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Original Research Article

Comparison of troponin 1 level among the patients who underwent coronary artery bypass grafting with and without adenosine as an adjunct to blood cardioplegia

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ABSTRACT

Background: Cellular injury is not avoidable with current cardioplegic solutions. No method of cardioplegia has been shown to completely protect the myocardium against cellular injury. The objective of the study is to evaluate the safety and efficacy of adenosine as an adjunct to blood cardioplegia during CABG.
Methods: A retrospective study at GMCT, Thiruvananthapuram in CABG patients for 3 years from January 1, 2016, to December 31, 2019, between the age of 40 and 70 years. Patients with other chronic diseases and pre-operative echo showing EF less than 40% were excluded. The study variables were level of troponin I intra and postoperative period, time taken for cardiac standstill, number of days in ventilator, ICU and on inotropic supports. Also, postoperative lactate levels, changes in RWMA and EF.
Results: Of the total 75 subjects, 40 got adenosine while 35 didn't. The mean post op EF for those who got adenosine is 55.30 and without is 56.46. The mean time of cardiac stand still with adenosine is 12.88 sec and without is 16.51 sec. The mean post op troponin I level in those who got adenosine is 6.43 and without is 12.94.
Conclusions: Decreased level of troponin I and inotropic requirement suggests that an optimal myocardial protection. Adenosine usage helps in early extubation but doesn't alter the number of days in ICU. Adenosine is safe, gives more rapid cardiac arrest but it will not alter the post op left ventricular function.

Keywords: Coronary artery bypass graft, Cardioplegia, Ejection fraction

INTRODUCTION

Re perfusion injury and myocardial ischemia after cardiac surgery is frequently noted and cause increased morbidity and mortality. After cardiopulmonary bypass procedure, the key issue in myocardial dysfunction is myocardial protection. Although new methods and strategies of myocardial protection have been developed and adopted in clinical work, the optimal method of myocardial protection is still uncertain. Our current study is to evaluate the role of adenosine in furthering the myocardial protection effects of cardioplegia in coronary artery bypass grafting cases. In 1910 Alexis Carrel first described the concept of operating on the coronary circulation, he successfully performed intra thoracic aortic and cardiac anastomosis in dog.[1] The first successful CABG surgery was performed by Robert Goetz at the Albert Einstein College of Medicine-Bronx Municipal Hospital Centre in New York using Rosenak (tantalum) rings.[2] The first clinical case of a direct hand-sewn coronary anastomosis was performed by David Sabiston on April 4, 1962, when he anastomosed the saphenous vein graft (SVG) to the RCA at Johns Hopkins.[3]

The development of cardiopulmonary bypass or a machine that could temporarily take over the function of the heart and provide oxygenation of the blood (bypass the pulmonary circuit) was a major development in clinical medicine. Dr. Gibbon's developed the heart-lung machine in the 1950s. Cardiopulmonary bypass (CPB) triggers deleterious effects that may potentially cause dysfunction in almost every organ such as kidney, liver, lungs, central nervous system, and cardiovascular system.[4] Systemic inflammatory response syndrome (SIRS) is considered as the main etiologic factor causing heart damage.[5]

Reactive oxygen species, detected as radical adducts or lipid peroxides in coronary venous blood after aortic clamp release, can cause reperfusion injury and affect myocardial recovery.[6] The objective of any type of myocardial management during CPB should be limiting injury during ischemia by some combination of myocardial hypothermia, electromechanical arrest, washout, O2 and other substrate enhancement, oncotic manipulation, and buffering. Cardioplegia induces electromechanical arrest. Therefore, myocardial metabolism is reduced, and intermittent ischemia is bearable.[7] Adenosine expresses numerous pharmacologic properties that render it useful for the protection of the ischaemic myocardium.[8] Endogenous adenosine is formed predominantly in myocardial cells from the degradation of adenosine triphosphate (ATP) and its release into the interstitial space, particularly during ischemia.[9] Exogenous adenosine has been shown to improve the function, viability, and metabolism when given as cardioplegic constituent or applied during reperfusion.[10]

Objective of the study is to evaluate the safety and efficacy of adenosine as an adjunct to blood cardioplegia during CABG. It will also investigate whether the addition of adenosine in blood cardioplegia would enhance myocardial protection.

METHODS

In this retrospective study, medical records of patients who underwent CABG in the Department of Cardiovascular and Thoracic surgery, Government Medical College Hospital, Thiruvananthapuram for the last 3 years from January, 2016, to December, 2019, were included.

The inclusion criteria were patients between the ages of 40 and70 who underwent elective CABG for Triple Vessel disease in the last 3 years from January 1, 2016, to December31, 2019.Also, patients with pre-operative ejection fraction of less than 40% and those with chronic diseases other than coronary artery disease were excluded. Minimum sample size calculated was 35 in each group.

The study variables were: level of troponin I during intraoperative and post-operative period, time taken for cardiac standstill, number of days in ventilator, number of days on inotropic support, post-operative serum lactate level, post-operative ECHO showing any improvement in RWMA, post-operative improvement in ejection fraction, number of days in ICU.

The study population comprises 75 patients who underwent elective coronary artery bypass grafting (CABG) surgery 3 years from January 1, 2016, to December31, 2019. The patients will be divided into two groups based on the administration of cardioplegia with adenosine and without adenosine during surgery and postoperative changes in the two groups. Institutional ethical committee clearance was obtained, confidentiality was maintained and insured throughout the study.

Statistical analysis

Categorical and quantitative variables were expressed as frequency (percentage) and mean±SD respectively. Independent t test was used to compare quantitative parameters between categories. Chi-square test and Fisher's exact test were used to find association between categorical variables. Mann-Whitney U Test was used to compare ordinal parameters between groups. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analyses were performed by using a statistical software package Statistical package for social sciences (SPSS), version 20.0 test.

RESULTS

A total of 75 patients were included (n=75) in the study. The mean age of patients who got adenosine was 57.55±5.58 and who didn't get adenosine was 57.71±5.45.

Table 1: Study variable with and without adenosine.

		With adenosine (n=40)	Without adenosine (n=35)	P value	
Preoperative mean troponin I		0.57±0.07	0.59±0.08	Less than 0.428	NS
Post-operative mean troponin I		6.43±4.03	12.94±6.45	Less than 0.01	S
Time taken for cardiac standstill		12.88±1.38 secs	16.51±1.27 secs	Less than 0.01	S
Number of days in ventilator	1	18 (45%)	9 (25.7)	0.06	NS
	2	19(47.5%)	13 (37.1)		
	3	3 (7.5%)	13 (37.1)		
	1	18 (45%)	9 (25.7)		

Continued.

		With adenosine (n=40)	Without adenosine (n=35)	P value	
Number of days on inotropic support	2	19 (47.5)	13 (37.1)	0.06	NS
	3	3 (7.5%)	13 (37.1)		
Number of days in ICU	3	30 (75)		0.081	NS
	4	7 (17.5)			
	5	2 (5)			
	6	1 (2.5)			

S: significant; NS: nonsignificant.

Table 2: Comparison on serum lactate level.

		Adenosine				Mann-Whitney U	P value
		Positive		Negative			
		Count	Percent	Count	Percent		
Post-operative serum lactate level	4	36	90.0	14	40.0	4.4	p<0.01
	5	2	5.0	13	37.1		
	6	2	5.0	8	22.9		

Table 3: Comparison on EF in patients who got adenosine and didn't get adenosine.

	Adenosine						t	P value
	Positive			Negative				
	Mean	SD	N	Mean	SD	N		
Pre-operative EF	52.70	5.38	40	55.86	6.02	35	2.4*	0.019
Post-operative EF	55.30	5.01	40	56.46	5.26	35	0.98	0.333
Increase in EF	2.60	3.28	40	0.60	3.31	35	2.62*	0.011

Of these patients 40 (53.3%) got adenosine and 35 (46.6%) didn't get adenosine. And of those who got adenosine 25 (33.3%) males and 15 (20%) females are there while from patients who didn't receive adenosine 28 (37.3%) males and 7 (9.3%) females are there.

Table 4: Various study on post op troponin I level.

Study	Troponin I value with adenosine	Troponin I value without adenosine
Present study	6.43±4.03	12.94±6.45
Ghasemi[13]	8.41±4.84	10.16±6.48
Idris[16]	14.751±6.7960 ng/ml	37.219±39.084 ng/ml

p value of number of days in ICU regarding gender is 0.726, which is statistically insignificant. P value of significance was only for two study variables, postoperative troponin 1 levels and time taken for cardiac standstill. P value of serum lactate level is <0.01, which is statistically significant. All the patients had elevated lactate level but the range of increase in lactate level was seen in those who didn't take adenosine as compared to those who took adenosine.

Adenosine as an adjunct to cardioplegia doesn't show an improvement in EF than without adenosine.

Table 5: Various study on cardiac standstill.

Study	Cardiac standstill time with adenosine	Cardiac standstill without adenosine
Present study	12.88±1.38	16.51±1.27 sec
Kaliti[17]	9.2±4.4	66.0±25.2sec
Ghasemi[13]	11.65±3.77	25.80±23.46
Jakobsen[14]	11±5 sec	44±18 sec
Liu[15]	19.9±4.6	29.3±10.6.

Table 6: Various study on time of extubation.

Study	Time of extubation with adenosine	Time of extubation without adenosine
Jin[12]	10.9±6.4 hrs	12.6±5.5 hrs
Ghasemi[13]	504.50±157.56 min	483.00±210.99 min
Jakobsen[14]	169±90 min	186±103 min

DISCUSSION

Surgery for revascularization of the myocardium continues to be an effective and lasting means of managing patients

with multi vessel coronary artery disease. Myocardial protection has clearly made open-heart surgery a safe and reproducible technique. There continue to be many modifications of the chemical composition of the cardioplegic solution, the optimal temperature (cold or warm), and the route of infusion (ante grade or retrograde).

This is a retrospective study undertaken to compare the outcome of patients who underwent coronary bypass surgery with adenosine as an adjunct in blood cardioplegia. The study was conducted in the Dept. of Cardiovascular and thoracic surgery, Government Medical College, Trivandrum. 75 case sheets were taken and analyzed with various study variables. Our results and observations were discussed and compared with various other studies.

In this study Mean post op troponin I level in those who got adenosine is 6.43±4.03 and Mean post op troponin I level in those who didn't got adenosine is 12.94±6.45 this shows that in both groups troponin I level are increased in the post op period but the value in those patients who received adenosine is less compared to those who didn't get adenosine.

A study conducted by Idris on 50 consecutive patients undergoing CABG under cardiopulmonary bypass he found out that there is a difference between 12 hours post-operative period Troponin I levels between those who got adenosine and those who didn't got adenosine.[16] 12 hours post-operative period Troponin I levels between two groups were 37.219±39.084 ng/ml and 14.751±6.7960 ng/ml, the differences were statistically significant, p=0.007. He concluded that adenosine has a better cardio protective action and will reduce the troponin I level significantly which is a marker for myocardial injury.

A study conducted by Kaliti on 40 patients between 20 to 40 years of age who underwent mitral valve replacement under cardiopulmonary bypass for severe mitral regurgitation to evaluate the safety and beneficial effect of Bolus Injection of Adenosine at Aortic Root for Fast cardioplegic Induction in Patients with "Sick Heart" undergoing cardiac heart valve surgery, he found out that the levels of troponin I were significantly higher in the control group than in the adenosine root injection group at time points of postoperative 6 and 24 h.[17]

Rinne et al conducted study in 40 patients with Adenosine as an adjunct to cold blood cardioplegia during coronary revascularization showed there were no significantly higher serial serum values of CK (MB) (p=0.33 troponin-T (p=0.23), and troponin-1 (p=0.10) in the adenosine group.[11]

A randomized single blinded clinical trial conducted by Ghasemi on 40 consecutive patients who were candidates for mitral valve surgery.[13] The patients were randomly assigned to receive cold blood cardioplegia in combination with or without adenosine or hyperkalemic cardioplegia as the control. Troponin I after 6 hours in patient who received adenosine is 8.41±4.84 and in control group is 10.16±6.48. Troponin I value after 24 hours in patients who got adenosine is 8.41±5.44 and in control group after 24 hours 8.98±6.49. After 48 hours troponin I in adenosine group is 5.03±4.51 and in control group is 7.15±5.67. They concluded that there is no statistically significant rise in troponin I when adenosine is given as an adjunct to cardioplegia.

In this study mean time of cardiac stand still with adenosine is 12.88±1.38 sec and the mean time of cardiac stand still without adenosine is 16.51±1.27 sec. This shows that the Adenosine as an adjunct to cardioplegia has faster cardiac standstill time as compared to that without adenosine.

A study conducted by Kaliti on 40 patients showed Cardiac standstill time of 9.2±4.4 on patients who got adenosine as compared to 66.0±25.2sec, respectively on patients who didn't got adenosine ($p<0.01$).[17] They concluded that adenosine could cause a faster cardiac stand still time. A randomized single-blinded clinical trial done by Ghasemi on 40 consecutive patients who were candidates for mitral valve surgery showed Cardiac standstill in patients with adenosine is 11.65±3.77 and those without adenosine is 25.80±23.46.[13] A study conducted by Jakobsen showed Cardiac standstill time in patient who didn't have adenosine is 44±18sec and who got adenosine is 11±5 sec.[14] A study conducted by Liu showed cardiac standstill time of 19.9±4.6 on patients who got adenosine while without adenosine cardiac standstill time is 29.3±10.6.[15]

In this study 24% of patients who got adenosine were on ventilator for first 24 hours while 12% of patients who didn't get adenosine were on ventilator for first 24 hours. Furthermore 25% of patients who got adenosine were on ventilator for initial 48 hours while 17.3% of patients who didn't get adenosine were on ventilator for initial 48 hours. 4% patients who got adenosine were on ventilator for initial 72 hours and 17.3% patients who didn't get adenosine were on ventilator for initial 72 hours. This shows that Patient who got adenosine has increased chance of extubating within first 24 hours compared to those who didn't get adenosine. Number of days on ventilator will be reduced in those patients who got adenosine when comparing with those who didn't get adenosine.

The study conducted by Jin showed patient who didn't get adenosine was extubated after 12.6±5.5 hours post-operative period while those who got adenosine was extubated 10.9±6.4 hours.[12] A study conducted by Ghasemi intubation time in adenosine is 504.50±157.56 minutes as compared to those who didn't got adenosine is 483.00±210.99, he concluded that there is no difference in mean intubation time when adenosine is given as an adjunct to blood cardioplegia.[13] A study conducted by Jakobsen showed extubation time in patient who didn't get adenosine was 186±103 min and who got adenosine was 169±90 min.[14]

In patients who got adenosine 30 patients were shifted to ward on 3rd post-operative day,7 patients on 4th post-operative day, 2 in 5th postoperative day and 1 in 6th post-operative day. While in patients who didn't get adenosine 20 patients were shifted to ward on 3rd post-operative day,8 patients on 4th post-operative day, 5 in 5th postoperative day and 2 in 6th post-operative day. This shows that Patients who got adenosine P value is 0.081 which is statistically insignificant. Hence there is no difference in ICU stay when patients were given adenosine as compared to those who didn't get adenosine.

A study conducted by Kalita showed that the ICU stay was significantly shorter in adenosine pre-treatment group compared to the control group.[17] Patient was shifted to ward on 3.2±1.2 days on patient who got adenosine as compared to patient who didn't got adenosine which is 3.9±1.2 days (p=0.013). A study conducted by Jin showed that Patient was shifted to ward on 3.1±0.9 days on patient who got adenosine as compared to patient who didn't got adenosine which is 4.4±3.1 days.[12] A study conducted by Fahimeh Ghasemi13 showed that patient was shifted to ward on 2.25±0.85 days on patient who got adenosine as compared to patient who didn't got adenosine which is 2.55±0.60 days concluding that there were no differences in length of ICU stay.

In our study mean increase in EF for those who got adenosine is 2.60±2.08 and mean increase in EF for those who didn't got adenosine is 0.60±3.31. This result shows that with adenosine there will not be an increase in ejection fraction in post-operative period as compared without adenosine. A study conducted by Ghasemi showed that in those patients who got adenosine post-operative EF is 49.75±5.95 as compared to those without adenosine is 48.50±9.04, hence concluded that there is no difference in left ventricular systolic function.[13]

In our study patients who got adenosine the level of serum lactate was 4 in 36 patients serum lactate was 5 for 2 patients, serum lactate was 6 in 2 patients. While in patients who didn't have adenosine the level of serum lactate was 4 in 14 patients serum lactate was 5 for 13 patients, serum lactate was 6 in 8 patients.

A study conducted by Rinne showed that there are no differences in post-operative lactate value between those who got adenosine as compared to those who didn't have adenosine.[11] A study conducted by Ahlsson showed that there is no significant effect on lactate value in post-operative period when comparing with patient who got adenosine with those who didn't got adenosine.[4] A study conducted by Ghasemi showed Serum lactate is patient who got adenosine is 1.23±0.67 as compared to those who didn't got adenosine which is 1.12±0.56, they concluded that there was no difference between lactate values in those who got adenosine as compared to those who didn't got adenosine.[13]

In our study number of patients who was on single inotropic support was 18 who took adenosine while 9 number of patients who didn't got adenosine was on Single inotropic support. Number of patients on dual inotropic support was 19 in those who got adenosine while number of patients who was on dual inotropic support was 13 who didn't have adenosine. Number of patients who required triple inotropic support was 3 in those who got adenosine while number of patients who required triple inotropic support was 13 in those who didn't got adenosine. This shows that usage of inotropes is reduced in patients who took adenosine as compared to those who didn't take.

A study conducted by Jin showed that the inotrope scores in the intensive care unit (ICU) were much lower ($p<0.01$) as comparing with those who got adenosine and those who didn't got adenosine.[12] A study conducted by Ghasemi showed there is no difference between usage of inotropic support when comparing with those who took adenosine and those who didn't took adenosine.[13] A study conducted by Idris showed that there is less usage of inotropes in patients who adenosine as compared to those who didn't took adenosine.[16] A study conducted by Mentzer showed outcome analysis demonstrated that patients who received high-dose adenosine were less likely to experience high inotropic support.

Limitations in our study is unpredictability of the amount of adenosine to heart due the obstructive coronary lesions in coronary artery disease. Further studies are needed.

CONCLUSION

Decreased level of cardiac enzymes and lower inotropic requirement suggests that an optimal myocardial protection with less cellular damage is obtained with adenosine pretreatment as adjunct to cold blood cardioplegia. Adenosine usage will help in early extubation but doesn't alter the number of days in ICU. Adenosine is safe, gives more rapid cardiac arrest but it will not alter the post op left ventricular function.

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