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Research Article / Araştırma Makalesi

Is Procalcitonin An Accurate Marker in the Diagnosis of Acinetobacter-Induced Bacteremia?

Acinetobacter Etkenli Bakteriyemilerin Tanısında Prokalsitonin Doğru Bir Belirteç Midir?

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Abstract

Nosocomial bloodstream infections are common in intensive care units, and a significant portion results in mortality. Procalcitonin is a biomarker used in the early diagnosis of bloodstream infections. Since different pathways release it, its level in the blood may differ in bloodstream infections caused by different agents. The present study was designed to demonstrate whether procalcitonin was an accurate marker in nosocomial bloodstream infections caused by *Acinetobacter spp.* The present study evaluated 214 bacteremia episodes of 145 patients diagnosed with nosocomial bloodstream infection. Nosocomial bloodstream infection agents were divided into four groups gram-positive bacteria, gram-negative bacteria, *Acinetobacter spp.*, and Candida spp. At the time of diagnosis, procalcitonin, C-reactive protein, neutrophil/lymphocyte ratio, and leukocyte values were measured on the 3rd and 7th days. The mean procalcitonin value measured at the time of diagnosis was 11.7±21.8 ng/ml, the highest in the gram-negative bacteria group. The mean procalcitonin value in the gram-positive bacteria group was 2.8±6.44 ng/ml, 2.5±3.35 ng/ml in the Candida spp. group, and 3.5±12.1 ng/ml in the Acinetobacter spp. group. A significant difference was determined between the four groups regarding procalcitonin values. It was determined that the blood procalcitonin level at the time of diagnosis did not increase as expected in *Acinetobacter spp.*-induced nosocomial bloodstream infections. In this respect, caution should be exercised in the early diagnosis of nosocomial bloodstream infections.
Keywords: *Acinetobacter spp.*; Bloodstream infection; C- Reactive protein; Procalcitonin

Özet

Nozokomiyal kan dolaşımı enfeksiyonları yoğun bakım ünitelerinde sık görülen ve önemli bir bölümü mortalite ile sonlanan enfeksiyonlardır. Prokalsitonin kan dolaşımı enfeksiyonların erken tanısında kullanılan bir biyobelirteçtir. Salınımının farklı yöntemlerle olması nedeni ile farklı etkenlerce oluşan kan dolaşımı enfeksiyonlarında kandaki seviyesi farklı düzeylerde olabilmektedir. Bizde *Acinetobacter spp.* etkenli nozokomiyal kan dolaşımı enfeksiyonlarında prokalsitonin iyi bir belirteç olup olmadığını göstermek amacı ile çalışmamızı planladık. Çalışmamızda nozokomiyal kan dolaşımı enfeksiyonu tanısı alan 145 hastanın 214 bakteriyemi epizodu değerlendirildi. Nozokomiyal kan dolaşımı enfeksiyonu etkenleri gram pozitif bakteriler, gram negatif bakteriler, *Acinetobacter spp.* ve Candida spp. olarak dört gruba ayrıldı. Tanı anında, 3. ve 7. günlerde prokalsitonin, C-reaktif protein, nötrofil/ lenfosit oranı ve lökosit değerlerine bakıldı. Tanı anında bakılan prokalsitonin değeri ortalaması 11,7±21,8 ng/ml ile en yüksek gram negatif bakteri grubunda idi. Gram pozitif STUDTbakteri grubunda ortalama prokalsitonin değeri 2,8±6,44 ng/ml, Candida spp. grubunda 2,5±3,35 ng/ml ve *Acinetobacter spp.* grubunda ise 3,5±12,1 ng/ml olarak tespit edildi. 4 grup arasında PCT değerleri açısından anlamlı fark saptandı. *Acinetobacter spp.* etkenli nozokomiyal kan dolaşımı enfeksiyonlarında tanı anında kan prokalsitonin düzeyi diğer etkenlere oranla beklenildiği kadar artmadığı tespit edilmiştir. Nozokomiyal kan dolaşımı enfeksiyonlarının erken tanısında bu açıdan dikkatli olunması gerektiğini düşünmekteyiz.
Anahtar Kelimeler: *Acinetobacter spp.*; C-reaktif protein; Kan dolaşımı enfeksiyonları; Prokalsitonin

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1. Introduction

The incidence of nosocomial infections (NI) has increased in recent years due to the prolonged life expectancy, newly developed techniques, prolonged stay in the intensive care unit (ICU), and the high number of invasive procedures applied. Among the causative agents of NI, *Acinetobacter spp*. are common since they can survive for a long time in hospital environments and can colonize the hands of hospital staff, the patient's environment, and the equipment used.

Nosocomial bloodstream infections (NBSI) develop 7-8 times more frequently in ICUs than in other hospital units. It ranks 3rd among ICU infections (1). NBSIs need to be well managed in terms of diagnosis and treatment. Since the treatment is urgent, they have a high mortality rate and are difficult to diagnose, so making a quick decision and starting empiric treatment is necessary. Although blood culture is the gold standard in diagnosing bacteremia, the time needed for the results could be late to initiate treatment. Hence, there is a need for biomarkers that will guide the clinician in the diagnosis of bacteremia and enable us to make the diagnosis quickly and accurately.

Procalcitonin (PCT) is a prohormone biomarker that can be used in the diagnosis of bacteremia and is released from thyroid C cells, which begins to increase in response to infection in 2-6 hours, peaks at 6-12 hours, and has a half-life of 24 hours (2). It is known that bacteremias caused by gram-negative agents increase more than those caused by gram-positive agents (3). In recent studies, PCT values are examined according to NBSI agents (4). Since it has been experienced in clinical practice that the PCT level does not increase sufficiently in *Acinetobacter spp*.-induced bacteremias, the present study was designed to investigate the accuracy of this hypothesis.

2. Material and Method

Study design and data collection

The study was performed among patients hospitalized in the 10-bed neurology ICU between January 2020 and November 2021 in our hospital, which is a tertiary hospital. Infectious diseases and clinical microbiology specialists of the patients were retrospectively reviewed from the ICU follow-up forms, and 214 NBSI episodes of 145 patients diagnosed with NBSI were evaluated. Patients diagnosed with NBSI were excluded from the study if more than one agent was grown in their blood culture. In our study, only primary or catheter-related BSIs were evaluated.

Patients with at least 14 days between two bloodstream infection episodes were included. If the causative agent reproduced in the second episode was the same as the first agent between these two episodes, it was also excluded from the study. NBSI were divided into four groups gram-positive bacteria (GPB), gram-negative bacteria (GNB), *Acinetobacter spp*., and Candida spp. PCT, C-reactive protein (CRP), leukocyte, and neutrophil-lymphocyte ratios (N/L ratio) were recorded from the blood tests taken routinely on the day of culture from the patients (Day 0) and on the 3rd and 7th days.

Demographic data, comorbid diseases, growth agents in blood culture, PCT, CRP, N/L ratio, and leukocyte values obtained on the day of blood culture, the 3rd and 7th days, were recorded.

In our hospital, blood is drawn routinely twice a week from patients hospitalized in the Neurology ICU and also for PCT in case of suspected sepsis.

Study population

Patients over the age of 18 who were diagnosed according to the Centers for Disease Control and Prevention (CDC) bloodstream infection diagnostic criteria were included in the study (5).

Exclusion criteria

Patients under the age of 18 years

Patients without measurement of PCT level on the day of blood culture

Patients with thyroid malignancies

Patients with lung malignancies

Patients with acute pancreatitis

Microbiological methods

Working principle of blood culture

The BACTEC 9240 automatic blood culture system was used to perform the blood culture (Becton Dickinson, SARKS, MD, USA). Whole blood was injected into aerobic blood culture bottles for each blood sample. All positive bottles were pulled out of the machine, and the samples were then subcultured on a regular solid medium for gram staining and further analysis. Then, pathogens and antibiotic sensitivity were determined using the VITEK II compact system (bioMérieux, Lyon, France).

Working principle of PCT

An automatic electrochemiluminescent immunoassay (COBAS E601, RoCH, Switzerland) was used to measure serum PCT levels per the manufacturer's recommendations. Combining the one-step sandwich method with the Enzyme-Linked Fluorescent Assay method allowed the detection of serum PCT. The limit of detection was 0.05 ng/ml.

Statistical analysis

SPSS (Statistical Package for Social Sciences) Windows 22.0 package program was used in all statistical analyzes. For statistical significance, $p<0.05$ was accepted. Quantitative data were expressed as mean ± standard deviation (SD) values, and qualitative data as numbers and percentages. Kolomogorov-Smirnow test was used for normality test. ANOVA test evaluated leukocytes, N/L, CRP, and PCT levels on days 0, 3rd and 7th according to the agents of NBSI when the assumption of normal distribution was provided. Kruskal Wallis test was used for non-parametric comparisons. In patients diagnosed with Acinetobacter-mediated nosocomial bloodstream infection, the curve of PCT intersection points was analyzed using Receiver Operating Characteristics (ROC). Sensitivity and specificity (sensitivity and specificity) values of the significant cut-off value were calculated. In the evaluation of the area under the curve, it was accepted that it was statistically significant in cases where the Type-1 error level was below 5%.

Ethics Committee Approval Approval for the study was obtained from the Ethics Committee of Antalya Training and Research Hospital with the number 2022-016.

3. Results

A total of 214 bacteremia episodes of 145 patients diagnosed with NBSI in our ICU between January 2020 and November 2021 were included in our study. The mean age of the patients was 70.4±15.7 (26-95) years, 53.1% of the patients were male, and 46.9% were female. The most common reason for hospitalization in the neurology ICU was acute stroke (74.5%). The second most common diagnosis of subarachnoid hemorrhage was found in hospitalized patients (9.7%). 75.9% of the patients had at least one comorbid disease. When the comorbidities were examined, hypertension (HT) was in first place at 44.8%, while diabetes mellitus (DM) was in second place at 31%. The mean duration of hospitalization in the neurology ICU of the patients was 37.6±33.1 (3-181) days. At the end of the follow-up period, 53.8% of the patients were discharged, and 46.2% died. Demographic data of the patients are presented in Table 1.

Two hundred fourteen microorganisms grown in blood cultures were divided into four groups GPB, GNB, Acinetobacter spp, and Candida spp. There were 107 (50%) agents in the GPB group, 45 (21%) in the GNB group, 44 (20.6%) in the Acinetobacter spp group, and 18 (8.4%) in the Candida spp group. The distribution of agents grown in blood cultures is summarized in Table 2.

The mean PCT value measured on day zero was 11.7±21.8 ng/ml, being the highest in the GNB group. The mean PCT value in the GPB group was 2.8±6.44 ng/ml and 2.5±3.35 ng/ml in the Candida spp. group, and 3.5±12.1 ng/ml in the Acinetobacter spp. group. A significant difference was determined between the four groups in terms of PCT values. GPB group,

Acinetobacter spp group, and Candida spp. group mean PCT value was lower than the GNB group (p:0.003). There was no statistical difference between the PCT values measured on the third and seventh days. There was no significant difference between these four groups regarding WBC, N/L ratio, and CRP values measured on the 0th, third, and seventh days. Laboratory values determined according to the groups are shown in Table 3.

In demonstrating Acinetobacter spp bacteremia, the zero-day PCT cut-off value was calculated as 0.69 ng/ml (Figure 1). The PCT value of 0.69 ng/ml was calculated to have a specificity of 44.7% and a sensitivity of 55.9% for Acinetobacter spp bacteremia (Table 4).

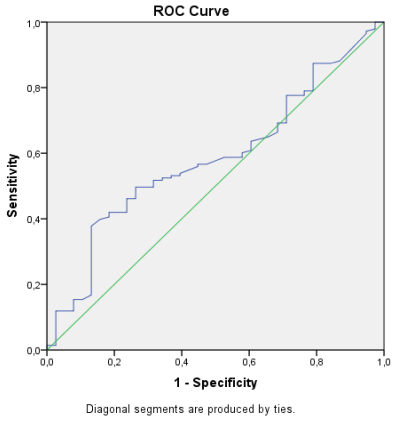

Figure 1. PCT ROC curve in *Acinetobacter spp* group

Table 1. Demographic data of the patients

	mean±SD	**Min-Max**
Age (years)	70.4±15.7	26-95
Intensive care hospital stay (days)	37.6±33.1	3-181
	Number (n)	Percentage (%)
Gender		
Female	68	46.9
Male	77	53.1
Hospitalization diagnosis		
Subarachnoid hemorrhage	14	9.7
Acute stroke	108	74.5
Myasthenia gravis	1	0.7
Epilepsy	10	6.9
Central nervous system infection	3	2.1
General condition disorder	9	6.2
Underlying disease		
Hypertension	65	44.8
Diabetes mellitus	45	31.0
Coronary Artery Disease	39	26.9
Chronic Kidney Failure	20	13.8
Heart failure	19	13.1
Chronic obstructive pulmonary disease	17	11.7
Malignancy		
Disease outcome	6	4.1
Discharge		
Mortality	78	53.8
	67	46.2

Table 2. Distribution of reproducing agents in blood culture

	Reproduced Agent	Number (n)	Percentage (%)
GPB	*Staphylococcus aureus*	27	12.6
	Staphylococcus epidermidis	24	11.2
	Staphylococcus hominis	25	11.4
	Enterococcus faecalis	14	6.5
GNB			
	Pseudomonas aeruginosa	19	8.9
	Klebsiella pneumoniae	9	4.2
	Proteus mirabilis	7	3.3
	Stenotrophomonas maltophilia,	5	2.3
	Escherichia coli	4	1.9
	Enterobacter spp.	1	0.5
Candida spp.	*Candida parapsilosis*	7	3.3
	Candida tropicalis	4	1.9
	Candida glabrata	5	2.3
	Candida albicans	2	1.0
Acinetobacter spp.		44	20.6

GPB: gram positive bacteria
GNB: gram negative bacteria

Table 3. Laboratory values determined as per the bacterial groups

	GNB (n=45)	GPB (n=107)	*Candida spp.* (n=18)	*Acinetobacter* spp. (n=44)	P
0th DAY					
WBC ($10^{3/}$ mm3)	13206.7±6797.57	13223.3±5670.14	12305.6±5826.35	11668.2±7452.66	0.537
N/L ratio	19.3±19.43	13.7±17.33	9.1±7.38	9.9±8.13	0.287
CRP (gr/l)	164.9±89.42	147.7±86.36	184.5±109.47	149.7±109.51	0.392
PCT (ng/ml)	11.7±21.08[a]	2.8±6.44[b]	2.5±3.35[b]	3.5±12.19[b]	**0.003***
3rd DAY					
WBC ($10^{3/}$ /m3)	12479.1±8707.23	12403.0±5600.90	12362.5±5127.29	10842.9±4751.69	0.545
N/L ratio	18.1±12.71	11.9±10.99	6.1±2.88	8.3±4.86	0.101
CRP (gr/l)	116.3±66.33	131.7±9.42	175.7±89.95	115.5±73.07	0.116
PCT (ng/ml)	5.3±8.05	3.1±9.47	2.6±2.66	2.0±4.35	0.369
7th DAY					
WBC ($10^{3/}$ mm3)	12937.8±8083.25	12404.8±5334.30	11292.3±5774.14	13027.8±5884.05	0.815
N/L ratio	11.0±7.99	9.6±7.00	3.6±2.51	5.5±2.88	0.090
CRP (gr/l)	107.9±65.27	110.3±101.96	155.8±119.15	118.5±92.90	0.474
PCT (ng/ml)	4.5±16.92	2.3±8.87	1.6±2.24	1.8±3.83	0.672

Table 4. Evaluation of PCT intersection points in the presence of *Acinetobacter spp*.-induced bacteremia

Risk factor	AUC (95%)	Cut off	p	Sensitivity (%)	Specificity (%)
Acinetobacter spp bacteremia	0.583 (0.488-0.679)	0.69	0.049	55.9	44.7

4. Discussion and Conclusion

NBSI is a severe life-threatening infection. Bloodstream infections constitute 30-40% of nosocomial infections and are a critical cause of mortality (6). Early diagnosis is vital for timely and appropriate treatment. Although blood culture is the gold standard for diagnosis, considering the time required for blood culture, it may lead to delays in diagnosis and treatment (7).

PCT is a biomarker used for early diagnosis of sepsis, and its use has recently increased for diagnosis and treatment follow-up. It is produced in response to bacterial endotoxins and inflammatory cytokines (8). GNBs and GPBs activate different Toll-like receptor pathways, thereby causing the release of different cytokines that stimulate PCT release (9). Since GNBs cause endotoxin release after cell death, it is thought that PCT may increase the blood level more (10). Therefore, PCT values can be different in blood stream infections (BSI) caused by different agents. In some studies, it has been shown that the increase in procalcitonin is less in infections caused by non-fermentative gram-negative bacteria than in infections caused by the enterobactericae family (11). There is no clear study yet to reveal the reason for this.

Our study revealed that the PCT value increased less in NBSIs caused by Acinetobacter spp than in NBIs caused by other GNB agents.

In a study performed in 2013, PCT and CRP values were compared between sepsis groups caused by GNB, GPB, and candida agents. In the study, the mean PCT value was 8.9 ng/ml in the GNB group, 0.73 ng/ml in the GPB group, and 0.58 ng/ml in the candida group (12). Similarly, in a study by Leli et al., the PCT value was significantly higher in GNB-induced BSIs compared to GPB-incluced BSIs and fungal-induced BSIs (mean 13.8 ng/ml). In the same study, when GNBs were separated by their types, the mean PCT value was 2.2 ng/ml in Acinetobacter baumannii-induced BSIs (11). In our study, consistent with the literature, it was revealed that PCT increased more in bloodstream infections caused by GNB than in BSIs caused by GPB and candida spp. A study by Watanebe et al. showed that individuals infected with extended-spectrum beta-lactamase-producing (ESBL) strains had more PCT release than those infected with non-ESBL-producing strains; however, they reported that the number of patients was insufficient (13). The present study aimed to examine the PCT value in the colistin-resistant and susceptible Acinetobacter spp group, and this evaluation could not be made due to the very low number of resistant *Acinetobacter spp.*

In a study on secondary bacteremias, PCT levels were demonstrated to vary according to the focus of infection (14). In our study, only primary or catheter-related BSIs were evaluated.

In a study from our country, GNB infections were divided into two groups Acinetobacter and non-acinetobacter-induced infections. In the Acinetobacter group, PCT levels measured 48 hours before, at the time of diagnosis, and 48 hours after diagnosis were significantly lower than in the other group. The mean PCT value measured at the time of diagnosis was found to be 1.6±2.5 ng/ml, and it was stated that the PCT level is not an appropriate marker for diagnosing Acinetobacter-induced infections (15). In our study, the mean PCT value in the Acinetobacter spp group at the time of diagnosis was 3.5±12.19. The reason for the difference in PCT cut-off values in various studies can be interpreted as the difference between the blood culture collection time and the time to reach the PCT peak level. It is considered that paying attention to this issue in new prospective studies may yield healthier results. Also, it would be essential to evaluate the patients using antibiotics separately in studies without the infectious diseases specialist evaluating them before PCT is examined. We think that the advantages of our study are that only patients with primary or catheter-related bloodstream infections were included.

In conclusion, it is known that PCT can be used in the early diagnosis of BSIs. We think that PCT increases differ in terms of the agent, causing less PCT increase, especially in Acinetobacter spp-induced BSIs compared to

other GNB agents, and this issue should be paid attention to in terms of early treatment.

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Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Republic of Turkey Ministry of Health University of Health Sciences Antalya Training and Research Hospital. (Decision no: 2/10, Date: 20.01.2022).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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