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Original article

Usefulness of Serum and Urinary Neutrophil Gelatinase -Associated Lipocalin in Detecting Acute Kidney Injury in Asphyxiated Neonates

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ABSTRACT

Objective: To determine the predictive value of serum and urinary NGAL in the detection of AKI in asphyxiated neonates. **Subjects and Methods:** Serum and uNGAL were measured in forty full term>37 week, both sexes, neonates had clinical and laboratory findings of perinatal asphyxia according to the criteria defined by the American Academy of Pediatrics and 20 apparently healthy neonates matched for gestational age and birth weight as a control group, in the neonatal intensive care unit of Benha university hospital within 24 hours after birth using ELISA. **Results:** Asphyxiated neonates had significantly higher serum NGAL and uNGAL than control neonates, (P<0.001). Serum and uNGAL level were higher in patients with AKI than those without AKI; (P<0.001). Serum and urinary NGAL correlated with serum creatinine at the day 3 in the AKI subgroup. A cutoff value 144 ng/ml for serum NGAL and a cutoff value 18 ng/ml for urinary NGAL could detect AKI in asphyxiated neonates with a sensitivity of 95% and a specificity of 94%. **Conclusion:** Serum and urinary NGAL obtained in the first 24 hours of life showed significantly high values in asphyxiated neonates, with great accuracy and high sensitivity and specificity.

KEYWORDS: AKI, Hypoxic Ischemic Encephalopathy (HIE), NGAL and Serum creatinine

INTRODUCTION

Kidneys and other tissue damage may occur in response to hypoxia and ischemia, hypoxic ischemic episode can cause renal insufficiency within 24 hours and if prolonged it may cause irreversible cortical necrosis [1]. It is important to diagnose AKI as early as possible in neonates with hypoxic ischemic encephalopathy (HIE) in order to start fluid and electrolyte treatment and keep a normal biochemical environment to improve their outcome [2]. Diagnosis of AKI is based on two factors: changes in serum creatinine (SCr.) and urine output, but both markers are not markers of the injury itself, they are considered as late effects of the injury and can be affected by the neonatal physiology [3].

The Glomerular filtration rate can be monitored by serum creatinine measurement, but its use is limited in the neonatal period as it reflects the maternal creatinine level for 48-72 hours after delivery and then decline over days with varying rates according to gestational age. This makes it difficult to interpret changes of serum creatinine or even lack of change in its level during the first week after birth. Moreover tubular secretion of creatinine can cause overestimation of the renal function at lower GFR, also, changes in serum creatinine concentrations may not occur until 25–50 % of the kidney function has been lost [4].

Identifying of new biomarkers for AKI is now an important area of research by many scientists as AKI incidence is high and its outcome is poor. Identifying of a new serum or urine biomarker that allow early AKI diagnosis can aid in detection and differentiate between causes of it and identification of different preventive methods [3]. Neutrophil gelatinase-associated lipocalin (NGAL) is a secretory glycoprotein, of about 25kDa molecular weight, it belongs to the lipocalin family of proteins. Human NGAL was originally isolated from the supernatant of activated neutrophils [5, 6]. In experimental models and human disease NGAL source is the injured distal nephron, and its level in plasma in urine is directly proportional to the severity and duration of renal injury, and decreases with

attenuation of the renal injury, this makes it a promising biomarker for early detection of AKI [7].

Objective of the study: This study was designed to determine the predictive value of serum and urinary NGAL in detection of AKI in asphyxiated neonates.

MATERIALS AND METHODS

This cohort study was conducted at the Neonatal Intensive Care Unit the Pediatric Department at Benha University Hospital, during the period from June 2013 till May 2014. The study was approved by the Ethical Committee of the Pediatric Department at Benha University. An informed consent was taken from the parents before enrollment of their neonates in the study.

This study was conducted on 60 neonates; they were divided into 2 groups:

(*a*) *Patient Group:* Included 40 term neonates with perinatal asphyxia according to the criteria of the American Academy of Pediatrics [8].

(*b*) *Control Group:* Included 20 apparently healthy neonates matched for gestational age and birth weight.

The study group was under the following inclusion and exclusion criteria:

Inclusion criteria: full term>37 week, both sexes, neonates had clinical and laboratory findings of perinatal asphyxia according to the criteria defined by the American Academy of Pediatrics [8].

Exclusion criteria: Neonates of a mother suffered from diabetes mellitus, pre-eclampsia, chronic kidney disease, or received nephrotoxic therapy, any neonate suffered from neonatal sepsis, inborn error of metabolism, taking a nephrotoxic drug, chromosomal abnormalities or congenital malformation including renal anomalies.

All participants were subjected to the following:

1) Full history taking, including gestational age, birth weight, sex and mode of delivery.
2) Full clinical examination and recording of Apgar scores at 1 and 5 min.
3) Laboratory investigations: included

Blood and urine samples were obtained as simultaneously as possible at day of life 1 (DOL 1) with the first urination.

Blood was used for measurement of:

a) Complete blood picture by automated hematology system (Sysmex XE 5000).[9]
b) C-reactive protein (CRP): using latex agglutination (CRP-Latex Cromatest)
c) Blood glucose, blood gases and serum electrolytes.
d) BUN, serum creatinine (done in first and third days of admission for diagnosis of AKI).
e) sNGAL: using commercially available enzyme-linked immunosorbent assays (ELISA) were used for NGAL measurements according to the manufacturer's instructions (Human Lipocalin-2/ NGAL, R&D Systems Europe, Ltd, Abingdon, UK) [10].

- Urine was used for the determination of uNGAL: Using the same ELISA kits

- Daily assessment of urine output (24 hours urine output measurement was done by applying plastic collection bag, and the nappies were weighed in case of leaking urine, especially in females to estimate the total urine volume). Oliguria was defined as urine output (<1 ml /kg/ hour for six consecutive hours). Anuria was defined as a passage of less than 50 mL of urine per day.[11]

Patients were divided according to level of serum creatinine 48 hours following admission in two groups:

AKI: level of serum creatinine > 1.5mg⁄dL for more than 48 hours or rising values>0.3 mg/dL from day of life (DOL) 1 (*n*=22) [12].

No-AKI: level of serum creatinine ≤1.5mg⁄dL (*n*=18)

Asphyxiated infants were neurologically examined daily over the first two postnatal weeks and were subsequently classified according to the Sarnat **[**13] into clinical stages as mild (grade I, *n*=31), moderate (grade II, *n*=7) and severe (grade III, *n*=2) hypoxic ischemic encephalopathy (HIE). In the first, AKI biomarkers were compared between asphyxiated neonates (asphyxia group) and healthy controls. In the second, biomarkers were compared among asphyxiated neonates with AKI (asphyxia-AKI subgroup) and without AKI (asphyxia no AKI subgroup). We also compared these subgroups to healthy controls.

Statistical analysis:

Data was analyzed using (SPSS) Statistical Package of Social Science for windows software Version 16 (SPSS, Inc, Chicago, USA). Descriptive data were expressed as number (no.), percentage (%) mean, standard deviation (SD), and range. Serum NGAL levels were expressed as median and interquartile range due to the nonparametric nature of the data. Analytical data were expressed as:

- Chi-Squared ($\chi 2$) it is used to compare between two or more qualitative variables in a 2x2 contingency table or r x c complex table,

- Student's t test: -It is used to test the difference between two means of normally distributed data.

- Mann-Whitney*:* nonparametric of Student's t test.

Values of p <0.05 were considered significant. The sensitivity and specificity for all possible cut off levels of NGAL were calculated and plotted as a Receiver Operating Characteristic curve (ROC curve) for visual analysis and for determination of optimal cutoff values of NGAL.

RESULTS

Of the enrolled asphyxiated neonates, 22 (55 %) developed AKI. Anuria or oliguria were observed in five (22.72 %) and eleven (50 %) asphyxiated neonates with AKI, respectively.

Perinatal-neonatal characteristics: Asphyxiated neonates (AKI and no AKI subgroups) were comparable to controls with respect to demographic-perinatal characteristics, except for Apgar score at 1 and 5 min that were significantly lower in the asphyxia group and subgroup compared to controls (Table 1).

Table 1: Demographic-prenatal characteristics of the studied neonates

	Cases (n = 40)	Controls (n = 20)	P value	AKI Subgroup (n = 22)	No AKI Subgroup (n = 18)	P1 Value
Gestational age (weeks)Range	37-41	37 – 40		37 - 41	37 - 40	
Mean ± SD	37.85 ± 1	37.95 ± 1	0.687	37.9 ± 1	37.85 ± 1	0.861
Birth weight (g) Range	2250 – 4300	2700 – 4100		2250 – 4300	2400 – 3800	
Mean ± SD	3133.8 ± 458	3242.5± 407	0.374	3145.5 ± 528	3133.8 ± 458	0.902
Delivery mode Vaginal *(n, %)*	22 (55%)	9 (45%)	0.469	14 (64%)	8 (44%)	
C.S *(n, %)*	18 (45%)	11 (55%)		8 (36%)	10 (56%)	0.231
Sex Male *(n, %)*	22 (55%)	8 (40%)		12 (56%)	10 (56%)	
Female *(n, %)*	18 (45%)	12 (60%)	0.277	10 (44%)	8 (44%)	0.950
Apgar 1 min Median (IQ range)	2 (0 – 3)	8 (7 – 9)	< 0.001	2 (1 – 2)	2 (2 – 3)	< 0.001
Apgar 5 min Median (IQ range)	4 (2 – 6)	9 (8 – 10)	< 0.001	3 (2 – 4)	5 (4 – 5)	< 0.006

P: asphyxia vs. control group, P1: asphyxia-AKI subgroup vs. asphyxia-no AKI subgroup

Serum Creatinine: Serum creatinine was significantly higher in asphyxiated neonates as compared to controls on DOL 1 and 3. Also, Serum Creatinine was significantly higher in the asphyxia-AKI subgroup versus the asphyxia no AKI subgroup on DOL1–3 (table 2)

sNGAL and uNGAL: There was a highly statistically significant difference in sNGAL level in the patient group (median= 147 ng/mL, IQR=59-195 ng/mL) as compared with control group (median= 46 ng/mL, IQR=39-56 ng/mL) being higher in patient group (*P*<0.001). It also, was significantly higher in patients having AKI, (median=180 ng/mL, IQR=163-225 ng ⁄ mL) than in those without AKI (median=56 ng/mL, IQR=40-73 ng/mL) (*P* < 0.001).

With respect to uNGAL, significant differences were observed between the asphyxiated neonates and control group, as well as between the asphyxia- AKI subgroup and asphyxia-no AKI subgroup (table 2). Serum and urinary NGAL were significantly correlated with the HIE severity in asphyxia AKI – subgroup (P<0.01). While there were significant positive correlations between both sNAGL (r=0. 890) and uNGAL (R=0. 867) and serum creatinine at day 3 only in AKI subgroup. Also, there was a significant correlation between sNGAL and creatinine on day 3 in No - AKI subgroup. On the other hand, there were no significant correlations between both sNAGL at day 1 (r=0. 467) and uNGAL at day 1 or 3 (r=0.036) (r=0.197) and serum creatinine in No - AKI subgroup (table 3).

ROC analysis of the data showed that the best cut off value of serum NGAL was value144 ng\ mL, this value could predict AKI in asphyxiated neonates**,** with area under the curve (AUC) of 0.985 and a confidence interval of (0.958-1.0); *P* < 0.001. Serum NGAL had a sensitivity of 95%, specificity 94 %, positive predictive value 85.7% and negative predictive value 92.3% (Fig.1) (table 4).

The second ROC curve shows that urinary NGAL can predict AKI at the cutoff point of *(*18 ng/mL*)* with sensitivity of 95*%* and specificity of 94*%* and accuracy of 95% (Fig.2) (table 4).

Table 2: Serum creatinine, serum and urinary NGAL in the asphyxia and control groups as well as in the subgroups of asphyxiated neonates with and without AKI on day of life (DOL) 1–3:

	Cases (n = 40)	Controls (n = 20)	P value	AKI subgroup (n = 22)	No AKI subgroup (n = 18)	P1 value
Serum Creatinine(mg/dl) Day 1 Day 3	 1.13±0.17 1.7±0.67	 0.71 ± 0.2 0.5 ± 0.14	 < 0.001 < 0.001	 1.2±0.13 2±0.34	 1±0.15 0.96±0.2	 < 0.001 < 0.001
sNGAL (ng/ml) Median IQ range	 147 59 - 195	 46 39 - 56	< 0.001	 180 163 - 225	 56 40 - 73	< 0.001
uNGAL(ng/ml) Median IQ range	 20 10 - 28	 9 6 - 11	< 0.001	 27 24 - 32	 10 9 - 12	< 0.001

P: asphyxia vs. control group, P1: asphyxia-AKI subgroup vs. asphyxia-no AKI subgroup (DOL 1, 3)

Table 3: Correlation between serum & urinary NGAL with apgar need to use capital letter where ever necessary score, sarnat staging and serum creatinine in asphyxia AKI – subgroup and asphyxia no - AKI subgroup:

	AKI subgroup (n = 22)				No - AKI subgroup (n = 18)			
	sNGAL		uNGAL		sNGAL		uNGAL	
	r	P value	r	P value	r	P value	r	P value
Apgar 1 min	-0.333	0.130	-0.465	0.029	0.076	0.763	0.002	0.992
Apgar 5 min	-0.245	0.272	-0.146	0.516	0.00	1.00	0.060	0.812
Sarnat staging	0.476	0.025	0.605	0.003	-0.119	0.639	0.031	0.904
Serum Creatinine (mg/dl) Day1 Day 3	 0.228 0.890	 0.308 < 0.001	 0.506 0.867	 0.016 < 0.001	 0.467 0.560	 0.051 0.016	 0.036 0.197	 0.888 0.432

Table 4: Validity and predictivity of serum NGAL and urinary NGAL: in detecting acute kidney injury in asphyxiated neonates

Variable	Sens.%	Spec.%	PPV%	NPV%	AUC	95%CI AUC	P
serum NGAL (cutoff=144 ng\ mL)	95%	94 %	85.7%	92.3%	0.985	0.958-1.0	<0.001 (HS)
urinary NGAL:(cutoff=18 ng/mL)	95%	94%	95%	94%	0.93	0.85-1.0	<0.001 (HS)

Figure 1: ROC curve for Serum NGAL

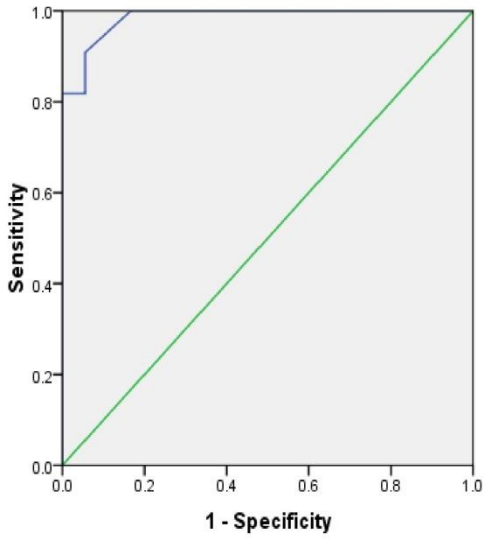
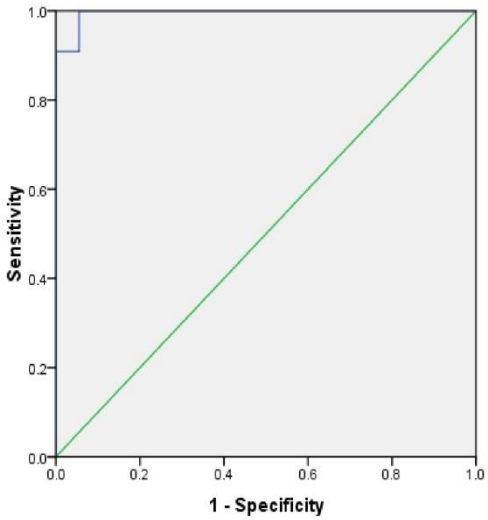


Figure 2: ROC curve for Urinary NGAL



DISCUSSION

AKI, previously named acute renal failure, occure in 70 % of severely asphyxiated neonates [14] with higher mortality in its oliguric type [1] and more adverse neurologic outcomes [15]. Clinically, SCr. is an unreliable marker of renal damage after birth [16]. This fact hampers not only the early documentation of AKI but also its management (e.g., fluid balance) or even the administration of drugs such as theophylline, potentially preventing kidney dysfunction [17].

In this context, neonatologists and nephrologists have focused their interest on the clinical utility of certain novel AKI biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL) [18], which is a 25-kD protein of the lipocalin superfamily, expressed in several tissues including kidney, but its renal expression is greatly enhanced in response to experimental kidney injury [6]. In humans, serum (sNGAL) and urine NGAL (uNGAL) are sensitive, early indicators of AKI in various situations, including cardiac surgery, [19] kidney transplants [20] sepsis [21], and following nephrotoxic drug administration [22].

In our study, serum and urinary NGAL obtained in the first 24 hours of life showed significantly higher values in asphyxiated neonates compared to controls, by following the patients, we observed that serum & urinary NGAL concentrations were also significantly higher in cases with acute kidney injury than cases without AKI.

In addition, serum & urinary NGAL concentrations were markedly increased showing significantly higher values in asphyxia no - AKI subgroup compared to controls. Higher values of serum and urinary NGAL irrespective of whether the asphyxiated neonates had AKI or not (based on serum creatinine levels) might hint at a spectrum of AKI that is being missed when the diagnosis is based solely on rising SCr. Our results go hand in hand with the study done by Dent and his colleagues**,** who found that plasma NGAL at 2 hours after cardiopulmonary bypass (CPB) was the most powerful independent predictor of AKI, they also concluded that Plasma NGAL is an early predictive biomarker of AKI, morbidity, and mortality after pediatric CPB.[23]

Bennett and his associates also found that the mean urine NGAL levels increased 15-fold within 2 h and by 25-fold at 4 and 6 h after CPB, they concluded that urine NGAL is an early predictive biomarker of AKI severity after CPB[24]. Our results also inconsistent with the results of Haase-Fielitz et al., study, as they found that plasma NGAL was an independent predictor of AKI in adult cardiac surgery and of excellent value in the prediction of the composite end point. [25]

Cruz and coworkers, results are also in agreement with ours as they found that plasma NGAL appears to be a useful early marker for the development of AKI in a large heterogeneous adult ICU population, allowing the diagnosis of AKI up to 48 h prior to a clinical diagnosis based on AKI consensus definitions. It is also correlated with AKI severity and overall severity of illness. [26] Moreover, in a meta-analysis involving 19 studies with approximately 2,500 patients, Haase et al., reported a high diagnostic accuracy of NGAL regarding diagnosis and prognosis of AKI, with better predictive ability in children than in adults [7]. On the other hand, Parikh et al., in a large study on AKI biomarkers in children undergoing cardiac surgery found that only uNGAL, and not sNGAL, was associated with subsequent AKI and poor outcomes [19]. A very good diagnostic performance of uNGAL in predicting AKI and mortality was also documented in premature infants, independent of gestational age and birth weight [27].

Our findings also come in agreement with the study of Sarafidis et al., on asphyxiated neonates, they found that

asphyxiated neonates had significantly higher serum and urinary NGAL values than the controls at all-time points [28]. Similarly, the study of Sweetman DU & Molloy EJ done on the biomarkers of acute kidney injury in neonatal encephalopathy, they observed that asphyxiated neonates had significantly elevated uNGAL; they concluded that these elevated urine biomarkers indicated that asphyxiated neonates did suffer acute tubular injury [29].

Renal failure in the neonate often occurs in the absence of oliguria [1], and a high index of suspicion is required. We depended mainly on serum creatinine levels because only 20% of our studied cases had oliguria in the first day of life while 80% had normal urine output.

In our study, ROC curve analysis suggested that a serum NGAL cutoff value of (144 ng/mL) within the first 24 hours of life in asphyxiated neonates can predict the development of AKI with sensitivity of 95%, specificity of 94%, positive predictive value of 95% and negative predictive value of 94%. While urinary NGAL can predict acute kidney injury (AKI) at the cutoff point of (18 ng/mL) with sensitivity of 95%, specificity of 94%, positive predictive value of 95% and negative predictive value of 94%.

Our results were comparable to the results of the study of Sarafidis et al., which showed that uNGAL at cutoff values of (> 18.61 ng/mL) had 100 % sensitivity, 83.3 % specificity, to detect acute kidney injury (AKI) in asphyxiated neonates, and also showed that sNGAL at cutoff values of (> 89.6 ng/mL) had 100 % sensitivity, 92.3 % specificity, to detect acute kidney injury (AKI) in asphyxiated neonates [28]. Also, our results were near the results of the study of Wheeler et al., which showed that serum NGAL levels at a cutoff value of 139 ng /ml within the first 24 hours of admission to the PICU is highly sensitive for predicting AKI (sensitivity of 86%) with relatively poor specificity 39% [30].

In our study we tried to investigate an important complication in the management of neonates, acute kidney injury (AKI), using NGAl as it has been emerging as a likely candidate biomarker to supplant creatinine.

Limitation: However, the present study has limitations as well. First, it was performed at a single center, thus limiting the number of the asphyxiated neonates that could be enrolled. Second, Serum Creatinine was used for AKI definition with all its known drawbacks. All these reasons would justify the validation of the AKI biomarkers studied mainly in the urine in larger multi-center clinical studies, especially in relation to clinically important end points such as the need for dialysis, length of hospital stay or mortality.

CONCLUSION

Serum and urinary NGAL obtained in the first 24 hours of life showed significantly high values in asphyxiated neonates, with great accuracy and high sensitivity and specificity. Serum & urinary NGAL concentrations were also significantly higher in cases with acute kidney injury.

Conflicts of Interest: NIL

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