Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

C-reactive Protein in Determining the Duration of Antibiotic Therapy in Neonatal Sepsis

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Abstract

Objectives: The objectives of this study were to evaluate the role of C-reactive protein (CRP) to decide the duration of antibiotic use in cases of neonatal sepsis (NS).

Materials and Methods: The hospital-based observational study was performed in the Sick Neonatal Care Unit and Neonatal Intensive Care Unit of a Tertiary Care Hospital in West Bengal from January 2020 to July 2021. Forty neonate fulfilling the criteria of clinical sepsis with or without laboratory confirmations with serum CRP >10 mg/L were selected. All the patients were started on empirical antibiotics after drawing samples for blood cultures and CRP. Serum CRP was done every alternate day until a normal CRP was achieved. Antibiotics were discontinued when two consecutive CRP were normal provided that there was clinical improvement. Culture positive NS was followed up after a week of antibiotics with serum CRP and then repeated every 24 h.

Results: Eighteen neonates had a negative CRP on day 2 and none of them had positive blood culture report. Six had a positive CRP on day 2 which became negative on day 5 all of whom had positive blood cultures. Seven patients had a positive CRP on day 2 and 5 which became negative on day 7 among which 6 had positive blood culture. Seven patients had a positive CRP on days 2, 5, and 7 which became negative on day 14 among which 4 had positive blood culture. Two patients had a positive CRP report on day 2, 5, 7, and 14 among which both were culture positive. The negative predictive value of CRP in NS according to our study was thus 100%.

Conclusion: Thus, we can conclude that serial estimation of CRP can act as a diagnostic parameter to decide when antibiotics can be safely discontinued in cases of NS which decreases antibiotic associated morbidity and cost of healthcare significantly by shortening hospital stay.

Key words: Antibiotics in neonates, C-reactive protein, Neonatal sepsis

INTRODUCTION

Any invasive bacterial infection occurring within the 1st month of life is defined as Neonatal Sepsis (NS), it is of early onset if it occurs within the 1st week of life and late onset if it occurs after the 1st week of 1 month.[1] NS is a very challenging scenario for neonatologists, because most of these neonates present with non-specific symptoms, and most of these mimic non-infectious causes with a lack of specific laboratory criteria, making the exact and timely diagnosis very challenging.[2,3]

The prevalence rate of NS has been reported to be 10/1000–15/1000 live births in developed countries and 15/1000–25/1000 live births in South Asia.[2,4] In India, the prevalence of NS is 11–24.5/1000 live birth.[5] NS is responsible for 30 to 40% of total neonatal mortalities in developing countries.[6]

Current recommendations for the treatment of neonatal septicemia include endpoints of 48–72 h for clinically stable children with negative blood culture results and 7–14 days for blood culture positive or clinically probable infection.[7-9] However, the rationale and safety of these recommendations have never been formally evaluated. According to different studies, about 11–23% of neonates

Access this article online

www.ijss-sn.com

Month of Submission : 05-2023
Month of Peer Review : 06-2023
Month of Acceptance : 06-2023
Month of Publishing : 07-2023

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are treated wrongly for sepsis, but they are not having it.[10-12] This not only results in antibiotic resistance but it also has many other short-term complications (e.g., pain and infection) and some long-term complications (e.g., hearing disorder and necrotizing enterocolitis).[13,14]

In addition, different organisms causing NS have a different spectrum of infection. Hence, instead of following the strict protocols of antibiotic duration, the antibiotic duration should also be regionalized according to the causing organism.[15] Therefore, there is a need to look for rapid diagnostic evaluation tests for NS instead of culture sensitivity reports. Over the past decades, a variety of laboratory tests have been developed to enhance the early and accurate identification and treatment of infants with sepsis. Various tests include micro-ESR, band neutrophil ratio (B/N ratio), procalcitonin, interleukin (IL)-6, IL-8, tumor necrosis factor-α, and C-reactive protein (CRP). Among them, serum CRP levels have become the front runner for the early diagnosis and in the determination of the duration of antibiotic treatment through various studies.[16,17]

Serum CRP, an acute-phase reactant, is synthesized in the liver within 6–8 h in response to inflammatory cytokines and may raise 1000 folds during an acute phase response. CRP level falls quickly after efficient elimination of microbial stimulus due to its short half-life of 19 h.[15] Thus, CRP levels may sufficiently reflect the individual balance between the microbes and the immune system of the neonate for monitoring the effect of antibiotic treatment and for guiding the duration of antibiotic therapy.[18,19]

The objectives of the present study were to determine whether CRP can be used as a parameter to identify the time point when antibiotic treatment can safely be discontinued in a defined major subgroup of neonates treated for suspected bacterial infection and to shorten the duration of hospital stay.

MATERIALS AND METHODS

The hospital-based observational study was performed in the Sick Neonatal Care Unit (SNCU) and Neonatal Intensive Care Unit (NICU) of a Tertiary Care Hospital in West Bengal from January 2020 to July 2021. Any neonate fulfilling the criteria of clinical sepsis with or without laboratory confirmations with serum CRP >10 mg/L were selected for the study. For clinical diagnosis of sepsis initial signs and symptoms of infection was considered. Forty neonates with clinically suspected septicemia were included in the study.

Inclusion Criteria

Neonates (0–28 days of life) with clinical signs and symptoms of sepsis with or without positive sepsis screen were included in the study.

Exclusion Criteria

The following criteria were excluded from the study:

a. Neonates who were <1.5 kg in birth weight and <32 weeks of gestational age due to high occurrence of comorbidities
b. Neonates who were diagnosed with meningitis (Lack of laboratory support to evaluate CRP in cerebrospinal fluid.)
c. Neonates who had undergone surgery due to the risk of Wound Infection
d. Neonates with congenital malformations predisposing to Infections
e. Neonates with hypoglycemia, hypocalcemia, or other metabolic derangements at presentation
f. Neonates with other comorbidities such as perinatal asphyxia, respiratory distress syndrome, bronchopulmonary dysplasia, meconium aspiration syndrome, hemolytic or hemorrhagic disease of newborn, acute kidney injury, congestive heart failure, and liver dysfunction.
g. Neonates who had all their CRP results negative
h. Parents who refused consent.

All patients included in the study were started on empirical antibiotics after drawing samples for blood cultures and CRP (as a part of sepsis screen). Strict aseptic measures were taken to rule out any systemic bias while taking blood cultures. A sample for serum CRP was taken every alternate day until a normal CRP level is achieved. CRP was read as negative when the level is ≤10 mg/L and positive when the level is >10 mg/L. Blood culture was followed for growth up to 7 days. The results of the CRP were verified by a laboratory technician of the microbiology department. The data collection tool was a pre-tested performa.

Suspected NS patients were started on empirical antibiotic therapy on admission after CRP and blood culture was sent for analysis. For NS without septicemia, serum CRP was monitored every 48 h. Antibiotics were discontinued when two consecutive CRP levels were within the normal range provided there is clinical improvement and with the senior consultant's permission. Culture positive NS was followed up after the 7th day of intravenous antibiotic with serum CRP and then every 24 h. With guidance from the visiting physician, antibiotics were discontinued when two consecutive results are normal. Single CRP value ≤10 mg/L was not considered as an endpoint. Neonates were kept up to 48 h after stopping the antibiotics to observe for recurrence of clinical features of septicemia.

For statistical analysis, data were entered into a Microsoft Excel Spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA). Data have been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A Chi-square test (2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a Chi-square distribution when the null hypothesis is true. Without other qualification, "Chi-square test" often is used as a short for the Pearson's Chi-square test. Unpaired proportions were compared by Chi-square test or Fisher's exact test, as appropriate. Z-test (Standard Normal Deviate) was used to test the significant difference of proportions. Correlation was calculated by Pearson correlation analysis. The Pearson product-moment correlation coefficient was a measure of the linear dependence between two variables X and Y. Multivariate analysis was performed by logistic regression method for calculation of risk factors. Once a t-value is determined using a one-tailed or two-tailed test, *P*-value can be found using a table of values from Student's t-distribution. If the calculated *P*-value is above the threshold chosen for statistical significance, then the null hypothesis is rejected in favor of the alternate hypothesis. $P \leq 0.05$ was considered for statistically significant.

RESULTS

In the study population, 12 (30%) neonates presented within 72 h of birth, 14 (35%) neonates presented between 72 h and 7 days of birth, 9 (22.5%) cases presented between 8 and 14 days while only 5 (12.5%) cases presented after 2 weeks of birth. The average age of presentation was 7.4 ± 6.06 days. Twenty-two (55%) of the neonates were male while 18 (45%) were female. Thirty-three (82.5%) of the neonates included were born by vaginal delivery while 7 (17.5%) were born by cesarean section.

Twenty-seven (67.5%) of the neonates were preterm while 13 (32.5%) were term. Eighteen (45%) of the neonates were born with a birth weight of ≥1.5–2 kg, 13 (32.5%) had a birth weight of >2–2.5 kg, 6 (15%) had a birth weight of >2.5–3 kg while only 3 (7.5%) had a birth weight >3 kg. The study population had an average birth weight of 2.19 ± 0.47 kg. A significant number of neonates admitted for NS were of low birth weight ($P < 0.05$). Fourteen (35%) of the neonates suffered from early-onset NS while 26 (65%) suffered from late-onset NS.

Among the study population, the most common risk factor for NS encountered was Vaginal delivery (82.5%), followed by prematurity (32.5%) and maternal urinary tract infection (UTI) during 3rd trimester (30%). Maternal fever (10%) and prolonged rupture of membrane (15%) and meconium stained liquor (15%) were the lesser found risk factors. The most common clinical feature with which a neonate presented was refusal of feed (55%), followed by jaundice (45%), lethargy (37.5%), and poor cry (35%).

Among the 14 neonates with early-onset NS, 5 (35.71%) had a positive blood culture report. Among the 26 neonates with late-onset NS, 13 (50%) patients had a positive blood culture report. Patients with late-onset NS had a significantly greater number of positive blood culture reports ($P = 0.013$).

Among the 18 culture-positive patients, 13 (72.22%) grew Gram-negative organisms while 5 (27.78%) grew Gram-positive organisms. Among the Gram-negative organisms, *Klebsiella* (27.78%) was the most common followed by *Escherichia coli* (22.22%), *Pseudomonas* (22.22%), and *Acinetobacter* (5.56%). Among the Gram-positive organisms, *Staphylococcus aureus* (22.22%) was the most common.

Twenty-two (55%) had a raised CRP >10 mg/L on day 2, 16 (40%) had raised CRP on day 5, and 9 (22.5%) had raised CRP on day 7 while only 2 (5%) had a positive CRP on day 14.

Among the study population, 18 had a negative CRP on day 2 and none of them had positive blood culture report. Six patients had a positive CRP on day 2 which became negative on day 5 among which all of them had positive blood culture reports. Seven patients had a positive CRP on day 2 and 5 which became negative on day 7 among which 6 had positive blood culture reports. Seven patients had a positive CRP on days 2, 5, and 7 which became negative on day 14 among which 4 had positive blood culture reports. Two patients had a positive CRP report on day 2, 5, 7, and 14 among which both were culture positive. The negative predictive value (NPV) of CRP in NS according to our study was thus 100%.

Eighteen (45%) received antibiotic therapy for <3 days, 6 (15%) for 5 days, 7 (17.5%) for 7 days, 7 (17.5%) for 14 days, and 2 (5%) for >14 days. This was guided as per serum CRP levels and antibiotic was discontinued after consultation with senior pediatrician. None of the subjects required retreatment until 48 h post cessation of antibiotic therapy.

DISCUSSION

The hospital-based observational study was conducted among 40 neonates presenting with clinical signs and

symptoms of sepsis with or without positive sepsis screen admitted at our SNCU and NICU wards were included in the study. This was in line with the incidence of NS in India which was 24/1000 as per epidemiological studies as on April 2019.[18]

In the present study, the average age of presentation in the study was 7.4 ± 6.06 days. In a study by Hisamuddin *et al.*, mean age of the neonates was 5.72 days + 3.86.94 27 (67.5%) of the neonates included were preterm while 13 (32.5%) were term. There was significantly more risk of developing NS in preterm neonates as compared to term neonates ($P = 0.027$).[20] Similarly, in a meta-analysis performed by Belachew and Tewabe, it was revealed that NS was significantly associated with the gestational age of newborns with odds ratio (OR) 3.36 (95% CI: 2.50, 4.54), that is, preterm babies were 3.36 more likely to develop NS than term babies.[21] In a study by Mehar *et al.*, preterm were having 1.49 (CI [0.95, 2.35]) times risk of developing septicemia as compared to term neonates ($P < 0.05$).[22]

Our study had 18 (45%) of the neonates born with a birth weight of ≥1.5–2 kg, 13 (32.5%) had a birth weight of >2–2.5 kg, 6 (15%) had a birth weight of >2.5–3 kg while only 3 (7.5%) had a birth weight >3 kg. The study population had an average birth weight of 2.19 ± 0.47 kg. A significant number of neonates admitted for NS were of low birth weight ($P < 0.05$). In a study by Hornik *et al.*, data of over 108,000 very low birth weight (VLBW) infants were compared. Early-onset sepsis occurred in 1032 infants, and late-onset sepsis occurred in 12,204 infants. Early and late-onset sepsis was associated with increased risk of death controlling for other confounders (odds ratio 1.45 [95% confidence interval 1.21, 1.73], and OR 1.30 [95% CI 1.21, 1.40], respectively). They concluded that (VLBW, <1500 g birth weight) infants are at high risk for both early and late-onset sepsis.[23]

In our study, 14 (35%) of the neonates suffered from early-onset NS while 26 (65%) suffered from late-onset NS. A retrospective study from the Netherlands showed a decrease in the incidence of EONS from 4% between 1978 to 1982 to 1.2% from 2003 to 2006. The incidence of LONS in this study increased from 7.1% between 1978 to 1982 to 13.9% from 2003 to 2006.23 A review from the United States in 2012 reported that EONS occurs in 1.5–2% of VLBW infants and LONS in 21% of VLBW infants.[24] In a cohort study by Delhi Neonatal Infection Study Collaboration, nearly two-thirds of total episodes were early onset while the rest one-third were late.27 In a study by Bangi *et al.* during 2003–2004, the incidence of EOS and LOS was 3.08% and 2.96%, respectively, while the same in 2013–2014 was 2.57% and 3.44%.[25]

The most common risk factor for NS in our study encountered was vaginal delivery (82.5%), followed by prematurity (32.5%) and maternal UTI during the 3rd trimester (30%). Maternal fever (10%) and premature rupture of membrane (15%) and meconium-stained liquor (15%) were the lesser found risk factors. In the study by Assa *et al.*, the major infection risk factor was premature rupture membrane >24 h (14.9%), and minor infection risk factor was gestational age <37 weeks (78%), very low birth weight (44.6%), and asphyxia (41.1%).[26] Murthy *et al.*, in their systemic review, found that male sex (OR: 1.3, 95% CI: 1.02, 1.68), outborn neonates (OR: 5.5, 95% CI: 2.39, 12.49), need for artificial ventilation (OR: 5.61; 95% CI: 8.21, 41.18), gestational age <37 weeks (OR: 2.05; 95% CI:1.40, 2.99), and premature rupture of membranes (OR:11.14, 95% CI: 5.54, 22.38) emerged as risk factors for NS.30 Leal *et al.* after logistic regression found that risk factors for sepsis included the following: low birth weight; prematurity; abnormal amniotic fluid; premature membrane rupture (PMR) for >24 h; respiratory complications; and the requirement of assisted ventilation, O2 Inspiration fraction (IF) >60%, or a surgical procedure.[27] Adatara *et al.*, the neonatal risk factors associated with sepsis were birth weight ($\chi^2 = 6.64$, $P = 0.036$), neonatal age ($\chi^2 = 38.31$, $P < 0.001$), meconium passed ($\chi^2 = 12.95$, $P < 0.001$), the reason for CS ($\chi^2 = 24.27$, $P < 0.001$), and the duration of stay on admission ($\chi^2 = 36.69$, $P < 0.001$).[28] In a cross-sectional study by Bangi *et al.*, highly significant risk factors were inadequate antenatal care, assisted vaginal delivery, and premature rupture of membranes, low birth weight, and associated complications.[25]

We observed the most common clinical features with which a neonate presented were refusal of feed (55%), followed by jaundice (45%), lethargy (37.5%), and poor cry (35%). In the study by Jajoo *et al.*, lethargy/refusal to feed (77%), hypothermia (47.5%), and respiratory distress (44%) were common clinical presentations.[29] The most common clinical manifestations in a study by Hematyar *et al.* were respiratory distress in 49 (44.5%), jaundice in 28 (25.5%), vomiting in 26 (23.6%), and poor feeding in 23 (20.9%) of the infants. Other clinical manifestations were lethargy (weakness), decreased sucking reflex, fever, tremor, abdominal distention, and seizure, found in 12 (10.9%), 10 (9.1%), 4 (3.6%), 4 (3.6%), 3 (2.7%), and 2 (1.8%) neonates, respectively. Early-onset sepsis was considerably associated with respiratory distress ($P < 0.001$), while LOS in neonates was followed by jaundice ($P < 0.001$), seizure ($P = 0.02$), and fever ($P < 0.001$).[30] In a retrospective chart review of VLBW infants by Lim *et al.*, apnea and/or bradycardia and/or cyanosis (65.8%), poor activity (48.7%), and increased respiratory effort (43.0%) were the most common presenting features of sepsis.[31]

Among the 14 neonates in the present study with early-onset NS, 5 (35.71%) had a positive blood culture while 9 (64.29%) had a negative blood culture report. Among the 26 neonates with late-onset NS, 13 (50%) patients each had positive and negative reports. Patients with late-onset NS had a significantly greater number of positive blood culture reports ($P = 0.013$). In a study by Kayange *et al.*, positive blood culture was found in 57 (47.1%) and 92 (51.4%) among neonates with early- and late-onset NS, respectively ($P = 0.466$).[32] Patel *et al.* found in his study found 276 positive blood culture reports in comparison to 546 negative blood culture reports in NS over a 4-year period.[33]

On the serial measurement of CRP, our study found that 22 (55%) had a raised CRP >10 mg/L on day 2, 16 (40%) had raised CRP on day 5 and 9 (22.5%) had raised CRP on day 7 while only 2 (5%) had a positive CRP on day 14. 18 had a negative CRP on day 2 and none of them had positive blood culture report. Six patients had a positive CRP on day 2 which became negative on day 5 among which all of them had positive blood culture reports. Seven patients had a positive CRP on day 2 and 5 which became negative on day 7 among which 6 had positive blood culture reports. Seven patients had a positive CRP on days 2, 5, and 7 which became negative on day 14 among which 4 had positive blood culture reports. Two patients had a positive CRP report on day 2, 5, 7, and 14 among which both were culture positive. The NPV of CRP in NS according to our study was thus 100%. In a study by Hisamuddin *et al.*, the sensitivity and specificity of CRP in the diagnosis of acute NS were determined as 76.92% and 53.49%, respectively. It had a positive predictive value (PPV) of 80% and a NPV of 48.94%. The overall diagnostic accuracy of CRP in the diagnosis of NS was 70.07%.[20] In a validation study by Ahmed *et al.*, CRP results were positive in 85 (62.9%) neonates on first baseline measurement and were positive in 103 (76.29%) neonates after 72 h of admission. The sensitivity of CRP in diagnosing sepsis was found to be 98.03%, specificity was 91.0%, PPV was 97%, and NPV was 93.7%.[34] In a cross-sectional study by Bunduki *et al.*, of the 228 neonates with suspected sepsis, 94 (41.2%) had a positive CRP. Among the 69 cases with positive blood culture, CRP identified 66 cases. The sensitivity, specificity, positive and NPVs of CRP were 95.7%, 82.4%, 70.2%, and 97.8%, respectively. The area under the curve for the CRP registrar of companies analysis was 0.948.[35]

In our study, 18 (45%) received antibiotic therapy for <3 days, 6 (15%) for 5 days, 7 (17.5%) for 7 days, 7 (17.5%) for 14 days, and 2 (5%) for >14 days. This was guided as per blood CRP levels and antibiotics were discontinued after consultation with a senior pediatrician. Ahmed *et al.* found that the mean duration of antibiotic treatment in the CRP-guided group was 5.03 days versus 7.02 days in the standard treatment duration group ($P < 0.001$).[34] Bomela *et al.* found that repeat CRP estimation correctly identified 99 of 100 infants in the study as not requiring further antibiotic therapy (NPV, 99%; 95% confidence intervals, 95.6–99.97%). The one infant with a positive blood culture was premature with a gestational age of 31 weeks. Eight babies required repeat evaluation for suspected sepsis, four presented on days 3–4 and one of these babies died. Thus, they concluded that the use of serial CRP measurements to guide antibiotic therapy is a safe and practical approach in neonates with suspected sepsis in a developing country.[36] Gyllensvärd *et al.* carried out a study between 2 periods, period 1: 2016–2017 where a conventional antibiotic protocol was followed and then after the introduction of the new CRP guided protocol (period 2: 11 June 2018 to 30 Sept 2019). The median CRP was 52 mg/L (37–62) in period 1 and 42 mg/L (31–56) in period 2 in the group that met the criteria of the guidelines. The duration of antibiotic therapy (Median: 7 vs. 5 days, $P < 0.001$) and hospital stay (Median: 7 vs. 5 days, $P < 0.001$), as well as healthcare costs, was reduced in the group who met the criteria after the introduction of the guidelines.[37]

CONCLUSION

Thus, it can be concluded that serial estimation of CRP can act as a diagnostic parameter to decide when antibiotics can be safely discontinued in cases of NS. The NPV of CRP in NS according to our study was thus 100%. This study has also shed light on the basic characteristics of NS by studying its risk factors and clinical features. It was observed that pre-term and low birth weight neonates had a significantly increased risk of NS. Serial estimation of CRP can, in turn, decrease antibiotic-associated morbidity and cost of healthcare significantly by shortening hospital stay for a neonate.

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How to cite this article: Chakraborty S, Ghosh T. C-reactive Protein in Determining the Duration of Antibiotic Therapy in Neonatal Sepsis. Int J Sci Stud 2023;11(4):66-71.

Source of Support: Nil, **Conflicts of Interest:** None declared.