Improvement in Creatinine Clearance after Open Heart Surgery in Infants as an Early Indicator of Surgical Success

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ABSTRACT: **Background:** Early surgical correction of congenital heart malformations in neonates and small infants may be complicated by acute kidney injury (AKI), which is associated with higher morbidity and mortality rates, especially in patients who require dialysis. Glomerular filtration rate (GFR) is considered the best measurement of renal function which, in neonates and infants, is highly dependent on heart function.

Objective: To determine whether measurements of creatinine clearance after open heart surgery in neonates and young infants can serve as an early indicator of surgical success or AKI.

Method: We conducted a prospective observational study in 19 neonates and small infants (body weight < 5 kg) scheduled for open heart surgery with cardiopulmonary bypass. Urine collection measurement of creatinine clearance and albumin excretion was performed before and during surgery and four times during 48 hours after surgery.

Results: Mean creatinine clearance was lowest during surgery (25.2 ± 4. ml/min/1.73 m^2) and increased significantly in the first 16 hours post-surgery (45.7 ± 6.3 ml/min/1.73 m^2). A similar pattern was noted for urine albumin which was highest during surgery (203 ± 31 µg/min) and lowest (93 ± 20 µg/min) 48 hours post-surgery. AKI occurred in four patients, and two patients even required dialysis. All six showed a decline in creatinine clearance and an increase in urine albumin between 8 and 16 hours post-surgery.

Conclusions: In neonates and small infants undergoing open heart surgery, a significant improvement in creatinine clearance in the first 16 hours postoperatively is indicative of a good surgical outcome. This finding has important implications for the early evaluation and treatment of patients in the intensive care unit on the first day post-surgery.

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Surgical correction of congenital heart malformations in neonates and small infants may be complicated by acute kidney injury (AKI), which increases hospitalization time and mortality risk, especially in patients who require dialysis [1-4]. Large pediatric series have reported a 30–40% rate of AKI after open heart surgery. Risk factors included young age and long cross-clamp and cardiopulmonary bypass times [1,2,5,6]. Other authors found that neonate and infant weight < 5 kg posed the highest risk for significant AKI and the need for dialysis [3,5,7].

Several studies have shown that changes in various biochemical factors in the first hours after surgery could serve as early indicators of AKI in the pediatric age group [2,8-10]. However, none of them focused on neonates, who account for nearly 20% of all congenital heart malformation repairs, and not all the markers identified are available in daily clinical work [2,8-10]. Although a recent study reported promising results using the urine albumin/creatinine ratio, a common clinical test [6], patients younger than 1 month were excluded because of the unique characteristics of proteinuria in this population [6].

Glomerular filtration rate (GFR) is the best measure of renal function. A significant (twofold) physiological increase in GFR has been reported from birth to age 6–8 weeks [11]. The increase is caused mainly by an increase in renal plasma flow which, in turn, is highly dependent on cardiac function [11]. The aim of the present study was to assess whether the trend in creatine clearance and albuminuria measured by timed urine collection can serve as an early marker of cardiorenal function in neonates and small infants (weight < 5 kg) after open heart surgery.

PATIENTS AND METHODS

A prospective observational study design was used. The study group comprised 19 infants admitted to the pediatric cardiac intensive care unit of a tertiary university-affiliated pediatric medical center for correction of a congenital heart anomaly. Other inclusion criteria were weight < 5 kg, absence of kidney, or electrolyte dysfunction. None of the infants was receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or aldosterone antagonist at the time of admission. The parents of all infants gave informed consent and the study was approved by the Institutional Ethics Committee.

PROCEDURE

Two methods of preoperative urine collection were used, depending on the method of patient management by the attending physician. When a Foley catheter was used to monitor urine output preoperatively (n=8), we performed an 8 hour urine collection. When a Foley catheter was inserted immediately after the patient was placed under general anesthesia (n=11), urine was collected for 30–60 minutes while the patient was prepared for surgery. Mean creatinine clearance was similar for the two methods of urine collection (31 ± 5.7 ml/min/1.73 m^2 for the 8 hour collection, 34 ± 4.7 ml/min/1.73 m^2 for the shorter collection). Similar results on the accuracy of 2 hour urine collection were reported [12].

Urine collection was repeated from onset of surgery until the patient arrived at the cardiac intensive care unit, and then again at 8, 16, 24, and 48 hours after surgery. Urine collection was stopped if the patient required peritoneal dialysis.

As a surrogate marker of surgical stress and AKI, we used values of microalbuminuria, which has been shown to predict disease severity and mortality in critically ill patients [13,14] and acute kidney disease after open heart surgery in children [6] and adults [15].

MEASUREMENTS

Levels of blood and urine creatinine were determined by the Jaffe method using the Beckman Creatinine Analyzer 2 (Brea, CA, USA). Urine albumin was determined using a double antibody radioimmunoassay kit (DPC, Los Angeles, CA, USA). In addition, the surgical severity score was calculated according to Hannan [16], and the Pediatric Risk of Mortality (PRISM) score was calculated 24 hours after surgery.

AKI DEFINITION

AKI was defined according to the Acute Kidney Injury Network (AKIN) study [17] as follows:

- stage 1: a 50% or 0.3 mg/dl rise in serum creatinine from the preoperative value
- stage 2: doubling of the serum creatinine value
- stage 3: tripling of the serum creatinine value or being on dialysis.

STATISTICAL ANALYSIS

Mean (± SD) values of the biochemical parameters were compared over time using analysis of variance (ANOVA) with repeated measures and the post-hoc Student-Newman-Keuls test. A P value < 0.05 was considered statistically significant.

RESULTS

CLINICAL CHARACTERISTICS AND SURGICAL SCORES

The study group included 7 males and 12 females whose mean age was 3.2 ± 2.3 months and mean weight 3.7 ± 0.6 kg. Eight children had a ventricular septal defect, three had transposition of the great arteries, two had an atrioventricular septal defect, and six had other cardiac anomalies. Mean bypass time for the whole cohort was 136 ± 48 minutes, and mean aortic cross-clamping time 93 ± 49 minutes. Mean surgical stress score was 3.6 ± 2.6 and mean PRISM score 24 hours after surgery 2.4 ± 1.

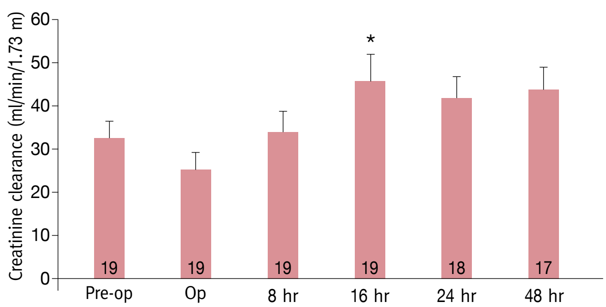
CREATININE CLEARANCE

Figure 1 shows the creatinine clearance results at the different time points of urine collection in the present cohort. Preoperatively, mean creatinine clearance was similar for the two methods of urine collection: 31 ± 5.7 ml/min/1.73 m^2 for 8 hour collection (n=8) and 34 ± 4.7 ml/min/1.73 m^2 for 30–60 minute collection at onset of general anesthesia. These values are lower than the normal. The normal mean GFR in the neonate/small infant age group is 39 ± 15.1 ml/min1.73 m^2 at age 3–4 days, 54.6 ± 7.6 ml/min1.73 m^2 at age 1–2 weeks, and 87.7 ± 22.3 ml/min1.73 m^2 at age 4–6 months [11]. The lowest mean creatinine clearance value was found during surgery (25.2 ± 4.6 ml/min/1.73 m^2) and the highest 16 hours post-surgery (45.7 ± 6.3 ml/min/1.73 m^2). The difference was statistically significant ($P < 0.05$). There was no significant change in creatinine clearance from 16 to 48 hours after surgery.

URINE ALBUMIN

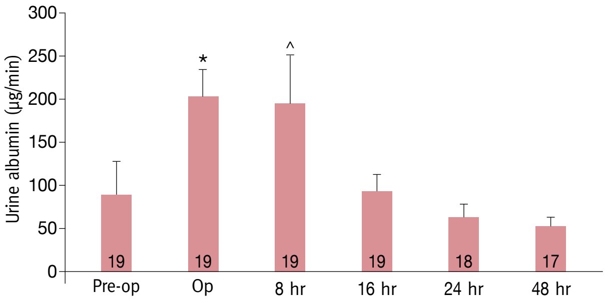
Albuminuria was calculated in two ways: albumin excretion rate (μg/min) and albumin-to-creatinine ratio (μg/mg). The normal albumin excretion rate in infants weighing < 5 kg is not known. The normal albumin-to-creatinine ratio in healthy newborns is 5 to 10 times higher than in adults (range 150–300 μg/mg), and at age 6 months 3 times higher than in adults [18,19]. The albumin excretion rates for the present sample at the six time points are shown in Figure 2. The highest rate was found during surgery (203 ± 31 μg/min) and the lowest 48 hours after surgery (53 ± 11 μg/min). The difference was statistically significant ($P < 0.05$). Most of the decrease occurred at 8–16 hours (level at 16 hours 93 ± 20 μg/min). Significant differences were also noted between early values,

Figure 1. Trend in creatinine clearance before, during and after open heart surgery in infants weighing < 5 kg. Creatinine clearance (mean ± SD) was measured by timed urine collections. The lowest value was noted during surgery and the highest 16 hours after surgery. The 16 hour value was nearly double the intraoperative value, and the difference was statistically significant



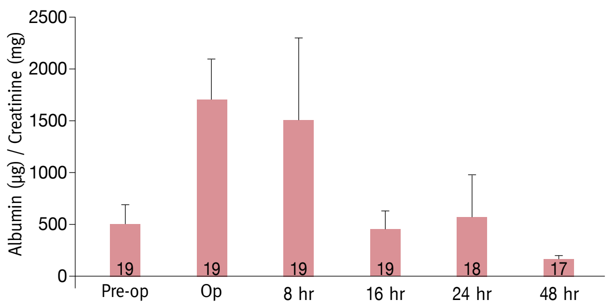
$P < 0.05$ Op vs. 16 hr

Figure 2. Trend in albumin excretion rate before, during and after open heart surgery in infants weighing < 5 kg. Albumin (mean ± SD) was measured by timed urine collections. The highest value was noted during surgery, and the lowest 48 hours after surgery. The main decrease occurred between 8 and 16 hours postoperatively. The intraoperative and 8 hour postoperative values were significantly higher than the values at the other time points. The level before surgery was higher than the level 48 hours after surgery



P < 0.05 Op vs. Pre-op, 16 hr, 24 hr, 48 hr
P < 0.05 8 hr vs. Pre-op, 16 hr, 25 hr, 48 hr

Figure 3. Trend in albumin-to-creatinine ratio before, during and after heart surgery in infants weighing < 5 kg. The results are mean and standard deviation. The trend was similar to that seem for albumin excretion rate [Figure 2], but the difference between the highest value (during surgery) and the lowest (48 hours after surgery) was not statistically significant



before and 8 hours after surgery, and later values, at 16, 24 and 48 hours ($P < 0.05$).

The albumin-to-creatinine ratios at the six time points are shown in Figure 3. The highest value was found during surgery (1706 ± 382 µg/mg) and the lowest 48 hours after surgery (174 ± 35 µg/mg). Although the pre-surgery value was nearly three times higher than the 48 hour post-surgery value, the difference did not reach statistical significance ($P = 0.059$).

ACUTE KIDNEY INJURY AND NEED FOR DIALYSIS

AKI occurred in four patients (21%); one patient had stage 1 disease, one patient had stage 2, and two patients had stage 3 disease. The patients with stage 3 disease received peritoneal dialysis because of low urine output (< 0.5 ml/kg/hr), starting between 18 and 24 hours after surgery. One died on the third postoperative day; the other required dialysis for only 3 days and was discharged home with normal renal function. These patients were the only ones in the group with creatinine clearance < 20 ml/min/1/73 m^2 8 hours post-surgery, and two patients requiring dialysis were the only ones whose creatinine clearance continued to decline 16 hours post-surgery.

DISCUSSION

The present study shows that neonates and small infants with congenital heart malformations who undergo successful early surgical correction exhibit a significant improvement in creatinine clearance and a reduction in albuminuria in the first 16 hours postoperatively. We found that severe AKI (usually requiring dialysis) developed only in the patients in whom creatinine clearance did not improve or who failed within the first 24 hours postoperatively.

To the best of our knowledge, this is the first study on changes in creatinine clearance before, during, and up to 48 hours after open heart surgery that focuses on neonates or infants weighing < 5 kg. Previous studies that measured GFR or creatinine clearance by timed urine collections included a wider range of patients of different ages and weights and usually concentrated on changes that occurred during surgery or the immediate postoperative period [6,8,10,20]. Their results are in line with ours when younger patients were evaluated [8,20] but not when older pediatric patients were evaluated [6,10].

An interesting observation in the present study was the abnormally low creatinine clearance preoperatively. As noted above, our search of the literature yielded no data on creatinine clearance prior to open heart surgery in patients weighing < 5 kg. The low values noted here may have been secondary to the considerable heart dysfunction in the patients, given the significant improvement noted already 24–48 hours after surgical repair [Figure 1].

Creatinine clearance measurement by timed urine collections is not a precise estimate of GFR, especially when GFR is abnormal and the patient is not in steady state [6,11]. However, our goal was not to accurately measure GFR but to identify a routinely available, easily measured biological factor that could potentially serve as a marker of overall cardiorenal function in the first 48 hours after heart surgery in neonates/small infants in the cardiac intensive care unit setting. We selected timed urine creatinine clearance based on previous reports of a strong correlation between cardiac function and GFR after open heart surgery in infants [21,22]. Furthermore, it is widely assumed that following a reduction in GFR, tubular creatinine excretion or back-leak is minimal relative to the reduction in filtrated creatinine [21,23,24]. Therefore, researchers hypothesized that an acute reduction in GFR is associated with a faster decrease in urine creatinine excretion and slower increase in serum creatinine hours and days later [23]. Our results support this hypothesis in neonates/small infants.

We also showed that the rate of urine albumin excretion increases during surgery, remains high up to 8 hours later, and returns to baseline 24 hours after surgery. Accordingly, previous studies reported that urine albumin levels rise in response to stress and are correlated with the surgical stress score [6,13,14,25]. Recently, studies in both children older than 2 years and adults noted that the presence of albuminuria soon after open heart surgery may serve as an equally good early marker of AKI as other tested biomarkers [6,15].

We found that the urine albumin level was abnormal before surgery, significantly increased at onset of surgery, and subsequently decreased to normal range 8–16 hours after surgery. Both the albumin-to-creatinine ratio and the albumin excretion rate varied widely between samples taken during surgery and in the first 8 hours after surgery, and there was no statistically significant difference between the four patients who developed AKI and the remaining patients. This observation supports the suggestion of Zappitelli and colleagues [6] regarding the problematic use of albuminuria as a marker of AKI in infants.

Our study has a number of limitations. The small sample and observational design precluded conclusions about an association of the trend in creatinine clearance with such surgical factors as cross-clamp and bypass time, with the primary disease, or with the development of AKI. Secondly, we did not compare the findings to any of the new early markers of AKI, such as neutrophil gelatinase-associated lipocalin (NGAL) which has also been found effective in infants and children after open heart surgery [9].

In summary, our study on infants weighing < 5 kg who undergo open heart surgery shows a statistically significant improvement in creatinine clearance in the first 16 hours postoperatively. The difference between a mean GFR of 25 and 48 ml/min/1.73 m^2 is indicative of a good surgical and renal outcome. This pattern can be utilized for clinical purposes in the setting of a cardiac intensive care unit. It may assist physicians in the evaluation of patients on the first day after surgery and instigating prompt early therapy to improve the hemodynamic status when necessary.

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