Effects of Dexmedetomidine on Biochemical Markers of Myocardial Injury after Pediatric Cardiac Surgeries

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Abstract

Background: Perioperative administration of alpha2-adrenergic agonist dexmedetomidine, has been shown to reduce anesthetic requirements, enhance hemodynamic stability and provide sedation during postoperative recovery following coronary artery bypass.

Biochemical markers are easily measured from blood samples and detect even minor levels of myocardial injury in all patients. Caveats concerning the myocardial specificity of biochemical markers after cardiac surgery (e.g., myoglobin and CK-MB are released predominantly but not exclusively from myocardium after cardiac surgery) can be resolved by the measurement of cTnT and cTnI, highly specific myocardial isoforms of the respective subunits of the troponin regulatory complex.

Methods: The present study included 40 pediatric patients undergoing repair of congenital heart defects with CPB including cyanotic and acyanotic patients, with average age of 6 months-8 years.

Patients were randomly allocated into 2 equal groups:
Group (A): Dexmedetomidine group (n=20).
Group (B): Control group (n=20).

Objective: To detect if there is a role of dexmedetomidine on biochemical markers of myocardial injury during cardiopulmonary bypass in infants and children undergoing corrective cardiac surgery.

Conclusion: Dexmedetomidine has a cardioprotective effect evidenced by lower values of biochemical markers of myocardial injury (cTnI, cTnT, CKMB and myoglobin) following pediatric cardiac surgeries.

Key Words: Dexmedetomidine – Biochemical – Myocardial – Pediatric – Cardiac surgeries.

Introduction

During repair of a congenital heart defects the child’s heart is exposed to myocardial hypoxia.

Impaired myocardial function after Cardiopulmonary Bypass (CPB) and surgical repair in children remain a commonly encountered clinical problem.

Alpha-2 agonists decrease central noradrenergic activity of the locus coeruleus with a decrease in systemic adrenaline and noradrenaline production. This may decrease the adrenergic response to the trauma of surgery and improve haemodynamic stability in the perioperative period. Decreasing the adrenergic response to surgery may also decrease the shear stress on vulnerable coronary plaques. Thus it is not surprising that alpha-2 agonists are potentially cardioprotective in the peri-operative period [1].

Perioperative administration of alpha2-adrenergic agonist dexmedetomidine, has been shown to reduce anesthetic requirements, enhance hemodynamic stability and provide sedation during postoperative recovery following coronary artery bypass [2].

The most popular biomarker for myocardial damage is Cardiac Troponin I (cTnI), with nearly total myocardial tissue specificity and extreme sensitivity, reflecting even a very small amount of myocardial necrosis. Postoperative serum cardiac troponin concentration is increased in all patients undergoing different types of cardiac surgery, an observation that highlights the essential sensitivity of the biochemical marker and a constant level of perioperative myocardial injury [3].

The cardiac specificity of these markers after pediatric cardiac surgery and release of troponins might be greater after pediatric than adult cardiac surgery [4].

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Patients and Methods

Patient population:
The study was conducted in Abou El-Resh Pediatric Hospital-Cairo University Unit of Congenital Heart Surgery, after approval of the local ethical committee and a written informed consent from the guardians of the patient. This study was conducted from September 2013 to June 2015. Patients were randomly allocated into 2 equal groups, 20 patients in each group using individual closed envelop randomization.

Inclusion criteria:
• All cases were performed using cardiopulmonary bypass (the study included cyanotic and acyanotic patients).
• Infants and children age from 6 months to 8 years.

Exclusion criteria:
• Ischemic time more than 1.30 hour.
• Pre-existing heart failure.
• Pre-operative CPR.
• Pre-operative use of inotropes or vasopressors.
• Pre-existing renal failure.
• Pre-existing cerebrovascular insult.

Pre-operative assessment:
All routine investigations include: CBC, coagulation profile, liver function tests, renal function tests, blood grouping, chest X-ray, recent echocardiography and angiography if available.

Anesthetic technique:
Premedication:
Ketamine 5mg/kg, midazolam 0.1mg/kg, atropine 0.02mg/kg IM 20min. before induction.

Preparation:
Upon the arrival to the operating theater:
- ECG lead II and V (with ST segment analysis), pulse oximetry, and non invasive blood pressure monitor were applied for all patients.
- The patient was put on a warm surface blanket (adjusted to 37º- 38ºC).
- An intravenous peripheral cannula was inserted and secured.
- Ceftriaxone was given as a slow bolus in a dose of 50mg/kg IV.

Patients were randomly allocated into 2 equal groups as follows:
Group (A): Dexmedetomidine group (n=20).
Group (B): Control group (n=20).

Induction:
- 2-3 µg/kg fentanyl and midazolam 0.1mg/kg IV were given.
- Pancuronium 0.1 mg/kg was given to facilitate the endotracheal intubation.
- Face mask ventilation for 3min., followed by tracheal intubation was done.
- End tidal capnography connected after endotracheal intubation.

Maintenance:
Inhalational: All patients received general anesthesia with mixture of Isoflurane 0.4%-1.5% in oxygen with the intent to maintain mean arterial blood pressure and heart rate within 20% ± of the base line.

Neuromuscular blocker: Boluses of pancuronium 0.01mg/kg/hr were given for maintaining neuromuscular blockade.

Opioids: Fentanyl boluses were supplemented at the time of skin incision, sternotomy, pericardial opening and the cannulation time at a dose of 2-3mcg/kg at each of these stages.

Mechanical ventilation: Pressure controlled ventilation was adjusted to maintain PaCO₂ between 30 and 35mmHg.

After insertion of a central venous catheter (internal jugular or femoral vein) and an arterial catheter (radial or femoral), in the DEX group, patients received an initial bolus dose of dexmedetomidine (0.5mcg/kg) over 10min., followed immediately by a continuous infusion of 0.5mcg/kg/h. The infusion started with the beginning of cardiopulmonary bypass and discontinued at the end of CPB. A similar volume of normal saline was given in the control group. Serum concentrations of Troponin T, Troponin I, CKMB and myoglobin were measured serially before and 1, 6 and 24 hours after the operation.

Intra-operative monitoring:
1- Cardiovascular system:
• Electrocardiogram: Standard five-leads system.
• Non-invasive blood pressure.
• Invasive arterial blood pressure.
• Central venous pressure.
• Urine output.
2- Ventilation:
- Oxygen saturation.
- End tidal carbon dioxide.
- Arterial blood gases analysis.
  A- After induction of anaesthesia and placement of central venous line and arterial line.
  B- Before cardiopulmonary bypass initiation.
  C- After surgical completion.

3- Temperature:
Nasopharyngeal and peripheral temperatures.

Extracorporeal circulation:
CPB was initiated after standard aorta-bicaval cannulation. A membrane oxygenator (Minimax Plus; Medtronic Inc., Anaheim, CA) and a non-pulsatile roller pump (model 10.10.00; Stöckert Instruments; Munich, Germany) were used. Fresh whole blood was added to the priming solution in appropriate amounts to achieve a hematocrit of 20% to 25% during CPB. Moderate hypothermia (28ºC to 30ºC) was used during CPB. Pump flows were 2.4 to 2.6L/min/m² during the normothermic period. Mean Arterial Pressure (MAP) was maintained by CPB flow adjustments between 30 and 50mmHg.

Measured variants:
Serum concentrations of Troponin T, Troponin I, CKMB and Myoglobin (measured by immunoassay methods). Serial samples as mentioned before.

Statistical method:
Categorical data was presented in the form of number (frequency) and analyzed using Chi-square test. Continuous data was presented as mean (standard deviation) and analyzed using unpaired t-test for single measures (of Troponin T, Troponin I, CKMB and Myoglobin) and two way analysis of variance (ANOVA) for repeated measures (hemodynamic parameters and blood gas analysis).

Sample size:
A total sample size of 40 patients, (20 in dex group, 20 in group control), was required to detect an assumed clinically significant dexmedetomidine induced effect on biochemical markers of myocardial injury during CPB in infants and children undergoing corrective cardiac surgery. The statistical test used is the power and sample size calculation (version 3.0.34) with a power level of 90% and a significance level (α) of 0.05. The proportion between the 2 groups was 1: 1.

Results

Demographic data:
Fourty patients were enrolled in the study. All demographic and operative data were comparable between both groups, (Table 1).

Effect on Cardiac Troponin I (cTnI) values:
The base line values of cTnI showed no statistically significant difference between the two groups. The cTnI values showed significant increase 1, 6 and 24 hours post CPB in both groups compared to the baseline values, with significantly higher levels in the control group [(Table 2) & Fig. (1)].

Effect on Cardiac Troponin T (cTnT) values:
The base line values of cTnT showed no statistically significant difference between the two groups. The cTnT values showed significant increase 1, 6 and 24 hours post CPB in both groups compared to the baseline values, with significantly higher levels in the control group [(Table 3) & Fig. (2)].

Effect on Creatinine Kinase MB (CKMB) values:
The base line values of CKMB showed no statistically significant difference between the two groups. The CKMB values showed significant increase 1, 6 and 24 hours post CPB in both groups compared to the baseline values, with significantly higher levels in the control group [(Table 6) & Fig. (5)].

Effect on Myoglobin values:
The base line values of Myoglobin showed no statistically significant difference between the two groups. The CKMB values showed significant increase 1, 6 and 24 hours post CPB in both groups compared to the baseline values, with significantly higher levels in the control group, except after 24 hours post CPB there were no significant difference between the two groups. [(Table 7) & Fig. (6)].

Table (1): Demographic data.

<table>
<thead>
<tr>
<th></th>
<th>Dex group</th>
<th>Control group</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age in months</td>
<td>31.60±29.85</td>
<td>49.90±36.66</td>
<td>0.095</td>
</tr>
<tr>
<td>Weight in kg</td>
<td>11.35±3.30</td>
<td>13.60±5.83</td>
<td>0.308</td>
</tr>
<tr>
<td>Gender male/female</td>
<td>12/8</td>
<td>12/8</td>
<td>1.000</td>
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Data expressed as mean (±SD).
p-value less than 0.05 is considered statistically significant.
Dex group: Dexmedetomidine group.
Dex group

Data were expressed as mean (±SD).

* : Statistically significant difference (p-value<0.05) between this variable at this time and baseline value in the same group.
The aim of the current prospective randomized single blinded clinical controlled study is to detect the role of dexmedetomidine on biochemical markers of myocardial injury in infants and children undergoing cardiac corrective surgery using cardiopulmonary bypass.

The main findings in the present study were the significant differences between dexmedetomidine group and control group regarding the biochemical markers of myocardial injury, where these markers showed significantly lower values in the patients who administered dexmedetomidine infusion during CPB.

Similar results were found by Hynek et al., it was an observational retrospective study comparing dexmedetomidine-ketamine group and sevoflurane-sufentanil group in adult patients undergoing coronary artery bypass grafting with the use of cardiopulmonary bypass. They concluded that ketamine-dexmedetomidine anesthesia during elective CABG resulted in lower postoperative levels of cTnI and CK-MB compared with sevoflurane-sufentanil anesthesia. They suggest that ketamine-dexmedetomidine anesthesia is a more favorable alternative to sevoflurane-sufentanil anesthesia in terms of cardioprotection in adult patients undergoing cardiac surgery [5].

Similarly, Hui et al., studied patients who were scheduled for mitral valve replacement under CPB. Patients were assigned to either the control group or the dexmedetomidine group. They concluded that dexmedetomidine has protective effects against myocardial ischemia/reperfusion injury during extracorporeal circulation evidenced by decreased levels of biochemical markers of myocardial injury and reactive oxygen species [7].

Another study was done by Kawasaki et al., had similar results. Patients had undergone elective cardiac surgery with CPB, and were randomly assigned into two groups. Patients in one group were received dexmedetomidine 1 µg/kg for 10min. after aortic cross-clamping, and 0.5 g/kg/h intraoperatively, while in the control group were received the same volume of saline. They concluded that perioperative dexmedetomidine infusion improves outcomes of cardiac surgery by lowering levels of biomarkers of myocardial injury and inflammatory mediators [8].

Similarly, Shen et al., studied the effect of dexmedetomidine in non-cardiac surgery. Patients having congenital heart diseases were scheduled for elective hip-replacement surgery and randomly allocated to receive a loading dose of 1 µg/kg dexmedetomidine followed by a 0.2 g/kg per h infusion (Dex group) or normal saline (control group). They concluded that Dexmedetomidine can reduce myocardial injury (confirmed by significantly decreasing values of cardiac troponin I and CKMB) and cytokine levels in patients with CHD undergoing non-cardiac surgery [9].
A recent study was done by Xiaohui et al., showed similar results. The study was done in patients undergoing off-pump coronary artery bypass grafting. Patients were randomly divided into three experimental groups that were separated by the dexmedetomidine administration protocol: A high-dose group (loading dose 1 \( \mu \)g/kg, maintenance dose 0.6 \( \mu \)g/kg/h), low-dose group (loading dose 0.6 \( \mu \)g/kg, maintenance dose 0.3 \( \mu \)g/kg/h), and control group (the same amount of 0.9% saline as placebo). They concluded that, dexmedetomidine decrease myocardial damage by lowering serum levels of cTnI and CK-MB [10].

Conversely Zeynep et al., showed different results. Adult patients undergoing elective CABG surgery were enrolled in the study, patients were divided randomly into 2 groups: The dexmedetomidine group or the placebo group. They concluded that, the administration of low-dose dexmedetomidine, 0.5mg/kg/10min of loading and 0.5mg/kg/h of infusion dose, did not reduce myocardial damage during CABG with CPB. These different results are most probably due to the difference in the primary outcome, in the current study the primary outcome was the effects of Dex on biochemical markers of myocardial injury, while the primary outcomes in their study were the cardiac index, central venous pressure and mean pulmonary arterial pressure [11].

**Conclusion:**

Dexmedetomidine has a cardioprotective effect evidenced by lower values of biochemical markers of myocardial injury (cTnI, cTnT, CKMB and myoglobin) following pediatric cardiac surgeries.

**References**


الملخص العربي

أشارت عدة دراسات تجريبية في السنوات الأخيرة إلى قربة عقار الديكسيدوميدين على الحد من متطلبات التخدير، تعزز استقرار الدورة الدمية وتوفير السكن للمريض أثناء التعافي بعد العمليات الجراحية للشرايين التاجية.

إن قياس الدلالات الكيميائية الحيوية الدالة على اصابة عضلة القلب عقب جراحات القلب للأطفال تم الاعتماد عليها في كثير من الدراسات لأنها تكشف عن وجود واب مستويات قليلة من اصابة عضلة القلب بجانب سهولة تحيلها عن طريق عينات الدم.

وقد شملت هذه الدراسة أربعين طفلاً خضعوا لعمليات القلب المقترح لإصلاح عيب خلقية في القلب مع تعرض الدورة الانتقالية للقلب والرثين وكان متوسط أعمارهم من بين ستة أشهر وثمانية سنوات. وقد شملت الدراسة الأطفال الذين يعانون من نقص الأكسجين بالدم.

وقد تم تقسيم المرضى عشوائياً إلى مجموعتين:
- المجموعة الأولى: مجموعة عقار الديكسيدوميدين.
- المجموعة الثانية: مجموعة التحكم.

النتائج: عقار الديكسيدوميدين له التأثيرات الواقية للقلب وذلك يتضح من انخفاض القيم للدلالات الكيميائية الحيوية الدالة على اصابة عضلة القلب.