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ORIGINAL ARTICLE

Urine neutrophil gelatinase-associated lipocalin to predict acute kidney injury in preterm neonates. A pilot study

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Abstract
Background The efficacy of urine neutrophil gelatinase-associated lipocalin (uNGAL) as an early acute kidney injury (AKI) biomarker in preterm neonates was evaluated.
Methods Thirty-five preterm neonates were prospectively evaluated for serum creatinine (sCre)-documented AKI during the first 14 days of life. Urine samples were collected daily throughout the study period. Of the neonates evaluated, we analyzed 11 who developed AKI (cases) and an equal number of neonates without AKI (controls) matched for gestational and postnatal age (case–control study). uNGAL was measured on the day of AKI occurrence (day 0) and on the 2 days preceding the event (day −1 and day −2, respectively) using an enzyme-linked immunosorbent assay.
Results Cases had significantly higher sCre levels than controls on day 0 (1.21±0.48 vs. 0.83±0.16 mg/dL, $p=0.031$) but not on days −1 and −2. Similarly, uNGAL levels (ng/mL) were significantly higher in cases than in controls only on day 0 (19.1±3.5 vs. 13.3±7.3, $p=0.017$) and not on days −1 (18.8±3.4 vs. 16.3±5.9, $p=0.118$) and −2 (19.3±1.8 vs. 19.4±0.8, $p=0.979$). The receiver operating characteristic curve analysis showed no significant ability of uNGAL to predict AKI on days −2 and −1.
Conclusions In this pilot study in preterm neonates, although uNGAL detected sCre-based AKI upon its documentation, it failed to predict its development 1–2 days earlier.

Keywords uNGAL · Biomarkers · Kidney injury · Diagnosis · Prediction · Creatinine

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Introduction

Acute kidney injury (AKI) is progressively recognized as a common and serious neonatal morbidity, especially in preterm infants [1] independently associated with reduced in-hospital survival [2, 3]. The true incidence of AKI is actually unknown in this age group, but the risk for this unfavorable complication is considerably higher in more immature and sick neonates [4]. In recent studies on extremely and very low birth weight infants, AKI was reported in 12.5 and 18 % of these populations, respectively [2, 3]. Nevertheless, the inadequate diagnostic performance of serum creatinine (sCre) may result in delayed AKI diagnosis, therefore precluding interventions to mitigate renal injury [5].

To overcome the diagnostic problems related to sCre, researchers have been testing the efficacy of several novel AKI biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), with promising results. NGAL is one of most robustly induced proteins by the kidney after experimental ischemic or nephrotoxic injury [6]. Studies performed hitherto have demonstrated increased NGAL in the urine (uNGAL) and/or blood of adults and children developing AKI compared to respective controls in various clinical situations, such as cardiac surgery [7, 8], critical illness [9, 10], sepsis [11], contrast nephropathy [12] and liver transplantation [13]. More interesting and clinically useful, however, is the fact that NGAL has the potential to predict kidney injury considerably earlier (1–3 days) than sCre [7–9].

The value of NGAL in diagnosing and predicting AKI, as well as other significant endpoints, such as mortality, has recently been demonstrated in critically ill preterm [14] and term infants [8, 15]. Nevertheless, very few studies have evaluated the temporal relation of the AKI biomarkers in the neonatal period with respect to the onset of kidney injury, as indicated by sCre which is considered to be the "gold standard." In one study on term neonates undergoing heart surgery, AKI diagnosis based on increased NGAL levels was possible 1 day earlier than that based on sCre [8].

We hypothesized that NGAL would be increased in the urine of preterm neonates suffering AKI considerably earlier than sCre. To examine this possibility, we prospectively evaluated uNGAL concentrations in a cohort of preterm neonates receiving intensive care before and upon laboratory (sCre) documentation of AKI.

Methods

Study design and population

This is a case–control study of uNGAL in preterm neonates (27–32 weeks gestational age) who were admitted to our tertiary neonatal unit between March 2010 and April 2011. Enrolled neonates were prospectively followed for AKI development during the first 14 postnatal days by measuring sCre at least once every other day. Urine samples were also collected on a daily basis, during a 3-h collection time, using cotton balls placed near the perineum or, more rarely, through a bladder catheter inserted for clinical reasons (Fig. 1). Neonates with any congenital anomaly, early-onset sepsis and severe perinatal asphyxia were a priori excluded from the study, as were those who showed persistently abnormal sCre values (>1.5 mg/dL) from birth or died within the first 3 days after birth. The study was approved by the ethical committee of our institution and informed written consent was obtained from all parents.

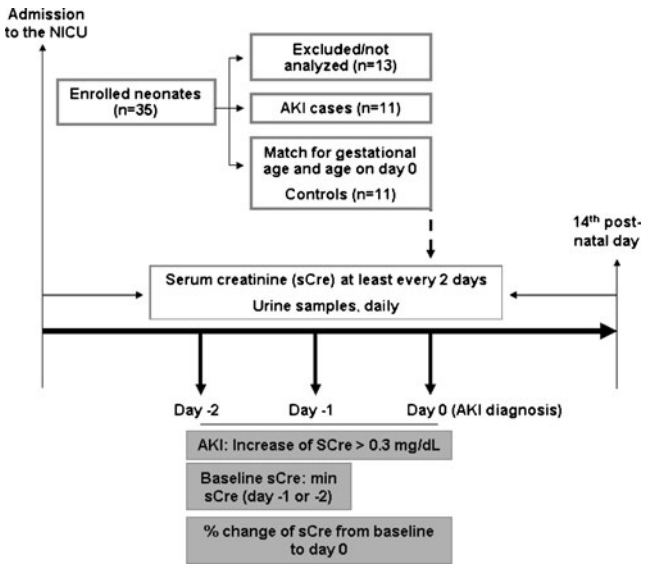


Fig. 1 Study design showing the selection of cases and controls as well as the time points of the study in which serum creatinine (*sCre*) and neutrophil gelatinase-associated lipocalin in the urine (uNGAL) were evaluated. The calculation of baseline sCre and its percentage (%) change is also given. *NICU* Neonate intensive care unit, *AKI* acute kidney injury

Group categories and estimation of AKI

Patients were categorized as having AKI (cases) according to the recently proposed classification of neonatal acute kidney injury (Table 1). In line with this classification, AKI was defined as an increase of sCr of ≥0.3 mg/dL from the previous measurement within 48 h or by a 150–200 % increase from the previous measured level [5]. Because urine biomarkers may vary by gestational age [16], each neonate with AKI was matched to one neonate of the same gestational age (± 1 week) without AKI (control).

In our study, day 0 corresponded to the day of life on which the AKI criteria were fulfilled in cases and the respective postnatal age in the controls, as postnatal age may also affect levels of urine biomarkers [17]. Measurements were performed in samples obtained on day 0 and on the two preceeding days (day −1 and day −2, respectively). In addition, the lowest sCre value either on day −1 or −2 (baseline sCre) was recorded and the percentage (%) change of sCre from baseline to day 0 was calculated (Fig. 1). In order to further evaluate the course of AKI, we also recorded the sCre levels during the period 1–2 days following day 0.

Data on demographic–perinatal characteristics (gestational age, birth weight, prenatal steroids, mode of delivery, Apgar scores, clinical chorioamnionitis, pre-eclampsia, gestational diabetes, large and small for gestational age neonates), prematurity-associated complications (respiratory distress syndrome, intraventricular hemorrhage ≥grade III, patent ductus arteriosus, late-onset sepsis, necrotizing enterocolitis) and interventions/drugs occurring up to day 0 (mechanical ventilation, exogenous surfactant, inotropes, ibuprofen,

Table 1 Proposed neonatal acute kidney injury classification definition[a]

Stage	Description
0	No change in sCre level or an increase of <0.3 mg/dL
1	↑ sCre 0.3 mg/dL or ↑ sCre 150–200 % from previous trough value
2	↑ sCre 200–300 % from previous trough value
3	↑ sCre 300 % from previous trough value or 2.5 mg/dL or dialysis treatment

SCre, Serum creatinine

[a] Adapted from Jetton and Askenazi [5] (used with permission)

vancomycin) were collected for both groups. The total number of urine samples evaluated was also recorded.

Urine NGAL and sCre assays

For both cases and controls, urine samples were centrifuged (3,000 rpm) for 15 min and the supernatants stored at −80° C until NGAL measurement using a commercially available enzyme-linked immunosorbent assay (ELISA) (Quantikine® Human Lipocalin-2/NGAL; R&D Systems Europe, Ltd, Abingdon, UK). The intra-assay coefficient of variation was <5 % and the lower limit of detection of uNGAL was 0.012 ng/mL. uNGAL was measured by an investigator blinded to the study design. sCre measurements were performed in the hospital's central biochemical laboratory using the Jaffe method.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation (SD) as all variables followed normal distribution assumptions (Kolmogorov–Smirnov test). Continuous and categorical variables between two groups were assessed using the paired *t* test and McNemar's test, respectively, as indicated in matched case–control studies [18, 19]. The diagnostic accuracy of uNGAL for identifying AKI was evaluated by constructing receiver operating characteristics (ROC) curves. *p* values of <0.05 were considered to be statistically significant. Statistical analysis was performed using MedCalc software (ver. 11.1.1; MedCalc Software, Ostend, Belgium).

Results

Study population

Of the 35 preterm neonates evaluated, eight were excluded from the study due to persistently high sCre from birth ($n=2$), death within 3 days after birth ($n=2$) and inadequate sCre measurements and/or urine samples ($n=4$). Of the 27 remaining neonates, 11 developed AKI and were matched with an equal number of neonates without AKI. As controls outnumbered cases, five neonates were not analyzed (Fig. 1). Cases ($n=11$) and controls ($n=11$) were comparable in terms of gestational age (29.6±1.8 vs. 29.8±1.9 weeks, $p=0.341$), as expected by the study design, but also in terms of birth weight (1416±273 vs. 1555±371 g, $p=0.101$). The incidence of the other demographical–perinatal characteristics, prematurity-associated complications and interventions are shown in Table 2. However, statistical comparisons of these parameters were not performed as the number of patients in the study was small.

Table 2 Demographic–perinatal characteristics and complications of prematurity and applied interventions observed up to day 0

Demographic–perinatal characteristics	Cases ($n=11$)	Controls ($n=11$)
Male sex	6 (54.5)	5 (45.4)
LGA/SGA	1 (9.1)/0 (0)	1 (9.1)/1 (9.1)
Caesarian section	10 (90.1)	9 (81.8)
Prenatal steroids	6 (54.5)	8 (72.7)
Gestational diabetes	2 (18.2)	0 (0)
Pre-eclampsia	1 (9.1)	1 (9.1)
Premature rupture of membranes	2 (18.2)	4 (36.4)
Clinical chorioamnionitis	2 (18.2)	1 (9.1)
Apgar score 1 min	6.2±2.2	6.9±1.2
Apgar score 5 min	8.0±1.2	7.9±1.1
Intubation in the DR	3 (27.3)	1 (9.1)
Mechanical ventilation	9 (81.8)	9 (81.8)
Respiratory distress syndrome	6 (54.5)	8 (72.7)
Exogenous surfactant	6 (54.5)	6 (54.5)
Patent ductus arteriosus	2 (18.2)	1 (9.1)
Necrotizing enterocolitis	0 (0)	0 (0)
Late onset sepsis	0 (0)	0 (0)
IVH grade 3–4	2 (18.2)	2 (18.2)
Inotropes	3 (27.3)	1 (9.1)
Ibuprofen for PDA	0 (0)	0 (0)
Vancomycin	2 (18.2)	2 (18.2)

LGA, Large for gestational age; SGA, small for gestational age; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; DR, delivery room

Continuous variables are expressed as the mean ± standard deviation (SD) and and categorical variables are expressed as numbers with percentages in parenthesis

AKI development and indicators

Age on day 0 was comparable between cases and controls (5.0± 2.4 vs. 5.5±2.3 days, respectively; $p=0.167$), as was expected by the study design. Cases had significantly higher sCre levels than controls on day 0 (1.21±0.48 vs. 0.83±0.16 mg/dL, respectively; $p=0.031$) but not on day −1 (0.76±0.15 vs. 0.81± 0.16 mg/dL, respectively; $p=0.423$) and day −2 (0.81±0.31 vs. 0.83±0.22 mg/dL, respectively; $p=0.819$). The % change in sCre level differed significantly between groups ($p < 001$), increasing by 58.5±24.8 % in cases and decreasing by −5.5± 17.5 % in controls. All but one case were considered to have stage 1 AKI. One neonate showing a 116.7 % increase in sCre level from baseline was classified with stage 3 AKI, as a sCre value of 2.6 mg/dL was observed on day 0 [5]. Although the sCre levels remained significantly higher in cases than in controls 1 to 2 days after day 0 (pooled values: 1.01±0.28 vs. 0.78± 0.15 mg/dL, respectively; $p=0.044$), none of the ten neonates with stage 1 AKI progressed to more advanced stages.

The analysis of 56 urine samples revealed that cases had significantly higher uNGAL concentrations than controls only

Table 3 Urine neutrophil gelatinase-associated lipocalin levels in acute kidney injury cases and controls from day −2 to day 0

Day	Cases ($n=11$)	Controls ($n=11$)	P value[a]
0	19.1±3.5	13.3±7.3	0.017
−1	18.8±3.4	16.3±5.9	0.118
−2	19.3±1.8	19.4±0.8	0.979

Urine neutrophil gelatinase-associated lipocalin levels (ng/mL) are presented as the mean ± SD

[a] Paired t test

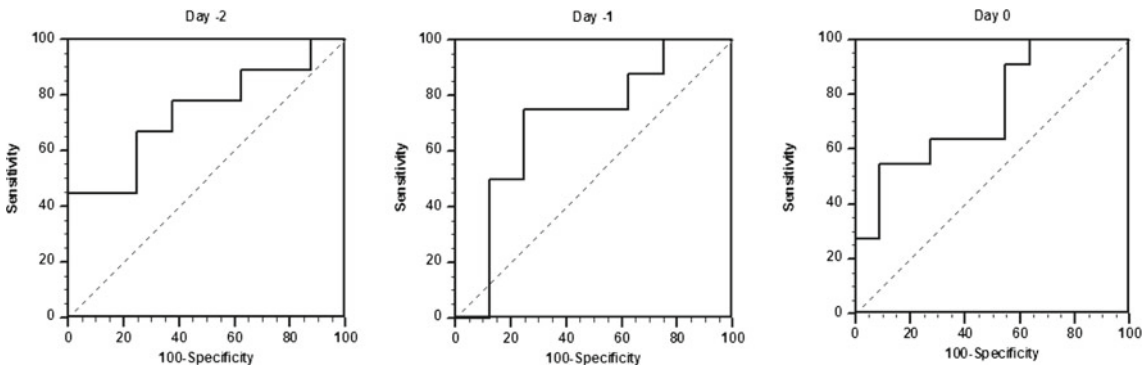
on day 0 (Table 3). Further analysis of uNGAL values as % change gave similar results (data not shown). Results of the ROC curve analysis showed that uNGAL had no significant efficacy to predict AKI 1–2 days prior to its development (Fig. 2).

Discussion

In this pilot, case–control study, we investigated the potential of uNGAL as a biomarker to detect and, therefore, predict AKI in preterm neonates, earlier than sCre. We found that significantly higher uNGAL concentrations were associated with the documentation of mild (stage 1) AKI cases, but the levels of this biomarker did not differ in the urine of neonates 1–2 days prior to the increase of sCre. This observation strongly indicates that the diagnostic value of uNGAL as an early predictor of AKI is limited relative to sCre.

uNGAL has recently emerged as a valuable AKI biomarker as it provides a significant advantage compared to sCre—its level increases much earlier than that of sCre in the urine of patients with AKI [20]. In studies on patient cohorts that included neonates developing AKI following cardiopulmonary bypass, uNGAL was found to increase as early as 1–2 h after the onset of the operation [7, 8, 21]. Our results are consistent with existing data showing increased uNGAL concentrations in neonatal AKI [14]. However, contrary to our hypothesis, we were unable to document any superiority of uNGAL over sCre in terms of the early detection of AKI. Severity of renal injury could provide an explanation, as this factor is associated with the rise in uNGAL levels. In our study, only one neonate had stage 3 AKI according to the neonatal AKI classification definition [5]. Overall, cases had an average increase of sCre of 58.5 %, corresponding to stage I AKI; this is much less than the increase (108 %) reported by Krawczeski et al. in his patient cohort of neonates undergoing cardiac surgery [8]. A correlation between uNGAL concentrations and severity of kidney injury was also observed by Zappitelli et al. in critically ill children [9]. In the latter investigation, even though uNGAL predicted the development of AKI within 48 h, 22.1 and 17.9 % of the patients were stratified according to the modified pRIFLE criteria as having "Injury" and "Failure," respectively [9]. However, the trend for decreasing uNGAL levels observed in our study between days −2 and 0 in cases versus controls (levels remained unchanged in the latter) provide some evidence that uNGAL could probably serve as an early AKI indicator had the number of studied neonates been larger (as discussed below) and/or renal damage more severe.

In our study, until the diagnosis of AKI was made, no neonate developed late-onset sepsis or necrotizing enterocolitis, while an equal number in each study group was given vancomycin. This is important as inflammation–sepsis and nephrotoxic drugs could influence uNGAL levels [11, 22]. Interestingly, our absolute values are considerably lower than those previously reported in preterm neonates by other investigators who used various assays: uNGAL was determined either alone (commercial ELISA kit) [23] or together with



Day	Area under the curve (AUC)	P value	Cut-off point	Sensitivity	Specificity
0	*0.744*	*0.023*	*>19.39*	*54.5*	*90.9*
-1	*0.703*	*0.129*	*>18.95*	*75*	*75*
-2	*0.736*	*0.055*	*>19.99*	*44.4*	*100*

Fig. 2 Diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin (uNGAL) in predicting acute kidney injury (AKI)

other AKI biomarkers (multiplex assay) [14, 16]. On the contrary, pooled uNGAL values (immunoblot) reported by other investigators in very-low birth weight infants largely approximate those determined in our study [23]. The authors of a recently published study comparing the accuracy of commercially available uNGAL assays in critically ill patients documented significant discrepancies among the assays [24]. This finding emphasizes the need for each center to develop reference values based on the laboratory technique used.

Our measurement—for the first time in preterm neonates—of uNGAL at pre-determined time points related to the increase in sCre is an important strength of this study. Previous investigations reporting on AKI in preterm neonates evaluated "maximal" uNGAL levels from urine samples obtained around the time of AKI confirmation or under conditions of no AKI [14], which do not enable the usefulness of uNGAL in the earlier (within days) prediction of AKI to be assessed. In addition, matching for the degree of pre- and post-natal maturation is another important factor in such studies as uNGAL/urine creatinine values decrease by around 23 and 1.33 % per week of gestational age [16] and postnatal day [17], respectively. Although the most common approach adopted to compare uNGAL levels would be the use of logistic regression analysis to adjust for a possible effect of gestational age and age after birth, matching in case–control studies allows better control of the confounding variables, especially in studies with small sample sizes [18, 19]. On the other hand, in our study the exclusion of controls (due to 1:1 matching with fewer cases than controls) as well as the a priori exclusion of neonates with AKI from birth and of those who died within the first 3 post-natal days resulted in a significant attrition rate. The limited number of neonates in which uNGAL was evaluated is indeed a weakness of our single-center study, as is the use of a sCre-based definition for AKI. Sampling analysis using MedCalc revealed that 60 and 82 subjects would be needed in each group at days −2 and −1, respectively, in order to achieve statistically significant areas under the ROC curves for AKI prediction. Therefore, larger (adequately powered) multi-center studies, also involving clinical settings with more severe cases of AKI (e.g following cardiac surgery) [25], are needed to overcome such issues and provide more insights into the value of uNGAL as an early AKI indicator. Practical difficulties in working with preterm neonates (limitations in blood volumes drawn and difficulties in collecting urine samples) greatly hamper research in this area. However, more frequent sampling to optimize the performance of AKI biomarkers in this age group might not be realistic in clinical terms and has a considerable cost. Lastly, other urine AKI indicators such as cystatin C, kidney injury molecule-1, interleukin-18 and liver fatty acid binding protein, which may be more appropriate for the evaluation of renal injury in this age group, should be explored alone or in combination [26].

In summary, based on the results of our study in preterm neonates with AKI, uNGAL may detect renal injury only upon its documentation by conventional sCre levels. Nevertheless, given the aforementioned limitations of this investigation, the inability to provide sufficient evidence of good diagnostic performance with uNGAL in predicting AKI 1–2 days prior to its development should be assessed with caution. Larger investigations that include the whole spectrum of AKI are needed in order to clarify the value of this specific urinary biomarker as an early AKI indicator in preterm neonates.

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