Research Article

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Predictive values of Ischemia modified albumin in neonatal sepsis
Yenidoğan sepsisinde İskemi modifiye albüminin prediktif değerleri

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Abstract

Objective: This study aims to identify whether ischemia-modified albumin (IMA) can be used as a marker in the diagnosis of sepsis in the term patient population.

Methods: In the study group 30 sepsis patients and 30 healthy neonatal, control group, whose gestational ages were ≥ 38 weeks were included. Blood samples were taken for IMA levels at baseline and on the 3rd and 10th days of the treatment. The IMA values obtained were compared with those for C-reactive protein (CRP).

Results: The baseline CRP, IMA, and adjusted IMA levels of the patients in the study group were statistically higher compared to the control group (p < 0.05). IMA and adjusted IMA values measured in the study group on the 3rd and 10th days decreased gradually and significantly compared to initial levels (p < 0.0001). There was a positive correlation between the baseline IMA levels and CRP values among the patients with sepsis (r: 0.371, p < 0.05). The diagnostic cut-off value of IMA in term of diagnosis of the neonatal sepsis was found to be 0.644 ABSU (p < 0.0001), with a sensitivity of 93.3% and specificity of 66.7%.

Conclusion: We suggest that IMA can be used as a useful biomarker in the early diagnosis of neonatal sepsis.

Keywords: Term birth; Sepsis; Ischemia-modified albumin; C-reactive protein; Biomarker.

Özet

Amaç: Bu çalışmanın amacı, term yenidoğan sepsisinin tanısında iskemi modifiye albuminin (IMA) bir biyomarker olarak kullanılabileceğini belirlemektir.

Yöntem: Çalışma, gestasyonel yaş ≥ 38 hafta olan 30 sepsisli (çalışma grubu) ve 30 sağlıklı term yenidoğan (kontrol) gerçekleştirildi. İMA seviyeleri tanı konulduğu anda, tedavinin üçüncü ve 10. günlerinde ölçüldü. Elde edilen IMA değerleri CRP ile karşılaştırıldı.

Bulgular: Çalışma grubunda hastaların başlangıçta ölçülen IMA, düzeltilmiş IMA ve CRP değerleri kontrol grubuna göre iyi istatistiksel olarak anlamlı derecede yüksekti (p < 0.05). Çalışma grubunda üçüncü ve 10. günlerde ölçülen ortalama IMA ve düzeltmiş IMA değerlerinin başlangıçta göre düşereden derecede azaldığı saptandı (p < 0.0001). Sepsisli vakaların başlangıçta ölçülen IMA değerleri ile CRP değerleri arasında anlamlı derecede pozitif korelasyon saptandı (r: 0.371, p < 0.05). Term hastalarda neonatal sepsis tanısı için IMA’nın cut-off değeri 0.644 ABSU (p < 0.0001), sensitivitesi 93.3%, spesifitesi 66.7%, pozitif prediktif değeri 73.7%, negative prediktif değeri 90.9% idi.

Sonuç: Bu çalışmanın sonucu IMA’nın neonatal sepsisin erken tanısında yararlı bir biyomarker olarak kullanılabilileceğini önermektedir.

Anahtar Kelimeler: Term doğum; Sepsis; Ischemia-modified albumin; C-reactive protein; Biyomarker.

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Introduction

Neonatal sepsis is one of the major causes of neonatal morbidity and mortality [1]. It is vital to identify infected neonates as early as possible, but unreliable clinical signs and the absence of good diagnostic tests hinder an accurate early diagnosis [1]. In the diagnosis of sepsis, various diagnostic tests are used; particularly C-reactive protein (CRP) level is frequently measured. However, none of these tests are adequate for the accurate diagnosis of sepsis [1, 2].

Recent studies have suggested that modified albumin can be a novel and sensitive marker for ischemia and oxidative stress [3]. In conditions such as ischemia, hypoxia, acidosis or superoxide radical damage; binding sites of albumin to metals are reduced and a metabolic variant with diminished metal binding capacity is formed. This alteration is called as ischemia-modified albumin (IMA) [4–6]. Previously, IMA levels have been reported to be increased in conditions such as myocardial ischemia, pulmonary embolism, obesity, hypercholesterolemia, perinatal asphyxia and necrotizing enterocolitis [5, 7–12]. Although there are several studies investigating the role of IMA in the diagnosis of sepsis, it has not been clearly demonstrated [13–15]. In this study, we aimed to investigate the value of IMA in establishing the early diagnosis of neonatal sepsis.

Materials and methods

The study was performed on patients at 5–28 days of age. This study included 30 newborns with sepsis (the study group) and 30 healthy newborns (control group) whose gestational ages were ≥ 38 weeks. All patients were evaluated according to their Tollner sepsis scores and CRP values [15]. Septic patients with Tollner sepsis scores ≥ 10 or patients with Tollner sepsis scores ≥ 5 and CRP values ≥ 0.5 mg/dL were enrolled [16, 17]. Exclusion criteria were neonates with conditions causing oxidative stress like acute renal damage, severe liver dysfunction, suspected or known congenital metabolic disease, cyanotic congenital heart disease, perinatal asphyxia, maternal diabetes, intracranial haemorrhage or necrotizing enterocolitis. In the sepsis group, blood culture, total blood count, the immature to total neutrophil (I/T) ratio and the CRP values were determined before treatment. Blood specimens were taken for IMA measurement from the study group at the start of the treatment and on 3rd and 10th days. In the control group, IMA levels were studied only once, when blood specimens were taken for routine tests. From the study group, blood specimens such as CRP, albumin and complete blood count were taken at the beginning of the treatment and on the 10th day. Complete blood counts were carried out by auto analyzer (Beckman Coulter, Brea, CA, USA). Albumin levels were measured using a colorimetric analysis method with a Cobas C701 auto analyzer (Roche, Mannheim, BW, DE). Serum CRP levels were determined by immunonephelometric measurement (Dade Behring, Marburg, HE, DE). The normal CRP values is <0.5 mg/dL.

The study protocol was approved by the institutional Ethics Committee (Decision Number: 2009/24-11-5) and a written informed consent was obtained from the parents of each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Ischemia modified albumin

The blood samples were centrifuged at 3000 rpm for 10 min and serum samples were collected. The serum samples were kept at −80°C until the IMA analysis. The rapid colorimetric method which was previously developed was used to determine the IMA levels [5]. Glass tubes were filled with 200 μL of patient serum and 50 μL of 0.1% CoCl₂·6H₂O (Sigma) was added. After this mixture was gently shaken, the mixture was left for 10 min to ensure sufficient cobalt albumin binding. Then, 50 μL of 1.5 mg/mL dithiothreitol (DTT) was added as a coloring agent. After 2 min 1 mL of 0.9% sodium chloride was added to quench the reaction. A control sample was prepared for each sample. At the DTT addition stage, 50 μL of distilled water was used instead of 50 μL of 1.5 mg/mL dithiothreitol (DTT) to obtain a control sample without DTT. The samples were analyzed for absorbance at 470 nm using a spectrophotometer (Shimadzu UV 1601, Ausburn, Australia). Color formation in the specimens containing DTT was compared with the color formation in the control tubes to which DTT was not added. The results were expressed in absorbance units (ABSU).

Adjusted Ischemia modified albumin

The adjusted IMA levels were used to eliminate the effects of hypoalbuminemia, which is frequently encountered in patients with sepsis. In this study the adjusted IMA is calculated using the formula [18]:

\[
\text{Adjusted IMA} = \frac{\text{Individual serum albumin concentration}}{\text{Median serum albumin concentration}} \times \text{IMA}
\]
Statistical analysis

Statistical analysis was performed using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistical analysis was carried out for all variables. The χ²-test was used to compare the ratio of categorical variables. The data obtained from the measurements are expressed in mean ± standard deviation. The Kolmogorov-Smirnov test was used for the eligibility of the variables. The normally distributed variables between the groups were compared using the Student's t-test, whereas abnormally distributed variables were analyzed using the Mann-Whitney U-test. The paired test was used to analyze the normally distributed intragroup data (pre-treatment and post-treatment) whereas the Wilcoxon test was used to analyze abnormally distributed data. The role of IMA in predicting the clinical and laboratory course of sepsis was investigated by determining IMA levels at different time intervals. Friedman’s test and Wilcoxon’s test were used to compare IMA levels of the study group in different periods. The significance level was adopted as p < 0.017 (0.05/3) with using Bonferroni correction. The Pearson test was used to analyze the correlation of the data. The discriminative ability of IMA levels in patients with sepsis was calculated using the area under the receiver operating characteristic (ROC) curve. A threshold value was determined for IMA in terms of diagnosis of sepsis in the patient group. To calculate the ROC curves, data was analyzed using MedCalc version 12.1.4 (MedCalc software bvba, Mariakerke, Belgium). Sensitivity, specificity, and negative and positive predictive values for IMA were calculated according to the ROC curves. p-Value of < 0.05 was considered statistically significant.

Results

Mean birth weight in study and control groups were 3142.0 ± 464.7 and 3269.3 ± 405 g, female to male ratio was 12/18 and 10/20 respectively (p > 0.05). There were no statistical differences with regard to demographic characteristics between the groups (p > 0.05) (Table 1).

Pre-treatment, the mean Tollner sepsis score was 8.00 ± 2.63 and the mean I/T ratio was 0.60 ± 0.24. Blood cultures were positive in 30% of sepsis cases. The microorganisms which were isolated from blood cultures were Staphylococcus epidermidis (n = 3), Staphylococcus hominis (n = 2), Staphylococcus aureus (n = 1), Klebsiella pneumonia (n = 2), Escherichia coli (n = 2), Citrobacter freundii (n = 1) and Candida albicans (n = 1).

The IMA (ABSU), adjusted IMA (ABSU), CRP, albumin, white blood cell count and platelet count levels of the patients and controls are shown in Table 2. This table

| Table 1: Demographic characteristics of the study and control groups [mean ± standard deviation (minumum–maximum)]. |
|---------------------------------------------------------------|
| Demographic characteristics | Study group (n = 30) | Control group (n = 30) | p-Value |
|-------------------------------|---------------------|----------------------|---------|
| Gestational age (week)        | 39.3 ± 1.1 (38–41)  | 39.2 ± 0.9 (38–41)   | 0.705   |
| Postnatal age (day)           | 15.2 ± 7.7 (5–28)  | 16.3 ± 8.4 (5–30)    | 0.599   |
| Weight (g)                    | 3096.5 ± 504.3 (2050–4330) | 3176.3 ± 397.4 (2500–6000) | 0.499 |
| Type of delivery              |                      |                      |         |
| Vaginal [n (%)]               | 13 (43)             | 15 (50)              | 0.796   |
| C/S [n (%)]                   | 17 (57)             | 15 (50)              |         |

| Table 2: Laboratory values of the study and control groups [mean ± standard deviation]. |
|---------------------------------------------------------------|
| Parameters | Pre-treatment | 3rd day | 10th day | Sepsis group (n = 30) | Control group (n = 30) |
|-------------|---------------|---------|----------|----------------------|------------------------|
| IMA (ABSU)  | 0.71 ± 0.08a  | 0.66 ± 0.05a | 0.61 ± 0.05a | 0.60 ± 0.05d          |                        |
| Adjusted IMA (ABSU) | 0.71 ± 0.10a  | 0.66 ± 0.10a | 0.60 ± 0.07a | 0.60 ± 0.08a          |                        |
| CRP (mg/dL) | 1.75 ± 0.96i  | –        | 0.29 ± 0.17i  | 0.31 ± 0.13k          |                        |
| Albumin (g/dL) | 3.19 ± 0.39i  | 3.19 ± 0.42a | 3.43 ± 0.26e  | 3.50 ± 0.31i          |                        |
| White blood cell count (/mm³) | 15386.67 ± 45188.83a | –      | 13380.00 ± 11994.00i | 16420.00 ± 15531.05i  |                        |
| Platelet count (/mm³) | 241600.00 ± 68517.60a | –      | 343766.70 ± 133778.69a | 283166.70 ± 61893.73a  |                        |

a,b,c,d,e,f,g,h,i,k,l,p < 0.0001; *p < 0.05; **p < 0.01; ***p < 0.001; ****p < 0.05; p > 0.05.
showed that the pre-treatment IMA and adjusted IMA levels of the patients in study group were statistically higher when compared to the control group (p < 0.05) and IMA and adjusted IMA values measured in the study group on the 3rd and 10th days decreased gradually and significantly compared to initial levels (p < 0.001). Pre-treatment mean CRP levels in the study group were statistically higher when compared to the control group (p < 0.05) (Table 2). Mean CRP levels measured on the 10th day in the study group were statistically significantly lower compared to initial levels (p < 0.05) (Table 2). In addition, pre-treatment mean albumin levels of patients in the study group were significantly lower compared to the control group and there was a significant increase on the 10th day, compared to the pre-treatment and on the 3rd and 10th day measurements (p < 0.05) (Table 2). No statistical difference was observed between the study and control group in terms of white blood cell counts, but there was a statistical difference with regard to platelet count between two groups. Furthermore, there was a statistically significant negative correlation between the pre-treatment albumin and IMA levels of patients in the study group (r: −0.399, p < 0.05). However, a positive correlation was identified between the pre-treatment IMA and CRP values in the same population (r: 0.371, p < 0.05).

The curve in the ROC analysis was performed for IMA as a marker for sepsis (Figure 1). According to the ROC curve analysis, the diagnostic cut-off value of IMA was found to be 0.644 ABSU (p < 0.001), with a sensitivity of 93.3% and specificity of 66.7%. The area under the ROC curve area under the curve (AUC) was 0.803 [95% confidence interval (CI): 0.680–0.894] while the positive predictive value was 73.69% and the negative predictive value was 90.9%.

**Discussion**

Sepsis is one of the diseases that cause an inflammatory response [19]. On that basis we hypothesized that IMA levels might be increased in septic patients and that this might be of diagnostic value. In our study, we found significantly higher pre-treatment IMA values in the sepsis group compared to control group values. Increased IMA levels in sepsis can be explained by the formation of the reactive oxygen products which are involved in the pathophysiology of sepsis, as well as hypoxia and ischemia [19, 20]. Microorganisms leading to sepsis cause inflammatory response and increased capillary permeability by directly and indirectly affecting the endothelial cells. Inflammatory response causes overproduction of reactive oxygen products, while increased vascular permeability leads to hypoxia and ischemia in tissues [19–22]. The overproduction of reactive oxygen species causes oxidative stress and consequently tissue hypoxia and ischemia [22]. It has been suggested that these events lead to the formation of IMA by modifying the albumin N-terminus, a powerful binding site for metal ions [23, 24].

In medical literature, various studies have reported the diagnostic and prognostic value of IMA in diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis and psoriasis which are characterized by inflammation, in the same way as sepsis do [25–27]. Leitemperguer et al. [26] reported higher IMA values in patients with rheumatoid arthritis compared to a control group. Likewise, Kaplan et al. [25] reported higher IMA values in patients with IBD and suggested that there was a correlation with the severity of the disease. The increasing of IMA, as a marker of oxidative stress in diseases with inflammatory conditions, reflects the fact that inflammation and oxidative stress are closely related in the pathogenesis of these diseases, as shown in our study [28].

To our knowledge, only one study in the literature has investigated IMA levels in newborns with sepsis [14]. Yerlikaya et al. [14] investigated IMA levels in premature infants (with gestational age less than 36 weeks) with sepsis. They reported higher IMA levels in septic premature babies compared to the control group. Whereas, septic term infants with 38 weeks gestational ages or over were included in our study. IMA levels in septic term infants were significantly higher compared to those of the control group. As far as we know, this is the first report...
about the assessment of diagnostic value of IMA in the diagnosis of sepsis in the term newborn population.

The most studied acute phase reactant in neonatal sepsis, and the most used in clinical practice is CRP [29]. It is secreted from the liver within four to 6 h with the induction of the inflammatory stimuli and reaches the peak level within 24–48 h [30]. CRP is a reliable marker of oxidative stress and systemic inflammation and increases in sepsis [10, 30]. As anticipated, mean CRP levels measured at the beginning of the study in our sepsis group were significantly higher compared to the control group and after treatment mean CRP levels returned to normal ranges as the control group have. There is a limited number of studies reporting any relationship between the IMA and CRP values in patients with sepsis [13, 31]. Erdem et al. [13] reported positive correlation between IMA and CRP levels in adult patients with sepsis. Likewise, Yerlikaya et al. [14] showed a positive correlation between IMA and CRP levels in premature newborns with sepsis. As in other studies, we determined a significant positive correlation between initial IMA and CRP levels in the sepsis group.

The most important factor affecting the reliability of serum IMA levels measured in sepsis is albumin. Studies have reported that IMA levels are not reliable in the presence of decreased or increased albumin levels (<2.0 or >5.5 g/dL) [28]. Zapico-Muñiz et al. [28] reported that every 1 g/dL change in albumin levels causes a corresponding 2.6% change in IMA values. Hypoalbuminemia has been shown to develop in association with decreased albumin production in the liver in inflammatory events, including sepsis [32]. Albumin levels measured in septic cases in this study were lower than those in the control group, and a significant negative correlation was determined between IMA and albumin levels. Also in this study, adjusted IMA was calculated in order to reduce potential error in IMA level measurement. Similarly to IMA, adjusted IMA levels in the sepsis group were also significantly higher than in the control group.

The most common screening tests used for neonatal sepsis are white blood cell counts and the I/T ratio in the blood. None of these tests particularly have been found to be useful in identifying the majority of septic infants [33]. Low white blood cell counts and high I/T ratios are associated with infection [34]. As in this study, there were no statistical differences with regard to white blood cell counts between the groups while ratio of immature to total neutrophils in the blood was significantly higher in the sepsis group.

The ROC plot has shown that IMA has a high degree of sensitivity and specificity. It is seen that IMA can be used as a very good discriminatory parameter for sepsis.

IMA could be assayed in patients with sepsis because the measurement of its level is simple and inexpensive.

In conclusion, we tried to assess the role of serum IMA in the early diagnosis of neonatal sepsis and we found that serum IMA level is a useful marker in neonatal sepsis at the time of diagnosis. Its estimation helps to identify and quantify oxidative stress and IMA could serve as a marker of ischemic damage of tissues and organs. But further studies are needed to confirm our results in larger groups of patients.

Conflict of interest statement: The authors have no conflict of interest.

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