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Original Research Article

The Role of C- Reactive Protein (CRP) in the Diagnosis of Neonatal Sepsis

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Abstract: ***Background:*** Neonatal sepsis or septicemia is the term that has been used to describe the systemic response to infection in a newborn infant during the first 28 days of life. Neonatal mortality is increasingly recognized as an important global public health challenge that must be addressed if we wish to reduce child death disparities between rich and poor countries. Most of the estimated 4 million neonatal deaths per year occur in low and middle-income countries. ***Objective:*** The aim of this study is to evaluate the role of C-reactive protein (CRP) in the diagnosis of neonatal sepsis. ***Method of the Study*:** This is a cross-sectional study carried out in the Department of Neonatology, BSMMU, Dhaka over a period of 6 months between January 2013 to June 2013. Newborns with suspected sepsis admitted to BSMMU were the study population. Clinically diagnosed cases of neonatal sepsis aged < 28 days of both sexes whose parents or guardians provided informed consent were eligible for enrollment in the study. The subjects were selected consecutively from the study population. Data were collected using a structured questionnaire containing all the variables of interest. Data were processed and analyzed using the computer software SPSS (Statistical Package for Social Sciences). The test statistics used to analyze the data were Chi-square ($\chi 2$) or Fisher's Exact Probability Test & Student's t-Test. ***Result:*** The sensitivity of CRP in correctly detecting neonatal sepsis of those who have the disease is 94.44%, while the specificity of the test in correctly differentiating neonates who do not have the disease is 13.72%. The positive predictive value (PPV) of the test is 27.86% and the negative predictive value of the test is 87.5%. The percentages of false positives and false negatives as yielded by the test are 72.13% and 12.5% respectively. ***Conclusion:*** The sensitivity of CRP was higher at 94.44% but specificity was low 13.72%. A combination of tests may increase the sensitivity, specificity, and positive predictive accuracy compared with a single test for the diagnosis of neonatal sepsis.

Keywords: Neonatal Sepsis, Neonatal Mortality, C-Reactive Protein, Newborns.

INTRODUCTION

Sepsis is the commonest cause of neonatal mortality and is responsible for 30-50% of total neonatal deaths each year in developing countries [1]. Neonatal sepsis or septicemia is the term that has been used to describe the systemic response to infection in a newborn infant during the first 28 days of life. Neonatal mortality is increasingly recognized as an important global public health challenge that must be addressed if we wish to reduce child death disparities between rich and poor countries. Most of the estimated 4 million neonatal deaths per year occur in low and middle-income countries. More than one-third of neonatal deaths are estimated to be due to severe infection and a quarter is due to the clinical syndrome of neonatal sepsis / pneumonia [2]. Currently, the infant mortality rate (IMR) in Bangladesh is 38/1000 live births out of them 70% of death occur in the neonatal period (<28 days), and the neonatal mortality rate (NMR) in our country 27/1000 live births [3].

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In Bangladesh Gram-negative bacteria and in particular, Klebsiella and enterobacter species are the leading causes of neonatal sepsis and almost all are resistant to commonly used antibiotics such as ampicillin, gentamicin, and third-generation cephalosporin [4-6]. The initial diagnosis of neonatal sepsis is challenging for physicians because clinical signs and symptoms are nonspecific. The gold standard for diagnosis of neonatal septicemia is the isolation of micro-organisms from blood and the site of infection but the result is available after 48-72 hours. Moreover, blood culture yields a positive result in only 10-60% of cases [7]. Hence, the diagnosis is missed or delayed. These factors stress the need for some early diagnostic measures with reasonable specificity and sensitivity. Therefore, for early initiation of therapy, certain indirect markers along with clinical diagnosis are essential.

CRP is an acute-phase protein synthesized in the liver in response to inflammatory cytokines. Its level may increase up to a thousand fold during an acute phase response. Any elevation of CRP in a newborn baby represents endogenous synthesis as CRP crosses the placenta in very low amounts. It takes 6 to 12 hours, even 24 hours for CRP to rise following the onset of infection. The hematological response to inflammation in neonates includes changes in total white cell count (WBC), total neutrophil count, immature to the total neutrophil ratio (IT ratio), and platelet numbers. Though the predictive value of white cell count is non-specific and it can be normal in up to 30% of the neonate with culture-proven sepsis, a decreased count is a more specific indicator of bacterial infection than leukocytosis. No doubt blood culture is still the gold standard but due to the emergence and dissemination of antimicrobial resistance that has been well-documented as a problem worldwide. This highly specific microbiological parameter is unavailable in our region and peripheral health centers are high-cost, have more chance of contamination, and are time-consuming. We need tests that are convenient, cost-effective, and whose results can be readily available. So this study is planned to evaluate the role of C-reactive protein (CRP) in the diagnosis of neonatal sepsis. So that prompt treatment can be initiated and neonatal deaths can be minimized.

OBJECTIVES

General Objective

- To evaluate the role of C-reactive protein (CRP) in the diagnosis of neonatal sepsis.

Specific Objective

- To observe the clinical and laboratory findings.

METHODOLOGY AND MATERIALS

This is a cross-sectional study carried out in the Department of Neonatology, BSMMU, Dhaka over a period of 6 months between January 2013 to June 2013. Newborns with suspected sepsis admitted to BSMMU were the study population. Clinically diagnosed cases of neonatal sepsis aged < 28 days of both sexes whose parents or guardians provided informed consent were eligible for enrollment in the study. The subjects were selected consecutively from the study population. After admission informed written consent from parents or guardians was taken and emergency management was given and septic screening was sent. Blood samples were collected by using an aseptic technique by applying povidone iodine and 70% alcohol at the site of the vein puncture. Four ml of venous blood was drawn from the peripheral vein. Two ml of blood were sent for CBC and CRP to the clinical pathology laboratory. Two ml of blood for culture were inoculated into a blood culture bottle containing tryptone soya broth (TSB). The specimen was transported immediately to the microbiological laboratory and incubated for 12-24 hours in 37 degree celcius and checked for evidence of bacterial growth. For positive broth cultures, subcultures were made on solid media (Blood Agar & Mac Conkey Agar) and incubated at 370c for 24 to 48 hours. The growth of bacteria were identified by colony morphology, Gram staining & biochemical test. Antimicrobial sensitivity testing was performed for all blood culture isolates according to the criteria of the National Committee for Clinical Laboratory Standards by the disk diffusion method. Data were collected using a structured questionnaire containing all the variables of interest. Collected data were analyzed using SPSS (version 20).

- **Inclusion Criteria:**
  - Newborns with suspected sepsis.
  - Neonatal sepsis aged < 28 days.
  - Neonatal sepsis of both sexes.

- **Exclusion Criteria:**
  - Prior treatment with antibiotics.
  - Developed the signs of sepsis within 72 hours of discontinuation of the antibiotics.
  - Newborns with perinatal asphyxia or meconeum aspiration syndromes.
  - Inborn errors of metabolism and
  - Baby with congenital anomalies.

RESULT

The present study intended to evaluate the role of WBC, IT ratio and CRP in the diagnosis of neonatal sepsis and included a total of 138 neonates (both preterm and term) of clinically diagnosed cases of sepsis. All the neonates were subjected to test for WBC, IT ratio CRP and blood culture. The findings of WBC, IT ratio and CRP were then compared against the blood culture report to see the diagnostic accuracies of these three diagnostic modalities in predicting neonatal sepsis. In terms of gestational age over 80% were preterm and the rest 19.6% were term neonates (Table

I). Male neonates were higher (57%) than females Figure I. Figure II demonstrates that 81% of the neonates were of low birth weight (< 2.5 kg). The predominant clinical finding at presentation was lethargy (89.1%) followed by tachypnoea (47.1%), poor feeding (43.5%), abdominal distension (34.1%), grunting (27.5%), hypothermia (25.4%), vomiting (23.2%), apnoea (20.3%), hyperthermia (14.5%). Other seldom observed signs were cyanosis (9.4%), convulsion (7.2%), bulged fontanel (2.9%) and tachycardia (2.9%) (Table II). Approximately 43% of the neonates were born by normal delivery and 57.2% by cesarean section (Table III). Among the neonates, 40 (29%) had early onset sepsis (EOS) and 98(71%) had late-onset sepsis (LOS) (Table IV). Of the 138 cases subjected to blood culture, 36(26.08%) yielded the growth of pathogenic microorganisms (Table V). Based on WBC count, IT ratio and serum CRP 21.7%, 31.1% and 88.4% cases were screened respectively as having sepsis (Table VI). About one-quarter (23.2%) of the neonates were released in less than 14 days, 29.7% in 14 – 21 days, and 47.1% in 3 or > 21 days' time. The mean duration of hospitalization was 21.2 days (Table VII). The distribution of neonates by CRP is shown in Table VIII. Meanwhile, Table IX shows the accuracy of CRP as a screening test in diagnosing neonatal sepsis. The sensitivity of CRP (at a cut-off value of 6 mg/dl) in correctly detecting neonatal sepsis of those who have the disease is 94.44%, while the specificity of the test in correctly differentiating neonates who do not have the disease is13.72%. The positive predictive value (PPV) of the test is 27.86% and the negative predictive value of the test is 87.5%. The percentages of false positives and false negatives as yielded by the test are 72.13% and 12.5% respectively.

Table I: Distribution of neonates by gestational age (n = 138)

Gestational age (weeks)	Frequency	Percentage
28-<37	111	80.43
37-42	27	19.6

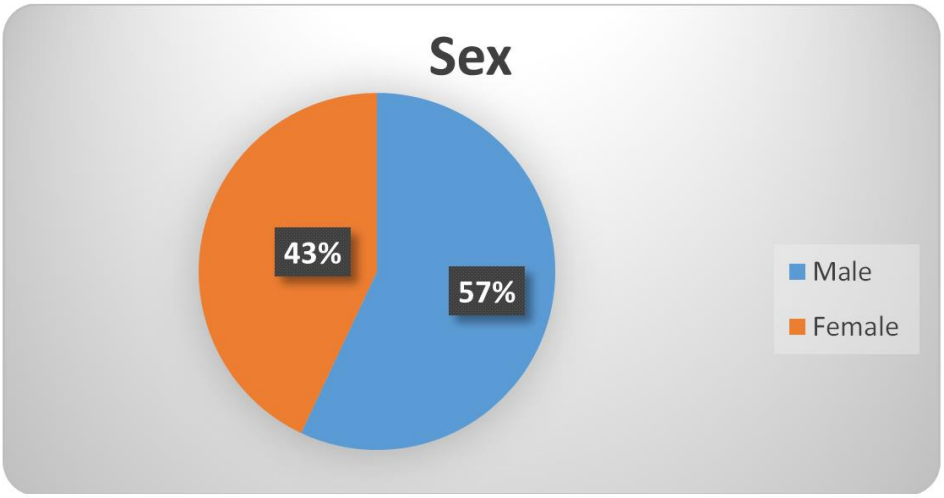

Figure I: Distribution of patients by their sex (n=138)

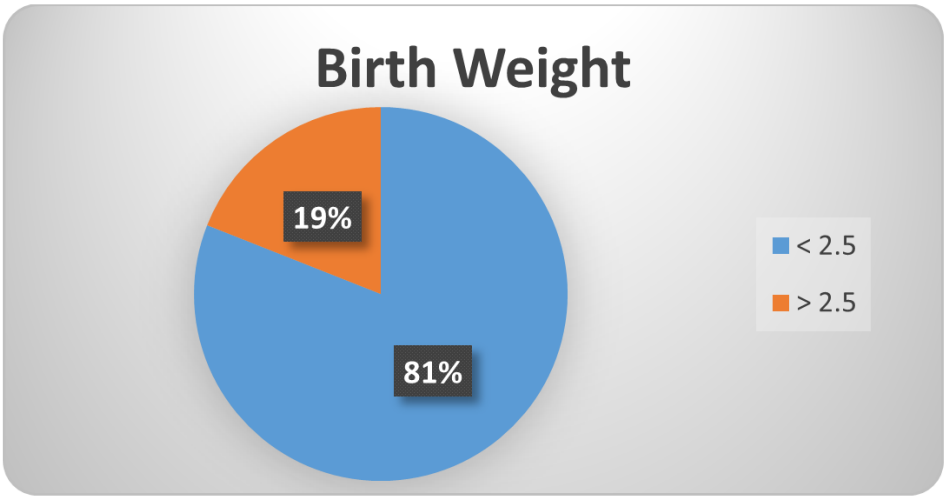

Figure II: Distribution of patients by birth weight (n=138)

Table II: Distribution of patients by clinical findings (n = 138)

Clinical Findings	Frequency	Percentage
Lethargic	123	89.1
Tachypnoea	65	47.1
Poor Feeding	60	43.5
Abdominal distension	47	34.1
Grunting	38	27.5
Hypothermia	35	25.4
Vomiting	32	23.2
Apnoea	28	20.3
Hyperthermia	20	14.5
Cyanosis	13	9.4
Convulsion	10	7.2
Bulged fontanel	04	2.9
Tachycardia	04	2.9

Table III: Distribution of neonates by mode of delivery (n = 138)

Mode of Delivery	Frequency	Percentage
Normal	59	42.8
LUCS	79	57.2

Table IV: Distribution of neonates by mode of onset of sepsis (n = 138)

Mode of onset of sepsis	Frequency	Percentage
Early onset sepsis (EOS)	40	29
Late onset sepsis (LOS)	98	71

Table V: Diagnosis of sepsis established by blood culture (n = 138)

Diagnosis	Frequency	Percentage
Culture proven sepsis	36	26.08
Suspected or Clinical sepsis	102	73.91

Table VI: Sepsis cases screened by total WBC count, IT ratio and serum CRP (n = 138)

Screening tests	Frequency	Percentage
WBC count		
<5000 cu-mm	5	3.6
5000 – 25,000 /cu-mm	108	78.3
> 25,000 /cu-mm	25	18.1
IT ratio		
> 0.2	43	31.1
< 0.2	95	68.9
Serum CRP		
> 6	122	88.4
< 6	16	11.6

Table VII: Distribution of the neonates by the duration of hospitalization (n =138)

Duration of hospitalization* (days)	Frequency	Percentage
< 14	32	23.2
14 – 21	41	29.7
≥21	65	47.1
* Mean = (21.2 ± 7.5) days; range = (9 – 35) days.		

Table VIII: Distribution of neonate by CRP

CRP (mg /dl)	Sepsis		Total
	Culture proven	Suspected or Clinical	
> 6	34	88	122
< 6	2	14	16
Total	**36**	**102**	**138**

Table IX: Accuracy of CRP in diagnosing neonatal sepsis

Validity of screening test	Percentage
Sensitivity	94.44
Specificity	13.72
Positive predictive value	27.86
Negative predictive value	87.5
False positive	72.13
False-negative	12.5

DISCUSSION

Neonatal sepsis with its high mortality rate still remains a diagnostic and treatment challenge for neonatal health care providers. An early diagnosis of neonatal sepsis helps the clinician in instituting antibiotic therapy at the earliest, thereby reducing the mortality rates in neonates. Early identification of infected neonates also helps in avoiding the unnecessary treatment of a non-infected neonate. Isolation of bacteria from blood is a standard and most specific method used to diagnose neonatal sepsis. An additional drawback of culture-based diagnosis is the 24-48 hour assay time. However, empirical treatment should not be delayed, because failure or delay in treatment may result in significant mortality and morbidity [8]. Many studies have investigated a variety of laboratory tests to enhance the early detection of neonatal sepsis [911].

The present study included a total of 138 neonates (both preterm and term) of clinically diagnosed cases of sepsis where male neonates were higher (57%) than females. These results are comparable with the observations made by other authors [12, 13]. It's possible that the X-linked immunoregulatory gene factor, which increases the host's vulnerability to infections in males, is responsible for the male preponderance in neonatal septicemia [14].

In the current study, newborns with Early-onset sepsis (EOS) had the highest percentage of culture-positive cases compared to neonates with Late-onset sepsis (LOS). This might be caused by an ascending infection after the membranes have ruptured, through an infected birth canal, or when the baby is being revived in the delivery room. Neonatal immune development throughout the first week of life renders children more prone to infections at this time [15]. Similar findings were found in other authors' investigations [12, 13, 16].

In our study, the rate of proven sepsis was 26.08%. Klebsiella Pneumoni is the common organism isolated and is consistent with other studies [4-6]. The diagnosis of sepsis required microbiological and clinical correlation. Among the neonates (73.91%) classified as having probable sepsis had clinical evidence but lacked microbiological proof of infection, which might have been due to late arrival, sample collection after giving antibiotics, and faulty technique in the collection procedure. But we cannot ignore these babies because the fatal infection has been reported in other studies in the presence of negative blood culture [17].

In this study, three screening tests were evaluated (WBC count, I/T ratio, and CRP) for use in the diagnosis of neonatal sepsis. None of these tests could be considered ideal in terms of their diagnostic accuracy (sensitivity, specificity, positive and negative predictive values). The sensitivities of WBC and I/T ratio are poor (27.7% and 38.88% respectively), although their specificities are optimum (80.3% and 77.56% respectively). While the sensitivity of CRP is appreciably higher (94.44%), its specificity is extremely low (13.72%). The CRP test was the most sensitive of the sepsis screen parameters but, had the lowest positive predictive value in diagnosing septicemia. Meanwhile, various studies by other authors show the opposite results to this test [18-21]. Because of variances in the diagnostic standards, the timing of illness onset (early or late), and the various CRP calculation techniques, several studies have produced diverse results for this parameter.

CRP production is a very early and sensitive response to most forms of microbial infection. CRP is found in very low concentrations in the sera of neonates. Fetus as early as 28 weeks of gestation has a high concentration of CRP in serum in response to a variety of infections. It does not cross the placenta. Its concentration in the mother and fetus is independent of each other. Recently many studies have considered CRP estimation to be of value in early diagnosis and monitoring of neonatal sepsis [22-24]. The frequent occurrence of raised CRP in sera of uninfected newborn infants eliminates it as a useful indicator of infection but may suggest an active tissue-damaging process.

CONCLUSION AND RECOMMENDATION

Neonatal sepsis is a life-threatening emergency and thus any delay in treatment may cause death. Clinical diagnosis of sepsis in newborns is not easy because symptoms and signs are non-specific. Blood culture is the gold standard for confirmation of diagnosis. In this study among 138 neonates who were diagnosed clinically had sepsis, 26.08% were proved to have sepsis on blood culture. The sensitivities of WBC count and IT ratio when compared against blood culture finding were found poor (27.7%, and 38.88% respectively), although their specificities were optimum

(80.3% and 77.56% respectively). The sensitivity of CRP was higher at 94.44% but specificity was low 13.72%. A combination of tests may increase the sensitivity, specificity, and positive predictive accuracy compared with a single test for the diagnosis of neonatal sepsis. A scoring system should be designed for our setup, using those tests that are easy to perform, economical, available, and should ideally identify all infected infants (high sensitivity), so that disease can be confidently excluded with negative test results (high negative predictive value) and stop the antibiotic early, thereby reducing the cost, duration of hospital stay and anxiety of the parents. A large-scale multicenter study should be carried out and the findings derived from the study should be extrapolated to formulate policy guidelines for the diagnosis and management of neonatal sepsis in our setting.

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