Original Article

Dexmedetomidine Pretreatment Confers Myocardial Protection and Reduces Mechanical Ventilation Duration for Patients Undergoing Cardiac Valve Replacement under Cardiopulmonary Bypass

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Purpose: The study aims to assess the effects of dexmedetomidine (Dex) pretreatment on patients during cardiac valve replacement under cardiopulmonary bypass.
Methods: For patients in the Dex group (n = 52), 0.5 μg/kg Dex was given before anesthesia induction, followed by 0.5 μg/kg/h pumping injection before aortic occlusion. For patients in the control group (n = 52), 0.125 ml/kg normal saline was given instead of Dex.
Results: The patients in the Dex group had longer time to first dose of rescue propofol than the control group (P = 0.003). The Dex group required less total dosage of propofol than the control group (P = 0.0001). The levels of cardiac troponin I (cTnI), creatine kinase isoenzyme MB (CK-MB), malondialdehyde (MDA), and tumor necrosis factor-α (TNF-α) were lower in the Dex group than the control group at T4, 8 h after the operation (T5), and 24 h after the operation (T6) (P <0.01). The Dex group required less time for mechanical ventilation than the control group (P = 0.003).
Conclusion: The study suggests that 0.50 μg/kg Dex pretreatment could reduce propofol use and the duration of mechanical ventilation, and confer myocardial protection without increased adverse events during cardiac valve replacement.

Keywords: cardiac valve replacement, dexmedetomidine, propofol, cardiopulmonary bypass, cardioprotection

Introduction

Valvular heart disease (VHD) is a common clinical entity in the cardiovascular field and affects millions of people around the world, showing a major impact on health care systems.[1)] The increase in prevalence of VHD has been accompanied by rapid population aging, and the proportion of valve interventions remains more than 20% of all cardiac surgeries.[2)] Although valve replacement surgery has been widely practiced in clinics, it is recommended for patients with VHD only when compatible symptoms dictate or when changes in left ventricular function occur and should be performed after a consensus discussion of cardiologists and cardiac surgeons.[3)] Due to VHD resulting from multiple heterogeneous etiologies and leading to cardiac dysfunction, hemodynamic changes in cardiac output and vascular resistance associated with anesthesia induction should be carefully managed during valvular surgeries, especially for patients typically elderly and with a higher American Society of Anesthesiologists physical status.[4,5)] During cardiac valve replacement, myocardial ischemia-reperfusion

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injury is likely to occur since cardiac valve replacement procedures involve clamping and declamping of the aorta concomitant with stopping and resuming of the heart pumping.[6] Additionally, cardiopulmonary bypass (CPB)-related myocardial ischemia-reperfusion injury is a leading contributor to postoperative morbidity.[7] During the surgery, the production of catecholamine usually causes hemodynamic instability as well as an imbalance between oxygen supply and demand in the myocardium, which also aggravates the myocardial injury.[8]

Anesthesia and analgesia for cardiac surgery have been one of six fields involving enhanced recovery after cardiac surgeries under CPB for reducing postoperative mortality and morbidity, decreasing the length of hospital stay, and improving patient satisfaction.[9] Hypnotics and opioids have been synergistically employed in painful procedures to block responses to surgery and different dose combinations may be used to induce anesthesia and analgesia, such as sufentanil, dexmedetomidine (Dex), or ketamine added to propofol-based sedation for elderly patients receiving gastrointestinal endoscopy.[10] During cardiac valve replacement, Dex pretreatment, posttreatment, and whole-course pumping were shown to exert myocardial protective effects, such as prolonged time to heart rebound and low incidence of arrhythmia.[11] Dex is a highly selective α2-adrenergic agonist that inhibits sympathetic activity and mimics natural deep sleep to produce anesthetic and analgesic effects, which has opioid-sparing actions and exerts a minimal impact on cardiorespiratory systems.[12,13] Dex was previously demonstrated to provide the desired attenuation of the hemodynamic response and result in a lower incidence of respiratory depression compared with sufentanil during percutaneous tracheostomy.[14] Dex administration before CPB could prevent cardiac injuries and reduce inflammatory response in valve replacement surgery with a sevoflurane postconditioning protocol.[15] However, the incidence of severe bradycardia, hypotension, and hypertension during the anesthesia management focusing on the combined usage of Dex still remains clinical challenge. In this study, we investigated the effects of Dex pretreatment in the setting of 0.50 μg/kg on patients undergoing for cardiac valve replacement under CPB.

Materials and Methods

Patient selection

This prospective study consisted of 104 patients undergoing cardiac valve replacement surgery between January 2021 and December 2022 based on sample-size calculation, and their medical records were reviewed with the approval of Zhongshan City People's Hospital. The included patients were: (i) those undergoing mitral valve replacement (MVR), aortic valve replacement (AVR), and double-valve replacement surgery on CPB; (ii) median sternotomy; (iii) those using propofol target-controlled infusion (TCI); (iv) those with cardiac function graded as New York Heart Association (NYHA) class II or III; (v) at the age of 18–72 years; and (v) those with the same myocardial protection method (500–1000 ml 4°C modified St. Thomas No 1 cardioplegic solution containing 0.058–0.23 mmol/L captopril). The exclusion criteria were: (i) preoperative pulmonary infection, pulmonary, kidney, and liver insufficiency; (ii) history of kidney or heart surgery; or (iii) complete electronic record for propofol TCI data. According to with or without Dex pretreatment during cardiac valve replacement surgery, eligible patients were randomly split into the Dex group (with Dex pretreatment) and the control group (without Dex pretreatment) by a table of random number. Participants, staff, and investigators were blinded to study group allocation.

Dex pretreatment and anesthesia method

For patients in the Dex group, 0.5 μg/kg Dex was given before anesthesia induction, followed by 0.5 μg/kg/h pumping injection before aortic occlusion. For patients in the control group, 0.125 ml/kg normal saline was given before anesthesia induction, followed by 125 ml/kg/h pumping injection before aortic occlusion. The plasma target concentration of propofol was maintained at 3 μg/ml by TCI until the end of the surgery, and 0.4 μg/kg sufentanil was injected by the intravenous pump when the eyelash reflex disappeared. Tracheal intubation was facilitated by administration of 0.15 mg/kg cisatracurium besylate.

Data collection

The patient variables recorded included demographic and clinical details. Hemodynamics and respiratory mechanics recorded included the mean arterial pressure (MAP), heart rate (HR), and pulse oxygen saturation (SpO2) before anesthesia (T0), 3 min after anesthesia induction (T1), 5 min after tracheal intubation (T2), before aortic occlusion (T3), at the end of the operation (5 min after cession of CPB, T4). The levels of cardiac troponin I (cTnI), creatine kinase isoenzyme MB (CK-MB), malondialdehyde (MDA), and tumor necrosis factor-α (TNF-α) at T0, T4, 8 h after the operation (T5), and 24 h

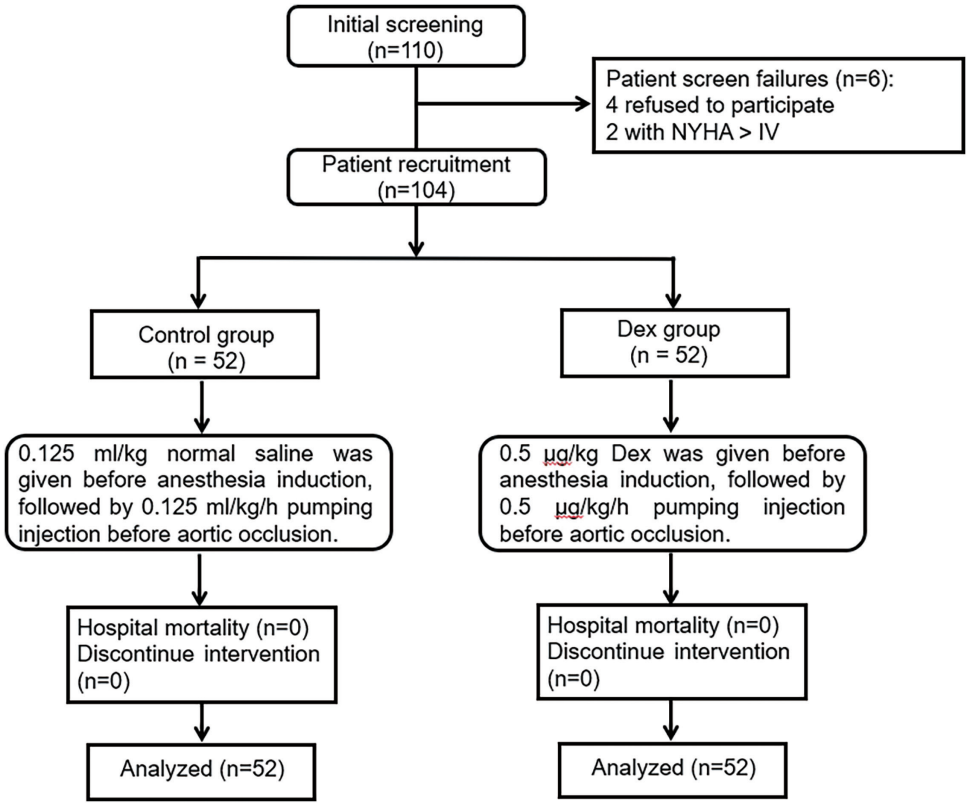

Fig. 1 Flow diagram of patient recruitment and analysis in this study. T0: before anesthesia; T1: 3 min after anesthesia induction; T2: 5 min after tracheal intubation; T3: before aortic occlusion; T4: at the end of the operation (5 min after cession of CPB); T5: 8 h after the operation; T6: 24 h after the operation. CPB, cardiopulmonary bypass

after the operation (T6) were measured by using two-site enzyme immunoassay, thiobarbituric acid, and enzyme-linked immunosorbent assay, respectively. Procedure-related data recorded included the time to first dose of rescue propofol, the total dosage of propofol, the time required for awaking from anesthesia, the time required for orientation recovery, the duration of mechanical ventilation, intensive care unit (ICU) stay time, and hospital stay time. Intra-procedural adverse events recorded were vomiting and headaches, hypoxia SpO2 <95%, hypotension (MAP <65 mmHg during anesthesia induction; 5–10 μg norepinephrine was administrated by intravenous injection), and bradycardia (HR <50 beats/min; 0.25 mg atropine was given intravenously).

Statistical analysis

The sample size was estimated based on a pilot study (15) in which the mean ± standard deviation (s.d.) of cTnI at 24 h after the operation in the Dex and non-Dex groups were 4.16 ± 1.58 and 6.90 ± 3.73, respectively. with a two-tailed α of 0.01 and β of 0.05, the power of >90% was achieved with 52 patients for each group (total n = 104 patients) by using G*Power 3.1.9.2 software. Continuous variables were presented as either mean ± s.d. and analyzed using t-test and one-way analysis of variance (ANOVA). Moreover, categorical variables were analyzed by the chi-square test. All statistical tests used a two-tailed P <0.05 as statistically significant in GraphPad prism, version 6.0 (GraphPad prism, San Diego, CA, USA).

Results

Patient baseline characteristics

A total of 110 patients scheduled for elective on-pump valve replacement surgery were initially screened for recruitment eligibility. Four patients (four from each group) were excluded due to their families' unwillingness to participate and two patients were excluded due to NYHA grade > IV. Finally, 104 eligible patients were randomly split into the Dex group and the control group (**Fig. 1**). During the study, no hospital mortality or discontinued intervention was observed. Their baseline characteristics are listed in **Table 1**, and two groups did not show significant differences

Table 1 Patient baseline characteristics between the control and Dex groups

Characteristics	Control	Dex	*P*
Age (year)	57.44 ± 9.57	55.06 ± 8.87	0.191
Gender distribution (male, n/%)	22 (42.31%)	24 (46.15%)	0.693
BMI (kg/m^2)	24.68 ± 3.04	25.23 ± 2.91	0.363
Current smoker (n/%)	6 (11.5%)	9 (17.3%)	0.402
Presence of diabetes (n/%)	13 (25.0%)	10 (19.2%)	0.478
Presence of hypertension (n/%)	16 (30.8%)	13 (25.0%)	0.512
Presence of dyslipidemia (n/%)	10 (19.2%)	8 (15.4%)	0.604
Previous stroke (n/%)	7 (13.5%)	6 (11.5%)	0.767
Cardiac function grade (n/%)			0.534
II	16 (30.8%)	19 (36.5%)	
III	36 (69.2%)	33 (63.5%)	
Valve lesion (n/%)			0.676
Stenosis	31 (59.6%)	28 (53.8%)	
Regurgitation	12 (23.1%)	16 (30.8%)	
Mixed	9 (17.3%)	8 (15.4%)	
Preoperative medication (n/%)			
ACEI	9 (17.3%)	10 (19.2%)	0.800
β-blocker	35 (67.3%)	32 (61.5)	0.539
Aspirin	38 (76.0%)	36 (69.2%)	0.665
Anticoagulant	4 (7.7%)	2 (3.8%)	0.674
Type of surgery (n/%)			0.636
MVR	29 (55.8%)	27 (51.9%)	
AVR	10 (19.2%)	14 (26.9%)	
DVR	13 (25.0%)	11 (21.2%)	

The value of *P* was yielded by unpaired t test and chi-square test. Dex: dexmedetomidine; BMI: body mass index; ACEI: angiotensin-converting enzyme inhibitor; MVR: mitral valve replacement; AVR: aortic valve replacement; DVR: double-valve replacement

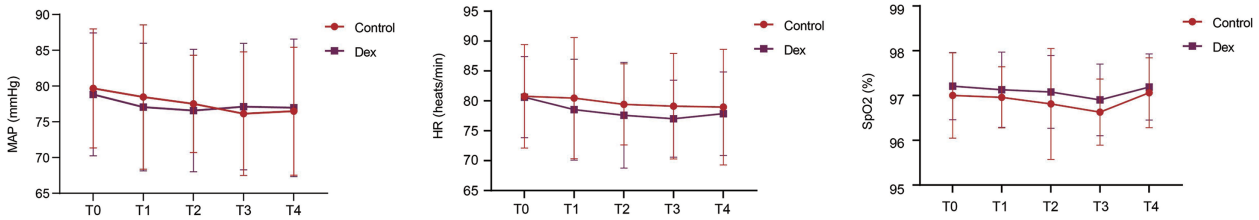

Fig. 2 The MAP, HR, and SpO2 of patients undergoing cardiac valve replacement on CPB at T0–T4 in the control and Dex groups. T0: before anesthesia; T1: 3 min after anesthesia induction; T2: 5 min after tracheal intubation; T3: before aortic occlusion; T4: at the end of the operation (5 min after cession of CPB); T5: 8 h after the operation; T6: 24 h after the operation. Statistical comparisons were performed by one-way ANOVA for different time points in a group and unpaired t-test for two groups at one time point. MAP: mean arterial pressure; HR: heart rate; CPB: cardiopulmonary bypass; ANOVA: analysis of variance

regarding age, gender distribution, body mass index (BMI), smoking status, comorbidities, previous stroke, cardiac function grade distribution, valve lesion, preoperative medication, and types of surgery (P >0.05).

The hemodynamic outcomes of patients after Dex pretreatment

The MAP, HR, and SpO2 of patients undergoing cardiac valve replacement on CPB under propofol TCI sedation with or without Dex pretreatment were monitored at T0–T4, and the results are shown in **Fig. 2**. The MAP, HR, and SpO2 values of patients did not show significant differences from T0 to T4 in the control and Dex groups, and two groups did not show significant differences at each time point (P >0.05).

The effect of Dex pretreatment on propofol use during cardiac valve replacement

The CPB time, aortic cross-clamp time, the time to first dose of rescue propofol, the total dosage of propofol,

Table 2 The surgical information of patients between the control and Dex groups

Variable	Control	Dex	*P*
Operating time (min)	285.62 ± 42.56	271.83 ± 47.33	0.121
CPB time (min)	116.39 ± 48.55	110.81 ± 50.24	0.566
Aortic cross-clamp time (min)	69.17 ± 45.20	73.06 ± 42.50	0.652
Time to first dose of rescue propofol (min)	12.19 ± 4.05	14.54 ± 3.79	0.003
Total dosage of propofol (mg)	1212.40 ± 225.24	1123.42 ± 196.57	0.034
Time required for awaking from anesthesia (min)	11.63 ± 3.38	12.04 ± 3.78	0.567
Time of orientation recovery (min)	23.87 ± 3.96	25.12 ± 5.33	0.178

The value of *P* was yielded by unpaired t-test. Dex: dexmedetomidine; CPB: cardiopulmonary bypass

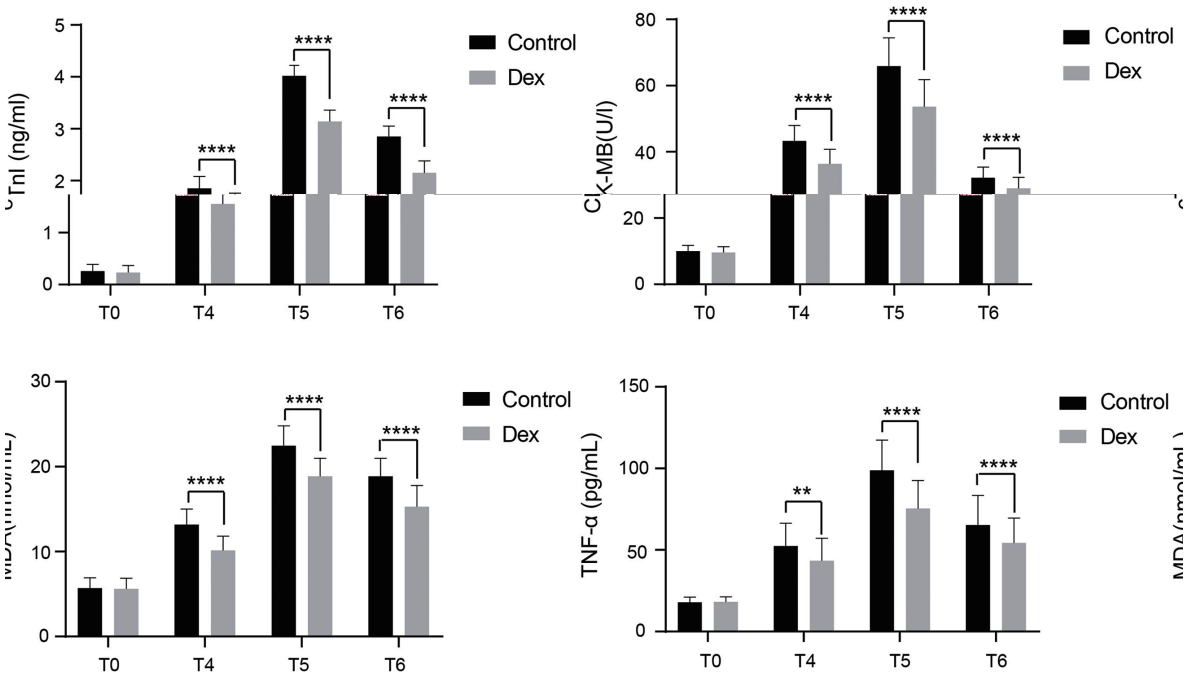

Fig. 3 The levels of cTnI, CK-MB, MDA, and TNF-α of patients undergoing cardiac valve replacement between the control and Dex groups were detected at T0, T4, T5, and T6. T0: before anesthesia; T1: 3 min after anesthesia induction; T2: 5 min after tracheal intubation; T3: before aortic occlusion; T4: at the end of the operation (5 min after cession of CPB); T5: 8 h after the operation; T6: 24 h after the operation. Statistical comparisons were performed by one-way ANOVA for different time points in a group and unpaired t-test for two group at one time point. ** *P* <0.01 and **** *P* <0.0001 by unpaired t-test for two groups at each time point. cTnI: cardiac troponin I; CK-MB: creatine kinase isoenzyme MB; MDA: malondialdehyde; TNF-α: tumor necrosis factor-α; CPB: cardiopulmonary bypass; ANOVA: analysis of variance

the time required for awaking from anesthesia, and the time of orientation recovery were compared between the control and Dex groups (**Table 2**). The patients in the Dex group had longer time to first dose of rescue propofol than the control group ($P = 0.003$). The Dex group required less total dosage of propofol than the control group ($P = 0.034$). As for the total operation time, CPB time, aortic cross-clamp time, the time required for awaking from anesthesia, and the time of orientation recovery, the Dex group did not differ when compared to the control groups ($P > 0.05$).

The myocardial protection by Dex pretreatment

The levels of cTnI, CK-MB, MDA, and TNF-α of patients undergoing cardiac valve replacement between the control and Dex groups were detected at T0, T4, T5, and T6. As shown in **Fig. 2**, the levels of cTnI, CK-MB, MDA, and TNF-α of two groups were all increased from T0 to T4, to T5, and to T6 ($P < 0.05$). These levels did not differ between two groups at T0 ($P > 0.05$). The patients in the Dex group had lower levels of cTnI, CK-MB, MDA, and TNF-α than those in the control group at T4, T5, and T6 ($P < 0.01$ or $P < 0.0001$, **Fig. 3**).

Table 3 The duration of mechanical ventilation, ICU stay time, and hospital stay time of patients between the control and Dex groups.

Variable	Control	Dex	*P*
Duration of mechanical ventilation (h)	11.14 ± 3.42	9.23 ± 3.05	0.003
ICU stay (d)	1.61 ± 0.70	1.44 ± 0.78	0.245
Hospital stay (d)	7.93 ± 2.40	7.56 ± 2.13	0.408

The value of *P* was yielded by unpaired t-test. Dex: dexmedetomidine; ICU: intensive care-unit

The time required for mechanical ventilation of patients after Dex pretreatment

The mean time required for mechanical ventilation in the Dex group was 9.23 h, which was less than the control group in which the mean time required for mechanical ventilation was 11.14 h ($P = 0.003$, **Table 3**). The Dex group required similar times for ICU stay and hospital stay compared to the control group ($P > 0.05$).

The incidence of adverse reactions of patients after Dex pretreatment

In the control group, three patients had vomiting and headaches and one patient with bradycardia. In the Dex group, there were two patients with bradycardia. The incidence rate of adverse reactions for patients undergoing cardiac valve replacement was similar between two groups ($P = 0.400$).

Discussion

This study demonstrated that Dex pretreatment at a dose of 0.50 μg/kg/h could reduce propofol use and the duration of mechanical ventilation, and confer cardioprotection against myocardial injury without increased adverse events during cardiac valve replacement.

The primary anesthetic considerations for cardiac valve replacement surgery on CPB is hemodynamic stability.[16] Nevertheless, Dex was shown to potentially associated with significant hypotension and bradycardia rather than propofol during transcatheter aortic valve implantation procedure.[17] A previous study provided contrary data that, except for the vasodilating effect, continuous Dex infusion did not significantly change hemodynamic conditions, and thus Dex could be used as a viable sedative drug after cardiac surgery.[18] In this study, we retrospectively reviewed hemodynamics and respiratory mechanics of patients undergoing cardiac valve replacement with or without Dex pretreatment. No significant difference from T0 to T4 was noticed for the values of MAP, HR, and SpO2 between patients undergoing cardiac valve replacement with or without Dex pretreatment, suggesting that pretreatment of 0.50 μg/kg Dex until aortic occlusion did not affect the hemodynamics stability of patients undergoing cardiac valve replacement. The propofol TCI protocols were still associated with in a higher prevalence of hypoxia and the respiratory function of patients was compromised.[19] As a highly selective α2-adrenergic agonist, Dex exerts a central activity on the locus coeruleus to achieve unique conscious sedation effect which allows patients to be awakened easily.[20] Dex possesses dose-dependent inhibition of sympathetic nervous system activity, cardiovascular stabilization, and significant reduction of postoperative delirium and agitation, without leading to occurrence of respiratory depression and agitation.[21] Dex sedation often causes bradycardia due to suppressive effects of sympathetic nerve activity, but the bradycardia may be a normal physiologic change and can be monitored rather than corrected when the dose of Dex was used appropriately.[22] In this study, although the HR was reduced after Dex pretreatment, this reduction did show significant difference compared to the control group, as well as the HR depression ratio from T0 to T1, T0 to T2, T0 to T3, T0 to T4 did show significant difference between two groups. Therefore, we believed that pretreatment of Dex at dose of 0.50 μg/kg was safe to use during cardiac valve replacement under CPB without adding significant HR changes.

Propofol can be rapidly distributed and metabolized in the body, with fast onset, short biologic half-life, and rapid awakening. However, propofol produces a significant respiratory depression during intraoperative period and its combination with opioids, such as sufentanil, may contribute to longer recovery time, respiratory depression, and higher doses of propofol.[23,24] Accordingly, the usage of high-dose propofol with opioids may contribute to an increased risk of postoperative respiratory depression, delayed awakening time from anesthesia, nausea, vomiting, and other adverse reactions.[25] In this study, the patients in the Dex group had longer time to first dose of rescue propofol than the control group. The Dex group required less total dosage of propofol than the control group.

During cardiac valve replacement, the patients, to a certain extent, encounter surgical stress response, myocardial injury, ischemia-reperfusion, a significant post-procedural inflammatory response, and imbalance between oxygen

supply and demand.[26] Postprocedural myocardial injury accompanied by certain degrees of cardiac biomarker elevations has been observed in up to two-thirds of patients after cardiac valve replacement, which is associated with worse outcomes.[27] The use of Dex during cardiac surgery on CPB could reduce postprocedural elevations of cardiac biomarkers, cTnI and CK-MB, and TNF-α.[28] Both clinical data and animal results demonstrated that Dex pretreatment attenuated oxidative stress as well as postischemic myocardial injury.[29] In this study, the patients undergoing cardiac valve replacement showed postprocedural elevations of cTnI, CK-MB, MDA, and TNF-α at T4–T6, whereas this elevation was attenuated by Dex pretreatment in the setting of 0.50 μg/kg as a loading dose until aortic occlusion. In agreement with other studies,[30] Dex pretreatment could significantly reduce the duration of mechanical ventilation for patients after cardiac valve replacement.

The study should be interpreted with caution due to several limitations. First, the era of valve plasty rather than valve replacement warrant further prospective studies in the setting of different dosages and different surgical curses of Dex administration during valve plasty. Second, lack of boarder follow-up data to identify patients with increased risk of prolonged mechanical ventilation and related complications, for example, postoperative delirium, and to implement prevention measures in these individuals. Third, the Dex group has fewer interventions on the mitral valve despite no statistically significant difference existing, the cardioprotection conferred by Dex against myocardial injury should be interpreted with caution due to MVR involves more incisions in the myocardium than AVR. Lastly, larger-scale studies in the setting of different doses and different time course of Dex treatment are need to ensure how much difference about total dose of propofol for clinical management.

In conclusion, the study provided evidence that Dex pretreatment at a dose of 0.50 μg/kg/h can be safely and effectively used during cardiac valve replacement. Dex, at this dose, could not only reduce propofol use and the duration of mechanical ventilation, but also confer cardioprotection against myocardial injury without increased adverse events during cardiac valve replacement.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhongshan City People's Hospital. Patients will be informed and requested to sign written informed consent before their participant. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Funding

Not applicable.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data used for the study are available in the present study.

Authors' contributions

YBL conceived the study and wrote the first draft of the manuscript, HXQ contributed to data collection and data analysis, WJL completed figure visualization, and PMZ did critical revisions for the manuscript. All authors reviewed the manuscript.

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