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STUDY OF EFFECTS OF POSTCONDITIONING THE HUMAN HEART WITH ADENOSINE IN HEART VALVE REPLACEMENT SURGERY

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ABSTRACT

The role of adenosine pretreatment in animal has been proven but its role in human has been controversial. We performed prospective randomised study to find out adenosine post conditioning usefulness in human. Twenty patients having rheumatic heart disease with severe mitral valve stenosis formed the study group. The adenosine group (n =10) received adenosine infusion (200 microgram/kg) after aortic cross clamp removal. The control group (n = 10) received only normal saline injection. Intraoperative and postoperative patient parameters compared. The adenosine group associated with less troponin I release, less inotropic use, shorter ICU stay and was well tolerated as a post conditioning adjunct to high potassium cold blood myocardial protection. Spontaneous rhythm recovery was more in adenosine group. Electrical defibrillation was required frequently in control group. Adenosine postconditioning appears to protect against reperfusion injury in human hearts and thus result in improved postoperative hemodynamics with less hospital stay.

Keywords: Heart Valve Replacement Surgery

Abbreviations

CPB-cardiopulmonary bypass

ICU-intensive care unit

SD -standard deviation

INTRODUCTION

The effect of post conditioning on myocardial protection in cardiac surgery remains uncertain. Adenosine can be used as an adjunct to predominantly used cold blood cardioplegic myocardial protection method in the setting of heart valve replacement operations. Current approaches to cardiac operations have aided by the two major developments of mechanical circulatory support and myocardial protection. Myocardial protection refers to all strategies that increase the heart's ability to withstand an ischemic insult, which together with reperfusion injuries are principally responsible for cardiac failure, morbidity and mortality after cardiac operations. The current strategy for myocardial protection during cardiac procedures is based on two methods of hypothermia and cardioplegia arrest. Cardioplegia protects the myocardium by providing continuous or intermittent oxygen while simultaneously reducing cardiomyocyte oxygen demand through both hypothermia and cardiac arrest, but is incapable in augmenting the tolerance of cardiomyocytes for ischemic reperfusion injury. Our study consist of administration of adenosine through an arterial catheter immediately after the aortic cross clamp removal was associated with less troponin I release, less inotropic use, shorter ICU stay and was well tolerated as a post conditioning adjunct to high potassium cold blood myocardial protection.

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Aims and Objectives

- 1} To study the effects of post conditioning with adenosine in Heart Valve Replacement surgery.
- 2} To study the release of Troponin I after adenosine postconditioning and in control patients with their comparison.
- 3} To compare the ICU stay, inotropic scores, post operative hospital stay, CPB time, aortic cross clamp time, total volume of cardioplegia, urine volume during first 24 hours after surgery, type of rhythm recovery [spontaneous or electrical defibrillation] and total hours of mechanical ventilation in post conditioned and control patients.

MATERIALS AND METHODS

Methodology

Study Design- This is a prospective study, this study will comprise of total 20 patients of all those who will undergo heart valve replacement over a period from December 2007 onwards for five years.

Inclusion Criteria- Patients [Men and Women] in age group 25 to 40 years diagnosed as RHD with severe mitral stenosis undergoing mechanical heart valve replacement surgery with intermittent horizontal mattress technic using ethibond 25 number needle plegetted suture.

Exclusion Criteria –Patients with co morbid heart disease, hypertension, diabetes mellitus or congenital heart disease or patients undergoing reoperation.

Study Procedure

All patients who meet the inclusion criteria will be enrolled in the study and studied prospectively. Twenty patients with rheumatic heart valve disease undergoing heart valve replacement operations will be randomized to two groups, first group will be given adenosine (200 micro gram /kg) bolus injection and second group will receive normal saline (0.9 %) bolus injection through an arterial catheter immediately after the removal of aortic cross clamp. Patients will be monitored for following characters.

1. The preoperative, intra operative and post operative data of patients will be collected prospectively.
 2. The preoperative data will include age, sex, body mass index, ventricular ejection fraction and occurrence of chronic atrial fibrillation.
 3. The intraoperative data will include valve replacement operation time, CPB time, aorta cross clamp time, total volume of cardioplegia, frequency of cardioplegia delivery and type of rhythm recovery [spontaneous or electrical defibrillation]
 4. The lowest mean arterial pressure and its duration after aortic cross clamp removal.
 5. Postoperative data include the hours of mechanical ventilation in ICU, urine volume over first 24 hours postoperatively, ICU stay, inotrope scores and total hospital stay.
- The data will be collected and analysed.

Statistical Analysis

The continuous and interval related variables are expressed as the mean $\pm$ SD and the catagorial variables were expressed as percentages.

RESULTS AND DISCUSSION

Results

Operative variable were comparable in both groups. No mortality was observed nor was there any intraoperative or post-operative complication in either group. There was no prebypass difference in any

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parameter (Table 1) between the two groups. The summarized intraoperative and postoperative parameters are shown in table 2 and table 3.

Table 1: Comparison of preoperative parameters between control and adenosine group

Parameters	Adenosine group (n=10)	Control group (n=10)	P value
Age (years)	25+-15	25 +-15	NS
Sex (M/F)	9/1	8/2	NS
Body mass index (kg/m ²)	25+-5	25+-5	NS
Ventricular ejection fraction	50+-10	50+-10	NS
Chronic atrial fibrillation	7/3	8/2	NS

NS-not significant

Table 2: Comparison of operative parameters between control and adenosine group

Variables	Adenosine group (n=10)	Control group (n=10)	P value
Operation time (min)	180+-10	178+-15	NS
CPB time (min)	72+-12	74+-10	NS
Aortic cross clamp time(min)	42.4+-7.6	43.2+-6.8	NS
Total volume of cardioplegia (ML)	1200+-500	1000+-700	NS
Frequency (number) of cardioplegia delivery	2+-1	2+-1	NS
Lowest MAP	95+-5	85+-5	<0.05
Type of Spontaneous rhythm	9	4	<0.05
recovery Electrical defibrillation	1	6	<0.05

CPB- cardiopulmonary bypass, NS - not significant, MAP - mean arterial pressure

Table 3: Comparison in postoperative parameters between control and adenosine group

Parameters	Adenosine group (n=10)	Control group (n=10)	P value
Troponin I (ng /ml)	10+-5	15+-10	<0.05
ICU mechanical ventilation (hours)	4+-2	6+-2	<0.05
Urine volume in first 24 hours (liters)	4+-1	4+-1	NS
ICU stay(days)	2+-1	4+-1	<0.05
Inotrope score	30+-20	50+-20	<0.05
Total hospital stay (days)	7+-2	10+-2	<0.05

ICU - intensive care unit, NS –not significant

In control group there was no significant change in aortic cross clamp time, CPB time, operation time, number as well as volume of cardioplegia but lowest mean arterial pressure was less as compared to

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adenosine group. Spontaneous rhythm recovery was more in adenosine group. Electrical defibrillation was required frequently in control group. The average troponin I level rise was less in adenosine group as compared to control group indicating that myocardial trauma was less in adenosine group.

All though the urine volume in first 24 hours was same in control and adenosine group but the mechanical ventilation duration, inotropic score, ICU stay and overall hospital stay was less in adenosine group as compared to control group.

Discussion

The term ischemic preconditioning was coined by Murry *et al.*, in 1986. Prior ischemic exposure made the myocardium more tolerant to subsequent prolonged ischemic episodes. Preconditioning has been reported in various animal studies.

There is now evidence indicating that the human heart can be preconditioned. Adenosine has been thought to be responsible for preconditioning.

Preconditioning has been seen to be beneficial by reducing the infarct size and preventing arrhythmias. It has also been shown to reduce myocardial acidosis and protect against post ischemic contractile dysfunction. Thus the preceding period of ischaemia prepared the myocardium and made it more adaptable for subsequent ischaemic episodes. Similarly it has been observed by Kloner *et al.*, in a retrospective analysis that patient who experienced angina 48 hr before infarction had smaller infarct and a more favourable outcome compared to patients who did not have angina before myocardial infarction. Therefore the hypothesis that the transient episode of ischaemia releases adenosine which then mediates the protective effect against ischaemic reperfusion injury is attractive.

Ischaemia results in a net depletion of ATP in the myocardial cells. There is delay in the de novo nucleotide synthesis resulting in low levels of adenosine, inosine and hypoxanthine because of their rapid washout from the tissue on reperfusion. Experimental studies in animals Isselhard *et al.*, has shown that adenosine reduce ATP degradation during ischaemia and it enhances post ischaemic ventricular function in crystalloid perfused and blood perfused hearts.

The cardioprotective effects of adenosine are well known. Adenosine delays the onset of ischaemic contracture, enhances post ischaemic function and reduces infarct size. All these effects of adenosine are mediated via ADO A1 receptors located on the myocytes. Cohen *et al.*, conceptualised hyperpolarisation of the myocyte membrane during ischaemic arrest. They found improved ventricular function using hyperpolarized cardioplegic arrest using a potassium ATP channel agent. Adenosine pretreatment is well known to cause hyperpolarisation by activation of outward potassium current, inhibition of inward calcium current and activation of specific A 1 adenosine receptors. Adenosine released by ischaemic myocyte has a protective effect when infused before ischaemia. This concept of pretreatment in various experimental and clinical setting has prompted the cardiac surgeons to implement a similar therapeutic concept in patients undergoing open heart surgery as post treatment(after release of cross clamp).Lee *et al.*, demonstrated an improved cardiac index in adenosine treated patients.

The current strategy for myocardial protection during cardiac procedures is based on two methods of hypothermia and cardioplegia arrest.

Cardioplegia protects the myocardium by providing continuous or intermittent oxygen while simultaneously reducing cardiomyocyte oxygen demand through both hypothermia and cardiac arrest, but is incapable in augmenting the tolerance of cardiomyocytes for ischemic reperfusion injury.

Keeping in mind that adenosine is a strong mediator of myocardial postconditioning we selected a group of patients in whom the possible beneficial result of adenosine could be observed. Based on this premise we post treated the human myocardium of these patients who has undergone mitral valve replacement under cardiopulmonary bypass Our study consist of administration of adenosine through an arterial catheter immediately after the aortic cross clamp removal was associated with less troponin I release, less inotropic use, shorter ICU stay and was well tolerated as a post conditioning adjunct to high potassium cold blood myocardial protection.

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Conclusion

Adenosine postconditioning appears to protect against reperfusion injury in human hearts and thus result in improved postoperative hemodynamics. Spontaneous rhythm recovery was more in adenosine post treatment. The average troponin I level rise was less in adenosine group as compared to control group indicating that myocardial trauma was less in adenosine group. The mechanical ventilation duration, inotopic score, ICU stay and overall hospital stay was less with use of adenosine post treatment.

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