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Evaluation of the Relationship Between the Causative Microorganism and Procalcitonin Levels in Intensive Care Patients

Yoğun Bakım Hastalarında Etken Mikroorganizma ile Prokalsitonin Düzeyleri Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Objective: In intensive care units, various inflammatory and immunological markers, along with the patient's clinic, are used to select the appropriate empirical antibiotic therapy until blood culture results are obtained. Of these markers, C-reactive protein (CRP) and procalcitonin (PCT) are frequently used. Our study aimed to evaluate the relationship between microorganism grown in blood culture and PCT level.

Material and Methods: In our study, following the approval of the ethics committee, the demographic data, blood culture growths, and CRP and PCT values of the patients who were followed up with a diagnosis of bloodstream infection in the intensive care unit for a six-month period between 15.11.2022 and 15.05.2023 were recorded retrospectively. Repetitive culture growths and contaminated cultures were excluded from the study.

Results: The total number of cultures included in the analysis was 510, of which 172 were Gram-negative, 304 were Gram-positive, and 34 were for fungal infection. When Gram-negative cultures were examined, the most common agents were *Escherichia coli* (29.0%) and *Klebsiella pneumoniae* (27.9%), respectively. When we looked at Gram-positive cultures, *Staphylococcus hemoliticus* (24.7%), *Staphylococcus hominis* (18.8%) and *Staphylococcus auerus* (14.4%) were the most common factors, respectively. All fungal cultures consisted of *Candida species*. When the PCT levels of the groups were examined, it was seen that the values were statistically significantly higher in the Gram-negative bacteria group ($p<0.001$). In comparisons between groups, CRP levels were found to be statistically higher in the Gram-negative group than in both the Gram-positive and fungal groups ($p<0.001$, $p<0.001$, respectively).

Conclusion: We think that looking at serum PCT levels will guide us in estimating the agent in choosing the empirical antibiotic therapy that should be started until the culture agent is identified.

Keywords: Procalcitonin, bacteremia, C-reactive protein, Gram-negative

ÖZ

Amaç: Yoğun bakımlarda kan kültürü üremeleri sonuçlanana kadar geçen zamanda uygun ampirik antibiyoterapinin seçimine yönelik hastanın kliniği ile birlikte çeşitli enflamatuvar ve immünolojik belirteçlerden faydalanılmaktadır. Bunlar arasında C-reaktif protein (CRP) ve prokalsitonin (PCT) sıkça kullanılmaktadır. Çalışmamızda kan kültüründe üreyen etkenler ile PCT arasındaki ilişkinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Çalışmamızda etik kurul onayını takiben 15.11.2022- 15.05.2023 tarihleri arasında altı aylık dönemde yoğun bakımda kan dolaşım enfeksiyonu tanısı ile takip edilmiş hastaların demografik verileri, kan kültürü üremeleri, kültür alımından 24. saat öncesine ait CRP ve PCT değerleri retrospektif olarak kaydedildi. Tekrarlayan kültür üremeleri ve kontamine kültürler çalışma dışı bırakıldı.

Bulgular: Analize dahil edilen toplam kültür sayısı 510 olup, bunların 172'si Gram-negatif, 304'ü Gram-pozitif ve 34'ü mantar enfeksiyonu idi. Gram-negatif etkenler incelendiğinde en sık etken sırasıyla *Escherichia coli* (%29,0) ve *Klebsiella pneumoniae* (%27,9) idi. Gram-pozitif kültürlere baktığımızda ise sırasıyla *Staphylococcus hemoliticus* (%24,7), *Staphylococcus hominis* (%18,8) ve *Staphylococcus auerus* (%14,4) en

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ÖZ

sık görülen etkenlerdi. Mantar kültürlerinin tamamı *Candida* türlerinden oluşmaktaydı. Grupların PCT düzeyleri incelendiğinde Gram-negatif bakteri grubunda değerlerin istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (p<0,001). Gruplar arası karşılaştırmalarda CRP düzeylerinin Gram-negatif grubunda hem Gram-pozitif hem de mantar gruplarına göre istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (sırasıyla p<0,001, p<0,001).

Sonuç: Bakteriyemi etkenini tahmin edilip kültür etkeni ortaya konuluncaya kadar başlanması gereken ampirik antibiyoterapinin seçiminde serum PCT değerlerine bakılmasının bize yol gösterici olacağı düşüncesindeyiz.

Anahtar Kelimeler: Prokalsitonin, bakteriyemi, C-reaktif protein, Gram-negatif

INTRODUCTION

Although bloodstream infections are common in patients followed in intensive care units, they are associated with high mortality (1). Early diagnosis and targeted empirical treatment are of high prognostic importance (2). Delay in initiating adequate antibiotic therapy is an independent indicator of high mortality. Various inflammatory and immunological markers are used, together with the patient's clinical information, for the selection of the appropriate empirical antibiotic therapy until the blood culture results are completed. Among these, C-reactive protein (CRP) and procalcitonin (PCT) are frequently used (3,4). Because PCT rises earlier in serum and has higher sensitivity and specificity than CRP against systemic bacterial infections, it guides us in the treatment and follow-up of bloodstream infections (2). In addition, high PCT concentrations have a positive predictive value for severe sepsis and septic shock, and distinguish between viral and bacterial infections (5). However, there are recent studies showing that PCT can also help predict the causative microorganism (6,7). In these studies, it is stated that the PCT level can be used to differentiate bacteremia caused by Gram-positive and Gram-negative bacteria, but more studies are needed on this subject. In our study, we aimed to evaluate the relationship between CRP and PCT levels according to the causative microorganism in the blood culture.

MATERIALS and METHODS

Ethical approval was obtained for the study from the Eskişehir Trainig and Research Hospital of Medicine Non-interventional Clinical Research Ethics Committee (decision number: ESH/GOEK2023/29, date: 20.06.2023). All procedures were performed according to the ethical rules and principles of the Declaration of Helsinki.

Study Population

In our study, patients who were followed up with the diagnosis of bloodstream infection in the intensive care unit for a six-month period between 15.11.2022 and 15.05.2023, demographic data, blood culture reproductions, CRP and PCT values 24th hours before culture were retrospectively recorded after following the approval of the ethics committee. The causative microorganisms were separated according to their Gram stain properties; examined in three groups, and their CRP and PCT values were compared.

Pathogenic microorganism growths in blood cultures not associated with another focus were included in the study, according to laboratory-confirmed bloodstream infection criteria defined in the Centers for Disease Control and Prevention guideline for patients over the age of 18 who were followed in intensive care units (8). Multiple blood cultures from the same patients, blood cultures suspected of contamination, and blood culture results from patients under 18 years of age were excluded from the study. Blood culture samples were studied with BD Bactec automated blood culture systems. The remaining blood culture growths were examined by dividing them groups: group 1, Gram-negative bacteria; group 2, Gram-positive bacteria; group 3, fungal organisms.

Statistical Analysis

The normality of the distributions of continuous variables was checked with the Shapiro–Wilk test, and the homogeneity of group variances was checked with the Levene test. Descriptive statistics for continuous variables with a non-normal distribution are expressed as the median (lowest-highest value), while categorical variables are expressed as the number of cases and percentage (%). In group comparisons, normally distributed data were compared with the t-test, and non-normally distributed data were compared with the Mann-Whitney U test. Logistic regression analysis was used to evaluate differences in PCT levels between groups. Statistical significance was set at p<0.05. All statistical analyses were performed using SPSS 22.0 (IBM SPSS Ver. 22.0, IBM Corp, Armonk, NY, USA).

RESULTS

The total number of cultures included in the analysis was 510, and 172 cultures were Gram-negative, 304 cultures were Gram-positive, and 34 cultures constituted the fungal infection group. When Gram-negative agents are examined, the most common agents are *Escherichia coli* (29.0%) and *Klebsiella pneumoniae* (27.9%). When we look at Gram-positive agents, *Staphylococcus haemolyticus* (24.7%), *Staphylococcus hominis* (18.8%), and *Staphylococcus aureus* (14.4%) were the most common ones, respectively. All of the fungal agents were *Candida species* (Table 1). There was no significant difference

between the groups in terms of age and gender. When the CRP and PCT levels among the groups were examined, it was found that these levels were statistically significant and higher in the Gram-negative bacteria group (CRP: p<0.001, PCT: p<0.001). In the comparison of CRP and PCT values between the groups, CRP and PCT values were found to be significantly higher in the Gram-negative group than in the Gram-positive group (p<0.001, p<0.001, respectively) (Table 2). It was also observed that the Gram-negative group was significantly higher than the fungal infection group with respect to CRP (p<0.001) (Table 3).

DISCUSSION

In our study, we showed that CRP and PCT levels were higher in the Gram-negative bacteria group than in the other groups. This is one of the pioneering studies showing that acute phase reactants can give clues not only about the severity of the infection but also about the causative agent.

Bloodstream infections are frequently seen and are serious causes of mortality and morbidity in intensive care; however, the factors vary in every region and even in every hospital. In studies conducted in Türkiye, it was stated that Gram-positive agents were the most common in intensive care units, while *Staphylococci* were the most common agents among them. The Gram-negative bacteria group was emphasized as the second most common, with *Acinetobacters* being the most common (9,10). In our study, in parallel with the literature, Gram-positive bacteria were mostly encountered in the intensive care unit, and *Staphylococc*i constituted the majority of them. When Gram-negative agents are considered, the most common agents in our hospital were *Escherichia coli* and *Klebsiella pneumoniae*.

Early diagnosis of bloodstream infections and initiation of an appropriate empirical antibiotic therapy significantly reduce mortality in studies conducted in intensive care units. Initiation of an inappropriate antimicrobial therapy at baseline, was found to be an independent risk factor for adverse outcomes in patients with bloodstream infections of *Staphylococcus aureus* and Gram-negative origin (11,12). Studies have emphasized that an inappropriate initial antimicrobial therapy is strongly associated with adverse outcomes in bloodstream infections caused by antibiotic-resistant nonfermenting Gram-negatives such as *Pseudomonas aeruginosa* (13). Therefore, the estimation of causative microorganisms is important for clinicians. In our study, the differences in serum PCT levels between the different agents were examined, and these levels were found

Table 1. Distribution of culture according to species

Group 1 Gram-negative bacteria (n=172)	Group 2 Gram-positive bacteria (n=304)	Group 3 Fungal group (n=34)
Escherichia coli (n=50) 29.0%	*Staphylococcus* hemolyticus (n=75) 24.7%	*Candida species* (n=34) 100%
Klebsiell pneumoniae (n=48) 27.9%	*Staphylococcus* hominis (n=57) 18.8%	
Acinetobacter baumanii (n=37) 21.5%	*Staphylococcus* aureus (n=44) 14.4%	
Pseudomonas aureginosa (n=14) 8.1%	The other *Staphylococcus. spp* (n=47) 15.4%	
Proteus mirabilis (n=7) 4.0%	*Enterococcus faecium* (n=28) 9.2%	
The other *spp.* (n=16) 9.5%	*Enterococcus faecalis* (n=27) 8.8%	
	Streptococcus spp. (n=16) 5.2%	
	The other *spp.* (n=10) 3.5%	

Table 2. Change of demographic data and acute phase reactants between groups

	Group 1 (n=172)	Group 2 (n=304)	Group 3 (n=35)	p value
Age	73 (62-82)	74 (66-82)	70 (60-79)	0.097
Gender (male, n)	87	150	16	0.868
Procalcitonin (ng/mL)	5.24 (1.06-16.09)	0.52 (0.14-2.57)	0.59 (0.36-3.14)	<0.001
CRP (ng/mL)	152 (75-218)	96 (49.5-160.5)	112 (75-178.5)	<0.001
CRP: C-reactive protein				

Table 3. Significance values of CRP, PCT values between groups

	CRP level	Procalcitonin level
Group 1 vs group 2	<0.001	<0.001
Group 1 vs group 3	<0.001	0.103
Group 2 vs group 3	0.288	0.119
CRP: C-reactive protein, PCT: Procalcitonin		

to be statistically significant in the Gram-negative bacteria group.

In recent studies, it has been emphasized that the PCT response is different in Gram-negative and Gram-positive bacteria (6,7). PCT expression is induced by the stimulation of various inflammatory *Cytokines,* and it is thought that the main reason for this difference is the activation of different pathways by bacteria (14,15). *Lipopolysaccharides* in Gram-negative bacteria stimulate Toll-like receptor-4, while lipoteichoic acid in Gram-positive bacterial cell walls stimulates Toll-like receptor-2 (16). This leads to differential production of inflammatory *Cytokines* in the respective *Leukocytes* (17). This concept suggests that different pathogens may lead to different levels of PCT production (18-20). Thomas et al. (14) found higher levels of IL-6 and IL-8 in Gram-negative bacterial infections, which further increased the accuracy of the variable response. The mechanisms of lower production of PCT by Gram-positive agents, have not been fully elucidated, and attempts have been made to explain different mechanisms of action regarding the immune response, such as the inhibitory effect of *Enterococci* on macrophage activation, antibodies activated by *Staphylococcus aureus*, and the innate immune response triggering effect of T-lymphocytes (21,22). In our study, in parallel with the literature, Gram-negative bacterial infections induced more severe PCT and CRP responses.

Martini et al. (23) found that a PCT limit of 2.0 ng/mL was able to differentiate between *Candida species* and bacterial sepsis in 48 intensive care patients with signs of sepsis at high risk for fungal infection. In contrast, Fu et al. (24) found a cut-off value of 8.06 ng/mL in the distinction between candidemia and Gram-negative bacterial sepsis in their study of 85 patients. Since PCT values can differ significantly in different clinical diseases and especially in intensive care patients, they said that making this inference depends on the clinical characteristics of the patient population studied, and furthermore, they predicted that a definite conclusion could not be reached. In our study, the PCT level was found to be high (especially in the Gram-negative bacteria group), but the patients were not separated according to their clinical characteristics (5.24 vs. 0.52, $p<0.001$).

The most important limitations of the study, including its retrospective type and the lack of homogeneity in numbers among the groups, can be listed as follows. The Gram-positive infection group is almost twice that of the Gram-positive group. In addition, the number of fungal groups is very small.

Study Limitation

Considering the limitations of the study, its retrospective type and the lack of homogeneity in numbers among the groups can be listed as the most important ones. The Gram-positive infection group is almost twice as high as the Gram-negative group. In addition, the number of fungal group is very small.

CONCLUSION

PCT levels were found to be higher in Gram-negative agents than in Gram-positive agents. We think that looking at serum PCT values will guide us in the selection of empirical antibiotherapy, which should be initiated while the bacteremia agent is being identified and the culture results are pending.

Ethics

Ethics Committee Approval: Ethical approval was obtained for the study from the Eskişehir Trainig and Research Hospital of Medicine Non-interventional Clinical Research Ethics Committee (decision number: ESH/GOEK2023/29, date: 20.06.2023).

Informed Consent: Informed consent was obtained from all participants.

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Footnotes

Author Contributions

Surgical and Medical Practices: A.A., A.D., Concept: A.A., A.D., Design: A.A., A.D., Data Collection or Processing: A.D., Analysis or Interpretation: A.D., Literature Search: A.A., A.D., Writing: A.A.

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