Evaluation of Serum Procalcitonin in Patients with Systemic Inflammatory Response Syndrome with and without Infection

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Abstract- Procalcitonin (PCT) is a precursor peptide for the hormone calcitonin and is frequently increased in overt sepsis. The aim of this study was to test diagnostic accuracy of procalcitonin among patients with positive systemic inflammatory response syndrome (SIRS) in identifying sepsis. In this cross sectional study, from 563 patients with positive SIRS admitted through the emergency department of a university hospital, we included 120 patients. Procalcitonin was measured semi-quantitatively. Two groups of patients (with and without infection) were defined based on clinical, laboratory and bacteriologic findings throughout the admission course; the serum PCT levels were compared between the two groups. Seventy two (60%) patients were male and 48 (40%) were female, and the mean age was 49.1 ± 20.2 years. Final diagnosis was infection in 71 patients (59.2%) and 49 (40.8%) had non-infectious SIRS. When considering PCT > 0.5 μg/L as the cut-off point, PCT had a sensitivity of 88.7%, a specificity of 77.6%, a positive predictive value of 85.1% and a negative predictive value of 82.6%. Serum level of procalcitonin in infectious group was significantly higher than in non-infectious group ($P < 0.0001$). PCT level was a predictor of mortality in patients with infectious SIRS. ($P = 0.01$) In summary, PCT is a useful marker for differentiating sepsis from other cause of SIRS. With change in the cut-off value of PCT in any situation its application can be maximized. Procalcitonin can also be a good marker for predicting outcome in patients with infection.

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Introduction

Bacterial infections and sepsis are major causes of morbidity and mortality in medical departments and intensive care units (ICUs) (1). Sepsis has been defined as the systemic inflammatory response to an active infectious process in the host. This inflammatory response has been named systemic inflammatory response syndrome (SIRS) (2). This systemic inflammatory response can also be induced in the absence of infection. Accurate and timely diagnosis of infectious SIRS remains challenging to the clinician. Clinical and laboratory signs of systemic inflammation, including changes in body temperature, tachycardia, tachypnea and leucocytosis, are sensitive. However, their use is limited because of their poor specificity for the diagnosis of sepsis (3).

A positive culture result has a relatively high specificity for infection, but even this finding is not the gold-standard, because it lacks sensitivity and the results are only available after 2 to 3 days (4). Delays in identifying the pathogens based on the specimen cultures add to the difficulty in establishing an etiological diagnosis in the Emergency Department (ED) and leads to inappropriate use of antibiotics. In addition, estimation of the severity of bacterial infection is mostly based on the presence of characteristics suggestive of systemic inflammatory response syndrome, which may not be apparent when the patient is seen early in the course of the infection (5).

Therefore Sepsis can be difficult to distinguish from other noninfectious conditions in critically ill patients admitted with clinical signs of acute inflammation (6). An ideal marker for bacterial infections should allow an early diagnosis, inform about the course and prognosis of the disease, and facilitate therapeutic decisions (4).

Procalcitonin (PCT) is a precursor peptide for the hormone calcitonin (CT) (7). It is finally cleaved enzymatically into smaller peptides to yield the thirty-two amino acid mature CT. (4) Most CT precursor peptides,

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including PCT, are not found in the serum of the normal population.

In microbial infections and in various forms of inflammation, circulating levels of several calcitonin precursors, including PCT but not mature CT, increase up to several thousandfolds. This increase correlates with the severity of the condition and with mortality (4, 8).

Procalcitonin is very frequently increased in overt sepsis; The onset of this rise is early in the course of sepsis (within 3 hr) (4). Furthermore, recent experiments have demonstrated that in contrast to the transient rise of classic cytokines, the massive increase in circulating PCT persists for several days (9). Beside helping early diagnosis of infection, an increase in serum PCT levels can predict the outcome and severity of infection (10-12) and guide a standard management without an adverse outcome and with fewer antibiotic-related side-effects. (13-16)

The aim of this study was to evaluate the changes in serum level of procalcitonin in patients with SIRS with and without infection.

Patients and Methods

Study design

The present study was a cross sectional study using a consecutive sample of adult patients admitted through the ED. The primary outcome was the infection status of the patients.

Study population and setting

The study was performed from July 2006 until September 2007 in the ED of a university-affiliated tertiary-care teaching hospital with an annual census of about 30000 visits. All adult patients with systemic inflammatory response syndrome (defined as the presence of at least two of the following criteria: Temperature of ≤36 or ≥38 degrees centigrade, pulse rate >90/min, respiratory rate >30/min or PCO_2 <32 mmHg, white cell count >12000/μL or <4000/μL) admitted to the ED of the hospital were included in the study. Patients with mechanical trauma, severe burns, heat stroke, cancer, surgical trauma, age less than 12 years, and those who received antibiotic therapy for more than 48 hours before study were excluded. A serum sample for measurement of PCT was collected in the ED.

Study protocols

All patients were examined for signs and symptoms of infection on ED admission. Samples were collected for cultures of blood, urine and of other body fluids, depending on the clinical presentation. Two groups of patients were defined based on clinical, laboratory and bacteriologic findings throughout the admission course. Infected patients had a definable source of infection and/or positive blood culture and received antibiotic treatment. Patients with clinical infection and a positive blood culture were considered to have bacteremia. The diagnosis of urinary tract infection (UTI) required the presence of symptoms such as urinary frequency, dysuria, costovertebral angle tenderness, and a significant growth of $10^{4–5}$ CFU/ml bacteria in urine culture or active urine analysis (≥ 10 white cells). The diagnosis of pneumonia was based on both respiratory symptoms such as a productive cough, dyspnea and chest pain, and a new pneumonic infiltrate on chest radiograph with or without a positive culture of plural fluid or blood. The diagnosis of cellulitis was based on clinical manifestation of erythema, warmth, tenderness and swelling in suspected site with or without positive blood culture. For diagnosis of endocarditis, duck criteria were used and for other foci, distinct radiological or microbiological documentation of the foci and recovery during the antimicrobial treatment were required.

Noninfected patients were those who, throughout their course of admission to the hospital or in the examinations performed, had no evidence of infection clinically with evidence for a diagnosis other than infection. The serum PCT levels were compared between infected and noninfected patients. The protocols comply with the recommendations of the Declarations of Helsinki and Tokyo for human research and are approved by Tehran University of Medical Sciences ethics committee.

Measurements

The clinical and laboratory data collected included age, sex, admission diagnosis, time of initiating symptoms, body temperature (BT), pulse rate (PR), respiratory rate (RR), leukocyte (WBC) count, blood culture, urine culture and analysis, chest radiograph (CXR), final diagnosis and outcome with a follow-up visit 48 hours or more depending on the case and other available samples. Procalcitonin was measured semi-quantitatively by B.R.A.H.M.S PCT-Q kit (B.R.A.H.M.S.-Diagnostica GmbH, Henningsdorf, Germany). Two milliliters of blood was collected and centrifuged for PCT determination. Six drops of separated serum were put in to the round cavity of the kit. Then it was incubated for 30 minutes at room temperature. After 30 minutes, the PCT concentration range of the samples was determined by comparing the color intensity of the test band with the color blocks of the reference card after checking the

validity of the test with the help of the clearly visible control band. Detection limit of this test is 0.5 ng/ml. All serum samples were processed by the same person who was blinded to the patients' clinical presentations and outcomes and the results of the diagnostic tests.

Data analysis

Data were analysed using the Statistical Program for Social Science (SPSS ver. 11.5) software. The Mann–Whitney U test was used to compare independent samples, and the chi-square test (with the confidence interval of 95%) was used to compare proportions. All variables were expressed as the median, and a P value of less than 0.05 was considered significant. A multiple logistic regression model was used to identify variables (including age, gender, BT, Time of initiating symptoms, WBC count, the presence of SIRS, and a PCT level that was higher than the cut-off value for identifying infection) independently associated with the outcome variables; namely, the presence of bacterial infection, and mortality.

Results

Among the 563 patients with SIRS who were examined in the ED during the study period, 120 patients were included in our study. Four hundred and forty three patients were excluded from the study because of receiving antibiotics (345 cases, 77.9%), trauma (55 cases, 12.4%) and a history of a known malignancy (43 cases 9.7%). Baselines characteristics of the remaining 120 patients were as follows: 72 (60%) were male and 48 (40%) were female, and the mean age was 49.1± 20.2 years.

Fifteen patients (12.5%) were diabetic and 8 (6.7%) had chronic renal failure. Asplenia, HIV infection and chronic liver disease were found in 2 (1.7%) patients each.

Overall in the 120 patients with SIRS, 15 patients (12.4%) had microbiological evidence of bacterial infection (6.7% of blood cultures and 5.8% of urine cultures were positive). The most frequently isolated microorganism was *staphylococcus aureus*. Ultimately, 111 patients (92.5%) were discharged from the hospital and 9 patients (7.5%) died during that hospitalization.

According to the diagnostic criteria, 49 (40.8%) had non infectious SIRS (NISIRS) and 71 patients (59.2%) had infectious SIRS (ISIRS). pneumonia (23.9%), UTI (16.9%) and cellulitis (11.3%) were the most common infectious diseases seen in patients with infectious SIRS.

Among 120 patients, 46 (38.3%) had a serum procalcitonin level below the detection limit of the test (PCT < 0.5 μg/L). Seven patients (15.2%) had ISIRS and 39 (84.8%) had NISIRS. Twenty three patients (19.2%) had PCT > 0.5 μg/L, 33 (27.5%) had PCT > 2 μg/L and in 18 (15%) patients PCT was more than 10 μg/L.

Mann-Whitney test showed that serum levels of procalcitonin in infectious SIRS group were significantly higher than non-infectious group ($P < 0.0001$) (Table 1).

Furthermore with Chi-Square statistical test Sensitivity, Specificity, positive predictive value (PPV) and negative predictive value (NPV) in various cut-off points were calculated, and the results have been shown in table 2. When considering PCT level of > 0.5μg/L as the cut-off point, PCT in our study had a sensitivity of 88.7%, a specificity of 77.6%, a PPV of 85.1% and a NPV of 82.6%. Patients who died had significantly higher levels of procalcitonin as compared to the patients who survived. ($P = 0.03$) Although with multivariate analysis, PCT level was a predictor of mortality in patients with ISIRS ($P = 0.01$) but not in NISIRS patients ($P > 0.05$).

Table 1. Procalcitonin level in patients with infectious and noninfectious SIRS

	Patients with ISIRS N (%)	**Patients with NISIRS N (%)**	**Total patients with SIRS N (%)**
PCT (μg/l)			
PCT<0.5	7 (9.9%)	39 (79.6%)	46 (38.3%)
0.5<PCT<2	14 (19.7%)	9 (18.4%)	23 (19.2%)
2<PCT<10	32 (45.1%)	1 (2.0%)	33 (27.5%)
PCT>10	18 (25.3%)	0	18 (15.0%)
Total	71	49	120

SIRS= systemic inflammatory response syndrome, ISIRS= infectious SIRS, NISIRS= non infectious SIRS

Table 2. Diagnostic value of Procalcitonin at various thresholds in patients with infectious SIRS

	Sensitivity	Specificity	PPV	NPV
PCT (µg/l)				
0.5<PCT<2	88.7%	77.6%	85.1%	82.6%
2<PCT<10	69%	95.9%	96.1%	68.1%
PCT>10	25.4%	100%	100%	48%

SIRS= systemic inflammatory response syndrome, PPV= positive predictive value, NPV= negative predictive value

Discussion

The main purpose of the present study was to test the efficacy of PCT in identifying bacterial/parasitic episodes among SIRS-positive adult patients presenting to the ED. According to our study, an increased serum level of procalcitonin is helpful in the diagnosis of the infections, even in when the infection is localized. Unlike the majority of studies published to date on PCT assay, we did not focus on an organ-specific infection.

The etiology of a presumed bacterial cause of fever cannot be detected in 50–80% of patients with suspected bloodstream infection (13). In our study overall 15 (12.4%) culture proven cases of infection were recognized. The low prevalence of bacteremia in our patients is expectable because the majority of them had a focal infection. However this is much lower than the rate of bacteremia in localized infections according to the studies reported in medical literature (13, 17). A previous unpublished study performed by the authors showed that even in bacterial endocarditis, the prevalence of bacteremia in our patients is much lower than the reported prevalence in literature (63.7% vs. more than 80%). Therefore culture results should not be considered central to the clinical care of infections in our center.

Parameters of diagnostic accuracy depend on the cut-off points applied (13). Therefore reports on the diagnostic accuracy of PCT in the literature are varied. Sensitivity ranges from less than 70% to 100%, and specificity varies between 50% and 100% (12, 13, 18-20). The likelihood of a bacterial infection increases gradually with increasing procalcitonin levels. We noticed that with choosing a higher cut-off point for serum PCT level, the sensitivity decreased (higher false negative) but specificity increased (lower false positive). When considering PCT > 0.5 µg/L as the cut-off point, the sensitivity, specificity, PPV and NPV were 88.7%, 77.6%, 84.6% and 82.6% respectively. When the cut-off point was increased to 10 µg/L sensitivity decreased to 25.4% and specificity increased to 100%, PPV was 100% and NPV was 48%. These finding represent that use of a cut-off value in serum procalcitonin for differentiating sepsis can be tailored according to the physicians' needs and the practicing situation. According to our application of this serum marker, we can change this figure for extreme benefit. For example in transplantation wards lowering cut-off points for screening of infections can be useful.

Sepsis is merely a syndromic diagnosis and the optimal cut-off point for procalcitonin probably depends on the origin of infection (13). A study performed on 243 febrile patients in an emergency room in France, the PCT assay, with a 0.2 µg/L cut-off value, had a sensitivity of 77% and a specificity of 59% in diagnosing bacterial/parasitic infection. The authors stated that the lower specificity reported (59%) could be explained by keeping the cut-off value for PCT assay low (5)

Another study in Spain on 100 infants aged between 4 and 28 days with clinical suspicion of neonatal sepsis of nosocomial origin, serum PCT concentrations were significantly higher at initial suspicion and at 12–24 h and 36–48 h after the onset of symptoms in neonates with confirmed sepsis than in neonates with clinically suspected but not confirmed sepsis. Optimal PCT thresholds according to ROC curves were 0.59 ng/mL at the time of suspicion of sepsis (sensitivity 81.4%, specificity 80.6%); 1.34 ng/mL within 12–24 h of birth (sensitivity 73.7%, specificity 80.6%), and 0.69 ng/mL within 36–48 h of birth (sensitivity 86.5%, specificity 72.7%) (18).

In a study using a cut-off point of 2 ng/mL, the sensitivity and specificity of PCT for distinguishing systemic bacterial infection from aseptic meningitis and from localized bacterial infection were 100%. Positive and negative predictive values for the diagnosis of systemic bacterial infection were also 100% in comparison to C-reactive protein (CRP) (cut-off value of 40 mg/l) with a sensitivity of 88% and specificity of 72.2% for distinguishing systemic bacterial infection from aseptic meningitis, and 50% to distinguish it from localized infection. The PPV was 63.6% and the NPV was 90.9 % (19).

In addition to a great number of studies that show a good and valuable diagnostic accuracy for PCT, there is some metaanalyses in which the authors concluded that procalcitonin is of low diagnostic value (21, 22). Conse-

quently, we agree with Hausfater that emergency physician's judgment is as efficient as or better than the PCT assay, and that biological markers must be considered as diagnostic and prognostic tools that assist physicians in their clinical practice, but cannot replace their clinical judgment (5).

Another important finding in our study was that PCT level was a predictor of mortality in patients with ISIRS ($P = 0.01$).

There are many published data that support the benefits of procalcitonin in predicting outcome, mortality or severity of the infections. In a study in Switzerland on 545 patients with suspected lower respiratory tract infections, authors showed that PCT, in contrast to highly sensitive C-reactive protein and leukocyte count, increased with increasing severity of community acquired pneumonia (CAP), as assessed by the pneumonia severity index ($P < 0.001$), and so they concluded that PCT is useful in assessing the severity of CAP (10). In a systematic review of the literature for assessing the possible role of PCT in detection of postoperative cardiac surgery complications and mortality, the authors noted that serum PCT levels increase with increasing severity of sepsis and the presence of organ dysfunction/failure and are higher in patients with a poor outcome or in those who develop postoperative complications (11). In a review on pediatric infections, Rossum and colleagues found that all studies on severe, invasive bacterial infections in children report higher sensitivities and specificities for procalcitonin than for CRP; so they concluded that procalcitonin is an excellent marker of severe, invasive bacterial infections in children (23).

Study Limitations

One of the limitations of the present study is that we did not perform quantitative measurement for PCT. However, a good correlation between the results of the quantitative and the more rapid semi-quantitative test has been shown in other studies (24, 25). In a study aimed at detecting the correlation between the quantitative and the rapid semi quantitative test by Gervaix and colleagues, no result above 0·5 ng/mL with the quantitative method was below the threshold of detection (0·5 ng/mL) by the rapid test (24). In a multicenter study in Spain researchers found that the PCT-Q test has a good correlation in 87% of cases with the quantitative values of the marker within the context of infectious diseases (25).

Another limitation of our study is that we did not study PCT kinetics in infected patients with low initial PCT levels. Because in such patients PCT may become positive or show higher levels on sequential samples (5). The major limitation of our study, however, is the choice of the gold standard against which sepsis was diagnosed. Any observational study and metaanalysis investigating the diagnostic accuracy of procalcitonin is biased by the choice of the gold standard. The etiology of a presumed bacterial cause of SIRS cannot be detected in 50–80% of patients with suspected bloodstream infections (13). We considered expert diagnosis to be more suitable, because a significant proportion of bacterial febrile episodes are never confirmed microbiologically in the setting of ED care. In conclusion, PCT is a useful marker for differentiating sepsis from other cause of SIRS, but only in combination with other clinical and laboratory markers. With changes in the cut-off value of PCT in any situation its application is maximized. However more studies for determining the exact cut-off point for PCT and its diagnostic accuracy is needed. Procalcitonin can also be a good marker for predicting outcome in patients with infection.

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