Clinical and Translational Science

ARTICLE OPEN ACCESS

Effects of Esketamine Combined With Remimazolam Tosylate on Hemodynamics During Cardiovascular Anesthesia

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Received: 7 November 2024 | **Revised:** 18 February 2025 | **Accepted:** 10 March 2025

Funding: The authors received no specific funding for this work.

Keywords: esketamine | heart valve replacement | hemodynamics | remimazolam tosylate

ABSTRACT

This study aimed to evaluate the effects of esketamine combined with remimazolam tosylate on hemodynamic stability, cerebral oxygen metabolism, and cognitive outcomes in patients undergoing heart valve replacement. Seventy-eight patients were randomized to Group C (dexmedetomidine hydrochloride) or Group R (esketamine + remimazolam tosylate). The following parameters were measured: multiple time points, including mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), arterial-jugular vein oxygen content difference (Da-jvO_2), cerebral oxygen uptake rate (CERO_2), and biomarkers of myocardial injury (cTnI, CK-MB, FABP) at baseline (T0), incision (T1), sternotomy (T2), pre-cardiopulmonary bypass (T3), and post-surgery (T4). Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and Confusion Assessment Method (CAM). Group R showed prolonged values of lower RR in T1 to T4 than Group C ($p<0.05$). The Da-jvO_2 and CERO_2 were found to be much higher in Group R in T2, T3, and T4 ($p<0.05$). This is an indication of improved cerebral oxygen metabolism. MMSE scores were elevated in Group R: the incidence of delirium and CAM Scores were lower compared with Group C ($p<0.05$). This indicates better cognitive outcomes. Also, cTnI, CK-MB, and FABP, myocardial injury markers, were significantly reduced in Group R at postoperative 24 and 72 h ($p<0.05$), indicating reduced myocardial injury. The combination of esketamine and remimazolam tosylate offers hemodynamic stability, enhances cerebral oxygen metabolism, improves cognitive function, and reduces myocardial injury in patients undergoing heart valve replacement surgery. This approach might provide significant benefits in cardiovascular anesthesia.

1 | Introduction

With the gradual improvement and development of cardiovascular surgical technology, heart valve replacement surgery has become an important surgical method for treating heart valve diseases. It is an invasive surgery and is usually performed under cardiopulmonary bypass (CPB) and general anesthesia [1, 2]. During the operation, factors such as blood contact with the CPB circuit under CPB, ischemia–reperfusion, etc., can cause the body to produce a stress response, thereby triggering severe hemodynamic fluctuations; in addition, long-term anesthesia can also affect the patient's brain function and cognitive function [3, 4]. Simultaneously, the selection of surgical anesthetic medications and the level of anesthesia will also substantially impact the likelihood of intraoperative problems [4, 5]. Most of the sedative drugs commonly used in clinical practice have

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Summary

- What is the current knowledge on the topic?
  - Cardiovascular anesthesia for heart valve replacement often poses risks such as hemodynamic instability, cognitive impairment, and myocardial damage. Existing sedatives, including midazolam and etomidate, have drawbacks like respiratory depression and delayed recovery. Esketamine and remimazolam tosylate offer promising stability with fewer side effects, but their combined impact on hemodynamics and cognitive function is not well-studied.
- What question did this study address?
  - This study investigated the combined effects of esketamine and remimazolam tosylate on hemodynamics, cerebral oxygen metabolism, myocardial protection, and cognitive function during cardiovascular anesthesia.
- What does this study add to our knowledge?
  - Findings show that esketamine with remimazolam tosylate stabilizes hemodynamics, enhances cerebral oxygenation, reduces myocardial damage markers, and lowers postoperative delirium risk, thus advancing understanding of this anesthetic combination.
- How might this change clinical pharmacology or translational science?
  - The study suggests that esketamine with remimazolam tosylate could enhance anesthesia protocols for heart surgery by improving patient stability and recovery, which may guide future research in anesthetic pharmacology and clinical practice.

certain defects. Long-term midazolam infusions can elicit adverse responses such as myoclonus and etomidate-induced nausea and vomiting, as well as respiratory depression, prolonged recovery times, substantial cardiopulmonary suppression, and injection pain [6, 7]. An ideal, fast-acting anesthetic drug should have sedative-hypnotic properties and a low risk of side effects [8]. Esketamine is the dextrorotatory form of ketamine, which has stronger anesthetic and analgesic effects, can preserve airway reflexes and spontaneous breathing, and reduces the occurrence of respiratory depression [9, 10]. Remimazolam is a new type of benzodiazepine that has the characteristics of stable hemodynamics, rapid onset, and elimination and does not increase the burden on the liver and kidneys. It may have certain advantages in anesthesia induction [11, 12]. The impact of remimazolam tosylate and esketamine on hemodynamics in clients having heart valve replacement during cardiovascular anesthesia, however, is not well documented in the literature at this time. Therefore, this study aims to explore it. The current report is as follows.

2 | Materials and Methods

2.1 | Study Design and Participant Selection

In this study, 78 patients with heart valve replacement were included. They hoped to survive elective surgery at Nantong First People's Hospital from January 2022 to November 2023. Their clinical data were analyzed retrospectively. There were 39 patients in the two groups, C and R, made by the random number table method to nondiscriminatory separate patients. Group C had 22 males and 17 females, with dual ratings in Group II and 28 in Group III, according to the American Society of Anesthesiologists (ASA). Twelve cases were graded II according to the New York Heart Association (NYHA) classification, and 27 were listed in the grade III group. The average age of patients in group R was (54.92 ± 9.73), 24 males and 15 females, with ASA having 14 cases in grade II and 25 cases in grade III. At the same time, under the New York Heart Association (NYHA), the classification included 10 cases in grade II and 29 in grade III. The general information was statistically insignificant ($p > 0.05$) between both groups Table 1.

2.2 | Inclusion and Exclusion Criteria

Inclusion criteria: (1) heart valve disease; (2) Meet the surgical indications and plan to undergo heart valve replacement; (3) First-time valve replacement; (4) NHYA grade II or III; (5) ASA grade II, Level III; (6) The clinical data are complete; (7) The hospital ethics committee approved this research, and informed consent was provided by all enrolled clients and their families regarding the study design.

Exclusion criteria: (a) Patients with AV nodal blockade ≥ II degrees; (b) patients with severe arrhythmias; (c) patients with long-term use of analgesics and/or sedatives; (d) patients with severe hypertension, diabetes, and/or other organ dysfunctions; (e) patients with mental disorders who cannot communicate normally; (f) Patients with known hypersensitivity to study drugs or any drugs used during the procedure; (g) patients unable to complete postoperative follow-up.

2.2.1 | Anesthesia and Surgical Procedures

The patients from both groups underwent heart valve replacement. They fasted for ≥ 8 h before the procedure and underwent oxygen supply where necessary. On entering the operating room,

TABLE 1 | Comparing the two teams' general information [n (%), ($x \pm s$)].

Team	n	Gender (men and women)	Age (years)	ASA rating (Level II/III)	NHYA rating (Level II/III)
C team	39	22/17	54.97 ± 8.90	11/28	12/27
R team	39	24/15	54.36 ± 8.74	14/25	10/29
χ^2/t		0.212	0.308	0.530	0.253
p		0.645	0.759	0.467	0.615

200–500 mL of Sodium Lactate Ringer's Injection was injected once the peripheral intravenous infusion catheter was opened. EEG bispectral index (BIS) was recorded via a disposable EEG sensor. The induction of anesthesia was comprised of intravenous injection of Sufentanil Citrate Injection (2 μg/kg), Midazolam Injection (1 mg/kg), Atracurium Besilate For Injection (0.15 mg/kg), and Etomidate Injectable Emulsion (0.3 mg/kg).

Group C received intravenous Dexmedetomidine Hydrochloride Injection in a 0.5 μg/kg loading dose and maintained at 1 mg/kg/h. Group R was initiated on intravenous Ketamine Hydrochloride Injection 0.5 mg/kg + Remimazolam Besylate for Injection 0.4 mg/kg, maintained at 0.5 mg/kg/h. The residual doses of 0.2 mg/kg cisatracurium were administered intravenously to the subjects in both groups after they were unconscious. Tracheal intubation was performed after the muscles were relaxed and the BIS value was below 60. After tracheal intubation, patients were conditioned for mechanical ventilation. For the duration of surgery, anesthetic maintenance consisted of Propofol Injectable Emulsion at 4 mg/kg/h, Remifentanil Hydrochloride for Injection at 0.1–0.3 μg/kg/min, and Sufentanil Citrate Injection in conjunction with Sodium Chloride Injection using infusion. Muscle relaxation was maintained by intermittent Cisatracurium Besilate for Injection at 0.1 mg/kg to maintain BIS values between 45 and 60.

2.2.2 | Evaluation Index

1. To determine the hemodynamic variables' causes, mean arterial pressure (MAP) and heart rate (HR) between groups were compared before induction of anesthesia (T0), at the skin incision (T1), at sternotomy (T2), just before CPB (T3), and at the closure of the wound (T4).
2. Comparison of respiratory rates (RR) of the two groups at T0, T1, T2, T3, and T4.
3. Comparisons of blood gas and cerebral oxygen metabolism indicators between the two groups: Cerebral oxygen uptake rates ($CERO_2$) and arterial-internal jugular vein blood oxygen content differences ($Da\text{-}jvO_2$) are calculated according to the Fick formula. $Da\text{-}jvO_2 = CaO_2 - CjvO_2$; $CERO_2 = (CaO_2 - CjvO_2)/CaO_2 \times 100\%$.
4. Comparison of cognitive ability of the two patient teams: Preoperatively, 24 h postoperatively, and 72 h later, cognitive functions in the two groups were evaluated based on Mini-Mental State Examination (MMSE) scores, in which a score of 30 represents high cognitive performance, while lower scores portray worse cognitive performance.
5. Myocardial damage indications between the two patient teams: 72 h postoperatively, patients had Fasting venous blood drawn before surgery, 24 h after surgery, and 72 h after surgery, and myocardial damage indicators were analyzed using an ELISA (troponin I [cTnI], creatine kinase MB isoenzyme [CK-MB], and heart-type fatty acid-binding protein [FABP]).
6. Delirium: The diagnostic criteria were: (i) a sudden onset of fluctuating conditions, (ii) a lack of concentration or attention, (iii) disordered thinking and/or levels of consciousness. If any patient met criteria (i) and (ii) plus either (iii) or (iv), delirium was diagnosed. The Delirium Scale (CAM) was used to assess the severity of postoperative delirium between the two groups, with scores greater than 22 indicating the presence of delirium, scores between 20 and 22 indicating possible delirium, and scores less than 20 indicating the absence of delirium.

2.3 | Statistical Methods

Data were analyzed using SPSS version 21.0. Categorical data were displayed as (*n* [%]), and the χ^2 test tested pairwise comparisons. Measurement data were reported as mean ± standard deviation ($x \pm s$), with a *t*-test used to compare pairs of values. No multiplicity adjustments were conducted. $p < 0.05$ indicates statistical significance.

3 | Results

3.1 | Demographic characteristics of both Team C and Team R

The demographic characteristics of both Team C and Team R were analyzed. Team C comprised 22 men and 17 women, while Team R comprised 24 men and 15 women. The average age of Team C was 55.48 ± 9.69 years, while Team R was 54.92 ± 9.73 years. The two groups were classified as grade II and grade III by the American Society of Anesthesiologists (ASA); the difference between them did not show statistical significance ($p > 0.05$). Such data on demographics are presented in Table 1.

3.2 | Comparison of RR Between Two Teams of Clients

The MAP and HR at T1, T2, T3, and T4 are lower in both Team C and Team R compared with T0 ($p < 0.05$). The MAP and HR at T1, T2, and T3 were statistically significantly lower in Team R than in Team C ($p < 0.05$). Detailed data are given in Table 2 and Figure S1.

3.3 | Comparison of Respiratory Rate (RR) Between the Two Teams of Patients

RRs from groups C and R were significantly higher on T1, T2, T3, and T4 than on T0 ($p < 0.05$). Given the comparison between Team R and Team C, RRs from Team R were significantly lower than RRs from Team C on T1, T2, T3, and T4 ($p < 0.05$). This comparison is provided in Table 3 and Figure S2.

3.4 | Comparison of Blood Gas and Cerebral Oxygen Metabolism Indicators Between the Two Teams of Patients

$Da\text{-}jvO_2$ and $CERO_2$ of Team D and Team R were statistically significantly lower at T1, T2, T3, and T4 compared to T0 ($p < 0.05$).

$Da\text{-}jvO_2$ and $CERO_2$ of team R showed statistical significance in their increase at T2, T3, and T4 compared to team C ($p<0.05$). These results are illustrated in Table S1 and Figure 1.

3.5 | Comparison of Cognitive Functions Between the Two Groups of Patients

In contrast, within Teams R and C, the MMSE grades were statistically significantly lower 24 and 72 h following surgery than before surgery ($p<0.05$). Within Team R, the MMSE grade was statistically significantly lower than that of Team C at 24 and 72 h, thus ensuring the anesthetic potency ($p<0.05$). This data is summarized in Table 4.

3.6 | Comparison of Myocardial Damage Indicators Between the Two Teams of Patients

The cTnI, CK-MB, and FABP levels in Team C were statistically significantly higher at 24 and 72 h following surgery than at the preoperative levels ($p<0.05$). The levels of cTnI, CK-MB, and FABP were statistically significantly lower in Group R compared to those in Group C at 24 and 72 h after surgery ($p<0.05$). The results are shown in Tables S3 and S4, and Figure S3.

TABLE 2 | Contrast of MAP and HR between two client teams at various intervals ($x \pm s$).

Index	T0	T1	T2	T3	T4
MAP (mmHg)					
C group ($n=39$)	94.36 ± 10.15	87.46 ± 9.77*	89.23 ± 8.26*	86.90 ± 7.49*	77.69 ± 7.44*
R group ($n=39$)	93.86 ± 11.02	75.15 ± 9.63*	78.94 ± 8.76*	82.17 ± 8.03*	75.92 ± 7.85*
t	0.174	5.586	5.363	2.688	1.051
p	0.862	0.000	0.000	0.009	0.297
HR (times/min)					
C group ($n=39$)	89.74 ± 9.51	83.79 ± 8.97*	84.97 ± 8.69*	80.62 ± 8.18*	84.26 ± 8.59 *
R group ($n=39$)	88.36 ± 10.04	75.50 ± 9.43*	76.87 ± 8.62*	75.11 ± 7.45*	83.85 ± 8.04*
t	0.636	3.988	4.124	3.090	0.191
p	0.527	0.000	0.000	0.003	0.849

*Shows a contrast with the same team's T0, $p<0.05$.

TABLE 3 | Comparing the RRs of two client teams at various intervals (%, $x \pm s$).

Index	T0	T1	T2	T3	T4
C group ($n=39$)	20.28 ± 2.24	26.00 ± 3.43*	30.51 ± 2.29*	27.05 ± 2.62*	23.49 ± 2.61*
R group ($n=39$)	20.33 ± 2.51*	23.21 ± 3.32*	25.77 ± 2.07*	22.90 ± 2.74*	22.85 ± 2.89*
t	0.117	3.659	9.674	6.907	2.543
p	0.907	0.000	0.000	0.000	0.013

*Shows the contrast with the same team's T0, $p<0.05$.

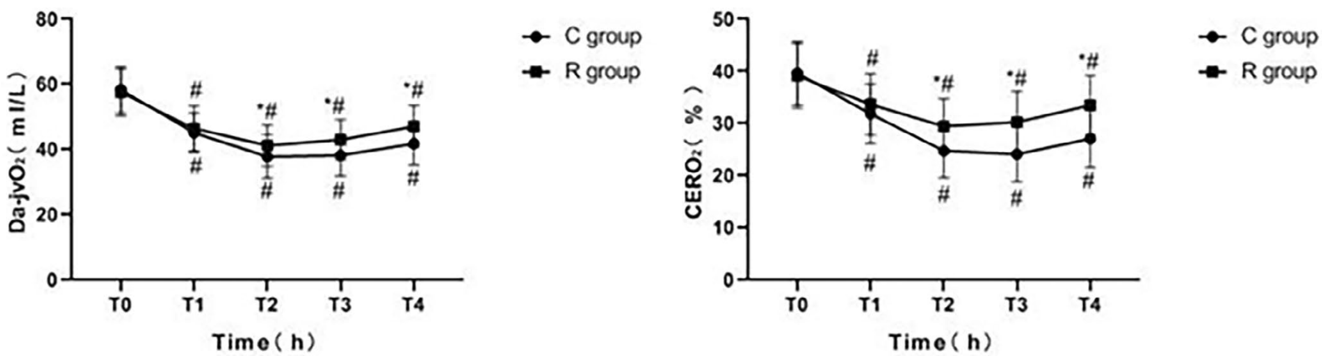

FIGURE 1 | Contrast of $CERO_2$ and $Da\text{-}jvO_2$ between two client teams at various intervals. *Indicates comparison with group C, $p<0.05$; #shows contrast with T0 of the same team, $p<0.05$.

3.7 | Postoperative Delirium

Team R, post-operatively, had statistically significantly lower cases of delirium than Team C, along with lower CAM grades ($p < 0.05$). Tables S1–S3, Figure S3, and Figure 2 all point to the direction of the risk. The p-value for the CAM grading Table S2 was carefully checked and was found to be accurate.

4 | Discussion

This involves draining venous blood out of the body through CPB-related instruments and devices and returning oxygenated blood into the arterial system after one has been stabilized, thus enabling smooth completion of the heart valve replacement operation. Studies have indicated that during surgical heart valve replacement under CPB, the patients are in a state of controlled shock, where hemodynamic fluctuations are easily induced. Reopening the aorta after CPB may also lead to myocardial ischemia–reperfusion and, thus, myocardial cellular injury.

Midazolam and etomidate are sedative agents commonly used for induction and maintenance of anesthesia. Midazolam may lead to prolonged recovery times and myoclonus, while etomidate has always been associated with side effects like nausea,

TABLE 4 | Da-jvO_2 and CERO_2 between two teams of clients at different time points ($x \pm s$).

Index	T0	T1	T2	T3	T4
Da-jvO_2 (mL/L)					
C group ($n = 39$)	58.36 ± 7.04	45.16 ± 6.80*	37.84 ± 6.64*	38.30 ± 6.34*	41.82 ± 6.05*
R group ($n = 39$)	57.5 4 ± 7.25	46.50 ± 6.93*	41.27 ± 6.29*	43.06 ± 6.13*	47.12 ± 6.43*
t	0.505	0.865	2.345	3.376	3.755
p	0.615	0.390	0.022	0.001	0.000
CERO_2 (%)					
C group ($n = 39$)	38.65 ± 6.03	31.86 ± 5.69*	24.79 ± 5.15*	2 4.13 ± 5.22*	27.12 ± 5.53*
R group ($n = 39$)	39.14 ± 6.22	33.70 ± 5.86*	29.47 ± 5.20*	30.27 ± 5.95*	33.53 ± 5.64*
t	0.354	1.407	3.991	4.843	5.067
p	0.724	0.163	0.000	0.000	0.000

*Indicates comparison with T0 of the same group, $p < 0.05$.

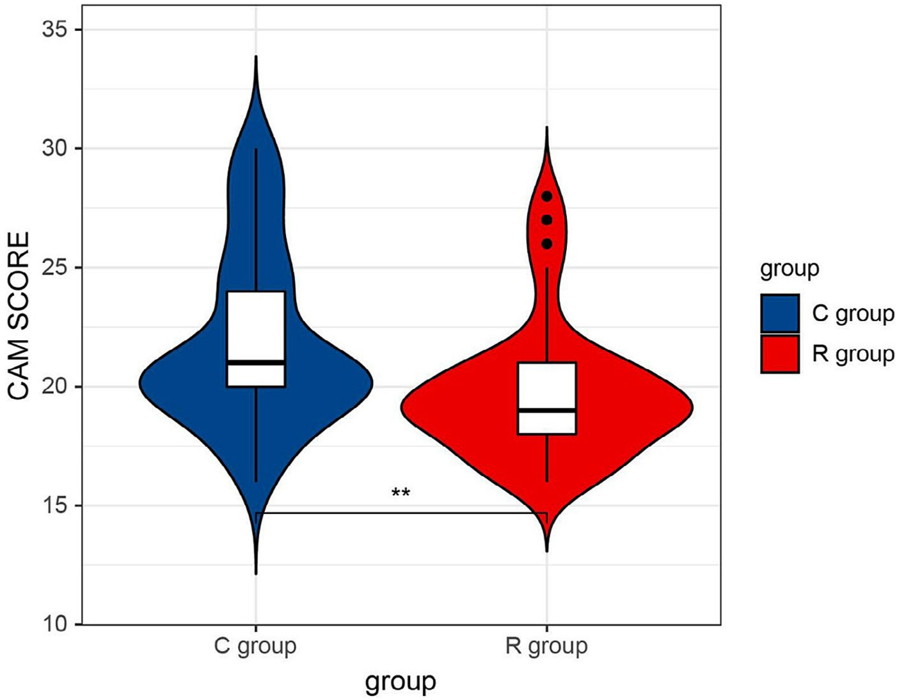

FIGURE 2 | Violin plot comparing CAM (Confusion Assessment Method) scores between the two groups of patients. This violin plot compares the distribution of CAM scores, reflecting the severity of delirium in the two patient groups postoperatively. The plot highlights the range, density, and median CAM scores, illustrating differences in delirium severity between groups C and R.

vomiting, and respiratory depression. Thus, an urgent need arises to search for newer anesthetic agents with much safer profiles and fewer side effects [13–16].

In Group C, dexmedetomidine was compared against esketamine and remimazolam tosylate (Group R). Dexmedetomidine is an α_2-adrenergic agonist known for its sedative and anxiolytic properties that dampen sympathetic outflow and maintain hemodynamic stability during surgery. Unlike midazolam, dexmedetomidine provides sedation and does not suppress respiration, making it the drug of choice in cardiovascular anesthesia [17, 18]; however, its long duration of action may delay recovery relative to newer agents like remimazolam.

Esketamine is an NMDA antagonist that manifests a distinctive dissociative anesthetic effect. An enantiomer of ketamine, esketamine has anesthetic effects that are about two times stronger and analgesic properties about three times stronger than ketamine due to stronger NMDA receptor activity [19, 20]. Studies suggest that esketamine produces fewer side effects and allows more rapid recovery than ketamine does in equivalent analgesic doses. Other studies have shown that esketamine administration improves hemodynamics and reduces respiratory depression due to its parasympathetic effects [21]. Esketamine also may help protect airway reflexes, thus decreasing the risk of respiratory depression and fast onset. It is, therefore, a helpful drug for maintaining intraoperative hemodynamic stability and improving outcomes.

Remazolam tosylate further develops imidazolium drugs that can deal directly with γ-aminobutyric acid type A (GABA-A) receptors. This increases chloride into the neuronal membrane, inhibiting neuronal excitability and producing sedative and analgesic effects [22–24]. Other studies show that remimazolam tosylate promotes faster patient recovery, better sedation success rates, and less postoperative sleepiness [25].

Statistical analyses revealed that at timestamps T1, T2, and T3, the MAP, HR, and respiratory rate of Team R were found to be statistically significantly lower than the values for Team C ($p<0.05$), while timestamps T2, T3, and T4 show that in Team C, Da-jvO_2 and CERO_2 were statistically significantly increased in comparison to Team C, ($p<0.05$). The parameters Da-jvO_2 and CERO_2 are indispensable indicators in the field of cerebral oxygen metabolism: an increase in Da-jvO_2 reflects an improved capacity to extract oxygen from the arterial supply; similarly, an increase in CERO_2 indicates improved oxygen utilization by the brain. These expected influences suggest improved cerebral oxygenation, reducing the risk of hypoxia-associated complications [26, 27].

The postoperative mean mini-mental state examination (MMSE) score was significantly lower in both groups than the preoperative scores ($p<0.05$). After surgery, the MMSE scores were significantly higher in Team R than in Team C ($p<0.05$). The findings implicate that dexmedetomidine-based sedation in Group C might lead to postoperative cognitive impairment. At the same time, the esketamine/remimazolam combination given to Group R demonstrated improved cognitive recovery rates based on MMSE. Team R had lower rates of postoperative delirium and CAM grades than Team C ($p<0.05$). The CAM score has been utilized to estimate the severity of postoperative delirium, and consequently, the lower the reduction in the grade, the more likely cognitive recovery will be improved. Given the report that dexmedetomidine appears to prolong the sedative effects, and this prolongation may negatively impact postoperative cognitive outcomes, these results further validate the improvement in cognitive recovery by a combination of esketamine and remimazolam [16, 18].

The study compared myocardial injury assessed in the groups before, 24 and 72 h after surgery. A statistically significant decline in cTnI, CK-MB, and FABP for Team R over Team C occurred 24 and 72 h after surgery ($p<0.05$). Those myocardial markers indicate the degree of myocardial damage; hence, a decline in cTnI, CK-MB, and FABP indicates better cardiac protection. Dexmedetomidine may provide hemodynamic stability but may not provide the same degree of myocardial protection offered by esketamine/remimazolam; conversely, the esketamine/remimazolam combination appears to reduce myocardial injury by minimizing oxidative stress and inflammation [28].

In conclusion, combined administration of esketamine with remimazolam tosylate ensures hemodynamic stability, contributes to cerebral oxygen metabolism, protects from myocardial damage, improves cognition, and potentially decreases the incidence of postoperative delirium among patients undergoing cardiac valve replacement under cardiovascular anesthesia. This study outlines the potential beneficial effects of these agents on hemodynamic and cerebral stability and makes a case for their broader use in high-risk cardiovascular surgical fields.

Author Contributions

L.X. and H.L. wrote the manuscript; H.L. designed the research; L.X. and Z.J. performed the research; Z.J. and X.T. analyzed the data; L.X. and Z.J. contributed new reagents.

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of Renmin Hospital, Hubei University of Medicine approves this study. Written informed consent was obtained.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

References

1. Z. Tugaoen, P. Nguyen, S. Arora, and J. Vavalle, “The Selection of Transcatheter Heart Valves in Transcatheter Aortic Valve Replacement,” *Trends in Cardiovascular Medicine* 32, no. 8 (2022): 513–522.

2. L. E. Dobson and B. D. Prendergast, "Heart Valve Disease: A Journey of Discovery," *Heart* 108, no. 10 (2022): 774–779.

3. J. T. S. Faustich, J. P. Carney, M. T. Lahti, B. L. Zhang, and R. W. Bianco, "Establishing Background Pathologic Changes of Valve Replacement Surgery in Sheep," *Cardiovascular Engineering and Technology* 13, no. 1 (2022): 181–190.

4. A. Pitsis, N. Tsotsolis, H. Boudoulas, and K. D. Boudoulas, "Totally Endoscopic Aortic Valve Replacement With Concomitant Trans-Aortic Mitral Valve Repair for Mitral Regurgitation," *Journal of Cardiothoracic Surgery* 16, no. 1 (2021): 318.

5. G. Liu and Y. Xiong, "Analysis of Stress Response and Analgesic Effect of Remazolam Combined With Etomidate in Painless Gastroenteroscopy," *Contrast Media & Molecular Imaging* 2022 (2022): 4863682.

6. Q. Hu, X. Liu, C. Wen, D. Li, and X. Lei, "Remimazolam: An Updated Review of a New Sedative and Anaesthetic," *Drug Design, Development and Therapy* 16 (2022): 3957–3974.

7. M. F. Bellolio, H. A. Puls, J. L. Anderson, et al., "Incidence of Adverse Events in Paediatric Procedural Sedation in the Emergency Department: A Systematic Review and Meta-Analysis," *BMJ Open* 6, no. 6 (2016): e011384.

8. X. Wu, L. Zeng, T. Zhang, W. Wu, Y. Tian, and S. Dong, "The Study of Different Dosages of Remazolam Combined With Sufentanil and Propofol on Painless Gastroscopy: A Randomized Controlled Trial," *Medicine (Baltimore)* 102, no. 34 (2023): e34731.

9. Y. Zheng, Y. Xu, B. Huang, Y. Mai, Y. Zhang, and Z. Zhang, "Effective Dose of Propofol Combined With a Low-Dose Esketamine for Gastroscopy in Elderly Patients: A Dose Finding Study Using Dixon's Up-And-Down Method," *Frontiers in Pharmacology* 13 (2022): 956392.

10. P. Liu, S. S. Zhang, Y. Liang, Z. J. Gao, W. Gao, and B. H. Dong, "Efficacy and Safety of Esketamine Combined With Antidepressants for Treatment-Resistant Depression: A Meta-Analysis," *Neuropsychiatric Disease and Treatment* 18 (2022): 2855–2865.

11. S. H. Gregory, N. Sodhi, J. K. Zoller, et al., "Anesthetic Considerations for the Transcatheter Management of Mitral Valve Disease," *Journal of Cardiothoracic and Vascular Anesthesia* 33, no. 3 (2019): 796–807.

12. Y. Hari, S. Satomi, C. Murakami, et al., "Remimazolam Decreased the Incidence of Early Postoperative Nausea and Vomiting Compared to Desflurane After Laparoscopic Gynecological Surgery," *Journal of Anesthesia* 36, no. 2 (2022): 265–269.

13. A. Harky, A. Hof, M. Garner, S. Froghi, and M. Bashir, "Mitral Valve Repair or Replacement in Native Valve Endocarditis? Systematic Review and Meta-Analysis," *Journal of Cardiac Surgery* 33, no. 7 (2018): 364–371.

14. J. H. Lee, J. E. Lee, J. Shin, et al., "Clinical Implications of Hypothermic Ventricular Fibrillation Versus Beating-Heart Technique During Cardiopulmonary Bypass for Pulmonary Valve Replacement in Patients With Repaired Tetralogy of Fallot," *Interactive Cardiovascular and Thoracic Surgery* 25, no. 3 (2017): 370–376.

15. Y. Lyu, M. Cao, C. Wei, H. Fang, and X. Lu, "High-Dose Ulinastatin Reduces Postoperative Bleeding and Provides Platelet-Protective Effects in Patients Undergoing Heart Valve Replacement Surgery," *International Journal of Clinical Pharmacology and Therapeutics* 60, no. 11 (2022): 463–468.

16. J. Wang, J. Huang, S. Yang, et al., "Pharmacokinetics and Safety of Esketamine in Chinese Patients Undergoing Painless Gastroscopy in Comparison With Ketamine: A Randomized, Open-Label Clinical Study," *Drug Design, Development and Therapy* 13 (2019): 4135–4144.

17. L. Zheng, Y. Wang, Q. Ma, et al., "Efficacy and Safety of a Subanesthetic Dose of Esketamine Combined With Propofol in Patients With Obesity Undergoing Painless Gastroscopy: A Prospective, Double-Blind, Randomized Controlled Trial," *Drug Design, Development and Therapy* 17 (2023): 1347–1356.

18. Y. Zhan, S. Liang, Z. Yang, et al., "Efficacy and Safety of Subanesthetic Doses of Esketamine Combined With Propofol in Painless Gastrointestinal Endoscopy: A Prospective, Double-Blind, Randomized Controlled Trial," *BMC Gastroenterology* 22, no. 1 (2022): 391.

19. S. Eberl, L. Koers, J. van Hooft, et al., "The Effectiveness of a Low-Dose Esketamine Versus an Alfentanil Adjunct to Propofol Sedation During Endoscopic Retrograde Cholangiopancreatography: A Randomised Controlled Multicentre Trial," *European Journal of Anaesthesiology* 37, no. 5 (2020): 394–401.

20. M. Feng, G. Shi, W. Cui, N. Zhang, Q. Xie, and W. Zhang, "The Median Effective Concentration of Propofol in Combination With Different Doses of Esketamine During Gastrointestinal Endoscopy in Adults," *Frontiers in Pharmacology* 13 (2022): 1034236.

21. A. Eisenried, J. Schüttler, M. Lerch, H. Ihmsen, and C. Jeleazcov, "Pharmacokinetics and Pharmacodynamics of Remimazolam (CNS 7056) After Continuous Infusion in Healthy Male Volunteers: Part II. Pharmacodynamics of Electroencephalogram Effects," *Anesthesiology* 132, no. 4 (2020): 652–666, https://doi.org/10.1097/ALN.0000000000003102.

22. G. Dai, L. Pei, F. Duan, et al., "Safety and Efficacy of Remimazolam Compared With Propofol in Induction of General Anesthesia," *Minerva Anestesiologica* 87, no. 10 (2021): 1073–1079.

23. M. Doi, N. Hirata, T. Suzuki, H. Morisaki, H. Morimatsu, and A. Sakamoto, "Safety and Efficacy of Remimazolam in Induction and Maintenance of General Anesthesia in High-Risk Surgical Patients (ASA Class III): Results of a Multicenter, Randomized, Double-Blind, Parallel-Group Comparative Trial," *Journal of Anesthesia* 34, no. 4 (2020): 491–501, https://doi.org/10.1007/s00540-020-02776-w.

24. T. Liu, T. Lai, J. Chen, et al., "Effect of Remimazolam Induction on Hemodynamics in Patients Undergoing Valve Replacement Surgery: A Randomized, Double-Blind, Controlled Trial," *Pharmacology Research & Perspectives* 9, no. 5 (2021): e00851.

25. M. Su, Y. Zhu, S. Liu, et al., "Median Effective Dose (ED50) of Esketamine Combined With Propofol for Children to Inhibit Response of Gastroscope Insertion," *BMC Anesthesiology* 23, no. 1 (2023): 240.

26. B. Hu, K. Jiang, W. Shi, et al., "Effect of Remimazolam Tosilate on Respiratory Depression in Elderly Patients Undergoing Gastroscopy: A Multicentered, Prospective, and Randomized Study," *Drug Design, Development and Therapy* 16 (2022): 4151–4159.

27. A. M. Wesolowski, M. P. Zaccagnino, R. J. Malapero, A. D. Kaye, and R. D. Urman, "Remimazolam: Pharmacologic Considerations and Clinical Role in Anesthesiology," *Pharmacotherapy* 36, no. 9 (2016): 1021–1027.

28. R. B. Kleiman, B. Darpo, M. Thorn, T. Stoehr, and F. Schippers, "Potential Strategy for Assessing QT/QTc Interval for Drugs That Produce Rapid Changes in Heart Rate: Electrocardiographic Assessment of the Effects of Intravenous Remimazolam on Cardiac Repolarization," *British Journal of Clinical Pharmacology* 86, no. 8 (2020): 1600–1609.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.