

Is Procalcitonin Useful in Early Diagnosis of Serious Bacterial Infections in Children?

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Introduction

Diagnosis of bacterial infections remains one of the greatest and most tantalizing challenges in medical science, especially in children, in whom clinical signs are often nonspecific and confusing and hence laboratory parameters become crucial^{1,2}. The currently used markers for diagnosis of sepsis in children are not very specific. Marshall et al published a thorough report from the fifth Toronto sepsis round table on measures, markers and mediators of clinical sepsis and suggested that many circulating or cell-associated molecules have been found to be useful markers for the presence, severity, or response to therapy of sepsis³. In recent years, several newer markers of infection have been investigated, such as procalcitonin (PCT) and interleukins (IL-6 and IL-8), which are easy to perform and in combination have high sensitivity and specificity^{4,5}. The aim of this study was to evaluate procalcitonin as early marker of serious bacterial infection in children.

Materials and Methods

This diagnostic evaluation study was carried out at a tertiary care hospital from Sep 2008 till Sep 2010, among newborns and children up to five years of age presenting with features suggestive of systemic inflammatory response syndrome (SIRS). All patients underwent standard tests / sepsis screen namely total leukocyte count (TLC), Differential leukocyte count (DLC),

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Abstract

Introduction: Diagnosis of bacterial infections remains one of the greatest challenges in medical science, especially in children, in whom clinical signs are often nonspecific. The currently used sepsis screen has poor predictive value. Recently introduced marker procalcitonin (PCT) with high sensitivity and specificity is evaluated as early marker of serious bacterial infection in children.

Materials and Methods: Children up to 5 years of age presenting with features of Systemic Inflammatory Response Syndrome (SIRS) were evaluated clinically and underwent standard sepsis screen namely total leukocyte count (TLC), peripheral blood smear for band count, C-reactive Protein (CRP) and newer tests like procalcitonin (PCT) and Interleukin-8 (IL-8). Results were analyzed using SPSS14.0. **Results:** One hundred patients suspected of sepsis were evaluated. Maximum cases were below one year (37%) with mean age of 27 months. Male:female ratio was 1.5:1. Respiratory system was the commonest system involved in (54%) followed by gastrointestinal (20%), genitourinary (10%) and central nervous system (5%). Seventy two cases were found to have confirmed sepsis, proven by blood culture (34%) and other investigations. Fifty two cases were diagnosed by conventional markers, while newer markers in 60 cases. Diagnostic evaluation revealed that newer markers have higher sensitivity and specificity as compared to conventional sepsis screen. **Conclusion:** Procalcitonin is a useful marker for diagnosis of serious bacterial infections in children and in combination with IL8 has a higher sensitivity and specificity as compared to standard sepsis screen. Therefore it is recommended that procalcitonin should be used for the screening of sepsis in children so that the treatment can be started earlier in order to prevent morbidity and mortality.

Key words: Systemic inflammatory response syndrome (SIRS), Sepsis screen, Procalcitonin, Interleukin-8

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peripheral blood smear for band count and C-reactive protein (CRP) by qualitative method using RHELAX-CRP kit. They were also subjected to newer markers like procalcitonin (PCT) by semi-quantitative assay using bedside immunochromatography kit (B.R.A.H.M.S. PCT-Q, B.R.A.H.M.S.-Diagnostica GmbH, Hennigsdorf, Germany) and Interleukin-8 (IL-8) by human IL8/NAP-1 kit by ELISA method. Blood culture positivity was taken as gold standard for sepsis. Other cultures or corroborative investigations for proven sepsis were also considered as definite evidence of sepsis. The data was statistically analyzed using SPSS 14.0 to determine the sensitivity, specificity, positive and negative predictive values and likelihood ratios of the tests.

Results

Total 130 patients were considered for the study, of which 30 patients excluded as they did not fulfill the inclusion criteria. Maximum numbers of cases were in the age group of one month to one year (37%) with mean age of 27 months and male:female ratio of 1.5:1. Maximum numbers of cases had involvement of respiratory system (54%) followed by gastrointestinal (20%), genitourinary (10%) and central nervous system (5%). Clinical profile of the study population is depicted in Figure 1 and 2.

Seventy two cases had evidence of proven sepsis by blood culture and other cultures (urine, CSF and other body fluids). Respiratory system was involved in the 41 cases (57%) (95% CI, 44.3 - 67.99), genitourinary in 12 (17%) (95% CI, 9.36 - 26.6) and central nervous system in 10 cases (14%) (95% CI, 7.28 - 23.36). Organisms were isolated from blood culture in 34 patients with commonest being staphylococcus aureus in 19 (55%) children. Fifty two cases (52%) (95%CI, 42 - 61) were

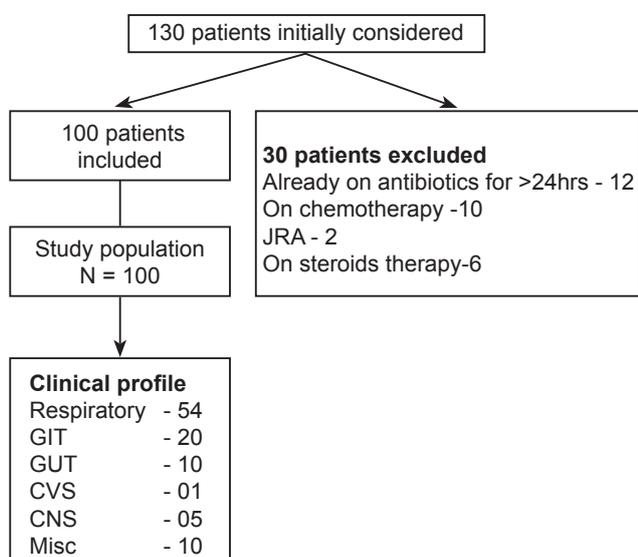


Fig 1: Clinical profile of the study population

diagnosed by the conventional markers namely total leukocyte count (TLC), band count and CRP, while 60 cases (60%) (95% CI, 50.18 - 69.25) were diagnosed by the newer markers like procalcitonin and IL-8 as shown in Table- 1.

Diagnostic evaluation of the conventional markers and newer markers was done and it was observed that CRP and band count have sensitivity of 69.7% (95% CI, 58-79.5) and 50.9% (95% CI, 41-60.5), which was lower than newer markers like PCT and IL8 with the sensitivity of 84.8% (95% CI, 73-92) and 90.9% (95% CI, 81-96) respectively. Similarly specificity of conventional markers CRP and band count was 54.8% (95% CI, 45-63) and 44.4% (95% CI, 34-55), which was also low as compared to the newer markers PCT and IL8 with specificity of 88.2% (95% CI, 72-96) and 82.4% (95% CI, 65-93). It was also observed that the PPV and NPV were high for the newer markers as compared to the conventional markers. On further analysis of newer markers PCT & IL-8, when combined together had improved sensitivity of 90.3% (95%, CI 79.5-85) and specificity of 73.4% (95% CI, 51.8-85.1) as shown in Table 2.

Sensitivity of newer markers PCT and IL8 with respect to CRP was also evaluated and found 82.1% (95% CI and 70.4-90) and 83.6% (95% CI, 72-91) and specificity 84.8% (95% CI, 67-94) and 90.9% (95%CI, 75-95) respectively showing the superiority of newer markers over conventional markers. Similarly sensitivity of PCT and IL8 with respect to band count was 84% (95% CI, 73-92) and 91% (95% CI, 82-97) whereas the specificity 83% (95% CI, 67-93) and 87% (95% CI, 68-95.6) showing the usefulness of newer markers over conventional markers as shown in Table 3.

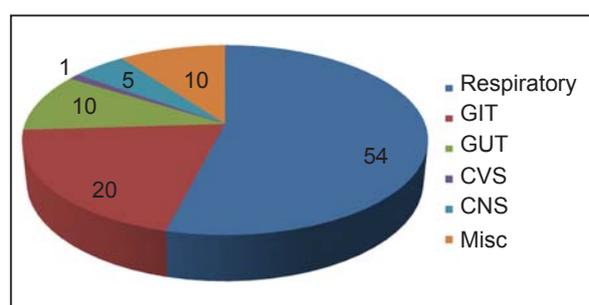


Fig 2: Showing the Clinical profile of sepsis in study population

Table 1: Sepsis in the study population

Diagnosis of sepsis	No. of cases	95% CI
Confirmed sepsis (Gold standard and other suggestive tests)	72	62 - 81
Diagnosed by conventional markers	52	42 - 61
Diagnosed by newer markers	60	50 - 69
Total number of cases	100	

Table 2: Sensitivity and specificity of single and combination markers of infection

Marker	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR value
CRP	69.7 (58-79.5)	54.8 (45-63)	48.6 (39-58)	74.7 (64-98.3)	1.56
Band forms	50.9 (41-60.5)	44.4 (34-55)	52.8 (43-62)	42.6 (32-53)	1.05
PCT	84.8 (73-92)	88.2 (72-96)	93.3 (83-98)	75 (58-87)	7.08
IL8	90.9 (81-96)	82.4 (65-93)	90.9 (81-96)	82.4 (65-93)	5.06
PCT + IL8	90.3 (79.5-85)	73.4 (51.8-85.1)	86.2 (74-93)	78.6 (58.5-91)	3.1

Table 3: Comparison of sensitivity and specificity of markers of sepsis

Combination markers	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Kappa coefficient (P value)	LR ratio
PCT Vs CRP	82.1 (70.4-90)	84.8 (67-94)	91.7 (81-97)	70 (53-83)	0.63 (P=0.00)	5.47
IL8 Vs CRP	83.6 (72-91)	90.9 (75-98)	95 (85-98)	73.2 (57-85)	0.70 (P=0.00)	9.33
PCT Vs BF	84 (73-92)	83 (67-93)	90 (79-96)	75 (56-87)	0.66 (P=0.00)	4.94
IL8 Vs BF	91 (82-97)	87 (68-95.6)	94.1 (85-98)	81 (63-92)	0.77 (P=0.00)	7

Discussion

Early diagnosis of the severe infections and the prompt initiation of adequate antimicrobial therapy are essential for the good outcome in infants and young children¹. Chiesa et al reported that an abnormal PCT concentration in early neonatal sepsis with a sensitivity of 92% and specificity of 97.5%⁹. These findings were in agreement with our study, which showed the sensitivity and the specificity of PCT to be 85% and 88% respectively. Suprin E et al compared PCT and CRP in ICU patients and found that PCT had better specificity and sensitivity (93% and 94%) than CRP (75% and 73%)¹⁰. Among the organisms isolated from the blood, staph aureus was the commonest isolated organism seen in 55% whereas in a study by Jose R gram negative organisms were found in maximum number of cases¹¹.

Our study demonstrated that newer markers namely PCT and IL8 were more sensitive than CRP, TLC and band counts for predicting sepsis in children. Similarly specificity of these newer markers were higher than that of CRP and band forms. Muller and colleagues investigated 101 patients admitted to medical ICU and found that PCT is a more reliable marker of sepsis than CRP, IL-6 and lactate levels¹². A systematic review was published in 2004 investigating the value of PCT as a marker of bacterial infection in children

and adults. Two of the 12 studies analyzed involved children, one of which had enrolled newborn infants, both demonstrated that PCT was more accurate marker than CRP for differentiating between viral and bacterial infections^{13,14}. When combination markers PCT and IL8 were used by Carcello et al, sensitivity and specificity increased to 94% and 90%. In our study the sensitivity increased to 90% and the specificity 73%⁴. The future lies in demonstrating whether assaying PCT improves the prognosis of patients, by making early diagnosis possible and aiding with monitoring treatment.

Conclusion

Procalcitonin is a useful marker for in diagnosis of serious bacterial infections in neonates and children. Alone or in combination with IL8 it has a higher sensitivity and specificity as compared to standard markers like CRP. Therefore it is recommended that procalcitonin should be used for the screening of sepsis in neonates and children so that the treatment can be started earlier in order to prevent morbidity and mortality.

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