Protective effects of dexmedetomidine on the ischemic myocardium in patients undergoing rheumatic heart valve replacement surgery

WEI CHEN[1*], YAN WANG[1*], ZHIGUO PAN[2*], XIYUAN CHEN[1], DIHUAN LUO[3] and HAIYING WANG[1]

[1]Department of Anesthesiology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000;
[2]Department of Anesthesiology, Guizhou Provincial People's Hospital, Guiyang, Guizhou 550002;
[3]Department of Anesthesiology, Affiliated Stomatological Hospital of Zunyi Medical University,
Zunyi, Guizhou 563000, P.R. China

Abstract. The aim of the present study was to compare the effects of two methods of dexmedetomidine (Dex) administration on myocardial injury, inflammation and stress in ischemic myocardium during rheumatic heart valve replacement. In total, 90 patients were included in the present study and were divided into the following three groups: i) Dex group (1.0 μg/kg Dex pre-administered 10 min prior to anesthesia, then 0.5 μg/kg/h Dex for maintenance); ii) Dex pre-conditioning group (Pre-Dex; 1.0 μg/kg Dex administered 10 min prior to anesthesia, then saline for maintenance); and iii) control group (saline 10 min prior to anesthesia and saline during maintenance), with 30 patients in each group. Heart rate (HR) and mean artery pressure (MAP) were recorded at eight time-points: i) T1, pre-medication; ii) T2, 10 min post-medication; iii) T3, immediately post-intubation; iv) T4, upon skin incision; v) T5, upon sawing the sternum; vi) T6, immediately post-cardiopulmonary bypass; vii) T7, immediately post-operation; and viii) T8, 24 h post-operation. The serum cardiac troponin I (cTnI), interleukin (IL)-8, IL-10 and malondialdehyde (MDA) levels were also detected at T1, T6, T7 and T8. Blood glucose levels were detected at T1, T5, T6 and T7. In comparison with the control group, patients in the Dex group exhibited a significant increase in cardiac function, as indicated by an increase in HR, MAP and IL-10 levels, and a significant decrease in cTnI, IL-8, MDA and glucose levels.

Both Dex perfusion and Dex preconditioning were able to reduce myocardial injury, inflammation, oxidative stress and stress response in rheumatic heart valve replacement surgery. However, Dex perfusion during the whole surgery was more effective than Dex preconditioning treatment. The study was registered with the Chinese Clinical Trial Registry (ChiCTR; no. ChiCTR-INR-17011955).

Introduction

Rheumatic heart disease frequently causes mitral stenosis and/or aortic regurgitation, which poses a serious threat to life. Heart valve replacement surgery under cardiopulmonary bypass (CPB) is a common form of surgical treatment for patients with rheumatic heart disease. However, the pathophysiological process of myocardial ischemia-reperfusion injury (MIRI) is inevitable during general anesthesia for CPB (1). MIRI is a complication of CPB and may worsen the prognosis of patients undergoing this surgical treatment. Surgeons should therefore reduce the risk of MIRI during cardiac surgery with CPB. Optimizing perioperative medications may represent an important strategy to decrease the risk of MIRI.

Previous studies have reported that ischemia preconditioning (IPC) is able to mitigate MIRI and improve cardiac function. The role of IPC in myocardial protection was first identified by Murry *et al* (2) using animal models and it was defined as one or more transient ischemic and reperfusion stimulations prior to ischemia. IPC is now considered to be the most effective endogenous protective measure against MIRI (3). However, the clinical application of IPC is limited due to the fact that there are no strict guidelines for the timing and duration of ischemia and the invasive nature of this complex operation. In 1997, Cope *et al* (4) investigated the effectiveness of drug pretreatment, which involves simulating endogenous protective factors in order to induce myocardial protection mimicking IPC. Therefore, the use of drug pretreatment to reduce MIRI has become a popular research topic.

Dexmedetomidine (Dex) is a highly selective α_2-adrenoceptor agonist, the effects of which are characterized

by sedation, analgesic and anxiolytic effects, as well as inhibition of the release of serum catecholamines (5). Dex is widely used in clinical scenarios and recent studies have indicated that the use of Dex is advantageous in reducing anesthetic requirements and enhancing hemodynamic stability following cardiac surgery (6). Dex pre-conditioning and Dex perfusion during the whole surgery have been examined in a variety of animal models of ischemia-reperfusion and have been demonstrated to protect multiple organs and provide a protective effect against MIRI (7-9). Furthermore, clinical study have suggested that Dex perfusion during the whole cardiac surgery under CPB reduces the risk of postoperative MIRI (10). However, few studies have investigated whether Dex pre-conditioning can reduce MIRI. Therefore, it has remained elusive whether Dex pre-conditioning is able to attenuate MIRI in patients undergoing rheumatic heart valve replacement surgery under CPB.

In the present study, a prospective trial was designed to investigate whether Dex pre-conditioning and Dex perfusion exert myocardial protective effects. The effects of these methods were investigated by assessing myocardial injury markers, inflammatory factors, oxidative stress and stress response in order to determine the best method of Dex administration.

Materials and methods

Study population. The present clinical study was a randomized double-blinded placebo-controlled trial that was approved by the Ethics Committee of the Affiliated Hospital of Zunyi Medical College (Zunyi, China; approval no. 8). All patients included in the present study or their relatives provided written informed consent prior to the onset of the study. In total, 105 patients were treated at the Affiliated Hospital of Zunyi Medical College (Zunyi, China) between May 2016 and August 2017. All patients were aged 18-65 years, underwent cardiac valve replacement surgery under CPB and were classified based on the American Society of Anesthesiologists (ASA) classification II or III and New York Heart Association (NYHA) classification II or III (11,12), and with an estimated operation time of ≥2 or ≤6 h. The exclusion criteria included patients with myocardial infarction occurring in the previous month, history of heart surgery, rheumatic activity prior to surgery, heparin resistance, history of drug allergy, preoperative severe anemia, termination of anticoagulant therapy <3 days prior to surgery, abnormal coagulation function, severe liver and kidney damage, preoperative inflammatory disease, systemic disease with increased catecholamine secretion, relapse issues (defibrillation >4 times), difficulty in stopping CPB, refusal to participate, lack of signed informed consent, withdrawal during the trial or missing data.

Patient grouping. The eligible patients were numbered sequentially according to the daily surgical schedule of the Affiliated Hospital of Zunyi Medical College (Zunyi, China) and were then randomly divided into the three study groups. Subsequently, a nurse prepared the appropriate drug and syringe, and they did not know the corresponding code. The patients and anesthesiologist were blinded to the contents of the syringe. The sample size was estimated using a statistical formula for estimating sample size for a complete randomized

design with multiple sample means. The mean and standard deviation (SD) of each indicator [heart rate (HR), mean artery pressure (MAP), cardiac troponin I (cTnI), interleukin (IL)-8, IL-10, malondialdehyde (MDA) and blood glucose] in the three groups were used in the statistical formula to obtain an estimated required sample size of ≥27 cases per group. In total, 90 patients were included in the trial (30 per group). These patients were blinded to their group identity. In the operating room, patients were anesthetized by the same anesthesiologist who was blinded to the patient group.

In the Dex group, patients received Dex intravenously at 1.0 μg/kg 10 min prior to the induction of anesthesia and then 0.5 μg/kg/h Dex during the entire operation. In the Dex pre-conditioning group, patients received Dex intravenously at 1.0 μg/kg until 10 min prior to the induction of anesthesia and then 0.9% normal saline (at the same dose as the maintenance dose of Dex in the Dex group) during the operation. In the control group, patients were injected with 0.9% normal saline at the same doses and time-points as Dex in the Dex group (prior to the induction of anesthesia and during the operation).

Surgery. Patients who met the inclusion criteria were routinely monitored in terms of electrocardiography (ECG), pulse oxygen saturation and non-invasive blood pressure after entering the operating room. In addition, the patients were monitored using a bispectral index (BIS) monitor to assess the depth of anesthesia. MAP was monitored by cannulation of the left radial artery under local anesthesia. A double-lumen central venous catheter was inserted to monitor the central venous pressure. In addition, patients were monitored for nasopharyngeal and rectal temperature and by arterial blood gas analysis, which was also used to determine the level of blood glucose.

Anesthesia was induced with 0.01 mg/kg penehyclidine hydrochloride, 0.1 mg/kg midazolam, 1.0 μg/kg sufentanil, 0.15-0.3 mg/kg etomidate and 1 mg/kg rocuronium. Drug use was reduced as appropriate in patients with severe conditions (such as ASA III and NYHA III), and tracheal intubation was performed when BIS ranged between 40 and 50. After successful tracheal intubation, volume-controlled mechanical ventilation was performed and the tidal volume was adjusted to 8-10 ml/kg, the inspiratory-to-respiratory ratio was maintained at 1:1.5-2 and the respiratory rate was maintained at 12-20 breaths/min to ensure an end-tidal carbon dioxide partial pressure of 35-45 mmHg. Subsequently, 1-2 μg/kg/h sufentanil, 4-6 mg/kg/h propofol and intermittent intravenous injections of rocuronium and midazolam, along with compound inhalation of isoflurane (if necessary), were used to maintain the appropriate depth of anesthesia. The target range of BIS was 40-50 and the fluctuation of blood pressure was maintained at <20%.

Furthermore, the induction and maintenance of anesthesia in the three groups were using the same protocols in order to limit variability among patients. All operative procedures were performed by the same surgical team, using a CPB machine (Jostra; Sorin Group Co., Ltd.), an extracorporeal membrane oxygenator (CAPIOX RXO5, Terumo Co., Ltd.), a blood ultrafilter (SORIN DHF0.2; Sorin Group Co., Ltd.), the domestic Ningbo Filar corresponding type of arterial microthrombus filter (Ningbo Filar Medical Products Co., Ltd.)
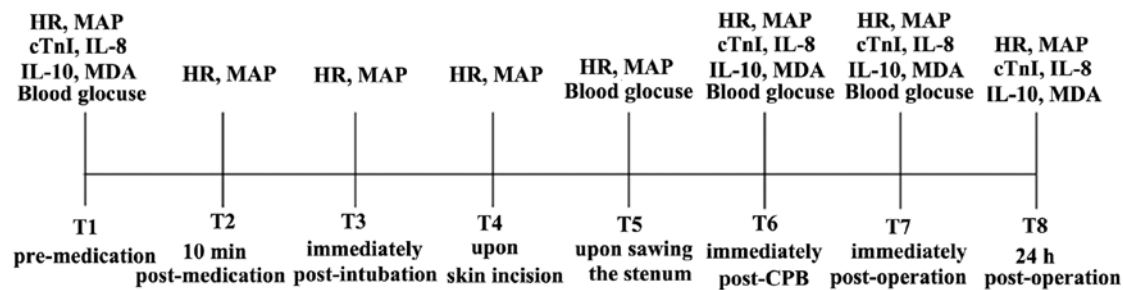
Figure 1. Timeline sketch indicating time-points and indicators detected. The time-points were as follows: i) T1, pre-medication; ii) T2, 10 min post-medication; iii) T3, immediately post-intubation; iv) T4, upon skin incision; v) T5, upon sawing the sternum; vi) T6, immediately post-CPB; vii) T7, immediately post-operation; and viii) T8, 24 h post-operation. HR, heart rate; MAP, mean artery pressure; cTnI, cardiac troponin I; IL, interleukin; MDA, malondialdehyde; CPB, cardiopulmonary bypass.

and the corresponding type of non-heparin coated circulation pipeline (Ningbo Filar Medical Products Co., Ltd.). Surgery was performed under standard hypothermic CPB (28-30˚C), with cannulation of the superior vena cava, inferior vena cava and ascending aorta. During CPB, the following parameters were maintained: Activated clotting time of >480 sec, hematocrit of 25-28%, MAP of 50-80 mmHg, hemoglobin of >80 g/l, pH of 7.35-7.45 and partial pressure of CO_2 of 35-45 mmHg. Adrenaline, dopamine and nitroglycerin were intravenously pumped to maintain hemodynamic stability after stopping the CPB.

Measurement of hemodynamic and blood parameters. HR and MAP were assessed in the three groups of patients based on ECG and invasive artery blood pressure at eight time-points: i) T1, pre-medication; ii) T2, 10 min post-medication; iii) T3, immediately post-intubation; iv) T4, upon skin incision; v) T5, upon sawing the sternum; vi) T6, immediately post-CPB; vii) T7, immediately post-operation; and viii) T8, 24 h post-operation. Blood samples (5 ml) were obtained from the radial artery at four time-points (T1, T6, T7 and T8), centrifuged and then stored in a refrigerator at 4˚C. After centrifugation and storage at -80˚C, the supernatant was collected to determine the serum levels of cTnI, IL-8, IL-10 and MDA. The concentrations of serum cTnI, IL-8 and IL-10 were assayed by ELISA using the cTnI, IL-8 and IL-10 detection kits (Beijing Biosic Biomedical Technology Co., Ltd.) according to the manufacturer's protocols. The serum level of MDA was measured using the thiobarbituric acid assay with the MDA determination kit (Beijing Solarbio Technology Co., Ltd.), according to the manufacturer's protocol. The concentration of blood glucose was detected by arterial blood gas analysis at four time-points: T1, T5, T6 and T7 (Fig. 1). All measurements were performed in duplicate.

Statistical analysis. Data analysis and statistical analyses were performed using SPSS software version 18.0 (SPSS, Inc.). Data with a normal distribution are presented as the mean ± SD. Mixed ANOVA was used to assess the main effect of treatment, main effect of time point and the interaction between these two main effects. Afterwards, Bonferroni's correction is used for post hoc inspection. The significance of differences among the three groups was determined by one-way analysis of variance (ANOVA), when obtaining a significant

result, Bonferroni's correction is used for post hoc inspection between the two groups. All tests were two-tailed. Differences in categorical variables were assessed using the χ^2 or Fisher's exact test. All tests were two-tailed. P<0.05 was considered to indicate statistical significance.

Results

General information of the patients and surgical conditions. A total of 105 patients were randomly allocated to the Control group (n=37), Pre-Dex group (n=32) and Dex group (n=36). After randomization, four patients (three in the Control group and one in the Dex group) did not meet the inclusion criteria, since three patients in the Control group had an operation time of >6 h and one patient in the Dex group had an operation time of <2 h. Therefore, these three patients were excluded. In addition, six patients were not followed up due to their families refused to participate after the operation and were therefore excluded due to incomplete data. Furthermore, three patients could not be followed up due to death of heart failure after operation, so they were excluded from this study. Mortality of each group [pre-Dex group, 1/32 (3.1%), Control group, 1/37 (2.7%) and Dex group 1/36 (2.8%)]. Of note, the cause of death was mostly due to heart failure and were not related to Dex treatment. In addition, two patients were discharged from hospital due to serious illness and poor prognosis and were therefore excluded. Finally, 90 cases were included in the present analysis and 30 patients were allocated in each of the three groups. All patients were surgically treated and none of the patients withdrew from the study (Fig. 2). As presented in Table I, the mean age of the patients in the Pre-Dex, Dex and Control groups was 50.01±9.97, 47.24±7.93 and 51.39±6.78 years, respectively. Male patients accounted for 87.5% of the Dex group and 76.5% of both the Pre-Dex and Control groups (P>0.05). The baseline demographic characteristics were similar among the three groups (P>0.05). There were no significant differences in ascending aortic cross-clamping duration, CPB duration, incidence of ventricular fibrillation after reperfusion, cardiac self-rejuvenation rate or operation duration across the three groups (P>0.05; Table I).

Dex perfusion and Dex pre-conditioning improve heart function after CPB. The HR was significantly reduced in the Pre-Dex and Dex groups at T2, T3, T4 and T5 compared

Table I. Baseline demographic characteristics, aortic cross-clamping duration, CPB duration, VF after reperfusion, self-rejuvenation rate and operation duration in the different groups.

Variables	Control group	Dex group	Pre-Dex group	P-value
Age (years)	51.39±6.78	47.24±7.93	50.01±9.97	0.151
Sex (M/F)	13 (43)/17 (57)	14 (47)/16 (53)	13 (43)/17 (57)	1.000
Bodyweight (kg)	55.51±8.43	53.79±8.92	57.81±10.06	0.239
NYHA (II/III)	11 (37)/19 (63)	14 (47)/16 (53)	12 (40)/18 (60)	1.000
LVEF (%)	57.87±7.14	58.60±5.54	61.33±6.58	0.097
Aortic cross-clamp duration (min)	71.58±17.25	68.52±20.65	71.77±19.07	0.760
CPB duration (min)	106.90±20.58	99.70±20.70	105.80±19.27	0.335
VF after reperfusion	5 (17)	5 (17)	6 (20)	1.000
Self-rejuvenation rate	25 (83)	25 (83)	24 (80)	1.000
Operation duration (min)	249.60±42.39	254.07±50.78	254.87±44.00	0.892

Values are expressed as n (%) or the mean ± standard deviation. Pre-Dex group, Dex pre-conditioning group; Dex, dexmedetomidine; CPB, cardiopulmonary bypass; NYHA, New York Heart Association classification; LVEF, left ventricular ejection fraction; VF, ventricular fibrillation; M, male; F, female.
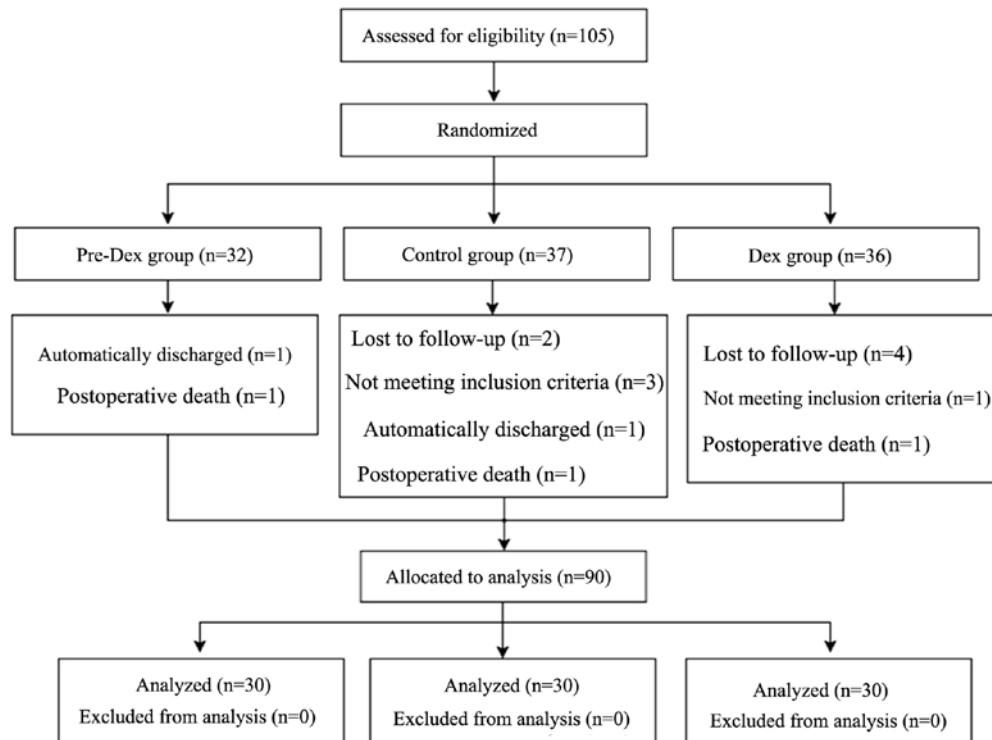

Figure 2. Flow diagram of the movement of patients in the present study. None of the randomized patients withdrew from the study (six were lost to follow-up). Pre-Dex group, Dex pre-conditioning group; Dex, dexmedetomidine.

with that of the Control group (P<0.00625), demonstrating the positive effects of DEX on myocardial oxygen consumption. However, the HR was not statistically significant among the three groups after CPB (T6, T7 and T8), suggesting that Dex had no influence on cardiac rejuvenation and HR after CPB (Fig. 3A). The HR was increased in the Pre-Dex and Dex groups after CPB (T6, T7 and T8) compared with that prior to CPB (T2-T5; P<0.00625). Furthermore, the HR was increased in control group after CPB (T6, T7) compared with that prior to CPB (T2; P<0.00625).

The MAP was reduced in three groups at T4, T5, T6 and T7 compared with T1 (P<0.00625), and there was no difference among the three groups. The MAP was reduced in the Control group at T8 compared with T1 (P<0.00625), while there were no differences in the Pre-Dex and Dex groups (P>0.05). Compared with the Control group, the MAP in Pre-Dex and Dex groups was increased at T8 (P<0.00625), suggesting that DEX treatment improved the MAP, thus enhancing cardiac perfusion after surgery, and had no influence on MAP during surgery (Fig. 3B).
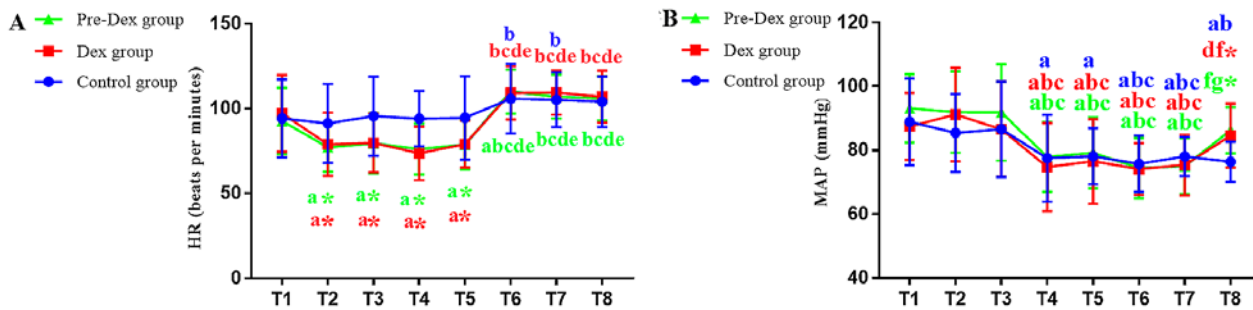
Figure 3. (A and B) Changes in HR and MAP in the three groups are shown respectively. HR and MAP in the three groups were recorded at eight time-points: i) T1, pre-medication; ii) T2, 10 min post-medication; iii) T3, immediately post-intubation; iv) T4, upon skin incision; v) T5, upon sawing the sternum; vi) T6, immediately post-cardiopulmonary bypass; vii) T7, immediately post-operation; and viii) T8, 24 h post-operation. Values are expressed as the mean ± standard deviation. [a]P<0.05 vs. T1, [b]P<0.05 vs. T2, [c]P<0.05 vs. T3, [d]P<0.05 vs. T4, [e]P<0.05 vs. T5, [f]P<0.05 vs. T6, [g]P<0.05 vs. T7. *P<0.05 vs. Control group at the same time point. Bonferroni's correction. HR, heart rate; MAP, mean artery pressure; Pre-Dex group, Dex pre-conditioning group; Dex, dexmedetomidine.
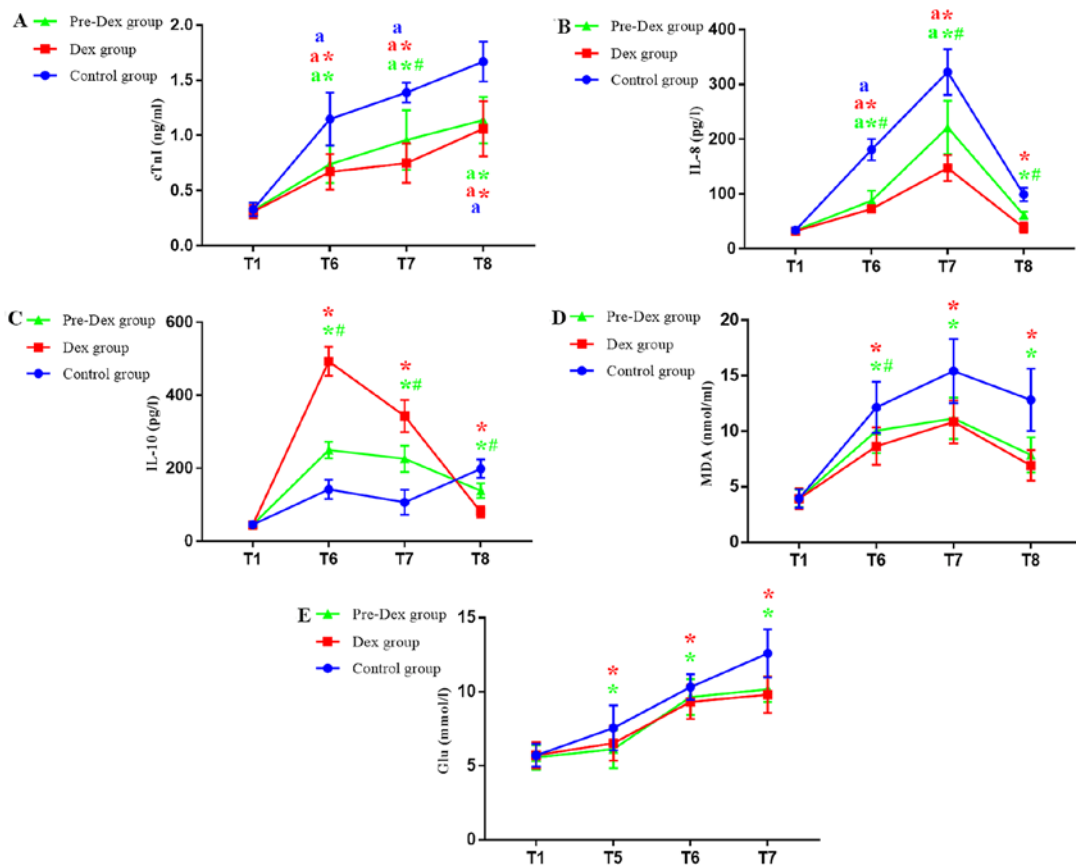

Figure 4. (A-E) Changes in the levels of cTnI, IL-8, IL-10, MDA and blood glucose in the three study groups are shown respectively. Levels of cTnI, IL-8, IL-10 and MDA in the three groups were measured at eight time-points: i) T1, pre-medication i.e. the time point before dexmedetomidine was used; ii) T2, 10 min post-medication; iii) T3, immediately post-intubation; iv) T4, upon skin incision; v) T5, upon sawing the sternum; vi) T6, immediately post-cardiopulmonary bypass; and vii) T7, immediately post-operation. Each reaction was performed three times for each patient at each time point. Values are expressed as the mean ± standard deviation. [#]P<0.05 vs. Dex group at the same time-point; [a]P<0.05 T5-T8 vs. T1. *P<0.05 vs. the control group at the same time-point. Bonferroni's correction. cTnI, cardiac troponin I; IL, interleukin; MDA, malondialdehyde; Glu, blood glucose; Pre-Dex group, Dex pre-conditioning group; Dex, dexmedetomidine.

Dex perfusion and Dex pre-conditioning decrease the levels of myocardial injury-associated markers. In comparison with T1, the cTnI levels were significantly increased at T6, T7 and T8 in three groups, indicating that CPB induced cardiac damage (P<0.0125). In comparison with the Control group, cTnI levels were decreased at T6, T7 and T8 in the Pre-Dex and Dex groups (P<0.0125). Compared with the Pre-Dex group, the cTnI levels were decreased

in the Dex group at T7 (P<0.0125). It was indicated that Pre-Dex and Dex treatments are able to prevent myocardial injury. In addition, the present results suggested that Dex treatment was more effective than Pre-Dex treatment (Fig. 4A).

Dex perfusion and Dex pre-conditioning regulates the levels of inflammatory factors. IL-8 gradually increased during the

surgical procedure, reached a maximum at T7 and decreased at T8. During the whole procedure, in the three groups, IL-8 levels increased significantly at T6 and T7 time points compared to T1. In the control group, the level of IL-8 was significantly higher compared with that in the Pre-Dex and Dex groups at the same time point. and the IL-8 levels in the Dex group were decreased compared with those in the Pre-Dex group (P<0.0125). IL-8 returned to baseline levels at 24 h post-operation, suggesting that CPB rheumatic heart valve replacement surgery stimulated the inflammatory response. However, Pre-Dex and Dex treatment downregulated the inflammatory response and Dex treatment significantly decreased the expression levels of the inflammatory marker IL-8.

IL-10 was increased at T6 in the three groups. A significant increase was identified in groups subjected to Dex treatment compared with the Control group (P<0.0125), suggesting that, after CPB, Pre-Dex and Dex treatment increased the release of anti-inflammatory factors and Dex treatment was more effective than Pre-Dex treatment. Compared with T6, the IL-10 levels were decreased in the three groups at the subsequent time-points, but the Pre-Dex and Dex groups presented with lower levels of IL-10 compared with those in the Control group (P<0.0125). At T8, the levels of IL-10 reached a maximum in the Control group and its levels were decreased in the Pre-Dex and Dex groups (P<0.0125; Fig. 4B and C).

Dex perfusion and Dex pre-conditioning suppress oxidative stress and the stress response. MDA, an indicator of oxidative stress, in the three groups, it increased from T1 to T7 and reached a maximum at the T7 time point before slightly decreasing at T8. In comparison with the Control group, the groups subjected to Dex treatment exhibited reduced MDA levels at T6, T7 and T8. Treatment by Dex perfusion during the whole surgery led to a more significant reduction compared with that in the Pre-Dex group at T6 (P<0.0125; Fig. 4D).

The glucose levels, an indicator of the stress response, increased during the whole procedure and reached a maximum at 24 h after surgery in all three groups. Compared with those in the Control group, the glucose levels in Pre-Dex and Dex groups were decreased (P<0.0125). The glucose levels were similar between the Pre-Dex and Dex groups (Fig. 4E).

Discussion

MIRI is a common pathophysiological process that occurs after cardiac surgery under CPB and involves multiple mechanisms, including cardiomyocyte apoptosis, inflammatory reactions, oxidative stress and stress responses (13-15). The pipeline for extracorporeal circulation is responsible for the process of cooling and rewarming, which causes cytokine release and promotes the occurrence and development of inflammatory and stress responses (16). Furthermore, when the blocked ascending aorta is re-opened, recanalization may promote additional production of inflammatory chemokines due to oxidative stress. The release of cytokines eventually causes damage to tissues and organs (17,18). For patients with rheumatic heart disease, cardiac reserve function is reduced and hemodynamic fluctuations tend to occur during the perioperative period (19). Therefore, reducing the stress response

and inflammation, and stabilizing the hemodynamics, may reduce the detrimental effects induced by MIRI.

It has been previously reported that Dex is able to inhibit the sympathetic activity of the nervous system and relieve oxidative stress reactions, inhibiting inflammation and stress response (20-22). This effect reduces the severe hemodynamic fluctuations during surgery and hemodynamic stability has a positive effect on the postoperative outcomes (23,24). Dex has an HR-slowing effect prior to CPB and at the concentration used in the present study, the HR in patients in the Pre-Dex and Dex groups was lower than that in the Control group at T2, T3, T4 and T5, but only had a negligible impact on MAP. After the ascending aorta opens (recovers blood flow to the heart), it has no effect on the heart's rebound rate and the HR. Therefore, reducing myocardial oxygen consumption prior to CPB may be beneficial for MIRI. Kehlet (25) pointed out that the application of Dex during the perioperative period may have important implications for Enhanced Recovery After Surgery (ERAS). Of note, using minimally invasive techniques and fast-track cardiac anesthesia for congenital heart disease surgery was reported to promote early extubation and accelerate patient recovery, which promoted ERAS (26,27).

Previous studies have indicated that Dex is able to reduce the levels of cTnI after myocardial ischemia-reperfusion, inhibit the release of the pro-inflammatory cytokine IL-8, promote the production of the anti-inflammatory cytokine IL-10 and exert antioxidant effects by reducing the level of MDA, thereby exerting cardioprotective effects (5,22,28,29). The most widely used clinical markers of myocardial injury are cTnI and creatine kinase-MB. Transesophageal echocardiography cardiac function monitoring and pro-brain natriuretic peptide may also be used as indicators of myocardial function in response surgery (30). However, cTnI is a highly sensitive and specific biomarker in the diagnosis of myocardial injury in the clinic (31). In addition, Dex inhibits the release of catecholamines to reduce HR (32), which prolongs coronary perfusion and simultaneously reduces myocardial oxygen consumption, thus improving the maintenance of the myocardial oxygen supply-demand balance (33,34). Dex is also able to increase the ischemic to non-ischemic myocardial blood flow ratio during myocardial ischemia in the perioperative period (35,36). The effect of Dex may be associated with the activation of α_2-adrenoceptors and its bidirectional regulation of the coronary artery diameter (37), thus preventing further aggravation of MIRI. The results of the present trial indicated that the levels of cTnI in the Pre-Dex and Dex groups were lower than those in the Control group at T6, T7 and T8, which means the application of DEX may reduce myocardial injury after CPB in patients with heart valve replacement surgery. This effect may be due to alterations in the timing of the release of myocardial injury markers into the blood, the peak time and the elimination half-life.

A systemic inflammatory response is able to aggravate myocardial damage (38). Previous studies have indicated that infiltration of inflammatory cells into the myocardium during MIRI leads to overproduction of reactive oxygen species, which are key in MIRI (39). IL-8 is a pro-inflammatory cytokine; mainly pro-inflammatory cells release a series of active products, leading to the occurrence of inflammatory reactions. IL-10 is mainly an anti-inflammatory cytokine

whose major role is to inhibit inflammatory responses. The present study indicated that the levels of IL-8 in the Pre-Dex and Dex groups were lower than those in the Control group at T6, T7 and T8, while the levels of IL-10 in the Pre-Dex and Dex groups were higher than those in the Control group at T6 and T7. Collectively, Dex administration alleviated MIRI by inhibiting the inflammatory response. In the Pre-Dex and Dex groups, IL-10 was lower compared with that in the control group at T8. This may be due to the application of DEX promoting the release of anti-inflammatory factor IL-10, inhibiting the pro-inflammatory reactions and reducing MIRI, thereby maintaining the inflammation at low levels. At T8, the level of IL-10 in the Dex group was suddenly significantly lower than that of the Pre-Dex group. This may be because the half-life of IL-10 in the body was only a few hours. The Dex group promoted IL-10 secretion during surgery. At T8 time, most were likely metabolized. In the Pre-Dex group, preconditioning induces myocardial the protection mechanism. At the T8 time point, new IL-10 is produced. Therefore, at the T8 time point, the IL-10 level of the Dex group is suddenly significantly lower than that of the Pre-Dex group. The control group demonstrated a strong inflammatory response, inducing anti-inflammatory defense mechanisms and maintaining high levels of IL-10. However, compared with those in the Dex group, the levels of IL-10 in the Pre-Dex group decreased at T6 and T7. The present results revealed that Dex perfusion is able to minimize the inflammatory response, which may protect cardiomyocytes from MIRI damage by inhibiting inflammatory factors.

MDA is an important product of lipid peroxidation in cell membranes and is associated with the level of oxygen free radicals. Due to defects in antioxidant defense mechanisms, an increased level of oxygen free radicals may promote the release of chemokines and cytokines via an inflammatory response, thus resulting in myocardial cell injury (40). The results of the present study suggested that the levels of MDA in the Pre-Dex and Dex groups were lower than those in the Control group at T6, T7 and T8. The present results suggested that the two Dex administration methods are able to attenuate the oxidative stress reaction and may serve a role in myocardial protection. However, the present results suggested that Dex administration during the whole surgery is more effective than Dex pre-conditioning. This effect may be caused by Dex-mediated improvements in antioxidant defense mechanisms, thereby reducing the production of MDA.

Previous studies have shown that reduced insulin sensitivity leads to elevated blood glucose in patients undergoing intracardiac surgery under CPB (41). The results of the present study suggested that the concentration of blood glucose in the Pre-Dex and Dex groups was lower than that in the Control group at T5, T6 and T7. This may be due to the fact that Dex application during the perioperative period may increase insulin sensitivity, thereby reducing the blood glucose levels.

In summary, the two Dex administration methods in CPB rheumatic heart valve replacement surgery were demonstrated to reduce myocardial injury, inhibit the release of pro-inflammatory factors, promote the release of anti-inflammatory factors, enhance the activity of anti-oxidant enzymes and reduce oxidative stress and stress responses. Dex perfusion during the whole surgery was more effective compared with Dex pre-conditioning. The study of perioperative myocardial protection is an important aspect of the application of ERAS in cardiac surgery. Therefore, the present study may be of great significance to the development of ERAS in cardiac surgery.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. This trial was registered at http://www.ChiCTR.org.cn under the clinical trial number ChiCTR-INR-17011955 (date of registration, July 12, 2017).

Authors' contributions

WC participated in the design and implementation of the trial. YW implemented anesthesia, including the preparation of various drugs for induction and maintenance of anesthesia, parallel arterial puncture and central venous catheterization and tracheal intubation after induction of anesthesia. ZP, DL and XC made substantial contributions to the acquisition of data and analysis and interpretation of the data. WC, YW, ZP and HW authenticate the raw data in this study. HW made substantial contributions to conception and design, provided guidance for the study and revised it critically for important intellectual content and gave final approval of the version to be published. All of the authors read the final manuscript and agreed to its submission.

Ethics approval and consent to participate

All of the research that was performed on the subjects followed national regulations in accordance with the relevant set of ethical principles. The Ethics Committee of the Affiliated Hospital of Zunyi Medical College (Zunyi, China; approval no. 8) approved the present study. All subjects provided written informed consent to participate in this clinical study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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