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RESEARCH ARTICLE

The Role and Significance of C – Reactive Protein in Neonatal Sepsis: A Clinical Investigation

***Jayanta Debnath[1], Tapan Debnath[2], Biswajit Majumdar[3], Jayanta Poddar[4]**

[1]Assistant Professor, Department of Microbiology, Tripura Medical College and Dr. B.R. Ambedkar Hospital, Hapania, Agartala, Tripura, 799014.

[2] Assistant Professor, Department of Biochemistry, Tripura Medical College and Dr. B.R. Ambedkar Hospital, Hapania, Agartala, Tripura, 799014.

[3]Professors, Department of Biochemistry, Gandaki Medical College, Tribhuvan University, Nepal.

[4] Associate Professor, Department of Pediatrics, Tripura Medical College and Dr. B.R. Ambedkar Hospital, Hapania, Agartala, Tripura, 799014.

ABSTRACT:

OBJECTIVE: To evaluate the role of CRP in the management of neonatal sepsis in a NICU setting where resources for diagnosis and monitoring prognosis is minimal.

METHODOLOGY: The study was conducted at Dr. B.R. Ambedkar hospital, Agartala for a period of one year from March 2010 to February 2011. The data included neonates born with definite risk factor who were clinically evaluated and subsequently transferred to NICU. The admitted neonates were evaluated for laboratory values, out of which serial C – reactive protein estimation (CRP) was particularly studied and correlated with initiation and duration of antibiotic therapy.

RESULTS: Of 1533 clinically evaluated neonates, 352 were transferred to NICU. In 120 neonates, antibiotics were either discontinued before 48 hours or not treated based on serial CRP concentration. The majority of neonates (206) were treated for 3 to 5 days and 26 treated for six days or more. Peak CRP concentration primarily determined the duration of antibiotic therapy, with the mean CRP level rising from 2.4 mg/dl to 10.8 mg/dl from third to above sixth day of treatment. The mean duration of treatment was 3.4 days. No infant discharged with normal CRP value was readmitted in this hospital with signs of sepsis within one month.

CONCLUSION: Serial CRP estimation has been evaluated out to be a low cost, effective and rapid prognostic marker in acute infection. It definitely helps in deciding the initiation and duration of antibiotic therapy, thereby reducing unwanted antibiotic exposure and duration of hospital stay of neonates.

KEYWORDS: C – reactive protein; neonate; antibiotic; sepsis

ABBREVIATIONS: NICU – neonatal intensive care unit ; CRP – C – reactive protein ; CBC – complete blood count ; WBC – white blood cell.

INTRODUCTION:

Perinatal causes are the most common causes of childhood mortality below age of five years in developing countries [(1)] and neonatal infections predominates the list.[(2)] Early clinical diagnosis of neonatal sepsis is a challenge due to nonspecific nature of clinical manifestations. Initiation of antibiotic therapy before diagnostic test results are available is recommended for the neonates with clinical signs or epidemiological factors associated with neonatal sepsis.[(3)] It has been observed that, due to nonspecific nature of clinical findings, empirical therapy may result in treatment of about 30 uninfected infants for everyone, who is later determined to be infected.[(4,5)] There have been attempts to develop screening tests or scoring systems to identify infected infants during initial assessment, sparing others from invasive diagnostic procedures and intravenous antibiotic therapy. Serial C – reactive protein (CRP) levels during this period may be useful for early identification of infants for whom antibiotic therapy can be safely discontinued.[(6)]

Also, a definitive diagnosis of neonatal sepsis has been complicated by increased use of prenatal antibiotics administered to mother. This poses a difficulty in management, because positive blood culture result becomes uncertain. In addition, false positive blood culture results due to contamination may be encountered. These can be distinguished by determining serial CRP levels.[(6,7)] The clinicians' dilemma for selecting infants who need antibiotic treatment and to decide the duration of antibiotic therapy may be solved by CRP estimation.

Acute phase proteins are mainly produced by the liver as part of an immediate inflammatory response to infection or tissue injury. The most extensively used and investigated acute phase reactant is CRP.[(8-12)] CRP is synthesized within 6 to 8 hours of exposure to an infective process or tissue damage. It has a half-life of 19 hours and may increase more than 1000 fold during an acute phase

* ***Corresponding author***: *Jayanta Debnath*

response.[13] CRP as a diagnostic marker in neonates has high sensitivity and specificity than total neutrophil count and I/T ratio.[14] Previous studies suggest that CRP is useful in managing late onset systemic bacterial or fungal infection.[12,15] As the concentration of CRP increases slowly in initial phase, the sensitivity at the time of sepsis screening is less.[15] So, serial measurement at 24 hours and 48 hours after onset of illness considerably improves sensitivity.[15] The change in pattern of CRP and normalization of raised concentrations are considered to be useful in monitoring the progress of treatment, thereby guiding the antibiotic therapy.[9,11,15,16]

METHODOLOGY:

A total of 1533 delivered neonates were enrolled for clinical evaluation of sepsis from March 2010 to February 2011 at Dr. B.R. Ambedkar hospital, Agartala. On clinical suspicion, the neonates were transferred to NICU for further evaluation and management, based on laboratory values. The data were collected prospectively and an observational study was conducted to correlate the laboratory values with the initiation and duration of antibiotic therapy in the neonates admitted in NICU.

The risk factors that necessitated clinical evaluation included preterm labour at 35 – 37 weeks of gestation, premature rupture of membranes for more than 18 hours, maternal pyrexia (>38^{o}C), fetal tachycardia (>180 beats/minute) and meconium stained liquor amnii. The clinical findings which aroused suspicion of sepsis in the neonate included tachypnea, dyspnea/apnea, cyanotic episodes, temperature instability, poor perfusion or unexplained hypoglycemia.

In all neonates with risk factor or clinical manifestation, serum concentrations of CRP were estimated immediately and 12 – 24 hours later. In case of abnormal values, another set of value was obtained by 48 hours. In such cases, antibiotics (ampicillin / ceftriaxone with amikacin) were started immediately on transfer to NICU. The antibiotics were started mostly due to increased CRP level and occasionally for abnormal complete blood count (CBC) in association with clinical finding.

The tests were performed following the recommended standard operating procedure of the clinical laboratory. About 0.5 ml of blood was collected using 24 gauge needle keeping all aseptic precautions. Within one hour, the blood was transferred to Serology section of laboratory. It was centrifuged at 2400g and serum pipetted out in Epindorff tubes. To maintain low cost, particle latex agglutination technique was adopted, with determination of titres using serial dilution method. In this, latex microparticles coated with anti – CRP mouse monoclonal antibodies reacts with the CRP in the sample to form an antigen – antibody complex. However, to minimize any error, automated nephelometric estimation was done randomly. The quality control was maintained with the supplied positive and negative controls during each batch of test sample.

Abnormal values were considered when the concentration of CRP was 0.6 mg/dl or more. The limit of detection by nephelometry was currently set at 0.6 mg/dl. Along with CRP estimation, a CBC was also performed by cell counter and later correlated by slides.

RESULTS:

The study period of one completed year included 1533 neonates who were evaluated clinically for presence of sepsis. Abnormal clinical findings or abnormal laboratory values necessitated the transfer of 352 (22.9%) neonates to NICU. The most common risk factors for evaluation is listed in Table 1.

Table 1: Major risk factors that required sepsis evaluation on clinical suspicion

Risk factor	Total number of neonates evaluated	Transfer to NICU (%)
35 – 37 weeks of gestation	176	11 (6.3%)
PROM > 18 hours[1]	260	53 (20.7%)
Maternal pyrexia[2]	297	87 (29.5%)
Hypoglycemia[3]	188	32 (17.2%)

[1]PROM indicates premature rupture of membranes
[2]Temperature > 38^{o}C
[3] Blood glucose screening tests < 50 mg/dl

Out of total NICU transfers, 165 neonates had clinical signs of tachypnea (92), oxygen requirement (79), dyspnea (43), temperature instability (14) and apnea (8), with some infants having more than one finding. The remaining 187 neonates had abnormal laboratory values, out of whom 181 had abnormal CRP or/and CBC and the other six had hypoglycemia.

In 18 neonates antibiotics were not administered, who were shifted to NICU for hypoglycemia (6) and rapid respiration (12) probably due to retained fetal lung fluid. None of these 18 neonates had an elevated CRP concentration. As total WBC count, immature / total neutrophil ratio and absolute neutrophil count couldn't determine the duration of antibiotic therapy; these parameters have not been cited.

Table 2: Relation of CRP level to duration of antibiotic administration

Peak CRP level (mg/dl)		Number of neonates	Duration of antibiotic therapy
Range	Mean		
-	< 0.6	18	None
-	< 0.6	71	< 2 days
0.6 – 2.4	1.28	31	2 days
0.6 – 4.8	2.46	76	3 days
1.2 – 4.8	3.67	87	4 days
1.2 – 9.6	5.82	43	5 days
1.2 – 19.2	8.66	19	6 days
4.8 – 38.4	10.40	7	> 6days

Antibiotics were administered for aduration of less than 48 hours in 102 neonates. Of them, 71 had normal CRP concentration (< 0.6 mg/dl), evaluated on atleast two occasions in first 36 hours. Mild elevation of CRP concentration in first 24 hours (0.6 – 2.4 mg/dl) was observed in 31 neonates, which then returned to normal values. Some of them also had abnormal CBC findings initially. The neonates with normal CRP concentration were evaluated for clinical findings like tachypnea, oxygen requirement, and unexplained hypoglycemia. In the neonates with mild elevation in CRP concentration, maternal pyrexia was frequently associated (11 cases ; 35%). Tachypnea was noted in 5, PROM in 7, hypoglycemia in 3, respiratory distress in 3 and neonatal fever in 2 patients.

The majority of neonates (206; 58%) were treated for 3 to 5 days, 19 were treated for 6 days and 7 for more than 6 days. From table 2, it has been observed that, there was considerable variation in range of peak CRP concentrations corresponding to each duration of antibiotic therapy, but the mean peak CRP concentrations increased with each day that treatment was required.

DISCUSSION:

Though life threatening, making a definitive diagnosis of neonatal sepsis becomes a difficult task, moreover where health care resources are limited and cost becomes an important factor before formulating the management. Also, intrapartum chemoprophylaxis received by mothers as per recommendation [3], may result in partially treated infant. In such cases, CRP has been implicated to be an important guide in formulating the course of management.

In the neonates who had abnormal laboratory test results, CRP was the major determinant to decide the duration of antibiotic therapy. This also determined the length of stay in the hospital. More than 34% (120 of 352) of those transferred to NICU were either not treated with antibiotics (n=18) or received antibiotics for only two days (n=102). About 46% of the neonates were administered antibiotics for 3 to 4 days and 12% treated for 5 days. With normal CRP concentrations, very few infants had antibiotic treatment beyond 48 hours. While deciding the duration of antibiotic therapy, it was the peak CRP level that primarily dictated, because high levels usually take several days to return to normal.[17,18] From our observations, we could formulate a strategy in our NICU that, rather than mandating an observation period combined with CBC, differential count and blood culture, a decision can be made within 24 hours using a low cost, easily available CRP estimation, differential count and clinical manifestation.

A previous survey indicated that there was little consensus while formulating the management of asymptomatic term- gestation infants whose mother's have received intrapartum antibiotics.[19] In a scenario in which the mother had a positive cervical culture result, many neonatologists would start antibiotics, with >70% in case of maternal pyrexia or PROM. [19]

Various authors have evolved strategies to decide the duration of antibiotic usage after investigating the admitted neonates. About two decades ago, in a study of newborn nurseries, in hospital A, antibiotics were given to 4.4% infants for a median duration of 7 days, whereas in hospital B, antibiotics were given to 10.5% infants for a median duration of 3 days. [4] In another study, it was possible to decrease antibiotic usage, by using sepsis screen that included estimation of CRP concentration. [20]
It was observed that maternal pyrexia was associated with NICU admission in 29% cases and when associated with another risk factor like PROM, resulted in about 50% neonates evaluated being transferred to NICU with abnormal CRP level. As noted by some authors [21,22], it was not usual to have an increased level of CRP at initial evaluation, indicating postnatal increase.

Many authors considered CRP as the best supportive criterion for discontinuation of antibiotic therapy.[6,10,11,22,23] In our observation, we also could find similar association. The mean duration of antibiotic usage in our study was 3.4 days, which can be correlated with findings of other authors.[10,24]
In some occasions, high clinical suspicion for neonatal sepsis inspite of normal CRP values resulted in prolongation of antibiotic therapy. But, to be importantly noted, only about 7% neonates were treated for more than 5 days. In this category, 7 of 26 had proven septicemia with no adverse outcome to result in mortality.

We observed that in addition to abnormal WBC counts and CRP levels, about half of the neonates treated were asymptomatic, though associated with risk factors. It

is difficult to rule out the possibility of elevation of CRP due to partially treated bacterial infection. It was also not feasible to find out by taking risk in our limited NICU setting, that how many asymptomatic neonates (at risk) included in this study would become sick if left untreated. Excluding the possibility of readmission in other hospital, no infant with two normal values of CRP, total WBC and differential counts, taken 12 – 24 hours apart was readmitted within one month of birth with sepsis or meningitis.

In this era of emerging multidrug resistant pathogens, posing threat to lives of many individuals, judicious and appropriate use of antibiotics should be mandatory in any health care setting. Incorporating CRP estimation to decide the duration of antibiotic therapy can minimize the unnecessary exposure of neonates to antibiotics and thereby reducing the emergence of drug resistant pathogens.[25]

CONCLUSION:

Serial CRP estimation has been evaluated out to be a low cost, effective and rapid prognostic marker in acute infection. It definitely helps in deciding the initiation and duration of antibiotic therapy, thereby reducing unwanted antibiotic exposure and duration of hospital stay of neonates.

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