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Original Research Article

Study of serum levels of CRP and procalcitonin as early marker of sepsis in children with sepsis above neonatal age group

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ABSTRACT

Background: Sepsis caused by infection remains a major cause of mortality and morbidity among children. Blood culture though gold standard requires lot of time for diagnosis, hence it's necessary to rely on early diagnostic markers such as blood counts, micro-ESR, CRP, Procalcitonin. The objective of this study is to evaluate the serum levels of CRP, Procalcitonin as reliable and as early marker of sepsis in pediatric patients above neonatal age group.
Methods: Children aged above neonatal age group with clinically suspected sepsis as per the definition given by the International Paediatric sepsis Consensus Conference were selected. Patients were classified as those with sirs, sepsis, severe sepsis and septic shock. Patients were divided into two groups one with culture proven sepsis and the other with non-culture proven sepsis. All patients had CRP, Procalcitonin levels measured at admission and 24hrs after admission. The primary outcome was to determine reliable marker in differentiating between the culture proven and non-culture proven sepsis, and to determine the early marker of sepsis.
Results: Total 104 patients formed the study group, of which 42 belonged to SIRS group, 26 were sepsis, 19 were severe sepsis and 17 were septic shock. A total of 36 cases had culture positive. In present study PCT was found to be more reliable marker of sepsis as the sensitivity and specificity of PCT was more than CRP and AUC for PCT was significantly higher than CRP. PCT was found to be early marker as the AUC for CRP at 24hrs was significantly more than AUC for CRP at admission and there was no statistically significant difference between AUC for PCT at admission and 24 hours after admission.
Conclusions: Both CRP and PCT levels have favourable test performance but PCT is more reliable. PCT is earlier to rise compared to CRP.

Keywords: C-reactive protein, Early marker, Paediatric sepsis, Procalcitonin, Reliable marker

INTRODUCTION

Sepsis caused by infection remains a major cause of mortality and morbidity among children.[1,2] Clinical experience and various studies have shown that the most important measure in reducing mortality from sepsis is early identification of the condition and prompt initiation of therapy.[3-6] Diagnosis of sepsis in children is difficult in everyday practice for many reasons, the clinical signs in children are very variable at the start of the infection; microbiological culture results are expected only after 48-72 hours; and false negatives are common. The turning-point in clinical recognition of sepsis is considered to have been the International Sepsis Consensus Conference in the USA in 2002, in which specific clinical definitions of systemic inflammatory response syndrome (SIRS) and sepsis in children were adopted.[3] Laboratory tests are as important as physiological parameters for the early

diagnosis of sepsis. During the last decade, measurement of C reactive protein (CRP), a good inflammatory marker, has been added to the set of hematological tests (total leukocyte count, neutrophils, band form counts) that have long been used in clinical practice. However, it does not have the specificity required to distinguish viral from bacterial infections. The calcitonin prohormone procalcitonin (PCT) has seldom been used clinically; its level is low in healthy individuals (<0.5ng/ml). Levels of procalcitonin rise during bacterial infections but are unchanged during viral infections.[7-9] The objective of this study is to evaluate serum levels of CRP, Procalcitonin as reliable markers of sepsis and to determine the early marker among the two in pediatric patients aged beyond neonatal age group.

METHODS

This is a prospective study carried out in PICU of S N medical college between January 2016 and December 2016. Children with age group above neonatal age group fulfilling the International Sepsis Consensus Conference in the USA in 2002, definition for SIRS, Sepsis and septic shock were selected. Proper consent was taken from the parents of all the children who formed the study group CRP and Procalcitonin levels were measured at admission and 24 hours later. Patients were divided into two groups as culture positive group and culture negative group, and the sensitivity, specificity, PPV and NPV of CRP and procalcitonin levels were compared. Also, the levels of CRP and procalcitonin were compared between culture proven and culture negative sepsis at admission and 24hours later to determine the early marker. Ethical committee clearance was taken. Method of collecting data: history and clinical examination using a systemically designed proforma, relevant laboratory investigations, serial measurements of CRP, procalcitonin levels at admission and 24hrs after admission.

Inclusion criteria

- Children with age group above neonatal age, fulfilling the International Sepsis Consensus Conference in the USA in 2002, definition for SIRS, Sepsis and septic shock

Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis and septic shock[10]

SIRS (systemic inflammatory response syndrome)

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count: Core temperature of >38.5°C or <36°C. Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or for children<1-year-old: bradycardia, defined as a mean heart rate<10th percentile for age in the absence of external vagal stimulus, blocker drugs, or congenital heart disease. Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anaesthesia. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or >10% immature neutrophils.

Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans).

Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

Septic shock

Sepsis and cardiovascular organ dysfunction.

Exclusion criteria

Non-infective causes that alter the levels of inflammatory markers like:

- Children with chronic inflammatory conditions: rheumatoid arthritis, inflammatory bowel disease, Wilson disease
- Children with malignancy.

RESULTS

This study included a total of 104 cases, 48 males and 56 females. Average age was 2.44years (2 months-12 years). Of the 104 cases 42 were SIRS, 26 were sepsis and 19 were severe sepsis and 17 were septic shock (Figure 1).

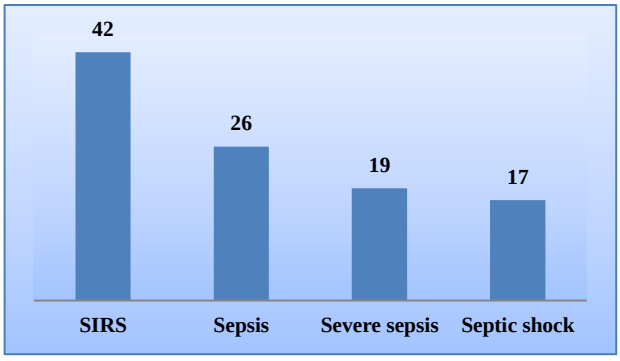


Figure 1: Distribution of study group according to the sepsis criteria.

There were 15 deaths. There was a total of 36 cases with positive culture.24 cases were blood culture positive, 4 were CSF culture positive, 5 were pleural fluid culture positive and 3 were urine culture positive (Figure 2).

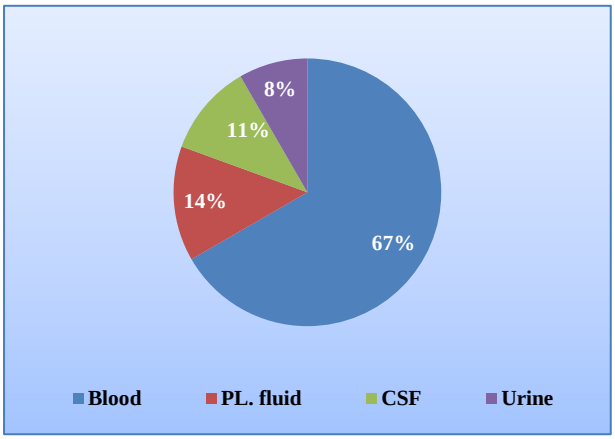


Figure 2: Culture positive cases.

The mean PCT level was 1.6ng/ml, 3.18ng/ml 14.17ng/ml and 23.85ng/ml for SIRS group, sepsis group, severe sepsis group and septic shock group respectively. The mean CRP levels were 9.76 mg/l, 18.59 mg/l and 50.6 mg/l and 105.8 mg/l respectively (Table 1).

The cases were divided into two groups definitive sepsis (culture proven) and probable sepsis (culture negative) and were compared. There was no statistically significant difference between the two group with respect to age, sex and duration of illness. The mean levels of CRP and PCT were significantly elevated in definitive sepsis group (Table 2).

Table 1: Mean levels of CRP and PCT.

	SIRS	Sepsis	Severe sepsis	Septic shock
Mean CRP (SD) mg/l	9.76 (6.38)	18.59 (19.26)	50.6 (23.78)	105.8 (62.26)
Mean PCT (SD) ng/ml	1.6 (1.56)	3.18 (2.89)	14.17 (8.83)	23.85 (17.22)

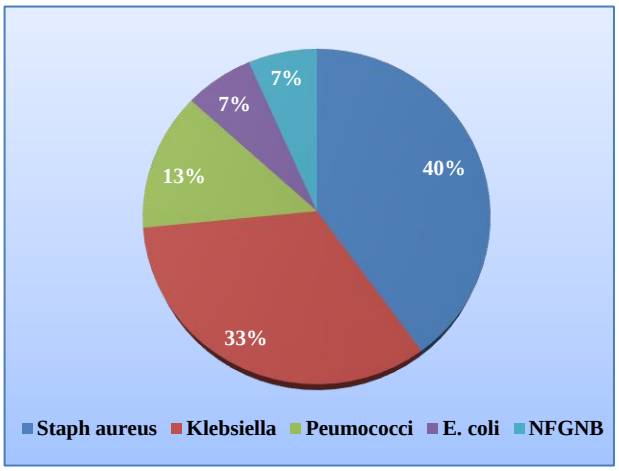


Figure 3: Organisms isolated.

Table 2: Comparison of data between definitive sepsis and probable sepsis.

	Definitive sepsis (culture positive) (n=36)	Probable sepsis (culture negative) (n=68)	P-value
Age-mean (minimal-maximal)	2.04 years (2 months-8 years)	2.85 years (3 months- 12 years)	0.34 (NS)
Gender girls/boys (number)	16/20	36/32	0.071 (NS)
Duration of illness- mean (minimal -maximal)	7.8 days (3 days-15 days)	6.6 days (2 days-10 days)	0.21 (NS)
Mean CRP levels mg/l (95%CI)	66.06 (59.06)	18.75 (21.83)	<0.0001 (S)
Mean PCT levels pg/ml (SD)	16.23 (15.54)	3.55 (4.78)	<0.0001 (S)

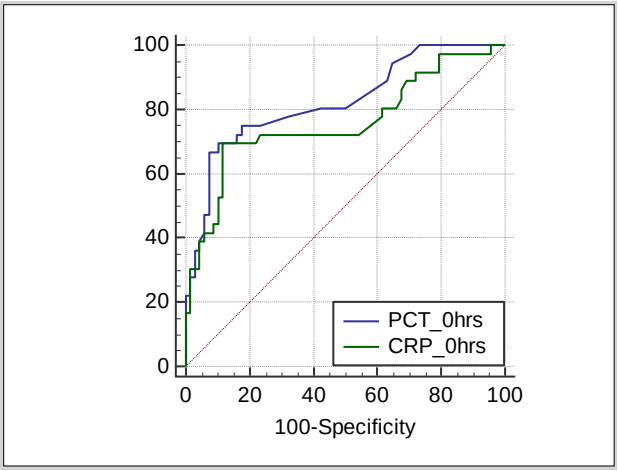
Table 3: Comparison of diagnostic accuracy between CRP and PCT.

Parameter	Sensitivity	Specificity	Positive predictive value	Negative predictive value	AUC*	P- value
CRP	72.22%	57.35%	47.27%	79.59%	0.648	0.0007
PCT	88.88%	83.82%	74.41%	93.44%	0.864	

*AUC-area under ROC curve.

The diagnostic accuracy of CRP and PCT were tested based on sensitivity, specificity, positive and negative predictive values and ROC curve.

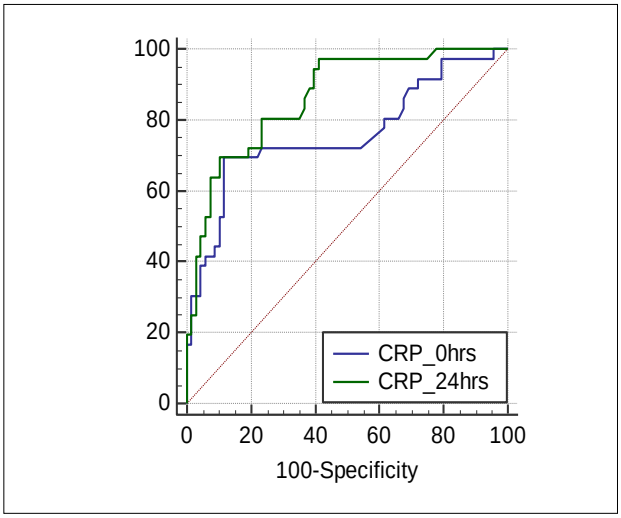
Cleary it was evident that PCT was significantly better than CRP (Table 3 and Figure 4).



PCT 0hrs ~ CRP 0hrs	
Difference between areas	0.0654
Standard error[a]	0.0193
95% Confidence interval	0.0276 to 0.103
z statistic	3.389
Significance level	P=0.0007

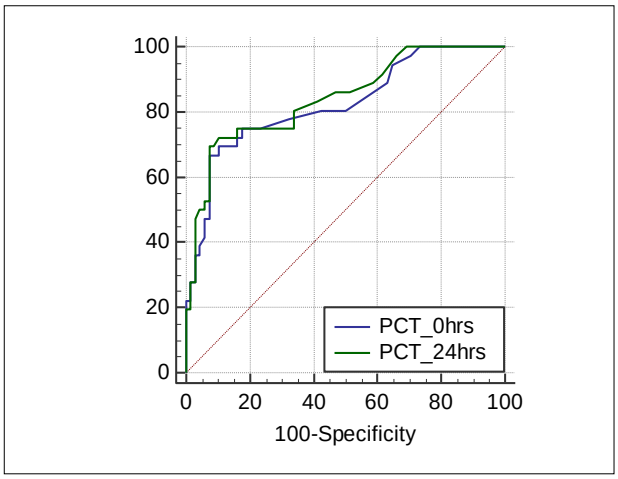
Figure 4: ROC curve comparing CRP and PCT.

The ROC curves for CRP and PCT were compared at 0hrs and 24hrs after admission. The AUC for CRP at 24hrs after admission was significantly higher than AUC at admission, whereas there is no statistically significant difference in AUC for PCT at admission and 24hrs after admission, indicating PCT as the early marker of sepsis (Figure 5 and 6).



CRP 0hrs ~ CRP 24hrs	
Difference between areas	0.105
Standard error[a]	0.0276
95% Confidence Interval	0.0511 to 0.159
z statistic	3.813
Significance level	P=0.0001

Figure 5: ROC curve comparing AUC for CRP levels at admission and 24hrs after admission.



PCT 0hrs ~ PCT 24hrs	
Difference between areas	0.0186
Standard error[a]	0.0214
95% Confidence interval	-0.0233 to 0.0605
z statistic	0.870
Significance level	P=0.3843

Figure 6: ROC curve comparing AUC for PCT levels at admission and 24hrs after admission.

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 of sepsis. This study saw the potential value of measuring the inflammatory markers C reactive protein (CRP), and procalcitonin (PCT) in patients with clinically suspected sepsis and was compared between culture positive and culture negative group. The results revealed that PCT was more superior biomarker than CRP in determining the presence of underlying infection in febrile pediatric patients. The sensitivity and specificity of PCT was significantly more than that of CRP in differentiating between culture positive and culture negative cases. In present study infection was proven by positive culture in 36% of the study group. Others had positive findings on clinical examination, imaging and laboratory tests. Pavare J et al, demonstrated 50% positive culture.[15]

In present study authors analyzed the acute phase reactants like CRP, procalcitonin in differentiating between culture positive and culture negative group at 0 hours and 24hours after admission. Procalcitonin had the best sensitivity and specificity among two. Procalcitonin of >2ng/ml had a sensitivity of 88.8% and specificity of 83.8% in differentiating between culture positive and culture negative group, with statistical significance ($p<0.0001$). Galetto-Lacour A et al, also had similar findings sensitivity of 93% and specificity of 74%.[11] Simon L et al, had sensitivity of 88% and specificity of 89%.[12] Suprin et al, had sensitivity of 89% and specificity

of 52%.[13] CRP>10mg/l had a sensitivity of 72.2% and specificity of 57.35% in differentiating between culture positive and culture negative groups which is statistically significant (p-0.035). Galetto-Lacour A et al, also had similar findings sensitivity of 79% and specificity of 79%.[11] Suprin et al, had demonstrated sensitivity 92% and specificity of 42% Simon et al found to have a sensitivity of 80% and specificity of 86%.[13,14] Early marker of sepsis: There was statistically significant difference between the ROC curves in differentiating between the culture positive and culture negative group at 0hrs and 24 hours of admission in case of CRP (p-0.0359) but there was no significant difference in case of PCT(0.556) indicating PCT as early marker. These results correspond to those of Casado-Flores J et al.[8]

The limitations of this study are the number of cases in the study group was very small, wide range of age group selection, to know the response to treatment the inflammatory markers must have been measured more frequently that is at least 12 hour.

CONCLUSION

Procalcitonin is clearly superior to CRP as biomarker of sepsis and it is earlier to rise compared to CRP.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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