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Evaluation of the Clinical Performance of an Automated Procalcitonin Assay for the Quantitative Detection of Bloodstream Infection

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Background : Bloodstream infection (BSI) is associated with a high mortality rate. Since the origin of infection is demonstrated in approximately 2/3rds of cases, early and established biomarkers are warranted. We evaluated the clinical performances of automated procalcitonin (PCT) and C-reactive protein (CRP) assays for the quantitative detection of BSI. Analytical performance of the VIDAS® B·R·A·H·M·S PCT assay (bioMérieux, France) was assessed and also compared with the semi-quantitative PCT-Q test (B·R·A·H·M·S Aktiengesellschaft, Germany).

Methods : We prospectively included consecutive patients divided into 3 groups at the Dong-A University Medical Center. Patients were categorized according to the criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM), and also on the basis of catheter-associated bacteremia.

Results : A total 77 patients were enrolled. All mean values of PCT and PCT-Q were consistent with the reference value. Measured PCT concentrations showed good linearity (r=0.983). The between-run, within-run, and total imprecisions were below 5%. The PCT levels in gram-negative bacteremia were significantly higher than those in gram-positive bacteremia. Furthermore, the PCT concentrations were significantly different among non-infection, bacteremia, sepsis, severe sepsis, and septic shock groups. Our study showed that PCT >0.3 ng/mL had 95.0% sensitivity and 97.3% specificity, whereas CRP >5.46 mg/dL had 85.0% sensitivity and 86.5% specificity for diagnosing sepsis.

Conclusions : We suggest that, compared with CRP, PCT is a better diagnostic and discriminative biomarker of sepsis categorized according to the ACCP/SCCM. Moreover, catheter-associated bacteremia could be discriminated from sepsis using PCT concentration. *(Korean J Lab Med 2010; 30:153-9)*

Key Words : *Procalcitonin, C-reactive protein, Sepsis, Bacteremia*

INTRODUCTION

Bloodstream infection (BSI) is associated with a high mortality rate of between 10% and 29% [1, 2]. Early diagnosis of BSI and prompt appropriate treatment lead to reduce morbidity and mortality [3, 4]. Although blood culture is the best method for the diagnosis of BSI, the test results are not rapidly available. Furthermore, since the origin of infection is only demonstrated in approximately 2/3rds of cases [5], early and established biomarkers are warranted for diagnosis, prognosis, and monitoring response to therapy.

Host response biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) are now being recognized as useful tools in the diagnostic process [5]. The most common biomarker is CRP, an acute-phase protein released by the liver after proinflammatory cytokine release. The CRP concentration rises within 24 hr of infection and is

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elevated in almost all cases of microbial infection; however, its reliability as a marker of infection is hampered by a very low specificity [6]. As another potentially specific biomarker of BSI, serum PCT, a 116-amino acid polypeptide, has been found to be low in the serum of healthy humans but elevated in persons suffering from severe infections, particularly sepsis [7].

The PCT assay used in prior studies had limited functional sensitivity of 0.3 ng/mL; however, a new automated rapid quantitative assay, the VIDAS® B·R·A·H·M·S PCT assay (bioMérieux, Lyon, France), is fully adapted for emergency conditions. This assay is based on an enzyme-linked fluorescent immunoassay (ELFA) and according to the manufacturers has a functional sensitivity of 0.09 ng/mL. A further assay, the BRAHMS PCT-Q (B·R·A·H·M·S Aktiengesellschaft, Hennigsdorf, Germany), is an immunochromatographic test for the semi-quantitative detection of PCT and is also easy to use under emergency conditions.

We evaluated the clinical performance of the automated quantitative PCT assay and a high sensitivity CRP assay for the quantitative detection of BSI. Analytical performance parameters of the VIDAS® B·R·A·H·M·S PCT assay, including normal value, linearity, and precision, were assessed and compared with those of the semi-quantitative PCT-Q test.

MATERIALS AND METHODS

We prospectively included consecutive patients divided into 3 groups at the Dong-A University Medical Center from September 2008 to February 2009 (Fig. 1). Group I included normal healthy subjects with no apparent clinical symptoms of infection; group II included all patients with blood cultures collected consecutively at the emergency department; and group III included those with blood cultures collected in the emergency department and general wards. Polymicrobial cultures and 1 positive for the same pathogen among 2 or 3 sets were excluded. Patients receiving antibiotic treatment prior to blood culture collection were excluded from the analysis. Prior to enrollment in this study, informed consent was obtained from all subjects in accordance with the guidelines of the Institutional Review Board.

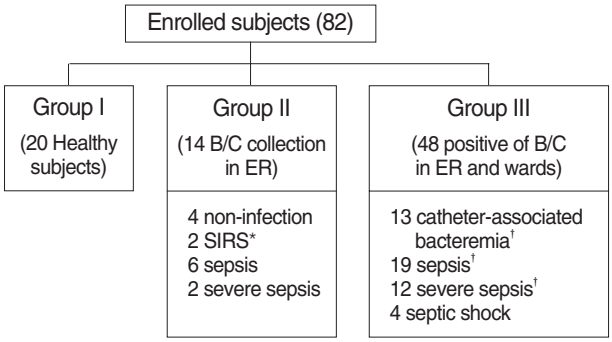

Fig. 1. Flow diagram of the subjects included in this study.
*The 2 SIRS patients were not included in this study since the sample size was too small for analysis. †Includes 3 patients receiving antibiotic treatment before blood culture collection.
Abbreviations: B/C, blood culture; ER, emergency room; SIRS, systemic inflammatory response syndrome.

For the clinical evaluation of the PCT assay, we categorized the patients with BSI as shown in Fig. 1. Patient records were reviewed in both groups II and III using a standardized data collection form to retrieve demographic, clinical, microbiological, radiographic, and laboratory data, including systemic inflammatory response syndrome (SIRS) criteria, the number and site (e.g., central or peripheral) of positive blood cultures, and the total sets of collected blood cultures. Patients were categorized into non-infection, SIRS, sepsis, severe sepsis, and septic shock groups using the criteria of the consensus conference of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) [8]. A further group of patients who were fitted with a central intravascular device were classified as having catheter-associated bacteremia, which we defined as BSI confirmed by blood culture but without SIRS. However, we did not include 2 patients with SIRS in this study since the sample size would have been too small to be representative.

The diagnostic categories were defined as follows:

Non-infection: healthy or blood culture-negative with no SIRS.

Catheter-associated bacteremia: BSI confirmed by blood culture without SIRS in patients with a central intravascular device.

To insure true blinding with regard to the PCT values, blood samples were collected from laboratory stock on the same day as blood culture collection and stored at −20℃. At the end of the study, serum PCT and CRP were measured. Serum PCT was measured using the new automated enzyme-linked fluorescent immunoassay reagent, VIDAS® B·R·A·H·M·S PCT. High-sensitivity CRP was measured using an immunoturbidimetric method (Toshiba, Tokyo, Japan). Blood cultures were processed using an automated colorimetric detection system, BacT/ALERT (bioMérieux, Durham, NC, USA). Bacteria and fungi were identified using the VITEK 2 automated system (bioMérieux) and standard methods, as appropriate.

For the comparison of serum PCT measured using the VIDAS® PCT and PCT-Q assays, a total of 12 patients from group I and all of the patients from group II were enrolled. The BRAHMS PCT-Q test is based on immunochromatographic principles for the semi-quantitative detection of PCT [9]. At a PCT concentration greater than 0.5 ng/mL, this complex can be visualized as a reddish band. The color intensity of the band is directly proportional to the PCT concentration in the serum and corresponds to the PCT concentration ranges ≥0.5 ng/mL, ≥2.0 ng/mL, and ≥10 ng/mL, which can be determined with the help of a reference card. The validity of the test must be checked with the help of the reddish control band. Interpretation of the results, which was based on a comparison of the color density with that of a reference card, was performed by 2 persons.

To evaluate the differences among groups, the Mann-Whitney U-test or Fisher's exact test for continuous or categorical variables was used. To compare the diagnostic value of individual laboratory markers for diagnosing sepsis based on the reviews of patients clinical records, we performed a ROC analysis and calculated the respective areas under the curves (AUCs). The results are expressed as the median and 95% confidence intervals (95% CI). A *P* value of <0.05 was considered significant. All calculations were performed using the statistical softwares MedCalc version 9.2 for Windows (MedCalc Software, Mariakerke, Belgium) and SPSS for Windows (version 10.0; SPSS, Chicago, IL, USA).

RESULTS

A total of 77 patients from an original 82 patients were enrolled in the study. These patients comprised 50 men (65.1%) and 27 women (34.9%) with an average age of 59.0 yr. As shown in Fig. 1, 2 patients with SIRS and 3 patients receiving prior antibiotic treatment were excluded from the study. The remaining 77 subjects were classified as follows: non-infection (N=24), catheter-associated bacteremia (N=12), sepsis (N=24), severe sepsis (N=13), and septic shock (N=4).

1. Reference groups

Evaluation of the PCT and CRP concentrations of a reference group was based on serum taken from 20 healthy group I subjects (12 men and 8 women; average age, 48.8 yr), 12 of whom were evaluated using the PCT-Q assay. For PCT, one of the 20 sera was not consistent with the manufacturers reference value of <0.05 ng/mL. All PCT-Q values were <0.5 ng/mL, which is consistent with the reference value. The mean (95% confidence interval) of CRP was 0.0935 mg/dL (0.0591-0.1279).

2. Linearity and precision

For an evaluation of linearity, we employed a CLSI EP6-A protocol [10]. The linearity was determined using a pati-

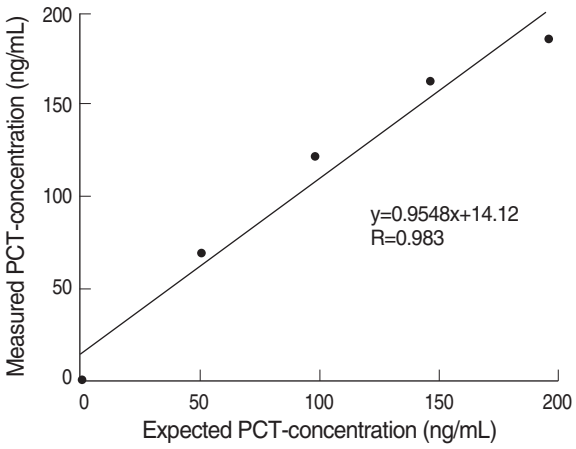

Fig. 2. Linearity of concentration in the PCT test.
Abbreviation: PCT, procalcitonin.

ent sample at a high concentration (195.53 ng/mL). This sample was diluted with PCT-negative serum pools (<0.05 ng/mL) in 4:0, 3:1, 2:2, 1:3, and 0:4 dilution steps, and then tested in duplicate. The expected value was plotted against the mean of the 2 measurements. Measured PCT concentrations showed good linearity (r=0.983) in the range from 0.05 to 195.53 ng/mL on the basis of the expected PCT concentration (Fig. 2).

For an evaluation of the between-run, within-run, and total precisions, we used a CLSI EP5-A2 protocol [11]. Two materials at a low and high concentration, respectively, were pooled from 2 calibrators (S1 and S2) and 2 controls (C1 and C2) included in the kit. Two pooled materials were tested in duplicate in 10 different runs (2 runs per day) with the same reagent lots using the same instrument (N=40). The between-run, within-run, and total CV determined by running 20 replicates were 4.2%, 1.7%, and 4.5% for the high-pooled materials and 2.5%, 2.8%, and 3.7% at the low-pooled materials, respectively.

3. Comparison of PCT values measured using the VIDAS® PCT and PCT-Q assays

Of the 28 patients in groups I (N=12) and II (N=16), agreement between the VIDAS® PCT and PCT-Q assays was observed for 22 (78.6%) and disagreement for 6 (21.4%) (Table 1). In particular, disagreements in the PCT ranges of 0.5-2 ng/mL and 2-10 ng/mL were observed in 5 (71.4%) of 7 patients and in 1 (25.0%) of 4 patients, respectively.

4. Evaluation of PCT and CRP concentrations based on 5 categories

The PCT and CRP concentrations in patients divided into the aforementioned 5 categories are shown in Fig. 3. The PCT concentrations increased in proportion to the severity of the category and enabled discrimination among the categories. Compared with CRP, the PCT concentrations were significantly different among non-infection, catheter-associated bacteremia, sepsis, severe sepsis, and septic shock categories (P<0.05).

Table 1. Comparison of procalcitonin measured using VIDAS® PCT and PCT-Q assays in 28 patients in groups I (N=12) and II (N=16)

	PCT-Q (ng/mL)				Total
	<0.5	0.5-2	2-10	≥10	
Agreement	15	2	3	2	22
Disagreement	0	5*	1†	0	6
Total	15	7	4	2	28

*PCT levels in disagreement with PCT-Q (0.05, 0.16, 0.19, 0.36, and 0.49 ng/mL). †PCT level in disagreement with PCT-Q (1.5 ng/mL).
Abbreviation: PCT, procalcitonin.

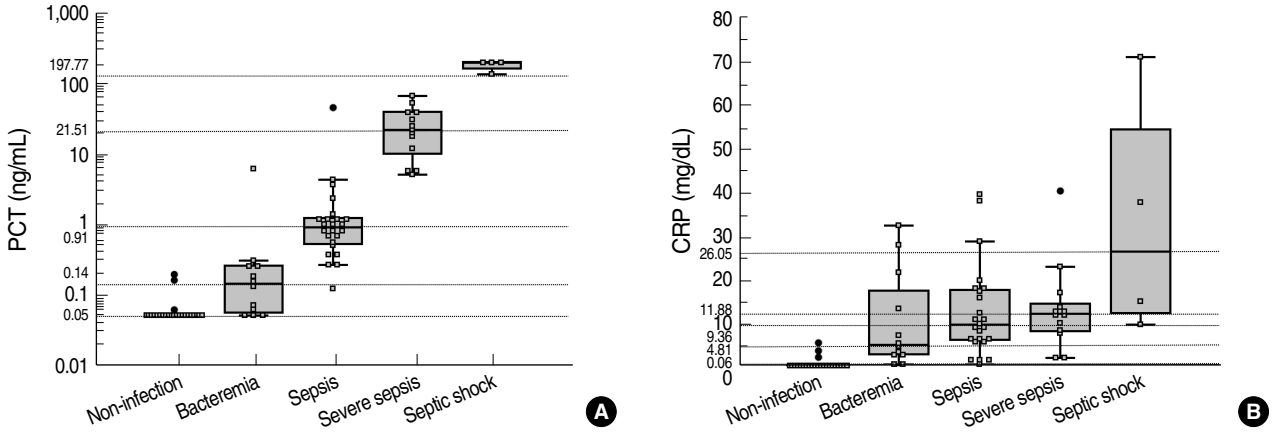

Fig. 3. Serum PCT level (A) and CRP level (B) in patients with no infection, bacteremia (catheter associated), sepsis, severe sepsis, and septic shock. Data are presented as box plots with median lines, 25- and 75-percentile boxes, and 10- and 90-percentile error bars. A log scale is used for the Y-axis in (A).
Abbreviations : PCT, procalcitonin; CRP, C-reactive protein.

5. Evaluation of PCT and CRP concentration based on isolated organisms

A total 49 organisms were isolated from the 77 patients (Table 2). Gram-positive organisms were isolated from 27 patients and gram-negative organisms isolated from 22 patients. The most common organisms were coagulase-negative staphylococci (CNS) (N=14), *Staphylococcus aureus* (N=11), and *Escherichia coli* (N=11). The PCT levels in gram-negative and gram-positive bacteremia were 0.79 ng/mL (0.25-2.11 ng/mL) and 4.96 ng/mL (0.47-35.41 ng/mL), respectively, and the PCT levels in gram-negative bacteremia were significantly higher than those in gram-positive bacteremia (P<0.05). CRP levels were, however, similar in both bacteremias.

6. Diagnostic accuracy of PCT and CRP

The ROC plots and respective AUCs for PCT and CRP in the diagnosis of sepsis are shown in Fig. 4. Respectively, sensitivities of 95.0% and 85.0% and specificities of 97.3% and 86.5% were achieved with a PCT cutoff value of 0.3 ng/mL and a CRP cutoff value of 5.46 mg/dL. The AUC for PCT was 0.982, which was significantly higher than that for CRP (0.871; P=0.003).

Table 2. Relationship of between PCT and CRP concentrations based on pathogens

Pathogen	N of patients	PCT (ng/mL)	CRP (mg/dL)
Gram- positive bacteria	27	0.79 (0.25-2.11)	8.78 (5.53-12.39)
Coagulase-negative staphylococci	14	0.63	8.30
Enterococcus faecium	1	2.30	10.6
Enterococcus fecalis	1	45.48	7.99
Staphylococcus aureus	11	0.82	8.78
Gram-negative bacteria	22	4.96 (0.47-35.41)	10.52 (2.85-14.47)
Acinetobacter baumannii complex	3	0.37	8.16
Acinetobacter junii	1	1.17	0.34
Sphingomonas paucimobilis	1	0.26	1.5
Klebsiella pneumoniae	4	29.17	25.51
Proteus mirabilis	1	200.0	14.76
Pseudomonas aeruginosa	1	1.36	17.67
Escherichia coli	11	5.70	9.48

Abbreviations: PCT, procalcitonin; CRP, C-reactive protein.

DISCUSSION

Recently, a few PCT studies using the newly introduced VIDAS® PCT assay have been reported [12, 13]. The VIDAS® PCT assay showed good correlation and concordance with the established Kryptor method [12]. In prior studies, samples were evaluated using a PCT test with a limited functional sensitivity of 0.3 ng/mL and according to obscure clinical sepsis syndrome criteria. The patients included in the present study were evaluated and diagnosed using a new automated rapid quantitative PCT measurement with a functional sensitivity of 0.09 ng/mL and based on the results of blood cultures.

PCT has been proposed as a diagnostic marker to be included in the international definition of sepsis [14], and its utility has been demonstrated in previous studies [15, 16]. From a meta-analysis in which PCT and CRP were evaluated as test markers to distinguish between bacterial infections and noninfective causes of inflammation, the pooled sensitivity and specificity of PCT markers were 88% and 81%, respectively, whereas those for CRP markers were 75% and 67%. PCT markers have a significantly higher accuracy than do CRP markers for discriminating bacterial infections from noninfective causes of inflammation [17].

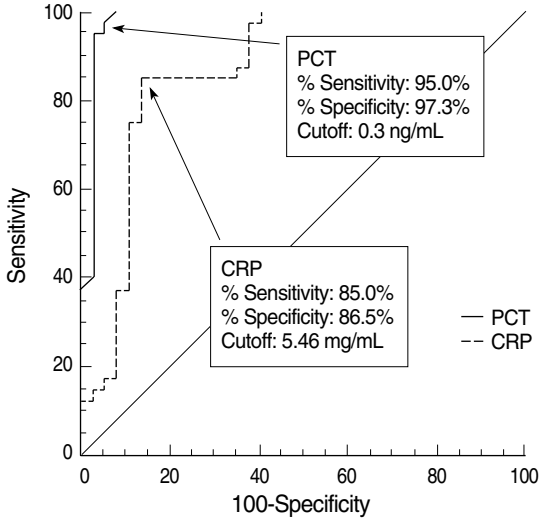

Fig. 4. The ROC curves of PCT (AUC, 0.982) and CRP (AUC, 0.871) for the diagnosis of sepsis.
Abbreviations: PCT, procalcitonin; CRP, C-reactive protein; AUC, area under the curve.

Our study showed that in terms of diagnosis, PCT >0.3 ng/mL had a sensitivity of 95.0% and a specificity of 97.3% and that CRP >5.46 mg/dL had a sensitivity of 85.0% and a specificity of 86.5%. Thus, both PCT and CRP showed good clinical sensitivity and specificity for diagnosing sepsis. However, our data also showed that PCT levels were a more sensitive and specific marker for diagnosing sepsis than were CRP levels (P=0.003).

From past meta-analysis of immunoluminometric assays, the optional cutoff values for PCT ranged from 0.6 to 5 ng/mL [18]. The most recent PCT study involving patients in an intensive care unit who were suspected of having bacteremia, to examine PCT's relationship with a blood culture or PCR reported the appropriate cutoff values of PCT for bacteremia were 0.38 μg/L [19]. Our PCT cutoff value (>0.3 ng/mL) is lower than the manufacturer's recommended value (PCT >0.5 ng/mL). From past to recent studies, the cutoff values for PCT have decreased owing to more sensitive assays, more homogeneous study design, and more evidence-based methods.

In the present study, we evaluated PCT and CRP concentrations in patients classified according to 5 categories. The PCT levels enabled significant discrimination among patients with no infection, catheter-associated bacteremia, sepsis, severe sepsis, and septic shock compared with the CRP levels (P<0.05).

Although bacterial culture is the best method for diagnosing infection, it does not indicate the host response well or differentiate between bacterial colonization and systemic bacterial infections. The early increase in PCT may reflect the colonization of the catheter with subclinical infection ultimately leading to BSI [20]. Thus, we investigated the diagnostic value of PCT as a discriminating marker for bacteremia and septicemia in patients with positive blood cultures as well as comparing it with CRP. The PCT levels in catheter-associated bacteremia (0.14 ng/mL) were significantly lower than those under septic conditions (0.91 ng/mL; P<0.01). The clinical symptoms and signs of catheter-associated bacteremia were erythema, edema, and purulent exudates around the catheter exit site, and these were not associated with SIRS. This diagnosis was confirmed microbiologically by recovery of indistinguishable microorganisms from the catheter or catheter tip and from blood culture obtained from a peripheral vein.

On analytical evaluation of PCT, the results of between-run, within-run, and total precisions on this PCT test were acceptable and the assay showed good linearity across the analytical range from 0.05 to 195.53 ng/mL. The mean PCT of the reference groups in this study was <0.051 ng/mL with a range from 0.0495 to 0.0515 ng/mL, which agrees with the information provided by the manufacturers.

Agreement between PCT measured semi-quantitatively and quantitatively was moderate. This is probably due to a subjective interpretation of the assay results. The PCT-Q concentration range is determined by comparing the color intensity of the test band with the color blocks of the reference card. We recommend using the respective reference cards supplied with each kit.

The present study suggests that PCT levels in gram-negative bacteremia could be significantly higher than those in gram-positive bacteremia, which is in accordance with a study by Charles et al. [21]. However, differences within the groups were observed; for example, more patients with catheter-associated bacteremia (N=10) had gram-positive bacteremia (N=10) than gram-negative bacteremia (N=2). Therefore, our results are suggestive rather then permitting a generalization to all patients with sepsis.

The limitations of this study were the small sample size and the heterogeneity of the patients regarding their groups and underlying diseases. Therefore, our results need to be confirmed in larger and more homogenous studies. Another limitation relates to the fact that we did not include 2 patients with SIRS in the categorization using the criteria of the ACCP/SCCM [8] due to the small sample size of the patients.

In conclusion, we confirmed that, compared with CRP, the measurement of PCT using the new ELFA is a better diagnostic biomarker of sepsis and discriminative biomarker of categories according to the ACCP/SCCM in BSI. Moreover, on the basis of the advanced functional sensitivity of the PCT measurements, we demonstrated that PCT levels can be used to discriminate catheter-associated bacteremia

from sepsis and guide therapy options.

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