ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 5.2
IJAR 2018; 4(8): 211-214
www.allresearchjournal.com
Received: 03-06-2018
Accepted: 04-07-2018

Dr. Jyoti Sharma
DNB Pediatrics, Institute of Child Health, Sir Ganga Ram Hospital, New Delhi, India

Dr. Roop Sharma
Fellow, PICU, Sir Ganga Ram Hospital, New Delhi, India

Correspondence
Dr. Roop Sharma
Fellow, PICU, Sir Ganga Ram Hospital, New Delhi, India

Procalcitonin: Biomarker in pediatric sepsis

Dr. Jyoti Sharma and Dr. Roop Sharma

Abstract
Introduction: Sepsis is a growing problem worldwide with a relatively high mortality rate. Immediate treatment is required, necessitating quick and accurate diagnosis. Taking into account the new definition of sepsis in children and evaluating the need for effective and rapid laboratory indicator, we studied the role of serum procalcitonin (PCT) as a biomarker in diagnosis and prognosis of sepsis in children.
Methods: This prospective study was done in a pediatric intensive care unit (PICU) of a tertiary care centre. 149 patients with sepsis were included for the study with an age >28 days and <16 years & PICU stay>24 hours. PCT was measured at the time of admission. Patients were followed up throughout their hospital stay and outcome data was obtained.
Results: Of the 149 patients, 93 survived while 56 died. PCT was not significantly associated with increased mortality in our study cases (p=0.346). Serum PCT values >2 ng/ml reported 52.6% sensitivity, 65.5% specificity, 55% positive predictive value and 65% negative predictive value to diagnose sepsis. Pediatric risk of mortality (PRISM) and pediatric logistics organ dysfunction **(**PELOD) scores were independently associated with mortality and also had a strong correlation with serum PCT values.
Conclusions: High serum PCT levels has poor association with mortality in patients of sepsis. Although, PCT has strong association with current prognostic score, more multicentre studies involving higher number of patients are needed to evaluate role of PCT in sepsis.

Keywords: Biomarkers, children, procalcitonin, sepsis

Introduction
Sepsis is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation therapies [1]. The events following sepsis involve pro-inflammatory and anti-inflammatory processes, humoral and cellular reactions and circulatory abnormalities [2, 3]. Diagnosis of sepsis in children is difficult in everyday practice for many reasons: the clinical signs and symptoms in children are very variable and nonspecific at the start of the infection; microbiological culture results are expected only after 48-72 hours and false negatives are common. In 2002, an International Sepsis Consensus Conference (ISCC) held in USA led to framing and adoption of specific clinical definitions for sepsis [4].
Early diagnosis and stratification of severity of sepsis is very important, increasing the possibilities of initiating timely and specific treatment [5, 6].
It remains difficult to differentiate sepsis from other non-infectious causes of systemic inflammatory response syndrome (SIRS). Laboratory tests are as important as physiological parameters for the early diagnosis of sepsis. Biomarkers have an important place because they can indicate the presence or absence or severity of sepsis [7, 8]. Other potential uses of biomarkers include roles in prognostication, guiding antibiotic therapy, evaluating the response of therapy and recovery from sepsis predicting sepsis complications and the development of organ dysfunction [9].
New research and novel understanding of the molecular basis of the disease reveals an abundance of exciting new markers that may be of utility in clinical practice. One such marker is serum procalcitonin (PCT). PCT, the pro-hormone of calcitonin, was described as a new and innovative parameter of infection in 1993 [10]. Serum levels are very low in healthy individuals (< 0.5 ng/ml) and in severe infections can reach up to 1000 ng/ml without changes in serum calcitonin levels [11]. Assicot *et al*. investigated its biosynthesis, molecular structure and amino acid sequence, and studies by Becker *et al*. [12] and Meisner *et al*. [13]

have related it to other pro inflammatory cytokines (interleukin- 6 and tumor necrosis factor-alpha). Rapid induction starting 3 hours after the injection of endotoxin in the bloodstream of healthy individuals has been demonstrated, with a peak at 6 hours and a half-life of 25 to 30 hours [14]. The same authors demonstrated that there was no increase in CRP levels 6 hours after the injection of endotoxin and that the drop in CRP concentrations was more delayed than that of PCT in these patients [14]. Because of its shorter half-life and the fact that elevated concentrations are achieved earlier than with CRP, PCT can offer advantages compared with CRP in the differential diagnosis of febrile syndrome in children. Several clinical studies have confirmed the superior diagnostic utility of serum levels of procalcitonin in sepsis and their greater reliability, compared to other markers, in following the course of illness [15, 16].

Taking into account the new definition of sepsis in children and evaluating the need for effective and rapid laboratory (quantitative) indicator, we studied the values serum PCT in diagnosis and prognosis of sepsis in children.

Methods

This was an analytical prospective study conducted in the pediatric intensive care unit (PICU) of Sir Ganga Ram Hospital, New Delhi over a period of 16 months from 1st May 2012 to 31st August 2013. Approval was taken from hospital ethics committee and written consent was obtained from parents.

Children were selected on the basis of sepsis definition defined by the International Pediatric Sepsis Consensus Conference.2 149 patients with sepsis were included for the study with an inclusion criteria of age >28 days to 16 years of age, who stayed for more than 24 hours in PICU. Exclusion criteria included (1) pediatric surgical, trauma and burn cases, (2) children dying within 24hours of PICU admission, (3) autoimmune diseases, (4) evidence of malaria, (5) diagnosis of hemophagocytic syndrome, (6) recipient of blood transfusion in the last 4 months, (7) cases of hepatitis, (8) children with other causes of shock, not due to sepsis itself, e.g., cardiogenic, anaphylactic, and dengue shock, (9) children with known malignancies and immunosuppressive treatment.

Following data was collected for the eligible enrolled patients: age, gender, primary organ involvement, duration of mechanical ventilation, length of stay in the PICU and hospital along with final outcome (survival/mortality). Pediatric risk of mortality score (PRISM) and pediatric logistic organ dysfunction score (PELODS) were used to assess the severity of illness and organ dysfunction. The results of all the investigations necessary for routine management sent by PICU team at admission and in the next 24 hours were recorded. Serum PCT was measured at the time of admission. Approval was taken from hospital ethics committee and written consent was obtained from parents.

Continuous variables were presented as mean ± standard deviation or median (minimum-maximum) as per the distribution. Categorical variables were expressed as frequencies (%). Differences between groups were assessed with Chi-square or Fisher's exact test for categorical variables. Unpaired t test was used for comparison of continuous variables between the two groups. For non-parametric data, Mann Whitney U test was used. Statistical analysis was performed with SPSS version 17.0 program for Windows (SPSS Inc., Chicago, IL, USA).

Results

149 children were enrolled in the study with a median age of 1.8 (0.5- 6) years with maximum cases (59.1%) below 3 years of age (Table 1). There were 104 (69.8%) boys. Out of 149 patients, total number of deaths were 56 (37.6%).

Table 1: Distribution of study group according to gender

Gender	Frequency	Percentage (%)
Male	104	69.8%
Female	45	30.2%
Total	149	100.0%

Respiratory system (RS) was involved in majority (34.9%) of the cases followed by central nervous system (CNS) (17.4%), gastrointestinal tract (GIT) (14.1%), genitourinary tract (GUT) (9.4%) and cardiovascular system (CVS) (1.3%). Although, higher PCT values were seen in patients with GIT and RS involvement, no statistically significant difference was found (p= 0.062 on admission, p =0.082 at 24 hours).

A bacteriological analysis from microbiology laboratory revealed culture positivity in 40.9% cases. The positive isolates were from blood, urine, pus, endotracheal secretion and bronchoalveolar lavage.

In our study, the median duration of stay in PICU was 6 days (range 4-12 days) and the hospital stay was 12 days (range 6-20.50 days). The duration of PICU and total hospital stay was significantly higher in survivors (p=0.001, $p<0.001$ respectively) as compared to non survivors. There was no significant correlation between duration of PICU and hospital stay with the PCT levels (p=.175, p=.078, respectively)

In the present study, requirement for mechanical ventilation was compared with outcome of patients. In 114 patients who required mechanical ventilation, 64 (56.1%) survived and 50 (43.9%) died. We also studied the association of prolonged duration of mechanical ventilation with PCT & it was found to be significant (p=0.001).

The median values of PRISM score at 12 hours and at 24 hours were 11 (range: 5-17) and 10 (range: 5-16) respectively. Median values of PELOD score on day 1 and day 2 were 21 (range: 11-31) and 21 (range: 10.50-31) respectively. We also tested the correlation of PRISM/PELODS with PCT values and found that serum PCT had a strong correlation with PRISM at 12 hours and 24 hours (p=0.001, $p<0.001$, respectively) and with PELOD score on day 1 (r = 0.642; p =0.03) and day 2 (r=0.568; $p<0.001$)(Table 2). Higher PRISM (> 15 at 12 hours) and PELOD (> 21 on day 1) scores were independently associated with increased mortality ($p<0.001$, p=0.001, respectively).

Table 2: Pearson correlation between PRISM, PELOD and serum PCT level.

		PCT (admission)
PRISM (12 hours)	Pearson Correlation Coefficient(r) p-value	0.746 0.001
PRISM (24 hours)	Pearson Correlation Coefficient(r) p-value	0.849 <0.001
PELODS (Day 1)	Pearson Correlation Coefficient(r) p-value	0.642 0.03
PELODS (Day 2)	Pearson Correlation Coefficient(r) p-value	0.568 <0.001

Median value of PCT on admission was 2.80 (0.48-34.20) ng/dl. Contrary to earlier studies, PCT was not significantly associated with increased mortality in our study cases (p=0.346) (Table 3). Furthermore, serum PCT values >2 ng/ml had a low diagnostic accuracy reporting 52.6% sensitivity, 65.5% specificity, 55% positive predictive value (PPV) and 65% negative predictive value (NPV).

Table 3: Comparison of PCT with mortality

	Survivor (n=93)		Non Survivor (n=56)		p Value
	Median	IQR	Median	IQR	
PCT (admission)	2.40	0.43-34.20	5.87	0.78-38.60	0.346

Discussion

Sepsis caused by infection remains a major cause of mortality and morbidity among children. Several inflammatory markers have failed to meet the requirements for early diagnosis and prognostication of sepsis. This study evaluated the potential value of measuring PCT in patients with clinically suspected and proven sepsis and correlated it with outcome of patients.

In our study the median age of presentation was 1.8 years (Table 1). The median age mentioned in study by Carvalho *et al* was 24 months [13] and 6(2–100) months in study by Garcia *et al*. [14] Number of males (69.8%) were greater than females (30.2%) in our study. There was no significant sex difference in other studies by Carvalho *et al* and Bennett *et al*. [13, 16] A higher proportion of male patients admitted in our PICU was probably due to socio-cultural gender inequality in northern India.

In our study maximum number of patients with sepsis had a primary focus of infection in RS, followed by CNS and GIT similar to the earlier studies by Farris *et al*. [17] and Bustamante *et al*. [15] No significant relation was found between PCT values and primary organ involved. We could not find any studies citing relation of PCT and organ affected.

Out of 149 patients in our study, 40.9% had culture positive sepsis. Lack of culture yield could be possibly due to influence of prior antibiotic treatment received. Total mortality in our study was 37.6%. In other studies done previously by Hartman *et al*. Bustamante *et al* and Bennett *et al*. total mortality reported was 8.9%, 18% and 22%, respectively [15, 16, 19].

Scores that assess clinical and biological variables, such as PRISM, are very useful for the prognosis of children with sepsis, and they are not difficult to perform, although they are time consuming. PCT levels had a strong correlation with the PRISM score as well as PELOD score in our study. Similar to our study, Juan *et al* found strong association of PCT values with PRISM score in children with sepsis [23].

While PCT levels 0.5 ng/ml to 2.0 ng/ml may indicate sepsis, levels above 2.0 ng/mL but less than 10 ng/ml indicate a high risk for progression to organ dysfunction [24]. PCT level > 2ng/ml has been shown to have low diagnostic accuracy in our study. This was contrary to the results of previous studies reporting sensitivity values of 74.8-100%, specificity values of 70-100%, PPV values of 55–100% and NPV values of 56.3-100% [25-28] One possible explanation for low diagnostic accuracy in our study could be that ours is a tertiary care centre and patients have received prolonged antibiotic treatment before being referred to our centre.

As a biomarker for bacterial infection, most studies find PCT to be accurate [29-31] and more useful than other common inflammatory markers [25-27]. Studies have also reported PCT being used as a prognostic marker, indicating severity of sepsis and mortality from sepsis [25, 28, 32]. There are some limitations of our study. Firstly, we studied only cases of clinical sepsis and no controls were included in our study. Secondly, we did not exclude cases who were admitted/treated elsewhere before being referred to our hospital.

The use of PCT in risk stratification and prognosis and/or mortality prediction has been increasingly evaluated, although more robust studies in pediatric patients are needed. The level of evidence published to date still preclude considering PCT a biomarker for routine use in clinical practice as a risk stratifier and a prognostic predictor or even to guide the duration of antibiotic treatment and bedside decision making. More multicentre studies involving higher numbers of patients, preferably in different regions of the world, are needed.

Funding: No funding sources

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29:1303-1310.
2. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003; 348:138-150.
3. Gullo A, Bianco N, Berlot G. Management of severe sepsis and septic shock: challenges and recommendations. Crit Care Clin. 2006; 22:489-501.
4. Randolph AG. The purpose of the 1st international sepsis forum on sepsis in infants and children. Pediatr Crit Care Med. 2005; 6:S1-S2.

5. Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S *et al*. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006; 34:1589-1596.
6. Zambon M, Ceola M, Almeida-de-Castro R, Gullo A, Vincent JL. Implementation of the Surviving Sepsis Campaign guidelines for severe sepsis and septic shock: we could go faster. J Crit Care. 2008; 23:455-460.
7. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001; 69:89-95.
8. Marshall JC, Reinhart K. Biomarkers of sepsis. Crit Care Med. 2009; 37:2290-2298.
9. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R *et al*. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med. 2008; 36:296-327.
10. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuhon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993; 341:515-8.
11. Meisner M. Procalcitonin. A new innovative marker for severe infection and sepsis: biochemical and clinical aspects. Brahms Diagnostica, 1996, 14-21.
12. Becker KL, Nylen ES, Thompson KA. Preferential hypersecretion of procalcitonin and its precursors in pneumonitis: A cytokine-induced phenomenon, Endotoxemia and Sepsis Congress, Philadelphia, 1995, 19-20.
13. Meisner M, Tschaikowsky K, Spiebl C, Schu ttler J. Procalcitonin: a marker or modulator of acute immune response. Intensive Care Med. 1996; 22:14.
14. Dandona P, Nix D, Wilson MF. Procalcitonin increase after endotoxin injection in normal subjects. J Clin Endocrinol Metab. 1994; 93:54-8.
15. Whang KT, Steinwald PM, White JC, Nylen ES, Snider RH, Simon GL *et al*. Serum calcitonin precursors in sepsis and systemic inflammation. J Clin Endocrinol Metab. 1998; 83:3296-301.
16. Werra I, Jaccard C, Corradin SB, Chiolero R, Yersin B, Gallati H *et al*. Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. Crit Care Med. 1997; 25:607-13.
17. Nakamura A, Wada H, Ikejiri M, Hatada T, Sakurai H, Matsushima Y *et al*. Efficacy of procalcitonin in the early diagnosis of bacterial infections in a critical care unit. Shock. 2009; 31:591-93.
18. Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. Crit Care Med. 2003; 31:1737-1741.
19. Tang BM, Eslick GD, Craig JC, McLean AS. Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis. 2007; 7:210-217.
20. Dahmet MK, Randolph A, Viatli S, Quasney MQ. Genetic polymorphisms in sepsis. Pediatr Crit Care Med. 2005; 6:61-73.
21. Ng PC, Lam HS. Diagnostic markers for neonatal sepsis. Curr Opin Pediatr. 2006; 18:125-31.
22. Carcillo JA, Planquois JS, Goldstein B. Early markers of infection and sepsis in newborns and children. Adv Sepsis. 2006; 4:118-25.
23. Juan CF, Blanco-Quirós A, Asensio J, Arranz E, Garrote JA**,** Nieto M. Serum procalcitonin in children with suspected sepsis: A comparison with C-reactive protein and neutrophil count. Pediatr Crit Care Med. 2003; 4(2):190-95.
24. Meisner M. Update on Procalcitonin Measurement. Ann Lab Med. 2014; 34(4):263-273.
25. Martini A, Gottin L, Menestrina N, Schweiger V, Simion D, Vincent JL. Procalcitonin levels in surgical patients at risk of candidemia. J Infect. 2010; 60(6):425-430.
26. Kim KE, Han JY. Evaluation of the clinical performance of an automated procalcitonin assay for the quantitative detection of bloodstream infection. Korean J Lab. Med. 2010; 30(2):153-159.
27. Fioretto JR, Martin JG, Kurokawa CS. Comparison between procalcitonin and C-reactive protein for early diagnosis of children with sepsis or septic shock. Inflamm. Res. 2010; 59(8):581-586.
28. Deis JN, Creech CB, Estrada CM, Abramo TJ. Procalcitonin as a marker of severe bacterial infection in children in the emergency department. Pediatr. Emerg. Care. 2010; 26(1):51-63.
29. Arnon S, Litmanovitz I. Diagnostic tests in neonatal sepsis. Curr. Opin. Infect. Dis. 2008; 21(3):223-227.
30. Limper M, de Kruif MD, Duits AJ, Brandjes DPM, van Gorp ECM. The diagnostic role of procalcitonin and other biomarkers in discriminating infectious from non-infectious fever. J Infect. 2010; 60(6):409-416.
31. Oshita H, Sakurai J, Kamitsuna M. Semi-quantitative procalcitonin test for the diagnosis of bacterial infection: clinical use and experience in Japan. J. Microbiol. Immunol. Infect. 2010; 43(3):222-227.
32. Schneider CP, Yilmaz Y, Kleespies A, Jauch KW, Hartl WH. Accuracy of procalcitonin for outcome prediction in unselected postoperative critically ill patients. Shock. 2009; 31(6):568-573.