Urinary neutrophil gelatinase-associated lipocalin is an early predictor of acute kidney injury in premature infants

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Abstract. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) is produced in response to tubular epithelial injury and is a biomarker of tubulointerstitial injury. The aim of the present study was to examine whether acute kidney injury (AKI) could be predicted by measuring uNGAL in very low-birth weight (VLBW) infants. Forty VLBW infants with birthweight below 1,500 g were enrolled in the present study. uNGAL and serum creatinine (sCre) were measured daily from postnatal days 0 to 8. Infants with sCre ≥ 1.2 mg/dl were diagnosed with AKI. The relationship of uNGAL with sCre was measured on the day after uNGAL measurement (next-day sCre) was examined. The results showed that 16 infants had sCre ≥ 1.2 mg/dl in this period. Logistic regression analysis revealed that uNGAL on postnatal days 2, 3, 4, 5 and 6 was correlated with next-day sCre ($P<0.05$). uNGAL corrected by urinary Cre (uCre) (uNGAL/uCre) was only correlated with an increase in next-day sCre on postnatal days 5 and 6 ($P<0.05$). For the logistic analysis, subjects with high and low uNGAL levels based on the median value for each day, uNGAL on post-natal days 2, 3 and 6 in the high uNGAL group was correlated with an increase in next-day sCre. Thus, AKI may be predicted by measuring uNGAL in VLBW infants. This measurement was non-invasive, and is potentially useful for the evaluation of renal function in VLBW infants.

Introduction

Renal function is immature in premature infants, and this can easily result in the development of acute kidney injury (AKI) due to changes in blood pressure and respiratory conditions, as well as administration of some drugs. It has been found that 8-24% of premature infants admitted to a neonatal intensive care unit (NICU) develop AKI (1,2). Additionally, AKI may contribute to the mortality of very low-birth weight (VLBW) infants with a birth weight of <1,500 g (3). Serum creatinine (sCre) is often used as a biomarker for renal function, albeit it is affected by parameters including muscle mass, gender, ethnicity, and medication (4). Additionally, several days are usually required before an increase in sCre level can be detected in infants with AKI (5).

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein from the lipocalin family that is primarily secreted by activated neutrophils (6). NGAL is produced in the granules of activated neutrophils and also by the nephron in response to any damage to tubular epithelium; therefore, NGAL can serve as a biomarker for tubulointerstitial injury (7). When the kidney is damaged, NGAL is mainly produced in the ascending thick limb of the loop of Henle and renal collecting tubule, and is immediately secreted into urine (8). Urinary NGAL (uNGAL) is increased with renal ischemia and associated acute tubular necrosis (9), and thus uNGAL is useful for the prediction of renal failure (10). uNGAL may also be an early marker of renal failure in adults and children after cardiac surgery or renal transplantation (11,12), and may be useful in the detection of chronic kidney failure in children (13), as well as the prediction of bronchopulmonary dysplasia in premature infants (14). The standard range of uNGAL in newborns, particularly VLBW infants, has been suggested to range between 2 and 150 ng/ml (15), albeit this has not been clearly established (16).

In the present study, we investigated whether an increase of uNGAL was useful for the early prediction of renal failure in VLBW infants.

Materials and methods

Subjects. The study subjects were infants who were born with a gestational age of 23 to <32 weeks and a birth weight of 500-1,500 g, and were admitted to the NICU of Dokkyo Medical University Hospital from January, 2009 to December, 2010. Infants with chromosomal abnormalities, external deformities and those with life-threatening diseases were excluded. Subsequently, a prospective single-center study was performed.

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Table I. Infant and maternal characteristics.

Characteristics	sCre ≥1.2 mg/dl (n=16)	sCre <1.2 mg/dl (n=24)	P-value
Gestational age (weeks)[a]	26.3±1.9	27.6±2.0	0.030
Birthweight (g)[a]	845±251	1,055±252	0.013
Normal spontaneous delivery (%)	7 (44)	14 (58)	0.520
1-min Apgar[a]	4.0±2.1	5.6±2.1	0.030
5-min Apgar[a]	6.9±1.1	7.8±1.7	0.029
Female (%)	9 (56)	10 (42)	0.520
Antenatal steroids (%)	9 (56)	18 (75)	0.305
Chorioamnionitis (%)	11 (69)	16 (67)	1.000
Indomethacin (%)	12 (75)	12 (50)	0.188
Aminoglycoside (%)	14 (88)	16 (67)	0.263
Mechanical ventilation (%)	11 (69)	8 (33)	0.051

[a]Mean ± standard deviation. sCre, serum creatinine.

This study was performed after obtaining approval from the ethics committee of Dokkyo Medical University (approval no. 25042) and informed consent from the infants' parents.

Methods. uNGAL and sCre levels were measured daily from postnatal days 0 to 8. For the measurement of uNGAL, urine was collected using cotton balls or a urine sampling bag and the samples were stored at -80˚C. When urine was collected with a cotton ball, the ball was applied to the vulva in the diaper and was collected after it was immersed in urine. uNGAL and urinary Cre (uCre) levels were unaffected by the measurement method (17,18). Furthermore, measurements of uNGAL levels in 23 subjects using urine sampling bags and cotton balls produced values of 134.5±128 and 132.1±125 ng/ml, respectively, with no significant difference (P=0.95). Based on these data, we collected urine using one of these methods.

uNGAL was measured using an NGAL ELISA kit 036 (BioPorto Diagnostics, Gentofte, Denmark) that specifically detects human NGAL. The urine sample was diluted 500 times using dilution solution provided in the NGAL kit. NGAL standards or diluted samples (100 μl) were applied to precoated microwells in duplicate, incubated for 1 h at 23±2˚C, and washed with washing buffer. Subsequently, biotinylated NGAL antibody and HRP-streptavidin were added to wells and incubated for 1 h via centrifugation using a shaking platform (200 rpm; Taiyo Micromixer, Taiyo Science Industrial Co. Ltd., Tokyo, Japan). TMB substrate was added for 10 min in the dark prior to adding stop solution. The NGAL concentration was then measured at 450 nm wavelength in each well with a reference reading at 620 nm in blank wells. The average was considered to be the uNGAL value. uCre was measured in the same samples.

sCre is generally used as an index of renal dysfunction in the first postnatal month (16) and is obtained using blood samples obtained in daily medical routine tests. AKI is diagnosed based on sCre ≥1.2 mg/dl (17). Subjects with sCre levels of ≥1.2 and <1.2 mg/dl were compared using U tests for gestational age, birth weight, and Apgar score, and Chi-square tests for gender. Indomethacin was employed for the treatment of patent ductus arteriosus in immature infants, and aminoglycoside antibiotics were used, as well as mechanical ventilation, antenatal steroid therapy, delivery method, and onset of chorioamnionitis for the diagnosis of AKI (17).

Statistical analysis. SPSS 11.0J for Windows (SPSS, Inc., Chicago, IL, USA) software was used for statistical analysis. Logistic regression analyses were performed for uNGAL and uNGAL/uCre with next-day sCre. Subjects were divided into low and high uNGAL groups based on the median uNGAL level on each day. Logistic regression analysis was then performed to calculate the odds ratio for next-day sCre as a predictor of high uNGAL, with the value for the low uNGAL group set to 1. Similar analyses were conducted for uNGAL/uCre. P<0.05 was considered to indicate a statistically significant difference.

Results

Subjects were stratified based on their weight into four groups: i) 500-750 g group (n=9); ii) 751-1,000 g group (n=15); iii) 1,001-1,250 g group (n=8); and iv) 1,251-1,500 g group (n=8). The gestational ages ranged from 23 weeks and 0 days to <26 weeks (n=13), 26 weeks and 0 days to <29 weeks (n=18), and 29 weeks and 0 days to <32 weeks (n=9). During the study period, 16 subjects had sCre ≥1.2 mg/dl. Groups with sCre ≥1.2 and <1.2 mg/dl had significant differences in gestational age, birthweight, and 1- and 5-min Apgar scores, but no significant differences in gender, delivery method, use of antenatal steroids, chorioamnionitis, use of indomethacin, use of aminoglycoside antibiotics, or mechanical ventilation were detected (Table I).

uNGAL levels measured in all subjects on postnatal days 0 to 8 are shown in Fig. 1. The median uNGAL was higher than the reported standard value in VLBW infants. There were significant differences in uNGAL between postnatal days 1 and 2, and between postnatal days 2 and 3 (Fig. 1). Based on logistic regression analysis, an increase in next-day sCre was significantly correlated with uNGAL on postnatal days 2, 3, 4, 5 and 6 (P<0.05), but with uNGAL/uCre only on postnatal days 5 and 6 (P<0.05).

Table II. Logistic analysis of uNGAL and next-day serum creatinine.

Postnatal	No.	uNGAL (ng/ml)		Odds ratio	P-value[a]
		Low	High		
Day 0	23	5.9-167.7	167.8-499.0	-	0.744
Day 1	40	6.6-193.2	193.3-542.1	3.00 (0.51-17.74)	0.063
Day 2	40	15.8-288.5	288.6-541.4	7.36 (1.34-40.55)	0.009
Day 3	40	14.3-359.6	359.7-572.6	15.52 (1.73-139.26)	0.010
Day 4	40	18.6-326.2	326.3-551.8	-	0.013
Day 5	40	17.0-239.9	240.0-542.2	-	0.011
Day 6	40	15.6-233.7	233.8-541.0	10.23 (1.12-93.34)	0.004
Day 7	40	15.0-237.6	237.7-542.0	6.33 (0.67-60.16)	0.122
Day 8	17	158.6-298.9	299.0-462.3	-	0.463

-, indicates no data because there were no cases with increased serum creatinine in the low group, and thus logistic regression analysis was not possible. [a]Urinary neutrophil gelatinase-associated lipocalin (uNGAL) was included as a continuous, rather than a categorical, variable in the logistic regression model.

Table III. Logistic analysis of uNGAL/uCre and next-day sCre.

Postnatal	No.	uNGAL/uCre		Odds ratio	P-value[a]
		Low	High		
Day 0	23	1.0-19.4	19.5-95.7	-	0.486
Day 1	40	0.8-18.9	19.0-82.4	1.42 (0.27-7.34)	0.228
Day 2	40	1.6-26.0	26.1-61.8	2.15 (0.52-9.00)	0.144
Day 3	40	0.9-21.2	21.3-73.1	3.05 (0.66-14.13)	0.159
Day 4	40	1.6-24.6	24.7-53.6	-	0.110
Day 5	40	1.7-18.1	18.2-52.6	8.14 (0.88-75.48)	0.031
Day 6	40	1.7-20.4	20.5-64.9	3.86 (0.67-22.11)	0.014
Day 7	40	1.3-21.5	21.6-78.0	2.53 (0.41-15.75)	0.065
Day 8	17	9.5-22.7	22.8-65.1	-	0.524

-, indicates no data because there were no cases with increased sCre in the low group, and thus logistic regression analysis was not possible. [a]uNGAL/uCre was included as a continuous, rather than a categorical, variable in the logistic regression model. uNGAL, urinary neutrophil gelatinase-associated lipocalin; uCre, urinary creatinine; sCre, serum Cre.
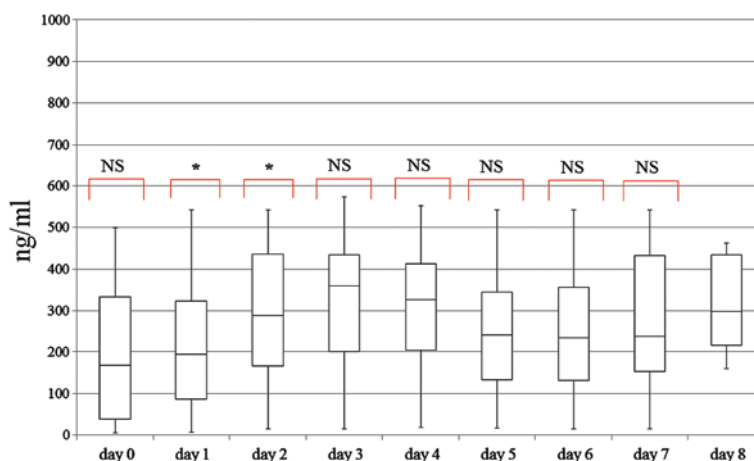

Figure 1. Urinary neutrophil gelatinase-associated lipocalin in infants on postnatal days 0 to 8. *P=0.02 for day 1 vs. day 2, and day 2 vs. day 3 by Mann-Whitney U test. NS, not significant.

Subjects were also divided into low and high uNGAL groups based on the median uNGAL measured each day. Calculation of the odds ratio showed that next-day sCre was a predictor of high uNGAL on postnatal days 2, 3 and 6 (Table II). No relationship with next-day sCre was detected for uNGAL/uCre on any day (Table III).

Discussion

The results of the present study have shown that, subjects with lower gestational age, lower birth weight, and lower 1- and 5-min Apgar scores had increased levels of sCre. Similar results were reported in previous studies (19,20). These results were consistent with findings showing that AKI occurs in 47-61% of cases of neonatal asphyxia with a 5-min Apgar score of <7 (20-22). It has been suggested that, compared to sCre, acute renal dysfunction in pediatric patients may be diagnosed more quickly based on NGAL in urine or blood after cardiac surgery (11). It was also reported that renal failure may be predicted more precisely with uNGAL because compared to blood NGAL levels, there was a marked increase in uNGAL levels (11). Thus, uNGAL is a more effective marker for renal dysfunction in children (11).

Higher levels of uNGAL have been detected in VLBW infants with a lower birth weight and lower gestational age (17), as well as in those with onset of AKI (23,24). The results showed that, uNGAL levels in the current study were higher than the recently reported standard value in VLBW infants (15,25). This difference may be explained by the fact that there were many premature infants with a gestational age <27 weeks among our subjects.

Next-day sCre, rather than sCre on the day of uNGAL measurement, was found to be a predictor for uNGAL. A difference in correlations of uNGAL with uNGAL/uCre and sCre were found (26), but our results support those of previous studies showing that correction of uNGAL with uCre was not necessary (15,17,27). An increase in uNGAL (a marker of proximal tubular epithelium disorder) may occur before an increase in sCre (a marker of glomerular disorder), because nephrogenic renal dysfunction may develop when prerenal failure is protracted (28). Additionally, Cre excreted due to tubular disorder may be reabsorbed due to insufficient tubular function, which can cause an increase in sCre in infants with LBW (29,30). uNGAL is excreted from renal proximal tubular cells as a response to AKI (31) and nephrogenic injury (32), and is increased in patients with late-onset sepsis (33).

uNGAL is not correlated with sCre in VLBW infants (16), however, our results suggested that uNGAL was a useful biomarker for the early diagnosis of renal failure in premature infants by predicting an increase in next-day sCre. The increase in sCre levels was significant in the high uNGAL group, and thus this group was likely to be at risk for AKI.

Further studies using bigger samples are needed to establish standard daily uNGAL levels for early postnatal days. Measurement of uNGAL has the advantage of being non-invasive for VLBW infants, and use of uNGAL in clinical practice may allow the prediction of renal failure, control of water intake, control of dosage of antibiotics that may induce renal failure, such as aminoglycosides and vancomycin for MRSA, and the need for use of indomethacin.

The most significant shortcoming of the present study was that we were not able to completely collect the maternal sCre data samples. This was because the sCre level of neonates 0 to 3 days after birth were influenced by the maternal sCre through the placenta, and data were not reflected adequately (34-36). In retrospect, this aspect should have been taken into consideration. Furthermore, because we only evaluated the relationship between uNGAL and sCre, the correlation with AKI was poor. We cannot disregard the possibility that AKI was overvalued. However, our results indicate that there was a correlation between uNGAL and sCre in VLBW infants, because it had the potential to function as the basic data for additional studies in the future. More clinical and basic studies on NGAL have been reported recently (37-43). In summary, more research on the biological mechanism of the NGAL is necessary.

Acknowledgements

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