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Is procalcitonin a good marker for *Acinetobacter* infections?

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ABSTRACT

Aim: Culture is the most important method in the diagnosis of infectious diseases, but diagnosis may be delayed with culture. Therefore, pro-inflammatory markers are used for early diagnosis of infections. Procalcitonin, a precursor of calcitonin, takes part in the systemic reactions caused by circulating endotoxins and inflammatory cytokines. The aim of this study is to investigate the utility of procalcitonin in the early diagnosis and treatment follow-up of *Acinetobacter baumannii* infections.

Material and Method: A total of 96 patients, 63 with *A. baumannii* and 33 with systemic infections caused by *Klebsiella spp*., *Escherichia* coli, *Enterobacter spp*., *Pseudomonas spp*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus* were included in the study. The cultured areas were endotracheal aspirate, sputum, bronchoalveolar lavage and blood culture. Leukocyte count, C-reactive protein and procalcitonin were used as inflammation markers.

Results: The procalcitonin levels in the group with infection due to *A. baumannii* were found to be significantly lower than the other group ($p<0.05$). There was no statistically significant difference between the two groups in terms of C-reactive protein and leukocyte levels.

Conclusion: Unlike other bacterial infections, procalcitonin may not increase in the early stages of *A. baumannii* infections. This situationshould be considered in the early diagnosis of systemic infections.

Keywords: *Acinetobacter*, procalcitonin, C-reactive protein, sepsis

INTRODUCTION

Microbiological sampling is the gold standard for the diagnosis of sepsis; however, identification requires time to result, and empirical antibiotics are needed to start for reducing mortality until obtained culture results. Some biomarkers are used to give an idea to start suitable empiric antibiotics while awaiting the culture results (1). White blood cell (WBC), procalcitonin (PCT) and C-reactive protein (CRP) are commonly used in the diagnosis of sepsis in the intensive care unit (ICU) (2). Procalcitonin is the precursor molecule of calcitonin and is produced mainly by the thyroid gland. Inflammation and tissue damage increases procalcitonin synthesis (1). Procalcitonin can be detected in the blood 2-4 hour after the onset of infections. Procalcitonin levels reach peak levels in serum within 6 to 24 hours and can be detected until seven days (3). Its production increases in response to a pro-inflammatory stimulus, especially of bacterial origin. While normal basal levels in most adults are <0.01 ng/mL, procalcitonin levels can rapidly increase by 400-fold (>4 ng/mL) when stimulated by an endotoxin (4).

MATERIAL AND METHOD

Ethics committee approval was obtained from Erciyes University by the decision number of 2018/617 on 05.12.2018. All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

Study design

The study was performed in the tertiary intensive care unit (ICU) of internal medicine in a university hospital. The ICU has a capacity of 16 beds. The data were obtained from the medical and laboratory records between January 2014 and December 2018 retrospectively. Sixty-three patients with *Acinetobacter baumannii* in any culture were included in the study group, and 33 patients with infections due to other bacterial agents (*Klebsiella spp*., *Escherichia* coli, *Enterobacter spp*., *Pseudomonas spp*, *Stenotrophomonas maltophilia*, *Staphylococcus aureus*) were included as the control group. Leukocyte, CRP and PCT count were used as inflammation markers. PCT and CRP levels were recorded in before 48 hours from culture,

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culture date, and daily white blood cell (WBC) count too. Patients who were previously receiving specific treatment for *A.baumannii* and patients with cancer, autoimmune diseases, trauma and under 18 years of age were excluded.

Procalcitonin, CRP are taken routinely at 48-hour intervals and WBC is evaluated daily in ICU. First samples of PCT, CRP and WBC were taken 48 hours before culture, second ones were taken the day of culture and third ones were obtained after 48 hours from culture. We used these data as a retrospectively. Cultures were taken in cases of deterioration in the patient's clinic, increasing body temperature, mechanical ventilatory support and/or inflammatory markers such as CRP, PCT, WBC (5,6). Serum procalcitonin was measured by the immune-luminometric method in the biochemistry laboratory. CRP was measured by nephelometry immunoassay, and white blood cell count was performed on K3EDTA-treated blood, using an automated Coulter JT hematology analyzer. An immune-luminometric assay and CRP concentrations obtained PCT levels by use of a nephelometric assay.

Statistical Analysis

Values were indicated as mean±standart error mean (SEM). Categorical data were analyzed by chi-square and nonparametric fisher exact test, numerical data by student-t-test, and nonparametric by the Mann-Whitney U test. A p-value <0.05 was considered significant. Spearman's rank correlation coefficient tested for associations of the biomarkers.

RESULTS

A total of 96 patients (63 patients in *A. baumannii* group and 33 patients in the *non-acinetobacter* group) were included in the study. Demographic data of both groups were summarized in **Table 1**. In the *A. baumannii* group, PCT values were measured before 48 hours from culture, day of culture and after 48 hours from culture 1.7±3.2, 1.6±2.5 and 8.1±21.7 ng/mL, respectively, and in the *non-acinetobacter* group, same parameters were measured at the same time 7.6±9.7, 3.6±3.7 and 9.4±16.5 ng/mL respectively. In terms of PCT value in three times between two groups, there was a statistically significant difference (p=0.01, 0.04 and 0.01 respectively). The *non-acinetobacter* group had higher PCT levels than *A. baumannii* group. Other parameters CRP and WBC were examined before 48 hours from culture and day of culture; there was no statistically significant difference between two groups among these parameters (p>0.05) (**Table 2**). In *A. baumannii* group before 48 hours culture, 41.8% of patients had PCT levels lower than 0.5 ng/mL, whereas during culture day 46.0% of patients had PCT levels lower than 0.5 ng/mL. In *non-acinetobacter* group before 48 hours culture, 28% of patients had PCT levels lower than 0.5 ng/mL, whereas, during culture day, 6% of patients had PCT levels lower than 0.5 ng/mL (p=0.03). There was a positive correlation in culture day between PCT and CRP levels in *non-acinetobacter* group (p=0.02 r:0.39) while, there wasn't any correlation in the *A. baumannii* group in terms of these parameters.

Table 1. Demographic features of the patients

Characteristics	*Acinetobacter* group	Control group	p
Subjects (n)	63	33	
Sex (male/female)	39 (62%)/24 (38%)	18 (54.5%)/15 (45.5%)	0.06/0.12
Age (years)	57.9±19.8	62.2±17	0.33
Comorbidity			
None (or N/A), n (%)	14 (22%)	4 (12.1%)	0.62
Hypertension	19 (30%)	17 (51.5%)	0.35
Coronary artery disease	17 (26.9%)	12 (36.3%)	0.42
Congestive heart failure	3 (4.7%)	4 (12.1%)	0.27
Diabetes mellitus	15 (23.8%)	11 (33.3%)	0.65
Chronic obstructive pulmonary disease	9 (14.2%)	8 (24.2%)	0.06
Duration of stay in intensive care (days)	24.9±18.5	18.9±10.4	0.31
Mechanical ventilation requirement	60 (95.2%)	29 (87.8%)	0.19
Mortality (%)	43 (68.3%)	20(60.6%)	0.45
Culture specimen (n)			
ETA*, bronchial lavage	41(65%)	11 (33.3%)	0.05
Peripheral blood	22 (34.9%)	12 (36.3%)	0.61
Catheter blood	14 (22%)	10 (30.3%)	0.19

* Endotracheal aspiration

Table 2. PCT, CRP, WBC levels of the groups

	Acinetobacter group	*Non-acinetobacter* group	p
PCTpre48	1.6±2.5	3.6 ±3.7	0.04
PCTx	1.7±3.2	7.6±9.7	0.01
PCTpost48	8.1±21.7	9.4±16.5	0.01
Median values			
WBCpre48	9.6 (0.25-45.5)	11.1 (3.20-32.7)	P>0.05
WBCpre24	10.5 (0.16-32.2)	11.1 (3-29.8)	P>0.05
WBCx	10.2 (0.34-27.6)	10.3 (1.24-30.9)	p>0.05
CRPpre48	94.5 (8-323)	99.7 (2.7-386)	p>0.05
CRPx	93.7 (4.5-400)	122 (13.4-400)	p>0.05
PCTpre48	0.75 (0.05-12.4)	2.09 (0.1-11.57)	p>0.05
PCTx	0.54 (0.04-20.1)	3.07 (0.05-32.7)	p>0.05

WBC: White blood cell, $\times 10^3/\mu L$ CRP=C-reactive protein (0-5 mg/L), PCT: Procalcitonin (0-0.5 ng/ mL) Pre48: 48 hours before culture day, x: culture day, post48: 48 hours after culture day. Data are presented as mean±SD and median (min-max).

Antibiotic susceptibility pattern of all patients in *A. baumannii* group showed multidrug resistance including carbapenems.

When the groups were compared in terms of bacteremia as considered culture results and septic shock, less bacteremia and more septic shock were observed in *A. baumannii* group (*A. baumannii* group, 57.1%, 65.0%; *non-acinetobacter* group 66.6%, 51.5% respectively.)

The most common comorbid conditions in both groups were diabetes mellitus, hypertension and coronary artery disease. There was no significant difference between the groups in terms of comorbid diseases (p>0.05) (**Table 1**).

According to the initiation of colistin (polymyxin E), patients with *A. baumannii* growing in their culture were divided into four groups. Group 1 was not administered any colistin (n:18), group 2 colistin was administered before 48-hour from culture (n:9), the third one was administered culture day, and up to 48-hour after culture (n:15) and the last group was administered after 48-hour from culture (n:21). There wasn't any statistically significant difference among groups in terms of PCT levels before 48-hour culture and culture day (p>0.05)

DISCUSSION

Procalcitonin, which is one of the proinflammatory markers expected to increase in bacterial infections (1). This presented study revealed that there was a less expected increase in *A. baumannii* infections compared to other agents. PCT was not a predictive marker for a new and resistant infection in patients with clinically and radiologically progressive in ICU according to this study findings. In a consensus report, clinical, radiological findings were reported as more critical than pro-inflammatory markers (1). To our knowledge, there wasn't any study about procalcitonin levels in *Acinetobacter* infections, in the literature.

In the presence of bacterial infection, PCT is produced in by the macrophage and monocytic cells throughout the body, especially in the liver, lung, and intestine (7). Its diagnostic and predictive value decreases in patients with severe sepsis (8). In a study, patients with procalcitonin levels below 0.25 were less likely to have an infection and recommended antibiotic discontinuation, Similarly, if procalcitonin level is between 0.25 and 0.5 mg/L, bacterial infection was unlikely while in this study, 25% of patients with *A. baumannii* infection had a lower PCT level below 0.25 mg/l, additional 20% of patients with *A. baumannii* buster had PCT levels between 0.25-0.5 mg/l (9). Choe et al. (10) demonstrated that the PCT was tending to increase in bacteremia and initial septic shock, while PCT levels were lower in local infections such as pneumonia. PCT concentrations should be interpreted differently depending on the source of infection. In a study showed that significantly higher PCT levels were found in patients with *Escherichia*, *Klebsiella* and Pseudomonas in blood cultures (11). The presented study showed that low PCT levels in *A. baumannii* group might be related that more local infections and septic shock were detected in that group.

Procalcitonin is used as a predictor marker for starting antibiotics in first studies (12). Some studies suggested that PCT is a useful marker for early sepsis while others did not offer as a criterion for starting antibiotics in terms of ventilator associated pneumonia (13,14). Also PCT for reduced antibiotic exposure in ventilator-associated pneumonia a randomised study (15). In a similar study, antibiotics were discontinued according to PCT levels, and they revealed that significantly lower antibiotic consumption and significantly lower 28-day and 1-year mortality rates (16). This study suggested that PCT is not suitable to start or stop antibiotics in patients with *A. baumannii* infections due to lower levels of PCT and low, an increasing trend. Furthermore, in the *A. baumannii* group, there was no significant difference in PCT levels between patients who had not started colistin, and who had started colistin before, during and after culture. For these reasons, the PCT may be not a useful marker for *A. baumannii* infections.

This study has some limitations such as relatively low number of patients and retrospective study. If the study was prospective, PCT levels could be measured more often, perhaps a specific cut-off value could be determined and factors affecting PCT would be better recorded such as antibiotics, drugs, or source of bacterial growth. If the culture results were more detailed, the agent specific PCT cut-off value might have been determined.

CONCLUSION

The fact that PCT levels do not show the expected increase in severe infections caused by *A. baumannii*, as in other agents, suggests that PCT is not a useful marker for *A. baumannii* infections. Since there was no significant difference between PCT levels in *A. baumannii* infections with and without empirical antibiotics, the predictive value of antibiotic initiation and discontinuation was poor. Further studies are needed for the importance and predictive value of PCT.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of local Ethics Committee of Erciyes University (Permission granted: 05.12.2018, Decision no: 2018/617).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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