Usefulness of procalcitonin and some inflammatory parameters in septic patients

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ABSTRACT

الهدف: قد يكون تشخيص المتلازمة الإنتانية صعباً عند المرضى المعتلين بشدة نظراً لأن الواصمات التقليدية للعدوى غالباً ما تكون مضللة. لقد أجريت الدراسة الحالية لتقييم مدى قدرة طليعة الكالسيتونين على تمييز هؤلاء المرضى المصابين بالمتلازمة الإنتانية و ذلك بالمقارنة مع تعداد الكريات البيض ودرجة حرارة الجسم و البروتين المتفاعل C و سرعة التثفل و الانترلوكين6.

الطريقة: تضمنت دراستنا المستقبلية خمساً وسبعين حالة مرضية تطورت لديهم أعراض استجابة التهابية جهازية و أدخلوا المستشفى بعدوى محتملة. كانت متلازمة الاستجابة الالتهابية الجهازية SIRS هي التشخيص النهائي عند 38 مريضا منهم و المتلازمة الإنتانية sepsis عند 22 مريضاً والمتلازمة الإنتانية الوخيمة الشديدة severe sepsis عند 10 مرضى و المتلازمة الإنتانية المتوقع أن سببها فيروسي suspected viral عند 5 الباقين. سحبت عينات الدم في اليوم الأول من قبول المرضى في مستشفى المواساة بدمشق في الجمهورية العربية السورية خلال الفترة الممتدة من شهر تموز 2006م إلى شهر كانون الثاني 2007م. لقد قدرت القيمة التشخيصية للمتثابتات المختلفة المدروسة من خلال تطبيق اختبار T–test ومعامل بيرسون للارتباط و المساحة تحت منحني Receiver Operating Characteristic (ROC).

النتائج: بلغ متوسط قيم طليعة الكالسيتونين عند الدخول0.37ng/ml عند مجموعة SIRS n=38 و 3.31ng/ml عند مجموعة sepsis n=22 و 40.2ng/ml عند مجموعة severe sepsis n=10 بفارق يعتد به إحصائياً بين المجموعات الثلاثة مثنى مثنى. كانت طليعة الكالسيتونين المتثابتة الوحيدة القادرة على التمييز بين المتلازمة الإنتانية sepsis و المتلازمة اللاعدوائية SIRS في حين أنها كانت أفضل المتثابتات المدروسة في التمييز بين المتلازمة الإنتانية sepsis و المتلازمة الإنتانية الوخيمة severe sepsis بمساحة تحت المنحني قدرها 0.966 يليها في ذلك الانترلوكين6 بمساحة 0.836. لم تلاحظ علاقة ارتباط بين طليعة الكالسيتونين و أية من المتثابتات المدروسة وذلك عند مجموعتيSIRS و sepsis.

خاتمة: إن تحديد قيم طليعة الكالسيتونين لتحري المتلازمة الإنتانية عند مرضى الالتهابات الجهازية الذين وفدوا حديثاً إلى المستشفى طريقة يمكن التعويل عليها بشكل أفضل مما هو عليه بالنسبة للمتثابتات المتداولة أو الانترلوكين6.

Objective: To evaluate the efficacy of procalcitonin (PCT) to identify critically ill patients with sepsis in comparison with leukocyte count, body temperature, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6).

Methods: We performed our prospective observational study in 75 patients admitted with acute systemic inflammatory response and suspected infection. The final diagnosis was systemic inflammatory response syndrome (SIRS) in 38 patients, sepsis in 22, severe sepsis in 10, and suspected viral sepsis in 5. Blood samples were taken on the first day of hospitalization in Al Mwasaa Hospital, Damascus, Syrian Arab Republic, from July 2006 to January 2007. We estimated the relevance of the different parameters by using the t-test, Pearson's correlation coefficient, and area under the receiver operating characteristic curves.

Results: Mean PCT concentrations on admission were 0.37 ng/ml for SIRS (n=38), 3.31ng/ml for sepsis (n=22), 40.2 ng/ml for severe sepsis (n=10), and significant differences existed in plasma PCT levels among the 3 groups. The PCT was the only distinguisher between sepsis and non-infectious SIRS, whereas it exhibited the best discriminative power between sepsis and severe sepsis with an area under the curve (AUC) of 0.966 followed by IL-6 with an AUC of 0.836. The PCT also do not correlate with any of the studied parameters within the SIRS group and the sepsis group.

Conclusion: Assessing PCT levels is a more reliable way to indicate sepsis in newly admitted patients with systemic inflammations compared with conventional inflammatory parameters and IL-6.

Saudi Med J 2008; Vol. 29 (4): 520-525

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Received 20th October 2007. Accepted 23rd February 2008.

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Mortality rates in sepsis are still high in spite of the improvements in experience, technology, and treatment procedures. It was estimated that there are more than 750000 cases of severe sepsis (sepsis with organ dysfunction) each year in the United States resulting in more than 500 deaths every day.[1] Acute respiratory tract infections (ARTI), which are among the most frequent reasons for consultations in primary care are often treated with antimicrobial agents although they are predominantly viral in origin. Moreover, the prophylactic prescription of antibiotics by clinicians is common in all patients with signs of sepsis without clear diagnosis since delaying treatment until definite microbiological evidence of infection is available can result in a higher rate of morbidity/mortality. It is well known now that this inappropriate use of antibiotic is the main cause of the spread of resistant microorganisms in addition to wasting huge amount of drugs and increasing the risk of adverse events.[2,3] The clinical and laboratory signs, which accompany infections and sepsis such as hyperthermia, changes in leukocyte count, increase in heart rate, and hyperventilation are just signs of systemic inflammation that might be due to an infectious or non-infectious cause, and are neither specific nor sensitive for sepsis.[4] Those who are suffering from pancreatitis for instance, major trauma, or burns without infectious complications have the same inflammatory response.[5] Bacteriological proof of infection, which is usually delayed may not resolve the problem because positive bacteriological results may be caused by contamination, and negative results do not exclude sepsis.[6] It is clear then that we are in need of other tests to be an early marker of the infectious etiology of the apparent systemic inflammatory symptoms. Among promising parameters, procalcitonin (PCT), which was first described by Hatherill et al[7] has obtained great interest as it could be a novel marker of sepsis. Procalcitonin is a 116-amino acid protein that is the precursor to calcitonin.[8] Its almost undetectable under physiological conditions,[9] however, rises to very high values in response to infection.[10] Several authors have postulated that this biomarker is superior to currently used clinical or biological indicators of sepsis and that it increases with the increasing severity of the inflammatory response to infection.[11-13] However, the diagnostic value of procalcitonin has been investigated by several studies ending with variable and sometimes conflicting findings according to the studied groups or patient population.[14-18] The current study aimed to assess the diagnostic value of this pro-hormone in a group of severely ill Syrian patients admitted with signs of acute severe inflammation. Specifically, we assessed whether PCT, interleukin-6 (IL-6), or standard parameters (leukocyte count, body temperature, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are helpful in distinguishing sepsis from systemic non-infectious inflammation, sepsis from severe sepsis, and viral from bacterial sepsis in newly admitted critically ill patients with suspected infection.

Methods.

Study setting and population. The study included all adult patients who were newly admitted to Al Mwasaa Hospital, Damascus, Syrian Arab Republic, from July 2006 to January 2007 and hospitalized in the Emergency Department with a clinically suspected infection if they fulfill at least 2 criteria of systemic inflammatory response syndrome (SIRS), which were provided by the American College of Chest Physician / Society of critical Care Medicine consensus conference in 1992 and confirmed again in 2001.[19] Every effort was made to identify patients with suspected sepsis as early as possible after admission. The healthy group was chosen from those who were donating their blood at the blood bank of Damascus University. Their routine laboratory analysis had to be within the normal range, and they also do not suffer from any illness. Cases which was clinically clear that it's not infection or those who died or were discharged without reliable diagnosis were excluded from the study. The study protocol was approved by the ethics committee of the University Hospital Damascus Syria and informed consent was obtained from all patients.

Data collection. At admission, the patient's age, gender, underlying diseases, clinical status (SIRS, sepsis, or severe sepsis), temperature, heart rate, respiratory rate, blood pressure, laboratory analysis including complete blood count, ESR, and CRP were recorded. Clinicians determined the patient's status before they became aware of the plasma cytokine and PCT levels according to the results of the routine investigations such as laboratory tests, microbiological cultures, chest radiographs, and ultrasound, when available.

Measurements of PCT and IL-6 plasma levels. Within 24 hours of study inclusion, blood samples were taken by venipuncture and centrifuged at 4000 r/min for 10 minutes before serum was frozen at -80^{0}C for future PCT and IL-6 measurements. Interleukin-6 concentrations were determined with a commercially available IL-6 ELISA test kit (Quantikine Human IL-6, R&D Systems Inc, USA). Procalcitonin levels were measured by a semiquantitative immunochromatographic assay (PCT-Q, Brahms Diagnostica GmbH, Berlin, Germany).

Statistical analysis. For the statistical evaluation of the results, the Statistical Program for Social Science (SPSS version 15) for windows has been used. Results were expressed as mean ± SD. Correlations between variables were assessed using Pearson correlation coefficient. T-test was performed to determine differences between variables. A p-value of <0.05 was

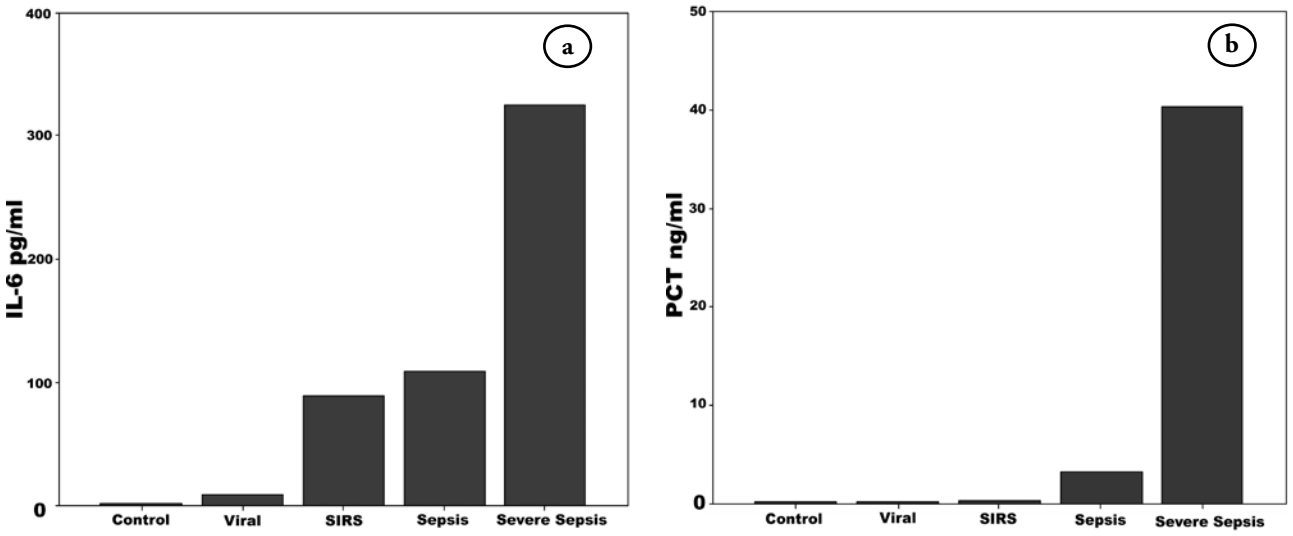

Figure 1 - Comparison of the plasma means of **a**) interleukin-6 (IL-6) and **b**) procalcitonin (PCT) with increasing severity of systemic inflammation and sepsis. The sepsis classification based on the bone classification criteria (5 groups). SIRS - systemic inflammatory response syndrome

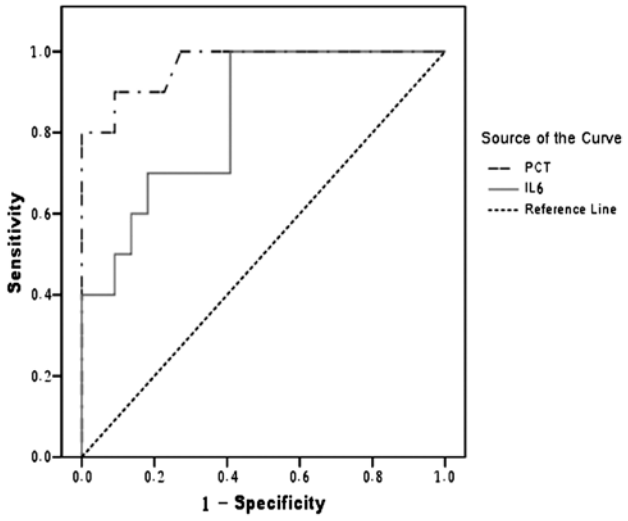

Figure 2 - Receiver operating characteristic curves of procalcitonin (PCT) and interleukin-6 (IL-6) for prediction of severe sepsis. Procalcitonin yielded the highest discriminative value with an area under the curve of 0.966 followed by IL-6 with 0.836.

considered statistically significant. The ability of PCT to predict sepsis was evaluated by performing receiver operating characteristic analysis. Furthermore, the areas under the receiver operating characteristic curve (AUCs) were determined.

Results. *Patient Population.* We evaluated a total of 75 patients, 38 of whom fulfilled the criteria of non-infectious SIRS, while the others suffered from sepsis (n=22) or severe sepsis (n=10) or suspected viral sepsis (n=5). The mean age of 75 patients (32 male and 43 female) included in the present study was 43.6 ± 19.14 years. Lower respiratory tract infection, intra-abdominal infection, blood stream infection, cellulitis, meningitis, and urinary tract infection constituted the most common infections.

Baseline plasma levels of PCT, IL-6, CRP, ESR, and white blood count (WBC). Mean PCT levels on admission were 0.25 ng/ml for control, 0.37 ng/ml for SIRS, 3.31ng/ml for sepsis, 40.2 ng/ml for severe sepsis (p<0.05 among the 4 groups), and 0.25 ng/ml for suspected viral sepsis (p<0.05 versus sepsis) (**Figure 1**). Procalcitonin appeared to be the sole one helpful in differentiating patients with sepsis from those with SIRS (**Table 1**). It yielded also the highest discriminative value between sepsis and severe sepsis with an AUC of 0.966 followed by IL-6 (AUC, 0.836) (**Figure 2 & Table 2**). Serum IL-6 concentrations increased from 89.47±124.38 pg/ml for SIRS to 109.17±136.8 pg/ml for sepsis to 324.6±237.8 pg/ml for severe sepsis, and it was 8.26±8.18 pg/ml in suspected viral sepsis (**Figure 1**). The difference was significant between sepsis & severe sepsis as well as between bacterial and viral sepsis (**Table 1**). On the other parameters (WBC, CRP, and ESR), their mean differences could not differentiate neither between SIRS and sepsis nor between sepsis and severe sepsis, however they all could differentiate bacterial from viral sepsis (**Table 1**). The accuracy of the candidate parameters to distinguish patients with viral from those with bacterial sepsis varied. Interleukin-6 yielded the highest discriminative value followed by PCT, ESR, CRP, and WBC (**Table 2**). Associations between PCT and the candidate parameters within SIRS group and

Table 1 - Serum values of the different sepsis indicators of the study.

Variables	SIRS (n=38)	Sepsis (n=22)	Severe Sepsis (n=10)	Suspected Viral (n=5)	Control (n=25)
			Mean ± SD		
Age (years)	44.7±21.82	42.6±21.34	50.2±19.14	26.8±14.34	31.16±12.66
Temperature	38.026±1.03	38.523±0.75	39.06±0.98	38.88±0.44	37.072±0.35
WBC (c/mm3)	12.6±7.24	14.32±8.67	18.89±11.41	8.46±4.9†	6.31±1.24
CRP (mg/dl)	60.22±62.84	99.34±89	137.02±105.9	27.54±41.8†	2.26±1.27
ESR (mm/h)	54.47±36.74	38.05±37.76	55.1±32.8	17.6±27.7†	5.56±2.8
PCT (ng/ml)	0.37±0.32	3.31±2.65*	40.2±22.5†	0.25†	0.25
IL-6 (pg/ml)	89.47±124.38	109.17±136.8	324.6±237.8	8.26±8.18 †	1.94±1.87

Data are expressed as means ± SD. *P<0.05, versus SIRS. † p<0.05 versus sepsis.
SIRS - systemic inflammatory response syndrome, WBC - white blood count, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, PCT - procalcitonin, IL-6 - interleukin-6.

Table 2 - Area under the ROC curve of the different parameters.

Variables	AUC (CI) SIRS versus sepsis	AUC (CI) Sepsis versus severe sepsis	AUC (CI) Viral versus bacterial sepsis
WBC	0.549 (0.392-0.706)	0.607 (0.393-0.821)	0.736 (0.514-0.959)
CRP	0.622 (0.468-0.776)	0.582 (0.337-0.826)	0.800 (0.584-1.016)
ESR	0.606 (0.455-0.758)	0.405 (0.197-0.613)	0.882 (0.713-1.051)
PCT	0.873 (0.765-0.982)	0.966 (0.908-1.024)	0.918 (0.811-1.025)
IL-6	0.596 (0.451-0.741)	0.836 (0.694-0.979)	0.945 (0.859-1.032)

AUC - area under the curve, ROC - receiver operating characteristic curve, CI - 95% confidence interval, SIRS - systemic inflammatory response syndrome, WBC - white blood count, CRP - C-reactive protein, ESR - erythrocyte sedimentation rate, PCT - procalcitonin, IL6 - interleukin-6

sepsis group were studied. No correlation was found between PCT and any of them within these 2 groups.

Discussion. Our study has shown the following main findings: 1) PCT has good diagnostic value in discriminating between SIRS and sepsis, sepsis and severe sepsis, and viral and bacterial sepsis, 2) Both, PCT and IL-6 plasma levels relate well to the severity of sepsis since they were the only ones able to discriminate between sepsis and severe sepsis, with PCT being the superior, 3) the ability of all the studied parameters except temperature to discriminate between viral and bacterial sepsis, with IL-6 being the superior followed by PCT, and 4) the finding of no correlation between PCT and any of the studied parameters within the SIRS group and the sepsis group.

The primary diagnosis of sepsis depends on clinical symptoms, which differ widely between cases and are sometimes misleading. Several laboratory parameters have been evaluated in order to find the right diagnosis of sepsis at an earlier time. White blood count, acute phase proteins, pro-inflammatory cytokines, and procalcitonin are among these tested parameters.[13] Leukocytosis is still considered as proof of infection despite that so many researches show that the elevation of white blood cell count is not specific or sensitive for infection. Furthermore, a left shift, which indicates increase in the new white cells released from the bone marrow does not have good diagnostic value in discriminating infectious from non-infectious systemic inflammation.[20] Body temperature is frequently changed in intensive care patients and may be due to noninfectious causes. In addition, hyperthermia can be induced by tumor necrosis factor-alpha (TNF-α) and IL-1 through stimulation of IL-6 production; it is seen that multiple factors may influence body temperature. As an acute phase protein, CRP may be elevated in a variety of inflammatory states of noninfectious etiologies. The dynamic concentration range of CRP is narrower than that of PCT. In particular, during the more severe stages

of infection, CRP fails to rise further. Furthermore, plasma levels of CRP increase up to 24 hours later than those of other markers such as cytokines and PCT, and often remain elevated for several days.[21] Interleukin-6 is one of the best markers of disease severity in patients with systemic inflammation.[22] However, concentrations of IL-6 have a short half-life in-vitro and in-vivo, and there is no preferential induction during bacterial infectious etiologies of inflammation.[12]

The present results confirm and extend earlier findings demonstrating that PCT is among the most promising sepsis markers in critically ill patients, capable of complementing clinical signs and routine laboratory parameters suggestive of severe infection at the time of ICU admission. Recently, Hausfater et al[23] investigated 243 patients admitted to an emergency department and suggested that PCT may provide additional, valuable information on the etiology and prognosis of infection in the emergency department. Another group from France[24] reported the sensitivity of PCT for infection as 89% and specificity as 93%, concluding that PCT might help to improve the diagnosis of sepsis in patients with SIRS, preventing unnecessary antibiotics, and hospital admission. Lastly, Bin et al[25] found PCT values similar to those in the present study: mean PCT serum levels and range were 0.5 (0.2-1.8) in patients with SIRS and 3.6 (1.8-27.5) in patients with sepsis.

One limitation of this study was the semi-quantitative way in which the assay of PCT was performed, as it prevented us from doing further statistical studies such as finding the cut-off and calculating the positive and negative predictive values. The other limitation could be the wide range of patients who suffer from many different diseases that may have different influences on PCT and the inflammatory response. More studies are required in each case alone to clarify this hypothesis.

In conclusion, PCT can be helpful to differentiate infectious from non-infectious causes of systemic inflammatory response. In this respect, it seems to be superior to other markers. Procalcitonin levels are closely correlated to the severity of sepsis and maybe to the degree of organ dysfunction. By assessing PCT levels in all patients in whom systemic infection is suspected, we might be able to achieve best management and consequently the best results.

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