ORIGINAL ARTICLE

Sensitivity and Specificity of C-Reactive Protein Against Blood Culture in Patients with Neonatal Sepsis - A Hospital-Based Study

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Abstract

Background: Neonatal septicemia is one of the primary causes of disease and death in low-income countries which makes early diagnosis an important factor to prevent microbial resistance and initiate antibiotic therapy. C-reactive protein is an essential biological indicator that might play an important role in the early detection of neonatal sepsis.

Objective: The present study was conducted to determine the sensitivity and specificity of CRP against blood culture in the identification of neonatal sepsis.

Methods: This study was carried out on 416 neonates identified with sepsis at the NICU and SICU of the National Institute of Child Health, Karachi, Pakistan for a span of 06 months from April 2022 to September 2022. The first blood sample for the evaluation of CRP and blood culture was drawn at the time of admission. The second sample of CRP and blood culture was drawn 72 hours after the first blood collection. The sensitivity and specificity of CRP were calculated on both occasions.

Results: Of the total 416 neonates, 165(39.6 %) patients' blood culture was positive and in 273 (65.9%) patients CRP was positive. The validation study of CRP in the diagnosis of neonatal septicemia reported sensitivity, specificity, positive predictive value, and negative predictive value to be 87.1%, 45.9%, 52.6%, and 83.7% 72 hours after the admission in comparison to 80.6%, 44.2%, 48.7%, and 77.6% at the time of admission.

Conclusion: The high specificity and sensitivity of CRP against blood culture make it an important diagnostic modality that might play a helpful role in the diagnosis of neonatal sepsis.

Keywords: *Neonatal septicemia, C-reactive protein, blood culture, sensitivity, specificity.*

INTRODUCTION

Neonatal sepsis is a medical condition that arises in the early 30 days of a newborn. The preterm neonates are found to be more susceptible to the invasion by micro-organisms and thus the resulting infections which can result in the death within a few hours or days [1]. Thus neonatal sepsis is considered a significant source of morbidity and mortality in the developing world. It is considered the second most frequent cause of neonatal deaths after prematurity in developing countries [2, 3]. Previously published literature revealed that 14.4% of infant mortality is attributed to neonatal sepsis [4].

Neonatal sepsis is a disorder that becomes a diagnostic dilemma on clinical grounds because of vague clinical manifestations that arise during infection. Therefore, laboratory investigations have a crucial role in the diagnostic process. The gold standard test performed frequently for the analysis of bacterial sepsis is blood culture analysis [5]. However, this test has a few disadvantages which include the two-week waiting period for the culture report to be generated which creates a delay in reaching an accurate diagnosis. Moreover, of the 7 - 13% of the neonatal population who are examined for sepsis, only 3 - 8% of the cases are confirmed by blood culture [6]. Thus the next logical step is a test that would help in the timely and rapid diagnosis of neonatal sepsis [7].

At present, C-reactive protein (CRP), an organic indicator has been recommended as a prospective indicator for the identification of neonatal infection [8]. It is a test that is easily accessible at many laboratory centers [9, 10]. In most medical facilities, CRP is performed only once on the arrival of the patient which in most cases may be negative. The reason behind the negative result is that the liver produces this protein almost eight to nine hours after the inflammatory or infectious event, and the enzyme reaches its peak levels in the next 48 to 72 hours. Therefore, it is essential to assess the validity of the CRP test on two separate occasions *i.e.* one at the time of admission and the other one after 72 hours of the first test. There is a dearth of local studies that have been conducted to evaluate the validity of CRP, particularly those which have been performed on two different occasions *i.e.* at the time of admission and the next 72 hours after the first CRP examination. So the present study aimed to examine the validity of elevated CRP for the diagnosis of neonatal sepsis (at 0 and 72 hours) with blood culture considered as the gold standard at a tertiary care hospital.

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MATERIALS AND METHODS

This diagnostic accuracy study was carried out at the Neonatal Intensive Care Unit (NICU) of the National Institute of Child Health, Karachi, Pakistan over six months spanning from April 2022 to September 2022. The study was approved by the Institutional Review Board and data collection was started after approval making it a prospective study design. The sample size was calculated by taking, sensitivity at 77.6%, specificity at 73.8%, and prevalence of neonatal sepsis at 33%, the margin of error d=7% for sensitivity and d=7% for specificity and confidence interval 95% [11] and the estimated sample size was 416.

Neonates with suspected septicemia are defined as a clinical syndrome characterized by systemic signs/ symptoms and bacteremia during the 1st month of life and those patients matching any 2 clinical and 1 laboratory criteria were believed to be the case suspected septicemia while signs and symptoms along with laboratory criteria may include:

- Fever (rectal temperature >38°C)
- Hypothermia (rectal temperature <36°C)
- Metabolic acidosis (base deficit of ≥4 meq/L)
- White blood cell (WBC) count ≥30,000/mm or <5,000/ mm, or >25% of immature cells
- Hypotension (mean blood pressure continues to be less than patient's gestational age after receiving 20 mL/kg of normal saline body weight and patient needs ionotropic support)
- Tachypnea (>60 breaths/min)

Were included by using nonprobability consecutive sampling. Neonates with hypoxic-ischemic encephalopathy, congenital heart illnesses, congenital abnormalities, and hyaline membrane disease and having birth weight less than 1.5 Kg were excluded from the study. Informed voluntary, and verbal consent was attained from parents/guardians of neonates before enrolment into the study. Empirical antibiotics were started after taking blood samples of CRP and blood culture. Sterilization was maintained to minimize the systematic bias while getting blood cultures.

Two blood samples were drawn for CRP *i.e.* one at the time of admission and the second 72 hours after the first sample collection. CRP level less than 5mg/dl was labeled as negative. Blood culture for the growth of microorganisms was followed up to 7 days. If the CRP test done at the time of admission reported negative results, the antibiotic therapy was continued, but in case of a second CRP report being negative, the antibiotic therapy was discontinued. However, if the CRP test performed 72 hours after the first CRP test was >5mg/ dL (positive) the antibiotic therapy was sustained or changed, depending on the clinical picture as assessed by the healthcare professionals. If both CRP tests (at the time of admission and 72 hours) were positive, the empirical antibiotic therapy was continued until the final culture and sensitivity report was received to decide the next antibiotic regimen.

Categorical variables such as the presence of neonatal sepsis on elevated CRP (Positive/Negative) and blood culture (Positive/Negative) were summarized using frequency and percentages while continuous variables such as age were presented as mean (±SD). Sensitivity, specificity, positive predictive value, and negative predictive values of CRP were determined with blood cultures considered as the gold standard. SPSS version 24.0 was used for statistical analysis.

RESULTS

In this study, 416 suspected patients of neonatal sepsis were studied. The present study displayed a male predominance *i.e.* 57.5% (n=239). The mode of delivery for the majority of the patient was vaginal (n=281; 67.5%). The mean age of participants was 11± 4 days. In terms of weight at birth, the majority of the study participants (n=222; 55%) weighed less than 2.5 kg. Socioeconomically, 64.8% of the patients were observed to be rural dwellers.

At the time of admission, the blood cultures and CRP were found to be positive in 39.6% (n=165) and 65.6% (n=273) cases. After 72 hours of admission, this frequency was found to have increased to 40.9% (n=170) and 67.5% (n=281) for blood cultures and CRP respectively. As per the blood cultures performed in the present study, Klebsiella Species accounted for 43% of cases, E coli 30% of cases, Staphylococcus Aureus 28% of cases, pseudomonas spp 16% of cases, Serratia 11% of cases, and Enterococcus spp 2% cases. There were no patients with polymicrobial sepsis in the study.

The accuracy studies of CRP performed at the time of admission reported a sensitivity and specificity of 80.6% and 44.2% respectively as displayed in Table **1**. After 72 hours, the validity tests were performed again and the sensitivity of CRP in diagnosing neonate sepsis had increased to 87.1% while the specificity was observed to be 45.9%.

An association was evaluated between the CRP and the blood cultures for both occasions and a statistical significance at 72 hours (p-value: 0.019) as displayed in Table **2**.

DISCUSSION

This hospital-based study was conducted in a pediatric facility of a tertiary care center in Sindh. In our study, the results of blood culture-confirmed neonatal sepsis in

Table 1: Validity of CRP in diagnosing the neonatal sepsis.

Validity	At Admission	After 72 hours
Sensivitiy (%)	80.6	87.1
Specificity (%)	44.2	45.9
Positive predictive value (%)	48.7	52.6
Negative predictive value (%)	77.6	83.7

Table 2: Association of blood culture and CRP in patients with neonatal septicemia (N = 416).

Blood Cultures									
CRP	Groups	At the time of admission				At 72 hours after admission			
		Frequency	Positive n(%)	Negative n(%)	p-value	Frequency	Positive n(%)	Negative n(%)	p-value
	Positive	273	133 (48.5)	140(51.2)	0.053	281	148 (52.7)	133 (47.3)	0.019*
	Negative	143	32 (22.4)	111(77.6)		135	22 (16.3)	113 (83.7)	

**Statistically significant*

39.6% of patients at the time of admission. The findings of the present study found a concordance with a study that reported a prevalence of 35.8% sepsis among neonates [12]. A study conducted by Bhatia *et al.* in India reported a much higher frequency of 50.7% of cases of neonatal sepsis [13]. These differences in the reported frequencies could be attributed to differences in sample size as well as the pattern of following the laboratory protocol for the evaluation of CRP and blood culture.

The present study reported 48.5% (n=133) patients as cases of neonatal sepsis as both their CRP as well as blood culture were found to be positive. However, there were 140 (51.2%) and 32 (22.4%) cases of neonatal sepsis in whom only CRP and blood culture were observed to be positive respectively. A study conducted by Lamicchane *et al.* in Nepal, confirmed the diagnosis of neonatal sepsis in 104 (42.5%) cases *via* blood culture while CRP was found to be positive in 92 cases (88.5%) of those cases which had already been labeled as having neonatal sepsis *via* blood culture [14].

In our study, the sensitivity of CRP in labeling a case of sepsis in the neonates was 80.6%, specificity of 44.2%, positive predictive value of 48.7%, and negative predictive value of 77.6%. In comparison, Sodani *et al.* reported the sensitivity to be 86.7%, specificity of 43%, positive predictive value of 45.5%, negative predictive value of 85%, and diagnostic accuracy of 69% [12]. Another study from a low-income country reported sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the CRP test in the diagnosis of neonatal sepsis to be 88.5%, 46.1%, 54.8%, 84.1%, and 64.1% respectively [14]. A study conducted by Bunduki *et al.* from Africa also reported the sensitivity to be 95.7%, specificity of 82.4%, positive predictive value of 70.2%, and negative predictive value of 97.8%, and stated CRP as being a useful test in diagnosing the neonatal sepsis [15]. Another local study conducted in Peshawar reported better screening accuracy of CRP in neonates who developed sepsis after 72 hours [11]. This was also observed in the present study as the sensitivity and specificity of labeling a patient with neonatal sepsis 72 hours after admission had increased to 87.1% and 45.9% respectively. Local studies reported 70% of diagnosis correctness of CRP in confirmation of neonatal sepsis [11, 16]. Rawat *et al.* aimed to evaluate the importance of routine blood investigations such as complete blood count (CBC), and CRP in the early detection of neonatal septicemia. They reported that of the one hundred neonates with suspected sepsis, 40 were found to be septic based on their blood cultures. They further reported that CRP had the highest sensitivity and NPV of 45% of 71% respectively, neutropenia had the highest specificity of 91.7% and leucopenia had the highest PPV *i.e.* 72% [17].

The current study reported Klebsiella Species, E coli, Staphylococcus Aureus, pseudomonas spp., Serratia, and Enterococcus spp., as the most frequent microorganisms observed in cases of neonatal septicaemia. In another study by Lamichhane *et al.* gram-negative organisms accounted for 57.6% of cases while gram-positive organisms were reported in 43.2% cases [14]. The authors further reported that early-onset (EOS) and late-onset sepsis (LOS) were observed in 79.2% and 20.8% of cases [14]. The most frequent micro-organisms observed in cases of EOS were Klebsiella, Pseudomonas, and methicillin-resistant Aureus and each was found in 17% of cases of the study cohort [17-19].

The strength of this study is that validation studies of the CRP test in the diagnosis of neonatal sepsis were done on two separate occasions *i.e.* first at the time of admission and second 72 hours after admission. The limitation of this study was that it was an observational single-centered research and its findings may not be generalized to all neonates suffering from sepsis in the entire country.

CONCLUSION

The high sensitivity and specificity of the CRP test in comparison to the blood culture supports the importance of this rapid test in the diagnosis of neonatal sepsis. This might impart an advantage to pediatricians to suggest the duration of antibiotic treatment, and thus help in the reduction of the mortality rate due to sepsis. Further multicenter analytic studies are suggested to formulate better protocols for the diagnosis and treatment of neonatal sepsis.

ETHICAL APPROVAL

Ethical approval was obtained from the Institutional Ethical Review Board of the National Institute of Child Health (NICH), Karachi (REF letter No. IERB-22/2021, Dated: 28-09-2021). All procedures performed in studies involving human participants were by the ethical standards of the institutional and/ or national research committee and with the Helsinki Declaration.

CONSENT FOR PUBLICATION

Voluntary informed consent was taken from the parents/ guardians/caretakers of the neonates who were enrolled in the study.

AVAILABILITY OF DATA

The data set may be acquired from the corresponding author upon a reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

DK: Conception or design of the work.

MK: Drafting the work or revising it critically for important intellectual content.

MS: the acquisition, analysis, and interpretation of data for the work.

MH: the acquisition, analysis.

WH: interpretation of data for the work.

All authors approve the final version of the manuscript to be published. All authors also agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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