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Original Research Article

Evaluation of C - Reactive Protein in Diagnosis of Neonatal Sepsis and Its Prognostic Value: A Prospective Study

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ABSTRACT

Introduction: Neonatal sepsis is considered to be the common cause of mortality and morbidity. Early diagnosis of neonatal sepsis will help to reduce the neonatal death. Microbial culture is the specific method for diagnosis of neonatal sepsis but these reports are usually available after 48-72 hours. Hence there is need for new biochemical marker for early detection of septic infants. One such marker is C-reactive protein (CRP) which rises rapidly in acute disease and cleared once the stimulus is aborted.
Aim: To assess role of CRP in diagnosis of neonatal sepsis and its prognostic value and also to study the co-relation of CRP with clinical findings.
Materials and Methods: Present cross sectional, prospective study was conducted on newborns suspected of sepsis in Department of Pediatrics and Microbiology. Study was conducted over a period of 2 years. Study group comprised of 200 neonates admitted in NICU who fulfilled criteria of neonatal sepsis as per guidelines of National Neonatology Forum. CRP estimation was done by Latex agglutination slide test, value of more than 0.6mg/dl was taken positive in our study. Out of 200 cases, 76 were both culture positive and CRP positive which were taken as proven sepsis, and 102 cases had only CRP positive (culture negative) so they were taken as probable sepsis and remaining 22 cases were both culture and CRP negative. In cases with CRP positive reports CRP was repeated on day 3, 7, 10, 14, 21 for its prognostic value.
Result: CRP was positive in 89% of babies with suspected sepsis and 100% in culture proven cases. Sensitivity of CRP in diagnosis of neonatal sepsis in our study was 100%, with specificity of 17.7% and positive predictive value of 42.7% with 100% negative predictive value. CRP was observed to be negative in neonates who responded to therapy. P= <0.05(statistically significant) (Chi-Square test).
Conclusions: Serial CRP measurement is good indicator for discontinuing antibiotic therapy in neonates with suspected sepsis, these neonates can be discharged from hospital earlier, with significantly reduced cost, complication of treatment and family anxiety.

Keywords: C-reactive protein, Blood culture, Culture positive, Neonatal sepsis.

INTRODUCTION

Neonatal sepsis is defined as clinical syndrome of bacteraemia with systemic signs and symptoms of infection in first month of life. [1-3] It is the commonest cause of neonatal mortality and morbidity in developing countries. [1] Neonatal sepsis is a great mimicker giving rise to signs and symptoms compatible with almost every other neonatal problem thus making clinical diagnosis of sepsis very difficult. [4] Blood culture remains the gold standard for

diagnosis of neonatal sepsis. As microbial culture reports are usually available after 48-72 hours, early identification of infected cases is a real diagnostic problem. [5] Many plasma proteins called Acute Phase Reactants become elevated acutely in response to illness, infection, and trauma and tissue necrosis. These proteins include α-1 acid glycoprotein, α-1 antitrypsin, ceruloplasmin, haptoglobin, fibrinogen and CRP. The most useful of this is CRP based on its rapid rise in response to acute disease and rapid clearance once that stimulus is been aborted. CRP is readily quantitated by immunological methods. [6] Although many authors proposed that, persistent positive CRP test indicates bad prognosis. But the possible role of CRP in diagnosis of neonatal sepsis and its prognostic value is not confirmed so far. Hence in this prospective study an attempt was made to evaluate role of CRP in diagnosis of neonatal sepsis and its prognostic value.

MATERIALS AND METHODS

Present cross sectional, non randomized, study was conducted over a period of two years from august 2010 to July 2012 in babies born and then admitted (up to 1 month of life) in NICU of Rajarshee Chhatrapati Shahu Maharaj Government Medical College and Chhatrapati Pramilaraje General Hospital, Kolhapur, India.

Ethical clearance was obtained from institutional Ethical Committee and informed consent was taken from parents of neonates. Sample size included two hundred neonates (all term and preterm babies) who shown signs and symptoms of sepsis. Babies suspected of other systemic illness were excluded from the study. A detailed history was obtained from the mother / guardian. Data regarding prolonged rupture of membrane (PROM), maternal pyrexia, gestational age and maternal urinary tract infection were obtained from history, antenatal case records and information from referral note. Type of delivery and birth order were noted. Detailed history regarding clinical features suggestive of sepsis and other relevant complaints were noted. Weight and sex of the baby were recorded. A detailed clinical examination was done at the time of admission. Blood cultures were collected from study groups at the time of admission. Complete blood investigation including haemoglobin, total leukocyte count and differential leukocyte count was carried out after 24 hours of life from all babies. C-reactive protein was assessed after 24 hours of admission. All diagnostic tests were repeated if required. For prognostic value C-reactive protein was repeated on day 3, 7, 10, 14 and 21. Normal value of CRP is upto 0.6mg/dl hence CRP value greater than 0.6mg/dl was taken as positive in our study.

During hospital stay babies were assessed every day for the evidence of clinical sepsis. If baby showed two or more features of clinical sepsis. They were classified as having suspected sepsis and once blood culture showed growth of micro-organism, babies were classified as having proven sepsis. Whenever sepsis was suspected lumbar puncture was done, and was repeated when indicated. Final diagnosis was noted at the time of discharge or when baby expired.

Proven septicemia: presence of clinical manifestations of sepsis plus either of the following two parameters: Isolation of the pathogens from a central body fluid, Autopsy evidence of sepsis.

Probable septicemia: indicative of clinical manifestations plus one or more of the following predisposing factors such as maternal pyrexia, prolonged rupture of membranes for over 18 hours, foul smelling liquor or gastric polymorphs. Positive sepsis screen, Radiological evidence of pneumonia.

RESULTS

Amongst 200 cases included in the study majority was preterm i.e. 118/200 (59%) while remaining 82 (41%) cases were full term babies. (p value <0.05)

Out of the total 200 cases, majority i.e 102 (51%) belonged to probable sepsis with CRP positive. This was followed by proven sepsis with CRP and culture positive as seen in 76(38%) cases while the remaining 22 (11%) cases were that of probable sepsis with CRP negative reports. [Table/Fig- 1]. We found that CRP was positive in 89% of babies with suspected sepsis (n=200). In 100 % culture proven sepsis cases CRP was positive.

Sensitivity of CRP in diagnosis of neonatal sepsis in our study was found to be 100% with specificity of 17.7% and positive predictive value of 42.7% with 100 % negative predictive value.

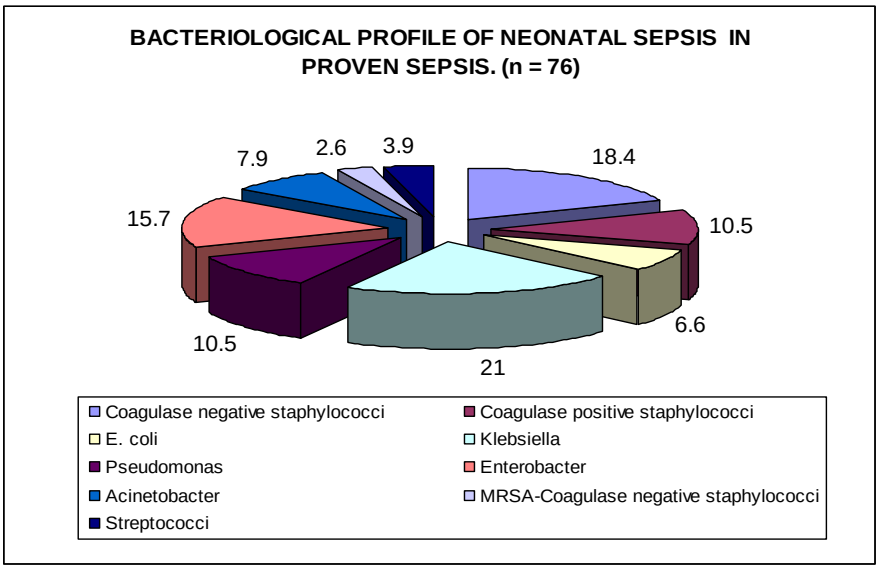
Table/Fig- 1: Showing Values of CRP in study group

Category	Proven sepsis with culture positive (n = 76)	Probable sepsis with culture negative (n = 124)	Total
CRP Positive	76	102	178
CRP Negative	0	22	22

Table/Fig- 2: days taken for CRP TO become negative

	Day 3	Day 7	Day 10	Day 14	Day 21
Proven sepsis (n = 58)	-	04	14	37	3
Probable sepsis (n - 97)	32	45	16	6	-

$x^2 = 30$, d.f. = 2, P = < 0.05 Statistically significant (Chi-Square test)



Table/Fig- 3: Bacteriological profile of neonatal sepsis. (N = 76)

Table/Fig- 4: Percentage of Risk factors in Suspected Septic Cases

Predisposing factors	No of cases	Percentage
Low Birth weight	147	73.5
Prematurity	118	59
Prolonged ruptures of membrane > 18 hrs	21	10.5
Home delivery	14	7
Congenital anomalies	11	5.5
Birth Asphyxia	7	3.5
Meconium stained liquour	6	3
H/O intrapartum maternal infection	4	2
Instrumental delivery	2	1

Of the 21 babies who expired remained positive throughout and most cases of proven sepsis required 14 days for CRP to become negative. Most cases of probable sepsis with CRP positive became negative on day 3 and day 7. So CRP has prognostic role for discontinuation of antibiotics. [Table/Fig- 2] The most common pathogen was klebsiella 21% followed by and Coagulase negative staphylococci 18.4% and enterobacter as seen in 15.7% cases. [Table/Fig- 3]

LBW was the most common risk factor as observed in 147/200 (73.5%) cases, this was followed by prematurity as seen in 118 (59%) cases. The third common risk factor was PROM as seen in 21 (10.5%) cases. [Table/Fig- 4]

DISCUSSION

We found that CRP was positive in 89% of babies with suspected sepsis. Out of them 100% of proven sepsis and 51% of culture negative probable cases had CRP positive and 11% had CRP negative. Sensitivity of CRP is diagnosis of neonatal sepsis in our study was 100%.

Out of 76 cases of blood culture positive sepsis, 58 were discharged and 18 expired. In 37 cases CRP became negative on day 14 following which the antibiotics were omitted. Amongst cases of sepsis where blood culture was negative but clinical parameters were positive. 3 cases expired, CRP became negative on day 3 in 32 cases, on day 7 in 45 cases, on day 10 in 16 cases and on day 14 in 6 cases.

In all the cases when repeated CRP value was negative, antibiotics were omitted based on CRP only. These babies were observed for a period of 48 hours, none of them showed any relapse of infection following normalization of CRP giving a negative predictive value of 100%. Similar findings were reported by squire et al., they were able to stop antibiotics in 65.5% of cases within 72 hours and could reduce the duration of treatment by 20% in cases of suspected neonatal sepsis. [7]

Our results concur best with a similar study conducted by Jaswal et al., [8] (2000) who revealed 100% negative predictive value with no relapse following discontinuation of treatment after normalization of CRP levels. Eh et al., [9] Study done at Johannesburg hospital reported NPV of 99%, Baptista Gonzales [10] et al., reported sensitivity of 91%, specificity of 93%, PPV of 87% and NPV of 95%, still other workers like Hindocha et al. [11] and Adhikari et al. [12] have reported sensitivities above 80%, specificities between 40 to 70%, PPV of 57% and Negative Predictive Value (NPV) between 73-95%.

Anita Sharma et al. reported that out of various test for rapid diagnosis of neonatal sepsis, CRP was one with maximum sensitivity 80%. Anita Chandna et al., found that CRP is the most useful single test with high degree of sensitivity (83%). [5,13] Similar study done by Chacha et al showed that higher rates of CRP positive were observed among neonates with confirmed neonatal sepsis than those with negative blood culture. [14] Present study results found that CRP is a useful marker for diagnosis of neonatal sepsis.

CONCLUSION

The results of our study signify the possible role of CRP in diagnosis of neonatal sepsis. The sensitivity of CRP in diagnosis of neonatal sepsis in our study was 100%, specificity of 17.7%, positive predictive value of 42.7% with 100% negative predictive value. Thus negative predictive value of CRP in deciding the duration of antibiotic therapy was 100% in present study. In most cases of probable sepsis with CRP become negative on day 3 and day 7. Hence CRP has prognostic value for discontinuation of antibiotics. Thus we conclude that serial CRP measurement is a good indicator for discontinuing antibiotic therapy in neonates with suspected sepsis and a useful diagnostic and prognostic marker in neonatal sepsis.

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