Original Article

Role of serial C-reactive protein measurements for determination of the duration of empirical antibiotic therapy in suspected neonatal sepsis

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ABSTRACT

Background: Neonatal sepsis (NS) is a clinical syndrome characterized by signs and symptoms of infection with or without bacteremia in neonatal age. At present, there are a variety of tests available for testing sepsis in neonates including C-reactive protein (CRP). **Objective:** The objective of the study was to decrease the antibiotic duration in a case of NS and to decrease the hospital stay and financial burden on the patient by measuring serial CRP levels**. Materials and Methods:** This case–control study was conducted in a tertiary care teaching hospital at a tertiary hospital of central India. A total of 103 neonates were considered as the study population. Estimation of serial CRP levels among neonates was assessed and correlated within two study groups. **Results:** CRP level at admission was able to successfully identify NS in 66.67% of the cases (sensitivity), while in 12.07% it was able to negate NS when it was absent on blood culture also (specificity). The positive predictive value (PPV) was low (37.04%) with a negative predictive value of 31.82%. The diagnostic accuracy of the CRP level at admission was 35.92% suggesting its accuracy to correctly identify the patient with NS in only 35.92% cases. The results show that CRP is having a good sensitivity, with a poor specificity, and overall low diagnostic accuracy. **Conclusion:** Our study showed a significant difference in the use of antibiotics in the two groups. The sensitivity of CRP was high with the low specificity and low PPV and high NPV, which makes CRP a vital screening tool, especially if used in conjunction with other screening parameters improving the overall sensitivity and specificity.

Key words: Antibiotics, C-reactive protein, Neonatal sepsis, Sensitivity, Specificity

According to the 2011 Census report, India comprises 17.5% of the world's population [1]. The current neonatal mortality rate (NMR) was 25.3/1000 live births accounting for two-thirds of the infant mortality in India. According to the data from the National Neonatal Perinatal Database (NNPD, 2002-03), sepsis is one of the predominant morbidities in neonates. The most common clinical category of systemic infection was septicemia found in 88.1%, while pneumonia was diagnosed in 32.8% of infants with systemic sepsis [2]. Neonatal sepsis (NS) or neonatal bloodstream infection is a pertinent reason behind death in neonates and children under 5 years of age. Sepsis ranks at the higher position among reasons causing avoidable mortality in neonates. Patients who are suffering from human immunodeficiency virus (HIV), tuberculosis, malaria, and other infectious diseases may ultimately result in death due to the clinical condition of sepsis. Every year 2·9 million newborns die because of bacterial infection indicating it as a leading cause of mortality among them [3].

Access this article online	
Received - 03 August 2020 Initial Review - 16 August 2020 Accepted - 28 August 2020	Quick Response code
DOI: 10.32677/IJCH.2020.v07.i09.008	

At present, there are a variety of tests available for testing sepsis in neonates such as complete blood count (CBC), C-reactive protein (CRP) test, absolute neutrophil count (ANC), immature to total neutrophil (I/T) ratio, erythrocyte sedimentation rate (ESR) [4], procalcitonin (PTC) test [5], and confirmatory tests like bacterial culture testing [3], and immune-histological test [4]. CRP test is one of the most trending tests in the study of NS.

CRP is a homopentameric acute-phase inflammatory protein and binds to polysaccharides such as phosphocholine and activates the classical complement pathway of innate immunity by triggering C1q [6]. Elevated expression levels of CRP denote inflammatory conditions such as rheumatoid arthritis, cardiovascular diseases, and infection [7]. In the case of some bacterial infections, blood serum contains high levels of CRP but also decreases exponentially with a reduction in infection [4,8]. According to Dagan *et al*. [9], children are discharged without any treatment if they are found negative for signs of sepsis or with a single dose of intramuscular antibiotics, but may potentially suffer from sepsis. CRP should be considered in such patients where the diagnosis of sepsis is not straightforward.

Our current research aims to determine the efficacy of short-term versus long-term antibiotic treatment using serial CRP as

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a simple, cost-effective, reliable method for evaluating the short versus long-term outcome of antibiotic treatment in suspected NS, as well as to minimize the efficacy of serial CRP.

MATERIALS AND METHODS

This randomized, case–control study was conducted in a tertiary care teaching hospital of central India from December 2017 to May 2019. A total of 103 cases divided into two groups (study and control) of 54 and 49 each based on the data of NICU for neonatal sepsis with positive and negative blood culture. The allocation to the two groups was done through computer generated randomization on http://www.random.org/.

Neonates with risk factors for NS such as born to mothers with intrapartum fever >38°C, asymptomatic bacteriuria, prolonged premature rupture of membranes (>18 h), high vaginal swab positive for the organism, foul-smelling liquor, and multiple per vaginal examination without using gloves/per speculum examinations were included in the study. Furthermore, preterm and very low-birth weight (<1500 g) neonates were included in the study. Newborns with surgical conditions such as congenital heart disease, trachea-esophageal fistula, imperforate anus, diaphragmatic hernia, necrotizing enterocolitis, congenital hypothyroidism, an inborn error of metabolism, chromosomal aberrations/syndromes, ventilated newborns, intraventricular hemorrhage, negative CRP, positive blood culture, and sensitivity were excluded from the study.

The prospective patient was identified and the study details including procedures and risks/benefits were explained to the parents of the patient, and consent was obtained. Suspected bacterial sepsis was screened using CBC, CRP, I/T ratio, ANC, PS for toxic granules at 6 h of life, or at presentation whichever was later and blood culture and sensitivity. CBC was done by the auto analyzer (Beckman Coulter LH750). CRP analysis was performed by agglutination technique using (Lab Care Diagnostics). A value of CRP >1 mg/dL was considered as positive. Blood culture and sensitivity were done by standard techniques using the disk diffusion method. The other investigations such as 2D ECHO, ultrasound (USG), and cerebrospinal fluid (CSF) analysis, were conducted, if required.

Group 1 (study group) included patients where antibiotics were initiated, but the use of antibiotics was stopped after 72/96 h, provided the infants were in good clinical condition. In the study group, when the blood culture became negative, two consecutive negative CRP levels (<0.6 mg/dL) or in case of decreasing titers of CRP last being (<0.6 mg/dL), antibiotics were stopped after 72/96 h provided that the infant did not exhibit signs and symptoms of NS. First-line antibiotics – ampicillin and gentamicin were started according to the NICU protocol for the management of bacterial sepsis. The CRP levels of study group patients were measured at presentation, 24 h, 48 h, 72/96 h, or until the blood culture results were made available.

Group 2 (control group) included patients where CRP level was recorded at presentation and if signs of NS were present, a full course antibiotic regimen for 7 consecutive days was given. CBC with peripheral smear was also done along with CRP. In the control group patients, first-line antibiotics were given for a fixed course of 7 consecutive days.

The patients of both the groups were followed weekly till 1 month postnatal age or for 4 weeks whichever was longer after discharge. At each follow-up, relapse of signs and symptoms of sepsis and the incidence of the same was compared within the groups to determine the statistical difference in outcomes (relapse of clinical signs and symptoms of sepsis) between the two groups treated with short (72/96 h) versus long course (7 days) of empirical antibiotic treatment.

The study protocol is summarized in Fig. 1.

The data were collected in a predesigned customized structured pro forma. Multivariant logistic regression was carried out to observe the predictive values and confirmed by the receiver operating characteristic (ROC) curve. $p<0.05$ was considered as significant using the Chi-square test to determine the statistical significance in the difference of outcome between the two groups treated with short (72/96 h) versus long course (7 days) of empirical antibiotic treatment.

RESULTS

In this study, various clinical features were compared in the two groups. In the study group, 11 (20.4%) patients had feeding difficulty, 5 (9.3%) patients had vomiting, 15 (27.8%) patients each had lethargy and excessive crying, 5 (9.3%) patients had fever, 8 (14.8%) patients had respiratory distress, 7 (13.0%) patients had mottling, 3 (5.6%) patients had sclerema, 4 (7.4%) patients had prolonged CRT, 8 (14.8%) patients had tachypnea, 23 (42.6%) patients had grunting, and 8 (14.8%) patients had retractions.

In the control group, 12 (24.5%) patients had feeding difficulty, 4 (8.2%) patients had vomiting, 12 (24.5%) patients had lethargy, 10 (20.4%) patients had excessive crying, 4 (8.2%) patients had fever, 5 (10.2%) patients had respiratory distress, 4 (8.2%) patients had mottling, 2 (4.1%) patients had sclerema, 5 (10.2%) patients had tachypnea, 21 (42.9%) patients had grunting, and 5 (10.2%) patients had retractions.

Various risk factors were compared to find significant correlation between them (Fig. 2).

Comparison of Mean CRP Levels at Different Time Intervals in the Study Group

Table 1 shows a comparison the comparison of mean CRP levels at different time intervals in the study group. There was a constant decrease in the CRP levels recorded serially at the different intervals. The differences were statistically significant between 0 and 24 h, 24 and 48 h, and 48 and 72 h.

Comparison of Mean duration of Antibiotic use between the Two Groups

The mean duration of antibiotic use in the study group was 80.44±11.57 h, while, in the study group, it was 168.00±0.00 h (Fig. 3). The difference was found to be statistically significant

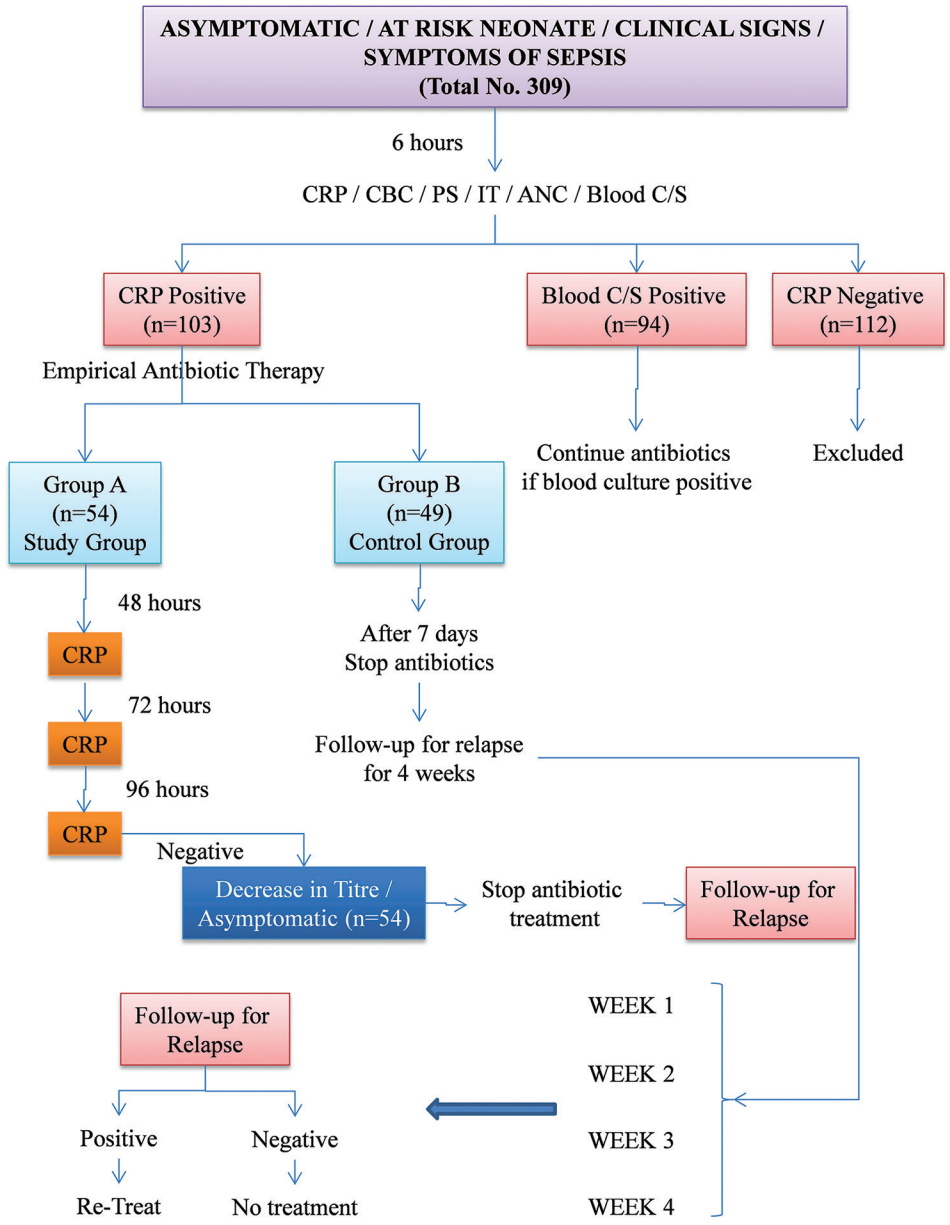

Figure 1: Algorithm for management of neonatal sepsis

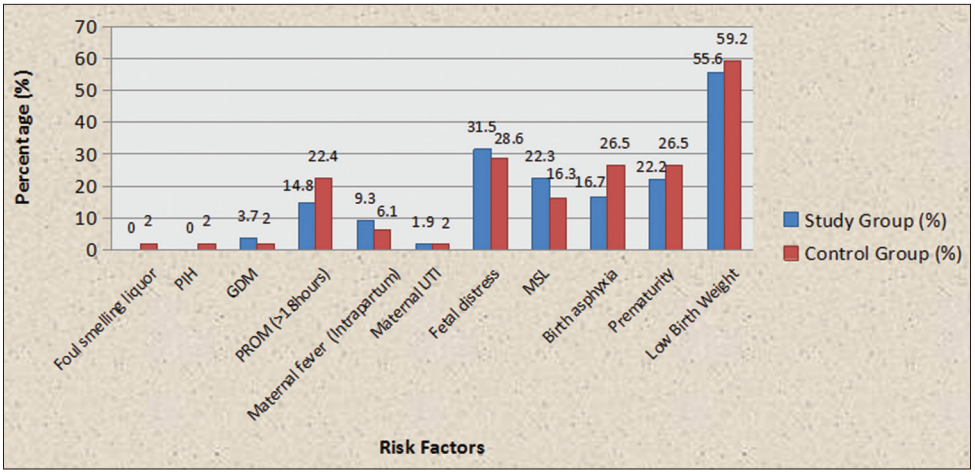

Figure 2: Bar diagram showing distribution of patients according to percentage of risk factors

Table 1: Comparison of mean CRP levels at different time intervals within the study group

Time interval (hours)	No.	Study group	p value
0	54	2.36±1.23	0.001*
24	54	1.34±0.65	
24	53	1.34±0.65	0.001*
48	53	0.78±0.34	
48	13	1.29±0.33	0.001*
72	13	0.60±0.00	

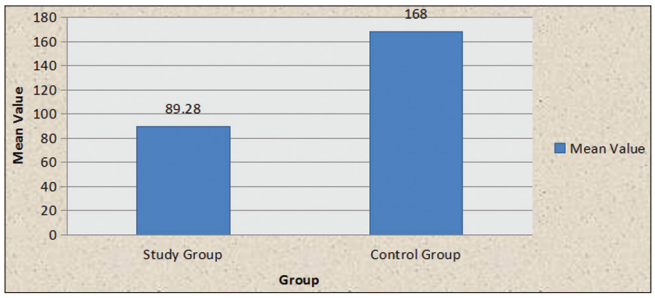

Figure 3: Bar diagram showing comparison of mean duration (in hours) of antibiotic use

(p=0.001), showing a significantly lower duration of antibiotic use in the study group in comparison to the control group.

Comparison of Sensitivity, Specificity, Positive Predictive Value (PPV), and Positive Negative Value (NPV) of CRP against Blood Culture at 0 h

CRP level at admission was able to successfully identify NS in 66.67% of the cases (sensitivity), in 12.07% it was able to negate NS when it was absent on blood culture also (specificity). The PPV was low (37.04%) with a high NPV (31.82%). The diagnostic accuracy of the CRP level at admission was 35.92% suggesting that the CRP level is able to correctly identify the patient with NS in only 35.92% cases.

The results show that CRP is having a good sensitivity, with a poor specificity, and overall low diagnostic accuracy.

Comparison of Sensitivity, Specificity, PPV, NPV, and Diagnostic Accuracy of CRP Level + I/T Ratio ± ANC (Any Two out of the Three) at Admission against Blood Culture Findings

CRP level + I/T Ratio ± ANC at admission was able to successfully identify NS in 95.92% of the cases (sensitivity), in 72.99% it was able to negate NS when it was absent on blood culture also (specificity). The PPV was good (62.25%) with a high NPV (97.47%). The diagnostic accuracy of the CRP level + I/T Ratio ± ANC at admission was 80.26% suggesting its accuracy to correctly identify the patient with NS in only 80.26% cases.

DISCUSSION

Out of 103 neonates, only two neonates presented with relapse, one in each study and control group.

Hisamuddin *et al*. [10] found that mean age of the neonates was 5.72 days + 3.86 in their study whereas in our study all the patients were of 1–24 h and 81 (55.1%) males and 66 (44.9%) females had sepsis with a slight male preponderance. With contrast to this, in our study 18 (33.3%) were females and 36 (66.7%) were males, while in the control group 23 (46.9%) were females and 26 (53.1%) were males. There was a female preponderance in the control group, while male preponderance was seen in the study group.

In the current study, various risk factors were compared between the study group and the control group. According to the recent study in 2019 by Murthy *et al*. [11], the need for artificial ventilation, gestational age <37 weeks and PRMO are risk factors for sepsis among neonates whereas, in our study, along with prematurity (26.5%), PROM (22.4%), and low-birth weight (59.2%), fetal distress (28.6%), birth asphyxia (26.5%) were also prominent risk factors for sepsis. Similar results were observed in several studies performed by Tallur *et al*. [12], Gerdes *et al*. [13], Anand *et al*. [14], and Gupta *et al*. [15].

The mean CRP level in the control group was 3.07±1.39, while in the study group it was 3.17±1.63. The difference was found to be statistically not significant (p=0.824), showing a comparable mean CRP level at 0 h between the two groups.

In the study group, the CRP levels were recorded serially, which at 0 h was 2.29±1.20, while at 48 h it was 1.34±0.65 and at 72 h 0.88±0.79. There was a significant fall in the CRP level at 48 h in comparison to 0 h (p=0.001) and further a significant fall at 72 h in comparison to the 48 h (p=0.001). The sensitivity of CRP to identify NS at admission was 66.67%, and specificity of 12.07% to negate sepsis in patients when it was absent on blood culture also. The PPV was low (37.04%) with a high NPV (31.82%). The diagnostic accuracy of the CRP level at admission was 35.92% suggestive of the CRP level which can correctly identify the patient with NS in only 35.92% cases. The study performed by Chacha *et al*. [16] found sensitivities of CRP assay in the diagnosis of septicemia using culture as the gold standard on days 1, 2, and 3 and any positive were 40.4%, 53.2%, 54.8%, and 62.9%, respectively, while specificities were 82.7%, 80.7%, 77.8% and 73.3%, respectively. The study concluded that in the place where blood culture is limited, neonates having clinical features of NS with positive qualitative CRP assay and increased white blood cells (WBC) should urgently be initiated on appropriate sepsis management to reduce morbidity and mortality, whereas our study results showed that CRP is having a good sensitivity, with a poor specificity, and overall low diagnostic accuracy. In contrast to our results, a study by Hisamuddin *et al*. [10] concluded that CRP estimation does have a role in the diagnosis of NS but the test is not specific enough to be relied on as the only indicator.

The mean duration of antibiotic use in the study group was 80.44±11.57 h, while in the control group it was 168.00±0.00 h. The difference was found to be statistically significant (p=0.001), showing a significantly lower duration of antibiotic use in the study group in comparison to the control group. This

implies that by recording CRP at serial intervals, the antibiotic regimen can be modified as per required and it is not necessary to follow the long course. The results were similar to the results of the study done by Jaswal *et al*. [17] in which they observed significant results in 44% cases. However, Brown *et al*. in a Cochrane systematic review concluded that the serum CRP level at initial evaluation of an infant was unlikely to be considered accurate to help in the treatment with antimicrobial therapy or other interventions [18].

The present study has limitations of a relatively small sample size. Furthermore, most of the neonates were term which precludes the extrapolation of results in the premature suspect sepsis cases. We also recommend that future studies should be conducted to assess the sensitivity and specificity of serial CRP, which in our study was recorded only for the levels at presentation.

CONCLUSION

The high sensitivity of CRP makes it a vital screening tool and can be used to curtail the duration of antibiotics in cases with culture-negative early-onset suspected/clinical NS and prevent the emergence of antibiotic resistance, thus helping in rationalizing the use of antibiotics. The serial CRP titers may assist to decide the duration of antibiotics.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Mehar V, Malhotra A, Mehta P, Thakur K, Malik R. Role of serial C-reactive protein measurements for determination of the duration of empirical antibiotic therapy in suspected neonatal sepsis. Indian J Child Health. 2020; 7(9):388-392.