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Fast Induction of Myocardial Arrest By Bolus Injection of Adenosine At Aortic Root in Patients With "Sick Heart" Undergoing Cardiac Surgery Enhances Myocardial Protection

Medical Science

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ABSTRACT

Fast Induction of Myocardial Arrest by Bolus Injection of Adenosine at Aortic Root in Patients with "sick heart" Undergoing Cardiac Surgery Enhances Myocardial Protection

Objective Adenosine is an endogenous purine nucleoside and a well known potent vasodilator. Adenosine pretreatment reduces the injury caused by ischemia-reperfusion of heart. The purpose of this study is to investigate that whether the aortic root administration of adenosine as bolus dose followed by routine cardioplegia after aortic cross-clamping has additional myocardial protection in cardiac surgical patients with "sick hearts" undergoing cardiac valve surgery under cardiopulmonary bypass.

Method: Patients of 20 to 40 years old who underwent mitral valve replacement under cardiopulmonary bypass for severe mitral regurgitation with ejection fraction (EF) of 35 to 45% were included in this study. In all patients Medtronic ATS valve was put after complete preservation of submitral apparatus. Twenty patients (Group A) were to receive adenosine solution (250 microg/kg) injection at aortic root followed by modified St. Thomas cardioplegic (20 mL/kg). Another twenty patients (Group B) to receive modified St. Thomas cardioplegic (20 mL/kg) alone. The anesthetic management was similar and surgeries were performed by the same team. The haemodynamic change, cardiac enzyme – Serum troponin I assay, post-bypass inotropic supplementation and total period of intensive care unit stay were recorded throughout the study period to evaluate the extent of myocardial ischemic injury.

Results: The mean time was taken to have cardiac asystole after aortic cross-clamping was significantly shorter for Group A compared to the Group B (9.2 +/- 4.4 vs. 66.0 +/- 25.2 sec, respectively; P< 0.01). To compare with the baseline value, the mean cardiac index immediately post CPB and 24 hours postoperatively was increased significantly for the adenosine group (from 1.8 +/- 0.4 to 2.0 +/- 0.3 and 2.3+/- 0.4 L/min/m2, respectively; P < 0.05), as contrasted with the control group (from 1.8 +/- 0.5 to 1.9 +/- 0.4 and 2.1 +/- 0.4 L/min/m2). Postoperative levels of serum troponin I was greater in Group B then Group A. Further, the requirement for inotropic support after CPB and postoperative serum troponin I release were significantly less in Group A. The ICU stay was significantly shorter in adenosine pretreatment group compared to the control group (3.2 ± 1.2 days vs 3.9 ± 1.2 days, p = 0.013). There were no adverse affects associated with adenosine administration.

Conclusions:This study demonstrates that immediate administration of adenosine via the aortic root following aortic cross-clamping followed by conventional cardioplegia quicken cardiac standstill, protective of the myocardium, and offer better postoperative myocardial performance during open-heart surgery in patients with left ventricular dysfunction.

Introduction

Cardioplegia is temporary cessation of cardiac activity and till date no cardioplegic agent can give complete protection to the myocardium against ischemic injury [1]. Ischemia and reperfusion injuries are principally responsible for cardiac failure, morbidity, and mortality following cardiac surgery. Hence, the primary principle of cardiac surgery under cardiopulmonary bypass is to preserve myocardial function by preventing ischemia by reducing cross-clamp time and use of certain cardioprotective agents in cardioplegia.

Adenosine is an endogenous purine nucleoside and it is a well-known vascular smooth muscle relaxant. Its cardioprotective action is independent of its negative chronotropic and dromotropic properties [2]. Adenosine action is mediated by activation of adenosine receptors coupled to guanine nucleotide inhibitory binding (G_i) proteins [3].

The beneficial effect of bolus injection of adenosine before cardioplegic induction has been demonstrated among patients undergoing coronary artery bypass grafting [4]. But the same has not been studied in patients with ventricular dysfunction undergoing cardiac valve replacement. Similarly though intensive studies are undergoing to look into the intracellular beneficial modulation by adenosine in animal models, it has not been conclusively demonstrated the cardioprotective affect of adenosine in humans.

The purpose of that study was 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.

Methods

Patient selections

All consecutive patients between 20 to 40 years of age who underwent mitral valve replacement under cardiopulmonary bypass for severe mitral regurgitation with ejection fraction (EF) of 35 to 45% were included in this study. Preoperatively all patients were evaluated clinically and left ventricular function was assessed by transthoracic echocardiography.

Study Design

Informed consent was obtained from each patient enrolled in the study. This was a single center clinical trial. A total of 40 patients were enrolled. They were divided into two groups. Twenty patients (Group A) were to receive adenosine solution (250 microg/kg) injection at aortic root followed by modified St. Thomas cardioplegic (20 mL/kg). Another twenty patients (Group B) to receive modified St. Thomas cardioplegic (20 mL/kg) alone. In all patients Medtronic ATS valve of size 27 or above were put after complete preservation of submitral apparatus. The trimmed head anterior papillary muscle chordaes were tied at the commissural area of mitral annulus and posterior mital chordaes are tied to the posterior mitral annulus with 3-0 prolene sutures. Sevoflurane anesthetic agent used at induction and maintained with a combination of intravenous fentanyl, propofol and inhaled sevoflurane in air and oxygen. Muscle relaxants were used in all patients.

Invasive hemodynamic monitoring included heart rate, systolic blood pressure, central venous pressure, pulmonary artery pressure, pulmonary capillary wedge pressure. Hemodynamic measurements were obtained in operating theatre and recorded just before establishment of cardiopulmonary bypass, and at 15, 30, 45, and 60 minutes and 2, 3, 4, 6, and 8 hours after cessation of cardiopulmonary bypass. There after the hemodynamic monitoring was continued with measurements of specified parameters every 2 hours for 24 hours and then every 4 hours until the inotropic medications were discontinued. Clinical parameters, including postoperative use of inotropic medicine and duration in the intensive care unit (ICU) were recorded. The pre and postoperative levels of serum troponin I level was measured. The blood samples were collected just before surgery and at 3, 6, 12, and 24 h after surgery for measurement of serum troponin I.

Results

The mean time was taken to have cardiac asystole after aortic cross-clamping was significantly shorter for Group A compared to the Group B (9.2 +/- 4.4 vs. 66.0 +/- 25.2 sec, respectively; P< 0.01). To compare with the baseline value, the mean cardiac index immediately post CPB and 24 hours postoperatively was increased significantly for the adenosine group (from 1.8 +/- 0.4 to 2.0 +/- 0.3 and 2.3+/- 0.4 L/min/m2, respectively; P < 0.05), as contrasted with the control group (from 1.8 +/- 0.5 to 1.9 +/- 0.4 and 2.1 +/- 0.4 L/min/m2). Further, the requirement for inotropic support after CPB were significantly less in Group A. The ICU stay was significantly shorter in adenosine pretreatment group compared to the control group (3.2 ± 1.2 days vs 3.9 ± 1.2 days, p = 0.013). Postoperative levels of serum troponin I was greater in Group B then Group A indicating that the control group suffered greater myocardial injury. 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. Though the decrease in level of troponin I concentration immediately after surgery was lower in GroupA then group B, it did not reach the statistical significance. There were no adverse effects associated with adenosine administration.

Discussion

The cardiovascular actions of adenosine have been well recognized and its property of vesodilatations is considered as primary mechanism of autoregulation of coronary blood flow [5]. The mechanisms by which adenosine exerts cardioprotection have become more intriguing and more complex. In all three windows of cardioprotection (pretreatment or preconditioning, ischemia and reperfusion), the adenosine can be effective. Adenosine exerts its cardioprotective action of prevention ischemic-reperfusion injury action by multiple ways, and the beneficial effects of this agent appear to be related to activation of specific adenosine receptor subtypes, at least three of which (A_1, A_{2a}, and A_3) may be involved and it has been demonstrated well in animal models[6, 7]. Experimental findings indicate that adenosine is most effective in protecting the reversibly injured heart when administered before ischemia [8]. Adenosine improves postischemic myocardial ventricular function in stunned myocardium [9]. Preischemic treatment of adenosine reduces myocardial infarct size and in addition its has ability to reduce platelet and neutrophil adherence to coronary endothelium [7, 10]. As being a potent nasodilator, adenosine increased coronary artery blood flow during reperfusion and thereby increasing the oxygen and the substrate delivery but also enhancing washout of toxic products of ischemia. In addition, its negative inotropic and chronotropic effects have been understood for many years [11].

Adenosine actions are mediated by activating membrane receptors coupled to G-proteins that differentially couple to adenylate cyclase [12]. There are four receptor subtypes: A1, A2A, A2B, and A. The A1 and A3 subtypes inhibits adenylate cyclase. The wide range of cardiovascular effects produced by adenosine interaction with receptors is due to either the inhibition or the stimulation of adenylate cyclase.

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The A1 receptor engages an adaptive mechanism of response making the myocardium more resistant to ischemia by extension to hypoxia and anoxia. Activation of the A1 receptor opens ATPsensitive potassium (KATP) channels, thereby causing membrane hyperpolarization with resultant bradycardia. The A1 and A3 receptor subtypes are coupled to kinases including protein kinase C (PKC). Leading to the opening of sarcolemmal KATP channels, resulting in transmembrane hyperpolarization. Adenosine via A1 receptor-mediated effects also suppresses the L-type calcium channels which have implications regarding calcium accumulation during ischemia-reperfusion. The A1 and A3 receptor subtypes are also coupled to tyrosine kinases that are responsible for phosphorylation and desensitization. The A2A receptor subtype is coupled to stimulatory G-proteins that stimulate adenylate cyclase, leading to an increase in cAMP. Stimulation of the high-affinity A2A receptors causes vasodilation in vascular smooth muscle.

Adenosine has been on clinical use for many purposes e.g. rapid termination of supraventricular arrhythmias, coronary perfusion imaging, and management of postoperative systemic and pulmonary hypertension [13, 14].

The suggestion of cardioprotective effect of adenosine as an adjunct to hyperkalemic crystalloid cardioplegia was proposed in 1976 [15]. However, there was always concern and doubt regarding effectiveness of this drug because of its rapid degradation by plasma adenosine deaminase and catabolism of adenosine in blood cardioplegia can be attenuated by hypothermia. In experimental studies on animal model of rats the bolus injection of adenosine prior to cardioplegia has shown enhances preservation of heart grafts [16].

Pretreatment adenosine administration preoperatively to patients with poor left ventricular function undergoing coronary artery bypass graft surgery for three-vessel disease has shown improved postoperative creatinine kinase pattern [17]. Adenosine rich conventional hyperkalemic cold blood cardioplegia in elective cardiac surgery is an established practice for some time. There are studies on adenosine supplemented blood cardioplegia in operation of coronary artery bypass grafting where it has shown improvements on post ischemic myocardial dysfunction after severe regional ischemia [18]. In our study also shows that the postoperative Troponine I release was significantly less in Group A.

In one double-blinded, placebo-controlled randomized study on patient undergoing coronary artry bypass surgery under cardiopulmonary bypass on cardioplegic arrested heart treated with graded dose of adenosine and without adenosine, it was found that patients who received high-dose adenosine were less likely to experience one of five adverse events: high-dose dopamine use, epinephrine use, insertion of intraaortic balloon pump, myocardial infarction, or death [8]. In our study too the requirement for inotropic support after CPB was significantly less and postoperative intensive care unit stay of patients was significantly shorter in adenosine pretreatment group compared to the control group.

The safety and tolerance of the adenosine as additive to cardioplegia is well documented, and additive concentration from 100 μM to 2 mM has been found to be safe [8]. Patients receiving adenosine cardioplegia are also given an infusion of adenosine prior and after removal of the aortic cross clamp. There is evidence of ventricular performance in both invasive and noninvasive measurements and post operative requirements of ionotropic supports are less.

It has been demonstrated that the adenosine pretreatment has significantly decreased postoperative Cardiac troponin T (cTnT) release in elective Coronary Artery Bypass Grafting patients [19, 20]. In a similar study of adenosine root injection before routine St Thomas cardioplegia in patients undergoing coronary artery bypass surgery, It was found that in the adenosine group, only 3 of 45 (6.6%) patients had elevated creatine phosphokinase (CPK) (MB) values greater than 50 U/L over preoperative CPK values compared with 3 of 15 (20%) in the control group [21]. In our observation too, 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 though this difference is not significant in immediate postoperative sample.

There is still controversy exists regarding effectiveness of pretreatment of adenosine in inhibition of inflammatory process and improvement of cardiac enzyme parameters while used as pharmacologic preconditioning agent administered before delivery of cardioplegia [22, 23]. Therefore it is advisable that the pretreatment modality of adenosine seems to be more effective than administration separated by a washout period.

The potent antineutrophil effects of adenosine at reperfusionhas been investigated and it is found that neutrophil accumulation in the ischemic reperfused area is attenuated compared with the unsupplemented blood cardioplegia group [24]. Also it is observed that the hearts treated with adenosine only during reperfusion has shown improved postischemic coronary artery endothelial function compared to the unsupplemented blood cardioplegia. The mechanisms of cell loss during ischemia-reperfusion injury are the apoptosis and it has been shown in both in animal models and humans early after cardioplegic arrest and open heart surgery [25, 26]. Myocardial upregulation of the proapoptotic gene bax and reduction of both bcl-2 and bcl-2/bax ratios are predisposing factor for apoptosis of cardiomyocyte [27]. It has been shown that by inducing rapid standstill of heart by aortic root injection of adenosine before cardioplegia inhibits apoptosis via modulation of antiapoptotic bcl-2 and proapoptotic bax genes and neutrophil accumulation, primarily mediated by an adenosine A2a receptor [28].

Conclusions

The adenosine pretreatment is protective of the myocardium during open-heart surgery in patients with ventricular dysfunction undergoing valve surgery. This finding supports the need for a larger study of adenosine precardioplegia root treatment in patients undergoing cardiac surgery on similar patients. Adenosine physiologic action extends beyond its plasma half-life. The adenosine used as an adjunct to cardioplegia has significant effects in attenuating reperfusion injury. The optimal dose of adenosine still needs to be defined to avoid unwanted side effects such as hypotension and bradycardia.

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