Impact of adenosine in controlled aortic root reperfusion on clinical outcomes among patients undergoing valvular heart surgery

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Background:

Adenosine is a vital medication in cardiac surgery, particularly in valvular heart procedures. While its use has been linked to improved postoperative cardiac function in some studies, there remains significant uncertainty regarding the adenosine usage in aortic reperfusion phase. This lack of consensus poses challenges for surgeons, perfusionists, and anesthesiologists alike. This study aims to explore the impact of adenosine on clinical outcomes in patients undergoing valvular heart surgery.

Method:

This prospective randomized controlled trial was conducted over a three-month period. Sixty patients undergoing valvular heart surgery were enrolled using a continuous sampling method and randomly allocated into two equal groups of 30 patients each. The intervention group received adenosine-enriched aortic root reperfusion immediately prior to aortic declamping, while the control group underwent standard warm blood aortic root reperfusion. Both groups were matched for demographic and clinical characteristics to ensure comparability.

Results: Results indicated no significant differences in mean cardiopulmonary bypass (CPB) time, aortic cross-clamping duration, or mechanical ventilation between the intervention and control groups. However, the intervention group that received adenosine had a higher rate of antiarrhythmic agent usage in the operating room ($P<0.05$). Inotropic agent usage was similar in both groups during surgery and in the ICU. Additionally, laboratory parameters on the first day of ICU admission were comparable between groups.

Conclusion:

Results in control group showed more favorable outcomes in terms of anti-arrhythmic drug usage, electroshock application, and arrhythmia prevalence. This study showed advantages for the standard warm blood aortic root reperfusion technique in managing post-operative cardiac rhythm disturbances in comparison with trial group.

Keywords: Adenosine; Aortic root reperfusion; Cardiac operation; Cardiopulmonary bypass

Introduction

Cardioplegia is commonly used to minimize myocardial damage during cardiac surgery, but both reversible and irreversible injuries such as myocardial edema and reduced cardiac function still occur

due to ischemia-reperfusion injury during cardiac operations(1). These complications might lead to cardiac dysrhythmia, a decrease in ejection fraction, cardiac attack, and increased recovery time for patients undergoing cardiac operations. Appropriate cardioplegia can be considered an important preventive measure for these complications; however, the optimal composition of cardioplegia fluid for myocardial protection has not yet been determined(2). Injection of warm blood before aortic root declamping can wash and remove anaerobic metabolites and improve myocardial function(3). Warm blood injection has had a significant impact on Troponin-I levels and significantly decreased the need for inotrope agents and intra-aortic balloon pumps (3). Despite these advantages of using warm blood, Rergkliang, in his study, reported that using warm blood did not cause significant changes in operation-related parameters (4). Although recent studies have suggested some additives such as Insulin, Nicorandil, and Amiodarone for modification of cardioplegia solution, there is no defined instruction for using warm blood within the CPB (Cardiopulmonary Bypass) among patients undergoing cardiac operations(1).

Adenosine, as an antiarrhythmic agent, has been used in managing cardiac arrhythmias and has recently been suggested for cardioplegia solution with warm blood injection(5). Adenosine improves cardiac rhythm and helps return to normal rhythm. Some studies have reported that adenosine during ischemia can increase ventricular function and ejection fraction and reduce myocardial damage size(6). Recent advances in LC-MS/MS-based metabolomics (liquid chromatography - mass spectrometry-based metabolomics) have enabled detailed profiling of biomolecules such as adenosine, which provides the necessary insights into their cardioprotective effects and potential as a therapeutic agent that could enhance myocardial protection and improve clinical outcomes associated with cardiac surgeries(7, 8). It seems that using adenosine in warm blood infusion during CPB can decrease cardiac operation complications. Accordingly, the present study was performed to assess the impact of reperfusion of the aortic root with and without adenosine among patients undergoing cardiac valve operations. In this study, we hypothesized that adenosine supplementation in warm blood reperfusion before aortic declamping provides superior myocardial protection compared with warm blood alone, by reducing ischemia-reperfusion–related myocardial injury and improving functional recovery.

Materials and methods

We conducted a prospective randomized controlled trial involving a total of 60 patients undergoing valvular heart surgery in 2020, who were consecutively sampled and randomly allocated into two equal groups of 30 patients . Study protocol was approved in ethical research committee of Shahid Rajaie Cardiovascular, Medical and Research Institute (IR.RHC.REC.1399.41) and all of participants signed informed consents. Study participants were selected via consecutive sampling method, according to inclusion criteria. Inclusion criteria were EF>35%, patients with 18-65 years old, primary valvular replacement or repair. Exclusion criteria were, ventricular hypertrophy, preoperative inotrope usage, cardiac pacemaker (ICD), and pulmonary hypertension (PAP>65 mmHg), and recent myocardial infarction, perioperative need for intra-aortic balloon pump, and cardioprotective mechanical devices. Randomization was performed with an accidental number table and a random block of four samples and participants randomly allocated to trial and control groups. Participants in both groups received mild hypothermia (15) and their acid-base balance was controlled by Alpha-stat method. The anesthesiology conditions and CPB settings were the same for all study patients. Del Nido cardioplegia was used for cardiac arrest and half of its first dose was repeated 60 minutes after the initial dose. At the end of the ischemic phase and before aortic declamping, patients in the trial group received warm blood with adenosine (150 µg/kg) directly through the cardioplegia delivery line using a roller pump, at a rate of 200 to 250 ml per minute, within a time frame of 5 to 10 minutes, under a pressure of 80 to 100 mmHg until sinus rhythm was restored. This was administered through the cardioplegia line using a roller pump as part of the trial intervention. In the control group, patients received warm blood same as the trial group without adenosine. For prevention of blood clotting, Heparin was injected (300-400 units/kg) to reach the ACT higher than 480 seconds.

Demographic and baseline variables including age, sex, weight, operation type, and cardiac disorder were gathered by researcher-made checklist via the medical documents and records. The pre and post operation cardiac ejection fraction of the patients was assessed by echocardiologist who was blinded to study groups by echocardiography. CPB-related data were gathered within the study period by the research team. Some operation related parameters including spontaneous sinus rhythm resumption time, antiarrhythmic and inotrope drugs usage, CPB time, frequency of cardiac shock and peacemaker usage after CPB, and cardiac muscle damage, and liver and kidney function markers were measured as study outcomes. Other clinical variables such as the need for blood transfusion and introp agents were recorded by the patient medical documents.

Statistical analysis

The data were analyzed using IBM SPSS Statistics software (Version 22.0; IBM Corp., Armonk, NY, USA).. Normality of study data were analyzed, and mean/standard deviation and frequency/percentages were used to describe quantitative and qualitative variables in normal distribution and median (IQR1- IQR3) for nonparametric variables. Independent sample t-test and chi-square statistical tests compared quantitative and qualitative variables between two groups for parametric and Mann–Whitney U test for non-parametric variables. All P-values less than 0.05 were assumed as significant results.

Results

60 patients in trial and control groups were entered into the analysis. Demographic and baseline variables were similar between patients of both groups.

(Table 1)

Mean of the CPB time was similar between patients of trial and control groups (80.87±20.07 vs. 74.90±21.43 minutes; P=0.27). There was no significant difference between aortic cross clamp time among patients of trial and control groups (53.40±19.07 vs. 50.63±16.81 minutes; P=0.55). There was no significant difference between the two groups in Mechanical ventilation time (10.0±4.0 vs. 8.87±3.48 hours; P=0.25). Ejection fraction of included patients had no significant differences at pre and post CPB and intensive care unit times.

(Table 2)

Study patients in the trial group received significantly higher antiarrhythmic agents in operation room ~~in~~ compared with patients in the control group (14, 43.3% vs. 5, 16.7%; P=0.024). Antiarrhythmic usage rate was similar in patients of both groups in the ICU and only one patient in the control group received antiarrhythmic agents (P=0.31). Inotrope agents' usage rate was similar between patients of trial and control groups in the operation room (20, 66.7% vs. 24, 80%; P=0.243) and ICU (10, 33.3% vs. 6, 20%; P=0.25). Although cardiac shock usage was significantly higher among patients of trail group in comparison with control group, pacemaker usage rate was similar between patients of both groups (P=0.99).

(Table 3)

Time of warm blood infusion among patients of both groups was similar. The type of cardiac resumption rhythm was significantly different among patients of trial and control groups. According to

that, Ventricular Tachycardia (VT), Ventricular Fibrillation (VF) and Dysrhythmia to sinus rhythm frequency were significantly higher among patients of trial group.

(Table 4)

In the first day to ICU entrance, laboratory parameters were similar between two groups.

(Table 5)

Discussion

In the present study, 60 patients in both trial and control groups were included and baseline variables were similar between study participants in two groups. Duration of operation, aorta cross clamping, ICU stay, and mechanical ventilation time were similar between the two groups. Our findings were similar to those reported by Givtaj et al. (10), which supports the validity of our results (9). In contrast to our results, Kalita et al. reported that patients who used traditional method without warm blood injection in aortic root, in their mitral valve operation, had significantly higher ICU stay time and therefore had higher operation related complications(10). Although EF of included patients was decreased after operation, there were not significant differences between two groups. Although, Givtaj et al. (9) had similar result with our study, Ammar et al, in their study reported that patients who received adenosine before aortic declamping had better systolic and diastolic function (11).

We found that the time of cardiac rhythm resumption was similar between patients of two groups. Elgariah et al., in their study reported that in patients who received adenosine, cardiac rhythm returning time and incidence of cardiac rhythm abnormalities were significantly lower than patients of control group(3). The frequency of ventricular fibrillation and tachycardia was significantly higher among our patients in the trial group compared to those in the control group. In contrast to our findings, Sallam et al., found that patients who used adenosine had been experienced lower frequency of cardiac rhythm abnormalities and atrial and ventricular arrhythmia (12). Ascione et al., reported that adenosine did not significantly influence the type of cardiac rhythm resumption (13). Rergkliang et al., in their study reported that patients who did not receive warm blood during operation, need lower time to cardiac rhythm resumption (4). Our findings suggest that adenosine administration might impair cellular metabolic conditions and contribute to non-sinus cardiac rhythm and delayed rhythm recovery.

Antiarrhythmic agents' usage in patients of trial group was significantly higher than patients of control group. In the other hand, incidence of dysrhythmia in the operation room among patients of trial group

was higher than patients of control group. There were no significant differences in incidence of arrythmia among patients of both groups in the ICU. In contrast to our findings, Ammar at al., in their studies reported that use of adenosine can decrease incidence of postoperative arrhythmia (11). Givtaj et al reported that there was no considerable relationship between incidence of arrythmia and adenosine usage among patients undergoing cardiac operation (9). Patients of both groups had similar inotropic usage rates in the operation room and ICU. Ascione et al., had similar findings with our study (13). Khairy, P et al in their study, reported that patients who did not get adenosine had significantly higher need to supportive and inotropic agents in comparison with patients who get adenosine in the operation (14).

Mean of the Troponin and CK-MB as two main myocardial damage markers were similar between patients of two groups. In the other hand, use of adenosine did not reduce postoperative troponin among patients. Ayman, S et al in their study reported that mean of troponin among patients who did not receive adenosine during their operation significantly was higher than other patients (12). Elgariah et al reported that frequency of troponin among patients of adenosine group was significantly lower than patients of control group (3). Cardiac enzymes are known as effective factors of cardiac function and can predict postoperative situations of patients undergoing cardiac operation. Although we had not seen any significant differences in postoperative troponin level between two groups.

In our study, the frequency of cardiac electroshock applications among patients in the trial group was significantly higher than that in the control group. This finding can be related to the decline in cardiac function and increase in cardiac enzymes among patients in the trial group who received adenosine during their operation. Although in our study the mean level of cardiac enzymes did not show significant differences between the two groups, higher cardiac rhythm abnormalities and more antiarrhythmic drug usage in the operating room indicate that patients who received adenosine required more therapeutic interventions to improve their cardiac rhythm; and we hypothesize potential

mechanisms including adenosine receptor desensitization, inter individual variability in response, and metabolic effects during reperfusion. Ammar et al. reported opposite results, noting that cardiac electroshock usage among patients who received adenosine was lower than in other patients. (11). Ascione et al., reported that usage of cardiac electroshock was similar between patients of both groups (13). It seems that theoretically, use of adenosine should reduce cardiac rhythm abnormalities after aortic decamping, and we need ~~to~~ more studies in the cellular and clinical settings for confirming impact of adenosine on the postoperative cardiac rhythm of patients. Use of adenosine in our study had no significant impact on postoperative cardiac ejection fraction of patients. Givtaj et al., study had similar findings (9) and in contrast to our findings, Ammar et al., in their study reported that patients who received adenosine had better postoperative systolic and diastolic functions (11).

Limitation

Due to patient recruitment restrictions and ethical limitations, the current study included 30 participants per group. We agree that this sample size may have limited statistical power for detecting differences in clinical outcomes and, we now acknowledge the lack of power analysis as a limitation.

Conclusion

In this randomized clinical study, adenosine administration during the reperfusion phase did not demonstrate a clear clinical advantage compared to the control group. Demographic variables, ejection fraction, ICU stay, and sinus rhythm recovery showed no significant differences between groups, while a higher rate of postoperative dysrhythmias were observed in the adenosine group. These findings suggest that adenosine, despite its well-documented cardio protective mechanisms through A1 and A3 receptor activation, may not uniformly confer antiarrhythmic benefits and could potentially exert pro-arrhythmic effects under certain physiological conditions such as receptor desensitization or individual dose-response variability. The present results emphasize the complexity of adenosine's actions in

myocardial reperfusion and highlight that timing, dosage, and patient-specific factors may critically determine its effects.

In conclusion, the findings of this study are specifically observed in patients undergoing valve heart surgery. These results highlight the clinical outcomes and implications of adenosine administration during the controlled aortic root reperfusion phase in this particular patient population

Given the relatively small sample size, the study may have been underpowered to detect subtle clinical benefits or adverse effects. Thus, larger randomized trials are warranted to confirm these observations and to clarify the risk-benefit balance of adenosine use during cardiac surgery, particularly in the reperfusion phase.

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Table 1- Comparison of demographic and baseline variables between included patients

Groups Variables		Trial group (n=30)	Control group (n=30)	P-value
Age (Mean±SD)		50.6±13.17	52.36±13.57	0.62
Sex	Male	17 (56.7%)	13 (43.3%)	0.30
	Female	13 (43.3%)	17 (56.7%)	
Underlying disease	Diabetes	1 (3.3%)	7 (43.3%)	0.42
	Hypertension	7 (23.3%)	4 (13.3%)	
	Hyperlipidemia	2 (6.7%)	5 (16.7%)	
Operation type	MVR	17 (56.6%)	15 (50.0%)	-
	AVR	9 (30.0%)	12 (40.0%)	
	MVR-TV repair	1 (3.33%)	-	
	MVrepaire	1 (3.33%)	-	
	TVR	1 (3.33%)	-	
	TVR-AVR	1 (3.33%)	-	
	PVR	-	1 (3.33%)	
	Resection AV	-	1 (3.33%)	
	MVR-AVR	-	1 (3.33%)	

Table 2- Comparison of ejection fraction between included patients at different measurement points

Ejection fraction		Trial group (n=30)	Control group (n=30)	P-value
Preoperation	35-45	11 (36.6%)	9 (30.0%)	0.72
	50	13 (30.0%)	8 (26.7%)	
	55-60	10 (33.3%)	13 (43.3%)	
Post operation	35-45	10 (33.3%)	3 (10.0%)	0.42
	50	10 (33.3%)	12 (40.0%)	
	55-60	10 (33.3%)	15 (50.0%)	
ICU	50-55	11 (36.7%)	11 (36.7%)	0.95
	40-45	7 (23.3%)	8 (26.7%)	
	15-40	12 (4.0%)	11 (36.7%)	
CPB (min)		80.87±20.07	74.90±21.43	0.27
Cross Clamp (min)		53.40±19.07	50.63±16.81	0.55
Mechanical Ventilation Time (day)		10.0±4.0	8.87±3.48	0.25

Table 3- Comparison of cardiac shock and pacemaker usage among patients of trial and control groups

Variable		Trial group (n=30)	Control group (n=30)	P-value
Cardiac shock	Yes	13 (43.3%)	2 (6.7%)	0.001
	No	17 (56.7%)	28 (93.3%)	
Number of shock usage	0	17 (56.7%)	28 (93.3%)	0.004
	1	8 (26.7%)	1 (3.3%)	
	2-5	5 (16.7%)	1 (3.3%)	
Pacemaker	Yes	4 (13.4%)	3 (10.0%)	0.99
	No	26 (86.7%)	27 (90.0%)	

Table 4- Comparison of warm blood infusion time and cardiac rhythm return among patients of trial and control groups

Variable		Trial group (n=30)	Control group (n=30)	P-value
Warm blood infusion time (Minute)	0-5	28 (93.3%)	28 (93.3%)	1.00
	5-10	2 (6.7%)	2 (6.7%)	
Cardiac rhythm resumption arrhythmia	Sinus Tachycardia	11 (36.7%)	16 (53.3%)	0.012
	VT	8 (26.7%)	4 (13.3%)	
	VF	5 (16.7%)	0	
	Dysrhythmia to sinus	4 (13.3%)	1 (3.3%)	
	Junctional	1 (3.3%)	6 (20%)	
	Sinus	1 (3.3%)	4 (13.3%)	
Returning time to cardiac rhythm (min)		2.94±1.93	3.19±1.72	0.59

Table 5- comparing laboratory parameters in the first day of ICU entrance among patients of trial and control groups

Variable	Trial	Control	P-value
Troponin (ng/mL)	3.6±0.93	3.1±1.93	0.17
Ck-mb (ng/mL)	44.03±16.64	39.81±14.93	0.305
CPK (ng/mL)	320.83±160.87	273.83±180.20	0.174
LDH (U/L)	600.80±229.12	577.27±132.77	0.629
SGOT(U/L)	38.23±17.41	36.07±10.57	0.563
SGPT(U/L)	21.87±15.80	18.50±7.47	0.298
Cr (mg/dl)	0.0 (0.9-1.4)	1 (0.7-1.2)	0.06
BUN (mg/dl)	15.1±5.44	16±9.07	0.65

Ck-mb: Creatine Kinase-MB, CPK: Creatine Phosphokinase, LDH : Lactate Dehydrogenase,

SGOT: Serum Glutamic-Oxaloacetic Transaminase Test, SGPT: Serum Glutamic-Pyruvic Transaminase, Cr: Creatinine, BUN: Blood Urea Nitrogen