The Role of Dexmedetomidine in Decreasing Acute Kidney Injury in Children with Acyanotic Heart Disease Undergoing Total Correction by A New Urinary Biomarker Kidney Injury Molecule-1

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Abstract

**Background:** Dexmedetomidine is an alpha 2 agonist with sedative properties. Some studies suggested that it has an organ protective effect. In this randomized controlled trial, we tested the protective effect of dexmedetomidine on the kidney in pediatric cardiac population.

**Patients and Methods:** Seventy two children with acyanotic heart disease were randomized into two groups, Group D (dexmedetomidine group) and Group C (control group) patients received an initial bolus dose of dexmedetomidine (0.5mcg/kg) over 10min in Group D and saline in Group C, followed by a continuous infusion of 0.5mcg/kg/h. Serum creatinine and KIM-1 were measured preoperatively and 24 hours postoperatively to diagnose AKI.

**Results:** Preoperative serume creatinine in Group D was (0.4±0.2) and (0.4±0.3) in Group C p=(0.1) while postoperative serum creatinine was (0.5±0.3) in Group D and (0.5±0.2) in Group C, p=(0.6). At twenty four hour KIM-1 (612.21 ±683.80) pg/ml in Group D and (576.89 ±686.78) pg/ml in Group C p=(0.8). In patients with prolonged bypass time >90 minutes, the level of KIM-1 was (666.8 ±734.15) in Group D and (986.7 ±691.13) in Group C (p=0.03).

**Conclusion:** Dexmedetomidine showed a protective effect on the kidney in children underwent prolonged cardiopulmonary bypass (>90min) assessed by KIM-1 at 24 hours post-bypass.

**Key Words:** Dexmedetomidine – Urinary biomarkers – KIM-1 – Pediatric cardiac patients.

Introduction

BASED on the evidence derived from post-operative AKI, which demonstrated a clinically relevant threshold of renal dysfunction in the setting of cardiac surgery, it is now widely accepted that even a mild increase in serum creatinine level (>0.3mg/dl) is an independent predictor of morbidity and mortality [1].

A recent proposal by the Acute Kidney Injury Network appears to have gained clinical acceptance. In that initiative, two options are outlined for measuring the abrupt (≤48 hour) reduction of kidney function which signifies AKI:

- Increased serum creatinine levels (absolute, ≥0.3 mg/dL; percentage, ≥50%; or 1.5-fold from baseline) or
- Oliguria (less than 0.5mL/kg/h for more than 6 hours).

The acronym RIFLE defines AKI by three grades of increasing severity (risk, injury, failure) and outlines two outcome variables (loss and end-stage). This system, much like that of the Acute Kidney Injury Network, describes the severity of renal dysfunction on the basis of increase in serum creatinine levels and decrease in urine output [2].

Necrosis and apoptosis of tubular cells lead to tubular obstruction, which contributes to the reduction of GFR. In addition, elevated intracellular calcium levels from tubular damage cause a series of cellular-level alterations that culminate in increased tubule-glomerular feedback, and thus, diminished GFR. These pathophysiologic mechanisms result in intrarenal vasoconstriction and, eventually, ischemia.

In order to facilitate the repair of congenital heart lesions, Cardiopulmonary Bypass (CPB) was developed. The extracorporeal circuit takes venous blood from the patient, pumps it through an oxygenator and filter, and returns it to the arterial system of the patient, thus bypassing the heart and lungs. Variation exists between types of pumps, oxygenators, venous reservoirs, and the size and coating of tubing and cannulae [3].
Cardiopulmonary bypass is still an unavoidable prerequisite for complete repair or palliation of many congenital cardiac defects. The current policy in cardiac surgery is to perform a complete repair of congenital heart defects early in life, preferably in neonate and infant patients, before the heart and other organs adapt and change according to the abnormal physiology.

Roller pumps, the most widely used type in pediatric perfusion, consist of two rollers oriented 180 degrees from each other. They provide continuous blood flow by partially occluding the tubing between the roller and the pump casing. Blood is displaced in a forward direction by the roller, resulting in continuous, nonpulsatile flow. During CPB reduction in plasma proteins and clotting factors, decreases in colloid osmotic pressure, electrolyte imbalance, and an exaggerated release of stress hormones, with activation of complement. Hematocrits of 40% coupled with hypothermia and the nonpulsatile flow of CPB impairs blood flow through the microcirculation including renal vasculature [4].

Serum creatinine levels can vary widely with age, gender, lean muscle mass, muscle metabolism, and hydration status. Serum creatinine concentrations may not change until about 50% of kidney function has already been lost, at lower rates of glomerular filtration, the amount of tubular secretion of creatinine results in overestimation of renal function. The use of serum creatinine as a therapeutic trigger has resulted in the failure of landmark clinical trials of interventions for AKI in humans.

Fortunately, the application of innovative technologies has uncovered several novel biomarkers. The most promising of these are included in a putative AKI Biomarker Panel, consisting of Neutrophil Gelatinase-Associated Lipocalin (NGAL), Interleukin-18 (IL-18), and Kidney Injury Molecule-1 (KIM-1). These biomarkers have completed initial validation, and have entered the prospective screening stage in the biomarker development process, facilitated by the development of commercial tools for their reproducible measurement across laboratories [5].

Conventional urinary biomarkers such as casts, fractional excretion of sodium, filtered high molecular weight proteins and tubular proteins or enzymes have been insensitive and nonspecific for the early recognition of AKI.

The kidney injury molecule-1 mRNA was identified using techniques of representational difference analysis, a PCR-based technique, which was carried out to find genes whose expression was markedly upregulated 24-48h after ischaemia in the rat. KIM-1 was the gene found to be most highly upregulated in this screen. There are a large number of studies in animals showing robust KIM-1 protein production in the affected segments of the proximal tubule whenever a toxin or pathophysiological state results in dedifferentiation of the epithelium. With injury KIM-1 mRNA is rapidly made and protein is generated and localized at very high levels on the apical membrane of proximal tubule in that region where the tubule is most affected [6].

Dexmedetomidine is a potent and highly selective α-2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties. It is the most recently developed and commercialized agent in this pharmacological class. It provides a unique “conscious sedation” without respiratory depression. It decreases Central Nervous System (CNS) sympathetic outflow in a dose dependent manner and has analgesic effects best described as opioid-sparing. There is increasing evidence of its organ protective effects against ischemic and hypoxic injury, including cardioprotection, neuroprotection and renoprotection [7].

By attenuating sympathetically mediated hypodynamic responses, α-2 adrenoceptor agonists ameliorate the hemodynamic profile during the perioperative period. Previous studies have shown that hemodynamic stabilization by the application of α-2 adrenoceptor agonists in the perioperative period leads to a reduction in perioperative myocardial ischemia episodes. However, theoretical considerations against the use of α-2 adrenoceptor agonists have been the vasoconstrictive and hypotensive properties, which are potentially proischemic. At present, a reduction in myocardial ischemia and improved outcomes for patients at risk of cardiac events has only been documented for clonidine as a clinically available α-2 adrenoceptor agonist. Future studies will have to be focused on whether dexmedetomidine provides similar properties in reducing the incidence of myocardial ischemia and postoperative mortality compared with clonidine [7,8].

The effects of dexmedetomidine on renal function are complex. α-2 agonists exert a diuretic effect by inhibiting the antidiuretic Action of Vasopressin (AVP) at the collecting duct most likely through α-2a receptors, resulting in decreased expression of aquaporin-2 receptors and decreased salt and water reabsorption [7,9].
Material and Methods

This study was dedicated to investigate the role of dexmedetomidine in decreasing AKI post bypass using KIM-1 and comparing it to serum creatinine. The study was conducted in the unit of congenital heart surgery, Abo El-Reesh Pediatric Hospital-Cairo University after the approval of the local ethical committee and a written informed consent from the guardians of the patients. It is a randomized controlled study that was conducted from November 2012 to April 2014. Seventy two Infants and children with ages ranging from 6 months to 8 years, weight ranging from 5 kilograms to 25 kilograms. Lesions included acyanotic heart disease (e.g ASD, VSD, Common AV canal) patients undergoing total corrective surgeries using CPB. We excluded Patients with pre-existing heart failure, pre-operative use of inotropes or vasopressors, pre-existing renal failure or hepatic failure and pre-existing thrombocytopenia.

The patients were randomly divided into two groups, Group D (dexmedetomidine group) and Group C (control group) using the sealed envelope method of randomization. Each group included 36 patients.

The children were sedated with 0.2mg/kg Midazolam, atropine 0.02mg/kg and 2mg/kg ketamine I.M. 20min before induction. Patients were put on full monitor and induction by 2-3 µg/kg fentanyl, Pancuronium 0.1mg/kg followed by tracheal intubation was done. Corticosteroid bolus 5mg/kg, tranexamic acid 10mg/kg followed by boluses of 1mg/kg after cardiopulmonary bypass were given.

Pressure controlled ventilation was adjusted to maintain PaCO2 between 30 and 35mmHg. A central venous line (internal jugular or femoral vein) and an arterial line was inserted for invasive blood pressure monitoring.

In the DEX Group (D), patients received an initial bolus dose of dexmedetomidine (0.5mcg/kg) (Precedex; Hospira Inc., Lake Forest, Illinois, USA Vial contains 200mcg/2ml) over 10min, followed immediately by a continuous infusion of 0.5mcg/kg/h. The infusion continued throughout the operation and has been discontinued at the end of CPB. A similar volume of normal saline was given in the control group. Three urine samples from each patient were then taken, the first sample after induction and before going on bypass and the second and third samples were taken 9 hours and 24 hours post operatively in the ICU.

In all patient median sternotomy was performed. CPB was initiated after standard aorto-bicaval cannulation. Moderate hypothermia (26°C to 28°C) was used during CPB. Pump flows was 2.4 to 2.6 L/min/m² during the normothermic period, Mean Arterial Pressure (MAP) was maintained by CPB flow between 30 and 50mmHg.

For quantitation of KIM-1, 1ml of urine from urine bag was collected in a vacutainer and stored at –80°C till quantitation of KIM-1 was done. Collected urine samples were allowed to sit at room temperature for 30 minutes to sediment, and the supernatant was aliquoted and stored at –70°C until analysis.

Urine samples were centrifuged at 3000xg for 10 minutes then the supernatant was separated for detection of human KIM-1 by ELISA kit. The ELISA kit was provided by Aviscera Bioscience Inc, Santa Clara, USA (Cat No SK00186-01). Our Reference Range Of Urine KIM-1 was 60-837 pg/ml.

Statistical analysis:

The data was analyzed and presented as mean, standard deviation SD, median and standard error of the mean SEM. The two studied groups were compared using Student's t-test. Repeated measures of the same group were compared using two way ANOVA followed by post-hock Tukey's comparison tests. p<0.05 were considered significant.

Results

Regarding demographic data, there was no significant difference between the two groups regarding age, weight, cardiac lesions and associated comorbidities (Table 1).

Table (1): Demographic data and patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group D</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>28.3±23.2</td>
<td>27.0±23.9</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kilograms)</td>
<td>11±4.6</td>
<td>11±5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Lesion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD</td>
<td>4 (11%)</td>
<td>10 (28%)</td>
<td>NS</td>
</tr>
<tr>
<td>CAVC</td>
<td>15 (42%)</td>
<td>14 (39%)</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>12 (33%)</td>
<td>10 (28%)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5 (14%)</td>
<td>2 (5.6%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comorbidities</td>
<td>33</td>
<td>27</td>
<td>NS</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>3 (8.3%)</td>
<td>9 (25%)</td>
<td></td>
</tr>
<tr>
<td>Antifailure drugs</td>
<td>12 (33%)</td>
<td>10 (28%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Group D : Dexmedetomidine group.
Group C : Control group.
VSD : Ventricular septal defect.
ASD : Atrial septal defect.
CAVC : Complete atrioventricular canal.
NS : Non significant.
There was no significant difference between the two groups regarding mean arterial blood pressure at skin incision and sternotomy, ischaemic time and bypass time on CPB (Table 2).

Table (2): Hemodynamics and CPB variables.

<table>
<thead>
<tr>
<th></th>
<th>Group D</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP 1</td>
<td>98±10.9</td>
<td>76±15.3</td>
<td>NS</td>
</tr>
<tr>
<td>MAP 2</td>
<td>72.8±8.3</td>
<td>71±13.5</td>
<td>NS</td>
</tr>
<tr>
<td>Ischemic time</td>
<td>50 (30-87)</td>
<td>45 (20-60)</td>
<td>NS</td>
</tr>
<tr>
<td>Bypass time</td>
<td>67.5 (60-120)</td>
<td>60 (32-87)</td>
<td>NS</td>
</tr>
</tbody>
</table>

MAP1: Mean arterial blood pressure during skin incision.
MAP2: Mean arterial blood pressure during sternotomy.

Regarding standard Kidney function tests plasma urea and creatinine and urine output, there was no significant difference between the two groups preoperatively or postoperatively (Table 3).

Table (3): Standard kidney function tests.

<table>
<thead>
<tr>
<th></th>
<th>Group D</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline creatinine</td>
<td>0.4±0.2</td>
<td>0.4±0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Baseline urea</td>
<td>19.1±5.9</td>
<td>20.1±5.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Postoperative creatinine</td>
<td>0.5±0.2</td>
<td>0.5±0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Postoperative urea</td>
<td>23.3±13.9</td>
<td>23.8±6.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Urine Output (ml/kg/day)</td>
<td>2.8±1.6</td>
<td>2.4±0.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Concerning Kidney Injury Molecule-1 it was measured in the urine preoperatively (baseline KIM-1), after nine hours and after twenty four hours postoperatively. The reference range for the normal values of KIM-1 that would be found in urine is 60-837 pg/ml.

Baseline KIM-1 in Group D was (165.71 ± 253.67) pg/ml urine and (173.20 ± 276.74) pg/ml in Group C with no significant difference between the two groups (p=0.8). Also after nine hours postoperative levels showed no significant difference between Group D and C in both groups with levels (256.32±395.08) pg/ml and (248.42±430.30) pg/ml in Group D and Group C respectively (p = 0.7). Although there was a noticeable rise between the nine hour KIM-1 and twenty four hour KIM-1; it was not statistically significant between the two groups where it was (612.21 ± 683.80) pg/ml in Group D and (576.89±686.78) pg/ml in Group C (p=0.8).

By subgroup analysis, patients with prolonged bypass time more than 90 minutes [17 (47%) of Group D and 16 (44%) of Group C], it was found that KIM-1 at 24 hours was significantly higher in Group C than in Group D (Table 4).

Table (4): KIM-1 in patients with prolonged bypass: Data presented as mean, standard deviation and frequency (%).

<table>
<thead>
<tr>
<th></th>
<th>Group D</th>
<th>Group C</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with prolonged bypass</td>
<td>17 (47%)</td>
<td>16 (44%)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline KIM-1</td>
<td>111.8±126.1</td>
<td>108.31±121.80</td>
<td>0.9</td>
</tr>
<tr>
<td>Nine hour postoperative KIM-1</td>
<td>163.3±274.7</td>
<td>403.52±590.79</td>
<td>0.1</td>
</tr>
<tr>
<td>Twenty four hours KIM-1</td>
<td>666.8±734.15</td>
<td>986.7±691.13</td>
<td>p=0.03</td>
</tr>
</tbody>
</table>

Discussion

This study showed that dexmedetomidine didn’t exert a protective effect on the kidney after CPB in children undergoing repair of congenital acyanotic cardiac lesions. This is shown by the non-significant difference in the standard kidney function tests (serum creatinine, urea and urine output) and in urinary KIM-1 at 0, 9 and 24 hours.

Dexmedetomidine exerted a protective effect on the kidney in the group underwent prolonged CPB >90mins as shown by the significant difference in KIM-1 at 24 hours between the groups.

So in the present study, the use of dexmedetomidine didn’t decrease AKI except in patients with
prolonged bypass time and only diagnosed when measured by KIM-1 and not detected by plasma creatinine.

Agreeable with the current study Ji et al., in a retrospective study involving adult and pediatric patients undergoing cardiac surgery, proved the renal protective role of dexmedetomidine during cardiac surgery and CPB. They studied the relationships among Acute Kidney Injury (AKI), chronic renal disease and potential benefits by post-bypass dexmedetomidine. AKI was divided into three stages based on Acute Kidney Injury Network (AKIN) criteria.

They found that post-bypass dexmedetomidine use was associated with significantly reduced incidence of total AKI (26.1% vs. 33.75%, \( p = 0.7033 \)) \((0.540 \text{ to } 0.916; \ p=0.0089)\). In addition, post-bypass dexmedetomidine use was more likely to reduce the incidence of AKI in these patients with preoperative normal kidney function and mild CKD. Also after cardiac surgery post-bypass infusion of dexmedetomidine was associated with significantly reduced incidence of any complication and 30-day mortalities \([10]\).

But Salah et al. \([11]\), in their study had a different result where eighty adult patients with mild to moderate renal impairment (serum creatinine between 1.5-2mg/dl) scheduled for elective CABG with cardiopulmonary bypass were randomly allocated to either dexmedetomidine infusion or placebo infusion groups (started at a dose 1mcg/kg bolus followed by a continuous infusion of 0.5mcg/kg/h until skin closure). Assessment of renal functions included serum creatinine, creatinine clearance, and urinary output in the 72h postoperatively. No significant difference was detected for any indicators of renal function between both groups, except for an increase in urinary output in the dexmedetomidine infusion group in the first 24h after surgery.

Similarly, Leino et al. \([12]\), tested the hypothesis that dexmedetomidine would improve kidney function in patients undergoing elective CABG during the first two postoperative days. Patients with normal renal function and scheduled for elective CABG were randomized to placebo or to infusion of dexmedetomidine to achieve a pseudo steady-state plasma concentration of 0.60ng/ml. The infusion was started after anesthesia induction and continued until 4h after surgery. The primary endpoint was creatinine clearance. No significant different results were recorded for any indices of renal function except for a mean 74% increase in urinary output with dexmedetomidine in the first 4h after insertion of a urinary catheter.

In the present study we used urinary KIM-1 as our primary determinant of AKI in addition to plasma creatinine and creatinine clearance like the previously mentioned studies; emphasizing the idea that dexmedetomidine does decrease the risk of AKI post-bypass. And as it is a fairly new addressed subject specially in the pediatric population \([13]\).

A bigger sample size with more versatile cardiac lesions can give us a better idea about the effect of dexmedetomidine in renal protection and more information about the possible side effects of its use specially in the pediatric population.

**Conclusion:**

Dexmedetomidine showed a protective effect on the kidney in children underwent prolonged cardiopulmonary bypass (>90min) assessed by KIM-1 at 24 hours post-bypass.

**References**


The Role of Dexmedetomidine in Decreasing Acute Kidney Injury in Children


