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Serum Procalcitonine Levels as an Early Diagnostic Indicator of Sepsis

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ABSTRACT
Introduction: Prompt and accurate diagnosis of sepsis is of high importance for clinicians. Procalcitonine (PCT) and C-reactive protein (CRP) have been proposed as markers for this purpose. Our aim was to evaluate the levels of PCT and CRP in early sepsis and its correlation with severity of sepsis. **Methods:** Levels of PCT and CRP were taken from 60 patients with sepsis criteria and 39 patients with SIRS symptoms from the University Hospital Center "Mother Teresa" in Tirana, Albania during 2010-2012. Sensitivity, specificity and predictive values for PCT and CRP were calculated. **Results:** PCT and CRP levels increased in parallel with the severity of the clinical conditions of the patients. The mean PCT level in patients with sepsis was 11.28 ng/ml versus 0.272 ng/ml in patients with SIRS symptoms, with a sensitivity of 97.4% and a specificity of 96.6% for PCT >0.5ng/ml. The mean CRP level in septic patients was 146.58 mg/l vs. 34.4 mg/l in patients with SIRS, with a sensitivity of 98.6% for sepsis and a specificity of 75 % for CRP >11mg/l. **Conclusion:** PCT and CRP values are useful markers to determine early diagnosis and severity of an infection. In the present study, PCT was found to be a more accurate diagnostic parameter for differentiating SIRS from sepsis and may be helpful in the follow-up of critically ill patients.
Keywords: Albania, C-reactive protein, procalcitonine, sepsis.

1. INTRODUCTION

Procalcitonine (PCT) and C-reactive protein (CRP) have been proposed as marker for the prompt and accurate diagnosis of sepsis (1), which remains a critical problem with significant morbidity and mortality even in the modern area of critical care management. The number of patients presenting with sepsis or septic shock is gradually increasing. For emergency medicine physicians the focus will likely be a differential diagnosis and investigating the strong clue of sepsis. Early diagnosis for sepsis not only decreases the mortality rate, but it is also necessary for emergency medicine physicians to perform further therapy steps (fluid therapy, appropriate antibiotic use) simultaneously (2).

Sepsis has been defined as the systemic response of the body to infection (3). The documentation of infection can be performed with positive culture, which is not an immediately available laboratory investigation in emergency department (ED).

Diagnostic uncertainly must be balanced with some biologic parameters. Researchers and clinicians have been investigating and implementing various methods of early diagnosis of sepsis before documentation of infection. There have been many described biologic parameters that facilitate a rapid diagnosis of sepsis beside the classic bacterial examinations (3, 4, 5).

We conducted the present prospective study to determine the accuracy of some inflammatory parameters among the patients who have at least two criteria of systemic inflammatory response syndrome (SIRS) and clinically suspected and non suspected sepsis. We determined the values of procalcitonine (PCT), C-reactive protein (CRP) and blood cells count (WBC) in all patients included in the study.

PCT corresponds to a group of proteins related to the calcitonine gene (CGRP) I and II. The transcription of the CALC-1 gene generates PCT and consequently mature calcitonine. PCT was discovered recently as a marker of bacterial infection. In the healthy individuals, it is secreted from the c-cells of the thyroid gland, in a very low plasma concentration less than 0.1ng/ml. Several animal and human studies have shown a sustained increase in the concentration of plasma PCT during serious infections and after stimulation with high concentration of bacterial endotoxins. When the infectious process has started, the liberation of lipopolisaccharides from the bacterial membrane is promoted, and that stimulate production of the proinflammatory cytokine, which allow the initial expression of the monocytes of the CALC-1 gene with the consequent transcription of ARN m -CT and production of PCT, which lasts about 3 to 5 hours, with maximal level at 6h and diminishes its production at 18 h. The local release of PCT acts as a chemokine and attracts additional activated monocytes, which penetrate the tissue. The migratory reaction triggered by PCT is time dependent and is deactivated after a few hours by the presence of PCT. The cells remain at the site of the inflammation. PCT also modulate the induction of proinflammatory cytokines. It has a halftime life in serum of 25 to 30 h (6, 7).

CRP as an acute phase protein has been used to perform the prognosis and diagnosis of several critical illness. This protein belongs to the pentatraxin family. It has five identical subunits codified by only one gene which is located in chromosome 1. It is part of the innate immunity and its synthesis is induced as a response to tissue damage. It is synthesized by hepatocytes and the vascular endothelium and its expression is regulated by cytokines, particularly interleukin 6 (IL 6), and to lesser degree by IL 1 and TNF – alpha. CRP level raises rapidly in response to inflammatory stimulus and this levels decreases rapidly when the inflammatory stimulus has resolved. CRP synthesis begins 6 h after the inflammatory stimulus started and reaches peak level at 24 to 72. The halftime life is approximately 19 hours, in plasma is stable, without regard to food intake and circadian cycle. Once the stimulus of IL 6 has ended, it returns to normal values in an average of 7 days (8, 9).

2. PATIENTS AND METHODS

With approval from the Local Research Ethical Committee, patients with signs of SIRS from Emergency Departments and Intensive Care Unit of the University Hospital Center "Mother Teresa" in Tirana, Albania, were enrolled in this study from April 2010 to April 2012.

Patients were included on the basis of clinical and laboratory findings, in line with the guidelines of the American College of Chest Physician Society of Critical Care Medicine Conference (10, 11).

Patients met at least two of the criteria for SIRS:

- fever >38 or<36,
- heart rate>90 beats/min,
- respiratory rate >20 breaths/min or PaCO2<32mmHg,
- WBC > 12000 cells/ mm3, <4000 cells/mm3 or> 10% immature forms (bands).

At admission, the patients age, sex were recorded. Data collection consisted of the following: clinical status (SIRS, SEPSIS or SEPSIS+MODS), Acute Physiology and Chronic Health Evaluation (APACHE0-II score: temperature, heart rate, respiratory rate, blood pressure), laboratory analysis (complete blood count, blood urea nitrogen, blood sugar, serum sodium, potassium and calcium, aspartate-aminotransferase, alanine-aminotransferase, prothrombine time, albumin and arterial blood gas analysis. The final determination of the patients' status was done retrospectively.

The patients were divided in two groups according to non suspected sepsis and suspected sepsis clinically. Categorization of patients was made without knowledge of PCT and CRP level on the basis of the patients complete charts, results of microbiological culture, chest radiographs and ultrasound, when available.

The term non suspected sepsis was used for patients who had minor infection, with only signs of SIRS and viral infection.. The non suspected sepsis group included 39 patients. This group was also designed as control group.

The second group, called the suspected sepsis group, was used for patients who had a higher risk for sepsis with concomitants diseases, previous hospitalization, and a strong suspicion of sepsis clinically but not documented bacterially at admission moment. This group included 60 patients. All patients included in the study has blood samples taken to determine PCT, CRP and WBC, as well as urine culture, blood culture and other routine examination before the treatment.

PCT was determined by an electrochemiluminiscent immunoassay in COBAS INTEGRA 6000 with Ellecsys BRAHMS PCT reagent, whose detection limit was 0.01ng/ml and normal range <0.5ng/ml. CRP was measured by immunometric method in IMMULITE 1000 with a normal range 0 to 11 mg/l.

WBC (leukocyte) was determined by using an automatic counter CELL-DYN 1800. The reference values were between 4000 and 12000 cells/mm^3.

Statistical analysis were conducted using the Statistical Program for Social Science (IBM SPSS 20).

Data were expressed as means at confidence intervals of 95%.

3. RESULTS

Of 99 patents included in the study 54(55%) were female and 44(45%) male. Average age was 44 year. We found that only 2 from 60 patents with sepsis and all patients with SIRS symptoms had PCT level less than 0.5 ng /ml . The result shown that 58 from 60 septic patients were PCT positive, with a mean of 11.128 ng/ml, compared with 0.272 ng/ml in patients with SIRS. We determined the sensitivity and specificity of PCT for distinguishing sepsis from SIRS. For PCT < 0.5 ng /ml we found a sensitivity of 97.4 % and a specificity of 96.6 %.

About the CRP, the results shown that the mean of CRP in septic patients was 146.58 ng/ml and 34.4 ng/ml in SIRS patients, with sensitivity 98.5 % and specificity 75 % for CRP <11 mg/l .

4. DISCUSSION

The results show that PCT and CRP are useful markers to determine if the infectious process is bacterial or not, with a relation between positive and negative cultures and the values of these tests. In our study all the patients that presented positive cultures had PCT levels greater than 0.5 ng/ml and most of them were greater than 2 ng/ ml. PCT levels increase 2-3 hours after installation of sepsis, that make PCT un accurate marker for diagnosis of bacterial infection and sepsis , than any clinical sign or routine laboratory test (12, 13). This is fundamental because by having this clear determination it is feasible to initiate early and efficient therapy prior to the infectious process being evident and having a positive culture. We correlate PCT values with the severity of the illness determined by APACHE II SCORE (14, 15). The correlation was significant (p 0.001). PCT levels in patients with positive blood cultures were higher than in patients with the same disease in whom no germs can be found in the blood. These patients usually also had a particularly severe progression or a poorer prognosis. Very low PCT concentration, on other hand, had a high negative predictive value for the exclusion of bacteremia. In sepsis PCT levels were on an average higher in patients with positive blood cultures, and positive blood cultures were more frequently seen in patients with high PCT levels or severe sepsis or those with severe organ dysfunction. For very low PCT levels, the presence of bacteremia was negative.

Our results are in accordance with results of other studies in a wide range of patients populations which have found that, PCT levels 2 or >2 have 100% specificity for diagnosis of sepsis. Due to high sensitivity and specificity PCT can be used for diagnosis and management of sepsis.

5. CONCLUSION

In the present study, PCT appeared to be a more accurate diagnostic parameter for differentiating between patients suffering from SIRS and those with sepsis in association with clinical and preclinical data. Routine determination of PCT may improve management of patients, for example by preventing the use of unnecessary antibiotics that are known to cause resistance strains.

PCT levels and their progression can provide important indication of the risk and progression of the disease, as well as can provide information about the success of therapy.

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