Plasma Neutrophil Gelatinase Associated Lipocalin in Neonates With and Without Sepsis

Nastaran Khosravi [1]; Hosein Karimi [1]; Nasrin Khalesi [1]; Rozita Hoseini [1]; Mitra Mehrazma [1]; Niloofar Khosravi [2,*]

[1]Pediatric Transplantation and Dialysis Research Center, Iran University of Medical Sciences, Tehran, IR Iran
[2]Ali-Asghar Children Hospital, Iran University of Medical Sciences, Tehran, IR Iran

Corresponding author: Niloofar Khosravi, Ali-Asghar Children Hospital, Iran University of Medical Sciences, Tehran, IR Iran. Tel: +98-2144297768, E-mail: niloofarkhosravi@rocket-mail.com

Background: Plasma neutrophil gelatinase associated lipocalin (NGAL) level is increased in sepsis irrespective of renal dysfunction. We investigated the effect of sepsis on the plasma level of NGAL in neonates.
Objectives: The aim of this study was to find whether serum NGAL is a reliable marker for early diagnosis of sepsis in neonates.
Patients and Methods: We conducted a prospective observational study in a university hospital neonatal intensive care unit. Serum NGAL was measured in 120 neonates admitted to the neonatal intensive care unit. Neonates were classified according to the presence of sepsis. Fifty-two Patients had sepsis.
Results: The NGAL levels were significantly higher in septic neonates compared with non-septic neonates (102.9 ± 69.9 ng/mL versus 29.2 ± 13.3 ng/mL, P value = 0.0001). An optimal cut off-point of 48 ng/mL for serum NGAL could potentially detect neonates with sepsis with a sensitivity and specificity of 92% and 91%, respectively.
Conclusions: Sepsis enhances the production of plasma NGAL in critically ill neonates. Thus Plasma NGAL can help clinicians diagnose sepsis in critically ill neonates during early phases.

Keywords: Neutrophil; Gelatinase; Lipocalin; Sepsis

1. Background

Neutrophil gelatinase-associated lipocalin (NGAL) is secreted by some cells in the body such as injured kidney cells and neutrophils in response to bacterial infections. Serum NGAL has been shown to be elevated in patients with sepsis and septic shock. Neonates are at risk of sepsis. Early diagnosis and treatment of neonates with sepsis is critical. Serum and urinary NGAL have been shown to be an ideal biomarker of infection in children and adults (1). A recent study by Parravicini et al. has introduced urinary NGAL as an early marker for neonatal sepsis (2). This markedly increased urinary NGAL in neonates at neonatal intensive care units occurs in the absence of renal dysfunction (3). However, there are only a few studies about the association between serum and/or urinary NGAL and neonatal sepsis. If we want to use NGAL as a predictive marker for early diagnosis of neonatal sepsis, we need more studies in this regard.

2. Objectives

We aimed to assess the influence of sepsis on plasma NGAL in neonates. In this regard we also aimed to evaluate the predictive ability of serum NGAL in diagnosis of sepsis in neonates.

3. Patients and Methods

One-hundred-twenty neonates were included in this prospective study. Sixty-eight neonates didn't have any manifestations of sepsis, and fifty-two neonates had clinical signs and symptoms of sepsis. Firstly, the diagnosis of sepsis was based on clinical signs and laboratory findings. All neonates had positive blood cultures. The clinical signs of sepsis were tachypnea, grunting, apnea, retraction, feeding problems, abdominal distension, seizure, irritability, lethargy, hypotension, cyanosis, fever and hypothermia. All included neonates had a minimum of three clinical signs. The laboratory manifestations of sepsis were elevated C reactive protein, leukopenia, neutropenia and thrombocytopenia. All cases had two or more laboratory findings. All neonates with negative blood cultures and renal dysfunction were excluded from this study. Serum NGAL was measured in both septic and non-septic neonates by NGAL rapid enzyme-linked immunosorbent assay (ELISA) kit (kit 037).

Table 1. The characteristics of the neonates [a]

	All Neonates	Septic Neonates	Non Septic Neonates	P Value
Gender, Male	68 (56.7)	34 (65.3)	34 (50)	0.09
Gestational age, week	36.7 ± 3.7	34.2 ± 4.3	38.7 ± 1.3	0.0001
Birth weight, kg	2796 ± 806	2315 ± 954	3163 ± 388	0.0001
Hospitalization duration, day	18.6 ± 20.7	39.9 ± 13.5	2.4 ± 0.5	0.0001
Death	2 (1.7)	2 (4.1)	-	0.18
Serum NGAL, ng/mL	61.2 ± 57.5	102.9 ± 65.9	29.2 ± 13.3	0.0001

[a] Data are presented as No. (%) or Mean ± SD.

3.1. Statistical Analysis

Statistical analysis was performed using the SPSS software version 16. Values were expressed as mean and standard deviations. Student t-test and Mann–Whitney U-test were used for quantitative data comparison. The discriminatory power and cut-off points for sepsis in neonates through the serum NGAL were evaluated by means of the Receiver Operator Characteristic (ROC) curve.

4. Results

NGAL was measured for 120 neonates. Sixty-eight cases were male. The mean gestational age was 36.7 ± 3.7 weeks (26-40 weeks). The mean weight was 2796 ± 806 grams (950-4030 gram). Fifty-two neonates had sepsis and sixty-eight neonates didn't have sepsis. The characteristics of these neonates are shown in Table 1.

The mean serum NGAL was 102.9 ± 69.9 ng/mL in septic neonates and 29.2 ± 13.3 ng/mL in non-septic neonates and this difference was significant (P Value = 0.0001). There was a significant relationship between serum NGAL and hospitalization duration (P value = 0.0001). There was no significant association between gestational age, birth weight and serum NGAL concentration. The ROC analysis demonstrated that serum NGAL could be a potentially useful index to diagnose sepsis in neonates (P < 0.05, AUC = 0.80). An optimal cut off-point of 48 ng/mL for serum NGAL could potentially detect neonates with sepsis with a sensitivity and specificity of 92% and 91%, respectively.

5. Discussion

Neutrophil gelatinase-associated lipocalin is released from secondary granules of activated neutrophils. It is an iron scavenger that prevents bacterial growth. This protein is also produced by renal tubular cells, secondary to injury, for instance as a result of ischemia. Thus it is used as an early marker of acute kidney injury. During sepsis, it appears that NGAL is also released by activated leukocytes. Severe sepsis is a major cause of mortality and morbidity in neonates at neonatal intensive care units. As the manifestations of sepsis are nonspecific in neonates and there are delays in taking cultures, there is difficulty with diagnosis of sepsis in neonates especially during early phases. On the other hand early diagnosis and intervention may be helpful in saving lives. On this basis, researchers have tried to find markers with high positive and negative predictive values for identifying neonates at risk of sepsis. One of these markers is serum and/or urinary NGAL. Parravicini et al. measured urinary NGAL in late onset sepsis in very low birth weight (VLBW) infants. They found a sensitivity of 75%, specificity of 84%, positive predictive value of 67% and negative predictive value of 89% (2, 3). They concluded that urinary NGAL is a suitable marker for early diagnosis of sepsis in VLBW neonates. To our knowledge, this is the first study to assess serum NGAL for the diagnosis of sepsis in neonates. We found that serum NGAL was low in neonates without sepsis and high in neonates with sepsis. This suggests that serum NGAL can be a biomarker of sepsis in neonates. We also found a cut-off value of 48 ng/mL for distinguishing septic from non-septic neonates with a sensitivity of 92% and specificity of 91%.

Authors' Contributions

All authors have read and agree with the content of this manuscript and there are no financial conflicts of interest to disclose.

References

1. Lentini P, de Cal M, Clementi A, D'Angelo A, Ronco C. Sepsis and AKI in ICU Patients: The Role of Plasma Biomarkers. *Crit Care Res Pract.* 2012;**2012**:856401.
2. Parravicini E, Nemerofsky SL, Michelson KA, Huynh TK, Sise ME, Bateman DA, et al. Urinary neutrophil gelatinase-associated lipocalin is a promising biomarker for late onset culture-positive sepsis in very low birth weight infants. *Pediatr Res.* 2010;**67**(6):636–40.
3. Parravicini E. The clinical utility of urinary neutrophil gelatinase-associated lipocalin in the neonatal ICU. *Curr Opin Pediatr.* 2010;**22**(2):146–50.