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The Effect of Infusion of Dexmedetomidine to the Aortic Root before Aortic Cross-Clamp Removal on the Myocardial Protection in Patients Undergoing Mitral Valve Surgery; A Triple-Blinded Randomized Clinical Trial

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Abstract

Background: Myocardial protection during cardiopulmonary bypass is a challenging dilemma. Some protective strategies have been introduced to ameliorate ischemic-reperfusion injury, although no optimal strategy has emerged.

Objectives: Herein, we evaluated the effect of aortic root infusion of Dexmedetomidine before cross-clamp removal on myocardial preservation.

Methods: This randomized, multicenter, triple-blinded controlled trial enrolled 56 patients who underwent mitral valve surgery. After randomization, the patients were allocated to the case group (Dexmedetomidine infusion in the aortic root before cross-clamp removal) and the control group (isotonic saline). Based on the study goals, Troponin-I and Creatinine kinase-MB were measured as primary outcomes at different time points during the study. Other clinical parameters were also measured as secondary outcomes. Statistical analysis was performed using SPSS software version 26.0 (Chicago, IL, USA). The significance level was considered as $P<0.05$.

Results: A total of 54 patients in the case and control groups were included in the analysis. The main finding of this study was that troponin-I levels at all time points showed statistical differences between the two groups (P=0.001). Also, evaluation of CK-MB levels showed a significant decrease at 1 hour (P=0.001), 12 hours (P=0.001), and 24 hours (P=0.001) after ICU admission, in the case group compared with the control group.

Conclusion: This study found that administering a Dexmedetomidine infusion before aortic cross-clamp removal can ameliorate ischemia-reperfusion injury-induced myocardial damage.

Keywords: Cardiac Surgery, Dexmedetomidine, Ischemia-Reperfusion Injury, Cardiopulmonary Bypass.

1. Background

Cardioprotection strategies aim to prevent and attenuate myocardial injury from ischemia and reperfusion (1). Despite the advanced approaches to cardio-myocyte protection from ischemic reperfusion injury (I/R Injury), morbidity and mortality from this unpleasant event are still remarkable (2,3).

I/R Injury may be seen in cardiac surgeries using cardiopulmonary bypass (CPB) and after cross-clamp removal (4). Various agents have been studied as pharmacological postconditioning approaches to ameliorate myocardial damage when exploited before, during, or even immediately after myocardial I/R Injury (5).

Dexmedetomidine is a specific short-acting alpha-2 agonist that reduces sympathetic output by decreasing serum levels of inflammatory biomarkers (6). It also acts as a sympatholytic during cardiovascular surgery, decreasing myocardial blood supply and tissue demand (7-8).

There is insufficient evidence to support the claim that many clinical studies reporting the attenuation of I/R injury following pharmacological interventions have not translated into better patient outcomes, especially after cardiac surgeries with CPB (9-13).

This study aimed to determine the effect of aortic root infusion of Dexmedetomidine on myocardial protection in patients undergoing mitral valve surgery.

2. Methods

This randomized multi center triple-blinded controlled trial was conducted on adults who underwent isolated mitral valve surgeries, including mitral valve replacement, due to the Severe mitral regurgitation, from November 2021 to January 2023, at the departments of Cardiac Surgery, Imam-Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, Razavi Hospital, Mashhad, Iran, and Rajaie Cardiovascular, Medical & Research Center, Tehran, Iran.

2.1. Study population:

The study population included patients scheduled for mitral valve replacement ranging from 18 to 75 years old, with an ejection fraction above 30%, without history of supraventricular dysrhythmias, history of cardiac surgery, contrast induced nephropathy (CIN), respiratory failure, stroke and TIA, coagulopathy, requiring vasopressors before the surgery, and intra-aortic balloon pump (IABP) before, during, and after surgery.

2.2. Sample size:

Considering 95% confidence interval, 80% power, also by using means space strategy and hypothesis of the same study (5) with the mean deviations S1 = 1.67 and S2 = 1.22 and means X1 = 2.32 and X2 = 5.78, as well as a drop-out rate of 15%, the sample size was calculated as 56 patients (28 in each group). Block randomization was performed after obtaining informed consent from the patients. Patients were randomized 1:1 to intervention and control groups using computer-generated block randomization. Sealed opaque envelopes ensured allocation concealment. The study maintained triple blinding: patients' families, perfusionists, surgeons, anesthesiologists, ICU teams, and data analysts were all blinded to the group allocation.

The trial managers placed the intervention assignments in sequentially numbered envelopes and arranged the facilities and data collection.

2.3. Study protocol:

Cardiopulmonary bypass (CPB) was initiated after the cardiac surgeon, anesthesiologist, and perfusionists confirmed favorable conditions. All patients underwent median sternotomy. Cannulation was performed after administration of three mg/kg heparin and when the activated coagulation time (ACT) was greater than 480 seconds.

Antegrade infusion of Del-Nido cardioplegia at the aortic root after the aortic cross-clamp was used for myocardial protection. The Fusion® oxygenator was used for all patients. Non-pulsatile

perfusion was used to maintain tissue perfusion at 2-2.8 L/m2/min. The alpha-stat strategy was administered during CPB to evaluate arterial blood gases to maintain PaCO2 and PaO2 at 35-45mmHg and 150-250 mmHg, respectively.

The induction of anesthesia was initiated with Ketamine 1-2 mg/kg, Fentanyl 10-15 mcg/kg, Midazolam 0.1 mg/kg, and Atracurium 0.5 mg/kg. Propofol 50-70 mcg/kg/min and Sufentanyl 0.2-0.5 mcg/kg were used to maintain anesthesia. Mild hypothermia (32-34℃ via nasopharyngeal prob) was considered in all the patients.

At the end of the surgical procedure, before removing the aortic clamp, either a solution of Dexmedetomidine (case) with a concentration of 4 µg / ml, at a rate of 1 µg/ kg/ h, or normal saline (20-30 mL)(control) for 10 minutes, was infused at the root of the aorta.

2.4. Outcomes:

As the primary outcomes, the laboratory levels of Troponin-I and Creatinine kinase-MB were measured before entering the operating room and at 1, 6, 12, and 24 hours after cardiac surgery at the Intensive Care Unit (ICU) entrance.

As a secondary outcome, the vasopressor-inotropic score (VIS), calculated as: *Dopamine + Dobutamine (µg/kg/min) ×1+ Milrinone ×15+ (Epinephrine+ Norepinephrine+ Isoproterenol) ×100*, was evaluated at 6 and 24 hours after ICU admission. Also, CRP and ESR levels were measured before surgery and at 6, 12, and 24 hours after ICU admission.

Also, the duration of CPB and cross-clamp, and hemodynamic parameters such as mean arterial pressure and heart rate, were recorded before anesthesia induction (T1), before CPB initiation (T2), and after CPB weaning (T3). Besides, the patients' Ejection Fraction (EF) was evaluated before surgery, 1 day after ICU admission, and on days 7, 28, and 180 after surgery by an echocardiologist who was unaware of the study protocol and patients' groups. The time to weaning from mechanical ventilation and the ICU stay were recorded.

2.5. Statistical analysis:

The patients, evaluators, and statisticians were unaware of the solutions. Statistical analysis was performed using SPSS software version 26.0 (Chicago, IL, USA). The quantitative results were presented as mean±SD and median (interquartile range (IQR)) for normal and non-normally distributed data, respectively. Categorical data were expressed as frequency (percentage). Normality of the quantitative data was assessed using the Shapiro-Wilks test, Q-Q plots, and Box plots. The Independent Student's T-test was used for normally distributed variables, and the Mann–Whitney test was used for non-normally distributed quantitative variables. The homogeneity of categorical variables across groups was analyzed using the chi-square test for independence or Fisher's exact test. After checking relevant assumptions, paired quantitative variables were compared using a paired-samples t-test or a Wilcoxon test. To investigate measurement time and its interaction with categorical group variables, a repeated-measures analysis of variance (RM-ANOVA) was used. Sphericity was also checked, and, based on Mauchly's test results, the Greenhouse-Geisser statistic was used. The significance level was considered as $P<0.05$.

3.Result

A total of 54 patients completed the study (N= 26 (46.42%)) in the case group and (N= 28 (50%)) in the control group, with a mean± age of 53.7±14.5 years, who underwent mitral valve replacement/ repair (Figure 1).

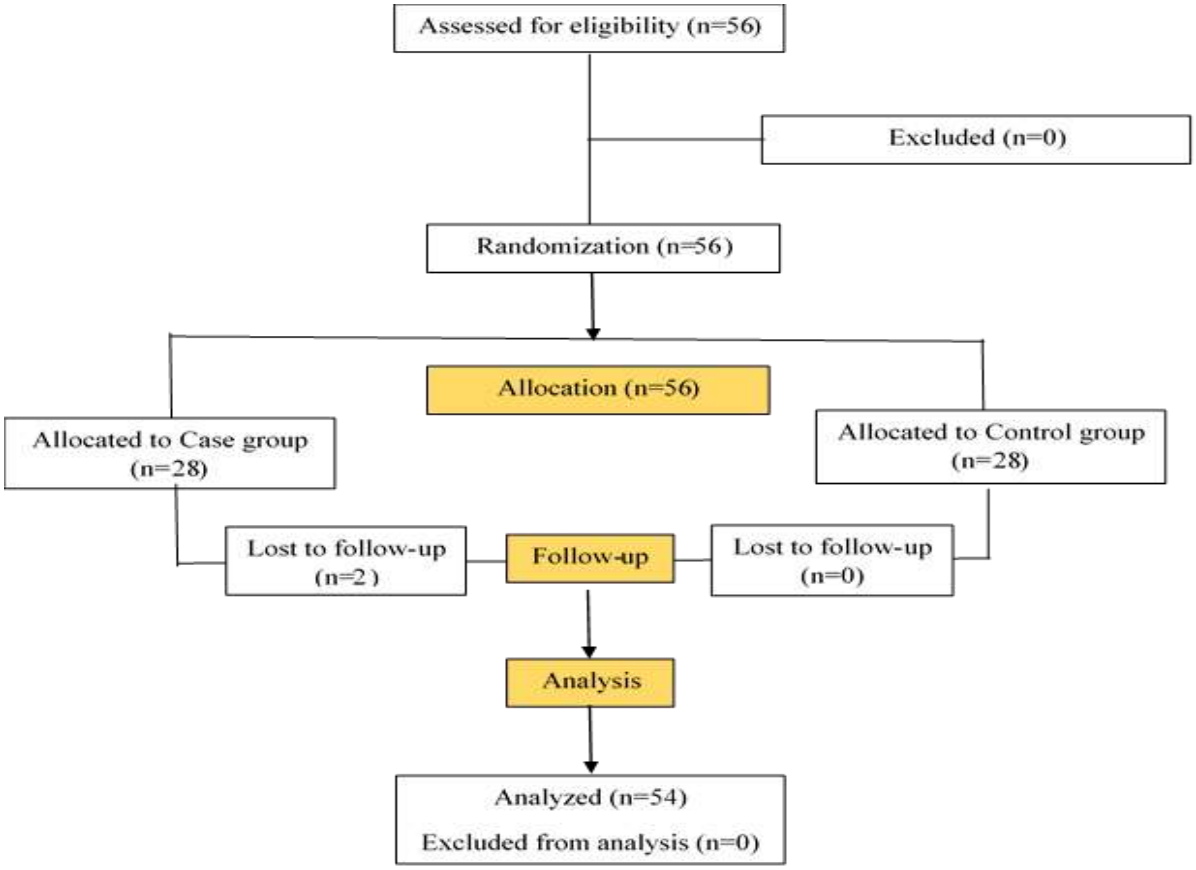


Figure 1: CONSORT diagram presenting the flow of participants in each stage of the randomized trial.

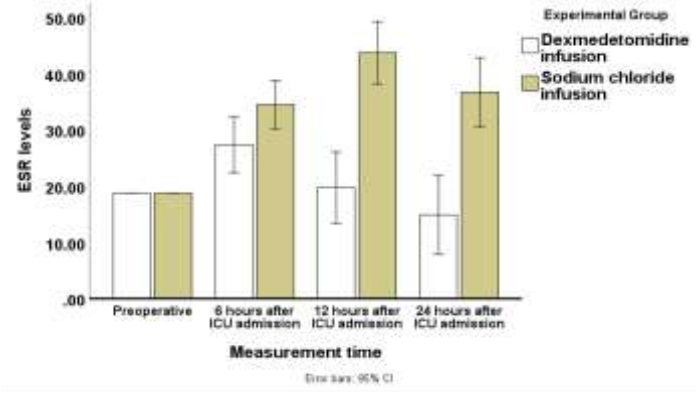
The two experimental groups had no significant differences in terms of age, sex, BMI index, body surface area, comorbidities (Hypertension, dyslipidemia, and diabetes mellitus), addiction and smoking status, and NYHA classification (Table 1).

Table 1: The comparison of the baseline characteristics between case and control group patients in this study

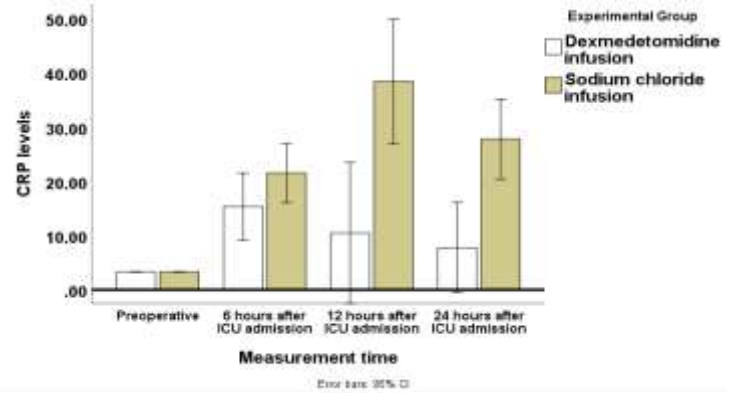
Variables		Case group (Dexmedetomidine infusion)	Control group (Sodium chloride infusion)	P
Age (mean± SD, years)		51.3±13.8	55.5±15	0.316
BMI (mean± SD)		27.4±3.5	26±5.1	0.294
Body surface area (mean± SD)		1.91±0.2	1.8±0.1	0.060
Sex, N(%)	Male	11(50)	15(53.6)	0.802
	Female	11(50)	13(46.4)	
Smoking history? ,N(%)	Yes	7(38.1)	7(25)	0.594
	No	15(68.2)	21(75)	
Narcotics addiction history N(%)	Yes	5(22.7)	7(25)	0.852
	No	17(77.3)	21(75)	
History of Diabetes mellitus N(%)	Yes	7(38.1)	13(46.4)	0.295
	No	15(68.2)	15(53.6)	
History of Hypertension N(%)	Yes	21(95.5)	23(82.1)	0.211
	No	1(4.5)	5(17.9)	
History of Dyslipidemia N(%)	Yes	3(13.6)	4(14.3)	1.000
	No	19(86.4)	24(85.7)	
NYHA classification ϯ N(%)	I	0	0	0.369
	II	6(27.3)	11(39.3)	
	III	15(68.2)	17(60.7)	
	IV	1(4.5)	0	

The means of Troponin-I (P=0.000), ESR (P=0.001), and CRP (P=0.000) at different measurement times were statistically different, and the interaction between measurement time and group was significant for these four factors (P<0.05). At the same time, the mean±SD of

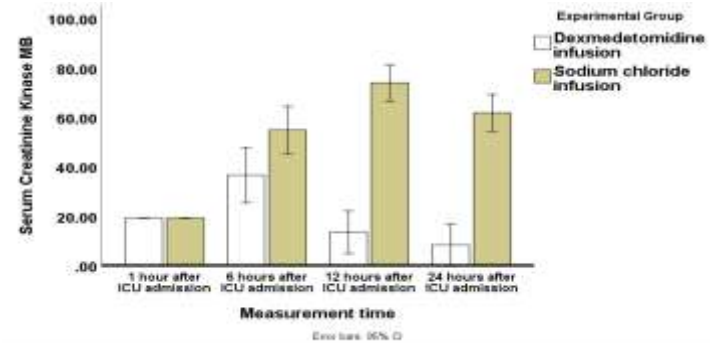
MAP(P=0.135) and CK-MB (P=0.637) had no significant variation during the time. The effect of measurement time on CK-MB (P=0.001) was different in patient groups (Figure 2).



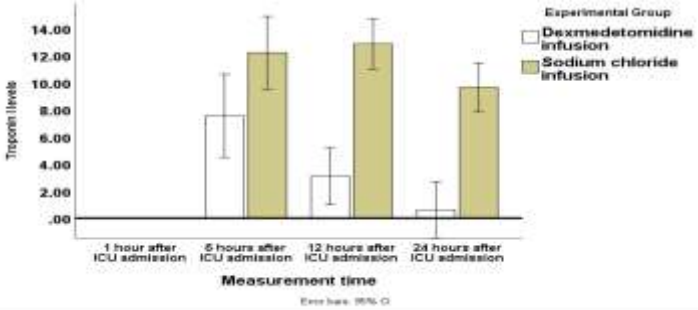
A. ESR measurement time*group (Greenhouse-Geisser p-value<0.001)
ESR measurement time (Greenhouse-Geisser p-value=0.001)



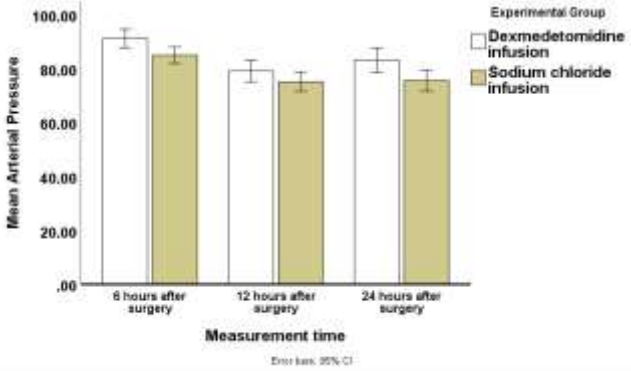
B. CRP measurement time*group (Greenhouse-Geisser p-value=0.001)
CRP measurement time (Greenhouse-Geisser p-value<0.001)



C. CK-MB measurement time*group (Greenhouse-Geisser p-value<0.001)
CK-MB measurement time (Greenhouse-Geisser p-value=0.637



D. Troponin I measurement time*group (Greenhouse-Geisser p-value<0.001)
Troponin I measurement time (Greenhouse-Geisser p-value=0.001)



E. MAP measurement time*group (Greenhouse-Geisser p-value=0.362).
MAP measurement time (Greenhouse-Geisser p-value=0.135).

Figure 2:Investigating the Measurement time variation and interaction between patient group and measurement time of clinical findings through Repeated Measure analysis of variance

=0.001), 6 hours (7.8±3.7 VS 12±8.2; P=0.018), 12 hours (3.9±2 VS 12.2±6.2; P=0.000), and 24 hours (0.9±0.5 VS 9.4±6; P=0.000) after ICU entrance were significantly lower in the Dexmedetomidine

group than in the control group (Table 2).

Also, evaluation of the CK-MB levels showed a significant plummet at the first hour (22.9±3.3 VS 16.3±4.8; P=0.001), and 24 hours (16.3±3.6 VS 55.4±25.6; P=0.001) after ICU entrance (Table 2).

On the other hand, regarding the evaluation of inflammatory markers, the results showed that ESR levels were only elevated at 12 hours (22.7±6.9 vs 41.5±18.2; P=0.001) and 24 hours (17.8±7 vs 34.5±20; P=0.001). The CRP levels at 12 hours (9.3±8 VS 39.4±39.3; P=0.001) and 24 hours (5.9±5.4 VS 29.2±26.6; P=0.001) after ICU entrance were significantly lower in the Dexmedetomidine group than in the control (Table 2).

The mean arterial pressure measurements in the Dexmedetomidine group revealed that in 6 hours (92.8±4.7 VS 83.9±9.8; P=0.000), 12 hours (80.9±6.6 VS 73.9±11; P=0.008), and 24 hours (84.1±4.2 VS 75±12.7; P=0.001) after ICU entrance were higher than in the control group (Table 2). Besides, the VIS showed a significantly greater range in the isotonic saline group than in the intervention at 6 hours (18.4±7.9 vs 9.8±5.8; P=0.001) and 24 hours (5.4±2.4 vs 2.9±2; P=0.001) after ICU admission (Table 2 and Figure 3).

Table 2: The comparison of the clinical findings of the studied patients between the two groups

Variables		Case group Dexmedetomidine+ Del-Nido	Control group Sodium chloride+ Del-Nido	P
Troponin-I	1 hour after ICU admission	0.05±0.00	0.1±0.1	0.001*
	6 hours after ICU admission	7.8±3.7	12±8.2	0.018*
	12 hours after ICU admission	3.9±2	12.2±6.2	0.001*
	24 hours after ICU admission	0.9±0.5	9.4±6	0.001*
CK-MB	1 hour after ICU admission	22.9±3.3	26.3±5.6	0.001 *
	6 hours after ICU admission	44.2±8.3	48.8±3.3	0.461
	12 hours after ICU admission	23.4±3.8	66.1±27.2	0.001 *
	24 hours after ICU admission	16.3±3.6	55.4±25.6	0.001 *
ESR	Preoperative	23.5±5.4	15.1±9.3	0.001 *
	6 hours after ICU admission	31.4±10.1	31.4±14	0.981
	12 hours after ICU admission	22.7±6.9	41.5±18.2	0.001*
	24 hours after ICU admission	17.8±7	34.5±20	0.001*
CRP	Preoperative	2.1±0.5	4.2±6.2	0.081
	6 hours after ICU admission	13.8±10.4	22.7±18.1	0.046
	12 hours after ICU admission	9.3±8	39.4±9.3	0.001*
	24 hours after ICU admission	5.9±5.4	29.2±6.6	0.001*
Mean Arterial Pressure (MAP)	6 hours after surgery	92.8±4.7	83.9±9.8	0.001*
	12 hours after surgery	80.9±6.6	73.9±11	0.008*
	24 hours after surgery	84.1±4.2	75±12.7	0.001*
Vasopressor-Inotrope Score	6 hours after ICU admission	9.8±5.8	18.4±7.9	0.001 *
	24 hours after ICU admission	2.9±2	5.4±2.4	0.001 *
Ejection Fraction	Preoperative	37.9±6.8	39.9±8	0.357
	One day after surgery	39.2↓6.3	37.1±7.6	0.311
	Seven days after surgery	40.1±6.1	37.2±7	0.123
	28 days after surgery	43.4±4.9	38±7.6	0.004 *
	180 days after surgery	44.1±4.8	37.7±7	0.001 *

* significant at α=0.05

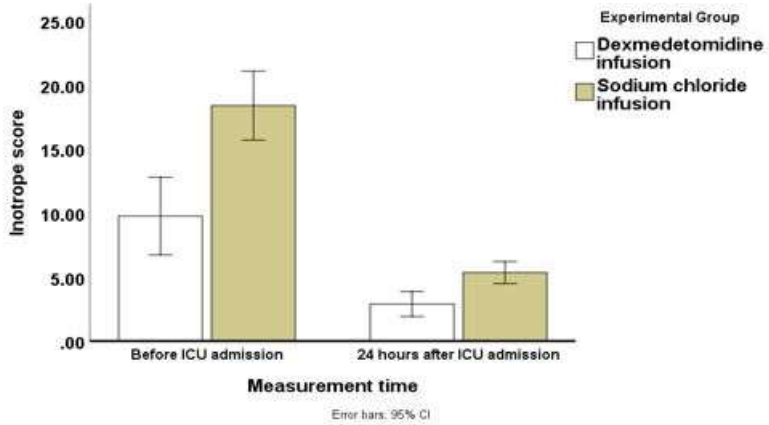
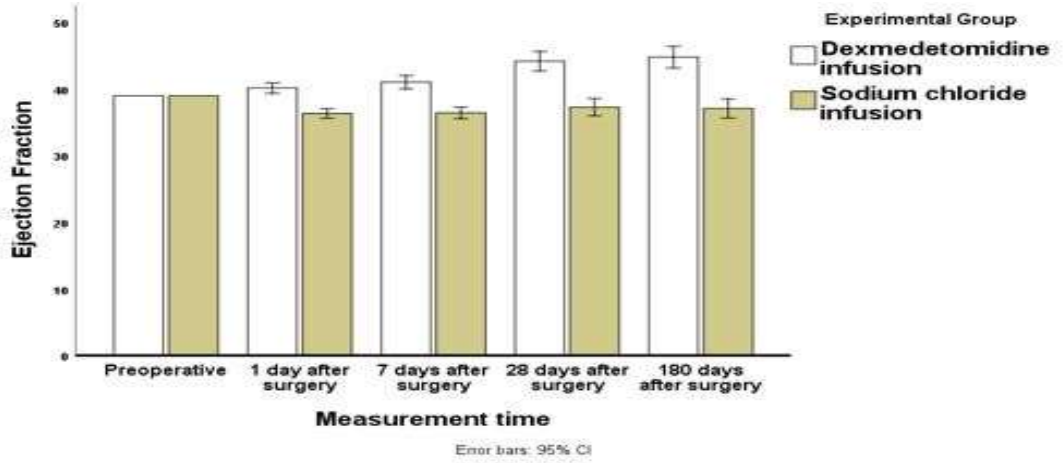


Figure 3: The mean±SD Inotrope score according to measurement time and group

The unique finding of our study was that the left ventricular ejection fraction was

significantly higher at 28 days (43.4±4.9 vs 38±7.6; p=0.004) and 180 days (44.1±4.8 vs 37.7±7; P=0.001) after cardiac surgery in the Dexmedetomidine group, compared with the control group (Table 2). Also, the left ventricular ejection fraction differed significantly across measurement times (P=0.001), and the interaction between measurement times and patient group was also significant (P=0.001) (Figure 4).



EF measurement time*group (Greenhouse-Geisser p-value<0.001). EF measurement time (Greenhouse-Geisser P-value=0.001).

Figure 4: Investigating the Measurement time variation and interaction between patients' groups and the measurement time of Ejection Fraction through Repeated Measure analysis of variance

The median (IQR) of weaning time (P=0.001), ICU stay (P=0.001), and hospital stay (P=0.003) were higher in the control group. The CPB time (P=0.09), Cross-clamp time (P=0.06), and Operation time (P=0.08) did not differ between the case and control groups (Table 3). Fortunately, no adverse events were observed in either group of the study.

Table 3: The comparison of the clinical outcomes after the surgical procedure in our study

variables	Case group Dexmedetomidine infusion	Control group Sodium chloride infusion	P
Weaning time, mean± SD, minutes	305(67.5)	600(263.7)	0.001*
Cross-Clamp time, median(IQR), minutes	39(7.2)	49.5(28)	0.06
CPB time, median(IQR), minutes	48.5(11)	67.5(49.7)	0.09
Operation time, median(IQR), minutes	61.5(10.2)	92.5(55)	0.08
ICU-stay, median(IQR), hours	50(10.7)	73(23.2)	0.001*
Hospital-stay, median(IQR),days	5(2)	6(2)	0.003*

*significant at α=0.05 IQR: Inter Quartile range

5. Discussion

Cardiac surgery using CPB has been shown to cause reversible post-ischemic myocardial dysfunction due to the I/R injury (14). It is crucial to attenuate myocardial metabolism and balance myocardial supply and demand to achieve myocardial protection (12). As there is no optimal strategy for reducing I/R injury risk during perioperative cardiac surgery (15), we sought to determine whether infusing Dexmedetomidine into the aortic root before aortic declamping can affect myocardial protection.

Dexmedetomidine has been considered an organ-protective agent against cytokine release syndrome that follows a tremendous inflammatory response during CPB and after cardiac surgery (16).

Changes in Creatinine kinase- MB concentration and cTn-I serum levels provide unequivocal diagnostic parameters indicating the extent of myocardial injury (17), and our study showed a statistical decrease in the myocardial injury followed by CPB use in patients treated with

Dexmedetomidine versus the control group based on these measures.

While some studies (8, 11, and 14) agree with our findings, Gong et al. (18) reported postoperative complications, including severe hypotension and bradycardia, in addition to cardioprotective effects in the Dexmedetomidine group. One probable reason for these complications may be due to using a higher dose of Dexmedetomidine in that study during and after cardiac surgery (19-22).

The evaluation of inflammatory markers (ESR and CRP) in this study showed that Dexmedetomidine acts as an anti-inflammatory agent. The anti-inflammatory mechanism of Dexmedetomidine can be explained by its inhibition of the NF-κB pathway and Toll-like receptors (23-25). As some studies have shown that inflammation is associated with cardiomyocyte dysfunction, followed by Systemic inflammatory response syndrome (SIRS), in cardiac surgery patients (26), it can be concluded that the anti-inflammatory role of Dexmedetomidine might decrease adverse cardiac outcomes after cardiac surgery.

The Mean Arterial Pressure (MAP) measurements during the post-cardiac-surgery period showed that patients in the Dexmedetomidine group had significantly higher blood pressure than those in the control group. Our results also showed a dramatic decline in VIS after surgery. It seems that our findings contrast with another study (18), which reported that this agent could cause detrimental effects on cardiomyocytes and the heart's electrical activity, a finding that a higher dose may explain than in our study. It is worth mentioning that using a standard dose of this drug not only demonstrated a destructive effect on cardiomyocytes but can also be considered a reliable factor in preserving cardiomyocytes during the perioperative period of cardiac surgery.

Our findings were consistent with other studies showing myocardial protection in patients treated with this drug compared with placebo during cardiac surgery (18, 26).

We found that his weaning time from mechanical ventilation was significantly shorter in the Dexmedetomidine group than in the control group, consistent with other reports (18, 28).

Our results revealed that ICU and hospital stays were significantly shorter in patients receiving Dexmedetomidine. Although other studies reported significant heterogeneity in their results (18, 26-28), most found that the ICU stay, despite the risk of cardiac complications, was significantly shorter in patients receiving perioperative Dexmedetomidine.

Limitations of the Study:

Overall, our findings add to the growing body of evidence that Dexmedetomidine, when integrated into the aortic root before cross-clamp removal, may provide synergistic myocardial protection and enhance postoperative recovery in patients undergoing valve surgery. However, certain limitations should be acknowledged. The sample size, although powered to detect differences in troponin I levels, limits the detection of rarer adverse events or nuanced subgroup effects. Moreover, while short-term biochemical and clinical outcomes were assessed, longer-term follow-up was not included to evaluate sustained myocardial function or late morbidity. Finally, although the study demonstrates biochemical and clinical benefits, the precise mechanistic pathways by which Dexmedetomidine confers myocardial protection when administered in different routes of administration warrant further investigation.

6. Conclusion

The main conclusion of this study is that administering Dexmedetomidine into the aortic root before declamping is an optimal approach to enhance myocardial protection in cardiac surgery patients on CPB.

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Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of interests: The authors declare that they have none.

Consent for publication: Not applicable.

Ethics approval and consent to participate: The Mashhad University of Medical Sciences ethics committee approved the study protocol under IR.MUMS.MEDICAL.REC.1400.186, which complies with the Declaration of Helsinki. The study was registered under the IRCT registration number: IRCT20210710051837N1.

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Author contributions: Sh.A.: Contributed to the conception of the work, revising the draft, approving the final version of the manuscript, and agreeing on all aspects of the work; F. H.: contributed to the critical revision, and approval of the final version of the manuscript; M. R. N. S.: Contributed to the conception and design of the study, critical revision, and approval of the manuscript's final version; M.Y.: Contributed to the conception and design of the study, drafting of the manuscript and critical revision, and approval of final version.

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