ORIGINAL ARTICLE

C-REACTIVE PROTEIN (CRP) IN EARLY DIAGNOSIS OF NEONATAL SEPTICEMIA

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ABSTRACT

Aim: Early diagnosis of sepsis in the neonate is often difficult because symptoms and signs are usually non-specific. A study was conducted to evaluate C-reactive protein (CRP) as a screening tool for neonatal sepsis.

Method: The prospective observational study was conducted at NICU, V. S. Hospital, Ahmedabad from January 2008 to June 2009. 75 neonates were included with the age group of first 28days (4week) of life (infant age) in study, all of which were suspected to have sepsis in clinical settings. All peripheral smear of neonate stained with Giemsa stain were reviewed .CRP performed by semi quantitative latex agglutination method. Positive cultures were the "gold standard" against which the performance of CRP , abnormal white blood cell counts (WBC) & absolute neutrophil counts (ANC) were compared.

Results: Among 75 septic screens, 39 (52%) patients had positive cultures. The sensitivity and specificity of CRP 0.6 mg/dL was 92.30% and 85.71% respectively. Abnormal platelet count had the lowest specificity(45%) and sensitivity(23.07%) among them.

Conclusion: CRP assay using semi quantitative latex agglutination method is a valuable adjunct in screening for neonatal sepsis, complementing clinical decision-making.

Keywords: C-Reactive Protein, Acute Phase Reactant, Infection, Neonatal Sepsis

INTRODUCTION

Early recognition of sepsis in the neonate is one of the most difficult problems facing clinicians today. Such infants often present with non-specific symptoms and signs so that failure or delay in treatment may result in significant mortality and morbidity [1]. Although various hematological indices had been utilized to screen for sepsis, most were neither highly sensitive nor specific and were commonly affected by perinatal factors like maternal hypertension, asphyxia and hemolytic disease[2]. C-reactive protein (CRP) has been used as an acute phase reactant to diagnose and follow the course of infection in neonates [3-7]. Its advantages include its very low serum levels in normal infants, a rapid rise within 12 to 24 hours of sepsis and a large incremental increase thereafter.

MATERIAL AND METHODS

The prospective observational study was conducted in NICU, V. S. Hospital, Ahmedabad from January 2008 to June 2009. 75 neonates were included with the age group of first 28days (4week) of life of infant in study. All of which were suspected to have sepsis in clinical settings. Patient with suspected sepsis having two or more of the following clinical features were used to identify patients for suspected neonatal sepsis: Respiratory and cardiovascular compromise, metabolic and Neurologic changes. Exclusion criteria include, age at the time of admission is greater than 28days, neonates who received antibiotic dose prior to septic workup and neonate diagnosed to have congenital malformation. Blood samples were drawn prior to administration of antibiotic therapy for blood culture by trained staff with all aseptic precaution in blood culture bottle and should be observed for 5 days after that they are reported as sterile, complete hemogram and routine biochemical investigations including glucose level.[8]

Investigation for CRP in newborn is sent after 12 hour if neonate is admitted on day one and it is performed by semi quantitative latex agglutination method. Results are given as negative, 0.6mg/dl, 1.2mg/dl etc. by serial dilution of serum of patient. The total leukocyte count and indices were counted on a cell counter and corrected for nucleated red blood cells. All peripheral smear of neonate stained with giemsa stain were reviewed by a pathologist. Differential counts were

performed by counting at least 200 cells. Various parameters of complete hemogram, as proved by many studies help in early diagnosis of neonatal sepsis. Blood of suspected neonate is collected at the time of admission prior to administration of antibiotic therapy. Alternate way is use of cord blood for hematological profile, which can reliable used as substitute of neonate blood collection[9]. Various parameters include absolute neutrophil & Total leucocytes count, Band cell & immature neutrophil count, neutrophilic shift to left, Band cell count & Band cells/Total Neutrophil Ratio (I: T Ratio), morphological changes in leucocytes - these include: toxic granulation, dohle Bodies, cytoplasmic vacuolation, and thrombocytopenia .As and when required, Chest X-Ray, Urine and CSF-routine and microscopy sent to rule out systemic/localized infection.

RESULTS

During study period, total 75 neonates admitted in neonatal intensive care unit were studied. They are divided in three groups based on clinical features and blood culture reports - proven sepsis, probable sepsis and clinically sepsis. **Proven Sepsis:** These are the patients among suspected neonatal sepsis in which blood culture confirms sepsis or there is definite evidence of localized infection. **Probable Sepsis:** These are the patients among suspected septic patient with CRP and/or hematological parameters suggestive of septicemia but negative blood culture. **Clinically Sepsis**: These are the suspected septic patient with CRP <0.6 mg/dl, almost normal hematological parameters and sterile blood culture.

The median birth weight was 2268gm & median age was 3.89 days. Out of 75 total cases 39 cases were proven sepsis, 4 cases have probable sepsis and rest of 32 cases having clinically sepsis.

Study confirms that low birth weight babies are prone to develop neonatal sepsis as compared to their counterpart with normal birth weight[18,19] Study reveals three out of four neonates with sepsis was low birth weight. Relation between birth weight and sepsis is shown in table 1.

Table 1: Relation between birth weight and sepsis

Birth Weight (gm)	Low <2500)	Normal (≥2500)
Neonates having proven sepsis (%)	74.35 (29/39)	25.65 (10/39)
Neonates having Probable sepsis (%)	75	25
Neonates having clinically Sepsis (%)	59.38	40.62
Jia-Horng Jiang et al (%) 16	75.9	24.1

Table 2: Gestational Age and Sepsis

Gestational age	Preterm (<36 wk)	Full term
Neonates having proven sepsis (%)	94.87 (37/39)	5.13 (2/39)
Neonates having probable sepsis (%)	25.0 (1/4)	75.0 (3/4)
Neonates having clinically sepsis (%)	46.87 (15/32)	53.13 (17/32)
Jia-Horng Jiang et al (%)[16]	76.7	23.3
E.J. Al- Zwaini et al (%)[17]	20	80

Table 3: Sensitivity & Specificity of Various Parameters of Investigation in Detecting Sepsis

Investigation	Sensitivity		Specificity	
CRP (>=0.6mg/dl)	92.30%	(36/39)	85.71%	(36/42)
Abnormal WBC count (<5000/ml or>20000/ml)	30.77%	(12/39)	63.15%	(12/19)
ANC (<1000/ml or >5500/ml)	64.10%	(25/39)	54.34%	(25/46)
Platelet count (< than 1.5L/cumm)	23.07%	(9/39)	45.00%	(9/20)
I:T ratio (>0.2)	28.20%	(11/39)	73.33%	(11/15)
Degenerative changes in neutrophils (+ to 3+)	64.10%	(25/39)	64.10%	(25/39)
Band flag estimate (>8%)	43.59%	(17/39)	62.96%	(17/27)
I:G region estimate (>1.0)	71.80%	(28/39)	58.33%	(28/48)

There is strong association of neonatal sepsis with prematurity. 94% of sepsis occurs in preterm neonate. Other studies do favor this conclusion but association however is not so strong. In clinical sepsis group, rate of prematurity is around 47% which is far more than incidence of prematurity in general population which may indicate predilection of suspecting sepsis more in case of premature neonate.

In this study, commonest causal organism for neonatal sepsis was Coagulase negative Staphylococcus[10] followed by Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus spp., and E.coli. Out of 39 proven sepsis cases streptococci, Citrobacter & Acinetobacter is responsible for one case each. Three cases were included in proven sepsis category because of presence of localized infection.

Sensitivity and specificity of various laboratory investigations in detection of neonatal sepsis is mentioned in table 3.

DISCUSSION

In this evaluation of CRP assay, the diagnosis of sepsis was based on positive blood culture, cerebro-spinal fluid or joint aspirate in the presence of signs of

infection. The definition excluded pneumonia, gastro-intestinal, urinary tract and skin infections which may not result in CRP changes [11, 12]. Comparison of the performance of CRP and abnormal hematology was thus made against a well-defined "gold standard". Like the report of Wagle et al[13], septic infants had significantly lower birth weight and gestational age than non-septic ones. Majority of infecting organisms were the Staphylococcus , which form a leading cause of nosocomial infections in the susceptible neonate[1].

The calculation of both sensitivity and specificity depend on knowing which infants were already septic when CRP assay was performed. Greater practical value is derived from knowing its predictive accuracy [8], although these are dependent on prevalence rate. In other words, when CRP showed a positive result, one wants to know what proportion of infants were in fact septic. Platelet counts had the lowest sensitivity (23.07%) and lowest specificity (45%) among the indices. These indices render them less valuable than CRP for screening purposes. Furthermore, Manroe [2] had reported that abnormal hematology may be affected by non-septic processes like steroid treatment as part of therapy for chronic lung disease. CRP on the other hand was unaffected by arterial catheterisation, intraventricular bleeding or steroid therapy[14,15].

This study showed that the measurement of C-reactive protein by semi quantitative latex agglutination method is a useful adjunctive tool in screening for neonatal sepsis. Quantitative assay of CRP is simple to perform at the bedside by medical staff. It is readily completed within 10 minutes, utilizing only 20 microL of the infants' blood. The optimum CRP value for screening of neonatal sepsis appeared to be 0.6 mg/dL. Abnormal hematology especially leucocyte indices did not have as comparable a sensitivity or specificity as CRP. Sound clinical judgment combined with quantitative CRP assay should provide a rational basis for treatment decisions in the management of neonatal sepsis [1]. Such a strategy may significantly reduce unnecessary antimicrobial therapy which could otherwise permit the emergence of resistant strains of organisms as well as place these immature infants at risk for allergic and adverse side-effects with increased hospitalization costs.

CONCLUSION

There are no ideal tests for the diagnosis of early or late-onset neonatal sepsis. Physical examination has an important role in identifying infants at low risk for sepsis who are asymptomatic. No sepsis marker can diagnose close to 100% of infected cases. The wide variations between studies in methods and results, the lack of precision in the definition of sepsis and the lack of standardized reference values makes it impossible to do a meta-analysis of existing studies using cytokine measurements for diagnosis of sepsis. Cytokine and chemokine determinations are expensive tests and are not routinely performed. Current sepsis markers like neutrophil indices, CRP are useful adjunct tests in identifying infants with a low probability of infection.

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