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Research Paper

Procalcitonin and C-reactive protein in differantiating to contamination from bacteremia

Lutfiye Oksuz[1], Ayper Somer[2], Nuran Salman[2], Osman Erk[3], Nezahat Gurler[1]

[1]Istanbul Faculty of Medicine, Department of Medical Microbiology, Istanbul, Turkey.
[2]Istanbul Faculty of Medicine, Department of Pediatric Infectious Diseases, Istanbul, Turkey.
[3]Istanbul Faculty of Medicine, Department of Emergency Internal Medicine, Istanbul, Turkey.

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Abstract

Procalcitonin (PCT) and C-reactive protein (CRP) are important biological markers used in the diagnosis of severe infections. The aim of this study was to evaluate the consistency of blood culture with PCT and CRP in differentiating contamination and non-bacteremia from true bacteremia. In this study blood samples were obtained from 809 febrile patients and analyzed using BACTEC 9120 system. All of positive blood cultures were performed Gram staining. The microorganisms were identified with conventional methods and automated systems. Antibiotic susceptibility tests were made by disc diffusion. PCT levels were analyzed by mini VIDAS device and PCT kit. PCT and CRP levels were analyzed with blood cultures in same times. Kruskal Wallis test, Mann-Whitney U test, Spearman's rho test and ROC curve were used for statistical analyses. The bacteremia group was found to be significantly different from non-bacteremia group and contamination group in terms of both PCT and CRP ($p<0.0001$). The p values of PCT and CRP in differentiating bacteremia from non-bacteremia were $p<0.001$ for PCT, $p=0.002$ for CRP and in differentiating bacteremia from contamination were $p<0.001$ for PCT, $p<0.001$ for CRP. PCT is a more useful marker than CRP in the differentiating of true bacteremia from contamination according to the results of this study.

Key words: Procalcitonin, C-reactive protein, bacteremia, blood cultures, contamination.

Introduction

Microbiological diagnosis in the patients with bacteremia is important for effective antimicrobial therapy (Llewelyn *et al.*, 2001). Although blood culture is known as the gold standard for the diagnosis of bacteremia, there are some problems, such as differentiating true infection from contamination, interpreting of the results of polymicrobial culture, interpreting the importance of microorganisms that normally has low virulence, etc (Cohen *et al.*, 2004). Necessary treatment can be rapidly started in case contamination is differentiated from bacteremia, unnecessary antibiotic use can be prevented in case of contamination, and resistance can be prevented by decreasing selective pressure on microorganisms (Schuetz *et al.*, 2007). Considering the necessity of experienced staff and long time for blood culture together with false negative and false positive results, a fast, sensitive and specific biological marker is needed for the identification of bacteremia. PCT and CRP are being widely used for this purpose in the recent years (Sakr *et al.*, 2008; Jeong *et al.*, 2012).

PCT is the precursor of calcitonin hormone and is normally produced by C cell of thyroid gland, as well as by certain cell types in response to infection. Some of the strongest inducers of PCT include inflammatory cytokines (TNF-α, IL-6, IL-2) and bacterial endotoxins and exotoxins (Kristoffersen *et al.*, 2009). PCT is considered to be a quite specific marker of severe bacterial infection in the patients with suspicious sepsis/bacteremia (Sakr Y *et al.*, 2008; Bouadma *et al.*, 2010). Comparing with widely used laboratory parameters, PCT has higher diagnostic accuracy (Schuetz *et al.*, 2007). Increasing in plasma PCT concentration occurs within post-infection 2-4 hours and continues until appropriate treatment is initiated or the infection is

Send correspondence to L. Oksuz. Istanbul Faculty of Medicine, Department of Medical Microbiology, Capa-34093 Istanbul, Turkey. E-mail: loksuz34@yahoo.com.

taken under control. Half-life of plasma PCT is approximately 24 hours (Kristoffersen *et al.*, 2009). CRP is an acute phase reactant known to respond to inflammation, infection and tissue injury (de Beer *et al.*, 1982). Increasings in PCT level in bacterial infections occurs faster than CRP. Whilst CRP is increased also in viral infections, PCT is increased in only bacterial infections (van Rossum *et al.*, 2004). Chronic non-bacterial infections, autoimmune diseases and other systemic diseases (vasculitis, SLE, etc.), and non-infectious and neoplastic diseases do not induce PCT, thus do not increase plasma PCT concentrations (Meisner M, 2000).

This prospective study aimed to investigation the consistency of blood culture with PCT and CRP, diagnostic performance of PCT and CRP, whether they are able to differentiate bacteremia from non-bacteremia, and difference in PCT and CRP in Gram positive and Gram negative bacteremia.

Methods

Blood samples were obtained from febrile patients (> 37 °C) in an 8-month period between November 2011 and June 2012. Blood samples taken from each patient were separated into two tubes (one was aerobic and the other one was anaerobic) and analyzed using BACTEC 9120 system (Beckton Dickinson, USA). In study, the term "bacteremia group" was used for positive blood cultures and the term "nonbacteremia group" for negative blood cultures. Positive blood cultures were inoculated in 5% sheep-blood and chocolated agars and were incubated on 35-37 °C in seven days. Gram staining, morphology of the colony, biochemical tests and automatic identification systems (API and VITEK 2 systems, bioMerieux, France), when needed, are used for bacterial identification. Antibiotic susceptibility tests were performed by disc diffusion in accordance with the recommendations of Clinical Laboratory Standards Institute (CLSI, 2011). Blood cultures without any growth at the end of 7^{th} day were considered negative. Isolation of microorganisms of skin flora (coagulase negative staphylococcus-CNS, *Corynebacterium spp*, viridans streptococcus, etc.), which have grown in a single blood culture bottle, was considered as contamination. Diagnosis of CNS-related bacteremia was done based on the isolation of strains from two blood cultures taken at two different times and their having similar antibiograms (Baron, 2005; Hall *et al.*, 2006; CLSI, 2007).

PCT concentration was analyzed by mini VIDAS device and PCT kit (bioMerieux, France) and CRP level was analyzed via Beckman Coulter AU Analyzer (USA) in blood samples taken simultaneously with blood cultures. Accepted cut-off values for PCT and CRP were 0.5 ng/mL and 5 mg/dL respectively. The lowest detection values for PCT and CRP were in turn 0.05 ng/mL and 0.05 mg/dL. Since the data have not been distributed normally, non-parametric Kruskal Wallis test was used for statistical analysis. Paired comparisons were done using Mann-Whitney U test and correlations were done using Spearman's rho test. ROC curve was used to determine diagnostic value of PCT and CRP. In statistical analyses, p values of 0.05 and lower were considered significant.

Results

Patients were divided into three groups according to the results of blood culture: Group 1; bacteremia group with positive blood culture (n = 88), Group 2; non-bacteremia group with negative blood culture (n = 672) and Group 3; contaminated blood culture group (n = 49). Bacteremia group was further divided into three subgroups: Gram positive bacteria (n = 35), Gram negative bacteria (n = 49), and yeasts (n = 4). Age ranged between 19 and 92 years and the mean age was 52.22 ± 17.86 years in adults, whereas the age ranged between 3 months and 18 years and the mean age was 6.34 ± 5.57 years in children.

Demographic and clinical data of pediatric and adult patients are demonstrated in Table 1 and microorganisms isolated in bacteremia and contamination groups are demonstrated in Table 2 and 3. Since the number of pediatric patients and ratio of bacteremia were low, statistical analyses of these patients were evaluated together with that of the adults. A total of 809 patients from all groups underwent statistical analysis. Median, minimum and maximum PCT and CRP values according to the groups are demonstrated in Table 4. Both PCT and CRP were found significantly different in bacteremia group *vs.* non-bacteremia group ($p < 0.0001$). There was a difference between Gram positive and Gram negative bacteremia in terms of both PCT and CRP in the bacteremia group, but the difference was not statistically significant ($p = 0.138$ for PCT and $p = 0.959$ for CRP) (Table 5). Evaluating PCT and CRP according to Kruskal Wallis test, at least one of the three groups was found different from the others ($p < 0.001$). Based on Post-hoc tests performed after Kruskal Wallis test, Group 1 was found to be significantly different from Group 2 and Group 3 in terms of both PCT and CRP ($p < 0.0001$). Evaluating the difference between the groups according to Mann-Whitney U test with Bonferroni correction (0.05/3 = 0.0166), statistically significant difference was found between Group 1 and Group 2 ($p < 0.0001$ for PCT and $p < 0.002$ for CRP) and between Group 1 and Group 3 ($p < 0.0001$ both for PCT and CRP). Both PCT and CRP were found significantly different in bacteremia group *vs.* non-bacteremia and contamination groups. Correlation between PCT and CRP according to Spearman's rho test revealed that, $r = 0.492$ and $p < 0.0001$ in bacteremia group (n = 88), $r = 0.442$ and $p < 0.0001$ in non-bacteremia group (n = 672), and $r = 0.422$ and $p = 0.003$ in contamination group (n = 49). A positive and extremely significant correlation was found between PCT and CRP in all three groups

Table 1 - The demografic and clinical characteristics of the patients.

Characteristics	Pediatric patients	Adult patients
The number of the patients	148	661
The age intervals of the patients	3 months-18 years	19-92 years
The median ages of the patients (years)	6.34 ± 5.57	52.22 ± 17.86
The number of bacteremic patients	11 (7.4%)	77 (11.6%)
The isolated microorganisms:		
Gram positives	6 (4%)	29 (4%)
Gram negatives	5 (3%)	44 (7%)
Fungi		4
The number of nonbacteremic patients	119 (80.4%)	553 (84%)
The number of contamined blood culture	18 (12.1%)	31 (4.6%)
Clinical conditions:		
Malignancy	30%	18%
Pulmoner disease	17%	17%
Renal disease	6%	11%
Congenital disorder	7%	
Metabolic disorder	6%	
Hematolojic disease	5%	2%
Epilepsy	5%	
Rheumatologic disease	1%	2%
Cardiovascular disease		11%
Pelvic disease		14%
Other diseases	23%	25%

Table 2 - The values of median, minimum and maximum of PCT and CRP

	Median (min-max)	
Groups	PCT (ng/mL)	CRP (mg/dL)
Bacteremia (Group 1) (n = 88)	1.25 (0.05-157.7)	93 (0-594)
Nonbacteremia (Group 2) (n = 672)	0.20 (0.05-114.63)	64 (0-715)
Contamination (Group 3) (n = 49)	0.08 (0.05-6.77)	19 (0-331)

Table 3 - The values of median, minimum and maximum of PCT and CRP for Gram positive bacteria, for Gram negative bacteria and for fungi in bacteremia group.

Bacteremia group (Group 1)	Median (min-max)	
	PCT (ng/mL)	CRP (mg/dL)
Gram positive bacteria (n = 35)	0.94 (0.05-103.15)	92 (0-552)
Gram negative bacteria (n = 49)	1.94 (0.05-157.73)	99 (3-594)
Fungi (n = 4)	0.43 (0.16-5.97)	70 (58-119)
p value	p = 0.174	p = 0.866

($p < 0.001$). PCT AUC was 0.755 (95% CI: 0.705-0.805) and CRP AUC was 0.601 (95% CI: 0.538-0.665) in differentiating bacteremia from non-bacteremia, and significance was $p < 0.001$ for PCT and $p = 0.002$ for CRP. PCT AUC was 0.864 (95% CI: 0.799-0.929) and CRP AUC was 0.744 (95% CI: 0.652-0.835) in differentiating bacteremia from contamination, and significance was $p < 0.001$ for PCT and $p < 0.001$ for CRP. It was found that both PCT and CRP can be used in differentiating the groups but PCT is more effective than CRP in differentiating bacteremia from both non-bacteremia and contamination (Figure 1 and Figure 2). When a cut-off value of 0.5 ng/mL was used for PCT and 5 mg/dL was used for CRP, sensitivity and specificity were 68.2% and 66.4% respectively for PCT and 93.2% and 9.5% respectively for CRP (Table 6).

Discussion

Both CRP and PCT are being used for a long time as biological markers for the diagnosis of severe infections. Whilst CRP is elevated in case of infection, inflammation and tissue damage, PCT is elevated only in bacterial infections (Pepys *et al.*, 2003; Sakr *et al.*, 2008; Jeong *et al.*, 2012). Since bacteria account for more than 90% of bacteremia cases, the use of PCT for the diagnosis of bacteremia seems more realistic (Llewelyn *et al.*, 2001). Although blood culture is known as the gold standard in detecting bacteremia, 24-48 hours are required for the results; thus, initiation of antibiotherapy is delayed (Riedel *et al.*, 2011; Jeong *et al.*, 2012). In addition, the present study was planned also considering that contamination, which is one of the most important problems encountered in evaluation of blood cultures, could be differentiated from bacteremia by the changes in PCT values.

Despite numerous studies that demonstrate the superiority of PCT over CRP in diagnosing bacteremia (Giamarellou *et al.*, 2004; Jimeno *et al.*, 2004; von Lilienfeld-Toal *et al.*, 2006; Schuttrumpf *et al.*, 2006), there are a few studies that investigate the relation between PCT and contaminated blood cultures (Schuetz *et al.*, 2007; Jeong *et al.*, 2012). The present study investigated the efficacy of PCT and CRP in differentiating true bacteremia from contamination and non-bacteremia. Based on our results, PCT is able to differentiate bacteremia from both non-bacteremia and contamination. Thus, decision for the initiation of antibiotherapy would be made in a short time owing to the fact that PCT is able to differentiate contaminated blood cultures from true bacteremia or unnecessary antibiotic use would be prevented. Followings are the favorable consequences of this: both resistance to antibiotics would be decreased, patients would be prevented against toxic effects of antibiotics, and economy of both the hospital and the country would have been protected (von Lilienfeld-Toal *et al.*, 2006; Schuetz *et al.*, 2011).

Many studies have reported higher PCT values in Gram negative bacteremia *vs.* Gram positive bacteremia

Table 4 - The number of Gram positive bacteria, Gram negative bacteria and fungi in bacteremia group (n).

Bacteremia group	Isolated microorganisms	Pediatric patients (n)	Adult patients (n)	Total
Gram positives	Methicillin-susceptible *Staphylococcus aureus*	1	14	15
	Methicillin-resistant coagulase negative staphylococci	4	1	5
	Methicillin-resistant *Staphylococcus aureus*		1	1
	Streptococcus pyogenes		3	3
	Enterococcus spp		6	6
	Corynbacterium striatum		1	1
	Streptococcus pneumoniae	1	2	3
	Listeria monocytogenes		1	1
Gram negatives	*Escherichia coli*		19	19
	Klebsiella pneumoniae	1	8	9
	Enterobacter spp		4	4
	Pseudomonas spp	1	6	7
	Pantoea spp	1		1
	Serratia spp	1		1
	Salmonella spp	1		1
	Proteus spp		1	1
	A.cinetobacter spp		2	2
	Haemophilus influenzae		2	2
	Bacteroides fragilis		1	1
	Brucella spp		1	1
Fungi	*Candida* spp		4	4
Total		11	77	88

Table 5 - The number of the isolated microorganisms in contamination group (n).

Contamination group	Isolated microorganisms	Pediatric patients(n)	Adult patients(n)	Total
	Methicillin resistant-coagulase negative staphylococci	14	17	31
	Methicillin susceptible-coagulase negative staphylococci	2	10	12
	Difteroid basil		3	3
	Alfa hemolytic streptococci	1	1	2
	Bacillus spp	1		1
	Total	18	31	49

Table 6 - The sensitivity, specifity, positive and negative predictive values of PCT and CRP.

	Cut off value	Sensitivity	Specifity	Positive predictive value	Negative predictive value
PCT	0.5 ng/mL	68.2	66.4	20.9	94.1
CRP	5 mg/dL	93.2	9.5	11.8	91.4

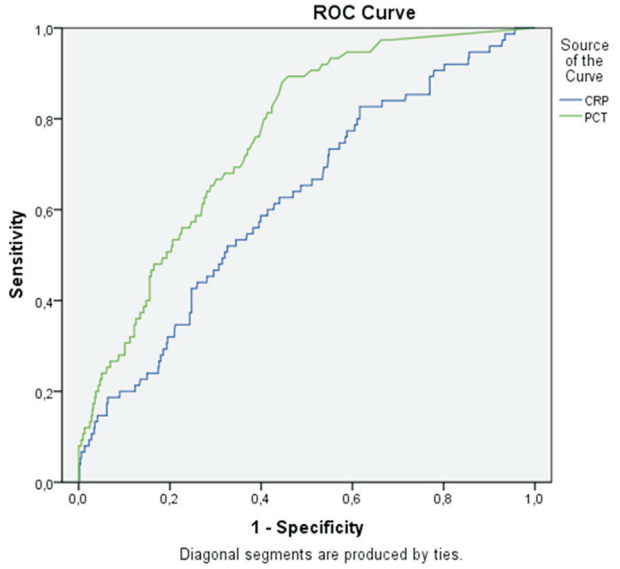

Figure 1 - The ROC curve of the PCT and CRP for discriminating between bacteremia group and non bacteremia group.

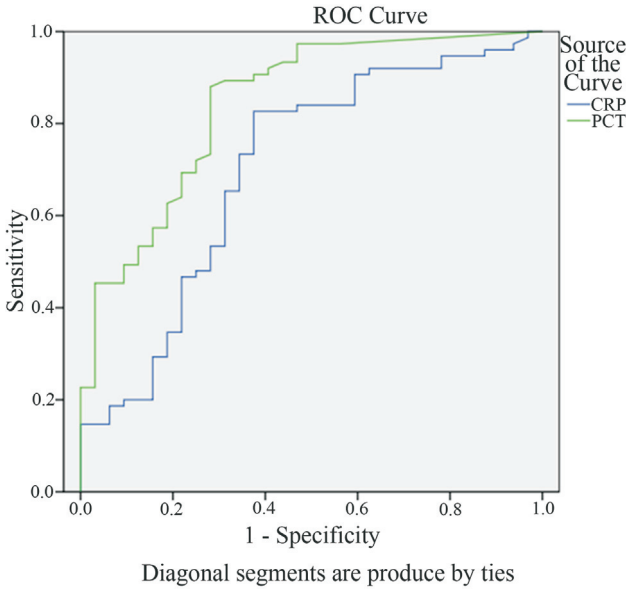

Figure 2 - The ROC curve of the PCT and CRP for discriminating between bacteremia group and contamination group.

(Engel *et al.*, 1999; Svaldi *et al.*, 2001; Jeong *et al.*, 2012). However, some studies (Al-Nawas *et al.*, 1996; Giamarellos-Bourboulis *et al.*, 2001; von Lilienfeld-Toal *et al.*, 2004) reported similar levels of PCT in Gram negative and Gram positive bacteremia. The present study failed to demonstrate statistically significant difference between Gram negative and Gram positive bacteremia in terms of PCT levels. This might have been resulted from various conditions. Bacteria such as *Brucella spp, H.influenze,* and *B.fragilis*, which have been isolated from the patients with Gram negative bacteremia and low PCT, are the microorganisms that grow late and difficult thereby induce PCT late. Moreover, there are patients with high PCT level and died before detection of any infectious agent other than contaminating bacteria. The blood samples might also have been obtained in early phase of infection.

In the recent years, there are numerous studies expressing that PCT is beneficial not only in defining bacterial infection, but also in determining the severity of underlying disease, guiding treatment, and predicting the result. Meta analyses suggest that PCT is superior over CRP in differentiating bacterial infection from other causes of infection in critical patients (Sakr *et al.*, 2008). Similar with the results of the studies conducted by Engel *et al.*, 1999 and Sakr *et al.*, 2008 the present study as well demonstrated that PCT is more effective than CRP in differentiating bacteremia from non-bacteremia. In a meta-analysis Simon *et al.*, 2004 reviewed 351 researches and reported that PCT has higher diagnostic accuracy as compared to CRP. Giamarellou *et al.* (2004) reported that PCT is a helpful marker for the clinician in detecting severe sepsis, bacteremia and local infection but bacteremia due to CNS does not increase the level of PCT. This might have resulted from the authors' considering every grown bacterium as an agent without differentiating CNS contamination from true bacteremia. Fleischhack *et al.* (2000) reported PCT was a more beneficial diagnostic parameter than CRP in cancer patients. Secmeer *et al.* (2007) reported that PCT, when measured periodically, was a more useful diagnostic parameter than CRP in pediatric neutropenic-fever patients. Von Lilienfeld-Toal *et al.* (2004) reported that PCT is a more reliable marker than CRP in predicting bacteremia in the patients with febrile neutropenia. In addition to the studies reporting high PCT levels in bacteremia (Giamarellou *et al.*, 2004; Jimeno *et al.*, 2004; von Lilienfeld-Toal *et al.*, 2006; Schuttrumpf *et al.*, 2006), there are studies defending just the opposite. de Bont *et al.* (2000) reported that PCT level showed no difference between bacteremia/sepsis group and the group with unknown fever among the patients with neutropenic fever but that there was significant difference in terms of CRP level.

In the present study, PCT AUC value was 0.755 in differentiating bacteremia from non-bacteremia. Jeong *et al.* (2012), Bossink *et al.* (1999) and Kim *et al.* (2011) obtained similar results (respectively; 0.76; 0.70; 0.77) with that of the present study. The present study found PCT ROC-AUC value to be 0.86 in differentiating bacteremia from contamination. This is exactly the same with the result of the study conducted by Jeong *et al.* (2012).

Based on the recommendations of manufacturer company, when a cut-off value of 0.5 ng/mL was used for PCT, sensitivity, specificity, and positive and negative predictive values were 68.2%, 66.4%, 20.9%, and 94.1% respectively. Other studies have found similar values for PCT (Kim *et al.*, 2011; Jeong *et al.*, 2012). Kim *et al.* (2011) used a cut-off value of 0.4 ng/mL and reached to a negative predic-

tive value of 95.4% and found that bacteremia could be excluded at a PCT level under 0.4 ng/mL. Likewise, the present study found that bacteremia could be excluded with an accuracy rate of 94.1% at a PCT level under 0.5 ng/mL. Using a cut-off value of 5 mg/dL, the sensitivity, specificity, and positive and negative predictive values for CRP were 93.2%, 9.5%, 11.8%, and 91.4% respectively. Low specificity of CRP despite high sensitivity might be explained by the variety of reasons other than bacteremia by which the CRP level is increased.

One of the unfavorable situations in the present study is high levels of PCT found in some patients of nonbacteremia group leading to a decrease in positive predictive value and specificity of PCT. It has been reported that high PCT levels might be explained by likely use of antibiotics or drugs that stimulate the release of proinflammatory cytokines, massive cell death, or probable failure in defining causative microorganism (Pihusch *et al.*, 2006; Schuetz *et al.*, 2011). It has been suggested that other clinical conditions may be in question in the patients with high PCT levels, or PCT may be induced by other reasons than bacteremia (pancreatitis, severe trauma, hepatic or renal disease, permanent shock and multi-organ failure, etc.) (Jeong *et al.*, 2012). It has been also reported that PCT may be elevated in medullary thyroid carcinoma, small-cell lung carcinoma, and carcinoid tumors (Becker *et al.*, 2008). In this study, malignancy was detected by 30% in pediatric patients and by 18% in adult patients. Renal disease was present by 6% in pediatric patients and by 11% in adult patients.

The present study displayed that PCT is more beneficial than CRP in diagnosing and excluding bacteremia. Moreover, PCT is more beneficial than CRP also in differentiating bacteremia from contamination. No statistically significant difference was found between Gram positive and Gram negative bacteria in the bacteremia group in terms of both PCT and CRP. Based on the results of this present study, early antibiotherapy can be initiated depending on PCT result, which is measured concurrently with blood culture.

In conclusion, PCT is a more useful parameter than CRP in differentiating bacteremia from contamination and nonbacteremia in febril patients.

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Ethical Consideration

This project was approved by the Ethical Commitee of Clinical Researches of Istanbul Faculty of Medicine (2010/805-260).

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