Value of Resistin in Early Onset Neonatal Sepsis

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Abstract

The diagnosis of neonatal sepsis is usually difficult because the sign and symptoms are nonspecific. Although C-reactive protein (CRP) and procalcitonin (PCT) are the most commonly used auxiliary tests, they are not reliable enough markers to be used for diagnosis of neonatal sepsis. This study aimed to evaluate the efficacy of resistin in diagnosing early onset neonatal sepsis and to compare its effectiveness to CRP and PCT. This prospective study was performed in the neonatal intensive care unit of Medicine Hospital between June and September 2016. Twenty-nine infants in the sepsis group and 33 infants in the control group were recruited. The Töllner scoring system was used for clinical signs. The hematologic parameters were evaluated using the Manroe and Rodwell scoring systems. The blood samples for CRP, PCT, and resistin were collected at admission (T0), and at 72 hours (T3). Mean plasma resistin level at T0 was 54.20 $\pm$ 39.3 ng/mL in the sepsis group and 34.92 $\pm$ 6.9 ng/mL in the control group. The sensitivity at T0 for resistin was 76%, and the specificity was 67%. The values of area under the curve (AUC) for CRP, PCT, and resistin were 0.84, 0.66, and 0.72, respectively. We found the diagnostic value of resistin to be lower than CRP, although its plasma levels were elevated. Therefore, we propose that resistin has limited value in diagnosis and follow-up of early-onset neonatal sepsis.

Keywords
- newborn
- neonatal sepsis
- resistin

Introduction

Neonatal sepsis is defined as systemic infection in the first month of life. This diagnosis is usually difficult because the sign and symptoms are nonspecific. It continues to be one of the major causes of morbidity and mortality. Blood culture is the gold standard for diagnosis of neonatal sepsis but factors such as the earliest positive culture results exceeding 24 to 48 hours, insufficient sampling, inability to culture the microorganism, and contamination can lead to delay in diagnosis. Therefore, many auxiliary tests are used to assist in the diagnosis of neonatal sepsis.[1–3]

The most commonly used tests are complete blood count and acute phase reactants such as C-reactive protein (CRP) and procalcitonin (PCT).[3,4] CRP is synthesized by the hepatocytes in response to inflammatory and infectious stimuli. However, it may also increase in trauma and ischemic tissue injury, meconium aspiration syndrome, and fetal distress. CRP begins to rise in 4 to 6 hours and reaches its peak values by 36 to 50 hours. Because the rise in CRP occurs in many varied conditions besides infection, it is preferably used in combination with another serum markers for diagnosis and monitoring.[2–4] PCT is the precursor protein of calcitonin, which is released by thyroid C cells and is produced by macrophages and hepatocytes. PCT's half-life is between 25 and 50 hours. Serum levels begin to increase with exposure to bacterial endotoxin, reach peak levels after 6 to 8 hours, and start to decrease after 24 hours. PCT increases earlier than CRP in infection and also falls quicker than CRP after the treatment.[3–5] Although CRP and PCT are the most commonly used auxiliary tests, they are not reliable enough to be used for the diagnosis of neonatal sepsis.

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Adipose tissue is a site for lipid storage and acts as an endocrine organ by secreting adipocyte-derived hormones and proteins called adipokines, such as adiponectin, resistin, leptin, visfatin, and apelin. Previous studies have suggested the role of some of the adipokines in immune system and inflammation.[6,7]

Resistin is a cysteine-rich protein and contains 108 amino acid with a weight of 12.5 kDa. It is also called as FIZZ3 or adipocyte-specific secretory factor. Resistin secretion was discovered in white adipose tissue in mice.[7] Its increasing levels in obese mice are associated with insulin resistance and impaired insulin sensitivity. However, the physiological role of resistin in obesity and insulin resistance is controversial. It is primarily produced by macrophages rather than adipose tissue in humans.[7,8] Recent studies have reported that lipopolysaccharide (LPS), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) could regulate the resistin messenger ribonucleic acid (mRNA) levels in human peripheral blood mononuclear cells.[9–11] The studies in adults have shown that the secretion of resistin was upregulated during inflammation, and elevated serum resistin level might be a marker of disease activity.[12–14]

This study aimed to evaluate the efficacy of resistin in early-onset neonatal sepsis (EOS) and also to compare its effectiveness with CRP and PCT in the neonatal period.

Methods

This prospective study was performed in the neonatal intensive care unit (NICU) of Medicine Hospital between June and September 2016. The study protocol was approved by the ethics committee of Biruni University, and informed consent was obtained for all infants from their family. A total of 62 term and near-term infants were randomly enrolled. The infants with clinical and laboratory findings of early-onset sepsis (<5 days) constituted the study group, and infants diagnosed as transient tachypnea of the newborn (TTN) were recruited as the control group. Fifty infants diagnosed as sepsis were initially included, but 21 infants of them were excluded from the study as 12 parents rejected inclusion of their babies, one infant had a metabolic disease, and there were insufficient blood samples for eight infants. Thus, a total of 29 term or near-term (>34 weeks) infants were included in the sepsis group, and 33 TTN infants with screen and culture negative were included in the control group. Exclusion criteria included premature newborns who were born ≤34 weeks gestation, antibiotic therapy at admission, serious congenital malformation, metabolic disease, admission after the first four days of life, and no parental consent. Gestational age, gender, birth weight, mode of delivery, Apgar score, history of premature rupture of membranes (PROM) and chorioamnionitis, and prenatal demographics were all recorded.

The infants with clinical and laboratory findings of infection were included in the sepsis group, whereas newborns without clinical and laboratory findings of sepsis served as the control group. The Töllner scoring system was used for classification of infants. According to this scoring system, a score of ≥10 indicates clinical sepsis, a score of ≤5 indicates no sepsis, and a score of 5 to 9 indicates possible sepsis.[15] The hematologic parameters were evaluated according to the Manroe and Rodwell scoring systems.[16,17] Leukopenia was defined as leukocyte count <5,000/mm^3, leukocytosis was defined as leukocyte count >25,000/mm^3 at birth, >30,000/mm^3 at 12 to 24 hours, and >21,000/mm^3 after the second day. The normal absolute neutrophil count was accepted as 7,800 to 14,500/mm^3 in the first 60 hours and 1,750 to 5,400/mm^3 after 60 hours. Thrombocytopenia was defined as platelet count <150,000/mm^3. Before initiating treatment (T0), blood samples for culture, whole blood count, CRP, PCT, and resistin were obtained from all neonates. This procedure was repeated at 72 hours (T3) in the sepsis group. Patients were treated with appropriated antibiotic therapies. The therapy was stopped once there was an improvement in the clinical and laboratory parameters.

Cultures were analyzed using automated BACTEC method by BacT/Alert (Biomeriux, France). CRP levels (reference range: <6 mg/L) were studied by an immunoturbidometry method using Cobas Integra 400 plus (Roche Diagnostics, Rotkreuz, Switzerland). PCT levels (reference range: <0.5 ng/mL) were determined by an immunoassay method using i-Chroma (Boditech Med. Inc., Korea). Whole blood count was performed by using a Sysmex XT-1800i (Sysmex Corporation, Japan). Resistin levels were determined by an enzyme-linked immunosorbent assay (Sunred Biological Technology, Shanghai, China) using a DAR800 Microplate (Cortez Diagnostics, United States). After centrifugation, plasma samples were stored at –80°C before analysis for resistin.

We used statistical G Power program to calculate the adequate sample size. We estimated a minimum sample size of 27 in each group to achieve an effect size of 0.55, the power of 0.8 and Type 1 error of 0.05. SPSS Statistics 22 and R were used for data analysis. Descriptive statistics were reported as mean, standard deviation, and minimum, maximum, and percentage. The significance between groups was evaluated with χ^2-test, continuity (Yates) correction, and Fisher's exact and with *t*-test where appropriate. The receiver operating characteristics (ROC) curve analysis was performed to identify the cut-off value.

Results

We recruited a total of 62 neonates: 29 infants (23 term and six near term) in the sepsis group and 33 infants (26 term and 7 near term) in the control group. There were no statistically significant differences between two groups concerning the gestational age, gender, birth weight, mode of delivery, presence of PROM, chorioamnionitis, apnea, hypoxia, jaundice, and support of mechanical ventilation except for the 5 minutes Apgar score. The clinical demographics are shown in ►**Table 1**. Nine patients (31%) had positive blood culture (four *Staphylococcus epidermidis*, three *Staphylococcus aureus*, two *Klebsiella pneumoniae*) in the sepsis group. There was no statistical difference between culture positive and negative patients ($p > 0.05$).

The initial leukocyte counts in the sepsis group (16307 ± 4898/mm^3) were similar to those in the control

Table 1 Clinical characteristics of study group

	Control group	Sepsis group	Total	*p*-Value
	Mean ± S ($n = 33$)	Mean ± SD ($n = 29$)	Mean ± SD ($n = 62$)	
Gestational age (wk)	37.58 ± 1.79	38.51 ± 1.96	38.02 ± 1.91	0.11[b]
Gender[a]				
Female	15 (45.45%)	7 (31.82%)	22 (35.48%)	0.14[c]
Male	18 (54.55%)	22 (68.18%)	40 (64.52%)	
Birth weight (g)	3016.67 ± 684.07	3213.10 ± 696.2	3108.55 ± 691.18	0.27[b]
Delivery route[a]				
Normal	6 (21.21%)	8 (27.59%)	14 (24.19%)	0.77[c]
Cesarean delivery	27 (78.79%)	21 (72.49%)	48 (75.81%)	
Apgar min 1	7.18 ± 0.85	7.62 ± 1.05	7.39 ± 0.96	0.078[b]
Apgar min 5	8.39 ± 0.70	8.83 ± 0.85	8.6 ± 0.8	0.034[b,d]
PROM[a]	1 (3.0%)	2 (6.9%)	3(4.8%)	0.56[c]
Choriamnionitis	0 (0%)	0 (0%)	0(0%)	
Apnea[a]	1 (3.0%)	3 (10.34%)	4 (6.45%)	0.32[c]
Hypoxia[a]	0 (0%)	2 (6.8%)	2 (3.23%)	0.16[c]
Invasive Ventilation[a]	2 (6.06%)	7 (24.14%)	9 (14.51%)	0.10[c]
Jaundice[a]	6 (18.2%)	7 (24.14%)	13 (20.98%)	0.78[c]
Feeding intolerance[a]	14 (42.42%)	19 (65.52%)	33 (53.22%)	0.38[c]

Abbreviation: PROM, premature rupture of membrane.
[a] *n* (%).
[b] Student's *t*-test.
[c] χ^2-test of independence.
[d] $p < 0.05$.

group (15,933 ± 6,421/mm^3). However, the leukocyte counts in the sepsis group decreased significantly at 72 hour ($p = 0.00$). No differences were found between sepsis and control group in the initial platelet counts ($p = 0.19$). Similarly, there was no difference between the initial and 72 hour values of platelet count ($p = 0.66$).

The T0 values of CRP and resistin in the sepsis group were significantly higher than those in the control group ($p = 0.00$ and $p = 0.01$, respectively). Although the initial PCT levels in the sepsis group were higher than those in the control group, there was no statistical difference. However, initial levels of CRP, resistin, and PCT were significantly higher than the values measured on the third day (T3) ($p = 0.02$, $p = 0.03$, $p = 0.00$, respectively) (►**Table 2**). Mean resistin level at T0 was found as 54.20 ± 39.3 ng/mL (median 40.56, range 27.75–180) in the sepsis group and 34.92 ± 6.9 ng/mL (median 31.35, range 20.72–52.02) in the control group (►**Table 2**). Also, there were no significant differences between patients with positive and negative cultures with respect to CRP, PCT, and resistin values in the sepsis group ($p > 0.05$).

The prevalence of sepsis for this study was found as 0.46. Thus, the sensitivities at T0 for CRP, PCT, and resistin were 83%, 76%, 76%, and the specificities were as 61%, 58%, and 67%, respectively. Also, the area under the curve (AUC) was estimated from the ROC analysis (►**Fig. 1**).The cut of value for resistin was determined as 36.79 ng/mL with 76% sensitivity and 67% specificity. The values of AUC for CRP, PCT, and resistin were 0.84, 0.66, and 0.72, respectively. Positive and negative predictive values for resistin were estimated as 0.86 and 0.52. All these values and confidence intervals (CI) were shown in ►**Table 3**.

Discussion

Blood culture is considered the gold standard for diagnosis of neonatal sepsis, but negative culture results do not exclude the diagnosis of sepsis. CRP and PCT are usually used as auxiliary tests for diagnosis. However, their reliability is limited in neonatal period.[1]

CRP is the most commonly used acute phase reactant for the diagnosis of neonatal sepsis. Early studies suggested that its sensitivity and specificity values for a single measurement vary from 29 to 100% and from 6 to 100%, respectively. Repeated CRP measurements are associated with better sensitivity (74–98%) and specificity (71–94%).[2] Early studies suggested that PCT levels increase earlier than CRP in sepsis. However, its value in neonatal sepsis is limited due to physiologic increase in PCT levels after birth. In previous studies, different values were reported for the sensitivity (83–100%) and specificity (70–100%) of PCT.[3,5] In this study, CRP and PCT levels in the sepsis group decreased during the study period, and their levels were higher than the control

Table 2 Table showing mean levels at 0 and 72 hours

	Sepsis group	Control group	*P*-Value
	Mean ± SD	Mean ± SD	
Leukocyte (mm^3)			
T0	16307.24 ± 4898	15933.64 ± 6421	**0.80**[a]
T3	10592.76 ± 3190		
p[b]	**0,00**[c]		
PLT (mm^3)			
T0	231137.9 ± 62029	256498.6 ± 88687	**0.19**[a]
T3	236344.8 ± 89421		
p[b]	**0.66**		
CRP (mg/l)			
T0	19.86 ± 25. 77	4.05 ± 2.57	**0.00**[a,d]
T3	8.05 ± 10.16		
p[b]	**0.02**[d]		
PCT (ng/ml)			
T0	15.89 ± 21.78	9.73 ± 14.7	**0.20**[a]
T3	1.46 ± 2.03		
p[b]	**0.00**[c]		
Resistin (ng/mL)			
T0	54.20 ± 39.31	34.92 ± 6.93	**0.01**[a,d]
T3	49.23 ± 38.53		
p[b]	**0.03**[d]		

Abbreviations: CRP, C-reactive protein; PCT, procalcitonin; PLT, platelet; SD, standard deviation.
[a]Student's t-test.
[b]Paired sample *t*-test.
[c]$p < 0.01$.
[d]$p < 0.05$.

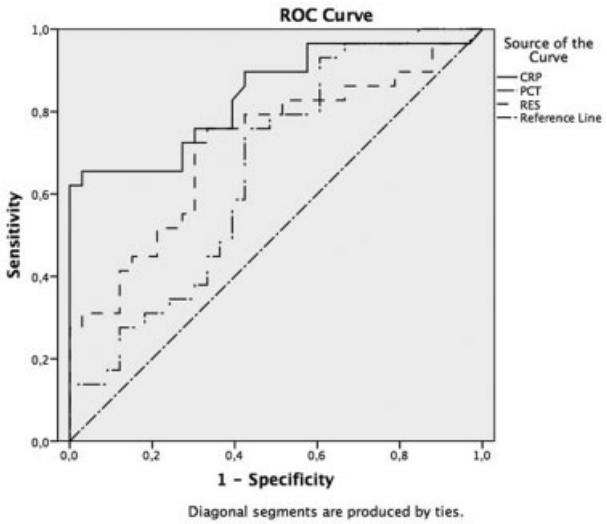

Fig. 1 ROC curve of CRP, PCT and resistin values in the EOS group. CRP, C-reactive protein; EOS, early-onset neonatal sepsis; RES, resistin; ROC, receiver operating characteristics; PCT, procalcitonin.

group. The sensitivity and specificity of PCT were significantly lower than CRP. Our results suggested that PCT had limited value in the diagnosis of EOS. This result may be related to the physiologic increase in PCT levels after birth.

Studies in human showed that resistin is mainly secreted from monocytic cells rather than adipocytes. Resistin mRNA expression was increased by proinflammatory cytokines, such as IL-1, IL-6, TNF-α, LPS, and its inflammatory functions is regulated by activation of nuclear factor kappa B. [18,19] Previous clinical studies suggested that resistin levels increased in inflammatory diseases.[14,20–22]

Koch et al.[23] showed that the resistin values were elevated in all critical care patients compared with healthy adults, and was significantly higher in patients with sepsis. Vassiliadi et al[24] reported that the resistin values of the adult patients with sepsis were higher than controls. Additionally, other studies in adults reported that the resistin levels were significantly elevated in patients with sepsis.[12,25,26] All of this evidence indicates that resistin may be used as a marker in infectious conditions; however, there was a limited number of studies in the neonatal period. Cekmez et al[27] reported that resistin levels of a term and near-term infants with late sepsis were higher than those of healthy infants, and they correlated positively with CRP. Also, Gokmen et al[28] and Aliefendioglu et al.[29] investigated the plasma resistin levels in premature infants with sepsis, and they reported that resistin could be used as a biomarker for sepsis in premature infants. In our study, resistin levels were higher in the sepsis group than in the control group, and its levels decreased with antibiotic treatment, similar to CRP and PCT. We could not find any differences between patients with positive and negative cultures in the aspect of resistin, CRP, and PCT levels. As our findings are consistent with the previous studies, we suggest that resistin may be used as an additional biomarker for the diagnosis of EOS in neonates.

Cekmez et al[27] reported that AUC value of resistin (0.91) was higher than CRP (0.84) and PCT (0.89). Also, Gokmen et al[28] found that resistin had a superior efficacy compared with CRP for sepsis diagnosis. In their study, AUC values of resistin and CRP were 0.98 and 0.71, respectively. However, Aliefendioglu et al[29] reported that AUC was 0.74 for resistin, and it had a limited value compared with CRP, PCT, and IL-6. Our cut-off value for resistin was 36.7 ng/mL. The sensitivity and specificity for this cut-off were found as 76% and 67%, respectively. The AUC for resistin was estimated as 0.72 from the ROC curve. According to our results, the diagnostic value of resistin was lower than CRP but higher than PCT in EOS. These results were similar to the findings of Aliefendioglu et al. The differences in cut-off and AUC values among the studies may be related to the fact that our study population included only cases with early-onset sepsis and term or near-term infants.

Our study has some limitations that should be mentioned. First, all of the infants in this study were >34 weeks of gestation, and second, this study included only a small number of patients. Therefore, further studies including a higher number of patients with EOS are needed to evaluate the limitations of this study. Also, there were not enough data

Table 3 Comparison of CRP, PCT and resistin

	Cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
CRP	>4.15	0.83 (0.79–0.87)	0.61 (0.52–0.70)	0.92 (0.85–0.99)	0.41 (0.36–0.46)	0.84[a] (0.74–0.94)
PCT	>1.58	0.76 (0.70–0.82)	0.58 (0.50–0.66)	0.78 (0.71–0.85)	0.55 (0.47–0.63)	0.66[b] (0.52–0.80)
Resistin	>36.79	0.76 (0.69–0.83)	0.67 (0.59–0.75)	0.86 (0.81–0.91)	0.52 (0.46–0.58)	0.72[a] (0.59–0.85)

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value.
[a] $p < 0.01$.
[b] $p < 0.05$.

to exclude viral infections. Therefore, we propose that resistin has limited value in the diagnosis and follow-up of EOS.

Conflict of Interest
None.

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