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Importance of Urinary NGAL Relative to Serum Creatinine Level for Predicting Acute Neonatal Kidney Injury

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ABSTRACT

Background: The diagnosis of acute kidney injury (AKI) is focused on the measurement of glomerular filtration rate based on serum creatinine; nevertheless, due to the effects of the underlying confounding parameters, this procedure tends to have some problems. Recent findings identified neutrophil gelatinase-associated lipocalin (NGAL) to be a critical marker for predicting AKI in humans. The aim of the present study was to evaluate changes in urinary NGAL levels in neonates with AKI and those without AKI.

Methods: This cross-sectional analytical study was conducted on a total of 75 neonates hospitalized for AKI and 81 neonates hospitalized for reasons not related to kidney disease. The serum concentrations of NGAL creatinine and urine were measured in both groups.

Results: The mean NGAL levels were 825.81±175.08 and 292.20±322.03 ng/ml in the case and control groups with a substantial difference, respectively. The NGAL had a sensitivity of 100%, specificity of 55.6%, positive predictive value of 67.6%, negative predictive value of 100%, and accuracy of 76.9% in predicting AKI. Assessing the region under the receiver operating characteristic curve (ROC curve) showed that measurement by NGAL effectively discriminated AKI from normal conditions (area under the ROC curve=0.899). The NGAL's best cut-off value for predicting AKI among neonates was estimated at 427 ng/ml, resulting in a sensitivity of 100% and specificity of 67.9%. Using Pearson's correlation coefficient test revealed a strong linear connection between the NGAL level and altered creatinine level (r=0.395; P<0.001).

Conclusion: The measurement of urinary NGAL in predicting AKI among neonates has high sensitivity and proper specificity, compared to that reported for the creatinine level.

Keywords: Acute kidney injury, Creatinine, Neonates, NGAL, Predicting AKI

Introduction

Acute kidney injury (AKI) is a leading cause of neonatal mortality and morbidity (1-4). The true etiology of acute neonatal kidney injury is multifactorial with a combination of many causes, such as ischemia, reperfusion damage, disturbance of homeostasis of the renal vasomotor, hypoxic and oxidative stress, and cytokine-driven impact. In other words, the identified mechanisms affecting kidney functional include altered renal perfusion, vasomotor nephropathy, severe sepsis, and drug-induced nephrotoxicity.

The diagnosis of this injury is routinely based on the calculation of glomerular filtration rate based on serum creatinine; however, this method appears to be unreliable due to the potential effects of underlying demographic and metabolic parameters on serum and urine creatinine levels. Therefore, recent studies have focused on new diagnostic specific markers with high sensitivity and accuracy for the early prediction of acute

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renal injury.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa lipocalin family protein that was initially identified in neutrophils but is also observed to be increased in other tissues in response to various conditions, such as ischemia and infection (12). The NGAL itself is stored within specific granules in certain cells, such as neutrophils (13), and is constitutively expressed in several organs, including the kidneys. In numerous cross-sectional studies, it has been shown that subjects with proven acute renal failure in the intensive care unit (ICU) showed a greater than 10-fold increase in NGAL plasma concentration and more than a 100-fold increase in urinary NGAL concentration, compared to normal controls.

The concentrations of NGAL plasma and urine both appear to be highly correlated with the concentrations of serum creatinine. In those cases, kidney biopsies showed the intense accumulation of immunoreactive NGAL in 50% of the cortical tubules. These outcomes described NGAL as a widespread and vulnerable human response to established AKI. However, the role of this marker in early predicting AKI in neonates remains uncertain. The purpose of this study was to determine and compare the amount of urinary NGAL in neonates with AKI and those without kidney injury admitted to the ICU in Ali-Asghar hospital in Tehran, Iran, and compare serum creatinine and urine NGAL among them.

Methods

This cross-sectional systematic study was carried out on a total of 75 consecutive neonates hospitalized due to AKI (defined as serum creatinine level higher than 1.5 mg/dl) at the neonatal department at Ali-Asghar hospital in Tehran in 2016. The neonates admitted to the hospital due to reasons not linked to kidney disease (with normal serum creatinine level) were randomly selected as the controls (n=81). By reviewing reported hospital files, baseline characteristics, including gender, gestational age, birth weight, underlying conditions of mothers, and mode of delivery, were collected.

The concentrations of serum creatinine and urinary NGAL were assessed in both groups on admission. The creatinine level was assessed using the enzymatic method, and the NGAL level was measured using the enzyme-linked immunosorbent assay. For statistical analysis, the obtained results were reported as mean±standard deviation for quantitative variables and summarized for categorical variables by absolute frequencies and percentages.

Data normality was evaluated using the Kolmogorov-Smirnov test. Using the Chi-square or Fisher's exact test, categorical variables were compared when more than 20% of cells with predicted counts of less than 5 were observed. In addition, quantitative variables were compared using the t-test or Mann-Whitney U test. The relationship between serum creatinine change and urinary NGAL concentration was evaluated using Pearson's correlation coefficient test.

The analysis of the receiver operating characteristic curve (ROC curve) was used to assess the NGAL value to differentiate AKI from normal conditions. Even the best cut-off value of NGAL was calculated yielding the most acceptable sensitivity and specificity. The SPSS statistical software (version 16.0; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p-value of 0.05 or less was considered statistically significant.

Results

A total of 156 neonates were included in this study. In all newborns, 75 subjects were categorized as the acute renal injury case group with an increased creatinine level, and 81 subjects were considered to be the normal creatinine control group. The demographic characteristics of the participants are shown in Table 1. All the subjects were term neonates, and none of them had a history of maternal kidney disease either during pregnancy or before pregnancy.

The mean NGAL levels were 825.81±175.08 and 292.20±322.03 ng/ml in the case and control groups with a substantial difference, respectively. The NGAL had a sensitivity of 100%, a specificity

Table 1. Demographic characteristics of participants

Group	n	Gender	Age (mean±standard deviation)	Gestational age (mean)	Birth weight (mean)	Maternal underlying disorders	Serum creatinine level (ng/ml)
Case	75	40 females 35 males	5±3 days	38 weeks	3.2 kg	No renal disease	>1.5
Control	81	36 females 45 males	4±2 days	39 weeks	2.9 kg	No renal disease	<1.5

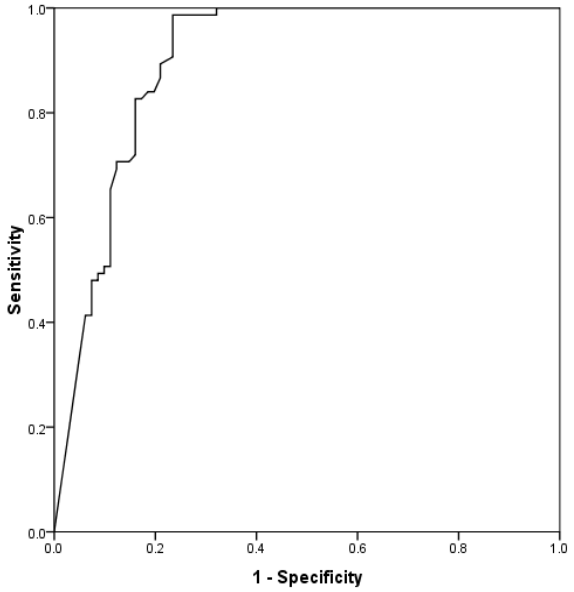

Figure 1. Analysis of area under receiver operating characteristic curve to determine value of urinary neutrophil gelatinase-associated lipocalin for prediction of neonatal acute kidney injury

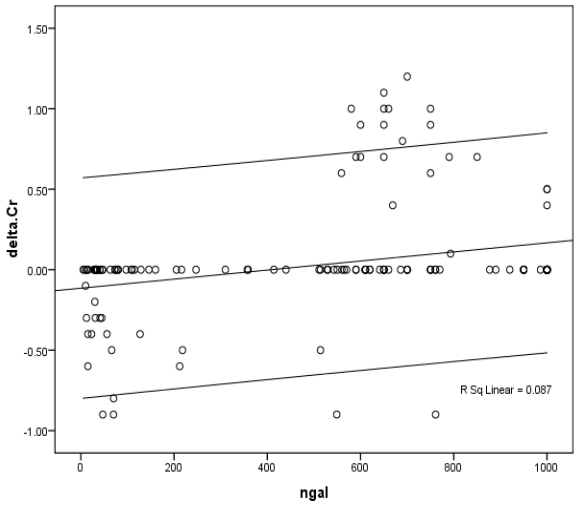

Figure 2. Correlation between urinary neutrophil gelatinase-associated lipocalin and change in serum creatinine

of 55.6%, positive predictive value of 67.6%, negative predictive value of 100%, and an accuracy of 76.9% to predict AKI using crosstabulation and basic formula. The area under the ROC curve (Figure 1) showed that NGAL calculation could effectively differentiate AKI from normal conditions (area under the ROC curve=0.899; 95% CI: 0.847-0.950; P<0.001).

The NGAL's best cut-off value for predicting acute kidney disease among neonates was estimated at 427 ng/ml, resulting in a sensitivity of 100% and specificity of 67.9%. There was a strong linear association between the NGAL level and changed creatinine level (r=0.395; P<0.001) using Pearson's correlation coefficient test (Figure 2).

Discussion

As previously demonstrated in both children and adults, creatinine levels may be influenced by a number of factors, such as demographic and metabolic parameters. Furthermore, raising creatinine level may occur by a significant delaying after injury leading reduce in accuracy of measuring creatinine to predict acute kidney injury as well as disability to early diagnosis, management and treatment of affected children.

In comparison to creatinine levels, the measurement of urinary NGAL as a more sensitive tool has recently been considered. Limited factors may affect NGAL levels; therefore, early and immediate increase has also been indicated following acute renal damage. In this study, we observed a strong association between the change in serum creatinine level and urinary NGAL level. In addition, the NGAL measurement of urine yielded a high sensitivity and acceptable specificity for predicting AKI.

Almost all similar studies have emphasized the role of NGAL as a sensitive tool for predicting AKI. In a study carried out by Rafiei et al., NGAL urinary levels were significantly higher in acute pyelonephritis with scars than in acute pyelonephritis without scars (16). The cut-off values were measured at 7.32 ng/ml, resulting in a sensitivity of 81.3% and specificity of 66% in groups with and without scars.

In a study conducted by Omerika et al., urinary NGAL level raised above cut-off value after heart surgery in a group of patients who developed AKI (17). There was a statistically significant difference between all four measurements. The positive association between urinary NGAL values and percentage difference between serum creatinine and creatinine clearance were also moderate.

In another study carried out by Zang et al. (18), the urinary NGAL levels in the AKI group increased significantly, compared to the levels obtained 3 days before the diagnosis of AKI; however, the serum creatinine levels did not change 2 days before the diagnosis. Urinary NGAL increased substantially, while serum creatinine levels did not change within the AKI group 1 day before the diagnosis (18). Two days before the diagnosis of AKI, the area under the urinary NGAL curve was 0.840 indicating that urinary NGAL was

AKI predictive, while serum creatinine was not AKI predictive.

Recently, Mishra et al. (19) suggested that the amount of NGAL in urine 2 h after cardiopulmonary bypass was the most powerful independent indicator of AKI. The area under the ROC curve was 0.998 for the urinary concentration of NGAL at 2 h. In addition, the sensitivity of 1.00% and specificity of 0.98% were reported for a cut-off value of 50 microg/L.

Conclusion

In conclusion, in predicting AKI among neonates, the NGAL measurement has high sensitivity and proper specificity, compared to the creatinine level. Consequently, the measurement of the urinary NGAL level will detect early kidney injury with high sensitivity and accuracy. This study was conducted in Ali-Asghar hospital that is a referral children hospital in Tehran (i.e., capital of Iran) with patients from all over the country; therefore, the results of this study can be generalized to all Iranian neonates. The mortality of neonates with AKI during the study and no long-time follow-up of the subjects were the limitations of the present study. It is suggested to carry out cohort studies with a longer time of follow-up.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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