Evaluation of the Relationship Between Microalbuminuria and Early Neonatal Sepsis, Respiratory Distress Syndrome in Preterm Infants

Prematüre Bebeklerde Mikroalbüminüri ile Erken Neonatal Sepsis, Solunum Sıkıntısı Sendromu Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: Early neonatal sepsis and respiratory distress syndrome lead to neonatal mortality in preterm infants during the first days of life. The objectives of this study were to identify whether spot urine albumin/creatinine ratio is an early diagnostic indicator of early neonatal sepsis and respiratory distress syndrome in preterm infants.

Material and Methods: This was a prospective longitudinal analysis of 126 preterm infants born at less than 34 weeks of gestation. In this study, we evaluated serum concentrations of albumin, creatinine, C-reactive protein (CRP) and spot urine albumin/creatinine ratio on the first, third and seventh day of life. We also investigated the association of these parameters with early neonatal sepsis and respiratory distress syndrome in preterm infants during the first days of life.

Results: There was a statistically significant difference between spot urine albumin/creatinine ratio and early neonatal sepsis group in the first and seventh day of life (p=0.01). Urinary albumin/creatinine ratios were not statistically significant in the respiratory distress syndrome group. Serum albumin concentrations and spot urine albumin/creatinine ratio were not correlated during the first days of life. There was also no relationship between gestational age, birth weight and spot urine albumin/creatinine ratio during the first days of life.

Conclusion: Our results suggest that spot urine albumin/creatinine ratio during the early postnatal period can identify early neonatal sepsis in preterm infants.

Key Words: Early neonatal sepsis, Hypoalbuminemia, Prematurity, Respiratory distress syndrome, Spot urine albumin creatinine ratio

ÖZ

Amaç: Erken neonatal sepsis ve solunum sıkıntısı sendromu, erken doğan bebeklerde yaşamın ilk günlerinde neonatal mortaliteye yol açmaktadır. Bu çalışmanın amacı, premature bebeklerde spot idrar albümin/kreatinin oranının erken neonatal sepsis ve solunum sıkıntısı sendromunun erken tanı göstergesi olup olmadığını belirlemektir.

Gereç ve Yöntemler: Gebeliğin 34. haftasından erken doğan 126 prematüre bebek prospektif olarak incelenmiştir. Bu çalışmada yaşamın birinci, üçüncü ve yedinci gününde serum albümin, kreatinin, C-reaktif protein (CRP) ve spot

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: The study protocol was approved by the Ethics Committee at Başkent University Faculty of Medicine and informed consent was obtained from the parents (KA10-180).

Contribution of the Authors / Yazarların katkısı*: *OZDEMIR B: Constructing the hypothesis or idea of research and/or article, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study,Taking responsibility in the writing of the whole or important parts of the study, Providing personnel, environment, financial support tools that are vital for the study. Biological materials, taking responsibility of the referred patients. ***ANUK INCE D:*** Reviewing the article before submission scientifically besides spelling and grammar. ***ECEVIT A:*** Planning methodology to reach the Conclusions. ***TEKINDAL MA:*** Taking responsibility in logical interpretation and conclusion of the results. ***TURAN O:*** Reviewing the article before submission scientifically besides spelling and grammar. ***KARAKAS MN:*** Taking responsibility in logical interpretation and conclusion of the results, ***TARCAN A:*** Constructing the hypothesis or idea of research and/or article. Planning methodology to reach the Conclusions. Organizing, supervising the course of progress and taking the responsibility of the research/study.

How to cite / *Atıf yazım şekli* : Ozdemir B, Anuk Ince D, Ecevit A, Tekindal MA, Turan O, Karakas NM, et al. Evaluation of the Relationship Between Microalbuminuria and Early Neonatal Sepsis, Respiratory Distress Syndrome in Preterm Infants. Turkish J Pediatr Dis 2020;14:359-365.

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Received / Geliş tarihi : 13.04.2020
Accepted / Kabul tarihi : 11.06.2020
Online published : 16.06.2020
Elektronik yayın tarihi
DOI: 10.12956/tchd.702590

idrar albümin/kreatinin oranlarını değerlendirdik. Ayrıca, bu parametrelerin erken doğan bebeklerde yaşamın ilk günlerinde, erken neonatal sepsis ve solunum sıkıntısı sendromu ile ilişkisini araştırdık.

Bulgular: Yaşamın ilk ve yedinci gününde spot idrar albümin/kreatinin oranı ile erken neonatal sepsis grubu arasında istatistiksel olarak anlamlı fark vardı (p=0.01). Solunum sıkıntısı sendromu grubunda idrar albümin/kreatinin oranları istatistiksel olarak anlamlı değildi. Serum albumin konsantrasyonları ve spot idrar albümin/kreatinin oranı yaşamın ilk günlerinde korelasyon göstermemiştir. Ayrıca yaşamın ilk günlerinde gebelik yaşı, doğum ağırlığı ile spot idrar albümin/kreatinin oranı arasında ilişki yoktu.

Sonuç: Bulgularımız, doğum sonrası erken dönemde spot idrar albümin/kreatinin oranının premature bebeklerde erken neonatal sepsisi tanımlayabildiğini göstermektedir.

Anahtar Sözcükler: Erken neonatal sepsis, Hipoalbuminemi, Prematürite, Solunum sıkıntısı sendromu, Spot idrar albumin/kreatinin oranı

INTRODUCTION

Prematurity is associated with increased neonatal mortality and morbidity (1). Premature infants are at high-risk for significant problems, such as intracranial-intraventricular hemorrhage, periventricular leukomalacia, hypoxic-ischemic encephalopathy, respiratory distress syndrome (RDS), neonatal infections and patent ductus arteriosus (2). Early neonatal sepsis and RDS are theimportant causes of mortality in preterm infants (3).

Sepsis is seen more frequently in preterm infants with comorbidities or prolonged hospitalization. Early neonatal sepsis (infection within the first 72 h of life) occurs in 1.5–2% of preterm infants and late neonatal sepsis (infection after 72 h of life) occurs with a prevalence of up to 21% in preterm infants (4). Diagnosis of early neonatal sepsis is difficult because the clinical signs and laboratory findings are non-specific.

Nephrogenesis continues until 36 weeks of gestation in infants. Thus, preterm infants are thought to have less glomeruli at birth than those born at full term and it has been shown that the renal cortical region undergoes accelerated growth after birth while the renal medulla growth lags behind in preterm infants (2,3). Several factors influence renal development and function after birth; in particular, gestational age and postnatal age seem to play a major role in the functional maturation of the kidneys (2). Asphyxia at birth, mechanical ventilation and respiratory distress and septicemia have adverse effects on kidney function (5,6).

Urinary albumin is used as a marker of glomerular permeability and transient albuminuria that occurs as a result of inflammation and such low rates of albumin excretion are termed microalbuminuria (MA). The degree of albuminuria can be assessed by a spot urine albumin/creatinine ratio (ACR). Microalbuminuria in children is defined as urinary albumin excretion rate of 30–300 mg/g creatinine (7). Microalbuminuria correlates with acute inflammation and is an early marker of diseases affecting the renal system. Several pediatric studies have been showed an association between low serum albumin concentrations and prolonged hospitalization and mortality (7,8). In addition, the degree of albuminuria can be used to predict disease severity in adult patients (9). There are currently no studies in the literature that investigate the relationship between early neonatal sepsis, RDS and ACR in preterm infants.

The purpose of this study is to compare the serum concentrations of albumin, creatinine, C-reactive protein (CRP) and urinary concentrations of albumin, protein and creatinine on the first, third and seventh days of life and to evaluate the influence of early neonatal sepsis and RDS in preterm infants of less than 34 weeks gestational age. This is the first study investigating the mean ACR during the first week of the neonatal period in preterm infants.

MATERIAL and METHODS

This prospective longitudinal study included 126 preterm infants of ≤34 weeks of gestational age who were born at Baskent University Hospital in 2 years period. The study protocol was approved by the Ethics Committee at Başkent University Faculty of Medicine and informed consent was obtained from the parents (KA10-180). The exclusion criteria were congenital anomalies, anuria, failure to collect urine samples, urinary tract infection, renal abnormalities and the presence of concomitant diseases. Information on demographic, clinical and laboratory variables was obtained prospectively for each patient. Birth weights were adjusted for gestational age and converted to standard deviation scores. Any infant whose birth weight was less than the 10th percentile for their gestational age was classified as small for gestational age (SGA) (10).

All samples were collected on the first, third and seventh days of postnatal life. Serum concentrations of albumin, creatinine and CRP were obtained from blood samples collected with proper technique and avoiding hemolysis. Urinary protein and creatinine concentrations and ACR were determined from spontaneously voided urine samples collected using urine bags. No pathological urine samples (proteinuria, hematuria or infection) were included in the analysis. The immune turbidimetric method (multigent microalbumin assay, Architect ci 8200 system, Abbott Laboratories Inc., Germany) was used to quantify MA. Urinary creatinine concentration was determined by the kinetic alkaline picrate method. Microalbuminuria in children is defined as urinary albumin excretion rate of 30–300 mg/g creatinine (1,7).

The diagnosis of early neonatal sepsis was based on blood culture results, hematological parameters (white blood cell

and neutrophil counts and CRP) and clinical signs. Early neonatal sepsis was defined as clinical signs of infection within 72 hours after birth combined with abnormal biochemical and hematological parameters (4). The clinical signs and symptoms included: lethargy, temperature instability, apnea, respiratory distress, bradycardia, feeding intolerance and glucose intolerance (11). RDS was diagnosed according to clinical findings during the first 24 h of life and typical radiological findings, including reduced pulmonary air content, a reticulogranular lung pattern and bronchogram (12).

Statistical Analyses

SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous data were expressed as mean ± SD and between-group differences in means were compared using Student's independent two-sample t-tests. The significances of between-group differences in repeated measures were analyzed using paired t tests, the Wilcoxon test and the Kruskal–Wallis test; Mauchly's sphericity test and Box's test for comparisons of repeated measures were used to assess the equivalence of the covariance matrices. Correlation analyses of serum albumin, creatinine, CRP concentrations and ACR were performed using a linear correlation model. The significance of relationships between variables was determined by linear regression. Differences were considered significant if $p<0.05$.

RESULT

One hundred twenty-six preterm neonates (57% males) were included in the study. Demographic and clinical characteristics of the neonates are shown in Tables I and II. Apgar scores were between six and nine at 5 minutes after birth. Fourteen of the subjects were born by spontaneous delivery. The mean (±SD) gestational age of the patients was 31.7 (±1.9) weeks. And the mean (±SD) birth weight was 1686.8 (±429.5) g. Four preterm infants died during the study period. Maternal diagnoses were preeclampsia (37 patients), gestational diabetes (4 patients), early membrane rupture (38 patients) and chorioamnionitis (2 patients).

Table I: Demographic and Clinical Characteristics of the preterm infants.

	Preterm (n=126) Mean (±SD)*n
Birth weight (g)	1686.8±429.5
Gestational age (weeks)	31.7±1.9
Male/female	57/69
Spontaneous delivery/cesarean	14/112
SGA (small for gestational age)	16
Apgar score at 1 min	6.7±1.3
Apgar score at 5 min	8±1.1
Surfactant treatment	54

*****Data Are Presented As Means ± Standard Deviation*

Table II: Maternal Characteristics.

	n (%)
Preeclampsia	37 (29.3)
Gestational diabetes	4 (3.1)
Early membrane rupture (>24 hours)	38 (30.1)
Chorioamnionitis	2 (1.5)
Multiple pregnancy	
twin pregnancy	21 (16.6)
triplet pregnancy	4 (3.1)

Median values for serum creatinine, albumin and CRP concentrations, ACR and urinary protein and creatinine concentrations during the first days of life are shown in Table III. The 126 infants were divided into two groups based on the presence or absence of RDS and early neonatal sepsis. There were 49 and 77 infants in the RDS and non-RDS group, respectively. There were 118 and 8 infants in the non-sepsis and early neonatal sepsis group, respectively. The infants in the early neonatal sepsis group were all proven sepsis. They had positive blood culture results. Escherichia coli (in 1 patient) and Klebsiella pneumoniae (in 7 patients) detected in blood cultures. There is a statistically significant difference between ACR in the first and seventh day of life in the early neonatal sepsis group ($p=0.01$) (Table IV). Early postnatal ACR significantly increased in the presence of early neonatal sepsis. Spot urine albumin/creatinine ratio correlated directly with birth weight in the first and seventh day (Spearman's rho: 0.714 and 0.886, respectively) and also gestational age in the first day of life in early neonatal sepsis group (Spearman's rho: 0.691).

Spot urine albumin/creatinine ratio was also high in both RDS and non-RDS group in preterm infants, however ACR did not significantly different between the RDS and non-RDS group during the first days of life (Table V).

There were no statistically significant differences between serum albumin concentrations and ACR on the first, third and seventh days of life. In premature infants, we did not find a significant correlation between ACR and gestational age. There was also no significant relationship between birth weight and MA. Cutoff values of ACR were found 70.35 mg/g on the first day, 37.5 mg/gon the third day and 43.25 mg/g on the seventh day of life in preterm infants, respectively.

Table III: Serum creatinine, albumin and CRP concentrations, ACR, urinary protein and creatinine concentrations on the first, third, and seventh days of postnatal life.

Preterm infants (n=126)	Postnatal day 1 mean ±SD (min–max)	Postnatal day 3 mean ±SD (min–max)	Postnatal day 7 mean ±SD (min–max)	p
Serum creatinine (mg/dL)	0.59 ±0.12 (0.55–0.63)	0.66 ±0.16 (0.61–0.71)	0.60 ±0.20 [ab] (0.56–0.63)	0.036*
Serum albumin (g/dL)	2.98 ±0.41 (2.81–31.6)	2.97 ±0.36 (2.89–3.06)	3.05 ±0.48 (2.94–3.16)	0.387
Serum CRP (mg/L)	1.10 ±2.56 (0.67–1.54)	6.55 ±6.53 [a] (4.24–8.85)	7.76 ±5.10 [ab] (4.30–11.22)	0.015*
ACR (mg/g)	160.73±252.84 (115.47–205.98)	129.19±111.59 (96.01–162.36)	118.35±199.46 (82.88–153.83)	0.980
Urinary protein (mg/dL)	25.43 ±37.22 (19.13–31.74)	28.51 ±25.30 (22.77–34.24)	22.47 ±15.86 (17.61–27.33)	0.554
Urinary creatinine (mg/dL)	17.40 ±7.87 (14.76–20.04)	16.30 ±8.00 (14.45–18.14)	15.39 ±12.31 (12.71–18.08)	0.621

Significant at p < 0.05.* ***SD:* *standard deviation,* ***CRP:*** *C-reactive protein,* ***ACR:*** *Spot urine albumin/creatinine ratio.*[a] **:** *p < 0.05 compared with the first postnatal day,*[b] **:** *p < 0.05 compared with the third postnatal day.*

Table IV: Spot urine albumin/creatinine ratio, urinary protein, creatinine concentrations and serum CRP levels on the first, third and seventh days of postnatal life in preterm infants with early neonatal sepsis and non-sepsis group.

Postnatal Day		ACR (mg/g)mean ±SDmedian(min-max)	Urinary protein(mg/dL) mean ±SDmedian(min-max)	Urinary creatinine(mg/dL)mean ±SDmedian (min-max)	Serum CRP(mg/L) mean ±SDmedian (min-max)
Early-onset sepsis group (n= 8)	1	236.32±332.81 65.00 (12.80-829.40)	26.28±19.28 15.00 (7.00-55.40)	12.97±8.17 12.40 (2.31-24.06)	3.44±4.54 1.65 (0.2-12.7)
	3	98.13±159.00 32.35 [a*] (24.00-422.10)	42.51±29.64 38.00 (9.00-92.00)	16.47±6.92 16.58 (7.88-27.48)	21.85±36.21 8.10 [a*] (4-103)
	7	96.53±159.07 34.20 [ab*] (11.70-418.30)	18.31±14.21 14.45 (4.00-43.00)	11.42±6.95 9.85 (5.05-23.20)	23.47±53 3.01 [ab*] (0.4-143.4)
p Repeated Measure Analysis		**0.01***	**0.07**	**0.09**	**0.01***
Non-sepsis group (n=118)	1	116.15±151.86 58.25 (6.8-870)	22.29±25.83 14 (0.40-204.90)	16.19±10.79 13.23 (3.20-66)	0.93±1.72 0.3 (0.1-13.8)
	3	113.89±132.60 48.3 (4.2-862.21)	24.99±26.48 16 (2-176.10)	15.62 ±7.56 14.44 (5-56.76)	2.65±4.27 0.85 (0.1-29.3)
	7	109.23±144.12 66.10 (4-914.40)	22.6±19.97 16.75 (0.23-119)	22.67±19.97 16.75 (0.23-119)	2.6±8.27 0.6 (0.2-84)
p Repeated Measure Analysis		**0.86**	**0.83**	**0.85**	**0.40**

** Significant p < 0.05,* ***SD:*** *standard deviation,* [a] *p < 0.05 with respect to the first postnatal day,* [b] *p < 0.05 with respect to the third postnatal day*

Table V: Spot urine albumin/creatinine ratio, urinary protein, creatinine concentrations and serum CRP on the first, third and seventh days of postnatal life in preterm infants with RDS and non-RDS group.

Postnatal Day		Urinary microalbumin/ creatinine (mg/mmol) mean ±SD median (min-max)	Urinary protein (mg/dL) mean ±SD median (min-max)	Urinary creatinine (mg/dL) mean ±SD median (min-max)	Serum CRP (mg/L) mean ±SD median (min-max)
RDS group (n= 49)	1	194.52±27.43 118.4 (6.80-1280.1)	21.72±17.65 14.7 (5.7-69.9)	14.44±9.24 11.45 (2.31-49.16)	1.18±2.29 0.2 (0.1-12.7)
	3	163.58±27.43 98.9 (8.7-862.21)	27.94±29.19 18.10 (4.00-176.10)	14.80±7.89 11.52 (5-36.07)	4.96±14.8 0.8 (0.2-103)
	7	167.24±35.54 106.35 (4.7-914.40)	21.04±18.82 15.50 (4.00-119.00)	12.81±7.64 10.82 (3.67-35.9)	5.15±20.43 0.9 (0.2-143.4)
p Repeated Measure Analysis		**0.68**	**0.40**	**0.40**	**0.057**
Non-RDS group(n=77)	1	90.28 ±139.23 47.3 (6.8-866.6)	23 ±29.49 13.6 (0.40-204.90)	16.94 ±11.44 14.30 (3.40-66)	1.02 ±1.92 0.30 (0.1-13.8)
	3	82.98 ±94.32 36.6 (4.2-409.4)	24.96 ±25.42 15.1 (2-141)	16.45 ±4.76 15.53 (5-56.76)	2.89 ±4.61 0.90 (0.1-29.3)
	7	72.30 ±72.13 38.70 (4-302.6)	23.31 ±20.18 17.8 (0.23-100)	17.73 ±12.12 14.33 (3.26-68.12)	2.89 ±10.0 0.5 (0.2-84)
p Repeated MeasureAnalysis		**0.34**	**0.86**	**0.71**	**0.094**

SD:*standard deviation*

DISCUSSION

In this study, we determined the ACR values during the first week of life in preterm infants. Tubular proteinuria during early postnatal life is predicted by low gestational age at birth and there are no previously reported reference values for the ACR, urinary protein and creatinine concentrations in preterm infants. Our results revealed an association between ACR and early neonatal sepsis in preterm infants in the first days of postnatal life. And also cutoff values of ACR were determined in preterm infants.

Microalbuminuria, which is characterized by increased glomerular permeability, has been demonstrated in many different pathological conditions; it has been also suggested as an early marker of systemic inflammation. The tubular reabsorptive mechanism for albumin from the ultrafiltrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine (2). The degree of albuminuria is dependent on the intensity of the inflammatory responses and MA. An early increase in MA during sepsis, acute pancreatitis, trauma and surgery has been also observed in adult studies. An early increase in MA during sepsis and sickle cell anemia in children has been observed in other studies (7,13). The studies have also shown that MA is associated with increased morbidity and mortality (7,9,13).

This is the first study that evaluate the role of MA in preterm infants with early neonatal sepsis. The highest ACR values were found on the first days of postnatal life in preterm infants. We found a statistically significant difference between ACR in the first and seventh day of life in the early neonatal sepsis. Increased urinary excretion of small molecular weight proteins may result from vascular and tubular damage.

Early postnatal ACR was also increased significantly in the presence of early neonatal sepsis. The increased prevalence of MA in preterm infants is probably the result of endothelial dysfunction arising from the effects of cytokines and other inflammatory mediators released during the intense inflammatory response associated with sepsis. Thus, ACR may be used for the diagnosis of early-onset sepsis. However, future studies are needed to investigate the relationship between the ACR and early-onset sepsis.

The studies indicate that the excretion of plasma proteins into urine results from increased glomerular permeability and impaired tubular reabsorption (14,15). When the ability of the proximal tubules to reabsorb albumin from the ultrafiltrate is exceeded, there is increased excretion of albumin in the urine. Nishimaki et al. (16) found that, in preterm infants, the urinary beta-2 microglobulin level at 48 h after birth was significantly higher in those with chorioamnionitis than in those without chorioamnionitis. Also, hypoalbuminemia has been shown to be associated with increased risk of necrotizing enterocolitis (17). Serum amyloid A is also increased in infants with neonatal sepsis (18). In neonatal sepsis, the degree of albuminuria is dependent of the severity of sepsis. In a study, the infants showed individual variation in their urinary protein excretion; however, in general, urinary excretion of albumin and protein were elevated in premature infants (14). This suggests that the proteinuria may be due to immaturity of the kidney, tubular dysfunction and renal immaturity. It has also been associated with renal tubular injury due to concomitant disease or sepsis. There are no previous reports of ACR in premature infants or the changes in these ratios during early postnatal life. Our results reveal that preterm infants have high ACR, as well as elevated urinary protein and creatinine concentrations.

In addition, our results showed that the early postnatal ACR was significantly elevated in both RDS and non RDS group. This may be due to the use of antenatal steroids and surfactant therapy, which was used to the infants in our study. The prevalence of antenatal steroid use may explain why there was no relationship between RDS and MA in our study. Increased permeability of the alveolar capillaries plays an important role in the pathogenesis of RDS in preterm infants (19). Protein levels are high in alveolar fluid because of the leakage of albumin and other proteins into the alveolar space (12,19). Albumin in the alveolar space then contributes to the pathogenesis of RDS by inactivating surfactant (20). Antenatal steroids are known to accelerate fetal lung maturity and have an important role in preventing RDS (19). Fluid and electrolyte balance is often impaired during the early postnatal period in preterm infants with RDS and previous studies have shown low levels of plasma proteins in neonates with RDS (6,19). In our study, there was also a significant correlation between the serum albumin level and ACR.

Studies demonstrated that protein excretion is greater in infants with lower gestational ages (21,22). Our results indicate that, although the ACR was not significantly associated with gestational age or birth weight, excretion of urinary protein is higher in preterm infants. Several pediatric studies have suggested an association between low serum albumin and prolonged hospitalization and mortality (8,9). However, no studies have shown the relationship between serum albumin concentrations and MA in infants. In the current study, we did not find a significant correlation between the ACR and serum albumin levels. This suggests that MA may be associated with tubular dysfunction rather than with serum albumin concentrations.

CONCLUSION

The association between clinical disorders and ACR in preterm infants remains undefined. In this report we demonstrated that the ACR in the first days of postnatal life increases in early neonatal sepsis. In this report we also determined cut off values of ACR in preterm infants. Our findings indicate that ACR is a simple, inexpensive and useful tool that may be useful for the prediction and early diagnosis of early neonatal sepsis. Further studies on this issue with a larger group of infants need to be initiated.

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