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Role of plasma neutrophil gelatinase associated lipocalin in the diagnosis of pediatric acute kidney injury

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Abstract

Background: Open heart surgery is usually indicated as treatment for congenital heart diseases in children, and one of the major complications of this procedure is cardiac surgery associated acute kidney injury (CSA-AKI). This is diagnosed late because there are no clear cut markers for early assessment of sudden decline in renal function. The aim is to assess the role of Neutrophil Gelatinase Associated Lipocalin (NGAL) in the diagnosis of cardiac surgery-associated AKI (CSA-AKI).

Method: Forty (40) children aged 15 years and below, who had open heart surgery for congenital heart diseases were recruited for this prospective longitudinal study. Concentrations of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in plasma were measured and compared at 0-, 4-, 8-, 12-, 24-, and 48- hours with plasma creatinine. Quantifications of NGAL were done using Enzyme-linked Immunosorbent Assay (ELISA) while creatinine was done on an automated analyzer (Cobas C311, Roche).

Results: Mean plasma NGAL concentrations at 0, 4, 8, 12, 24 and 48 hours were 70.50±21.47ng/ml, 105.32±24.95ng/ml, 113.58±28.51ng/ml, 103.47±26.49ng/ml, 94.43±22.78ng/ml and 89.18±20.44ng/ml respectively with peak concentration at 8hrs while that of creatinine were 48.98±11.6µmol/L, 59.65±13.06µmol/L, 63.00±16.53µmol/L, 64.90±17.65µmol/L, 68.50±19.99µmol/L and 70.78±21.86µmol/L respectively with peak concentration at 48hrs. NGAL had a better diagnostic ability with an AUC of 0.987, while creatinine had an AUC of 0.429.

Conclusion: The findings being reported in this study showed that NGAL predicted AKI earlier, at 8hrs after surgery and with a higher sensitivity and specificity, compared to creatinine in children who had open heart surgery for congenital heart diseases.

Keywords: NGAL; Paediatrics; AKI; Creatinine

1. Introduction

Congenital heart disease (CHD) accounts for about 30%-40% of all congenital defects worldwide.[1], affects about 1% of newborns and it is a significant cause of morbidity and mortality.[2,3], and the commonest cause of infant death from birth defect.[4], clinical presentation is often late with only 58.1% presenting in infancy.[2], 43% having a diagnosis before 5yrs.[4], and 6.9% progressing to definitive intervention.[5].

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Acute Kidney Injury (AKI) is an abrupt loss of the functions of the kidneys that is usually evidenced by a sudden increase in the value of serum creatinine.[6]. It is a sustained decline in renal function leading to the retention of nitrogenous and non-nitrogenous waste products as well as the dysregulation of cellular volume and electrolyte handling.[7]. Acute kidney injury is a serious and common complication of cardiac surgery.[8]. The widely acceptable staging of AKI in paediatric patients in clinical practice uses serum creatinine level and urine output.

Multiple factors have been identified as being responsible for the pathophysiology of postoperative AKI after cardiac surgery including a combination of tubular and vascular injury.[9]. Exposure of the kidneys to interruptions and alterations in the blood flow during cardiopulmonary bypass (CPB) due to changes in pump flow and lack of pulsatility causes ischaemia-reperfusion injury.[10].

The diagnosis of AKI generally is based on a reduced Glomerular Filtration Rate (GFR), increased serum creatinine and the presence or absence of oliguria.[7]. However, these parameters are limited in their clinical utility to diagnose AKI. Glomerular Filtration Rate estimation may not be accurate during the non-steady state of AKI, over estimation by serum creatinine measurement is a possibility.[7]. Also, using the established criteria of increased serum creatinine with or without oliguria for the diagnosis of postoperative AKI may take hours to days, leading to delayed recognition of renal dysfunction, which may be partly responsible for the limited progress in preventing and treating postoperative AKI.[10]. This underscores the need for more sensitive markers of AKI.[10].

The new biomarkers of AKI include Neutrophil Gelatinase Associated Lipocalin (NGAL), which is a new member of the lipid carrier protein superfamily and is highly expressed in damaged renal tubules.[11,12]. It is produced in response to ischemic kidney injury by the renal tubules and secreted in the urine and it can be measured in both urine and blood.[13].

Its evaluation in pediatric cardiac surgery patients has shown good sensitivity and specificity in diagnosis of AKI with an earlier rise (within 2hours) compared to serum creatinine rise (over 1-3 days) following renal injury.[14]. The use of NGAL to diagnose AKI following cardiac surgery has been extensively studied, with a rise in concentration within three hours following renal tubular injury, preceding creatinine rise by more than twenty-four hours.[15].

The aim of this study is to evaluate the role of NGAL as a biochemical marker of acute kidney injury while the objectives are to measure the levels of NGAL and Creatinine at 0-, 4-, 8-, 12-, 24-, 48hrs in plasma and compare their means in children undergoing cardiac surgery for congenital heart diseases. Despite widespread works and evaluation on the role of NGAL as a renal biochemical marker, it is not a routine marker in our center mainly because of the affordability, the difference in cost as compared to creatinine is 15,000:1,500 and this is the first work in our center in this cohort of study participants.

2. Methods

This study was approved by the Obafemi Awolowo University Teaching Hospital Ethical Committee (ERC/2020/03/16). Forty (40) consecutive patients aged 4wks to 14yrs undergoing open heart surgery for congenital heart disease, who did not have chronic kidney disease were enrolled and informed consent was obtained from the parents.

Anthropometric parameters (height and weight in centimeter and kilogram) were obtained from study participants' case files. The haemodynamics parameters of the study participants were optimized before surgery and a normal value of C-Reactive protein value was a pre-requisite for surgery, they were monitored peri-operation and post operation using multi-parameters monitors. The cardiopulmonary bypass (CPB) time ranged from 50-64 minutes for those with atrial and ventricular septal defects, 66-142 minutes for those with tetralogy of Fallot, and weaning off mechanical ventilation occurred from immediate post operation to 6hrs post operation in those with atrial and ventricular septal defect and 12-24hrs in those with tetralogy of Fallot. Two milliliters (2 ml) of blood was collected from the central venous line of each participant, over six time points for the measurements of NGAL and creatinine assays. The time points were baseline zero hour (pre-operative blood collected immediately after passing the central line in the operating room), 4hrs, 8hrs, 12hrs, 24hrs and 48hrs post operation. Collected blood specimens were discharged into heparinized bottles and centrifuged at 1500 g for 10 minutes. Subsequently, separated supernatants were harvested by Pasteur's pipette and dispensed into cryovials for storage at -70^{0}C. The aliquoted plasma was thawed at room temperature immediately prior to analysis. Determination of plasma concentrations of creatinine and NGAL were done using an auto-analyzer, Cobas c311 and Enzyme Linked Immunosorbent Assay (ELISA) respectively. Participants were stratified using a 50% rise in creatinine above baseline into those with and without cardiac surgery associated acute kidney injury (CSA-AKI). Data was analyzed by IBM Statistical Product and Service Solutions (SPSS) version 20.0. Comparison of the sensitivity and specificity of the different biomarkers in predicting CSA-AKI was done statistically by the Receiver

Operating Characteristic (ROC) curve, p-value of ≤0.05 was considered to be statistically significant and an AUC-ROC OF 0.900 or greater was considered to represent an excellent biomarker.

3. Results

The anthropometric parameters of the study participants are as shown in Table 1. 50% of the study participants had ventricular septal defect, 32.5% had Tetralogy of Fallot and 17.5% had atrial septal defect. NGAL had a peak at 8hrs while that of plasma creatinine was at 48hrs, with the mean plasma concentrations at the different time points as shown in Table 2.

As shown in Table 3 and 4, NGAL and creatinine in those with and without CSA-AKI revealed that patients with CSA-AKI had higher NGAL levels over the entire time points than patients without CSA-AKI which was statistically significant. The ROC curve in Figure 1 showed that NGAL had an AUC of 0.987 compared to that of creatinine which was 0.429 and this difference was statistically significant. The specificity and sensitivity for NGAL at a cut-off level of 149 ng/mL were 97 % and 100 % respectively, suggesting a better predictive capacity of NGAL for CSA-AKI.

Table 1 Anthropometric Parameters of Study Participants

Variables	**Frequency**	**Percent (%)**
Male	22	55
Female	18	45
	Mean	±1S.D
Weight (Kg)	17.66	9.05
Height (m)	0.99	0.31
BMI (Kg/m^2)	14.74	3.12

Table 2 Mean Concentration of Measured Biomarkers over Time

	Time(Hour)					
Biomarker	0	4	8	12	24	48
NGAL (ng/ml)	70.50±21.47	105.32±24.95	113.58±28.51	103.47±26.49	94.43±22.78	89.18±20.44
Creatinine (µmol/L)	48.98±11.6	59.65±13.06	63.00±16.53	64.90±17.65	68.50±19.99	70.78±21.86

Table 3 Comparison of NGAL at different time points in those with and without CSA-AKI

Renal Biomarker at time points (hours)	**CSA-AKI**		**P value**
	Present (n = 7)	Absent (n = 33)	
0	110.34±39.00	62.04±22.38	0.000*
4	215.29±39.31	81.99±27.37	0.000*
8	244.57±38.39	85.79±39.58	0.000*
12	204.43±26.44	82.05±32.49	0.000*
24	179.76±42.57	76.33±29.55	0.000*
48	177.57±27.37	70.43±33.75	0.000*

*Significant at p-value ≤0.05

Table 4 Comparison of Creatinine at different time points in those with or without CSA-AKI

Renal Biomarker at time points (hours)	CSA-AKI		p-value
	Present (n = 7)	Absent (n = 33)	
0	46.57±9.54	50.09±12.03	0.579
4	55.57±13.21	60.52±14.27	0.511
8	68.00±50.02	60.15±19.43	0.473
12	64.29±47.37	65.21±14.30	0.349
24	96.14±85.36	64.52±28.47	0.277
48	95.29±64.89	65.58±29.86	0.066

* Significant at p-value ≤0.05

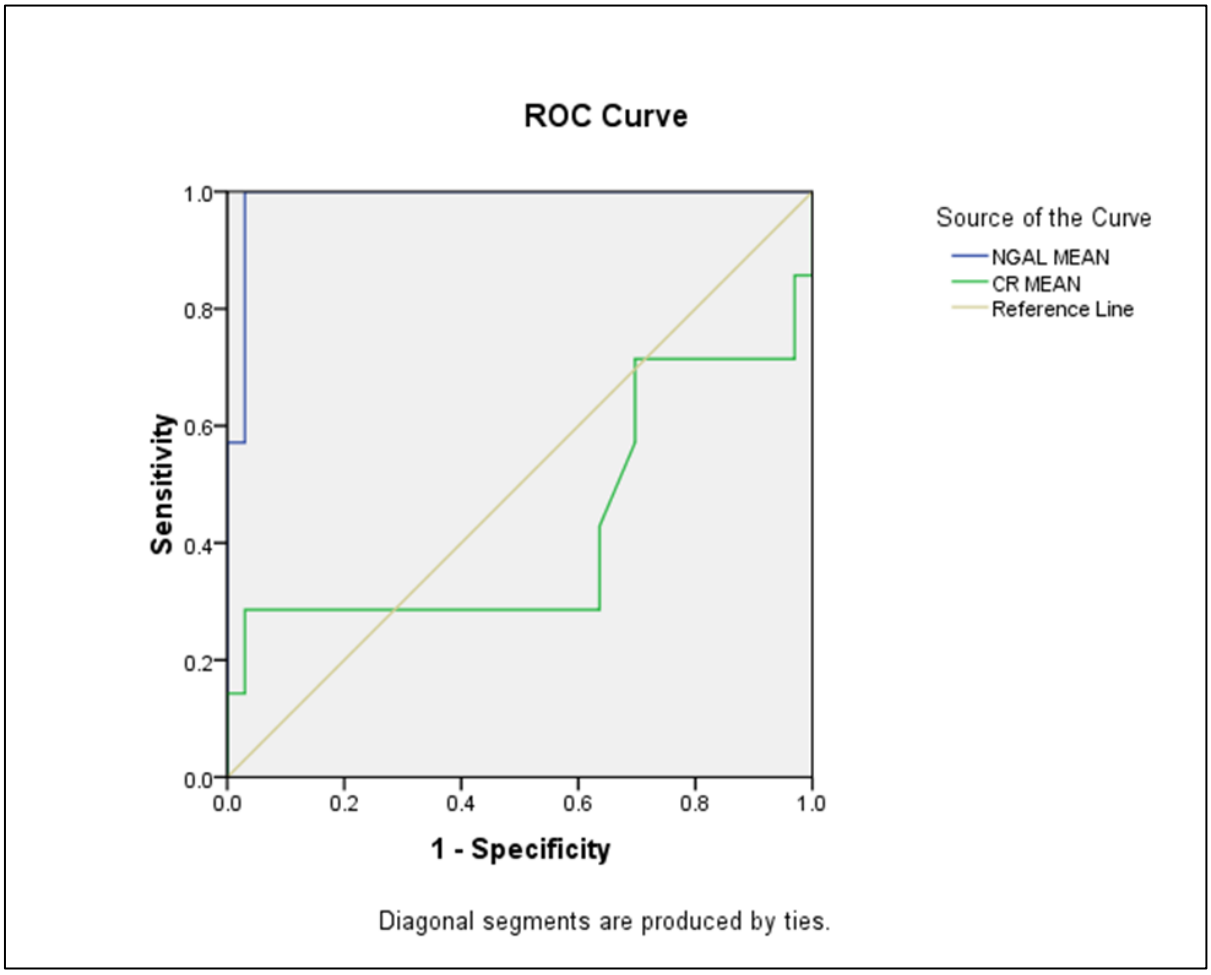

Figure 1 Receiver Operating Characteristics Curve of NGAL and Creatinine

4. Discussion

From this study, an increase in the mean plasma level of NGAL at 4hr post operation compared to that at the baseline was noted, which is similar to what was observed in earlier studies in which a twofold increase in NGAL value following open heart surgery was noted.[16]. Another study showed a rise in serum NGAL at 2hrs post cardiopulmonary bypass (CPB).[17] which is in accordance with what was observed in this study. The results from this study in the comparison of the diagnostic performance of different biomarkers in the prediction of CSA-AKI showed the p-value of mean plasma NGAL to be .000 which is less than p-value of <0.005 and is therefore statistically significant as compared to the p-value

of mean plasma creatinine from this study which is 0.557 and more than the p-value of <0.005 and is therefore not statistically significant, meaning that novel biomarkers like plasma NGAL are early markers of CSA-AKI as opposed to traditional marker like plasma creatinine.

Also, a meta-analysis study noted an increase in the mean plasma values of NGAL which is comparable to the increase in the mean plasma level of NGAL value following open heart surgery.[18]. Another study in Egypt showed a rise in serum NGAL at 2hrs post cardiopulmonary bypass (CPB).[19] which is in accordance with what was observed in this study and not different from another study in which a rise in serum NGAL was noted at 3hrs post operation which showed that sampling for NGAL as early as 2,3,4 hrs post operation can detect a rise in NGAL which can predict CSA-AKI.[20,21,22].

Urinary neutrophil gelatinase-associated lipocalin (uNGAL) is recently demonstrated as an early biomarker of AKI after cardiopulmonary bypass, increasing 25-fold within 2 h and declining 6 h after surgery in a study by earlier workers.[23] which though of different sample matrix with plasma NGAL value that was assayed in this study, the early rise between the two is similar, though the rate of decline is different.

The peak mean plasma level of NGAL was observed at 8hrs post operation in this study. This is slightly longer than what was obtained in a study in Egypt with a peak NGAL value at 6hrs post operation and this difference could be attributable to the fact that the participants in the study in Egypt were adults who had coronary artery bypass graft.[20]. Another study reported that NGAL appeared in urine after 3 hr from kidney injury, peaked at 6 hr and maintains elevation for a longer time.[24].

A steady decline in the mean plasma level of NGAL was noted in this study from 12hrs post operation to 48hrs post operation, with the decline greatest between 24hr and 48hrs which was different from that of a study in Egypt that had continuous rise in the level of serum NGAL post-CPB until 48hrs. [19]. The ideal sampling time for plasma NGAL that can be deduced from the significant statistical analysis of mean comparison in this study is between 4hrs and 8hrs post open-heart surgery, in children with congenital heart diseases for the prediction of CSA-AKI.

In this study, the area under the curve (AUC) of NGAL in the Receiver Operating Characteristic (ROC) curve is 0.987 (at 95% confidence interval) with 100 % sensitivity and 97% specificity at a cut-off value of 149ng/ml and this is similar to data reported in an earlier work in Egypt that reported a sensitivity and specificity of 98.1% and 91.9% at a cut-off value of 62ng/ml respectively. [20]. In both studies, ELISA method of quantification was used, and the samples were collected after cardiac surgery using cardiopulmonary bypass. The AUC of 0.987 that was obtained in this study is different from what was obtained in a study in Finland with adult population that reported AUC of 0.64.[25] which is different from this study population that comprised only of children participants.

Furthermore, the overall pooled sensitivity of NGAL for the diagnosis of AKI was 68% [95% confidence interval (CI), 65%-70%], and specificity was 79% (95% CI, 77%-80%) in a meta-analysis reported by some earlier workers.[[26] which was also similar to a meta-analysis of 24 studies that found an overall sensitivity of 68% (95% confidence interval (CI), 65%–70%) and a specificity of 79% (95% CI, 77%–80%), in which the performance characteristics were found to be superior in children over adults.[27].

In another meta-analysis of 19 studies in 8 countries involving 2,538 patients, the incidence of AKI was 19.2% overall, while the AUC of NGAL to predict AKI was 0.815(0.732-0.892) (95% CI); and the AUC-ROC when standardized platforms were used was 0.830 (95% CI, 0.741-0.918), and in cardiac surgery patients, the AUC-ROC of NGAL was 0.775, (0.669-0.867) (95% CI).[28].

Another study showed a dramatic increase in both urine and plasma NGAL detected within 2–6 hours of cardiopulmonary bypass in children predisposed to AKI, with a predictive area under the receiver operating characteristic curve (AUC) of >0.900, and these findings have now been confirmed in more than 7500 patients, with measurements obtained within 4–6 hours after initiation of CPB, yielding an overall predictive pooled AUC of 0.860. The predictive performance for CS-AKI was similar for both urine and plasma NGAL. Subgroup analyses revealed that NGAL displays the highest predictive accuracy for CS-AKI in children compared to adults (AUC 0.890 versus 0.830). [29,30]. Furthermore, another study showed that NGAL demonstrated a near-perfect performance for identifying AKI after pediatric cardiac surgery with an area under the receiver operator characteristic curve (AUC ROC) of 0.990 and 1.00 at 2 and 4 h after cardiopulmonary bypass (CPB), respectively.[31] which is very similar to what was obtained in this study with NGAL having an AUC of 0.987 at 8hrs.

The limitations of the study include being a single center study, the non-availability of NGAL as a routine marker, and blood sampling times in a narrower postoperative interval would have been of use.

5. Conclusion

From our study, NGAL was able to identify patients with CSA-AKI earlier, peaking 40hrs before creatinine, with a better correlation and ROC-AUC values, the time difference is highly significant in the clinical setting most especially in pediatric age groups. Though, the difference in the cost of the two biomarkers with creatinine about ten times cheaper than NGAL in this environment may give creatinine a relative advantage, but the diagnostic performance of NGAL from this study demonstrates its advantages over creatinine; it may be practically difficult to completely replace creatinine with NGAL, but high consideration should be given to the use of NGAL in pediatric age groups.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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