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Original Article

Impact of Adenosine Injection on the Clinical Outcome and Myocardial Protection in Patients Undergoing Coronary Artery Bypass Graft Surgery

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ABSTRACT

Background: Cellular damage is inevitable during cardiac surgery due to cardioplegic solutions and subsequent ischemia-reperfusion injury. There are controversies regarding the cardioprotective impact of adenosine addition to cardioplegic solutions in patients undergoing coronary artery bypass graft surgery (CABG). We aimed to assess the impact of adding adenosine to antegrade cardioplegia and before aortic declamping to the aortic root on the clinical outcomes of patients undergoing CABG.

Methods: The present single-blinded randomized clinical trial was performed on 99 patients of both sexes undergoing isolated CABG. The patients were randomly allocated to 2 trial groups and 1 control group: Group A, adenosine injection with antegrade cardioplegia (n=30); Group B, adenosine injection before aortic declamping by the surgeon at the aortic root (n=26); and Group C, control (n=30). In the course of the study, 13 participants lost their eligibility according to exclusion criteria. The patients' plasma creatine kinase (CK-MB), troponin T, lactate, and clinical outcomes were measured as trial outcomes.

Results: The frequency of patients with antiarrhythmic drug usage was significantly lower in trial groups A and B than in the control group (P = 0.001). The cardiac rhythm resumption time was significantly longer in the control group (344.37 ± 260.45) than in Group A (193.43 ± 297.73) and Group B (170.12 ± 103.58) (P = 0.02). Adenosine injection before aortic declamping (Group B) had the lowest time of cardiac rhythm resumption between the trial groups.

Conclusions: Our findings showed that adenosine injection enhanced the efficacy of cardioplegic arrest and myocardial protection during CABG. ***(Iranian Heart Journal 2023; 24(4): 26-33)***

Keywords: Adenosine, Cardiac arrhythmias, Cardiac function, CABG

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Coronary artery disease has the highest mortality rate across the globe. [1] Although coronary artery bypass graft surgery (CABG) with cardiopulmonary bypass (CPB) is suggested as the principal surgical procedure in patients who do not adequately respond to medical and minimally invasive therapeutic methods, some adverse outcomes, such as cardiac arrhythmias and myocardial damage due to ischemia-reperfusion injury, might occur during CABG and after aortic declamping. [2-7] Atrial and ventricular fibrillations are the common postoperative arrhythmias and cause hemodynamic instability and heart failure and increase hospitalization in one-third of patients. [8,9] Cardioplegic solutions play a crucial role in preventing myocardial damage among patients undergoing CABG. [10-13] The exact mechanism of arrhythmias is not fully recognized; nonetheless, factors such as the serum level of electrolytes and conductive anomalies might be responsible. Recent studies have reported that adding different substances to cardioplegic solutions can protect myocardial tissue from ischemic damage during CABG and after aortic declamping. [14]

Adenosine administration positively impacts systolic and diastolic functions since it provides cardiac protection, diminishes cardiac troponin I and creatine kinase-MB release, lowers the incidence of arrhythmias, and shortens the duration of postoperative mechanical ventilation and intensive care unit (ICU) stays. [15,16] Mentzer et al [17] used adenosine in cardioplegic solutions and reported enhanced cardiac output and reduced postoperative hemorrhage and dopamine and nitroglycerin usage. Chen et al [18] reported that using adenosine before the injection of cardioplegic solutions diminished postoperative inotrope usage and troponin I release. It seems that determining what constitutes the optimal time for adenosine injection in cardioplegic solutions can improve myocardial protection against ischemia-reperfusion lesions. [17] Our literature review showed that researchers have encountered formidable challenges in finding the optimal time for adenosine injection. Accordingly, we performed the present study to compare the impact of adenosine injection before and after aortic declamping on the clinical outcomes of patients undergoing CABG.

METHODS

Trial Design

The present open-labeled randomized clinical trial was performed with a parallel design on patients between 18 and 70 years old who had become candidates for elective CABG at Rajaie Cardiovascular Medical and Research Center. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences, and all the participants signed written informed consent.

Participants

According to our inclusion criteria, all patients without a history of severe renal or heart failure, sternotomy, previous cardiac surgery, myocardial infarction with electrocardiographic changes, an ejection fraction of less than 30%, and a forced expiratory volume in the first second (FEV1) of more than 65% were included in the study. Among the included patients, those who had pacemakers or sensitivities to adenosine or similar drugs, cross-clamping duration exceeding 100 minutes, CPB duration longer than 120 minutes, and cardiac arrest during cardiac surgery were excluded.

Intervention

The study population was randomly allocated by creating a randomization list with computer software and randomization blocks to 3 groups. In the post-clamping group, 250 µg/kg of adenosine was injected

after aortic clamping with the cardioplegia solution. In the pre-clamping group, 250 µg/kg of adenosine was injected into the root of the aorta before clamping. In the control group, the patients only received the cardioplegia solution without adenosine injection. [19,20] Del Nido was used as the cardioplegia solution for all the patients. In the trial groups, 6 mg of adenosine was injected by the perfusionist into the cardioplegia line. [20] The CPB cycle was primed with the crystalloid (ringer lactate) solution. The cardiac index was established continuously at 2-2.4 lit/min/m^2. Membrane oxygenators and the alpha acetate $PaCo_2$ strategy were employed during the surgical operation, and brain oxygenation was measured and recorded continuously. The patients' hematocrit level was maintained at higher than 24 mg/dL. Anesthesia, CABG, and cardioplegia injection were the same in the 3 study groups.

Trial Outcome

The trial outcomes consisted of the volume of the cardioplegic solution needed for cardiac arrest; pre and postoperative ejection fractions; the lowest temperature during CPB; CPB duration; cross-clamping; the spontaneous resumption of the cardiac rhythm time; the number of arrhythmias following aortic declamping; post-aortic declamping arrhythmia occurrences and their frequency; the need for the defibrillator; the need for potassium, magnesium, or lidocaine for restarting the cardiac rhythm; inotrope drugs usage in the operating room or the ICU; electrocardiographic changes; the amount of troponin and CK-MB before and then 6 and 24 hours after CABG; and the number of postoperative atrial fibrillation occurrences.

Sample Size

In the process of the sample-size calculation, firstly, the standard deviation of the time to arrest in the patients who received adenosine after aortic cross-clamping and before declamping was estimated (σ^1 = 3.77 s and σ^2 = 23.46 s). Then, the standard deviation of the time to arrest was estimated in the control group (K = 1). Then, the difference in time to arrest between the 2 intervention groups was calculated to be 14.15 seconds. According to the sample size formula (α=0.05 and β=0.2), similar studies, [21] and the sample size formula considering a 20% additive sample for the loss of follow-up, at least 90 patients were calculated to comprise the sample size in 2 trial groups and 1 control group.

Randomization and Blinding

Randomization was performed with randomization blocks (n = 6) in 2 trial groups and 1 control group with 30 patients. The randomized list of the patients was inserted in a sealed envelope and given to the researchers. The present study was open-labeled, and only patients were blinded to their study groups.

Statistical Analysis

The data were inserted into the SPSS, version 20, software, and mean ± standard deviation and frequencies and percentages were used to describe quantitative and qualitative variables, respectively. The Kolmogorov-Smirnov test was utilized to assess the normality distribution of the study variables. The comparison of the mean of the variables between the study groups was performed with one-way repeated measure ANOVA between different measurement points. The χ^2 and Fisher exact tests were used to compare qualitative variables between the 3 study groups. Repeated measure analysis was applied to compare the study variables between the different times measured. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Thirty patients in the post-clamping group, 26 in the pre-clamping group, and 30 in the control group were included in the data analysis. The mean values of age, weight, height, and body surface area were similar between the 3 study groups. Additionally, sex frequency was similar between the 3 trial groups. The details of the comparison of baseline variables between the groups are presented in Table 1.

During CPB, the frequency distributions of arrhythmias and drug usage were similar between the study groups. The mean cardiac arrest time and the mean time of the resumption of the first cardiac rhythm in the control group were significantly higher than those in the trial groups. After CPB, the mean values of the intubation time, postoperative hemorrhage, the ICU length of stay, and the hospitalization length of stay were similar between the study groups. Antiarrhythmic drug usage in the control group was significantly higher than that in the trial groups (P = 0.001). The mean frequency of the need for reoperation was similar between the trial groups. None of the trial participants needed cardiac shocks. The details of the comparisons are presented in Table 2.

The mean ejection fraction at preoperative, postoperative, and discharge times was similar between the study groups. The repeated measure analysis showed that mean ejection fraction at different measurement times had significant differences between the study groups (P = 0.004). On the other hand, time exerted a significant impact on the mean ejection fraction in the study population. The time and group impact on the mean ejection fraction between the study groups was not significantly different, and the mean ejection fraction change slope was similar between the study groups.

The mean lactate volume in CPB cooling and warming and on the first postoperative day was similar between the study groups. The mean lactate volume had significant differences between different measuring times between the study groups (P = 0.001). The time and group impact together was not significantly different between the study groups, and the slope of the mean lactate changes was similar between the groups.

The mean CK-MB before surgery and then at 6 and 12 hours postoperatively was similar between the study groups (P = 0.20). The time and group impact was not meaningfully different between the study groups, and the slope of CK-MB changes was also similar between the study groups (P = 0.32). The mean troponin level before surgery and at 6 and 12 hours postoperatively was similar between the 3 study groups (P = 0.80). The time and group impact was not significantly different between the study groups, and the slope of troponin changes was also similar between the study groups (P = 0.65).

Table 1: Frequency of baseline variables in the studied groups

Variable		Post-Clamping Group (n=30)	Pre-Clamping Group (n=26)	Control Group (n=30)	*P* value
Age, y		61.13±8.64	61.31±6.96	61.33±8.68	0.99
Sex	Male	25 (83.3%)	18 (69.2%)	20 (66.7%)	0.29
	Female	5 (16.7%)	8 (30.8%)	10 (33.3%)	
Weight (kg)		76.20±11.68	75.94±10.29	74.23±12.03	0.77
Height, cm		165.83±13.90	168.38±8.78	167.20±10.53	0.70
Body surface area, m^2		1.87±0.18	1.88±0.16	1.85±0.19	0.82

Table 2: Comparison of the study variable between the study groups at CPB and afterward

Variable	Post-Clamping Group (n=30)	Pre-Clamping Group (n=26)	Control Group (n=30)	*P* value
Cardiac arrest time, s	25.77±31.73	25.01±17.47	42.97±27.14	0.02
Resumption of the first cardiac rhythm, s	193.44±297.73	171.12±103.58	344.37±260.45	0.18
Post-declamping cardiac rhythm Sinus bradycardia Others Sinus rhythm	 10 (33.3%) 3 (10%) 17 (56.7%)	 2 (7.7%) 3 (11.5%) 21 (80.8%)	 6 (20.0%) 5 (16.7%) 19 (63.3%)	0.18
Post-declamping inotropes need	13 (43.3%)	8 (30.8%)	13 (43.3%)	0.55
Cardiac shock need	0	2 (7.7%)	2 (6.7%)	0.45
ST-depression	1 (3.3%)	1 (3.8%)	3 (10%)	0.62
ST-elevation	1 (3.3%)	0	1 (3.3%)	0.99
Post-declamping antiarrhythmic drug usage	27 (90.0%)	26 (100%)	28 (93.3%)	0.37
Cardiac balloon pump	2 (6.7%)	0	0	0.33
Pacemaker	1 (3.3%)	0	2 (6.7%)	0.78
ECMO	1 (3.3%)	0	0	0.99
ICU cardiac rhythm Sinus tachycardia Others Sinus rhythm	 5 (16.7%) 2 (6.7%) 23 (76.7%)	 4 (15.4%) 1 (3.8%) 21 (80.8%)	 4 (13.3%) 3 (10%) 23 (76.7%)	0.97
Antiarrhythmic drug usage	3 (10.0%)	1 (3.8%)	12 (40.0%)	0.001
Mechanical ventilation time, h	16.01±4.80	13.30±3.35	14.84±4.18	0.06
ICU stay, h	53.43±41.93	49.93±15.78	54.36±19.07	0.83
Cardiac shock need	0	0	0	-
Postoperative hemorrhage, mL	470.67±312.97	463.85±354.66	479.01±356.02	0.98
Reoperation need	2 (6.7%)	1 (3.8%)	2 (6.7%)	0.99
Hospitalization, d	12.93±7.58	11.77±4.87	12.23±4.42	0.75

CPB: cardiopulmonary bypass; ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit

Table 3: Frequency of ejection fraction at different time points in the study groups

Variable	Post-Clamping Group (n=30)	Pre-Clamping Group (n=26)	Control Group (n=30)	Group Impact	Time Impact	Time and Group Impact
Preoperative ejection fraction	45.50±9.50	46.54±6.13	47.01±7.02	0.88	0.004	0.08
Postoperative ejection fraction	48.33±10.45	47.50±7.91	46.33±10.33			
Discharge ejection fraction	49.33±9.71	49.04±7.35	47.01±10.64			

Table 4: Frequency of lactate (mmol/L) at different time points in the study groups

Variable	Post-Clamping Group (n=30)	Pre-Clamping Group (n=26)	Control Group (n=30)	Group Impact	Time Impact	Time and Group Impact
Cooling time (Pump I)	1.57±0.64	1.76±0.52	1.69±0.52	0.89	0.001	0.89
Warming time (Pump II)	1.70±0.88	2.01±0.81	1.81±0.85			
First postoperative day	2.66±2.06	2.54±1.94	2.63±2.31			

Table 5: Frequency of CK-Mb and troponin (unit/L) at different time points in the study groups

Variable	Post-Clamping Group (n=30)	Pre-Clamping Group (n=26)	Control Group (n=30)	Group Impact	Time Impact	Time and Group Impact
Preoperative	29.01±18.01	32.98±31.80	24.98±8.41	0.82	0.001	0.33
Postoperative (6 h)	36.08±16.04	35.75±19.34	35.71±14.75			
Postoperative (12 h)	36.95±16.69	37.17±16.06	37.40±15.06			

DISCUSSION

In the present trial, we assessed the impact of adenosine injection in the cardioplegic solution on the incidence of cardiac arrhythmias and cardiac output among patients undergoing CABG. Atrial fibrillation is the most common postoperative complication. Our results chime with those reported by Malhotra et al, [22] who concluded that adenosine had no significant impact on the frequency of atrial fibrillation among patients undergoing CABG. Nonetheless, in contrast to our findings, Jakobson et al [23] reported that adenosine could decrease the frequency of atrial fibrillation among CABG patients. Adenosine exerted no significant effect on the mechanical ventilation time of our patients, in concordance with studies by Ghasemi et al, [21] Idris et al, [19] Jakobson et al, [23] and Malhotra et al. [22] Ejection fraction was similar between our 3 study groups and had a significant difference between the 3 measurement times, in line with investigations by Abdalwahab et al, [1] Ghasemi et al, [21] and Shalaby et al. [20]

The first cardiac rhythm in patients who received adenosine had a significantly sooner return than in other patients. Accordingly, we suggest that adenosine exerts a positive impact on cardiac rhythm resumption among patients undergoing CABG. Some investigators, such as Idris et al [19] and Jakobson et al, [23] have reported similar findings and confirmed our hypotheses. Ghasemi et al [21] reported that adenosine increased the resumption time of cardiac rhythm, which contradicts our findings. Although the number of patients who returned to their sinus rhythm was higher in the pre-clamping group, the frequency of cardiac arrhythmias had no significant differences between the study groups. In line with our findings, the frequency of different arrhythmias in a study by Ghasemi et al [21] was similar between the adenosine and control groups. We hypothesize that adenosine may not have significant effects on the frequency of arrhythmias among patients undergoing CABG. Inotropic drug usage was similar between our 3 study groups. Our findings are in accord with studies by Abdelwahab et al, [1] Ghasemi et al, [21] Malhotra et al, [22] and Jakobson et al. [23]

Idris et al [19] reported that using adenosine could significantly decrease inotropic agent usage. In our study, the lactate level only in different measurement times had significant differences and was similar between the study groups. Similarly, adding adenosine to antegrade and retrograde adenosine cardioplegia had no impact on myocardial oxygen metabolism and lactate production in a prior investigation. [24] Ghasemi et al [21] reported that adenosine had no protective impact on the myocardium, and the lactate level was similar between patients with and without adenosine cardioplegia.

We measured the level of cardiac enzymes to assess the impact of adding adenosine to the cardioplegic solution. The CK-Mb level in different measurement times and groups was similar between the study participants. Nevertheless, whereas the troponin level was similar between the study groups, troponin had a significantly lower level in the pre-

clamping group than in the other groups. Abdelwahab et al [1] found different results and reported that the troponin level only in the adenosine group was significantly higher than the baseline level and remained at that level until 3 days after CABG. The troponin level in the adenosine group was significantly lower than that in the control group in all the measurement times. In line with our findings, Ghasemi et al [21] found that the troponin I level was similar between the adenosine and control groups. Jakobsen et al [23] reported that the release of endothelial activation markers (troponin T and CK-MB) had no significant differences between the adenosine and control groups. Investigators in the Malhotra study [22] reported that troponin I and CK-MB levels were nonsignificantly lower in the adenosine group than in the St Thomas cardioplegia group. Patients who received adenosine in an investigation by Shalaby et al [20] had a nonsignificantly lower CK-MB level than the control group. In contrast to our findings, some investigators have concluded that adding adenosine to cold cardioplegia fails to improve myocardial protection among patients undergoing aortic valve surgery. [24] In a prior study, patients who received adenosine before cold cardioplegia with potassium had a significantly lower troponin level than other patients. [19] Our findings and similar studies confirm this theory that adenosine could confer myocardial protection impacts and might not increase the release of cardiac enzymes, including CK-MB and troponin. Adenosine in our study shortened the time of cardiac arrest in patients undergoing CABG. Thus, we think that low adenosine may decrease cellular injury in myocardial tissue by reducing the cardiac arrest time in patients undergoing CABG. Ghasemi et al, [21] Jakobson et al, [23] and Idris et al [19] showed that cardiac arrest induction in the adenosine group was significantly lower than that in the control group and confirmed the potential of adenosine for enhancing cardioplegic arrest.

CONCLUSIONS

We concluded that adenosine had a significant impact on rapid cardiac arrest induction, coronary artery vasodilation, and myocardial injury prevention without adversely impacting the frequency of cardiac arrhythmias.

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