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Original Article

Cardioprotection with Adenosine during Coronary Revascularization

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Key Words : *Cardio protection, Adenosine, Cardioplegia, CABG.*

Abstract:

Background: *Postoperative cardiac dysfunction is a common cause of mortality and morbidity associated with CABG Surgery. Adenosine enhances tolerance of the myocardium to ischemic arrest. Therefore, the study on adenosine pre-treatment as an adjunct to cardioplegia in patients undergoing CABG will definitely help to provide better myocardial protection for better postoperative outcome.*

Methods: *Quasi experimental study was done in the Department of Cardiac Surgery, NICVD during July 2012 to June 2014 with patients who underwent conventional CABG surgery. Patients were divided in two groups. Group A: Patients received at regular institutional high-potassium ([K+] = 20 mol/ l) cold (12 °C) blood cardioplegia. and Group B: Patients received 250 µg /kg bolus dose of adenosine pre-treatment, which was immediately followed by high-potassium cold (12 °C) blood cardioplegia after clamp-on. Patients were followed up to evaluate the degree of myocardial damage by measuring perioperative Troponin I, amount of inotropic support, time of assisted ventilation, arrhythmia and mortality.*

Results: *Most of the patients in each group belongs to 51-60 years of age range. There was no difference regarding operative parameters in two groups. Time to arrest was significantly shorter in group B compared to group A, indicating that adenosine has the potential to enhance the efficacy of cardioplegic arrest. Plasma level markers of myocardial damage: cardiac Troponin I (cTnI) obtained from serial venous blood samples post-operatively were significantly lower in group B than group A ($p<0.05$). There was significantly decreased requirement of inotrope in group B during first 24 hrs ($p <0.05$).*

Conclusion: *Decreased level of cardiac enzymes and lower inotropic requirement suggests that an optimal myocardial protection with less cellular damage is obtained with adenosine pre-treatment as adjunct to cold blood cardioplegia.*

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Introduction:

Coronary artery bypass graft (CABG) surgery remains the preferred strategy for coronary revascularization.[1] Myocardial protection strategies play a pivotal role to protect the heart from the acute global ischemic injury, which is accomplished with the use of hyperkalaemic and hypothermic cardiac arrest and induced by cross-clamping the aorta to temporarily isolate the heart from the systemic circulation. Myocardial protection strategies are also required to protect against the subsequent acute global myocardial reperfusion injury induced by unclamping the aorta when restoring circulation to the heart.[2] Despite the modern cardioprotective techniques of cardiopulmonary bypass (CPB) postoperative cardiac dysfunction is a common cause of mortality and morbidity associated with CABG surgery. In-

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hospital/30-day mortality rates are around 1% for CABG.[3] About 10% of CABG surgery patients will have significant left ventricular dysfunction lasting several hours, days, or weeks. These patients are also more susceptible to the complications of surgery such as low cardiac output in 3-14 % of patients,[4] renal dysfunction in 4–40 % of patients, transient cognitive dysfunction or delirium in 10–40 % of adult patients, and stroke in 2–13 % patients.[5]

The underlying reason for the impaired cardiac function following CPB and cardioplegic arrest may be due to continued myocardial fibrillation after aortic cross-clamping that results in rapid exhaustion of myocardial ATP stores leading to anaerobic metabolism, acidosis, myocardial ischemia, oedema, and myocardial dysfunction and ultimately to ischemic cell death. However, significant portion of the damage occurs also during the reperfusion period. This has been termed as "ischemic-reperfusion injury" (IRI), and is probably responsible for the prolonged cardiac dysfunction or "myocardial stunning" after the termination of CPB,[6] which manifest postoperatively as depressed myocardial performances (e.g., low cardiac output), requiring inotropic or mechanical support to maintain acceptable hemodynamics.[7]

The cardioprotective agent to be considered along the development of new cardioplegic solutions is the nucleoside adenosine. Adenosine or adenine riboside is an endogenous nucleoside. Bolus administration of adenosine produces negative chronotropic and dromotropic effects by activation of potassium channels and by inducing hyper polarization, which ultimately inhibits myocardial contractility and also enhances tolerance of the myocardium to ischemic arrest.[2,8,9] While several mechanisms have been implicated, the cardioprotective effect appears to be mediated, in part, by activation of the adenosine A1 receptor coupled to the inhibitory guanosine (Gi) proteins,[10] which slow the sinoatrial nodal pacemaker rate, delay atrioventricular nodal impulse conduction and reduce atrial contractility, all of these contribute to rapid arrest of the heart.[11]

Activation of the A2a and A3 receptors have been found to be associated with attenuation of endothelial activation and neutrophil activation and adherence.It also decreases oxygen-derived free radical production by neutrophils, an effect that could minimize the free-radical–induced damage believed to occur during reperfusion.[12] Further evidences have shown that adenosine could reduce cardiac TNF-± production and it may inhibit the release of the pro inflammatory cytokines (IL-6 and IL-8) involved in the response to ischemia and reperfusion. Adenosine also has a direct metabolic effect (i.e., it enhances the myocardial phosphorylation potential) and thereby improves myocardial energetics in the stunned heart.[13]

Adenosine also ameliorate reperfusion injury because of decreased calcium influx during ischemia and provide better distribution of cardioplegic solution by coronary vasodilatation, resulting in an increased coronary artery blood flow, which may be beneficial not only for increasing oxygen and substrate delivery but also for enhancing the washout of toxic products of ischemia. Thus, adenosine alters fundamental processes that occur in the myocyte before, during, and after ischemia such that post ischemic damage is significantly attenuated.[3] In several experimental studies, aadenosine has been used for pre-treatment of human myocardium in CABG surgery in which aadenosine-treated patients were found to have reduced time of arrest and better myocardial protection in the perioperative period.[3,14,15]

Study Methods:

It is a Quasi-experimental study was done in the Department of Cardiac Surgery, National Institute of Cardiovascular Diseases (NICVD), Dhaka, from July 2012 to June 2014. Purposive sampling were done and the patients having coronary artery disease and recieving conventional CABG as inclusion criteria selected and exclusion criteria were Off-pump CABG, patients with left main disease, ejection fraction <30%, recent MI (<2 months), requiring inotropes or IABP preoperatively, emergency and re-do CABG, any other surgery performed simultaneously with CABG, contraindications of Adenosine (Bronchial asthma/ chronic obstructive airway disease.2nd and 3rd degree heart block and sick sinus syndrome.Patients having known prior history of hypersensitivity to Adenosine).

25 patients were in **G**roup **A:** Patients who receiveded regular institutional high-potassium ([K+] = 20 mol/ l) cold (12 °C) blood cardioplegia. 25 patients were in **G**roup B**:** Patients who received 250 μg/ kg bolus dose of adenosine pre-treatment, which was immediately followed by high-potassium cold (12 °C) blood cardioplegia after clamp-on. Regarding variables – other than demographic variables preoperative variables were Diabetes mellitus, Hypertension, LV ejection fraction, CAG finding; peroperative variables were time required to achieve cardiac arrest (Seconds), number of grafts, Extracorporeal circulation time (ECCT) in minutes, Aortic cross-clamp time (XCT) in minutes, cardiac injury markers (Troponin I) which was measured during induction, 10 minutes after declamping of aortic crossclamp, 12 hrs postoperatively, 24 hrs postoperatively. Post-operative variables were Mechanical ventilation time (In hours), post-operative inotropes requirement, post-operative aarrhythmia, duration of ICU stay (In hours) and in- hospital mortality. Regaring eithical issue Ethical clearance for the study was taken from the Ethical Committee of NICVD. Data was processed using software SPSS-17.0 Inc (Statistical Package for Social Sciences). The test statistics used to analyse the data are Chi-square (c^2) test and Student's t test for all analytical tests, the level of significance was set at 0.05 and a p value of < 0.05 was considered significant.

Results:

In both group maximum numbers of patients belong to 51-60 years 40% and 36% respectively. Mean (± SD) age was found 55.64 ±8.036 years in group A and 55.72±8.961 years in group B. The mean age difference between two groups were not statistically significant (p>0.05). Male predominance was seen in the study subjects. Out of 50 patients, in group A 21 (84%) were male and 4(16%) were female. In group B, 20 (80%) were male and 5(20%) were female. Male – female ratio was 4.5:1. No significant difference was found between two groups (p>0.05). The mean (± SD) height (cm) and weight (kg) were identical in the both groups: 164.72±4.306 vs. 162.52±5.221 (p=0.111) and 66.76±6.313 vs. 66.64±7.571 (p=0.951). Regarding height and weight no significant difference was not found between two groups.

Comparison of risk factors between two groups which demonstrates that hypertension and diabetic history of patients were not statistically significant; p=0.529 and 0.529 respectively. comparison of preoperative investigations between study populations which demonstrates mean (± SD) ejection fraction was 55.92±4.490 in group A and 56.28±5.877 in group B. The mean ejection fraction difference between two groups was not statistically significant (p>0.05). Coronary angiogram (CAG) finding between group A and group B were also almost identical. Difference between two groups were not statistically significant (p=0.552). Comparison of preoperative variables which reveals, mean (± SD) time required to achieve cardiac arrest in group B (11.92±3.546) sec. was less than group A (28.64±4.79) sec. and statistically result was significant (p<0.001). The mean (± SD)

Table-I

Patient's characteristics (N=50).

Preoperative parameters	Group A (n=25) Mean ± SD	Group B (n=25) Mean ± SD	p-value
Age(yrs)	55.64 ±8.036	55.72±8.961	0.974^{ns}
Male	21 (84)	20 (80)	0.713 ^{ns}
Female	4 (16)	5 (20)	
Ht (cm)	164.72±4.306	162.52±5.221	0.111 ^{ns}
Wt (Kg)	66.76±6.313	66.64±7.571	0.951 ^{ns}
Echocardiography : EF (Mean ± SD)	55.92±4.490	56.28±5.877	0. 809 ^{ns}
CAG (%)	0.552 ^{ns}		
1	0 (0)	0 (0)	0.552 ^{ns}
2	1(4)	2 (8)	
3	24 (96)	23 (92)	

XCT and ECCT time between two groups are almost identical: 119.04±12.670 min vs. 115.96±20.134 min and 158.40±16.90min vs. 150.04±19.542, respectively. However, difference of XCT and ECCT time between two groups were not statistically significant (p=0.520 and p=0.112, respectively). Data were analysed using student's t-test. (n=number of patients, S= Significant, NS=Not significant). Comparison of no. of grafts between study populations which demonstrates mean (± SD) no. of grafts was 2.96 ± 0.200 in group A and 2.92 ± 0.277 in group B. The difference between two groups was not statistically significant (p-value=0.561).

Measurement of cardiac injury markers (Troponin I) Table I shows comparison of Troponin I values between group A and group B which reveals, during induction Troponin I level were similar: 0.6937±0.755 ng/ml vs. 0.5389±0.6956 ng/ml, respectively. The difference was not statistically significant (p=0.455). At 10 min after declamping of cross clamp and 12 hours post-operative period Troponin I levels between two groups were: 4.004±1.989 ng/ml vs. 2.576±1.602 ng/ml and 37.219±39.084 ng/ml vs. 14.751±6.7960 ng/ml, respectively. In both periods, the differences were statistically significant, p=0.007 and p=0.007, respectively. At 24 hours post-operative period Troponin I level were: 13.74± 9.22 ng/ml vs. 9.02±4.38 ng/ml, respectively and the difference was not statistically significant (p=0.251).

Table-II

Comparison of Troponin-I level between two groups of study population (N=50).

Parameters (Troponin I) (ng/ml)	Group A (n=25) Mean ± SD	Group B (n=25) Mean ± SD	p-value
During induction	0.6937 ± 0.755	0.5389 ± 0.6956	0.455 ns
10 min after declamping	4.004 ± 1.989	2.576 ± 1.602	0.007s
12 hr. postoperative	37.219 ± 39.084	14.751 ± 6.796	0.007s
24 hr. postoperative	13.74 ± 9.22	9.02 ± 4.38	0.251 ns

Data were analysed using student's t-test. (n=number of patients, S=Significant, NS=Not significant) Inotropic support (Dose of Dopamine in 1st 24 hrs).

Table-III

Comparison of dose of Dopamine (in 1st 24 hrs) between two groups of study population (N=50).

Parameters (ng/ml)	Group A (n=25) Mean ± SD	Group B (n=25) Mean ± SD	p-value
Dose of Dopamine µgm/kg/min (in 1st 24 hrs.)	6.0419±1.61	4.7080±1.20	0.002 s

Data were analysed using student's t-test. (n=number of patients, S=Significant, NS=Not significant)

Table-IV

Comparison of postoperative variables between two groups (N=50).

Parameters (ng/ml)	Group A (n=25)	Group B (n=25) Mean ± SD	p-value Mean ± SD
Mechanical ventilation (hrs)	8.56±1.78	7.56±1.44	0.344 ns
ICU stay (hrs)	58.36±17.299	54.00±19.849	0.412 ns
In- hospital mortality (%)			
Yes	3 (12)	2 (8)	0.637 ns
No	22 (88)	23 (92)	

Table II shows that the mean (± SD) dose of Dopamine (in 1st 24 hrs) between group A and group B were 6.0419±1.61 and 4.7080±1.20, respectively. The difference between two groups was statistically significant ($p<0.05$).

Comparisons of postoperative variables which reveal mean (± SD) mechanical ventilation period (hrs) and mean (± SD) ICU stay (hrs) between group A and group B were almost identical:8.56 ± 1.78 vs. 7.56 ± 1.44 and 58.36 ± 17.299 vs. 54.00 ± 19.849, respectively. The difference of mean (± SD) mechanical ventilation (hrs) and mean (± SD) ICU stay (hrs) between two groups were not statistically significant ($p=0.344$ and $p=0.412$, respectively). Comparison of postoperative arrhythmia between study populations which reveals; incidence of arrhythmia between group A and group B was almost identical. Difference between two groups were not statistically significant ($p=0.221$). in-hospital mortality between two groups were almost identical. Difference between two groups were not statistically significant ($p=0.637$).

Discussion:

The present study was conducted at NICVD from July 2012 to June 2014.They were grouped according to adenosine pre-treatment. Group A received regular institutional high-potassium ([K+] = 20 mol/ l) cold (12 °C) blood cardioplegia and group B received 250 µg/ kg bolus dose of adenosine pre-treatment which was immediately followed by antegrade high-potassium cold (12°C) blood cardioplegia after clamp-on. The preoperative preparation, technique of operation and postoperative care followed standard protocol in both groups. No significant difference was not found between two groups with respect to age, height, weight and sex.

Risk factors comparison showed that 76% of patients in group A had hypertension and 32% had diabetes mellitus compared to 68% had hypertension and 24% had diabetes in group B. No significant difference was not found between two groups. In this study, comparison of preoperative investigations between study population demonstrates mean (± SD) ejection fraction % was in group A 55.92 ± 4.490 and 56.28 ± 5.877 in group B. The mean ejection fraction difference between two groups were not statistically significant. Comparison of preoperative Coronary angiogram between two groups revealed, most of patients have triple vessels disease(TVD),i.e.96% patients in group A have TVD and 92% patients in group B have TVD. Only 12% of patients in group A and 8% of patients in group B have double vessels disease (DVD). No patients with single vessel disease were operated. Another study, done by Mahbub 2006 in NICVD, also showed that about 76-80% patients had triple vessels disease and 20% had double vessel disease, which is similar to our study.[15,16]

Mean (± SD) time required to achieve cardiac arrest in group B (11.92±3.546) sec. was less than group A (28.64±4.79) sec. and statistically result was significant. In the study, conducted by Ruifang et al. time of arrest was significantly shorter in group B compared with that in group A.[3] Another prospective, controlled study comparing the effect of adenosine on myocardial protection with cold blood cardioplegia during CABG by Chauhan *et al*. also showed, time taken to achieve cardiac standstill after aortic cross-clamping was significantly greater, 18.7 ± 3.1 seconds in the control group compared with the adenosine group, 3.4 ± 0.9 seconds. Results of both the studies were consistent to our study.[3,16] This demonstrated that, adenosine as an adjunct to blood cardioplegia has the potential to enhance the efficacy of cardioplegic arrest. The mean (± SD) XCT and ECCT time between two groups were almost identical. This was different to study done on cardio-protective effect of adenosine pre-treatment in CABG by Wei *et al*. which compared CPB time (107.6 ± 21.9 min. in control group and 109.9 ± 24.5 min. in adenosine group) and ischemic time (89.6 ± 19.1 min. in control group and 90.4 ± 19.7 min. in adenosine group) between two groups. Variations of XCT and ECCT time may be due to differences of experiences and expertise of operating surgeon, surgical techniques, experiences and expertise of perfusionist and other auxiliary support. Comparison of number of grafts showed, there was no significant difference of no. of grafts between groups. In the study, done by Lee *et al*., also showed that there was no significant difference of no. of grafts between two groups, which was similar to our study.[14]

We studied cardiac enzyme Troponin I level between two groups during induction, 10 minutes

after declamping of aortic cross clamp, 12 hrs postoperative and 24 hrs postoperatively. Comparison of Troponin I (cTnI) values between group A and group B reveals, during induction Troponin I level were almost identical. But it was significantly different at 10 min after declamping of cross clamp and 12 hours post-operative period. At 24 hours post-operative period Troponin I level were: 13.74 ± 9.22 ng/ml vs. 9.02 ± 4.38 ng/ml, respectively and the difference was not statistically significant. In the study, conducted by Ruifang et al., revealed before induction, cTnI in both groups were baseline. After CPB, the levels of cTnI and CK-MB in both groups increased indicating myocardial injury.[3] Other studies on the effect of adenosine on myocardial protection by Wei *et al.* and Chauhan *et al.* also showed decreased level of cardiac enzymes in adenosine group, which was similar to our study.[16] Early cardiac standstill in the patients given adenosine before cardioplegia probably helped to conserve myocardial substrate. This, in turn, helped to maintain cellular integrity compared with the control group, in which the heart continued to fibrillate on cross-clamp, using up metabolic substrate and worsening myocardial ischemia.

The difference between two groups regarding inotropic support was statistically significant. This was consistent with the study by Chauhan *et al.*[15] In our study, in neither group Dopamine, greater than 10μg/kg/min was required probably may be due to exclusion of left main disease and severe left ventricular dysfunction from our study population. But decreased requirement of dopamine in a group without adenosine pre-treatment was similar to previous study. This suggests rapid electromechanical arrest with adenosine reduces the rate of prolonged cardiac dysfunction or "myocardial stunning" after the termination of CPB, thus decreasing requirement of inotropic support to maintain acceptable hemodynamics. Assessments of postoperative variables reveal mean mechanical ventilation (hrs) and mean (± SD) ICU stay (hrs) between groups were similar. A prospective study, reported by Chauhan *et al.*, comparing the effect of adenosine on myocardial protection with cold blood cardioplegia during CABG, showed similar result with that of our present study.[16] Incidence of arrhythmia between group A and group B was almost identical. 20% patients in group A and 8% patients in group B had postoperative arrhythmia. Difference between two groups were not statistically significant. But in the study, conducted by Chauhan *et al.* showed postoperatively sinus tachycardia was present in both groups.[17] According to Peretto *et al.* atrial fibrillation has been reported in up to 15 to 40% of patients in the early postoperative period after CABG, which was similar to our study.[18] In-hospital mortality between two groups was almost identical. This variable was not included in previous studies. But in the study, done by Mahbub 2006 in NICVD, also showed, there was 8% mortality even in patients with more than 40% ejection fraction after conventional CABG, which was compatible to our study.[16]

Conclusion:

The study has demonstrated that adenosine has the potential to enhance the efficacy of cardioplegic arrest. Decreased level of cardiac enzymes and lower inotropic requirement suggests that myocardial protection with less cellular damage is obtained with adenosine pre-treatment as adjunct to cold blood cardioplegia. However, it appears advantageous and at this moment, it may be recommended as adjunct to cold blood cardioplegia for better myocardial protection during conventional CABG.

Conflict of Interest - None.

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