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ORIGINAL ARTICLE

Effect of Fast Cardioplegic Arrest Induced by Adenosine on Cardiac Troponin Levels After Heart Valve Surgery

Amr A. Abdelwahab, MD [a,1], Mohab Sabry, MD [a], Hatem A. Elshora, MD [b], Amr A. Arafat, MD [a,1*]

[a]Cardiothoracic Surgery Department, Tanta University, Egypt
[b]Anesthesia and Surgical ICU Department, Tanta University, Egypt

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Background Cellular injury is not avoidable with current cardioplegic solutions. The effect of adenosine on reducing cardiac injury post-surgery is controversial. The objective of the current study is to evaluate the effect of fast cardioplegic arrest induced by adenosine on high sensitive cardiac troponin I after heart valve surgery.

Methods Forty-five (45) patients with rheumatic heart diseases underwent heart valve surgery using conventional approach through median sternotomy. They were classified into two groups, group I (n = 21) patients received 0.25 mg/kg adenosine into the aortic root just after aortic cross-clamping and before infusion of the cold hyperkalaemic crystalloid cardioplegia via antegrade route and group II (n = 24) who received cold crystalloid hyperkalaemic cardioplegia without adenosine. Cardiac troponin I was measured preoperatively and on postoperative days 0, 3 and 7.

Results There was no significant difference between both groups in the demographic, preoperative and operative data. Adenosine significantly reduced arrest time. Postoperative high sensitive cardiac troponin I increased significantly in both groups compared to the preoperative levels and the rise continued till postoperative day 3. Troponin levels were significantly lower in the adenosine group compared to the control at all measurements. The clinical outcomes were non-significant different between groups.

Conclusions Using adenosine in inducing fast cardioplegic arrest in heart valve surgery after aortic cross clamp and prior to infusion of the cold cardioplegia had significantly decreased postoperative cardiac troponin levels which was used as a proxy for cellular injury compared to the control group.

Keywords Adenosine • Cellular injury • Cardiac troponin I • Heart valve surgery

Introduction

Myocardial cell injury after cardiac surgery is unavoidable with the currently available hyperkalaemic cardioplegic solutions [1]. Several modifications to the cardioplegic solutions were made to decrease this cellular injury [2]. Adenosine causes fast cardioplegic arrest which was supposed to improve postoperative cardiac recovery. The effect of adenosine when added to the high potassium cardioplegic solution is variable. Some studies have demonstrated the beneficial effects of adenosine on improving clinical outcomes [3,4], and other studies have found better protection against cellular injury but not reaching significant levels [5].

*Corresponding author at: Faculty of Medicine, Tanta University, Cardiothoracic Surgery Dept., Al-Geish Street, Tanta, Gharbyia 31529, Egypt. Tel.: (+20100) 2415848; Fax: (+2040) 3337403., Email: amr.arafat@med.tanta.edu.eg

[1] First and last author have equal contribution to the manuscript.

Cardiac troponin I (cTn I) is one of the biomarkers used for risk assessment of several cardiac diseases and post cardiac surgery [6]. It is released whenever myocardial injury occurs regardless of the mechanism of injury and its release post cardiac surgery was found to be associated with increased mortality and morbidity [7].

The objective of our research is to study the effect of fast cardioplegic arrest induced by adenosine on myocardial cellular injury expressed as the level of the high sensitive cTn I after heart valve surgery.

Materials and Methods

From January 2016 to December 2016, 45 patients who had valve surgery for rheumatic heart disease were included in this prospective non-randomised cohort study. We excluded patients who had valve replacement for non-rheumatic aetiologies, concomitant non-valvar procedure, minimal invasive valve surgery, redo valve operations, patients with infective endocarditis, cases with severe aortic regurgitation and patients with renal or hepatic impairment.

Patients were divided into two groups based on adenosine administration. Twenty-one (21) patients received 0.25 mg/kg adenosine as a single bolus dose into the aortic root just after cross-clamping and before running the cardioplegia (group I, Adenosine group). Twenty-four (24) patients served as the control group (group II, Non-adenosine group) who received cold hyperkalaemic cardioplegia without adenosine. Adenosine was administered based on surgeon's preference and the choice of adenosine was not related to patients' specific factors. The dose was chosen according to our pilot study to determine the lowest effective dose to induce cardiac arrest.

All patients received cold crystalloid cardioplegia as per our protocol which consists of 20 mEq NaHCO3, 18 mEq potassium, 25 ml glucose 25%, 13 g mannitol 20% and 60 mg lidocaine hydrochloride 20%. Those components were added to 1 litre of Ringer lactate and were given at initial dose of 20 ml/kg with maximal flow of 300 ml/min and pressure of 60–80 mmHg. Half of the dose was repeated every 20 minutes and the solution was delivered at temperature 4–8 °C through antegrade route.

The study received approval from the Research Ethical Committee at our institution prior to patients' enrolment.

Anaesthesia, Cardiopulmonary Bypass and Surgical Technique

All surgical interventions were done through a conventional median sternotomy and cardiopulmonary bypass (CBP) was established with standard cannulation technique under full heparinisation (4 mg/kg heparin). The procedure was performed under mild to moderate hypothermia, with non-pulsatile flow, membrane oxygenator, and cold crystalloid cardioplegia as described before. All patients underwent mechanical valve replacement in the aortic and/or mitral position and tricuspid repair was done if moderate to severe tricuspid regurgitation was associated with the aortic or mitral valve disease.

A radial artery line and the right internal jugular vein central line were inserted for haemodynamic monitoring. Anaesthesia was induced with propofol (0.5–1.0 mg/kg), fentanyl (0.6–0.8 g/kg), and cis-atracurium and was maintained by intravenous propofol and inhaled isoflurane. No inhaled anaesthetic was utilised during the cardiopulmonary perfusion.

High Sensitive Cardiac Troponin I Assay

High sensitive cTn I was measured preoperatively and at postoperative days (POD) 0, 3 and 7 in all patients using ARCHITECT-STAT troponin I assay (Abbott Diagnostics, Chicago, IL, USA).

Study Outcomes

Time to induce cardiac arrest and to wean from CPB, need of inotropic support, intensive care unit (ICU) stay, and ventilation time were compared between groups. Arrest time was defined as the time from cardioplegia or adenosine administration to flat electrocardiogram (EGC). Troponin levels were measured preoperatively, post cardiopulmonary bypass (day 0), postoperative day 3 and postoperative day 7 in all patients. Primary outcomes were arrest time and postoperative cTn I levels and secondary outcomes were the postoperative clinical outcomes.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as numbers and percentages. Categorical variables were compared using Chi-square or Fisher exact test for events less than 5. Continuous variables were compared using a t-test for normally distributed variables or Wilcoxon rank-sum test for non-normally distributed variables. The treatment effect of adenosine on postoperative troponin level was estimated by propensity score matching after adjusting for the preoperative troponin, gender, age, hypertension, chronic obstructive pulmonary disease (COPD), CBP time and preoperative creatinine. A mixed effect model was used to test the changes in the levels of troponin and factors affecting the change. A p-value of 0.05 was considered significant. Statistical analysis was performed using STATA 14 software. (Statacorp, College Station, TX, USA)

Results

There was no statistically significant difference in the preoperative and operative characteristics between patients who received adenosine plus cold cardioplegia and patients who received cold cardioplegia only (Table 1).

Patients who received adenosine had significantly shorter arrest time ($p < 0.001$) (Figure 1) and lower troponin levels in all measurements at postoperative day (POD) 0, 3 and 7 ($p = 0.001$, 0.02 and 0.03 respectively). (Table 2)

Table 1 **Preoperative and operative characteristics of patients in adenosine and non-adenosine group.**

Variables	Adenosine group (n = 21)	Non-adenosine group (n = 24)	P-value
Male	16 (76.19%)	12 (50%)	0.07
Age (years).	37.28 ± 9.1	43.54 ± 13.4	0.08
Diabetes mellitus	3 (14.29%)	7 (29.16%)	0.296
Hypertension	4 (19.05%)	11 (45.83%)	0.068
COPD	5 (23.8%)	1 (4.16%)	0.053
Preoperative creatinine (mg/dl)	0.98 ± 0.17	1.05 ± .12	0.1
Preoperative urea (mg/dl)	29.48 ± .99	31.4 ± .72	0.1
Ejection fraction (%)	57.8 ± 5.4	57.5 ± 5.1	0.8
Ischaemic time (min)	80 ± 33.1	93.3 ± 28.9	0.2
Preoperative troponin (ηg/dl)	0.0014 ± 0.0005	0.0012 ± 0.0004	0.06
CPB time (min)	124.8 ± 37.8	147.7 ± 48.2	0.09
K++ before declamping (mmol/dl)	4.4 ± .2	4.4 ± 0.2	0.6
Surgery performed			0.1
AVR	4 (19.05%)	12 (50%)	
DVR	3 (14.29%)	3 (12.5%)	
MVR	6 (28.57%)	7 (29.16%)	
DVR + tricuspid repair	4 (19.05%)	1 (4.16%)	
MVR + tricuspid repair	4 (19.05%)	1 (4.16%)	

Abbreviations: COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; AVR, aortic valve replacement; MVR, mitral valve replacement; DVR; double valve replacement.

No difference was found between groups as regards inotropic support ($p = 0.06$), ICU stay ($p = 0.8$) and ventilation time ($p = 0.3$) (Table 2).

Troponin (cTn I) levels increased significantly postoperatively compared to the preoperative level in all patients and the increase was higher in patients who didn't receive adenosine (Figure 2). Changes in cTn I levels from day 0 through postoperative day 7 were affected by adenosine administration ($p = 0.02$) and the time of measurements ($p < 0.001$) (Table 3). The rise in cTn I continued till POD 3 then declined.

The treatment effect of adenosine on postoperative cTn I measured post cardiopulmonary bypass was estimated by propensity score matching with adjustment for the preoperative cTn I, gender, age, hypertension, COPD, CBP time and

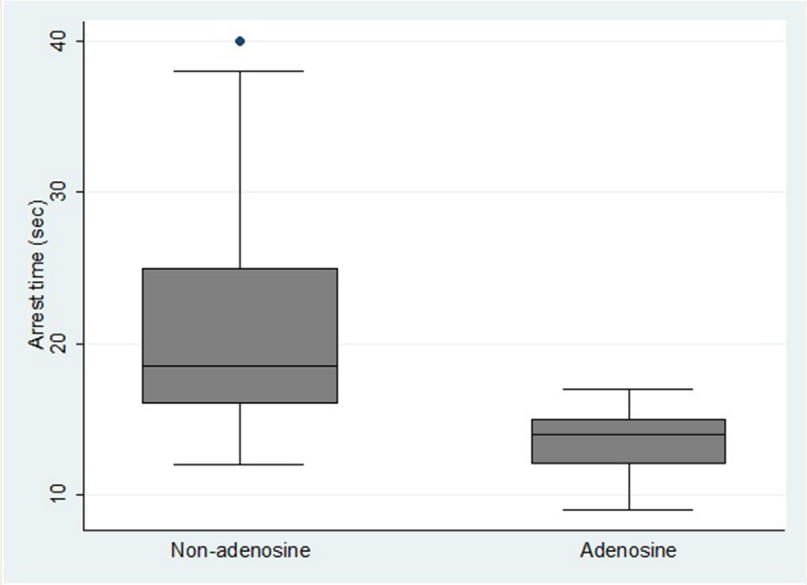

Figure 1 Box plot of arrest time in adenosine and non-adenosine groups.

Table 2 Outcomes in adenosine and non-adenosine group.

	Adenosine group (n = 21)	Non-adenosine (n = 24)	P-value
Time to arrest (sec)	13.4 ± 2.1	20.7 ± 7.2	<0.001
Cardiopulmonary bypass weaning time (min)	31.1 ± 5.7	39.8 ± 24.9	0.7
Auto resuscitation (n)	15 (71.43%)	10 (41.66%)	0.07
Ventilation time (hours)	7.9 ± 1.5	8.3 ± 1.3	0.3
Intensive care unit stay (days)	3.2 ± 0.9	3.2 ± 0.8	0.8
Inotrope use (n)	4 (19.05%)	11 (45.83%)	0.06
Postoperative ejection fraction (%)	51.9 ± 3.7	49.4 ± 4.8	0.14
Troponin (day0) (ηg/dl)	0.8 ± 0.19	1.08 ± 0.38	0.001
Troponin (day3) (ηg/dl)	1.16 ± 0.33	1.4 ± 0.36	0.02
Troponin (day7) (ηg/dl)	0.53 ± 0.17	0.68 ± 0.22	0.03

preoperative creatinine. Adenosine was an independent predictor of lower postoperative cTn I ($p < 0.001$) (Table 4).

Discussion

Cardiac function perseveration in open heart surgery is the main target of cardio-protection and several strategies have been evolved to achieve this goal. Ischaemic reperfusion injury causes rapid reduction of the expression of apoptosis regulating genes and induces cardiac cell apoptosis [8]. Adenosine was found to reduce apoptosis and cellular injury when added to the cardioplegic solutions [9]. On the other hand, other studies have shown the effect of adenosine on apoptosis didn't reach a significant level compared to patients who didn't receive adenosine [5]. The impact of the cellular changes of adenosine on the clinical outcome is a matter of controversy.

High sensitivity cardiac cTn I is a marker of myocardial injury and it has a prognostic role in several cardiac pathologies and after cardiac surgeries [6,10]. Our study focussed on the effect of adenosine added to the cold hyperkalaemic cardioplegic solution on postoperative cTn I as a marker for the degree of myocardial injury. We selected patients who had valve surgery for rheumatic valve disease to decrease the variations of troponin levels after different cardiac surgical procedures.

There is no consensus on the optimal dose, temperature, time and routes of administration of adenosine as a protective strategy for the myocardium in cardiac surgery. The variability of the results of adenosine could be attributed to the difference of its administration protocols among the published studies. Our protocol consisted of injection a dose of 0.25 mg/kg adenosine into the aortic root just after aortic cross-clamping and before infusion of the cold crystalloid

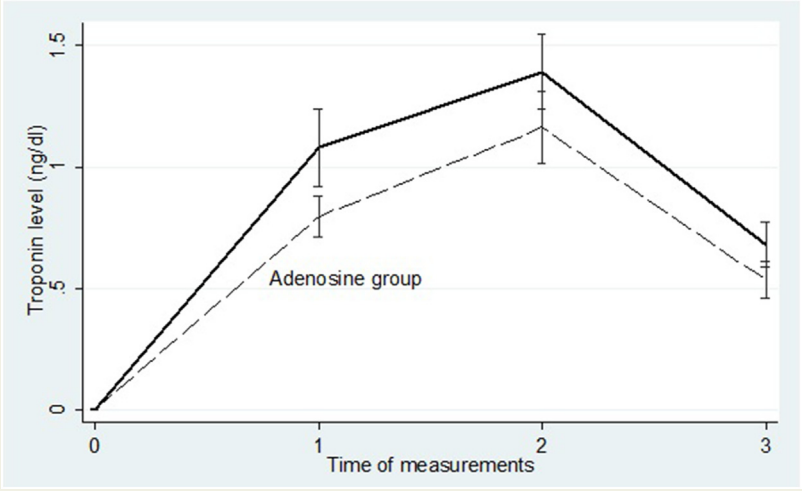

Figure 2 Change in the troponin I level in patients in adenosine and non-adenosine groups.
0 = preoperative
1 = postoperative day 0
2 = postoperative day 3
3 = postoperative day 7

Table 3 **Mixed effect model of the effect of adenosine on the changes of the postoperative troponin I measured at different time points (postoperative day 0, 3 and 7).**

	Coefficient	z-statistics	p-value	95% CI
Adenosine	−0.16	−2.29	0.02	−0.3–0.02
Time of measurements	0.22	6.74	<0.001	0.15–0.28

Table 4 **Treatment effect of adenosine on postoperative troponin I measured post cardiopulmonary bypass estimated by propensity score matching and adjusting for the preoperative troponin I, gender, age, hypertension, COPD, CBP time and preoperative creatinine.**

Troponin postoperative	Coefficient	z-statistics	p-value	95% CI
Attributable treatment effect of adenosine	−0.32	−4.69	<0.0001	−0.46–0.19

Abbreviations: COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass.

cardioplegia via antegrade route. This protocol was based on our previous pilot study to determine the minimum adenosine dose required to achieve cardiac arrest. We inject adenosine into the aortic root prior to cardioplegia infusion to achieve rapid cardiac arrest which we think plays a role in the cardioprotective effect of adenosine [4]. Adenosine was found to protect against cold cardioplegic injury to the endothelial cells and exerts its effects after a time window of 5 minutes [11]. Other studies injected adenosine prior to removal of the aortic cross clamp [7].

The major significant finding in our study is fast cardioplegic arrest induced by adenosine. The effect of adenosine on arrest time was consistent with no outliers and lesser variability as compared to the control group. Patients who received adenosine had better postoperative haemodynamics and lower inotropic support, although this didn't reach a statistically significant level. Adenosine had significantly reduced postoperative cTn I levels at POD 0, 3 and 7 days than patients who received hyperkalaemic cardioplegia only. Similar to our results, Liu et al. found that adenosine had reduced cardiac troponin I in patients who underwent heart valve surgery [4]. Moreover, adenosine reduced levels of interleukin-8 and interleukin-6.

During two decades of research on adenosine for cardioprotection, adenosine was mixed with different pharmacologic agents such as lidocaine and procaine. In several studies, it was not clear whether the cardioprotective effect was offered by adenosine solely or it could be attributed to other chemicals [12]. In our study, the difference between groups was the adenosine administration prior to aortic cross clamp and after adjusting for possible confounders, adenosine was found to be an independent predictor of low postoperative cTn I levels. In contrast to our results, a randomised controlled trial of adenosine in cold blood cardioplegia versus placebo didn't find any difference whether for levels of postoperative enzymes nor the clinical outcome [13].

Recently, cellular injury was attributed to the hyperkalaemic content of the cardioplegia [12]. Adenosine was found to be a safe alternative to hyperkalaemic cardioplegia with similar cardio-protection effects and lower incidence of atrial fibrillation [14]. In a randomised trial published in 2016, normokalaemic cardioplegia containing adenosine, lidocaine and Mg2+ was found to be superior to hyperkalaemic cardioplegia as regards spontaneous return to sinus rhythm, lower coronary and peripheral blood troponin I, lactate and potassium at reperfusion and better haemodynamics and lower ICU stay [1].

Research on the cardioprotective effect of adenosine continues and our study found a decreased cellular injury associated with adenosine administration prior to cold cardioplegia. The effect of this cellular protection on the clinical outcomes needs further investigation on a larger study population. The study recommends the concomitant administration of adenosine with cold cardioplegia which is safe and effective in inducing fast arrest and significantly lowers postoperative cardiac troponin I.

Study Strengths and Limitations

The design of the study is a prospective, non-randomised cohort study in which the choice of adenosine injection was entirely dependent on surgeon's preference, however, the choice of adenosine was not related to patient's specific risk factors. Randomised studies have higher levels of evidence compared to observational studies. However, we had rigorous inclusion criteria to make the study groups comparable regarding the preoperative characteristics. Moreover, the effects of adenosine on the postoperative troponin levels were assessed using propensity score matching with adjustment of possible measured confounders. Another limitation is the small number of patients which may or may not be powered to test the effect of adenosine on the clinical outcome. However, the study was sufficiently powered to demonstrate the high significant effect of adenosine in reducing the troponin levels. Further studies are required to clearly demonstrate the benefits of adenosine on the clinical outcome after showing a good effect at the cellular levels. Moreover, the measurements of cardiac troponin I at different time points up to POD 7 were complete in all patients and we don't have missing patients' data.

Conclusion

Using adenosine in inducing fast cardioplegic arrest in heart valve surgery administered after aortic cross clamp and prior to infusion of the cold cardioplegia had significantly decreased myocardial cellular injury expressed as decrease in cardiac troponin levels compared to the control group.

Conflict of Interest

None.

Funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.08.017.

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