The myocardial protective effects of adenosine pretreatment in children undergoing cardiac surgery: a randomized controlled clinical trial

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Abstract

Objective: Adenosine pretreatment reduces injury caused by ischemia-reperfusion. To investigate the hypothesis that adenosine pretreatment would modulate injury induced by cardiopulmonary bypass (CPB) and myocardial ischemia/reperfusion, we conducted a randomized controlled trial on the effects of adenosine pretreatment in children undergoing surgery to repair congenital heart defects.

Methods: Children undergoing surgery to repair congenital heart defects were randomized to adenosine pretreatment or control treatment. Adenosine pretreatment was performed by infusing a total of 2.45 mg kg⁻¹ of adenosine over 10 min. Serum troponin I was measured pre- and postoperatively. Multiple clinical parameters, including postoperative use of inotropic medicine and duration in the intensive care unit (ICU), were recorded.

Results: A total of 82 patients were enrolled in the study. There were 42 control patients and 40 patients in the adenosine pretreatment group. The mean age and weight of the two groups were not significantly different, nor were cardiopulmonary bypass and cross-clamp times. There were no deaths and severe complications in both groups. The adenosine pretreatment protocol caused significant hypotension but had no significant effect on heart rate. One patient had severe tachycardia shortly after the adenosine pretreatment protocol was completed, and adenosine infusion was continued until CPB was started. Postoperative levels of serum troponin I were greater in the control patients than in the adenosine pretreatment group, indicating that the control group suffered greater myocardial injury. Control group patients required more postoperative inotropic agents than those in the adenosine pretreatment group at 0, 1, and 3 h, indicating that the adenosine pretreatment group had a better cardiac function. The adenosine pretreatment group also required significantly less time in the ICU (3.2 ± 1.2 days vs 3.9 ± 1.2 days, p = 0.013).

Conclusions: This study demonstrates that adenosine pretreatment is protective of the myocardium during open-heart surgery in pediatric patients.

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Keywords: Cardiovascular surgery; Child; Adenosine; Myocardial protection; Randomized clinical trial

1. Introduction

Ischemia and reperfusion injuries (IRIs) are principally responsible for cardiac failure, morbidity, and mortality following cardiac surgery [1]. Ischemic preconditioning (IPC) was first described in 1986 by Murry et al. [2], who reported that the size of myocardial infarcts decreased from 29% to 7% in anesthetized dogs undergoing open-chest surgery after three brief episodes of ischemia and reperfusion prior to 40 min of coronary artery occlusion. Yellon et al. subsequently demonstrated that this effect is also observed in human myocardial tissue [3]. Meta-analysis shows that IPC may provide more myocardial protection than cardioplegia alone. Most of the patients selected for these clinical trials have coronary artery disease and undergo selective coronary artery bypass grafting. Given the potential embolic risks of manipulating the aorta, most surgeons and clinicians are reluctant to precondition the heart in the clinical setting. The ultimate therapeutic goal has been to develop a pharmacologic mimetic of IPC [4]. Adenosine, an endogenous nucleoside, is of particular interest because it protects...
against cellular injury at multiple sites and levels during ischemia and reperfusion [5] in addition to triggering early and delayed IPC [6].

Adenosine preconditioning has ameliorated IRI in several experimental animal models and also in patients with acute myocardial infarctions after undergoing interventional or surgical therapy [7]. In 1995, adenosine was first used as a pharmacological preconditioning agent to mimic the protective effects of IPC in clinical settings [8]. This study showed that adenosine infusion (250–350 μg kg\(^{-1}\) min\(^{-1}\) × 10 min) just prior to cardiopulmonary bypass (CPB) resulted in immediate improvements in post-bypass cardiac index (CI) in the operation room and improved postoperative ventricular performance, lowered postoperative myocardial energy demand, and decreased myocardial injury. Similar results are reported by Wei et al. [9], who pretreated patients with adenosine (total, 650 μg kg\(^{-1}\) via central vein infusion) before initiating CPB, and Liu et al. [10], who infused adenosine (100 μg kg\(^{-1}\) min\(^{-1}\) × 10 min) before aortic cross-clamping and delivering antegrade cold-blood cardioplegia solution in patients undergoing valvular operations. Administering adenosine directly into the aortic root immediately after aortic cross-clamping and just before initiating cardioplegia can also optimize the myocardial protective effect of conventional cardioplegia and offer better postoperative myocardial performance after CPB [11,12].

Based on these pilot clinical studies, we hypothesized that adenosine pretreatment would protect against myocardial IRI in children undergoing CPB for repair of congenital heart defects. We found that adenosine pretreatment could decrease postoperative troponin I release, inotropic drug use, and intensive care unit (ICU) time compared with control patients. The results might imply that adenosine pretreatment has a protective effect on myocardial IRI induced by cardiac operation and CPB.

2. Methods

This randomized controlled trial was reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) checklist (version 2001). From 1 December 2006 to 8 March 2007, we recruited consecutive pediatric patients with congenital heart disease referred to us for surgical repair. Children who weighed ≤10 kg, waiting to undergo congenital heart defects repair under CPB were eligible for recruitment. Children who weighed more than 10 kg with diagnoses of isolated atrial septal defect (ASD), isolated pulmonary stenosis, or bidirectional cavopulmonary shunt undergoing Fontan completion were excluded. These patients were excluded because bypass times are relatively short and the duration of stay in the ICU is often less than 24 h. Patients with chromosomal defects, airway and parenchymal lung disease, and immunodeficiency or blood disorders were also excluded.

The study protocol was approved by the ethics committee of Xijing Hospital. Informed consent was obtained before enrollment in the study. Eligible children were randomized to the adenosine pretreatment group or the control group. The randomization was realized by messages in sealed envelopes given to the anesthesiologist just before the operation. Staff involved in clinical care including surgeons, perfusionists, intensive care physicians, and members of the study group obtaining functional data were blinded to randomization for the period of data acquisition and analysis. Group allocation was not revealed until the final statistical analysis was completed.

All subjects were under general anesthesia at the time of surgical repair. Anesthesia was induced with sevoflurane and maintained with a combination of intravenous fentanyl and inhaled sevoflurane in air and oxygen. Muscle relaxants were used in all patients.

2.1. Adenosine pretreatment protocol

Adenosine was supplied by Guangda Pharmacy (Shenyang, China) in 90 mg/30 ml vial. After anesthesia was successfully administered, adenosine pretreatment was carried out by the anesthesiologist, who was aware of what was infused. Adenosine was infused through central venous catheter at 50 μg kg\(^{-1}\) min\(^{-1}\) for the first minute, and then the dosage increased by 50 μg kg\(^{-1}\) min\(^{-1}\) per minute up to 350 μg kg\(^{-1}\) min\(^{-1}\). This dosage rate was maintained for an additional 4 min. The total dose of adenosine was 2.45 mg kg\(^{-1}\). Control patients underwent saline infusion in the same fashion. There was a 5- to 10-min interval between completion of the adenosine pretreatment protocol and initiation of bypass.

2.2. Surgical repair

All children underwent surgical repair by the same surgical team with standard cardiopulmonary bypass techniques and crystalloid cardioplegia supplied by the clinical pharmacy of Xijing Hospital. The duration of cardiopulmonary bypass and aortic cross-clamping was recorded. Conventional and modified ultrafiltration was performed in all patients.

2.3. Body weight

Fluid retention caused by the surgical procedure was determined by measuring changes in body weight before and after the operation in the operating room.

2.4. Blood samples

Blood samples were collected in dry glass tubes before surgery and 3, 6, 12, and 24 h after surgery. Serum was immediately separated and stored at −70 °C for later determination of troponin I (cardiac troponin I (cTnI)). The troponin I concentrations were measured quantitatively by a one-step enzyme immunoassay based on electrochemiluminescence technology (Beckman Instruments Inc., Fullerton, CA, USA).

2.5. Postoperative assessment

All measurements were repeated at 3, 6, 12, and 24 h after arriving in the ICU. Urine output was also measured. Inotropic support at each time point was quantified by calculating the inotropic score as described previously [13,14].
2.6. Statistical analysis

The serum concentrations of cTnI were non-normally distributed. They were presented as mean ± SE. After logarithmically transformed to fit normal distribution, they were compared with repeated measurement data analysis of variance (ANOVA). Other normally distributed data were presented as mean ± SD and compared with unpaired \( t \)-test. A \( p \) value < 0.05 was considered significant.

3. Results

Fig. 1 shows the characteristics of patients enrolled in the trial. A total of 92 children were assessed for eligibility. Of these patients, 82 were actually recruited and randomly assigned to the adenosine pretreatment group (\( n = 40 \)) or control group (\( n = 42 \)). There were no significant differences between the groups with respect to preoperative characteristics, surgical repair of congenital heart defects, or intraoperative characteristics (Table 1). The time between termination of the adenosine pretreatment protocol and initiation of aortic cross-clamping did not exceed 20 min in any of the patients. The adenosine pretreatment protocol significantly decreased systemic blood pressure but had little effect on heart rate, compared with the pretreatment values (Table 2). None of the patients experienced significant hypotension (systolic arterial pressure <60 mmHg) requiring immediate intervention during or after the adenosine pretreatment protocol. One of the patients who underwent adenosine pretreatment had tachycardia (255 beats/min) after adenosine pretreatment. To maintain a normal heart rate, we had to infuse adenosine continuously until CPB was started. The child recovered completely after the operation.

3.1. Patients

A total of 82 children were studied. There were 42 patients in the control group and 40 in the adenosine pretreatment group. All of the children survived the operation without severe complications. Two children in the adenosine pretreatment group underwent ventricular septal defect (VSD) repair through right ventricle incisions. One VSD patient experienced complete atria ventricular block (IIIAVB) and was treated with a preliminary epicardial pacemaker. He reverted to normal sinus rhythm 3 days later. Two children in the control group experienced sinus bradycardia after either tetralogy of Fallot (TOF) repair or VSD repair. They were treated with isoprenaline infusion for 1 or 2 days, respectively, and normal sinus rhythm was restored uneventfully.

3.2. Myocardial function and injury

The levels of troponin I were significantly higher in the control group than in the adenosine pretreatment group at time points of postoperative 6 and 24 h (Figs. 2 and 3). Although the serum concentrations of cTnI in pretreatment patients were also decreased compared to untreated patients at time points of immediately (\( p = 0.07 \)) and 1 h (\( p = 0.08 \)) after operation, their differences did not reach statistical significance. Previous studies have reported that patients undergoing right ventricle incisions for TOF [15] experienced increased release of troponin I; these data were reanalyzed, and data from the patients who underwent right ventricle incision were excluded. Although there was a tendency of decreased troponin I concentration in adenosine pretreated patients, it did not reach the statistical significance compared with the control group (Fig. 4). The urine volumes of first 24 postoperative hours in adenosine pretreatment group were much more than that of control group (77.2 ± 17.5 ml kg\(^{-1}\) vs 59.8 ± 10.8 ml kg\(^{-1}\) \( p = 0.009 \)). However, the control group did require significantly more inotropic support than the adenosine pretreatment group at 0, 1, and 3 h after arriving in the ICU (Table 3).

4. Discussion

This study is the first demonstration of the clinical effectiveness of adenosine pretreatment in children patients. Our simple protocol for adenosine pretreatment protected against myocardial IRI in children undergoing open-heart surgery.

4.1. Safety of adenosine pretreatment in children undergoing cardiac surgery

No deaths or other severe complications occurred during the operations or postoperative period. The main side effects of adenosine administration are hypotension and bradycardia, and rapidly infusing adenosine intravenously is known to induce transient cardiac arrest [16]. To avoid these side effects of adenosine, we began adenosine pretreatment at a very low dose (50 \( \mu g \) min\(^{-1}\) kg\(^{-1}\)) and increased the dose gradually up to 350 \( \mu g \) min\(^{-1}\) kg\(^{-1}\). This infusion was accompanied by intensive monitoring of blood pressure and heart rate of the patients. We found that this adenosine pretreatment protocol significantly decreased blood pressure but had little effect on heart rate (Table 2). Although the blood pressure of adenosine patients decreased significantly, none of them decreased to less than 60 mmHg. A few minutes after the completion of adenosine infusion, the blood pressure resumed to normal levels. As indicated above,
one patient had tachycardia after the completion of adenosine pretreatment. We cannot explain this phenomenon as it might have been an adaptive reaction to the cessation of adenosine infusion and it might also imply that the adenosine pretreatment protocol used in this study was well tolerated. Only one adenosine patient with VSD had contemporary IIIAVB after operation, which could be explained as a complication related to the operation rather than the side effect of adenosine pretreatment. These data suggest that our adenosine pretreatment protocol is clinically safe.

4.2. Myocardial protective effects of adenosine pretreatment in congenital heart surgery

Myocardial IRIs are the primary cause of cardiac failure, morbidity, and mortality following cardiac surgery. Other studies have shown [17] a measurable degree of left ventricular dysfunction, even after repair of ‘simple’ congenital defects. Furthermore, many studies have demonstrated global myocardial damage following cardiac surgeries by monitoring surrogate markers such as troponin I and T. In

Table 1. Pre- and intraoperative characteristics of children in both groups.

<table>
<thead>
<tr>
<th>Congenital heart defects</th>
<th>Control (n = 42)</th>
<th>Adenosine pretreatment (n = 40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSD</td>
<td>24</td>
<td>28</td>
<td>NS</td>
</tr>
<tr>
<td>VSD + PDA</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>VSD + ASD</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TOF</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>TOF + PDA</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TOF + ASD</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CAVCD</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TAPVC</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Age (months)</td>
<td>6.6 ± 3.5</td>
<td>8.1 ± 5.0</td>
<td>0.13</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>6.4 ± 1.2</td>
<td>6.2 ± 1.6</td>
<td>0.54</td>
</tr>
<tr>
<td>Male/female</td>
<td>24/18</td>
<td>18/22</td>
<td>NS</td>
</tr>
<tr>
<td>Preoperative oxygen saturation</td>
<td>0.94 ± 0.03</td>
<td>0.95 ± 0.04</td>
<td>0.87</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>68.3 ± 26.5</td>
<td>67.5 ± 19.3</td>
<td>0.87</td>
</tr>
<tr>
<td>Heart arrest time (min)</td>
<td>39.4 ± 16.3</td>
<td>35.5 ± 12.8</td>
<td>0.22</td>
</tr>
<tr>
<td>Lowest body temperature during CPB (°C)</td>
<td>27.4 ± 1.5</td>
<td>27.7 ± 2.0</td>
<td>0.35</td>
</tr>
<tr>
<td>Ultrafiltration volume (ml)</td>
<td>207 ± 77</td>
<td>229 ± 87</td>
<td>0.24</td>
</tr>
</tbody>
</table>

VSD: ventricular septal defect; PDA: patent ductus arteriosus; ASD: atrial septal defect; TOF: tetralogy of Fallot; CAVCD: complete atrioventricular canal defect; TAPVC: total anomalous pulmonary venous connection; CPB: cardiopulmonary bypass.

Table 2. Hemodynamic changes before and after adenosine pretreatment.

<table>
<thead>
<tr>
<th></th>
<th>Before pretreatment (n = 42)</th>
<th>After pretreatment (n = 40)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>143 ± 24</td>
<td>140 ± 23</td>
<td>0.66</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)</td>
<td>96 ± 9</td>
<td>84 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)</td>
<td>54 ± 11</td>
<td>39 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>71 ± 10</td>
<td>54 ± 11</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

![Fig. 2. Scatter diagram of serum cTnI concentration before operation and after arrival at the ICU in control and adenosine pretreated patients.](image-url)

![Fig. 3. Serum cTnI concentrations at different time points in both groups. The serum concentrations of cTnI were non-normally distributed; they were presented as mean ± SE. After logarithmically transformed to fit normal distribution, they were compared with repeated measurement data ANOVA. *: compared with control group at the same time point, p < 0.05.](image-url)
the current study, we used levels of troponin I as the primary measure of myocardial injury. Patients in the control group had significantly higher levels of troponin I in the postoperative period. The patients in the pretreatment group required significantly less inotropic agents at 0–3 h after arriving at the ICU, less time of ICU stay than the control patients (3.2 ± 1.2 days vs 3.9 ± 1.2 days, p = 0.013). These results indicate that adenosine pretreatment has a significant myocardial protective effect in combination with crystalloid cardioplegia arrest, and it also had some beneficial effects on postoperative recovery.

4.4. Clinical study of remote ischemic preconditioning (RIPC)

Some groups hypothesized that remote ischemic preconditioning could provide systemic protection against multiorgan IRI. Günaydın et al. [20] first showed that RIPC could decrease Lactate dehydrogenase (LDH) release 5 min after aortic cross-clamp removal in elective coronary artery bypass patients (n = 8). Hausenloy et al. [21] and Venugopal et al. [22] separately demonstrated that RIPC significantly decreased postoperative Cardiac troponin T (cTnT) release in elective CABG patients. Redington et al. [23] showed that RIPC provides myocardial and pulmonary protection in addition to reducing the systemic inflammatory response in patients who undergo congenital heart surgery. Recently, Zhou et al. [24] reported that RIPC protects against myocardial and pulmonary IRI (n = 60). A meta-analysis carried by Takagi et al. [25] demonstrated that RIPC significantly reduced biomarkers of myocardial injury in cardiovascular surgery patients over control treatment. Whether adenosine pretreatment provides better protection than RIPC against IRI in the clinical setting of congenital heart surgery warrants further investigation.

![Graph](image-url)
4.5. Study limitations

In this preliminary study of the effects of adenosine pretreatment in a clinical setting, we purposely chose children undergoing surgical repair of a diverse range of congenital heart defects. A larger multicenter study would enable us to discern variations in the effects of adenosine pretreatment in discrete subgroups of patients. After we finished this trial, we continued to use this adenosine pretreatment protocol in our clinical practice for half a year. But now, we do not use this protocol any more, partially because of the worry by some of our surgeons on the significant hypotension induced by adenosine pretreatment.

Furthermore, although there are reports of preconditioning properties of inhalational anesthetics and other stimuli, patients in this study were randomized to adenosine pretreatment or control groups. All patients received the same anesthetic, CPB, and intensive care management protocols to minimize bias. It is impossible to determine the optimal timing and administration protocol for adenosine pretreatment from the current study. The risk-benefit ratio of this therapy is so favorable that further studies should be focused on optimizing the pretreatment protocol.

4.6. Summary

We have demonstrated that pretreatment with a 10-min infusion of adenosine has myocardial protective effects for cardiac surgery. This novel finding supports the need for a larger study of adenosine pretreatment in patients undergoing cardiac surgery, and additional attention should be paid to the potential benefit of second-window preconditioning.

Acknowledgments

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

References


Appendix A. Conference discussion

Dr P. van de Woestijne (Rotterdam, Netherlands): As a congenital heart surgeon, I’m very interested in your results. In Rotterdam we participated in a trial, the adult part, with the use of adenosine in CABG patients to reduce ischemia-reperfusion injury. In fact, the inclusion was stopped by the company very recently. The preliminary results are not yet clear, but one of the reasons was that there was too little advantage for the company to expect some profits I think.
You showed some significant differences in the early parameters, the troponin I and inotropic use, but no real significant differences in long-term outcome, functional status, or left ventricular function. Do you think that these early differences are enough to use adenosine routinely, also in relation to the cost/benefit ratio?

Dr Jin: Our data concerns the beneficial effect of adenosine pretreatment from our preliminary results. Do you mean this?

Dr van de Woestijne: Well, with your early results, is that enough to use the adenosine routinely now regarding probably cost/benefit ratio?

Dr Jin: We continued this study, after we finished this work, for another half a year, and the data are still being collected and analyzed. Now, we do not perform adenosine pretreatment as a routine protocol because some of the surgeons think that the pressure decrease may be a risk in our routine practice. After this study we performed another 200 or more cases also in these settings.

Dr van de Woestijne: That brings me to one other short question. What is your practical strategy now, do you use it for specific indications, or can you elaborate on that?

Dr Jin: Can you repeat your question.

Dr van de Woestijne: Do you use adenosine in specific indications, in specific congenital cases where you expect most benefit from the ischemia—reperfusion injury, or just study-based?

Dr Jin: We use this kind of adenosine pretreatment in congenital heart disease, and we also use adenosine to enhance blood cardioplegia in adult heart disease, CABG and valve replacement procedures.

Dr J. Pepper (London, United Kingdom): Very interesting study. I just wondered, if you’re interested in cost-effectiveness, why you didn’t place a blood pressure cuff around the thigh of the child and use the method of remote preconditioning, which Andrew Reddington and colleagues in Toronto have shown produces the sort of reduction in troponin that you’ve demonstrated with the much more expensive adenosine?

Dr Jin: You mean the remote preconditioning method in children when they are undergoing cardiac surgery?

Dr Pepper: Correct.

Dr Jin: Actually we also performed some of these studies and we want to compare these two kinds of methods to show whether one has much more advantages over the other, but we have not got understandable results at present.