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Procalcitonin – A Reliable Marker for Diagnosis of Neonatal Sepsis in Compare to CRP

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Abstract

Background: *Early recognition and diagnosis of neonatal sepsis are difficult because of the variable and non-specific clinical presentation of this condition. It is extremely important to make an early diagnosis of neonatal sepsis for prompt institution of anti-microbial therapy. So the objective of the study was to evaluate the efficacy of serum procalcitonin as a reliable marker in diagnosis of neonatal sepsis.*

Methodology: *This cross sectional analytical study was carried out in the Special Care Baby Unit of a tertiary level care hospital in Bangladesh from September 2012 to May 2013. Total 75 newborn with suspected sepsis were included in the study. Specimens of blood were obtained from each neonate prior to commencement of antibiotic for sepsis work up. Serum CRP and procalcitoninlevels were measured. The data from blood cultures were used as the gold standard to evaluate the optimum sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the Receiver Operative Characteristic (ROC) curves.*

Results:*Among total 75 newborns included in this study, 49.3% (37) newborn were diagnosed as proven sepsis and 50.7% (38) newborn as clinical sepsis.The procalcitonin (PCT) was high in 58.7% (500-<2000 pg/ml) newborn and remarkably high (2000-<10000) in 36% newborn with sepsis. At a cut-off value > 500pg/ml, the sensitivity of PCT in detecting sepsis was 48.6%, its specificity 76.3%, positive predictive value was 66.7%, and negative predictive value was 60.4% whereas the sensitivity of CRP for predicting sepsis was 35.1%, specificity 78.9%, positive predictive value 61.9% and negative predictive value was 55.6%. The area under the ROC curve for procalcitonin(0.653) was significantly higher than CRP (0.571).*

Conclusion:*Serum PCT was superior to serum CRP level in terms of early diagnosis of neonatal sepsis, in detecting the severity of sepsis. PCT is a reliable marker than CRP in the diagnosis of neonatal sepsis.*

Key words: *Sepsis, Procalcitonin, CRP*

Introduction

Neonatal sepsis is the commonest cause of neonatal mortality and it is responsible for 30-50% of the total neonatal death in developing countries.[1,2] It is estimated that 20% of all neonates develops sepsis and approximately 1% die of sepsis related causes .[2] Neonatal septicemia is a clinical syndrome of systemic illness accompanied by bacterium occurring in the 1st 28 days of life .[3]Neonatal sepsis may be categorized as early onset and late onset sepsis. Eighty five percent of newborns with early onset infection present within 24 hours and smaller percentage of patients present between 48 hours and 6 days of life.[4]

Sometimes infection in neonates is difficult to identify solely on the basis of physical finding, because signs are not specific and may be absent when the infection is identified just before delivary.[5] Definitive diagnosis of neonatal sepsis is based on blood culture which take at least 48-72

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hours and yields a positive result in only 10-60% of cases.[6] It is also possible that a pseudo-negative result may be obtained in some cases.[7]In addition to the blood culture, other tests that are usually used for the diagnosis of neonatal sepsis include estimations of the white blood cell count, the absolute neutrophil count (ANC), micro ESR and I/T ratio. Unfortunately, these tests do not have a high sensitivity and specificity in diagnosing neonatal sepsis. [8]

C-reactive protein (CRP) is a good marker for diagnosis of neonatal sepsis. CRP is the most extensively used and investigated acute phase reactant.[9,10,11] and synthesized by the liver. It can be considered as a specific but late marker of neonatal infection .[12] CRP level rises 12-24 hours of infection and remain elevated for 3-7 days. Elevated CRP levels are seen in infection, in autoimmune disease, in surgery, meconium aspiration syndromeand recent vaccination.[13,14]

Several serum biomarkers have been identified in recent years with potential uses to help diagnose local and systemic infections; differentiate bacterial from viral or fungal infections and guide antibiotic therapy. The serum biomarker that has been most extensively studied recently is procalcitonin.[15,16]Procalcitonin (PCT), a precursor of calcitonin is a 116 amino acid protein secreted by the C cells of thyroid gland in normal situation but its levels may increase during septicemia, meningitis, pneumonia and urinary tract infection . Macrophage and monocyte cells of various organs such as the liver, lungs, kidney, adipocytes and muscle cells are the potential sources of procalcitonin in severe bacterial infection .[17,18] Serum procalcitonin levels appeared to correlate with the severity of microbial invasion.[18]The increase level of procalcitonin (PCT) has been observed before the rise in CRP.[19] The unique feature that PCT increase in bacterial and fungal infections but remain unchanged even in severe viral infections and other inflammatory diseases, make PCT attractive as a potential diagnostic variable for the diagnosis of bacterial infection.[20] The measurement of procalcitonin is reliable and so can be used for early and rapid diagnosis of systemic infection in neonates in a short period of time.So the objective of the study to evaluate the efficacy of serum procalcitonin as a reliable marker for diagnosis of neonatal sepsis.

Materials and Methods

A prospective cross-sectional study was conducted at Special Care Baby Unit (SCABU) BIRDEM from Sept 2012 to May 2013.Total 75 cases were taken as consecutive sampling. The inclusion criteria were neonate who admitted into SCABU with clinical signs and symptoms of sepsis or who had maternal risk factors such as prolonged labour, PROM > 18 hour, maternal fever, urinary tract infection, chorioamnionitis and neonatal risk factors such as prematurity, low birth weight. The exclusion criteria were neonates with congenital malformation, severe jaundice due to blood group incompatibilities, antibiotic therapy prior to admission. The study was approved by the ethical review committee of BIRDEM and informed parental consent was obtained prior to the enrollment in the study. Before initiation of antibiotic therapy, blood sample was taken for total leucocyte count, absolute neutrophil count, blood culture, CRP and serum procalcitonin. The newborns under study were classified into two groups – group I as proven sepsis (who had clinical sign and symptom and positive blood culture) and group II clinical sepsis (who had clinical sign and symptom of sepsis but negative blood culture). Normal serum level of PCT are less than procalcitonin 500 pg/ml, test result interpretation is procalcitonin <500 pg/ml- normal, 500-<2000 pg/ml-progress to sepsis, 2000- < 10000 pg/ml – sepsis and > 10000 septic shock. PCT level is compared between the categories of infection.

Statistical Analysis

Data analysis was performed by using SPSS for windows version 15. Chi-square test, Mann- Whitney U test and Validity test was done to measure the level of significance. Area under the ROC (Receiver operating characteristics) was evaluated. A p value ≤ 0.05 was considered level of significance.

Results

The study included a total 101 newborns who met the inclusion criteria. Of which 15 were excluded because of incomplete data such as missing blood C/S,PCT and CRP report and 12 patient died. Therefore 75 newborn were included in the final statistical analysis. The study subject divided into two group- proven sepsis group and clinical sepsis group. 50.7% newborn were diagnosed as clinical sepsis and 49.3% as proven sepsis (fig-1). In proven sepsis group, bacterial growth was found in 21.3% , fungal growth in 28% and no

growth observed in 50.7% newborn with sepsis (Figure 2). Among the bacterial growth, commonest organism was acinobactor (12%) followed by klebsiella(8%), pseudomonas(1%) and 28% new born had fungal growth(fig-3). The serum level of procalcitonin was high(500-d" 2000 pg/ml) in 58.7% newborn with sepsis and remarkably high(2000-d" 10000 pg/ml) in 36% newborn with sepsis and only 5.3% new born had normal procalcitonin level(Table-I).There was no significant difference of mean WBC count, ANC platelet count and CRPbetween two group of patients and only mean of procalcitonin was significantly high in proven sepsis group p-0.023(Table-II).The raised procalcitonin was observed in 48.6% new born with proven sepsis and 23.7% new born with clinical sepsis and it was statistically significant between two groups of newborn. On the other hand, raised CRP observed in 35.1% new born with proven sepsis and 21.1%(8) new born with clinical sepsis and it was not statistically significant in two groups(Table-III).The sensitivity of PCT in predicting sepsis was 48.6%, its specificity was 76.3%, positive predictive value(PPV) was 66.7% and negative predictive value(NPV) 60.4%. The sensitivity of CRP in predicting sepsis was 35.1%, its specificity was 78.9%. its positive predictive was 61.9% and negative predictive value was 55.6%. The sensitivity, PPV, NPV were higher for procalcitonin whereas specificity was lower in comparison to CRP (Table IV). Receiver operating characteristic(ROC) curves of procalcitonin and CRP was made according to the sensitivity and specificity of procalcitonin and CRP values using data from all study subject showed on Fig-4. The area under ROC curve for procalcitonin(median: 0.653, 95% confidence interval CI: 0528 to 0.778) was significantly more(0.653) than CRP(median: 0.571, 95% CI: 0.441 to 0528) on the ROC curve, p value 0.023 which was significant (Table-V).

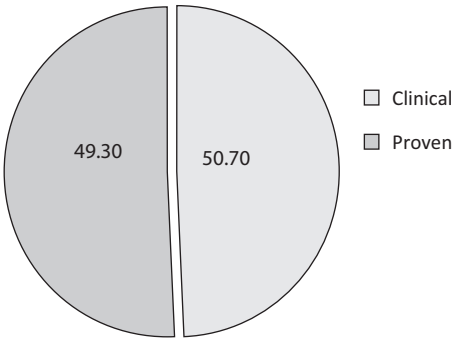

Fig.-1: *Distribution of neonates according to the type of sepsis.*

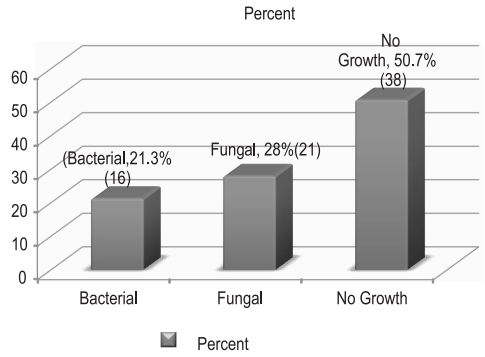

Fig.-2: *Distribution of microbial growth pattern in newborn with sepsis*

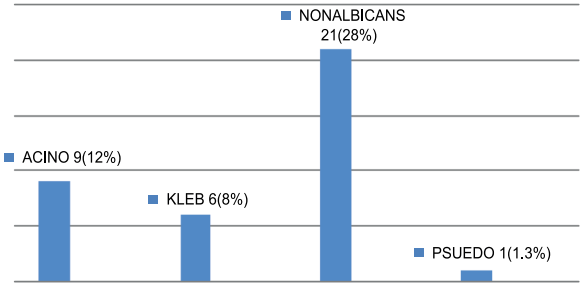

Fig.-3: *Distribution of organism pattern in proven sepsis.*

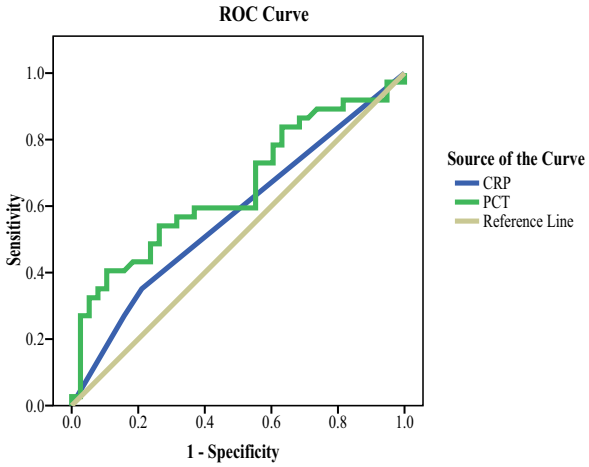

Fig.-4: *Receiver operating characteristics (ROC) curves of procalcitonin and CRP was made according to the sensitivity and specificity of procalcitonin and CRP values using the data from all study subjects.*

Table I

Distribution of procalcitonin level in newborn with sepsis

Procalcitonin cat	Frequency	Percent
Normal(<500 pg/ml)	4	5.3%
Progress to sepsis (500-<2000 pg/ml)	44	58.7%
Sepsis(2000-<10000 pg/ml)	27	36.0%
Total	75	100.0%

Table II

Comparision of mean of WBC count, ANC count, platelet count, CRP and procalcitonin in proven sepsis and clinical sepsis group

	Pro3ven Sepsis n=37, mean±SD	Clinical Sepsis n=38, mean±SD	P value
WBC count	15880.14±13986.30	13952.95±9160.11	0.874
Absolute neutrophil count	6980.24±5460.92	6675.24±4706.64	0.853
Platelet count	123786.49±96747.07	162307.89±90971.67	0.057
CRP	11.35±7.97	9.16±6.65	0.177*
PCT	2451.00±1938.95	1529.55±1168.37	0.023*

*Mann-Whitney U test

Table III

Distribution of raised CRP and PCT in clinical sepsis and proven sepsis

	Proven		Clinical	P value*
	Sepsis n=37(%)	SepsisTotal n=38 (%)	n=75 (%)	
CRP- Raised	13(35.1)	8(21.1)	21(28.0)	0.174
PCT-Raised	18(48.6)	9(23.7)	27(36.0)	0.024

*Chi-Square test was done
CRP- raised> 6 mg/L
PCT- raised > 500 pg/ml

Table IV

Comparision of validity tests of procalcitonin (pg/ml) and CRP (mg/L) in sepsis

Validity tests	CRP	PCT
Sensitivity	35.1% (23.6-45.2)	48.6% (36.3-59.1)
Specificity	78.9% (67.7-88.7)	76.3% (64.3-86.5)
PPV	61.9% (41.6-79.6)	66.7% (49.7-81.0)
NPV	55.6% (47.6-62.4)	60.4% (50.9-68.5)
Accuracy	57.3% (45.9-67.2)	62.7% (50.5-73.0)

Table V

Area under curve

Test Result Variable(s)	AUC	p value	95% Confidence Interval	
			Upper Bound	Lower Bound
CRP	0.571	0.289	0.441	0.701
PCT	0.653	0.023	0.528	0.778

AUC (area under curve)
Null hypothesis: true area= 0.5.

The area under the ROC curve for procalcitonin (median: 0.653, 95% confidence interval CI : 0.528 to 0.778) was significantly more (0.653) than CRP (median : 0.571, 95% CI : 0.441 to 0.528) on the ROC curve. Pvalue 0.023 which was significant.

Discussion

There is no single reliable test for the early definite diagnosis of neonatal sepsis. The C-reactive protein has been the most analyzed parameter for the detection of bacterial infections for many years[22,26].Procalcitonin (PCT) has been proposed as a marker of bacterial sepsis.

In this present study,among 75 newborns, 49.3% (37)newborn were diagnosed as proven sepsis and 50.7% (38) newborn as clinical sepsis. Almost half of the newborn were diagnosed as culture proven sepsis due to early arrival in hospital, sample collection before giving antibiotic and proper aseptic technique in collection procedure. Bacterial growth was found in 21.3% newborn with sepsis. Commonest bacteria were acinetobacter (12%) followed by klebsiella (8%) and pseudomonas (1%). This finding is similar with the study done by Sucilathangam et.al [24]and Misra A et. al[29] Begum S etal[23]. In our study, acinetobactor was the leading cause of neonatal sepsis and non albicans candida was isolated in 28% cases. As most of the newborn were exposed to broad-spectrum antibiotics, especially third generation cephalosporins, mechanical ventilation and not receiving enteral feeds were the risk factor for non-albicans candidal growth.[22]

In the present study, PCT was high (500-<2000) in 58.7% newborn with sepsis and remarkably high (2000-<10000) in 36% newborn with sepsis. Previous studies done by Chiesa C et al.[30], Lapillonne A et al.[31] and Monneret G et al.[33]had shown high PCT levels in neonates with proven or clinically diagnosed neonatal sepsis.

The comparison of mean of WBC count, ANC count, platelet count, CRP and procalcitonin in proven sepsis and clinical sepsis showed in table III. There was no significant difference of mean of WBC count, ANC count, platelet count and CRP in two groups patients but only mean of procalcitonin was significantly high in proven sepsis group and statistically significant, p-0.02. This finding was similar with Mohammed I A et al. study.[35]

In our study, PCT was high in most newborn with proven sepsis (48.6%) and in clinical sepsis (23.7%) and it was statistically significant, p-0.024 in two group of patients and this finding was similar with Carol et al. study,[22] Koksel et al. [36], Kawezynski et al. [37] and Lopez Sastre et al. [38] studies.

In the present study, the PCT levels were remarkably high in the neonates with proven sepsis (48.6%) and also in clinical sepsis cases (35.1%). This finding was comparable with that of the study which was conducted by YadollaZahadpasha et al.[40] and Monneret et al.[33] There was a significant correlation between the serum PCT level and the proven sepsis (p-0.02) in our study which was comparable with Koksal et al. study. [36]

In the present study, the sensitivity of PCT for detecting sepsis (more than 500 pg/ml) was 48.6%, its specificity 76.3%, its positive predictive value was 66.7% and negative predictive value was 60% and the sensitivity of CRP for predicting sepsis (more than 6mg/ L) was 35.1%, its specificity was 78.9%, its positive predictive value was 61.9% and negative predictive value was 55.6%. To evaluate the test performance ROC (receiver operating characteristic) curve using sensitivity and specificity of two test like PCT and CRP for cut off value of >500 pg/ml and >6mg/L respectively. The area under the ROC for PCT (median: 0.653, 95% confidence interval CI: 0.528 to 0.778) was significantly more (0.653) than CRP (median: 0.571, 95% CI: 0.441 to 0.528), p value 0.023 which was significant. Such finding are similar with the study done by Hatherill et al.[41], Sakha et al, [42]Naher BS et al [23] and Boo NY et al [43] studies.The present study confirmed the findings of other investigators that PCT was more sensitive than CRP in the detection of neonatal sepsis, earlier as the PCT level rose than the CRP level during sepsis. Among the 75 cases, an elevated PCT was detected in 71 cases whereas an elevated CRP level was noticed only in 21 cases. In 37 culture positive cases, an elevated serum PCT level was noticed in 18 (48.6%) cases whereas an elevated CRP level was noticed in only 13 (35.1%) cases.

Conclusion

The findings of the present study suggest that the serum levels of PCT is a more reliable marker than the CRP or WBC counts in the early diagnosis of neonatal sepsis. As this study included a small group of population, we recommend further large scale, multi centered and follow up study to confirm the role of PCT in the diagnosis of neonatal sepsis.

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