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A STUDY TO ASSESS THE IMPORTANCE OF CRP MONITORING IN THE TREATMENT OF NEONATAL SEPSIS IN PRETERM BABIES

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ABSTRACT

INTRODUCTION: *Newborns with the gestational age of less than 32 weeks are by default immune compromised, and possess only approximately one half of the cord blood Ig G seen in term infants. Furthermore, extremely preterm infants are immunologically immature manifested by decreased immune components, reduced poly morphonuclear chemotaxis and decreased ability to fight infections.*

AIM AND OBJECTIVES: *That is why, the purpose of this study was to evaluate the effectiveness of such approach as repeated consecutive monitoring of the C-reactive protein level together with the antibiotics administration to improve the sepsis outcomes in premature infants.*

MATERIALS AND METHODS: *Sixty preterm infants clinically diagnosed with sepsis were taken randomly in the study group and control group during one year (May 2019 to April 2020) in Fauji Foundation Hospital Neonatal Intensive Care Unit. In addition to the treatment, the study group's ENT was monitored with CRP levels.*

RESULTS: *The mean neonatal age distribution was 5.72 days ±3.86/ SI Units. Of the 60 neonates a, 32 (53.3%) were male while 28 (46.7%) were female. Sepsis was proved in 42/60; 70% through blood culture while sepsis was negatives through blood culture in 18/60; 30%. After 72 hours, 41 (68%) neonates had a positive CRP result, while 19 (32%) were negative. The sensitivity of CRP at 72 hours in diagnosing acute neonatal sepsis was 73.17%. The specificity was 42.10%. The positive predictive value (PPV) of CRP was 73.17%, and the negative predictive value (NPV) was 42.10%, and overall, the diagnostic accuracy of CRP in diagnosing neonatal sepsis at 72 hours was 63.33%.*

CONCLUSION: *This study demonstrates that CRP is a valuable tool for diagnosing neonatal sepsis in preterm babies, with decent sensitivity (73.17%) and a positive predictive value of 73.17%, making it effective in identifying true sepsis cases. However, its lower specificity (42.10%) and negative predictive value (42.10%) indicate limitations in ruling out non-sepsis cases. With a diagnostic accuracy of 63.33%, CRP can be used alongside clinical assessment and blood cultures to guide effective management of neonatal sepsis.*

Key words: *CRP, natal sepsis, premature babies.*

INTRODUCTION

Neonatal sepsis is characterized by disease in newborns who are less than 28 days old, are clinically ill and have positive blood cultures for culture the incidence of neonatal sepsis varies from 2.2 / 1000 live births in developed countries to 10-50 / 1000 live births in developing countries; however, reporting is most common in both countries [1-2]. The incidence of premature babies rises to 4/1000 premature births. Notwithstanding the steady and significant advances in hygiene, the demonstration of more recent effective antimicrobials, and supported strategies in early analysis and treatment, neonatal sepsis remains one of the most important causes of mortality in this age group. The high mortality and morbidity despite improved anti-infective agents and innovative advances in life-support therapies have prompted the search for different treatments[3-4]. Nonspecific signs/symptoms make it very challenging to formulate a timely clinical diagnosis[5.] Newborns are viewed as immune compromised in terms of their moderately immature defense mechanism. In particular, they show a quantitative and additionally subjective inadequacy in their humoral insensitivity.

MATERIALS AND METHODS

This prospective, randomized, controlled study was conducted among sixty preterm infants with sepsis and randomly assigned to study and control groups in the Neonatal Intensive Care Unit of Fauji Foundation Hospital, Rawalpindi for one-year duration from May 2019 to April 2020. SPSS version 20 was used for statistical analysis of the collected data. Mean and standard deviation were calculated for numerical variables i.e. age and weight of baby. Frequency and percentages were presented for categorical variables i.e. qualitative CRP and blood culture results. Sensitivity, specificity, negative and positive predictive values for CRP in identifying babies with culture proven neonatal sepsis were also calculated.

Study population: Preterm infants less than 33 weeks of age with suspected sepsis were eligible for inclusion. After admission to the hospital, the gestational age was determined on the basis of maternal dates (time from the main day of the last menstruation) and confirmed using the Ballard scale. A point-by-point history was collected, a thorough physical examination was performed and recorded in a standardized questionnaire. Sepsis has been associated by the presence of clinical signs that are reliable with possible true bacterial disease, including lethargy, refusal to eat, stomach bloating, heaving, snorting, grimacing, breathing problems, hypothermia, fever, or Sclerema neonatorum with or without risk confirmation on for example, maternal asphyxia, inflammation of the membranes of the mother's membranes (maternal fever or potentially rotten vaginal discharge) and delayed bursting of the layers. Meningitis has been associated with a history of seizures, screeching crying, and protruding / taut anterior fontanelles along with various sepsis components. Patients with respiratory distress (RDS), internal net abnormalities, and prior antitoxin treatment were avoided. The infants were sorted according to the associated sepsis risk factors: sex, birth weight, gestational age, origin, and mode of transmission. After admission to the study, the patients underwent the following diagnostic procedures: blood count, blood culture. C- reactive protein (CRP) determination was done in case group. In the case of suspected meningitis, CSF culture was performed. Neonatal sepsis was diagnosed when the clinical suspicion was confirmed by a positive blood and / or cerebrospinal fluid culture or by a clinical and biochemical tests leukocytosis or leukopenia.

Procedures

Following their inclusion in the study, all participants received immediate treatment with antibiotics even though samples for blood cultures were taken and completing the CRP projection assigned to laboratory services. In collecting blood culture, every effort was made to eliminate all forms of systemic bias. In addition, a second sample of blood was extracted for CRP 72 hours after the first sample was taken. Two CRP samples were taken, one immediately upon admission and another 72 hours after the first sample. A CRP level of <5mg/dl was construed as negative while a CRP level of more than 5 mg/dl was interpreted as positive. Thereafter, the blood culture was monitored for growth for seven days. The readings of CRP were confirmed by the laboratory technician and by the head of the pathology department. A pre-tested performa was used as the data collection tool. Patients suspected to have neonatal sepsis were immediately started on

empirical antibiotic therapy after admission and first CRP and blood culture sent for analysis. When the first CRP was negative, the onslaught of antibiotics would continue but when the second CRP was also negative, the antibiotics would be stopped. If, however, the second CRP turned positive, which indicates the presence of an infection, treatment with antibiotics was either continued or a different antibiotic was administered depending on the clinical picture of the patient. If both first CRP and second CRP were positive, therapy was maintained awaiting results of culture and sensitivity before deciding on course of antibiotic therapy.

RESULTS

A total of 60 patients were enrolled in the study, 30 in the study and 30 in the control group. Days. In this study, 60 neonates with suspected neonatal sepsis were included. Males were 32 (53.3%) and females were 28 (46.7%), with a male-to-female ratio of 1.14:1. Neonatal age was categorized into four groups, with the majority presenting in the younger age group, i.e., less than or equal to 5 days, which accounted for 38 (63.3%) of the neonates. 14 (23.3%) neonates were aged between 6-10 days, 4 (6.7%) were in the 11-15 days range, and 4 (6.7%) presented at ages greater than 15 days. The study included neonates aged from 1 to 27 days, with a mean age of 5.83 days ± 4.23. Age-wise distribution of results shows that 38 (63.3%) neonates with sepsis were in the less than or equal to 5 days age group. 12 (20%) neonates with sepsis were aged between 6-10 days, 3 (5%) were in the 11-15 days age range, and 3 (5%) neonates had sepsis at ages greater than 15 days. Similarly, 10 (50%) neonates who did not have neonatal sepsis were in the less than or equal to 5 days age group, 5 (25%) were in the 6-10 days range, 1 (5%) was in the 11-15 days group, and 4 (20%) neonates who did not have sepsis were aged greater than 15 days.

Table 1: Gender and Age wise Distribution of Neonatal Sepsis

Category	Neonates with Sepsis (n = 60)	Neonates without Sepsis (n=60)
Gender		
Male	32 (53.3%)	28 (46.7%)
Female	28 (46.7%)	32 (53.3%)
Age Distribution		
<5 days	38 (63.3%)	10 (50%)
6-10 days	12 (20 %)	5(25%)
11-15 days	3 (5%)	1 (5%)
>15 days	3(5%)	4(20%)

Table 2: Cross-tabulation for determining the accuracy of CRP keeping culture positive as gold standard

CRP Levels at 72 hrs	Culture Positive (n = 42)	Culture Negative (n = 18)	Total (n = 60)
Positive	30 (True Positive)	11 (False Positive)	41
Negative	11 (False Negative)	8 (True Negative)	19
Total	41	19	60

At the time of admission, CRP testing was positive in 38 (63.3%) neonates and negative in 22 (36.7%) neonates. After 72 hours, 41 (68%) neonates had a positive CRP result, while 19 (32%) were negative. The sensitivity of CRP at 72 hours in diagnosing acute neonatal sepsis was 73.17%. The specificity was 42.10%. The positive predictive value (PPV) of CRP was 73.17%, and the negative predictive value (NPV) was 42.10%, and overall, the

diagnostic accuracy of CRP in diagnosing neonatal sepsis at 72 hours was 63.33%.

Table III: Diagnostic Performance of CRP at 72 Hours (n = 60)

CRP Test Timing	Positive (n)	Negative (n)	Total (n = 60)
At Admission	38 (63.9%)	22 (36.1%)	60
After 72 Hours	41 (68%)	19 (32%)	60

- **Sensitivity**: 73.17%
- **Specificity**: 42.10%
- **Positive Predictive Value (PPV)**: 73.17%
- **Negative Predictive Value (NPV)**: 42.10%
- **Overall Diagnostic Accuracy**: 63.33%

DISCUSSION

Neonatal sepsis is a leading cause of illness and death among newborns, particularly in developing nations. Timely diagnosis and prompt treatment are essential for improving outcomes, as delays in identifying and treating the condition are major factors contributing to high mortality rates [6]. Although blood culture is considered the gold standard for diagnosing neonatal sepsis, several hematologic markers, inflammatory cytokines, and acute-phase reactants are also utilized. Among these, C-reactive protein (CRP) has been extensively researched for its potential in diagnosing neonatal sepsis[7].

Benitz et al. found that CRP had a sensitivity of only 40% when measured at the time of presentation. Typically, CRP levels in the serum do not increase until up to 24 hours after the onset of symptoms[8]. The sensitivity of CRP rises to 90% when tested 24 hours later. This finding aligns with a study by Mather NJ and colleagues, which demonstrated an increase in sensitivity from 22% to 61% as time progressed after admission[9].Wagle S and colleagues examined CRP in very premature infants and discovered that its sensitivity and specificity increased from 62% and 87.7% on Day 1 to 70.2% and 97% on Day 2[10]. One limitation of our study was that we recorded CRP as either positive or negative, without measuring exact CRP levels, so we cannot assess how CRP titers changed over time in neonatal sepsis.

Chan DK and colleagues established a CRP cutoff level of 7 mg/L, reporting sensitivity and specificity values of 56% and 72%, respectively, along with a positive predictive value of 57% and a negative predictive value of 71%[11]. In our study, CRP was found to be positive in 46.5% of culture-negative cases, while it was negative in 23.7% of culture-proven sepsis cases. In three culture-confirmed cases, CRP was positive at 0 hours, and levels continued to rise at 72 hours despite empirical antibiotic treatment. Clinically, these neonates deteriorated, and two developed fulminant sepsis.

Jave DL proposed that tracking CRP levels over time could be beneficial in evaluating the response to treatment following the initial diagnosis[12]. Their study found that neonates were discharged after receiving 5 days of intravenous antibiotics. Similarly, Jin Cherdze and colleagues concluded that quantitative CRP is a quick and sensitive diagnostic marker for identifying sepsis in preterm infants[13]. Our findings also suggest that CRP is a valuable indicator of neonatal sepsis, as the qualitative CRP status helped in identifying the infection and guiding management decisions.

Given the high mortality associated with neonatal sepsis, treatment is often initiated based on clinical suspicion. In our study, CRP was positive in 20 culture-negative cases, which may be attributed to the administration of intrapartum antibiotics influencing blood culture results. These neonates could not be excluded from the study, as fatal infections have been reported even when blood cultures are negative [14]. Infants with intrapartum risk factors (such as oxytocin use, epidural anesthesia, maternal fever, and meconium-stained amniotic fluid) as well as clinical signs of sepsis were also included. Elevated CRP levels are observed in 50-90% of neonates within six hours of bacteremia; however, these elevated levels are not specific to bacterial infections and can also be

found in other conditions, including asphyxia, shock, intraventricular hemorrhage, surgery, and meconium aspiration.

In this study, the latex agglutination slide test was used to detect CRP. This method is simple, cost-effective, and widely available. A more specific but expensive and time-consuming alternative is radioimmunoassay. According to our study results, CRP alone cannot be regarded as a reliable screening test for early diagnosis of neonatal sepsis. However, it can be incorporated into a broader scoring system. Along with hematologic parameters and clinical criteria, such a scoring system could help reduce unnecessary antibiotic use and minimize delays in starting appropriate therapy. Manucha and colleagues[15] emphasized the importance of a scoring system and evaluated one developed by Rodwell et al.[16] Ahmed Z and colleagues[17] also assessed CRP as a diagnostic marker in combination with hematological parameters. Considering the findings from this study and others, we propose that a panel of experts develop a scoring system for detecting neonatal sepsis. This system should include simple, cost-effective tests in addition to CRP to facilitate early and accurate identification of sepsis in neonates.

CONCLUSION

These results underscore the importance of CRP monitoring as part of a comprehensive diagnostic approach in neonatal sepsis. While CRP alone may not suffice as a standalone diagnostic test due to its limited specificity, its high sensitivity and PPV make it a valuable adjunct in the clinical decision-making process. Timely CRP testing can guide therapeutic interventions and improve outcomes in preterm neonates with suspected sepsis. Future studies integrating CRP with other biomarkers or clinical parameters may enhance diagnostic accuracy and provide more robust strategies for the management of neonatal sepsis.

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