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Original Article

Study of acute phase reactants in children with sepsis, with special reference to C-reactive protein and procalcitonin

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Abstract

Background: Several inflammatory markers have failed to meet the requirements for an early diagnosis of sepsis in children. Study results and trends show that measurement of the combination of biochemical markers offers the best prospects for research on early diagnosis of sepsis. **Objectives:** To evaluate the serum levels of C-reactive protein (CRP) and procalcitonin (PCT) as markers of early sepsis in pediatric patients. **Methods:** All the hospitalized children aged more than 28 days with clinically suspected sepsis, as per the definition given by International Pediatric Sepsis Consensus Conference, were selected. The patients were divided into two groups; one with culture proven sepsis and the other with culture negative sepsis. CRP and PCT levels were measured at the time of admission and 48 h after admission. **Results:** A 40 patients were studied, out of that 15 had culture positive and 25 had culture negative sepsis. The mean PCT level was significantly higher at admission than at 48 h after admission, and the mean CRP level was significantly lower at admission than at 48 h after admission indicating PCT as early marker of sepsis. **Conclusion:** CRP and PCT levels have favorable test performance in differentiating between culture positive and culture negative sepsis. PCT is earlier to rise compared to CRP and PCT is best in predicting the severity followed by CRP.

Key words: *Acute phase reactants, C-reactive protein, Procalcitonin, Sepsis*

Sepsis remains a major cause of mortality and morbidity among the children [1,2]. Clinical experience and various studies have shown that the most important measure in reducing the mortality from sepsis is early identification of the condition and prompt initiation of therapy [3-6]. However, early diagnosis of sepsis in children is difficult in everyday practice for many reasons such as variable clinical signs during initial period of infection, lag period of 48-72 h in getting microbiological culture results and false negative results.

Laboratory tests are as important as physiological parameters for the early diagnosis of sepsis. We may be close to finding the biological markers that will make the diagnosis more objective and more reliable than various clinical signs and symptoms. During the last decade, measurement of C-reactive protein (CRP) has been added to the set of hematological tests (total leukocyte count, neutrophils, and band form counts) that have long been used in clinical practice. CRP is an acute phase reactant released by the liver after the onset of inflammation or tissue damage. This protein is frequently used to differentiate between viral and bacterial infections [7,8].

The calcitonin prohormone procalcitonin (PCT) was described as a new and innovative parameter of infection in 1993. Serum levels are very low in healthy individuals (<0.5 ng/ml) which can reach up to 1000 ng/ml in severe infections without changes in serum calcitonin levels [9]. Levels of PCT rise during bacterial infections but are unchanged during viral infections [10-12]. Simon et al. have found that PCT and CRP can be used as markers to distinguish bacterial from viral infections with PCT having a higher sensitivity and specificity than that of CRP (92% vs. 86% and 73% vs. 70%) [13]. We planned this study to evaluate the beneficial effects of the combination of CRP and PCT to make an early diagnosis of sepsis in children.

METHODS

This prospective study was conducted at Indira Gandhi Institute of Child Health over a period of 1 year after obtaining approval from institutional ethics committee. All the children beyond neonatal age presenting with clinical features of sepsis and its different spectrum like severe sepsis and septic shock were included in the study after obtaining informed consent from the parents. Data were collected by taking the history and by clinical examination using a systemically designed proforma.

Inclusion Criteria

Children beyond the neonatal age group with suspected sepsis in the presence of at least one absolute criterion and additional criterion as defined by international pediatric sepsis consensus conference [14]. Absolute criteria include: (1) Core temperature of >38.5°C or <36°C or, (2) elevated or depressed leukocyte count for the age (not secondary to chemotherapy induced leukopenia) or >10% immature neutrophils. Additional criteria include tachycardia or tachypnea (defined as an increase in heart rate and respiratory rate respectively by more than 2 standard deviations above the values normal for that age).

Exclusion Criteria

Non-infective causes that alter the levels of inflammatory markers, such as chronic inflammatory conditions (including rheumatoid arthritis, inflammatory bowel disease, and Wilson's disease). Conditions with iron overload whether primary, e.g., hereditary hemochromatosis or secondary, e.g., transfusion overload, porphyria cutanea tarda, and ineffective erythropoiesis (in sideroblastic anemia or thalassemia), and hematological malignancy.

Relevant laboratory investigations were done such as total white blood cells count, differential count, erythrocyte sedimentation rate, platelet count and serial measurements of CRP and PCT levels at admission and 48 h after the admission. CRP and PCT were performed by using fully automated immunoturbidimetric assay. CRP level was considered raised if the result was >6 mg/L. PCT level was considered raised if the result was >2 ng/ml. Blood culture was performed by using agar based growth mediums. The volume of 5 ml of blood was collected into bile broth using standard techniques from all the patients with clinically suspected sepsis.

Diagnostic accuracy of the test was assessed by using ROC curve which denotes the diagnostic performance of a test or the accuracy of the test in sepsis cases. Accuracy is measured by the area under the ROC curve.

RESULTS

Total 40 cases met the inclusion criteria and were recruited in the study. Of these, 42.5% (n=17) cases had fever with tachypnoea, 67.5% (n=27) had fever with tachycardia while 67.5% (n=27) cases had fever and abnormal leukocyte count. Hypothermia was not noted in any patient. Clinical and demographic details of the study population are presented in Table 1. Out of 40 patients, 15 (37.5%) had culture-positive and 25 (62.5%) had culture-negative sepsis, and these had positive findings on clinical examination, imaging and laboratory tests.

Mean age in culture-positive group was 2.04 years while in culture-negative group, it was 2.85 years. Mean duration of illness was 7.8 and 6.6 days. Out of 40 patients, 17 were found to have a septic shock at the time of admission. The most common sources of sepsis were pneumonia (n=22) followed by urinary tract infection (n=12) and bacterial meningitis (n=6). Organisms isolated were *Staphylococcus aureus* (40%), *Klebsiella* (33%), *Escherichia coli* (13%), *Pneumococci* (7%), and non-lactose fermenting Gram-negative bacilli (7%).

Mean CRP level at admission (57.5 mg/L) was significantly lower (p=0.0074) as compared to mean CRP at 48 h later (73.4 mg/L), whereas mean PCT level at 0 h (35.3 ng/ml) was significantly higher (p=0.0094) as compared to mean PCT level at 48 h after admission (5.6 ng/ml).

The mean CRP level was significantly higher in culture positive group compared to culture-negative group at admission (p=0.0482) and 48 h after admission (p<0.0001). The mean levels of CRP were also significantly higher in septic shock group compared to non-septic shock group at admission (p=0.0008) and 48 h after admission (p=0.0183). Similarly, mean PCT levels were significantly higher in culture positive compared to culture-negative group at admission (p=0.0127) and 48 h after admission (p=0.0008). Mean PCT levels were also significantly higher in septic shock group compared to non-septic shock group at 0 and 48 h of admission.

However, total leukocyte count and band cell count were not significantly different between culture positive and culture-negative group at 0 h and 48 h after admission. There was also no significant difference in total leukocyte count between septic shock and non-septic shock patients at 0 and 48 h after admission. Although band cell count was not significantly different between septic shock and non-septic shock patients (0.1156) at 0 h, it was significantly higher in septic shock group compared to non-septic shock group (0.00018) at 48 h after admission.

Table 1: Clinical and demographic data of the study population

Clinical and demographic data	Culture positive	Culture negative	p value
Number of patients	15	25	
Age - mean (range)	2.04 years (2 months-8 years)	2.85 years (3 months-8 years)	0.34 (NS)
Male:Female ratio	11/4	11/14	0.071 (NS)
Duration of illness mean, (range)	7.8 days (3-15 days)	6.6 days (2-10 days)	0.21 (NS)
Receipt of antibiotics	73.33% (n=11)	68% (n=17)	0.721 (NS)

As depicted in Table 2, mean PCT levels were significantly higher in non-survivors as compared to survivors (p<0.0001). However, this difference was not significant in the case of CRP levels. Relative risk of mortality for PCT level >2 ng/ml was 2.77 (p<0.0001) while it was 1.7 (p=0.0027) for CRP level >40 mg/L.

Table 3 shows the sensitivity, specificity, positive and negative predictive values of different septic markers. The cut-off value of PCT at >2 ng/ml showed the highest sensitivity, specificity, positive as well as negative predictive values.

DISCUSSION

Sepsis remains a major cause of mortality and morbidity among children. Several inflammatory markers have failed to meet the requirements for an early diagnosis of sepsis. This study shows the potential value of measuring the inflammatory markers, CRP and PCT in patients with clinically suspected cases of sepsis.

CRP, an acute phase protein, was discovered by Tillet and Francis in 1930 in patients infected with *Streptococcus pneumoniae* [7]. CRP is synthesized in response to interleukin-6 which is produced following most of the bacterial infections. It is used routinely as a good marker of infection but lacks specificity for differentiating between viral and bacterial infections. If used alone as a marker, it can result in over judicious use of antibiotics. PCT, the prohormone of calcitonin was described as a new and innovative parameter of infection in 1993 [15]. Its serum levels can reach up to 1000 ng/ml in severe infections without changes in serum calcitonin levels, which was demonstrated by other authors [16,17]. Same authors demonstrated the rapid raise in serum PCT level within 3 h after injection of endotoxin to the healthy individuals with peak levels attaining at 6 h.

Table 2: Mean PCT and CRP levels of survivor and non-survivor group

Group	Number	PCT level		CRP level	
		Mean (ng/ml)	SD	Mean (mg/L)	SD
Non-survivor	7	149.6	103.8	72.6	6.13
Survivor	33	11.14	21.15	54.45	24.68

PCT: Procalcitonin, CRP: C-reactive protein, SD: Standard deviation

We demonstrated that PCT levels were high with a sensitivity of 93.3% and specificity of 84% initially which is in accordance with the study done by Simon et al. [13]. CRP levels were high in a later phase of infection as compared to PCT with a sensitivity of 86.6% and specificity of 52% which is comparable to the findings of Simon et al. [13]. Mean CRP levels at admission were significantly lower as compared to that at 48 h. In our study, infection was proven by positive culture in 37.5% of the study group. Others had positive findings on clinical examination, imaging and laboratory tests. Pavare et al. demonstrated 50% positive culture in their study [18].

In our study, we analyzed the acute phase reactants like CRP and PCT, total counts and the band forms in differentiating between culture positive and culture-negative sepsis at 0 and 48 h after admission, and also between patients with septic shock and non-septic shock at 0 and 48 h after admission. We found that both CRP and PCT levels were significantly higher in culture positive group than in culture-negative group both at the time of admission and 48 h later. Thus, both CRP and PCT levels were able to differentiate culture positive and negative sepsis.

We also concluded that PCT levels can be used a prognostic indicator if children with sepsis as in our study, admission PCT levels were significantly higher in non-survivors than in survivors. Although CRP could not be able differentiate these two groups. Casado-Flores et al. also demonstrated significantly higher levels of serum PCT levels in non-survivors than in survivors [10]. In our study, Mean CRP level at admission was significantly less as compared to levels at 48 h after admission, whereas mean PCT level at 0 h was significantly higher than the PCT level at 48 h, indicating slower rise of CRP levels than PCT levels. Therefore, we can say that PCT can be used as a better early marker of sepsis than CRP. These results were supported by the study conducted by Carvalho et al. [19].

CONCLUSION

Estimation of inflammatory markers like CRP and PCT can help to diagnose sepsis as early as possible and early initiation

Table 3: Optimum cut off values for the diagnosis of sepsis

Parameter	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	p value
Total count>15,000/<5000 cells/ul	53.33	24	29.63	46.15	0.176
Band cells>10%	53.3	52	40	65	1.00
CRP>40 mg/L	86.67	52	52	86.67	0.035
PCT>2 ng/ml	93.33	84	77.78	95.45	<0.0001
CRP>40 mg/L, PCT>2 ng/ml	80	84	75	87.5	<0.0001

PCT: Procalcitonin, CRP: C-reactive protein

of treatment can prevent the mortality and morbidity among these children.

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