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Prognostic Markers of Sepsis: Procalctionin vs C - Reactive Protein

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Abstract

The utility of procalcitonin as a diagnostic marker of sepsis has been studied widely. However, there is limited literature on the role of procalcitonin as a prognostic marker in sepsis. The aim of this study was to assess the utility of procalcitonin in predicting mortality in patients of sepsis and to compare it with C-reactive protein. A total of 250 children aged 2 months to 5 years and clinically suspected of sepsis admitted in the paediatric emergency ward of a tertiary care hospital in North India were enrolled in the study. Blood sample was collected at the of admission for performing blood culture by conventional method and for estimation of serum procalcitonin and C-reactive protein by a fluorescence based immunoassay. Each patient was followed for a period of 30 days. Procalcitonin was found to be a better predictor of mortality than C-reactive protein in patients of sepsis. There was a significant difference in mean PCT value in patients who died during hospital stay and those who survived ($p<0.0001$). Patients who expired had mean PCT value 15 times that of patients who survived (mean= 72.78 ng/ml vs 5.43 ng/ml in survivors). The mean CRP level was higher in patients who died during hospital stay (mean= 68.22 mg/l vs 3.37 mg/l in survivors) but the difference was not statistically significant ($p=0.018$). Hence, the study showed that CRP is not a good predictor of mortality in children with sepsis. A high level of procalctionin in patients of sepsis at the time of admission is a predictor of high risk of mortality and hence must be taken as a warning sign to provide necessary treatment to the patient.

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Sepsis mortality

Introduction

Sepsis has been identified as a major cause of mortality in children (Riedel and Carroll, 2010). There is a need for early identification of patients of sepsis with high risk of mortality. Various biomarkers have been studied for the early diagnosis of sepsis (Harbarth *et al.,* 2001; Ho and Towler, 2009; Guignant *et al.*, 2009; Seligman *et al.*, 2008; Wu *et al.*, 2009; Koch *et al.*, 2009). Recently, procalcitonin has emerged as a potential biomarker for the diagnosis of sepsis. The timely identification of sepsis and its related mortality can help in facilitating antimicrobial stewardship and improving patient outcome. However, the utility of procalcitonin for predicting sepsis related mortality has not been studied much. Moreover, the studies conducted to assess the prognostic role of procalcitonin in sepsis have mainly been carried out in intensive care units and the value of a single level of procalcitonin on admission has not been assessed. Sepsis patients usually present in the emergency department and there is substantial delay in admission to the intensive care unit. Therefore, the early

prediction of sepsis related mortality in the emergency room can help in improving the patient outcome by timely initiation of antibiotics. The aim of the present study was to assess the role of procalcitonin as a biomarker for the early prediction of sepsis related mortality and to compare it with C-reactive protein.

Materials and Methods

An observational study was conducted in the Department of microbiology and Paediatrics of a tertiary care hospital in North India. 250 patients between 2 months to 5 years of age, presenting to paediatric emergency room with a probable clinically diagnosis of sepsis were taken up for study. Sepsis in these children was clinically defined by the presence of atleast two of the following age dependent signs of sepsis as suggested by the International pediatric consensus conference (Goldstein *et al.,* 2005): Fever (>38^{o}C) or hypothermia (<36.6^{0}C) for <15 days. (Table 1)

Patients with a history of fever for more than 15 days and patients who had received antibiotics before admission were excluded from the study. A detailed history was taken and clinical examination performed according to the pre-designed proforma based on the clinical criteria for sepsis. Blood sample was collected after taking an Informed Consent from the patient's guardian. Approximately 2ml blood collected in blood culture bottle containing brain-heart infusion broth such that the blood: broth ratio is 1:5for culture and sensitivity. 2-3 ml blood collected in plain vial was used for the study of biomarkers. The blood sample was allowed to clot and serum was separated by centrifuging at 3000 rpm for 15 minutes. In case of delay in processing, the sample was stored at -20^{0} C until use. Serum sample was used for testing Procalcitonin (PCT) and C-Reactive Protein (CRP). PCT and CRP were detected using the quantitative QDx Diasys Instacheck fluorescence based immunoassay test. The procedure was carried out as per the manufacturer's instruction manual. The working range of QDx Instacheck PCT test is 0.25-100 ng/ml.

Statistical analysis

The data was analyzed by using SPSS, ver. 21.0 (IBM Chicago, Illinois, USA) software package. Logistic regression analysis was used to assess the association between procalcitonin and C-reactive protein levels and the outcome of hospital stay. The Mann Whitney U Test was used to study the difference in the levels of biomarkers among the patients who survived and those who expired. Pearson correlation coefficient was used to study the association of procalcitonin with mortality.

Results and Discussion

Out of 250 patients, 156 (62.4%) were males and 94 (37.6%) were females. The median age of the study sample was 6 months. The most common clinical presentation was fever (90%), followed by respiratory distress (42%). Other presenting complaints were lethargy, poor cry, refusal to feed, loose stools, tachycardia and hypothermia. (Table 2)

During the study period, total 250 samples of blood and 29 samples of CSF were processed. Out of these, 59 blood samples (23.6%) were positive on culture and 4 CSF samples (13.7%) were positive on culture. Overall 63 samples (25.2%) were culture positive. The culture positive and culture negative groups did not differ statistically in terms of age in months (p=0.18). 21 patients (9.2%) expired during their hospital stay while 229 (91.6) patients survived. The culture positive and culture negative groups were statistically different in terms of mortality which was greater in culture positive group (11/63, 17.5%) as compared to that in the culture negative group (10/187, 5.3%) (p<0.01). Relative risk of mortality with culture positivity was 3.3.The Mann Whitney U Test was used to study the difference in the levels of biomarkers among the patients who survived and those who expired. The mean CRP level was higher in patients who died during hospital stay (mean= 68.22 mg/l vs 3.37 mg/l in survivors) but the difference in CRP levels was not statistically significant (p=0.018) among survivors and non-survivors.

There was a significant difference in mean PCT value in patients who died during hospital stay and those who survived (p<0.0001). Patients who expired had mean PCT value 15 times that of patients who survived (mean= 72.78 ng/ml vs 5.43 ng/ml in survivors). Our results showed that serum procalcitonin concentrations were higher in patients with unfavorable outcomes than in patients with favorable outcomes. The Pearson correlation for PCT vs mortality was found to be r= 0.5855 which was statistically significant with a p-value <0.0001.

The use of biomarkers to predict the prognosis of patients of sepsis can be helpful in reassessing the diagnosis of complications and to change the line of treatment, which may help in improving the outcome of the patient during the hospital stay. Most of the studies

related to procalcitonin have focused on its role in the diagnosis of sepsis rather than its prognosis. The studies using procalcitonin as a biomarker to predict mortality in sepsis patient are very few (Dahaba *et al.*, 2006; Castelli *et al.*, 2006; Meisner *et al.*, 1999; Oda *et al.*, 2000; Lee *et al.*, 2004; Oberhoffer *et al.*, 1996). In our study, we found a relatively higher risk of mortality in culture positive individuals as compared to culture negative individuals. Also, the procalcitonin levels showed a significant correlation with mortality.

Table.1 Age dependent signs of sepsis

Age	Temperature for <15 days	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	TLC ($x10^3/mm^3$)	SBP (mm of Hg)
1month-2yr	>38^{0}C or <36.6^{0}C	>180 or <90	>35	>17.5 or <5	<75
2yr-5yr	>38^{0}C or <36.6^{0}C	>140	>30	>15.5 or <5	<75

SBP= Systolic Blood Pressure, TLC= Total Leucocyte Count

Table.2 Characteristics of the study population

	Number	%
Male	156	62.4
Female	94	37.6
Age :		
2-6months	120	48.0
6-12 months	34	13.6
1-2 year	28	11.2
2-5 years	68	27.2
Clinical diagnosis		
Pneumonia	105	42.0
Blood stream infection	69	27.6
Diarrhoea	39	15.6
Meningitis	29	11.6
Enteric fever	8	3.2

Our study showed that the PCT level on admission is a better predictor of mortality than CRP in children with sepsis presenting to the emergency room. The study supports previous observations (Claeys *et al.*, 2002).

Elevated levels of procalcitonin are a good indicator of mortality associated with sepsis. We suggest that procalcitonin should be evaluated in children with sepsis presenting to emergency room to aid in early prognosis and prevent poor outcome by starting timely treatment.

List of abbreviations

PCT = Procalcitonin
CRP = C-reactive protein
SBP = Systolic Blood Pressure
TLC = Total Leucocyte Count

Declarations

Ethics approval and consent to participate: Approval from the Institutional Ethics Committee, MAMC was taken before performing the study.

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