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

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Submitted: October 22, 2013; Approved: April 17, 2014.

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; Boudama 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
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 chocolate 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 7th 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.
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 (Giamarello et al., 2004; Jimeno et al., 2004; von Lilienfeld-Toal et al., 2006; Schuttermpf 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 1 - The demographic 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 contaminated blood culture | 18 (12.1%) | 31 (4.6%) |

| Table 2 - The values of median, minimum and maximum of PCT and CRP |
|-----------------|-----------------|
| 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) | 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 (0.05-157.7) | 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).
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      |                        |                    |       |
|                  | Streptococcus pyogenes                           |                        |                    |       |
|                  | Enterococcus spp                                 |                        |                    |       |
|                  | Corynbacterium striatum                          |                        |                    |       |
|                  | Streptococcus pneumoniae                         |                        |                    |       |
|                  | Listeria monocyogenes                            |                        |                    |       |
| Gram negatives   | Escherichia coli                                 | 1                      | 19                 | 20    |
|                  | Klebsiella pneumoniae                            | 1                      | 8                  | 9     |
|                  | Enterobacter spp                                 |                        |                    |       |
|                  | Pseudomonas spp                                  |                        |                    |       |
|                  | Pantoea spp                                      | 1                      | 1                  | 1     |
|                  | Serratia spp                                     | 1                      | 1                  | 1     |
|                  | Salmonella spp                                   | 1                      | 1                  | 1     |
|                  | Proteus spp                                      | 1                      | 1                  | 1     |
|                  | A.cinetobacter spp                               | 2                      | 2                  | 4     |
|                  | Haemophilus influenzae                           | 2                      | 2                  | 4     |
|                  | Bacteroides fragilis                             | 1                      | 1                  | 1     |
|                  | Brucella spp                                     | 1                      | 1                  | 1     |
| Fungi            | Candida spp                                      | 4                      | 4                  | 8     |
| 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         |                        |                    |       |
|                     | Haemophilus influenzae  |                        |                    |       |
|                     | Alfa hemolytic streptococci | 1                      | 1                  | 2     |
|                     | Bacillus spp            | 1                      | 1                  | 1     |
| Total               |                                                      | 18                     | 31                 | 49    |

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

|                  | Cut off value | Sensitivity | Specificity | 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                       |
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.influenzae, 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. Giamarello 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. Seeme 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 (Giamarellos-Bourboulis 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.

A part of this study was presented in 23rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) in Berlin-Germany on April 27-30, 2013 (R2744).

Acknowledgement

This study was supported by the Research Fund of Istanbul University (Project Number: 2010/7541). The authors would like to thank to Mr Kamber KASALI, MSc, from Department of Biostatistics and Medical Informatics, Istanbul Faculty of Medicine for helpful studies on statistical analyses.

Ethical Consideration

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

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