Early Prediction of Acute Kidney Injury using Serum Phosphorus as a Biomarker in Pediatric Cardiac Surgical Patients

Abstract

Background: Acute kidney injury (AKI) is a strong predictor of morbidity and mortality after cardiac surgery. Lack of valid early biomarkers for predicting AKI has hampered the ability to take therapeutic measures for preventive cause. Hyperphosphatemia that occurs in AKI due to renal excretion defect was not studied in this context and could be simple marker of AKI. Therefore, we tested role of serum phosphorus in prediction of AKI as a biomarker after cardiac surgery in children. **Methodology:** We prospectively evaluated 51 children aged between 3 weeks and 12 years undergoing elective cardiac surgery. Serum creatinine and phosphorus were measured preoperatively and postoperatively at 24 and 48 h. As per the Kidney Disease Improving Global Outcomes criteria, patients were grouped into AKI and non-AKI on the basis of the development of AKI within 48 h postsurgery. The postoperative diagnostic performance of phosphorus thresholds was analyzed by the area under receiver operating characteristic curves (AUC-ROC). **Results:** From 51 children included, 10 developed AKI. In AKI group, serum phosphorus increased significantly from 4.47 ± 0.43 baseline to 6.29 ± 0.32 at 24 h postsurgery ($P = 0.01$) while serum creatinine increased from baseline 0.33 (0.24–0.46) to 0.49 (0.26–0.91) at 24 h which is statistically insignificant ($P = 0.16$). ROC analysis showed that serum phosphorus at 24 h, the AUC was 0.84 with sensitivity 0.75 and specificity 0.93 for a cutoff value of 6.4 mg/dl. Whereas serum phosphorus at 48 h, the AUC was 0.86 with sensitivity 66.67% and specificity 97.62% for a cutoff value of 5.4 mg/dl. **Conclusion:** Serum phosphorus can be an alternative biomarker as early as 24 h for early prediction of AKI in pediatric cardiac surgery.

Keywords: *Acute kidney injury, biomarker, Kidney Disease Improving Global Outcomes, phosphorus*

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Introduction

Acute kidney injury (AKI) is a common complication after pediatric cardiac surgery with the incidence between 9.6% and 52%.[1] It is an independent predictor of morbidity and mortality in children who undergo cardiac surgery with mortality rate of 8% compared with 0.9% in patients without AKI.[2] Pathophysiology includes decreased renal perfusion, lack of pulsatile flow, oxidative stress, hypothermia, embolism, and inflammatory response.[2] Variables such as increased duration of surgery, aortic cross-clamp, and intraoperative hypotension cause AKI. There are various scoring systems based on serum creatinine and urine output to define AKI in children such as Pediatric Risk Injury Failure Loss End Stage (PRIFLE), Acute Kidney Injury Network (AKIN), and Kidney Disease Improving Global Outcomes (KDIGO).[1] However, serum creatinine is imprecise, suboptimal test as it does not accurately reflect glomerular filtration rate in those renal function is constantly changing.[3] More than 26 new biomarkers of AKI were studied till now.[4] Among them, cystatin C, urine and plasma neutrophil gelatinase-associated lipocalin (NGAL), interleukin-6 (IL-6), liver fatty acid-binding protein, homovanillic acid sulfate, and kidney injury molecule-1 (KIM-1) are available to predict and relate to severity of AKI. The scarcity of early and expensive biomarkers of AKI has hindered ability to take therapeutic, prophylactic measures in a timely manner which is potentially reversible cause.[5] Plasma and urine NGAL has shown to raise in 6 h of Intensive Care Unit (ICU) stay. In infants <6 m age, low levels of IL-18 at 2 h postsurgery had 91% negative predictive value. Similarly, homovanillic acid sulfate peaked to twice at 4 h postsurgery.

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Following AKI, urinary KIM-1 concentration is markedly increased in an hour of surgery.[6] Most of these markers need serial evaluation which is not cost-effective.

There are electrolyte and metabolic disturbances occurring during cardiac surgery as well as in acute renal failure. Numerous electrolytes have been investigated as evaluation for AKI. Most common cause for hyperphosphatemia is renal failure. Limited literature is being available on hyperphosphatemia with respect to kidney injury. Therefore, the aim of the present study was to evaluate whether serum phosphorus (Ph) could predict AKI as compared to serum creatinine in pediatric cardiac surgery.

Methodology

This was a prospective diagnostic observational study of 51 children aged between 3 weeks and 12 years undergoing elective cardiac surgery in a tertiary care center who were enrolled in the study. Exclusion criteria were preoperative AKI, use of nephrotoxic drugs or contrast material before or during the study period, steroids, insulin, diuretics, preoperative inotropic support, children with end-stage renal disease, dialyzed, solitary kidney or nephrectomy, hyperbilirubinemia, hemolytic disorders, leukemia, and thyroid and parathyroid disorders. The institutional ethics board approval was taken before study initiation, and parental written informed consent was obtained for all participants. Children were recruited during preoperative evaluation. Blood samples were collected for serum creatinine and phosphorus postanesthetic induction after central venous access insertion. After surgery, blood samples were collected for serum creatinine and phosphorus at 24 and 48 h in postoperative recovery unit. Variables collected include age, sex, weight, risk adjustment for congenital heart surgery-1 (RACHS-1) category, duration of surgery, aortic cross-clamp time, urine output (intraoperative period, 24 h, and 48 h), inotropic score, requirement of renal replacement therapy (RRT), ICU stay, and mortality. Serum creatinine was measured at our laboratory by modified Jaffe method while serum phosphorus is determined photometrically.

The primary outcome variable was development of AKI, defined as follows: Stage 1 is 0.3 mg/dl rise in 48 h or at least 50% rise from baseline in 7 days, Stage 2 is doubling value, and Stage 3 being tripling/requiring dialysis according to the KDIGO criteria.[7] Children were grouped into AKI and non-AKI based on this criteria. Other outcomes included were requirement of RRT, ICU stay, and mortality.

Statistical analysis

Statistical analyses were performed using MedCalc version 12.2.1.0 (Ostend, Belgium). Continuous data were analyzed using unpaired *t*-test or ANOVA for parametric data or Mann–Whitney U-test for nonparametric data. The Kolmogorov–Smirnov test was used to confirm normality.

Serum phosphorus and serum creatinine were compared between AKI and non-AKI. Sensitivity and specificity of serum phosphorus at 24 and 48 h to detect AKI were evaluated by the area under receiver operating characteristic curve (AUC-ROC). Categorical data were analyzed by Chi-square test. $P < 0.05$ was considered as statistically significant. The percentage of maximum elevation of phosphorus (%Ph = maximum-minimum/minimum ×100) was calculated at 24 and 48 h postoperatively. Continuous variables were expressed as mean ± standard deviation or median and percentile or geometric mean with 95% confidence interval (CI).

Results

Among 51 children aged between 3 weeks and 12 years who underwent elective cardiac surgery, 10 (19.6%) developed AKI in 48 h postoperatively according to the KDIGO criteria. Patients who developed postoperative AKI were comparable to the non-AKI group with regard to age, weight, cardiac risk score (RACHS-1), preoperative serum creatinine (cr), and serum phosphorus (Ph).

As summarized in above Table 1, patients who had AKI had longer duration of surgery and aortic cross-clamp time which were statistically significant with $P = 0.03$ versus 0.0006, respectively. Eight patients required RRT among AKI group (peritoneal dialysis = 7; hemodialysis = 1).

Receiver operating characteristic curves for serum phosphorus (24 and 48 h)

AUC of the ROC curve for serum phosphorus to predict AKI at 24 h was 0.84 (95% CI: 0.711–0.982; $P = 0.0112$) as shown in Figure 1.

Sensitivity and specificity of serum Ph at 24 h were 75% and 93.62%, positive predictive value was 50%, and negative predictive value was 97.8% with cutoff value of >6.4.

AUC of the ROC curve for serum phosphorus to predict AKI at 48 h was 0.86 (95% CI: 0.734–0.941; $P < 0.0001$) as shown in Figure 2.

Sensitivity and specificity of serum Ph at 48 h were 66.67% and 97.62%, positive predictive value was 85.7%, and negative predictive value was 93.2% with cutoff value of >5.4.

Comparison of prediction of acute kidney injury using serum creatinine and phosphorus

Preoperative serum creatinine and phosphorus levels in children with and without AKI were within normal ranges and did not differ between those two groups. In AKI group, serum Ph levels increased significantly at 24 h from baseline (6.29 vs. 4.47) with $P = 0.01$ [Table 2]. However, serum Cr at the same point in AKI group was not statistically significant ($P = 0.16$). Serum Ph at 48 h could not show a statistically significant increase ($P = 0.23$) although serum Cr had significant increase statistically at 48 h in AKI ($P = 0.0001$) [Table 2].

Table 1: Patient characteristics

Characteristics	AKI (*n*=10)	Non-AKI (*n*=41)	*P*
Demographic data			
Age (years)			
Median	0.99	0.75	0.73
(25th-75th percentile)	(0.17-1.99)	(0.35-1.40)	
Sex			
Female	2	24	0.028
Male	8	17	
Weight (kg)	9.51±8.16	6.93±4.62	0.18
Cardiac risk score (RACHS 1)	2.70±0.94	2.34±0.85	0.25
Preoperative data			
Serum creatinine (mean; 95% CI)	0.33 (0.24-0.46)	0.30 (0.26-0.34)	0.45
Serum phosphorus (mean±SD)	4.47±1.36	4.78±1.30	0.50
Intraoperative data			
Duration of surgery (h)	5.55±1.62	4.43±1.43	0.03
CPB time (min)	163.33±70.60	99.89±45.21	0.0015
ACC time (min)	110.56±44.18	65.34±30.0	0.0006
Type of surgery:			
VSD	2	27	
TGA	4	5	
TAPVC	1	5	
TOF	3	4	
Urine output (ml/kg/h)	4.22±3.33	4.68±3.07	0.67
Postoperative data			
RRT	8	0	<0.0001
ICU stay (days)	8±3.29	6.07±2.27	0.03
Mortality (days)	1	0	0.44
Urine output (24 h) ml/kg/h	1.96±1.27	2.95±1.07	0.01
Urine output (48 h) ml/kg/h	1.35±0.811	2.95±1.12	0.0001

AKI: Acute kidney injury, RACHS: Risk assessment for congenital heart surgery, ACC: Aortic cross-clamp, CPB: Cardiopulmonary bypass, SD: Standard deviation, CI: Confidence interval, ICU: Intensive Care Unit, VSD: Ventricular septal defect, RRT: Renal replacement therapy, TGA: Transposition of great arteries, TAPVC: Total anomalous pulmonary venous connections, TOF: Tetralogy of fallot

Percentage increase in serum Ph from baseline to 24 h in AKI group was 55.14 when compared with 0.87 in non-AKI group with *P* = 0.0011, while from baseline to 48 h in AKI, it was 62.95 with *P* = 0.0007 being statistically significant.

Discussion

AKI is an independent predictor of mortality in children undergoing cardiac surgery under cardiopulmonary bypass (CPB).[1] The factors involved in pediatric AKI are preoperative, CPB, postoperative, inflammatory, and neuroendocrine responses. It is common postcardiac surgery in children due to renal hypoperfusion, reperfusion injury, and inflammatory responses.[2] Degree of hemodilution and
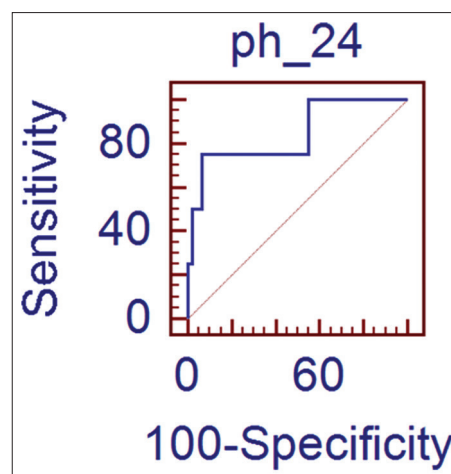
Figure 1: Receiver operating characteristic curve for serum phosphorus to predict acute kidney injury at 24 h (ph-24)

hormonal response to CPB in pediatric population makes it vulnerable for AKI. Thus, early AKI diagnosis is of great significance for prognosis of patients. Serum creatinine and urine volumes are nonspecific indicators of staging criteria of AKI and susceptible to external factors.[8] Serum creatinine is the main diagnostic test of AKI which is suboptimal and raising late in course of disease, leading to delay in evaluation, treatment, and application within narrow therapeutic window.[3] Although various criteria have been used for the diagnosis of AKI, the KDIGO classification has recently been introduced as a standard diagnostic tool.

Incidence of AKI by PRIFLE ranged from 20% to 64.6% and KDIGO from 29% to 86%. Using the KDIGO criteria for the diagnosis of AKI, the present study found that hyperphosphatemia at 24 h could be used as an early predictor of AKI after cardiac surgery in children. In the present study, incidence of AKI was 19.6%, while Zappitelli *et al*. found incidence being as high as 40% following cardiac surgery in children. The probable reason for low incidence of AKI in the present study could be accounted for volume of sample size.

In the present study, authors evaluated the performance of serum phosphorus as AKI biomarker in pediatric postcardiac surgery cohort. The AUC-ROC value for serum phosphorus at 24 h after surgery being 0.84 (95% CI: 0.7–0.92; *P* = 0.001) with a sensitivity of 75% and specificity of 93.6%. The cutoff value at this time was 6.4 mg/dl, while at 48 h (AUC = 0.86; 95% CI: 0.73–0.9; *P* < 0.0001), cutoff value was 5.4 mg/dl. Ibrahim *et al*. found AUC 0.375 for plasma renalase while serum NGAL had AUC 0.663 at 24hrs after surgery for prediction of AKI.[2] Wang *et al*. investigated diagnostic role of urinary IL-18 after CPB with AUC = 0.90 as early as 2 h after CPB and with AUC of urinary NGAL being 0.83.[8] The AUC of urine albumin ranges 0.57–0.76 for AKI detection.[9]

Risk factors of AKI after pediatric cardiac surgery are low bodyweight, young age, increased RACHS-1 score,

Table 2: Variation of serum creatinine and serum phosphorus in acute kidney injury group at 24 and 48 h

AKI group	0 h	24 h	*P*	48 h	*P*
Serum creatinine (mean and 95% CI)	0.33 (0.24-0.46)	0.49 (0.26-0.91)	0.16**	0.85 (0.51-1.39)	0.0001*
Serum phosphorus (mean±SE)	4.47±0.43	6.29±0.32	0.01**	6.78±1.2	0.23*

*P value between 0 and 48 h, **P value between 0 and 24 h. SE: Standard deviation, CI: Confidence interval, AKI: Acute kidney injury

Table 3: Variation of serum creatinine and phosphorus between acute kidney injury and nonacute kidney injury group

Value	AKI	Non-AKI	*P*
24 h (mean±SD)			
Serum creatinine	0.74±0.91	0.29±0.09	0.002
Serum phosphorus	6.29±1.02	4.53±1.18	0.0001
48 h			
Serum creatinine mean (95% CI)	0.84 (0.51-1.39)	0.23 (0.19-0.27)	<0.0001
Serum phosphorus (mean±SD)	6.78±3.8	3.62±0.87	<0.0001

SD: Standard deviation, CI: Confidence interval, AKI: Acute kidney injury

Figure 2: Receiver operating characteristic curve for serum phosphorus to predict acute kidney injury at 48 h (ph-48)

preoperative pulmonary hypertension, preoperative inotrope, and preoperative mechanical ventilation.[10] In the present study, we found that duration of surgery in AKI versus non-AKI (5.55 vs. 4.43; *P* = 0.03) is statistically significant. Similarly, increased aortic cross-clamp time noted in AKI group (110.56 vs. 65.34: AKI vs. non-AKI; *P* = 0.006).

AKI is associated with systemic complications including volume overload, electrolyte, and metabolic disturbances.[3] Hyperphosphatemia is a common complication of AKI, developing as a direct consequence of decreased renal excretion. Persistent hyperphosphatemia (>12 h) occurs in impaired kidney function. Normal values of phosphorus in infant 6–8 mg/dl, child 4.5–5.5mg/dl, adolescent 2.7–4.5mg/dl. It is the sixth most abundant element in the human body. Levels are expressed in terms of mg/dl. The removal of phosphate by dialysis may vary by >400 mg per treatment. Estimation of serum phosphorus is a simple, easily available, and cost-effective.[11]

In AKI group as early as 24 h, there is a statistically significant increase in serum phosphorus in comparison to non-AKI with *P* = 0.0001 [Table 3]. Serum Ph values from baseline to 24 h have shown statistically significant increase in AKI group with *P* = 0.01. However, at 48 h in AKI, serum phosphorus levels could not show statistical significance (*P* = 0.23). urine output analysed at bas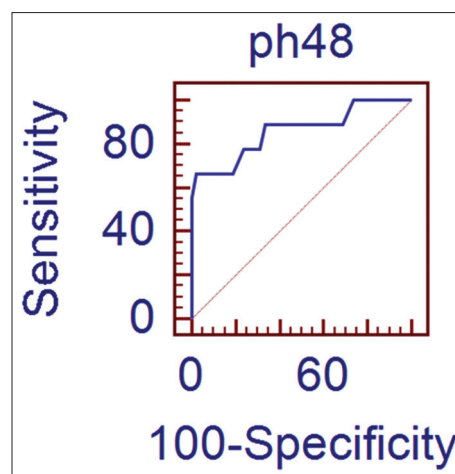eline being 4ml/kg/hr had decreased to 1.96ml/kg/hr at 24hrs ,therefore therapeutic interventions were aimed at increasing urine output could have led to increased phosphorus excretion and rendering serum Ph level insignificant at 48 h.

Apart from absolute serum Ph values, percentage increase in serum Ph levels could also implicate AKI. The present study showed 55% increase in serum Ph levels in AKI when compared with 0.87% in non-AKI with *P* = 0.0011 at 24 h. While at 48hrs,in AKI group 62.95% increase was observed in comparison to -15.8% change in non-AKI with respect to serum Ph levels(*p*=0.0007).

The authors would recommend that minimizing CPB duration, aortic cross-clamp time, and total surgical duration and maintaining optimal mean arterial pressure could prevent renal injury.

Limitations

Sample volume analyzed could be insufficient (*n* = 51) to stage AKI and determine the predictable cutoff value of serum phosphorus at each stage for defining AKI criteria earlier than serum creatinine.

To determine pattern of change of serum Ph at various time points with respect to AKI was not analysed.

Conclusion

Serum phosphorus level estimation being simple, easy, and cost-effective predicts AKI as early as 24 h in comparison with serum creatinine level in children undergoing cardiac surgery. Future research on its evaluation for its association with other new biomarkers is required and determined the specific value of serum phosphorus to extent to which its elevation leads to changes in patient management.

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Conflicts of interest

There are no conflicts of interest.

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