

Procalcitonin as a prognostic biomarker of severe sepsis and septic shock

Procalcitonina como biomarcador de prognóstico da sepse grave e choque séptico

JOSÉ RAIMUNDO ARAUJO DE AZEVEDO¹; ORLANDO JORGE MARTINS TORRES, TCBC-MA²; NICOLAU GREGORI CZECZKO, TCBC-PR³; FELIPE FRANCISCO TUON³; PAULO AFONSO NUNES NASSIF, TCBC-PR³; GLEIM DIAS DE SOUZA⁴

A B S T R A C T

Objective: To evaluate the tendency of the plasma concentration and clearance of procalcitonin (PCT-c) as biomarkers of prognosis of patients with severe sepsis and septic shock, compared to another early prognosis marker, the number of SIRS criteria at sepsis diagnosis. **Methods:** We conducted a prospective, observational, cohort study, with patients with severe sepsis and septic shock. The serum procalcitonin was determined at diagnosis of sepsis and after 24 and 48 hours. Demographic data, APACHE IV, SOFA score on arrival, number of SIRS criteria at diagnosis, site of infection and microbiological results were recorded. **Results:** Twenty-eight patients were included, 19 clinical and nine surgical. In 13 (46.4%) the source of sepsis was pulmonary, abdominal in seven (25.0%), urinary in five (17.9%) and soft tissue in three cases (10.7%). Fifteen patients had severe sepsis and 13 septic shock. Overall mortality was 17.9% (five patients), three with septic shock. Twenty-eight PCT determinations were performed at sepsis diagnosis, 27 after 24 hours and 26 after 48 hours. The initial concentration was not significantly different between survivors and non-survivors groups, but the differences between the two groups after 24 and 48 hours were statistically significant. There was no difference in the number of SIRS criteria. The 24-hour procalcitonin clearance proved to be significantly higher in the group of survivors (-3.0 versus -300.0, $p = 0.028$). Although the 48-hour procalcitonin clearance has shown to be higher in the group of survivors when compared to non-survivors, the difference did not reach statistical significance. **Conclusion:** Persistently high procalcitonin concentrations in plasma, as well as reduced 24-hours PCT clearance, were associated with a significant increase in mortality in patients with severe sepsis and septic shock.

Key words: Patients. Prognosis. Sepsis. Septic shock. Biological markers.

INTRODUCTION

Procalcitonin (PCT), the precursor peptide of calcitonin, a hormone involved in calcium homeostasis, is present in normal subjects in extremely low serum levels (0.1 to 0.5ng/ml). In response to bacterial infectious stimulation serum procalcitonin rises substantially and its role in inflammatory response includes chemotactic function, modulation of inducible nitric oxide synthase and induction of cytokines, among other¹⁻⁵.

Several studies have shown that the measurement of procalcitonin is highly sensitive and specific for distinguishing SIRS (systemic inflammatory response syndrome)⁶ from sepsis, bacterial pneumonia of other inflammatory lung conditions⁷ and pancreatic necrosis from septic pancreas necrosis⁸. Serial PCT assessments have been

used to determine the time of treatment of pneumonia and other infections⁹.

More recently, PCT has been used as a biomarker of prognosis. In severe sepsis and septic shock isolated determinations of serum PCT have shown variable results¹⁰⁻¹⁵. Most studies say that it is not possible to predict the outcome of critically ill patients based on high levels of PCT. Encouraging results were obtained from studies involving small numbers of patients and showed that serial determinations of PTC correlated with prognosis^{12,13}.

In recent studies, Guan *et al.*¹⁶ and Ruiz-Rodriguez *et al.*¹⁷ suggested, by analyzing small case series, that dynamic changes of PCT could be predictive of outcome in patients with severe sepsis and septic shock.

The identification of a prognostic marker that may predict the outcome at the end of 24 to 48 hours of

Work done at the Intensive Care Unit, Santo Domingo Hospital, São Luis, Maranhão State – MA, and at the Post-Graduation Program in Principles of Surgery, Faculdade Evangélica do Paraná / Hospital Evangélico de Curitiba, Curitiba, Paraná State – PR, Brazil.

1. Coordinator, Intensive Care Unit, São Domingos Hospital; 2. Surgeon, Department of Surgery, São Domingos Hospital; 3. Permanent Professor, Post-Graduation Program in Principles of Surgery, Medical Research Institute, Evangelical Faculty of Paraná; 4. PhD, Post-Graduation Program in Principles of Surgery, Medical Research Institute, Evangelical Faculty of Paraná / Evangelical Hospital of Curitiba, Curitiba, PR, Brazil.

treatment of severe sepsis and septic shock could be very useful in order to provide a reassessment of the patient, identifying perpetrators of gravity, permitting interventions and conduct reorientation. The addition of this marker for the routine evaluation of patients with severe sepsis and septic shock treated according to the Surviving Sepsis Campaign¹⁸ strategies might bring additional contribution towards reducing morbidity and mortality.

Some studies have attempted to establish the relationship between the intensity of the systemic inflammatory response and outcome of sepsis and septic shock. Rangel-Frausto *et al.*¹⁹ analyzed more than 2500 patients with SIRS of infectious cause and found a significant correlation between severity of SIRS translated by the number of positive criteria and mortality. Sprung *et al.*²⁰, in a study that included more than 3000 patients from 198 ICUs of 24 European countries, showed that the presence of more than two SIRS criteria in infected patients was associated with increased risk of developing severe sepsis and septic shock, and was also associated with significantly increased mortality. In conclusion, the authors suggested that the criteria for SIRS, which are easy to measure, should be compared with other markers for diagnosis and prognosis of sepsis in future studies.

The analysis of dynamic changes of procalcitonin can predict the outcome and provide early interventions to change the course of patients with severe sepsis and septic shock.

The aim of this study was to evaluate the usefulness of procalcitonin (PCT-c) as a biomarker of prognosis of patients with severe sepsis and septic shock through trend analysis of plasma concentration and clearance of PCT in the first 24 and 48 hours of treatment, comparing to another early marker of prognosis, the number of SIRS criteria at sepsis diagnosis.

METHODS

This was a cohort, prospective and observational study, whose project was approved by the Research Ethics Committee of the São Domingo Hospital, São Luís, MA on 16/4/12 under number 009/2012.

The study included 28 patients admitted to a general ICU of 37 beds in a tertiary hospital in São Luís, Maranhão State, in the period between May 1 and September 30, 2012.

Inclusion criteria were: patients aged 18 years or more, not pregnant, that met criteria for severe sepsis or septic shock from the American College of Chest Physicians / Society of Critical Care Medicine²¹, ie, sepsis associated with at least one organ dysfunction and / or signs of tissue hypoperfusion unresponsive to intravenous administration of 20ml/kg of fluid, requiring infusion of vasoactive drugs.

All patients were treated according to the institutional protocol for management of severe sepsis and

septic shock, based on recommendations from the Surviving Sepsis Campaign, modified to meet recent evidence from the literature^{22,23}.

The form of data collection included demographics, length of stay, outcome, patient clinical or surgical APACHE IV, death risk, SOFA score on arrival, number of SIRS criteria at diagnosis, site of infection, cultures (including results of blood cultures taken in the first hour), bacterial isolates, checklist package of six hours, use of corticosteroids for septic shock, use of protective ventilation, blood glucose control, blood glucose average in the first 24 hours and PCT clearance of 24 and 48 hours .

Dosages of procalcitonin in serum were performed at diagnosis of sepsis and repeated at the end of the first 24 and 48 hours of treatment beginning. The determinations were carried out by the technique of electrochemiluminescence (ECLIA). The reagent used in these assays was developed in collaboration with Brahms Diagnostica, Berlin, Germany.

The procalcitonin clearance (PCT-c) was calculated using the formula: initial PCT less than PCT of 24 and 48 hours, divided by the initial and PCT, then multiplied by 100.

Results were expressed as mean \pm standard deviation, median with interquartile ranges or proportions. Comparisons between categorical variables were performed with Fisher's exact and chi-square tests, and between continuous variables with Student's t or Mann-Whitney U. tests

To calculate the sample size we used results of study comparing PTC-c between survivors and non-survivors, analyzing population of patients with septic shock¹⁷. We reached $n = 28$ by using the two-samples ratio test (test power of 0.8 and alpha level of 0.05).

RESULTS

Twenty-eight patients were included. Table 1 shows the characteristics of the study population. Nineteen patients were clinical, nine surgical; in 13 patients (46.4%) the source of sepsis was pulmonary, abdominal in seven patients (25.0%), urinary infection in five (17.9%) and soft tissue in three cases (10.7%). Fifteen patients had severe sepsis and septic shock¹³. Overall mortality was five patients (17.9%), three with septic shock.

Twenty-eight PCT determinations were performed at diagnosis of sepsis, 27 after 24 hours and 26 after 48 hours. The initial median concentration of 24 hours and 48 hours is shown in Table 2. The initial concentration was not significantly different between survivors' and non-survivors' groups, but the differences between the two groups after 24 and 48 hours were expressively statistically significant. There was no difference in the number of SIRS criteria. The 24-hour procalcitonin clearance proved to be significantly higher in the survivors' group (3.0 versus -

300.0, $p = 0.028$). Although the 48-hour procalcitonin clearance has shown higher results in the survivors' group when compared to the non-survivors', the difference did not reach statistical significance.

DISCUSSION

This study corroborates the results of previous analyzes showing that dynamic changes of procalcitonin, translated by plasma concentrations and clearance after 24 and 48 hours, are effective biomarkers for prognosis of severe sepsis and septic shock. This study failed to demonstrate efficiency of the number of SIRS criteria identified in the initial assessment of the patient to distinguish survivors from non-survivors.

Sepsis and its complications represent the main cause of death in intensive care units. Although initiatives such as the Surviving Sepsis Campaign have brought substantial improvement to patient survival, they do not incorporate indicators that can identify patients with early unfavorable prognosis. This would allow reassessments of patients regarding diagnosis of complications and need for changes in treatment that could, in time, reverse the unfavorable course.

Several prognostic indices are now used in intensive care units. The two most widely in use and are validated APACHE (Acute Physiology and Chronic Health Evaluation) and SAPS (Simplified Acute Physiology Score), which, however, have limited their utility to the first 24 hours of treatment and do not offer the possibility to inform about the progress of patients in response to the first few hours of treatment. The SOFA score (Sequential Organ Failure Assessment), which assesses organ dysfunction, has been proposed as a prognostic score of evolutionary value, and several studies have shown that, for example, the delta SOFA (72-hour SOFA minus admission SOFA) can separate survivors from no survivors with enough accuracy^{24,25}. Nonetheless, SOFA as an assessment of organ dysfunction, which typically have several phases including periods of little or no clinical and laboratory manifestations, may depend on an excessively long time to identify an unfavorable progression, thereby undermining the possibility of early identification of adverse developments.

From the definitions of SIRS and sepsis by consensus conferences, several studies have tried to establish the relationship between inflammatory response and progression of sepsis to severe sepsis (sepsis associated with organ dysfunction) and septic shock (sepsis complicated by

Table 1 - Characteristics of the study population (n = 28).

	n	(%)
Women	12	(42.8)
Clinical / Surgical	19 / 9	
APACHE IV. mean (SD)	74.9	(34.7)
Number of SIRS criteria. mean (SD)	2.7	(0.7)
Number of organ dysfunctions. mean (SD)	2.5	(0.9)
Site of sepsis		
lung	13	(46.4)
abdomen	7	(25.0)
urinary	5	(17.9)
Soft tissue	3	(10.7)
Severe sepsis / septic shock. n	13 / 15	
ICU mortality. n (%)	5	(17.9)

Table 2 - PCT results in survivors and non-survivors (n = 28).

	Survivors n =23		Non-Survivors n = 5		p value
Number of SIRS criteria. mean (SD)	2.77	(0.75)	2.60	(0.54)	0.63
PCT i. median (IIQ)	8.8	(2.1 – 12.7)	10.8	(2.2 – 55.0)	0.41
PCT 24 h. median (IIQ)	8.2	(3.4 – 14.8)	68.6	(15.8 – 82.3)	0.003
PCT 48 h. median (IIQ)	4.6	(2.4 – 9.4)	31.0	(16.2 – 83.9)	0.003
PCT-c 24 h. median (IIQ)	- 3.0	(-371.0 – 32.5)	- 300.0	(- 1.080.0 – 48.0)	0.028
PCT-c 48 h Mediana (IIQ)	- 0.0	(- 158.0 – 58.5)	- 290.0	(- 1.175.0 – 13.5)	0.10

PCTi, PCT 24 h, PCT 48 h = Initial, 24-hour and 48-hour concentrations of procalcitonin (ng / ml), respectively.
PCT-c 24h, PCT-c 48 h = Procalcitonin clearance at 24 and 48 hours (%)

hemodynamic instability) and their impact on mortality. Rangel-Frausto et al.¹⁹ analyzed more than 2500 patients with SIRS of infectious cause and found a significant correlation between severity of SIRS translated by the number of positive criteria and mortality. Patients with four SIRS criteria had twice the mortality rate of those who had three criteria, and the latter, on their turn, displayed mortality 50 % higher than those with only two SIRS criteria. Sprung et al.²⁰, in a study that included more than 3000 patients from 198 ICUs of 24 European countries, showed that the presence of more than two SIRS criteria in infected patients was associated with increased risk of subsequent development of severe sepsis and septic shock and was also associated with significantly increased mortality. The authors conclude by suggesting that the criteria for SIRS, which are easy to measure, should be compared in future studies with other markers for diagnosis and prognosis of sepsis.

Procalcitonin has been proposed as a biomarker specific for bacterial infections. In normal individuals its concentrations are very low or undetectable (0.1 to 0.5 ng/ml). In the situation of colonization and viral infections its levels remain below 2ng/ml. In sepsis levels are generally above 3ng/mL and may reach more than 100ng/ml in septic shock.

More recently, PCT has been used as a biomarker of prognosis. In severe sepsis and septic shock, isolated determinations of serum PCT have shown variable results^{10,11}. Most studies consider it not possible to predict the outcome of critically ill patients based on high levels of PCT. On the other hand, the evaluation of serial PCT values proved to be more useful in assessing prognosis. In patients with pulmonary sepsis, reductions in PCT concentration above 30% between the second and third day of were identified as determinants of survival, with odds ratio of 2.9²⁶. In patients with community-acquired pneumonia with decreased PCT from day one to day three, it was related to survival with 89% specificity, 82% negative

predictive value and 71% positive predictive value²⁵. Karlsson et al.¹² showed in a recent study that mortality in patients with severe sepsis is smaller than in those whose PCT concentrations decreased by over 50% when compared to initial values. Claeys et al.¹³, analyzing patients with septic shock, showed that after 48 hours of admission, PCT levels only decreased substantially in the surviving. Guan et al.¹⁶ prospectively analyzed 37 patients with septic shock and showed that all survivors had lower levels of PCT during ICU stay and all non-survivors showed progressive elevation of PCT levels. Recently, Suberviola et al.²⁶ and Ruiz-Rodriguez et al.¹⁷ introduced the concept of procalcitonin clearance in order to assess the evolutionary behavior of PCT and its relationship with mortality. In both studies the clearance of PCT was determined by the formula: (initial value - final value) / initial value X 100. Suberviola et al.²⁶ studied 88 patients with septic shock admitted to a general ICU. The study showed that the mortality in patients with increased clearance of PCT in the first 72 hours of treatment was significantly lower than in patients with reduced clearance in the same period (15.4% versus 58.8%, p < 0.01). Ruiz-Rodriguez et al.¹⁷ determined the clearance of PCT after 24, 48 and 72 hours of treatment of 27 patients with septic shock and showed a significant increase in PCT clearance in survivors and reduction in non-survivors.

This study has limitations. The most important of these is the small sample size that limits the required rigorous statistical analysis. However, it stimulates analysis with larger samples and comparison of procalcitonin clearance with other markers of outcomes, such as delta SOFA.

In conclusion, persistently elevated concentrations of plasma procalcitonin in patients with severe sepsis and septic shock are associated with significantly higher mortality. The prognosis of severe sepsis and septic shock can be evaluated by 24-hour PCT clearance.

R E S U M O

Objetivo: Avaliar a tendência da concentração plasmática e do clearance de procalcitonina (PCT-c) como biomarcadores de prognóstico de pacientes com sepse grave e choque séptico, comparado a um outro marcador precoce de prognóstico representado pelo número de critérios de SIRS no momento do diagnóstico da sepse. **Métodos:** Estudo de coorte prospectivo observacional onde foram incluídos pacientes com sepse grave e choque séptico. A concentração sérica de procalcitonina foi determinada no momento do diagnóstico da sepse e após 24 e 48 horas. Foram coletados dados demográficos, escore APACHE IV, escore SOFA na chegada, número de critérios de SIRS no momento do diagnóstico, sítio da infecção e resultados microbiológicos. **Resultados:** Vinte e oito pacientes foram incluídos, 19 clínicos e nove cirúrgicos. Em 13 (46,4%) a fonte da sepse foi pulmonar, em sete abdominal (25,0%), em cinco urinária (17,9%) e de partes moles em três casos (10,7%). Quinze pacientes tinham sepse grave e 13 choque séptico. A mortalidade global foi cinco pacientes (17,9%), três deles com choque séptico. Vinte e oito determinações de PCT foram realizadas no momento do diagnóstico da sepse, 27 após 24 horas e 26 após 48 horas. A concentração inicial não se mostrou expressivamente diferente entre os grupos sobreviventes e não sobreviventes, mas as diferenças entre os dois grupos após 24 e 48 horas alcançaram significância estatística expressiva. Não se observou diferença em relação ao número de critérios de SIRS. O clearance de procalcitonina de 24 horas mostrou-se expressivamente mais elevado no grupo de sobreviventes (-3,0 versus -300,0, p=0,028). Embora o clearance de procalcitonina de 48 horas tenha mostrado resultado mais elevado no grupo de sobreviventes comparado aos não sobreviventes, a diferença não alcançou significância estatística. **Conclusão:** Concentrações persistentemente elevadas de procalcitonina no plasma, assim como, redução do PCT-c 24 horas, associaram-se à elevação expressiva da mortalidade de pacientes com sepse grave e choque séptico.

Descritores: Pacientes. Prognóstico. Sepse. Choque séptico. Marcadores biológicos.

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Address for correspondence:

Orlando Jorge Martins Torres

E-mail: o.torres@uol.com.br