Pediatrics and Neonatology (2016) 57, 207–212

Available online at www.sciencedirect.com

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journal homepage: http://www.pediatr-neonatol.com

ORIGINAL ARTICLE

Urinary Neutrophil Gelatinase-Associated Lipocalin Levels in Neonates

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Received Apr 28, 2015; received in revised form Aug 25, 2015; accepted Sep 13, 2015
Available online 9 October 2015

Key Words
acute kidney injury;
biomarkers;
neonate;
neutrophil gelatinase-associated lipocalin

Background: Acute kidney injury (AKI) is common in preterm infants and is associated with high mortality and morbidity. New biomarkers for the early detection of AKI have been identified. Specifically, urinary neutrophil gelatinase-associated lipocalin (uNGAL) is a new and powerful biomarker for AKI and sepsis. Our study evaluated the reference range of uNGAL in healthy neonates in Taiwan.
Methods: This study examined 24 preterm and 38 term infants without clinical complications. Urine samples were collected and the uNGAL values were measured at postnatal age (PNA) 3 days, 7 days, 14 days, and 21 days in the preterm infants and at PNA 3 days in the term infants. The uNGAL values were tested using enzyme-linked immunosorbent assay.
Results: The median uNGAL values in the preterm infants at PNA 3 days, 7 days, 14 days, and 21 days were 41.52 ng/mL, 35.82 ng/mL, 43.79 ng/mL, and 30.85 ng/mL, respectively. The median value at PNA 3 days in the term infants was 88.1 ng/mL. No significant differences associated with gestational age, birth body weight, or PNA were observed among the preterm infants. However, the uNGAL values in the female term infants were higher than those in

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http://dx.doi.org/10.1016/j.pedneo.2015.09.003

the male term infants ($p = 0.003$).
Conclusion: This study presents preliminary data on uNGAL levels in neonates in Taiwan. A large-scale study investigating the correlations between uNGAL and with gestational age, birth body weight, sex, and PNA is recommended.

1. Introduction

New biomarkers have been developed for detecting renal function impairment in neonates. These biomarkers are used in the early detection of acute kidney injury (AKI) and are less invasive.[1,2] The survival rate of preterm infants has also increased with advances in perinatal care and the development of new biomedical technology.[3] However, preterm infants remain vulnerable to renal impairment because of their underdeveloped kidneys, with medications for renal toxicity such as aminoglycoside, indomethacin, and ibuprofen sometimes being required. Hypotension and hypoxemia are common in preterm infants during the first few days of life; these conditions may also contribute to AKI. The incidence of AKI in neonates is 6–24%, and neonates with AKI may experience long-term complications such as chronic kidney disease.[4,5] Higher mortality and morbidity rates were found in preterm infants with AKI.[6] Therefore, the early detection of AKI is crucial for avoiding further organ damage and extending the lives of infants with AKI.

Serum creatinine (SCr) and urine output are the main detectors of AKI.[7–9] The true renal function of preterm infants is difficult to evaluate.[10] SCr levels in infants are unreliable as a detector of AKI in the first few days of life because they may continue to reflect maternal SCr levels. Furthermore, SCr levels in infants may not change until renal function decreases below 25–50% that of normal levels. In addition, SCr levels are correlated with muscle mass and sex.[1] New methods of identifying AKI in preterm infants are thus required.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein that was first discovered by a Danish scientist in 1983,[11] and is a novel biomarker used for detecting AKI. It can be detected in serum and urine specimens and used as a biomarker for detecting AKI, sepsis, and urinary tract infections in adults and children.[12–18] Serum NGAL was determined to be related to the occurrence of bronchopulmonary dysplasia in preterm infants.[19] Levels of NGAL can be detected a few hours after renal injury, before the SCr levels become elevated. A strong correlation between serum and urinary NGAL (uNGAL) concentrations was reported.[12]

Although NGAL appears to be a useful biomarker for AKI, scant reference data on NGAL in preterm infants exist, and previous studies have yielded conflicting results. Some studies have correlated NGAL with gestational age (GA), postnatal age (PNA), and sex, whereas others have revealed no such associations.[1,15,20–22] Furthermore, no studies have determined the normal levels of uNGAL in Asian neonates. Therefore, our study aimed at determining the reference ranges of uNGAL in healthy preterm and term neonates in Taiwan.

2. Methods

2.1. Participants and NGAL measurement

We conducted a prospective, observational study on neonates admitted to the National Taiwan University Hospital between December 2003 and January 2007. Ninety-nine neonates were initially enrolled in our study. Thirty-seven participants with congenital anomalies, proven (with a positive blood culture) or suspected neonatal sepsis, maternal infection (if the mother had a urinary tract infection, fever, or chorioamnionitis), AKI (urine output < 1 cm^3/kg/h for 24 hours),[23] prolonged ventilator use (intubated with mechanical ventilator support for >7 days) or severe hypoxic ischemic encephalopathy, a low Apgar score (Apgar score < 4 at 1 minute and/or < 7 at 5 minutes after birth), incomplete data (unrecognized or missing data of clinical parameters in medical records), post indomethacin treatment or surgical ligation for patent ductus arteriosus, or necrotizing enterocolitis were excluded. A total of 62 neonates with no clinical complications were enrolled and subgrouped into preterm ($n = 24$) and term infants ($n = 38$; Figure 1).

All of the preterm infants underwent a renal function test (verifying that their SCr levels were <1.0 mg/dL) when possible or had their urine output recorded (verifying an output of >2 cm^3/kg/h) during their hospital stay. The term infants were admitted to the nursery and had their urine output recorded at least once on Day 1, two times on Day 2, and three times on Day 3 as a general routine evaluation of renal function and hydration. Based on these measurements, we assumed that the infants had normal renal function and were sufficiently hydrated.

Urine samples were collected from the term infants at PNA 3 days and from the preterm infants at PNA 3 days, 7 days, 14 days, and 21 days. The preterm infants were stratified into the following two groups according to GA: Group 1 (GA < 32 weeks, $n = 11$) and Group 2 (GA 32–36 weeks, $n = 13$). The term infants comprised Group 3. This study was approved by the Institutional Review Board of National Taiwan University Hospital, and written consent was obtained from the parents of each infant.

Urine samples were collected using urine bags or cotton balls and were stored at -80°C until analysis. The NGAL values were tested using a sandwich enzyme-linked