	<0.001		
SP ( $\mu\text{g/mL}$ )					
Preoperative	4.20 ± 0.35	4.17 ± 0.24	4.22 ± 0.30	0.265	0.768
Intraoperative	5.55 ± 0.44*	5.61 ± 0.52*	6.78 ± 0.45*▲	80.515	<0.001
Postoperative 1 h	7.11 ± 0.62*#	7.07 ± 0.75*#	8.35 ± 0.51*#▲	49.274	<0.001
F	317.878	262.079	896.548		
p	<0.001	<0.001	<0.001		

Notes: Prostaglandin E2 (PEG2); Substance P (SP). \*The difference is statistically significant at  $p < 0.05$  compared with this group preoperatively; #The difference is statistically significant at  $p < 0.05$  compared with this group intraoperatively; ▲The difference is statistically significant at  $p < 0.05$  compared to Groups A and B at the same time point.

**TABLE 4. Comparison of VAS scores of the three assessed groups ( $\bar{x} \pm s$ , scores).**

Stage	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	F	p
Postoperative 2 h	3.05 ± 0.22	3.07 ± 0.20	3.01 ± 0.19	0.848	0.431
Postoperative 6 h	2.45 ± 0.17*	2.40 ± 0.16*	2.81 ± 0.19*▲	61.841	<0.001
Postoperative 12 h	1.47 ± 0.15*#	1.53 ± 0.13*#	1.80 ± 0.18*#▲	47.649	<0.001
F	669.279	758.842	422.309		
p	<0.001	<0.001	<0.001		

Notes: \*The difference is statistically significant at  $p < 0.05$  compared with 2 h postoperative in this group; #The difference is statistically significant at  $p < 0.05$  compared with 6 h postoperative in this group; ▲The difference is statistically significant at  $p < 0.05$  compared with Groups A and B at the same time point.

**TABLE 5. Comparison of surgery-related indicators in the three groups ( $\bar{x} \pm s$ ).**

Indicator	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	F	p
Operation time	65.27 ± 6.35	62.74 ± 6.06 <sup>▲</sup>	64.02 ± 6.20	1.498	0.228
Wake up time	13.08 ± 1.37	10.71 ± 1.13	12.67 ± 1.35	35.400	<0.001
Time to extubation	13.26 ± 1.45	13.44 ± 1.17	13.77 ± 1.05	1.629	0.201
24 h cumulative morphine dosage	22.42 ± 2.17	22.02 ± 2.13	22.14 ± 2.45	0.296	0.745

Notes: <sup>▲</sup> The difference is statistically significant at  $p < 0.05$  compared with Groups A and C at the same time point.

**TABLE 6. Comparison of the incidence of adverse reactions in the three groups.**

Adverse reactions	A Group (35 cases)	B Group (37 cases)	C Group (38 cases)	$\chi^2$	p
Nausea and vomiting	2	2	2		
Chills	2	1	1		
Dizziness	1	1	0		
Incidence (%)	5	4	3	0.615	0.735

these patients could lead to a shorter awakening time, possibly because selecting a relatively lower dose of esketamine (0.6 mg/kg) not only ensures effective anesthesia but also facilitates faster patient recovery. In clinical practice, the assessment of mean arterial pressure and heart rate plays a crucial role in evaluating the hemodynamic status of patients. In the context of this study, it was observed that patients in Group B displayed significantly lower heart rates at 30 min intraoperatively and 1 h postoperatively compared to Groups A and C. Furthermore, their mean arterial pressure was lower than that of Groups A and C, suggesting that 0.6 mg/kg esketamine for anesthesia could improve hemodynamic stability, possibly due to the potent dissociative anesthetic effects of esketamine, its non-competitive antagonism of glutamate (mediated by NMDA receptors in the central nervous system), and the maintenance of a 0.6 mg/kg dose, which appears to be more conducive to maintaining hemodynamic stability. Previous studies have also explored the use of low-dose esketamine administered before anesthesia induction in children undergoing surgical procedures and demonstrated the efficacy of low-dose esketamine in suppressing the somatotropic response triggered by propofol [16, 17]. Additionally, in a separate investigation, low-dose ketamine in combination with propofol was employed for epidural anesthesia in patients undergoing laparoscopic appendectomy, resulting in a significant reduction in anesthesia recovery time and improved hemodynamic stability [18].

This study revealed significant findings regarding SP and PEG2 levels. SP and PEG2 were lower in Groups A and B compared to Group C during the intraoperative and 1-hour postoperative periods. Importantly, no significant differences were observed when comparing Groups A and B within these timeframes, suggesting that both 0.6 mg/kg and 0.8 mg/kg dosages of esketamine effectively mitigated nociceptive hypersensitivity induced by remifentanyl in patients undergoing laparoscopic resection for benign ovarian tumors. The mechanism behind this effect lies in esketamine's unique properties. Esketamine, a chiral cyclohexanone, exhibits remarkable

analgesic efficacy by inhibiting the tyrosine phosphorylation of the NR2B subunit and regulating NMDA receptor activity in the spinal cord's dorsal horn. Additionally, it suppresses the supercation channel activity in subcortical centers, countering nociceptive sensitization induced by propofol through early inhibition of corresponding neural activity in these subcortical centers.

The drug also hinders the activity of subcortical centers, including supercritical cation channels, while speeding up the reduction of the imbalanced inhibition process induced by propofol and lowering postoperative nociceptive sensitization.

Furthermore, the study revealed that Groups A and B had lower VAS scores at 6 hours and 12 hours after the surgery than Group C. When comparing Groups A and B directly, no significant difference was observed, suggesting that administering esketamine at either 0.8 mg/kg or 0.6 mg/kg could effectively reduce postoperative pain perception due to esketamine's impact on pain stress indicators, such as PEG2 and SP, which likely contribute to reducing postoperative pain.

Importantly, this study demonstrated that the incidence of adverse reactions did not significantly differ among the three groups, indicating that administering esketamine anesthesia at either 0.6 mg/kg or 0.8 mg/kg did not significantly increase the risk of adverse reactions in patients, highlighting the high safety profile of these dosages.

## 5. Conclusions

In patients undergoing laparoscopic resection for benign ovarian tumors, both the 0.6 mg/kg and 0.8 mg/kg doses of esketamine effectively alleviate nociceptive hypersensitivity induced by remifentanyl, resulting in significant pain reduction. Importantly, the drug exhibits outstanding safety. However, it's worth noting that the 0.6 mg/kg dose outperforms the 0.8 mg/kg dose to promote hemodynamic stability and expedite the awakening time, making it a more valuable choice.

The limitations of this present study include a small sample size, a relatively short study duration, and its single-center

nature. Future research could address these limitations by expanding the sample size, extending the study duration, and involving multiple medical centers. While the findings of this study have certain therapeutic implications, their application in clinical practice should be tailored to individual circumstances, taking into account the various factors that may influence their implementation to establish a scientific and comprehensive approach.

## AVAILABILITY OF DATA AND MATERIALS

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

## AUTHOR CONTRIBUTIONS

LL and XTR—designed the study and carried it out; LL, XMH and QQS—supervised the data collection, analyzed the data, interpreted the data, prepared the manuscript for publication, and reviewed the draft of the manuscript. All authors have read and approved the manuscript.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was obtained from the Ethics Committee of Wenzhou Central Hospital (Approval no. L2023-02-032). Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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