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RESEARCH ARTICLE

ROLE OF C-REACTIVE PROTEIN IN EARLY DIAGNOSIS OF NEONATAL SEPSIS

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ABSTRACT

Sepsis is a major problem in neonates. Clinical criteria alone could not establish the diagnosis of neonatal sepsis. C-reactive protein, an acute phase protein increases in inflammatory disorder and tissue injury. The present study was conducted to evaluate C- reactive protein (CRP) as a screening tool for neonatal sepsis. A prospective study included newborn infants, aged <90 days and diagnosed with sepsis, who were admitted in neonatal intensive care unit at GCS Medical College Hospital and Research Center, Ahmedabad from 1stJanuary 2015 to 15th April 2015. This study included 100 cases in which 50 were culture proven sepsis and 50 normal newborn. Investigation for infection included CBC, Blood culture, and urine culture. As per the present study, sensitivity of serum CRP was found to be 88% and specificity 84% with NPV of 87.5 suggesting its beneficial role in diagnosing sepsis. Serum CRP was positive in 88% of culture proven sepsis and negative in 12% of cases. P-value of the test applied for the statistical significance is <0.0001 which implies that the result is statistically significant for CRP. Results of the current study indicates that despite the continuing emergence of newer markers of sepsis, CRP still plays a central role in the diagnosis of early onset neonatal sepsis.

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INTRODUCTION

Neonatal Sepsis is a disease that starts with usually minimal & non-specific symptoms & poses a high risk of morbidity & mortality due to its fulminant course. Early and efficient diagnosis of neonatal bacterial sepsis still remains a difficult task. A number of laboratory tests have been used in attempts to facilitate the early diagnosis of Sepsis. However there is neither a single laboratory test that will identify with certainty about sepsis, nor is there any single technique that excludes bacterial disease. Sepsis results from the complex interaction between the invading microorganism and the host immune, inflammatory, and coagulation response. During the last decades, efforts were made to improve laboratory diagnosis of sepsis and a variety of the markers like total leukocyte count (TLC), absolute neutrophils count (ANC), Band cell to total neutrophils count (BC/NC) ratio, Micro-ESR, cell surface antigen, and Acute phase reactants like C-reactive protein (CRP), Alpha1-acid glycoprotein and Alpha1-antitrypsin etc. were studied with different degrees of success. Despite the promising result of some of them, current evidence suggests that none of them can consistently diagnosis 100% of infected cases. C-reactive protein (CRP) is the most extensively studied acute phase reactant so far and despite the ongoing rise (and fall) of new infection markers it still remains the preferred index in many neonatal intensive care units (NICU).

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MATERIALS AND METHODS

The present study was conducted at Department of Clinical Biochemistry and Microbiology laboratory, GCS Medical College, Hospital and Research Center, Ahmedabad. This study included 50 cases which were neonates with culture proven sepsis and 50 normal newborn. Neonates selected for the study were those admitted during 1st January to 15th April , with clinical signs or symptoms of sepsis like fever, lethargy, poor feeding, jaundice, hypothermia, poor perfusion, diarrhoea, vomiting, abdominal distension, prolong capillary refill, weak or excessive cry, grunting, apnea, bulging anterior fontanelle or any maternal risk factor like maternal pyrexia

(within first week or prenatal and 48 hours of postnatal, foul smelling vaginal discharge, premature rupture of membranes (PROM), maternal UTI in last month, instrumental delivery). All the neonates were examined in detail by the pediatric trainees in NICU. The data was recorded on a data sheet. Each neonate was carefully examined according to the criteria screened for sepsis. Neonates with birth asphyxia, meconium stained liquor, low birth weight (<1500 grams), preterm babies (<32 weeks) or neonates who were already on antibiotic therapy were not included in the study. Blood for blood culture and C-reactive protein was taken under strict aseptic condition. A standard procedure was followed for both CRP and Blood culture. No special preparation of the patients required prior to specimen collection techniques. Only serum was used for testing. All the samples were tested for CRP by Turbidimertic immunoassay (quantitative) method which is based on the principle of agglutination reaction by using QUANTIA^{R}-CRP UV kits and ERBA XL-640 ANALYZER. Blood Samples were also processed for culture/sensitivity by BACTEC 9050 which is based on the principle of Fluorometric Detection System.

RESULTS

During the study period, 100 neonates were included based on selection criteria; these comprised 62 (62%) males and 38 (38%) females with ages ranging from 1day to 90 days. Their age and gender distribution are displayed in Table 1 & 2.

Table 1. Age distribution of subjects studied

AGE IN(DAYS)	NEONATES (n=100)	
	NO.	%
0-20	64	64
21-40	12	12
41-60	20	20
61-80	0	0
81-100	4	4

Table 2. Gender distribution of subjects studied

Gender distribution	Cases	
	No.	%
Male	62	62
Female	38	38
Stotal	100	100

Comparison of Mean value of CRP in test group and control group is shown in Table 3 (>0.6 mg/dl)

Table 3. Comparison of CRP (>0.6 mg/dl) in test group and control group

Variables	Mean ± S.D	P value	T value
Test group (CRP high/ Blood culture positive)	5.5323± 4.93400	<0.0001	5.425
Control group (CRP normal/ Blood culture negative)	0.5114± 0.9932		

P value of the test applied for the statistical significance is <0.0001 which implies that the result is statistically significant for CRP.

Table 4 provides data of laboratory investigations of neonates (Blood culture and CRP levels).

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of CRP levels were calculated as shown in Table 5.

Table 4. CRP levels in positive blood culture and negative blood culture cases

		Blood Culture		Total
		Positive	Negative	
CRP	High	(a) 44	(b) 8	52
	Normal	(c) 6	(d) 42	48
	Total	50	50	100

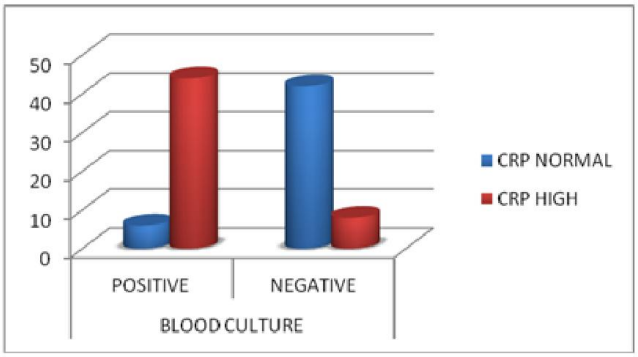

Table 5. Performance of CRP

Test	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Serum CRP (>0.6 mg/dl)	88	84	84.61	87.5

As per present study, sensitivity of Serum CRP is found to be 88% and specificity being 84% with NPV of (87.5) suggesting its beneficial role in diagnosis of neonatal sepsis.

DISCUSSION

Neonatal sepsis is a serious and potentially life threatening condition. Early diagnosis of neonatal sepsis is very difficult and essential for reducing the mortality and morbidity in neonates. No doubt blood culture is still the gold standard but because of its non-availability in most peripheral setups, high cost, more chances of contamination and delayed results, a need more convenient, cost effective and whose results are available in time. A large number of methods are available for the determination of CRP in the serum. Although, electro immune precipitation assay, immunometric assay, and laser nephelometry are sensitive and quantitative methods and latex agglutination is semi- quantitative method for the estimation of CRP. The facilities for such specialized investigations are not available at all centres. In the present study, serum CRP was done by Turbidimertric immunoassay method quantitatively and the concentration of 6 mg/dl or more was considered as positive similar to other study. In this study, 48 % (48 of 100) healthy neonates as a control group were selected and 50 % (50 of 100) neonates were proved to have neonatal sepsis which was based on positive blood culture. Other studies

showed a proved sepsis ranging from 20-30 % (Pavenik-Arnol *et al*., 2004; Naher *et al*., 2011; Abdollahi *et al*., 2012). This study showed that C-reactive protein was positive in 52% (52 of 100) of neonates. 84.61% (44 of 52) neonates were having confirmed sepsis. C-reactive protein was best single marker with an overall sensitivity and specificity of 88% & 84%. Our results are comparable with the study done by William E, Benitz *et al*, which was done in Stanford, California that shows C-reactive protein had higher sensitivity 92.9% and 85%. for proven and probable sepsis and 78.9% and 84.4% for proven sepsis in early and late onset episodes. Low Total leukocyte count (leucopenia) gave indication of infection in 46% of cases while no leucopenia was found in control group. High ESR count gave indication of infection in 40% of cases whereas normal ESR was found in control group. Positive CRP and raised micro-ESR in our study was similar to that reported by Bhartia. Similarly, CRP was positive in all culture positive cases. The comparison of both CRP and micro-ESR or CRP and TC (WBC) with positive blood culture was statistically significant ($p < 0.0001$).

In our study, 44 out of 50 (88%) cases that required longer duration of antibiotic therapy (>7 days) had positive blood culture suggesting that, those with positive blood culture and raised CRP needed longer duration of antibiotics therapy. No study comparing the blood culture positive and raised CRP with duration of treatment is available. Further studies are required to determine the duration of antibiotics therapy in neonatal sepsis with raised CRP level even after 7 days of therapy. As compared to the studies done by Boraey *et al* 18, our result have a NPV (87.5 %) of and comparatively low PPV (84.61 %). The marked difference of result among studies evaluating C-reactive protein as useful marker can be explained by non-availability of universally acceptable definition of neonatal sepsis, difference in reference range values and environmental influence on the results in different setups. We used quantitative technique for C-reactive protein determination. This is easy to perform and results are available in an hour time. Furthermore, it can also be used effectively in neonates who had already used antibiotics. Both CRP and WBC were found useful for the diagnosis of late neonatal sepsis and accuracy increased when CRP and WBC were combined and sequential CRP assay results were used.

Conclusion

CRP is one of the most widely available, most studied, and most used laboratory tests for neonatal bacterial infection and despite the continuing emergence of new markers of infection, it still plays a central role in the diagnosis of early onset sepsis of the neonate. CRP has the advantage of being well characterized in numerous studies and the extensive knowledge on its properties and limitations makes it safer compared to other newer markers. Although blood culture is still a gold standard test in diagnosing sepsis, its main drawback is its delayed result, more chances of contamination, high cost and non-availability in most peripheral setups in our country. This has prompted evaluation of surrogate markers of inflammation as possible tool for diagnosis of bacterial sepsis. Our study suggests that CRP should be used as a preferred marker in evaluating a neonate for sepsis. Despite the high sensitivity C-reactive protein we would still stress upon clinical correlation and laboratory findings should be used simultaneously for the diagnosis of neonatal sepsis.

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