

Effects of Remimazolam Tosilate Combined with Esketamine on Anesthetic Efficacy and Psychiatric Symptoms in Patients Undergoing Ambulatory Surgery: A Randomized Controlled Study

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Background: The choice of anesthetic drugs is crucial in ambulatory surgery. Esketamine has anesthetic, analgesic, and sedative effects, but it is associated with dose-dependent psychiatric symptoms. Benzodiazepines can alleviate these symptoms, but traditional drugs like midazolam may prolong the recovery time. Remimazolam tosylate as a novel benzodiazepine, has not been fully explored in terms of its effects when combined with esketamine and its impact on psychiatric symptoms.

Methods: A total of 249 patients undergoing elective laparoscopic surgery were enrolled. Randomly divided into the esketamine group (Group E), the esketamine plus midazolam group (Group EM), and the esketamine plus remimazolam tosylate group (Group ER). The primary outcome was the incidence of adverse reactions. The secondary outcomes included hemodynamics at different time points: at rest in the room (T0), immediately post-intubation (T1), immediately post-extubation (T2), 30 minutes following extubation (T3), and immediately after leaving the PACU (T4). Moreover, we also documented the Riker Sedation-Agitation Scale (SAS) scores at T2-4, as well as extubation time and PACU stay duration.

Results: Patients in Group ER had a significantly lower incidence of postoperative diplopia and blurry vision compared to Groups E and EM ($p < 0.05$). Postoperative psychiatric symptoms were significantly lower in Groups EM and ER than in Group E ($p < 0.05$). At the T1 time point, Groups EM and ER displayed significantly lower MAP and HR, compared to Group E ($p < 0.05$). Groups E and ER displayed a shorter extubation time than Group EM ($p < 0.05$); the PACU stay of Group ER was shorter than those of Groups E and EM ($p < 0.05$). The SAS scores decreased from T2 to T4 in Groups EM and ER than in Group E ($p < 0.05$).

Conclusion: The combination of remimazolam tosylate and esketamine effectively reduces postoperative psychiatric symptoms, enhances hemodynamic stability, and improves recovery quality, making it a viable anesthetic strategy for ambulatory surgery.

Keywords: remimazolam tosylate, esketamine, ambulatory surgery, psychiatric symptoms

Introduction

Ambulatory surgery is a surgical approach, in which patients undergo admission, surgery, and discharge within a single working day. It is beneficial for reducing hospital stays, accelerating bed turnover, and enhancing the efficacy of medical resource utilization.¹ The rational selection of anesthetic drugs is crucial for link in ensuring the anesthesia effect of ambulatory surgery and the rapid recovery of patients. Abdominal surgeries (such as laparoscopic cholecystectomy and hernia repair) are common types of ambulatory surgeries. However, due to situations like pneumoperitoneum irritation and visceral traction reflex, they place greater demands on the selection of anesthetic drugs and also pose greater challenges.

Traditional induction drugs for ambulatory surgery, such as propofol, often cause hypotension. Esketamine, with its advantages of providing anesthesia, analgesia, and sedation without suppressing cardiopulmonary function,² has become one of the ideal choices for anesthesia management in ambulatory surgery. However, the dose-dependent psychiatric

symptoms induced by esketamine, such as nightmares and dissociative phenomena,³ have attracted the attention of anesthesiologists.

Studies have shown that benzodiazepines can reduce adverse psychiatric reactions to esketamine through the non-specific central inhibitory effects mediated by the gamma-aminobutyric acid type A (GABAA) receptor.⁴ Midazolam is the most widely used benzodiazepine sedative in clinical practice. Research indicates that its sedative-hypnotic effects help reduce the use of general anesthetics during surgery, and its unique anterograde amnesia can prevent patients from experiencing intraoperative awareness.⁵ However, its metabolites remain highly active and continue to exert sedative-hypnotic effects within the body, thereby significantly prolonging the patient's recovery time.⁶

Remimazolam tosylate is a novel ultrashort-acting benzodiazepine. Compared with midazolam, it has higher clearance efficiency, a smaller volume of distribution, and a shorter half-life.^{7,8} In the fast-paced environment of ambulatory surgery, which demands rapid patient turnover, these characteristics give it an advantage in reducing postoperative recovery time and improving the efficiency of anesthesia recovery.

Although previous studies have focused on the interaction between benzodiazepines and esketamine, the effects of the combination of remimazolam tosylate and esketamine in ambulatory surgery, as well as its potential impact on the adverse reaction to esketamine, remain underexplored. This study aimed to investigate the specific effects of the combination of remimazolam tosylate and esketamine in reducing dose-dependent psychiatric symptoms associated with esketamine and the impact of this coadministration regimen on patient's recovery quality, thereby providing scientific evidence for optimizing anesthesia protocols in ambulatory surgery and promoting rapid patient recovery.

Methods

Study Design

The present unicentric, double-blind, randomized, controlled trial was carried out between July 2023 to February 2024 in Second Affiliated Hospital of Zunyi Medical University. This study was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) criteria and adhering to the Declaration of Helsinki. This study has been approved by the Ethics Committee of the Second Affiliated Hospital, Zunyi Medical University, China (number: KYLL-2022-026). It has been registered with the Chinese Clinical Trial Registration Center (<https://www.chictr.org.cn>, ChiCTR2300073319, registration date: July 6th, 2023). After understanding the study's objectives, procedures, and potential risks, all enrolled patients or their family members provided signed informed consent.

Patient Eligibility

The inclusion criteria were: Patients scheduled for day-case abdominal surgery under general anesthesia; aged 18–60 years, participants without sex discrimination, and those categorized as grade I–II, according to American Society of Anesthesiologists (ASA) guidelines. The exclusion criteria were: patients with preoperative dysfunctions of major organs like heart, lungs, liver, and kidneys; those contradicted for esketamine and benzodiazepines; patients who used sedative-analgesic drugs recently; those with cognitive impairment or mental disorders; those who underwent laparotomy; patients with surgery duration >1 hour, and participants with missing postoperative follow-up data.

Randomization and Blinding

Before anesthesia, we randomized all patients into Group E, Group EM or Group ER at the 1:1:1 ratio. Random numbers were generated using SPSS 26.0 software, and then random envelopes were created. During the grouping process, an anesthesiologist who did not participate in the research opened the envelopes. An anesthesiologist who was not involved in this study was responsible for the drug preparation. It is worth emphasizing that throughout the entire study period, neither the surgeons, nurses, patients, anesthesiologists, nor the outcome observers were aware of the specific grouping of the patients.

Anesthetic Procedure

All patients were instructed to abstain from drinking and eating for six and eight hours before surgery, respectively. In the operating room, we established an intravenous line and carried out fluid resuscitation as needed. Routine monitoring of

patients' basic vital signs included mean arterial pressure (MAP) and heart rate (HR). The anesthetic induction protocol was the same for all patients. All the patients were administered intravenous sufentanil (0.3 µg/kg), propofol (0.2 mg/kg), and rocuronium (1 mg/kg) consequently. Groups E, EM, and ER were administered esketamine (0.3 mg/kg, Jiangsu Hengrui Pharmaceutical Co., Ltd., China),⁹ esketamine (0.3 mg/kg) plus midazolam (0.08 mg/kg, Jiangsu Enhua Pharmaceutical, Co., Ltd., China),¹⁰ and esketamine (0.3 mg/kg) and remimazolam tosylate (0.3 mg/kg, Jiangsu Hengrui Pharmaceutical Co., Ltd., China).¹¹ After, anesthesia was induced, the three groups underwent tracheal intubation and pressure control mode ventilation. The ventilator parameters were adjusted to maintain the $P_{ET}CO_2$ at 35–45 mmHg. Anesthesia was sustained with propofol (4–12 mg/kg/h), remifentanyl 0.2–0.5 (µg/kg/h), and sevoflurane (1–2 MAC); the muscle relaxants were used whenever needed. The target blood pressure was maintained at $\pm 20\%$ of the baseline value, and the target heart rate was 60–100 beats/min. A decrease in MAP of 20% from baseline or a drop to below 60 mmHg for at least 1 minute is considered hypotension, which will be treated with ephedrine until the MAP returns to the normal range. A heart rate that drops below 50 beats per minute is considered bradycardia, and will be managed with 0.3 mg of atropine, which can be repeated based on the patient's heart rate. All patients received an anesthetic loading dose of tropisetron (5 mg) and flurbiprofen axetil (50 mg), ten minutes before the operation's completion. However, propofol, remifentanyl, and sevoflurane were immediately discontinued postoperatively, and the patients were transferred to the Post-Anesthesia Care Unit (PACU). If a patient's postoperative VAS score was >3 points, a rescue analgesic plan comprising intravenous ketorolac tromethamine (30 mg) injection was implemented. In case of postoperative psychiatric adverse reactions, propofol sedation was administered as a corrective measure.

Observational Indicators

Our primary outcome was the incidence of adverse reactions in patients (during the induction and postoperative recovery periods). To assess specific psychiatric symptoms such as hallucinations and nightmares, observers conduct interviews with patients upon awakening and make preliminary judgments based on the patients' self-reports. For the evaluation of symptoms like delirious speech, a comprehensive consideration of the patients' behavior, mental status, and clinical observations is required. For example, observers examine the patients' eye contact, emotional stability, and awareness of the surrounding environment.

The secondary outcomes included recording patients' demographic data, MAP, and HR at rest upon admission (T0), immediately after intubation (T1), immediately following extubation (T2), 30 minutes post-extubation (T3), and immediately before leaving the PACU (T4). Additionally, the quality of patients' postoperative awakening was assessed through several measures, including the Riker Sedation-Agitation Scale (SAS) scores at time points T2 to T4. The Riker Sedation-Agitation Scale Criteria are as follows: 1 point, unarousable, with no or only minimal response to noxious stimuli, and inability to communicate or follow commands; 2 points, very sedated, responding only to physical stimuli, unable to communicate or follow commands, with spontaneous movements; 3 points, sedated and drowsy, responsive to verbal stimuli or gentle shaking, able to follow simple commands but quickly returning to sleep; 4 points, calm and cooperative, easily arousable, and able to follow commands. 5 points, agitated and anxious or physically restless, but calmed with verbal reassurance; 6 points, very agitated, requiring protective restraints and repeated verbal reassurance, possibly biting on the endotracheal tube; 7 points, dangerously agitated, characterized by pulling at the endotracheal tube, attempting to remove various catheters, climbing over window bars, attacking medical staff, or struggling in bed. Additional parameters included postoperative extubation time, defined as the interval from the cessation of anesthetic drug administration to removal of the endotracheal tube, and the duration of stay in the post-anesthesia care unit (PACU), defined as the time from PACU admission until the patient meets discharge criteria and is released.

Sample Size Calculation and Statistical Analysis

Based on the results of the preliminary trial, this study used the incidence of postoperative adverse reactions in patients as the main observation index. The proportion in Group E was 62%, that in Group EM was 43%, and that in Group ER was 33%. With a significance level of $\alpha = 0.05$ and a power of $1 - \beta = 90\%$, the PASS 15.0 software was used to calculate the sample size, and the result was $n = 73$ patients per group. Considering a dropout rate of 20%, it was calculated that 91 patients were planned to be included in each group of this study.

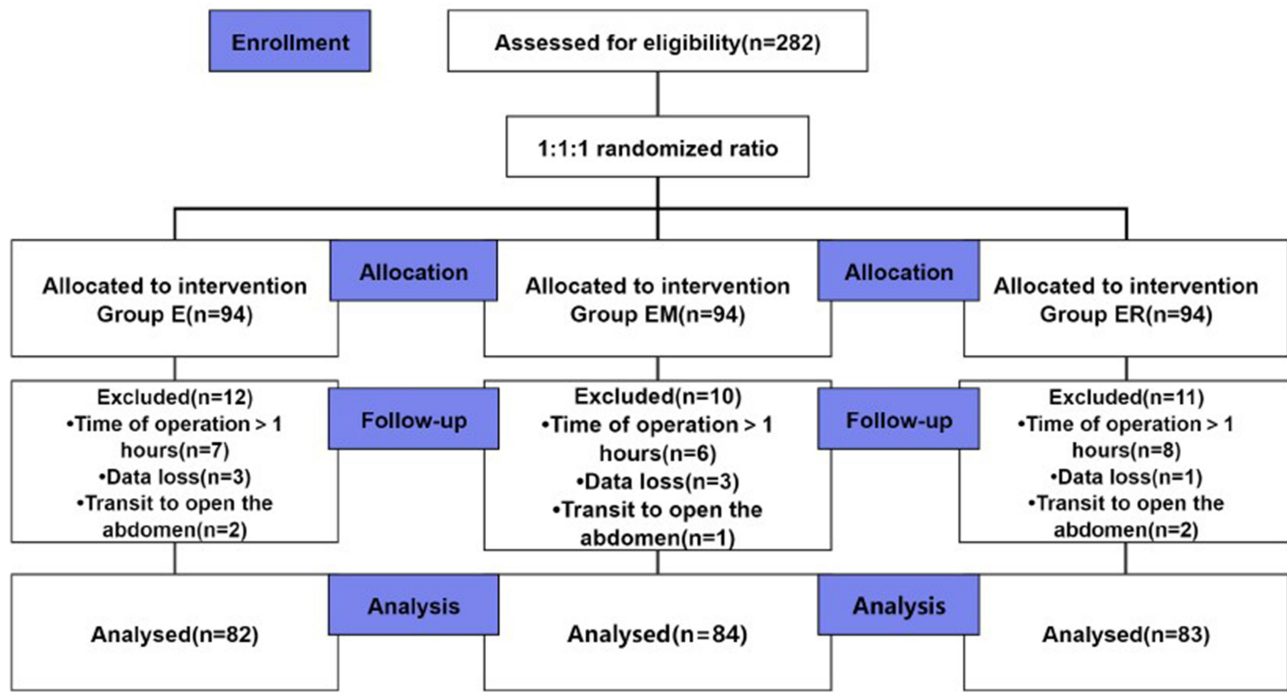


Figure 1 Flowchart depicting the study's procedure Baseline characteristics.

The PASS 15.0 software was used to calculate the sample size. Postoperative adverse reactions were the primary observational indicators. We enrolled 94 patients in each group, based on the results of a preliminary pre-trial, with a significance level of $\alpha = 0.05$, a power of $1 - \beta = 90\%$, and a dropout rate of 20%.

Data analysis was conducted using SPSS 26.0 software. The normally distributed data were represented as mean $\pm$ standard deviation ($\pm s$). Inter-group comparisons were made using one-way ANOVA. However, non-normal data were represented as a median and interquartile range [M(IQR)], followed by the Kruskal–Wallis test. Categorical data were expressed as the number of cases (%), and inter-group comparisons were made using the chi-squared (χ^2) test. A p-value < 0.05 indicated statistical significance.

Results

Initially, we enrolled 282 patients. However, 21, 7, and 5 patients were excluded due to surgery duration > 1 hour, missing data, and implementation of open surgery, respectively. Finally, 249 patients were included and 82, 84, 83 patients were categorized into Groups E, ER, and EM, respectively. [Figure 1](#) shows the flowchart depicting the study's procedure.

No statistically significant differences were observed in gender, age, BMI, ASA classification, type of surgery, surgery duration, or vasoactive drug perioperative use among the three groups ($p > 0.05$, [Table 1](#)).

Table 1 Comparison of the General Characteristics of the Three Groups

	Group E (n=82)	Group EM (n=84)	Group ER (n=83)	H/F/ χ^2	P value
Age (years)	38.94 (21)	37.93 (19)	40.64 (20)	2.481	0.289
Sex, [n (%)]				0.582	0.748
Male	42 (51.22)	39 (46.43)	43 (51.81)		
Female	40 (48.78)	45 (53.57)	40 (48.19)		

(Continued)

Table 1 (Continued).

	Group E (n=82)	Group EM (n=84)	Group ER (n=83)	H/F/ χ^2	P value
BMI (kg/m ²)	24.13±2.86	23.09±3.00	24.49±3.08	0.621	0.538
ASA class, n (%)				1.479	0.477
I	55 (67.07)	49 (58.33)	50 (60.24)		
II	27 (32.93)	35 (41.67)	33 (39.76)		
Operation time (min)	29.09±5.92	28.07±7.68	27.12±6.03	1.85	0.16
Type of Surgery [n (%)]				2.859	0.826
Cholecystectomy	26 (31.71)	24 (28.57)	21 (25.30)		
Herniorrhaphy	21 (25.61)	18 (21.43)	16 (19.28)		
Appendectomy	18 (21.95)	20 (23.81)	22 (26.51)		
Conization of the Uterus	17 (20.73)	22 (26.19)	24 (28.92)		
Perioperative vasoactive drugs [n (%)]					
Atropine	2 (2.44)	6 (7.14)	3 (3.61)	2.365	0.307
Ephedrine	3 (3.66)	8 (9.52)	4 (4.82)	2.398	0.301

Notes: Variables presented as mean ±SD, median (interquartile range) or number of patients (%).

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists.

Primary Outcomes

Group ER experienced a significant reduction in postoperative diplopia/blurry vision compared to the groups E and EM ($p<0.05$). Groups EM and ER showed a significant reduction in postoperative psychological reactions ($p<0.05$) than Group E. There was no statistically significant difference in the incidence of adverse reactions like postoperative nausea, vomiting, and increased secretions during the induction and postoperative phases among the three groups ($p>0.05$, Table 2).

Secondary Outcomes

Groups EM and ER had significantly lower MAP and HR at the T1 time point than Group E ($p<0.05$). And there were no statistically significant differences in vital signs at any other time points ($p>0.05$, Table 3).

Groups E and ER had quicker extubation times than Group EM ($p<0.05$); Group ER stayed less in PACU, compared to Groups E and EM ($p<0.05$). Groups EM and ER showed significantly reduced SAS scores at T2-4 ($p<0.05$) than Group E; however, no statistical differences were observed at other time points ($p>0.05$, Table 4).

Table 2 Incidence of Adverse Reactions

	Group E (n=82)	Group EM (n=84)	Group ER (n=83)
Induction phase of anesthesia [n (%)]			
Coughing	3 (3.66)	2 (2.38)	1 (1.20)
Lacrimation	2 (2.44)	1 (1.19)	1 (1.20)
Body movement	1 (1.22)	0 (0)	0 (0)
Bradycardia	0 (0)	2 (2.38)	1 (1.20)
Tachycardia	5 (6.10)	2 (2.38)	1 (1.20)
Hypertension	4 (7.5%)	2 (2.38)	0 (0)
Hypotension	1 (1.22)	4 (4.76)	2 (2.41)
Postoperative recovery period [n (%)]			
Diplopia/Blurry vision	21 (25.61)	12 (14.29)	2 (2.41) ^{b,c}
Psychiatric symptoms (Nightmares, Incoherent speech, Hallucinations)	13 (15.85)	2 (2.38) ^a	0 (0) ^b
Nausea/Vomiting	5 (6.10)	3 (3.57)	2 (2.41)
Increased secretions	3 (3.66)	3 (3.57)	2 (2.41)

Notes: Variables presented as median (interquartile range) or number of patients (%). ^a $P < 0.05$, ^b $P < 0.05$ vs Group E; ^c $P < 0.05$ vs Group EM.

Table 3 Comparison of MAP and HR at Different Time Points

		Group E (n=82)	Group EM (n=84)	Group ER (n=83)
MAP	T0	80.41±6.36	81.89±6.20	82.25±7.50
	T1	83.90±6.81	79.77±8.59 ^a	80.94±9.68 ^b
	T2	85.44±8.09	83.21±6.83	84.73±10.50
	T3	81.21±8.35	83.30±6.29	82.02±5.66
	T4	79.63±8.55	79.12±6.64	78.55±6.21
HR	T0	75.89±8.66	76.00±8.41	73.98±7.73
	T1	78.00±10.56	73.69±7.62 ^a	72.60±5.48 ^b
	T2	81.44±5.51	80.80±4.34	79.95±5.07
	T3	74.76±7.64	77.33±9.25	76.23±8.27
	T4	75.90±7.60	74.11±6.90	73.76±7.33

Notes: Variables presented as mean ±SD. ^aP < 0.05, ^bP < 0.05 vs Group E.

Abbreviations: MAP, mean arterial pressure; HR, heart rate.

Table 4 Comparison of the Quality of Postoperative Awakening Among Three Groups

	Group E (n=82)	Group EM (n=84)	Group ER (n=83)
Extubation time (min)	21.18±6.22	24.82±4.78 ^a	19.41±4.29 ^{b,c}
PACU stay time (min)	39.60±5.75	40.45±8.23	33.64±6.79 ^{b,c}
Riker Sedation-Agitation Scale Scores			
T2	4 (1)	4 (0) ^a	4 (0) ^b
T3	4 (0)	4 (0)	4 (0)
T4	4 (0)	4 (0)	4 (0)

Notes: Variables presented as mean ±SD, median (interquartile range). ^aP < 0.05, ^bP < 0.05 vs Group E; ^cP < 0.05 vs Group EM.

Discussion

Ambulatory surgery emphasizes rapid recovery and safety. Ideal drugs should take effect quickly, allow for a rapid recovery of consciousness, and have few side effects. The common anesthesia regimen for day surgery, which combines propofol, midazolam, and opioids, aims to achieve rapid awakening and adequate analgesia. However, it can cause hemodynamic changes in patients, affecting perioperative physiological stability and postoperative recovery.¹²

Esketamine, a new type of anesthetic, sedative, and analgesic drug, is a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist. It does not inhibit respiration, mildly stimulates circulation, and results in a short awakening time.¹³ Multiple domestic and international studies have shown that esketamine, a novel anesthetic sedative and analgesic drug,¹³ has no impact on postoperative recovery, has minimal side effects, and exhibits favorable safety characteristics when used at a dose of 0.3 mg/kg for anesthesia induction.^{14–16} Therefore, this study selected 0.3mg/kg of esketamine as the induction dose. However, this result is inconsistent with our study findings. The results of this study show that compared with the two groups using midazolam or remimazolam tosylate in combination, the incidence of postoperative diplopia/blurred vision and psychiatric symptoms such as speech confusion, nightmares, and hallucinations was higher in Group E, which used esketamine alone, with statistically significant differences.

Gastaldon¹⁷ found that the FAERS database contains 962 cases of esketamine-related adverse reactions, among which 18 were esketamine-related neurological adverse reactions. Xu¹⁸ indicated that intravenous injection of 0.25mg/kg esketamine before skin incision in cesarean section could produce sedative and analgesic effects, but it significantly increased the incidence of intraoperative neurological and psychiatric symptoms. We speculate that the esketamine's psychoactive effects might be related to its function as an NMDA receptor antagonist. As an NMDA receptor antagonist,

esketamine interacts with a receptor involved in several perceptual, emotional, behavioral, and cognitive alterations.¹⁹ It is worth noting that the elimination half-life of esketamine is 2–3 hours.²⁰ And our selected surgeries were ambulatory surgery, this might be related to the drug's metabolism. In addition, the differences in drug metabolism among individuals are a factor that cannot be ignored. Due to reasons such as genetic polymorphism, the activities of enzymes involved in drug metabolism vary among different patients.

The research indicates that medications capable of GABA receptor activation can be utilized to mitigate the esketamine-induced psychiatric side effects.²¹ Our study revealed that the concomitant usage of various benzodiazepines can effectively reduce postoperative diplopia/blurry vision and psychiatric symptoms. Midazolam and remimazolam tosylate were GABA receptor agonists,²² may exert its effects on the brainstem reticular formation and the limbic system through GABA receptors. This inhibits the excitability of the central nervous system and reduces esketamine's excitatory actions.²³ Furthermore, might mitigate esketamine's psychoactive adverse effects by inducing calcium (Ca^{2+}) influx and activating glutamate NMDA receptors as well as counteracting the antagonistic effects of esketamine on these receptors.²⁴

However, when different benzodiazepines are used in combination with esketamine, there are differences in their effects on patients' awakening time and recovery quality. Studies have shown that although midazolam can prevent the psychiatric symptoms caused by esketamine, it may prolong the patient's awakening time and even affect postoperative cognitive function.^{25,26} The results of this study show that, the group EM significantly reduced the incidence of postoperative diplopia/ blurred vision and psychiatric symptoms. However, the time to extubation and the length of stay in the PACU were significantly longer in the group EM than in the group ER. This may be due to the fact that the metabolites of midazolam still retain some pharmacological activity.²⁷ In contrast, remimazolam tosylate, with its high clearance rate and short duration of action, has attracted much attention. Its main metabolites exhibit almost no pharmacological activity and can be rapidly hydrolyzed by nonspecific esterases in the blood,²⁸ accelerates the patient's awakening process. Consequently, remimazolam tosylate displays a more rapid recovery than midazolam. In addition, the extubation time in Group E was also significantly shorter than that in Group EM, which may be closely related to the pharmacological properties of esketamine. Compared to the traditional racemic ketamine, esketamine exhibits potent pharmacological properties and has a higher body clearance rate. This contributes to faster postoperative recovery in patients.²⁹ Additionally, when esketamine was co-administered with different benzodiazepines, the SAS scores during the recovery period were significantly lower than those in the control group. This might be potentially related to the increased incidence of postoperative agitation due to esketamine's sympathomimetic effects. Moreover, benzodiazepines might significantly prevent postoperative agitation by reducing sympathetic tone and inhibiting catecholamine release.³⁰

In terms of hemodynamics, esketamine maintains stable vital signs during the anesthesia induction period. However, there is a slight increase in MAP and HR immediately after intubation, which may be due to its sympathomimetic effect and the stimulation of intubation. After the combined use of benzodiazepines, MAP and HR at time T1 are lower compared to when esketamine is used alone, and the hemodynamics are more stable. This benefits from the synergistic sedative effect between benzodiazepines and esketamine, as well as the balancing effect of benzodiazepines on the sympathomimetic stimulation of esketamine.²⁶

Limitations

Our study had several limitations. First, our sample size was a single-center trial. Thus, increasing the sample size can bolster the results' statistical power and external validity. Second, the optimal induction dose of esketamine remains unclear. Future studies can further explore this to reduce adverse reactions and optimize the quality of recovery from anesthesia. Furthermore, the postoperative follow-up period in this study was relatively short, making it difficult to evaluate the long - term recovery of patients and potential delayed adverse reactions. Therefore, it is highly necessary to extend the long-term postoperative follow-up. In addition, this study has certain limitations in the assessment of subjective endpoints such as psychiatric symptoms. In this study, psychiatric symptoms were mainly judged through patients' self-reports and observations by medical staff. There is a lack of more objective and quantitative assessment indicators. Future studies can adopt more standardized and objective assessment tools.

Conclusions

In summary, the combination of remimazolam tosylate and esketamine effectively reduces postoperative psychiatric symptoms, enhances hemodynamic stability, and improves recovery quality, making it a viable anesthetic strategy for ambulatory surgery.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests in this work.

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