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ORIGINAL ARTICLE

Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: A randomized, double-blind, controlled trial

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Abstract

Background: The stability of hemodynamics during anesthesia induction in patients undergoing valve replacement surgery is particularly important. Remimazolam is a new type of benzodiazepine drug, with supposed advantages of rapid induction, rapid recovery, stable hemodynamics, and mild respiratory inhibition.

Aim: To evaluate the effect of remimazolam anesthesia induction on hemodynamics in patients undergoing valve replacement surgery.

Methods: This randomized, double-blind, controlled trial enrolled consecutive patients undergoing mitral valve replacement (MVR)/aortic valve replacement (AVR)/double-valve replacement (DVR) surgery on cardiopulmonary bypass (CPB). The study was conducted according to the Consolidated Standards of Reporting Trials statement. Participants were randomly assigned to receive either remimazolam or propofol induction of 30 patients each. All patients, data collectors, and data analyzers were blinded to the group allocation. The primary outcomes were the fluctuations in hemodynamic parameters (the difference of maximum or minimum heart rate to baseline, ▲HR, the difference of maximum or minimum mean arterial pressure to baseline, ▲MAP), the occurrence of cardiovascular events (hypotension, severe bradycardia), and the cumulative norepinephrine doses used per patient, averaged per group during induction. The secondary outcomes were hemodynamic parameters (heart rate, HR, mean arterial pressure, MAP, bispectral index, BIS, plasma lactic acid, Lac, and blood glucose, Glu values).

Results: A total of 60 patients with heart valve replacement were included in the final analysis, with 30 patients in each group. The ▲MAP was significantly lower in the remimazolam group than in the propofol group during induction ($p < .05$). The incidences of hypotension and the cumulative norepinephrine doses used per patient,

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averaged per group during induction were significantly lower in the remimazolam group than in the propofol group ($p < .05$).

Conclusion: Remimazolam may be safe and effective for induction and may as an alternative to propofol during anesthesia induction in patients undergoing valve replacement surgery.

KEYWORDS
anesthesia induction, cardiovascular events, hemodynamics, propofol, remimazolam, valve replacement surgery

1 | INTRODUCTION

The overall ageadjusted prevalence of valvular heart disease (VHD) was estimated to be 2.5% (95% CI 2.2%–2.7%).[1,2] Heart valve replacement surgery has been widely practiced in clinics with its obvious effects. The proportion of valvular surgeries has accounted for more than 20% of all cardiac surgeries.[3] Many patients with VHD have varieties of underlying diseases and cardiac dysfunction, so the stability of hemodynamics during anesthesia induction is particularly important.[4] Remimazolam is a new type of benzodiazepine drug.[5] It mainly acts on the GABA-A receptor and has the advantages of rapid induction, rapid recovery, stable hemodynamics, and mild respiratory inhibition.[5,6] Moreover, remimazolam has no accumulation after long-term infusion and its metabolite has no pharmacological effect. Therefore, it should have a wide application prospect in clinical anesthesia.[5,7–9] At present, there is little literature on its practice in cardiac surgery anesthesia.

Our study aimed to evaluate the effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery.

2 | MATERIALS AND METHODS

The study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University (2020 No. 064) and conducted according to the Declaration of Helsinki. The trial was registered in the Chinese Clinical Trial Registry on December 6, 2020 (ChiCTR2000040650) and conducted according to the Consolidated Standards of Reporting Trials statement. Written informed consent was obtained from all participants after having been provided with detailed information about the study aims, procedures, and risks before enrolling for the study.

2.1 | Study design and patients

This randomized, double-blind, controlled trial enrolled consecutive patients undergoing mitral valve replacement (MVR)/aortic valve replacement (AVR)/double-valve replacement (DVR) surgery on cardiopulmonary bypass (CPB) at the Department of Anesthesiology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China between December 2020 and February 2021. The inclusion criteria were as follows: (1) Scheduled for MVR/AVR/DVR on CPB; (2) Age 35–65 years; (3) Cardiac function graded as New York Heart Association class II or III; and (4) American Society of Anesthesiologists (ASA) grade III. The exclusion criteria were as follows: (1) Severe cardiac dysfunction, ASA grade IV or above; (2) Allergic or contraindicated to benzodiazepines, opioids, propofol or their components; (3) Hypertension of grade 3 or above; (4) Dysfunction of the liver or kidney; and (5) Participation in another study within 4 weeks before the current trial.

2.2 | Randomization and grouping

Participants were randomly assigned to receive either remimazolam or propofol induction of 30 patients each. First, the random number table method was used to ensure equal distribution in the two groups (group remimazolam and group propofol). Randomization was done by opening a sealed envelope just before entry to the operating room by a nurse anesthetist, who did not involve in the anesthesia of study participants, and then she/he prepared the medications and recorded the data according to the instructions inside the envelope and put the recorded data back in the envelope to reseal. The anesthesiologist induced the patient into anesthesia according to the instructions in the envelope. Finally, after the data of all the enrolled patients were collected, envelopes would only be opened by the good clinical practice (GCP) monitor and by the investigators. Thus, all patients, data collectors, and data analysts were blinded to the group allocation.

2.3 | Anesthesia induction and maintenance

One day before the operation, a routine preoperative visit was carried out to obtain the understanding and cooperation of patients, and all preoperative preparations were made. After entering the OR, peripheral venous access was routinely achieved, five lead electrocardiogram (ECG) heart rates, noninvasive blood pressure, pulse oxygen saturation, and bispectral index (BIS) were monitored. Radial artery catheters were inserted under local infiltration anesthesia with lidocaine, and arterial blood pressure was continuously monitored by the arterial sensor. The central venous pressure was monitored. Baseline hemodynamic data were recorded after at least 5 min without further changes in HR or arterial pressure. Samples

for baseline values of plasma lactic acid (Lac) and blood glucose (Glu) were obtained before induction.

Anesthesia induction: After preoxygenation, patients in group remimazolam received a total dose of 0.3 mg/kg of remimazolam[10] (Jiangsu Hengrui Pharmaceutical Co. Ltd., approval number: H20190034) by constant speed pump at the speed of 1.8 mg/kg/h and in group propofol received target-controlled infusion (TCI) of propofol (Sichuan Guorui Pharmaceutical Co. Ltd., approval number: H20091713) 2.5 μg/ml. At the same time, the total dose of 1 μg/kg sufentanil (Renfu Pharmaceutical Group Co. Ltd., approval number: H20054171) was pumped at a constant rate of 0.1 μg/kg/min in both groups. Seven minutes later, patients received an intravenous injection of cisatracurium (0.2 mg/kg; Jiangsu Hengrui Pharmaceutical Co. Ltd., approval number: H20060869), and after 3 min, tracheal intubation (when BIS index below 60) and mechanical ventilation were performed to control PetCO2 in the range of 35–45 mmHg. The BIS index was maintained at a value of 40–60. The time from the beginning of anesthesia to tracheal intubation was 10 min for both groups. Hypotension was considered when the mean arterial pressure (MAP) was lower than 60 mmHg during induction, and 50 μg norepinephrine was given intravenously. When HR was lower than 45 beats/min, it was considered as severe bradycardia, and 0.25 mg atropine was administrated by intravenous injection. The occurrence of hypotension and severe bradycardia was recorded. The cumulative norepinephrine doses used per patient were recorded.

Anesthesia maintenance: in both groups, sufentanil 0.2 μg/kg/h and dexmedetomidine 0.5 μg/kg/h were injected intravenously, and propofol was target-controlled injected to maintain a BIS index of 40–55.

2.4 | Outcome measures

The primary outcomes were the fluctuations in hemodynamic parameters (▲HR, ▲MAP), the occurrence of cardiovascular events (hypotension, severe bradycardia), and the cumulative norepinephrine doses used per patient, averaged per group during induction. The secondary outcomes were hemodynamic parameters (HR, MAP), BIS index, Lac, and Glu values.

HR, MAP, and BIS index were recorded at baseline, 3 min after the induction of anesthesia, immediately before tracheal intubation (10 min after the induction of anesthesia), 1 min after tracheal intubation, and 5 min after tracheal intubation. The maximum or minimum HR and MAP after administration was recorded during induction. ▲HR was the difference of maximum or minimum HR to baseline. ▲MAP was the difference of maximum or minimum MAP to baseline. Lac and Glu values were recorded at baseline and 5min after tracheal intubation.

2.5 | Statistical analysis and sample size calculation

IBM SPSS Statistics version 25 was used to test the normality of data by the Kolmogorov–Smirnov test. The normally distributed data were expressed as the mean ± SD and were compared between groups using Student's unpaired t test, whereas nonparametric data were compared by the χ^2 test or Fisher's exact test for intergroup differences. $p < .05$ was taken to indicate statistical significance.

The sample size was calculated based on a pilot study. In this pilot study, the mean ± SD ▲MAP in the remimazolam group and the propofol group was 16.8 ± 7.2 mmHg and 23.6 ± 9.1 mmHg, respectively. For a difference in the 20% reduction of ▲HR and ▲MAP at a significance level of 0.05 (two-sided) and power of 0.9, we required a minimum of 25 patients in each group.

3 | RESULTS

3.1 | Baseline clinical characteristics of the study participants

According to the inclusion criteria and exclusion criteria, a total of 60 patients with heart valve replacement were included in the final analysis, with 30 patients in each group (Figure 1). There were no significant differences between groups in sex, age, height, weight, or type of surgery (Table 1).

3.2 | Primary outcomes

The ▲MAP was significantly lower in the remimazolam group than in the propofol group during induction ($p < .05$; Table 2). The incidences of hypotension and the cumulative norepinephrine doses used per patient, averaged per group during induction were significantly lower in the remimazolam group than in the propofol group ($p < .05$; Table 2). There was no significant difference between the remimazolam and propofol groups in ▲HR (Table 2). No severe bradycardia was recorded.

3.3 | Secondary outcomes

There were no significant differences between the remimazolam and propofol groups in HR, MAP, or BIS at all time points (Table 3). There were no significant differences between the two groups in Lac and Glu values at baseline and 5 min after tracheal intubation (Table 4).

4 | DISCUSSION

Cardiac output and functional reserve of patients undergoing valve replacement surgery under CPB are often reduced.[11] For this kind of patient, the stability of hemodynamics during anesthesia induction is particularly important.[4] Propofol is a commonly used clinical intravenous anesthetics, with the advantages of fast induction and recovery, but it has a strong inhibitory effect on the myocardium,

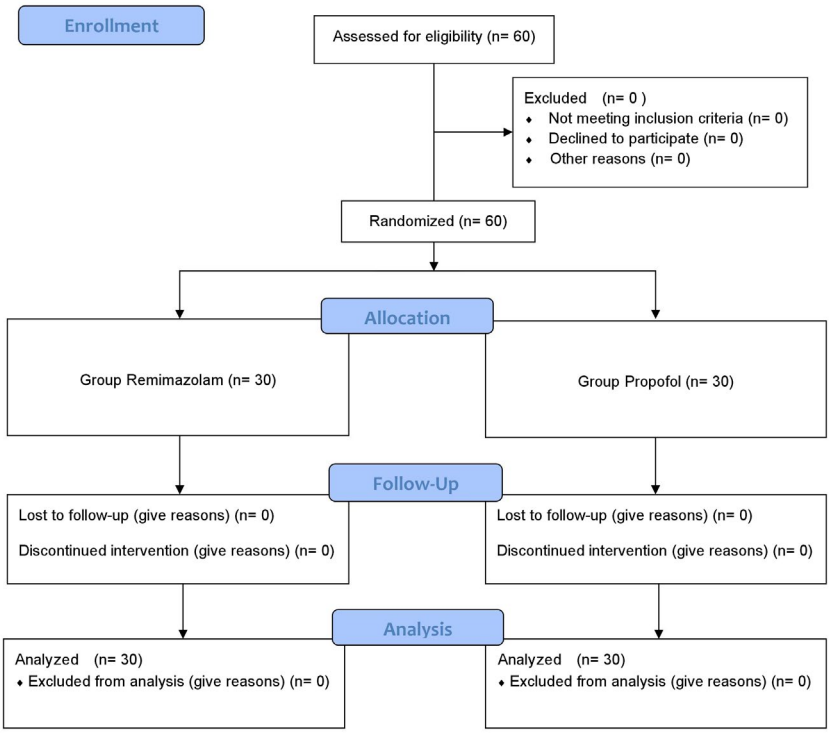

FIGURE 1 Consort flow diagram of patients

TABLE 1 Baseline clinical characteristics of the study participants

Group	Male/Female (*n*)	Age (years)	Height (cm)	Weight (kg)	MVR (*n*)	AVR (*n*)	DVR (*n*)
Remimazolam	14/16	54.9 ± 11.3	160.7 ± 9.4	59.1 ± 11.5	13	8	9
Propofol	17/13	50.6 ± 10.5	159.1 ± 20.0	64.7 ± 23.6	15	8	7
p value	.4383	.1299	.6932	.2469	.7961	>.9999	.7710

Note: Data are presented as the mean ± SD ($n = 30$ in each group).

TABLE 2 Fluctuations in hemodynamic parameters and incidence of cardiovascular events during induction

Group	▲HR (beat/min)	▲MAP (mmHg)	Hypotension, n (%)	Norepinephrine use (μg)
Remimazolam	9.3 ± 9.9	19.5 ± 7.5	5 (16.7%)	8.3 ± 18.9
Propofol	6.5 ± 8.4	26.7 ± 9.1	13 (43.3%)	33.3 ± 42.2
p value	.2380	.0016	.0242	.012

Note: Data are presented as the mean ± SD ($n = 30$ in each group).

Abbreviations: ▲HR, maximum change of heart rate; ▲MAP, maximum change of mean arterial pressure.

resulting in a drop in blood pressure and significant circulation fluctuations.[12] It also has obvious injection pain.[13]

Remimazolam is an ultra–short-acting novel benzodiazepine, similar to midazolam and remifentanil's complementary advantages.[14] It mainly acts on the GABA-A receptor and has the advantages of rapid induction, rapid recovery, stable hemodynamics, and mild respiratory inhibition.[5,6] A study has shown that the pharmacokinetic half-time of remimazolam is about one-fifth of midazolam after three hours of constant rate infusion.[15,16] And the half-times of both remimazolam and propofol are 7.5 min.[16] Unlike propofol, remimazolam undergoes organ-independent metabolism to an inactive metabolite.[6] Additionally, remimazolam does not affect liver and kidney function. And there was no accumulation after a long time infusion. At present, it has been increasingly widely used in clinical anesthesia, such as induction and maintenance of general anesthesia,[10] gastrointestinal endoscopy,[8,17] bronchoscopy,[18] and intraoperative wake-up during neurosurgical craniotomy.[19] However, there is little literature on its practice in cardiac surgery anesthesia.

In this study, we use the BIS index as an electroencephalographic (EEG) monitor to assess the effect of anesthetics. Appropriate ranges of BIS index for remimazolam anesthesia remain unclear, the ranges may be higher, for example 60–70 or 50–60 of BIS index.[20]

TABLE 3 Comparison of hemodynamic parameters between groups

Group	Baseline	3 min after the induction of anesthesia	Immediately before tracheal intubation (10 min after the induction)	1 min after tracheal intubation	5 min after tracheal intubation
MAP (mmHg)					
Remimazolam	83.4 ± 10.8	72.7 ± 8.7	65.1 ± 7.7	72.4 ± 7.8	71.3 ± 6.8
Propofol	89.7 ± 12.7	76.7 ± 10.8	65.1 ± 10.1	74.5 ± 11.3	71.5 ± 11.1
p value	.3815	.3493	.9773	.4134	.9444
HR (beats/min)					
Remimazolam	80.4 ± 13.5	78.7 ± 13.2	72.6 ± 11.3	74.6 ± 11.9	70.9 ± 11.5
Propofol	85.0 ± 18.9	82.7 ± 19.4	79.7 ± 21.4	81.3 ± 21.4	77.5 ± 19.0
p value	.2835	.3807	.0957	.1416	.1500
BIS index					
Remimazolam	95.6 ± 2.2	72.7 ± 6.6	49.9 ± 6.1	50.3 ± 6.4	49.6 ± 6.0
Propofol	96.4 ± 1.8	73.9 ± 5.7	48.2 ± 6.7	47.6 ± 6.4	48.4 ± 5.4
p value	.1765	.4599	.3025	.1461	.4610

Note: Data are presented as the mean ± SD ($n = 30$ in each group).

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

TABLE 4 Comparison of Lac and Glu between groups

Group	Baseline	5 min after tracheal intubation
Lac (mmol/L)		
Remimazolam	1.4 ± 1.0	1.1 ± 0.6
Propofol	1.0 ± 0.4	1.0 ± 0.3
p value	.0770	.1745
Glu (mmol/L)		
Remimazolam	5.4 ± 0.5	5.6 ± 0.6
Propofol	5.4 ± 0.6	5.6 ± 0.6
p value	.8172	.8773

Note: Data are presented as the mean ± SD ($n = 30$ in each group).

Abbreviations: Glu, blood glucose; Lac, lactic acid.

Our study showed that when BIS was maintained at 40–60, the hemodynamics of the remimazolam group was also stable, which indicated that the BIS index could well reflect the anesthesia depth of remimazolam. In the present study, all patients underwent anesthesia induction safely, no severe bradycardia was recorded, which indicated that remimazolam was safe and effective for anesthesia induction in patients undergoing valve replacement surgery.

Dai et al. found that propofol-based anesthesia was associated with significantly higher incidences of bradycardia, hypotension, ST-T segment abnormalities, and ventricular premature beats in patients with coronary heart disease undergoing noncardiac surgery under general anesthesia.[21] Kleiman RB et al. confirmed that remimazolam did not prolong QT interval and did not increase the risk of ventricular arrhythmia.[22] In this study, the hemodynamics of the remimazolam induction group was more stable, the incidences of hypotension, and the cumulative norepinephrine doses used per patient, averaged per group were lower than those in the propofol induction group during anesthesia induction of patients undergoing valve replacement surgery under CPB, which was undoubtedly more favorable for patients undergoing valve replacement surgery.

There were no significant changes in Lac, and Glu values before and after endotracheal intubation, which indicated that no hypoxia or excessive stress resulting in tissue perfusion dysfunction during the induction. The results were similar to the effect of propofol.[23] This study has several limitations. First, this was a single-center study, so the generalizability of the findings is not known. Second, some cardiac functional indicators were not measured, such as ST-T segment changes, the level of cardiac troponin I, and ventricular premature beats. Third, the sample size of this study was small and the age range of the included patients was narrow. Therefore, additional studies should be conducted to expand the sample size and the age range of the included patients to better evaluate the benefit/risk of remimazolam in patients undergoing valve replacement. Fourth, in this study, only one intravenous pumping injection speed was set for remimazolam. Whether other intravenous pumping injection speeds can better maintain hemodynamics stability while maintaining sufficient sedation depth during anesthesia induction remains to be further clinical study. Fifth, like other observational studies, some confounding factors may have influenced the results.

5 | CONCLUSION

Remimazolam may be safe and effective for anesthesia induction and may as an alternative to propofol during anesthesia induction in patients undergoing valve replacement surgery. However, additional studies should be conducted to expand the sample size and the age range of the included patients to better evaluate the benefit/risk of remimazolam in patients undergoing valve replacement.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

All authors participated in the whole process of this study and approved the final version. Tianxiao Liu, Ting Lai, Yanhua Chen, and Yubo Xie involved in planning, conducting, reporting, conception, design, acquisition of data, data analysis, interpretation of data, and writing of the manuscript. Jing Chen, Yizhi Lu, Fang He involved in conducting, acquisition of data, and data analysis of the manuscript.

DATA AVAILABILITY STATEMENT

All data generated and analyzed in the study are available from the corresponding author upon reasonable request.

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