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Original Article

Paediatrics Section

Correlation of C-Reactive Protein and Blood Culture in Neonatal Sepsis

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ABSTRACT

Introduction: In neonates, septicaemia is one of leading cause of morbidity and mortality. Therefore, timely diagnosis is important to prevent fatal outcome. C-reactive protein is an important biomarker that aids in the timely diagnosis of neonatal septicaemia.

Aim: The present study was carried out to determine the accuracy of CRP in the diagnosis of neonatal septicaemia and to compare it with blood culture.

Materials and Methods: One hundred neonates suspected of neonatal sepsis were included in the study over a period of one year. Blood culture and qualitative assessment of CRP was done for all the patients. CRP quantification was done for the patients who were CRP positive.

Results: Of the 100 neonates studied, 47 were blood culture positive while 70 were CRP positive. The sensitivity, specificity, positive and negative predictive values and diagnostic accuracy of CRP were 85.11%, 43.40%, 57.14%, 76.67% and 63% respectively.

Conclusion: CRP estimation is a rapid test with good sensitivity and aids in rapid diagnosis of neonatal septicaemia.

Keywords: **Biomarkers,** Neonates, Septicaemia

INTRODUCTION

Neonatal sepsis is defined as a blood infection that occurs in newborn in the first four weeks of life [1]. The sign and symptoms of neonatal septicaemia are non-specific and patients presents with fever or hypothermia, respiratory distress, feeding difficulties, lethargy or irritability, hypotonia, seizures, bulging fontanel, poor perfusion, bleeding problems, abdominal distention or unexplained jaundice [2].

After prematurity and intrapartum complications, neonatal sepsis is the third leading cause of mortality in neonates and is liable for 42% of deaths in the first week of life and 13% of all neonatal mortality [3].

Diagnosing neonatal sepsis is a difficult task because of nonspecific signs and symptoms. The gold standard method to diagnose neonatal sepsis is blood culture however it is time consuming, requires well equipped laboratory and trained personnel. It can be false negative due to the small amount of blood drawn from neonates, prenatal antibiotic use or low level of bacteraemia [4].

In last few years, various biomarkers like white blood cell count, CRP, procalcitonin and Interleukin-6 triggered by the host immune system have been targeted as potential indicators for diagnostic and prognostic purposes in the early diagnosis of sepsis [5].

CRP was first demonstrated in 1930 by Tillet and Francis at Rockefeller University [6]. It is an acute phase reactant and an inflammatory marker synthesised in the liver in response to inflammatory cytokines (IL-1, IL-6 and TNF-α) and plays a major role in innate immunity [7]. CRP stimulates cell-mediated cytotoxicity. It leads to the activation of neutrophils, promotion of platelet degranulation and enhancement of natural killer cell activity. It is produced rapidly after a single stimulus by the hepatic cells. The half life of CRP is 19 hours and in acute response its level increases up to thousand fold and comes down rapidly as the source is removed. After effective treatment, its levels can fall rapidly in 5-7 hours. CRP crosses through placenta in very low quantities, so any elevation in a newborn always represents endogenous synthesis [8].

CRP level can be assessed both quantitatively and qualitatively. Quantitative method provides fast, highly sensitive and precise result but is more costly and requires technical proficiency, so it is mostly used in developed countries and well equipped modern hospitals. The qualitative method is simple, rapid, easy to perform, easy to interpret and can be performed as a bedside test. It is cheaper and requires less skill. The qualitative method may

therefore, be more feasible in resource poor countries and where there are no laboratory equipments or trained manpower [9].

This study was planned to evaluate the role of CRP in the blood as an early marker of neonatal sepsis and to find its correlation with blood culture.

MATERIALS AND METHODS

This hospital based observational study was carried out in the Department of Microbiology of a tertiary care teaching hospital, Jaipur, Rajasthan, India from September 2016 to September 2017. The study protocol was approved by the Institutional Ethics Committee. One hundred neonates with suspected sepsis or those coming to hospital with signs and symptoms of sepsis up to 28 days of life were included in the study. Babies who had suffered from birth asphyxia, birth weight less than 1500 grams, extremely premature (less than 32 weeks of gestation) and neonates who were already given antibiotics were excluded from the study.

After written informed consent from the patient's parents, detailed history, clinical examination findings and laboratory findings were noted on pre-designed proforma. 1-2 mL of blood collected aseptically was inoculated into blood culture bottle containing 5 mL of Brain Heart Infusion Broth. Blood culture bottles were incubated at 37°C aerobically. After overnight incubation blood culture bottles were examined for indicators of growth like turbidity, gas production, haemolysis or discrete colonies on the surface of sedimented red cells. If any of these were present subculture was done on to blood agar and MacConkey agar. If indicators of growth were not present primary subculture was done after 48 hours of incubation on blood agar and MacConkey agar. If no growth occurred on plates after overnight incubation, bottles were incubated further and observed daily for indicators of growth till 7 days. A final subculture was done at the end of day 7 or at appearance of indicators of growth which ever was earlier. The colonies grown on blood agar and MacConkey agar were identified by conventional methods according to the standard laboratory protocol, including colony morphology, Gram staining and biochemical reactions [10].

CRP estimation was done by Latex Agglutination Card test. CRP was reported as positive if agglutination particles were detected and negative if no particles were seen. Samples positive for CRP were further subjected to CRP estimation using Automated Clinical Chemistry Analyser (ERBA Diagnostics Mannheim GmbH- Germany) [11].

RESULTS

In the present study, the male to female ratio was 1.6:1. The mean age of the study population was 7.10 days. Out of the total 100 neonates, 47 were blood culture positive from which 40 were positive for CRP also. Among the blood culture negative samples, 30 were CRP positive. The mean value of CRP in blood culture positive neonates was 48.7 mg/l (8.6mg/L-180.1 mg/L) whereas in blood culture negative neonates

Demographic Details (n=100)	No. of Neonates
Gender	
Male	62%
Female	38%
Age (in days)	
0-7	71%
8-14	11%
15-21	6%
22-28	12%
Preterm (<37 weeks)	52%
Term (>37 weeks)	48%
Maternal Risk Factors	
PROM	34%
MSAF	30%
Febrile illness in mother	17%
More than 3 vaginal examinations	6%
Preterm labour	3%
Delivery at home	2%
Risk factors not identified	5%
Birth Weight	
Low birth weight	39%
Normal birth weight	61%

[Table/Fig-1]: Demographic details of patients with neonatal sepsis. *PROM- Premature Rupture of Membranes; MSAF-Meconium Stained Amniotic Fluid

Variables	Blood Culture Positive	Blood Culture Negative	Total
CRP Positive	40	30	70
Mean Value	48.7 mg/L	16.0 mg/L	34.7 mg/L
CRP Negative	07	23	30
Total	47	53	100

[Table/Fig-2]: Comparison of blood culture and CRP in patients with neonatal septicaemia.

Parameters	Value
Sensitivity	85.11%
Specificity	43.40%
Positive Predictive Value	57.14%
Negative Predictive Value	76.67%
Diagnostic Accuracy	63.00%

[Table/Fig-3]: Predictive values of CRP in patients with neonatal septicaemia.

	Blood Culture Positive (n=47)	CRP Positive (n=40)	Mean (in mg/L)
Gram Negative Bacteria	20	17	96.3
Gram Positive Bacteria	27	23	36.15

[Table/Fig-4]: Mean value of CRP in relation to organisms isolated in patients with neonatal septicaemia.

were 16.0mg/L (6.6mg/L-44.8mg/L) [Table/Fig-1-4].

DISCUSSION

Neonatal sepsis is one of the leading causes of morbidity and mortality among the newborns in the developing countries. It is a life threatening clinical emergency that demands urgent diagnosis and treatment [12].

The present study was carried out in the Department of Microbiology of a tertiary care teaching hospital to evaluate the diagnostic accuracy of CRP in neonatal septicaemia.

In the present study male babies (62%) were affected more than female babies (38%) who were similar to findings of other studies reported from India [13-15]. The development of thymus and antibody production is X-linked which may be the reason for male preponderance [16].

In our study, incidence of septicaemia was higher in preterm neonates (52%) compared to term neonates (48%). Our results were consistent with studies conducted by Patel BM et al., [13] and Shah AJ et al., [17], who reported 67.37% and 70% blood culture positivity rates respectively in preterm babies. Preterm neonates are more prone to septicaemia because they have increased susceptibility to infection due to an immature immune system, inefficient neutrophil function and lack of antigen type-specific antibodies to pathogens in their environment [18-20].

In the present study, Premature Rupture of Membranes (PROM), Meconium Stained Amniotic Fluid (MSAF) and febrile illness in mother were the commonest risk factors. Our results were similar to Bodkhe A et al., who also reported PROM as the most common risk factor(30%) followed by MSAF(28.3%) and prolonged labour (15%) [5]. PROM is a major risk factor for sepsis because it increases the risk of ascending infection.

In our study, incidence of suspected neonatal septicaemia was more common in normal birth weight neonates (62%) but incidence of culture proven sepsis was significantly higher in low birth weight than normal weight neonates which was similar to the studies conducted by Patel BM et al.,[13].The rate of infection is inversely proportional to birth weight. Low birth weight neonates have low IgG level and are more susceptible to infections [21].

In the present study, out of 100 neonates suspected of neonatal septicaemia, 47% were blood culture positive. Our results were comparable with many studies conducted in India [1,22,23]. Low blood culture positivity in our study might be due to the low amount of blood drawn or possibility of infection with anaerobes or presence of fastidious organisms.

For definitive diagnosis of septicaemia, blood culture is the gold standard method but it takes at least 48-72 hours for reporting and by that time the infection may progress, especially if antibiotic treatment is not started. So there is a need of a screening test which can diagnose septic neonates rapidly and prevent injudicious antibiotic therapy in non septic neonates.

CRP is a screening test that can be used to assess neonatal sepsis as it is easily available, cost effective and results are readily available. In our study, 70% of the suspected cases of neonatal sepsis were CRP positive which was comparable to the studies done by Jan AZ et al.,[7], Shah AJ et al.,[17] and Hisamuddin E et al.,[23].

In our study, out of the 47 blood culture positive samples, 40 (85.1%) were positive for CRP which was similar to studies done by Gowsami Y et al.,[22] and Hisamuddin E et al.,[23]

In present study, the sensitivity and specificity of CRP against blood culture was 85.11% and 43.40% respectively. The positive and negative predictive value was 57.14% and 76.67% respectively. The diagnostic accuracy of CRP against blood culture in detecting neonatal septicaemia was 63%. Our results were comparable to studies done by Younis S et al., [24] and Chauhan S et al., [25].

The underlying pathogen in sepsis greatly influences the magnitude of CRP. In the present study, the magnitude of CRP was significantly higher in gram negative organisms (mean value=96.3 mg/L) than gram positive organisms (36.15 mg/L). Sabel and Hanson also reported higher CRP positivity in gram negative organisms than gram positive organisms [26].

LIMITATION

The limitation of our study was low sample size and to correlate it, large number of samples may be tested.

CONCLUSION

Early diagnosis of neonatal sepsis with the aid of biomarkers like CRP may serve as an important tool in reducing the mortality and morbidity among neonates. In the present study mean CRP value was higher in gram negative organisms as compared to gram positive organisms. So the estimation of CRP can help in providing a presumptive diagnosis as to whether a gram negative or gram positive organism is the cause of septicaemia and the antibiotic therapy can be started even before the blood culture comes positive.

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