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Assessing the Diagnostic Accuracy of C-Reactive Protein (CRP) in Neonatal Sepsis Detection

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Abstract:

Objective: The purpose of this study was to evaluate how well C-reactive protein (CRP) levels diagnose newborn sepsis.

Methods: At the KRL General Hospital's Neonatology unit, a validation study was carried out over the course of seven months, from February to August 2012. Using purposive sampling, a sample size of 147 neonates was established based on a 95% confidence level, 50% predicted prevalence, 75% sensitivity, 95% specificity, and 10% desired accuracy.

Results: The neonates' mean age was 5.72 days ± 3.86. Of the patients, 81 (55.1%) were male and 66 (44.9%) were female. Through blood culture, 43 neonates (29.25%) had neonatal sepsis confirmed, whereas 104 neonates (70.75%) did not test positive for the condition. When it came to identifying acute neonatal sepsis, CRP's sensitivity and specificity were 76.92% and 53.49%, respectively. 48.94% was the negative predictive value and 80% was the positive predictive value. In terms of identifying neonatal sepsis, CRP had an overall diagnosis accuracy of 70.07%.

Conclusion: Although it lacks specificity, CRP estimation can be helpful in identifying newborn sepsis; nevertheless, it should not be the only method used.

Keywords: C-reactive protein, Neonates, Neonatal Sepsis.

Introduction:

Newborns in underdeveloped nations are particularly vulnerable to septicaemia, which causes high rates of morbidity and mortality. It is typified by systemic infection signs and symptoms, which frequently appear in the first month of life. While late-onset septicemia manifests after the first week, early-onset septicemia happens within five to seven days. Early detection of newborn sepsis is essential for successful therapy; yet, because of its vague symptoms, diagnosis is sometimes delayed. In order to make the best treatment decisions for their neonatal patients, doctors need diagnostic techniques that can quickly and reliably confirm or rule out sepsis. (Shete et al., 2009)

Diagnostic delays are partly caused by the time-consuming nature of conventional diagnostic techniques, such as blood cultures. Furthermore, the diagnosis is made more difficult by the comparatively low prevalence of sepsis confirmed by culture. When combined with additional tests including thrombocytopenia, total leukocyte count (TLC), and absolute neutrophil count (ANC), C-reactive protein (CRP) exhibits potential in the diagnosis of newborn sepsis, especially when it comes to excluding negative instances. However, because CRP is a generic indicator of inflammation, it is not advised to rely too much on it alone for diagnosis. (Mahmood et al., 2002)

An acute-phase protein called CRP was initially identified in 1930 and rises in reaction to inflammation. Elevated CRP levels, although not specific to septicaemia, can identify the illness when paired with clinical signs. Repeated CRP levels help with diagnosis and can monitor the infection's course. But it's important to take into account when CRP rise occurs following infection, since it usually peaks 48–72 hours after inflammation begins. (Shirazi et al., 2010)

The purpose of this research is to assess CRP's diagnostic value for neonatal sepsis and its ability to help determine how long an antibiotic should be used. A single CRP test is often used by healthcare facilities upon admission, which may cause antibiotics to be stopped too soon before peak levels are achieved. Ensuring the effectiveness of qualitative CRP tests is crucial for optimizing antibiotic care and preventing the return of severe sepsis in newborns. This is especially true when the tests are conducted twice, upon admission and 72 hours later. (Tappero & Johnson, 2010)

Methods

At the Maternity and Pediatrics Hospital in Tabuk, a cross-sectional validation research was carried out for the period of seven months, from February 2012 to August 2012. The WHO sample size calculator yielded a sample size of 147 with a 75% sensitivity, 95% specificity, 50% predicted prevalence, 10% desired accuracy, and 95% confidence level. Purposive sampling was used to choose newborns admitted to the neonatology unit after parents gave their informed written agreement and the hospital's ethics council gave its approval.

Included were all infants suspected of having neonatal sepsis and aged 0 to 28 days. Neonatals with clinical and pathological characteristics of perinatal risk factors, such as maternal pyrexia (within 1 week of delivery and/or 48 hours after delivery), prolonged rupture of membranes (18 hours), foul-smelling vaginal discharge, or maternal urinary tract infection diagnosed within the last month, were considered suspected cases of suspected neonatal sepsis. Furthermore, included were infants exhibiting unexplained hypothermia/hyperthermia, lethargy, irritability, poor feeding, respiratory problems, cardiovascular problems, poor peripheral circulation, hypotonia, or circumoral cyanosis or pallor. Babies who had previously received antibiotics, had a history of birth asphyxia, were extremely preterm (less than 32 weeks gestation), or had a very low birth weight (less than 1500 grams) were not included.

Following the laboratory measurement of CRP levels and the collection of blood samples for blood cultures, all included patients received empirical antibiotic medication. To reduce systemic bias, strict aseptic procedures were used for collecting blood samples. Seventy-two hours after the first CRP sample was taken, another one was taken. If the CRP level was less than 5 mg/dl, it was considered negative; if it was greater than 5 mg/dl, it was considered positive. For up to seven days, blood cultures were observed for growth.

The head of the pathology department and lab techs confirmed the CRP measurement results. Data was gathered using a pre-tested data collecting form. Upon admission, patients who had been diagnosed with probable newborn sepsis were put on empirical antibiotic therapy, and the first blood culture and CRP samples were sent for study. Antibiotic medication was continued if the initial CRP result was negative. Antibiotic medication was halted if the results of the second CRP test were also negative. On the other hand, depending on the patient's clinical and pathological

presentation, antibiotic medication was either modified or continued if the second CRP test came back positive. Antibiotic therapy was continued if the results of the first and second CRP readings were positive until culture and sensitivity reports were available to inform the choice of additional treatments.

Characteristics	Neonatal Sepsis on Culture	
	Yes	**No**
Gender		
• **Female**	43 (41.3%)	23 (53.5%)
• **Male**	61 (58.7%)	20 (46.5%)
Patient Age (in days)		
• **<= 5**	66 (63.5%)	25 (58.1%)
• **6 - 10**	27 (26.0%)	15 (34.9%)
• **11 - 15**	6 (5.8%)	1 (2.3%)
• **16+**	5 (4.8%)	2 (4.7%)

Table-I: Gender and age wise distribution of culture results (n=147)

The acquired data were statistically analyzed using SPSS version 20. The age and weight of the newborn were examples of numerical variables for which mean and standard deviation were computed. For categorical variables, such as blood culture results and qualitative CRP, frequency and percentages were shown. Calculations were also made for the sensitivity, specificity, negative and positive predictive values of CRP in identifying infants with culture-proven neonatal sepsis.

RESULTS

147 patients with suspected newborn sepsis were enrolled in this study. 81 patients, or 55.1%, were male, and 66 patients, or 44.9%, were female. Ratio of men to women: 1.22:1.

There were four categories for newborn age, and 91 (61.9%) of them presented in the youngest age group, which is less than or equal to five days. Of the patients, 42 (28.6%) were between the ages of 6 and 10 days, 7 (4.8%) were between the ages of 11 and 15 days, and 7 (4.8%) were older than 15 days. The age range included in the study was 1 to 27 days. The average age was 3.86 ± 5.72 days.

The results' age distribution reveals that 66 neonates, or 63.5%, with sepsis were determined to be younger than or equivalent to five days old. Twenty-seven (26%) of the neonates with sepsis had an age range of six to ten days, six (5.8%) had an age range of eleven to fifteen days, and five (4.8%) had an age range of more than sixteen days.

As indicated in Table I, similarly, 25 newborns (58.1%) with ages less than or equal to 5 days, 15 neonates (34.9%) with ages 6–10 days, 1 neonate (2.3%) with ages 11–15 days, and 2 neonates (4.7%) with ages more than 15 days were found to not have neonatal sepsis.

According to the gender-wise distribution of newborn sepsis on culture results, males were exposed at rates of 58.7% and 41.3%, respectively, higher than females. Details are provided in Table-II. Of the cases, 104 (70.75%) had confirmed neonatal sepsis, whereas 43 (29.25%) did not have confirmation through culture reports.

	Positive	**Negative**	**Total**
CRP Positive	80	20	100
CRP Negative	24	23	47
Total	104	43	147

Table-II: Accuracy of CRP in diagnosis of neonatal sepsis (n=147).

CRP results obtained 72 hours after the initial test showed 100 (68%) positive results and 47 (32%) negative results. At the time of admission, CRP results were 94 (63.9%) positive and 53 (36.1%) negatives. CRP exhibited a positive predictive value of 80% and a negative predictive value of 48.94% when used to diagnose acute neonatal sepsis (after 72 hours of arrival). Its sensitivity and specificity were 769.2% and 53.49%, respectively. As indicated in Table-III, the overall diagnostic accuracy of CRP in the diagnosis of newborn sepsis was 70.07%.

	Value (%)
Sensitivity	76.92
Specificity	53.49
Positive Predictive Value	80.00
Negative Predictive Value	48.94
Accuracy	70.07

Table-III: Validity and predictive outcomes of CRP.

DISCUSSION

The primary and frequent cause of illness and death in neonates is sepsis. The developing world has a far greater incidence. Minimizing morbidity and death can be achieved most effectively by early diagnosis and efficient treatment. The primary causes of the high death rate are delays in diagnosis and treatment initiation. For diagnosis, blood culture is still considered the gold standard. In this context, several inflammatory cytokines, levels of acute phase reactants, and various hematologic markers are employed. The role of CRP in newborn sepsis has been extensively researched among the several tests. (Sakha et al., 2008)

This study examined 147 newborns to determine the validity of CRP in the diagnosis of sepsis. A total of 104 cases of neonatal sepsis with confirmed blood culture results were assessed. The majority of the patients that were assessed exhibited sepsis-related clinical characteristics and established risk factors. In one investigation, CRP was found to have a sensitivity of 58.33% and a specificity of 56.52%. Positive predictive values for the test were 48.27% and 67.74%. (Ahmed et al., 2005)

According to Benitz and colleagues, the test's sensitivity is only 40% when conducted during presentation. The time interval between the start of infection symptoms and the rise in serum CRP is typically as much as 24 hours. A 24-hour delay increases the sensitivity by up to 90%. Research by Mather NJ and colleagues13 found the same thing, with sensitivity rising from 22% to 61% as the amount of time following admission increased. Wagle S. and Colleagues14 investigated the relevance of CRP in sepsis in very young infants and found that on Day 1, CRP had a sensitivity and specificity of 62% and 87.7%, rising to 70.2 and 97% on Day 2. One of our shortcomings was that we didn't measure the precise value of the CRP result; instead, we only recorded the positive and negative results. Therefore, we are unable to remark on the CRP's growing titer in newborn sepsis. (Benitz et al., 1998)

Chan DK and associates (2015) provided a 7 mg/L threshold CRP level. The results were 56%, 72%, 71%, and 57% for the sensitivity, specificity, negative, and positive predictive values, respectively. In our investigation, CRP was found to be positive in 46.5% of cases where the culture was negative and negative in 23.7% of cases when the culture proved sepsis. Despite receiving empirical antibiotic treatment, CRP was detected as positive at 0 hours and increased at 72 hours in three patients

with culture proof. The state of the newborns also declined clinically, and in two instances, the outcome was fulminant sepsis. (Chan & Ho, 1997)

After the initial diagnosis, time can be utilized to assess how the treatment is working. Following five days of intravenous antibiotic therapy, they were sent home. In their investigation, Jin Cherdze and colleagues came to the conclusion that quantitative CRP is a quick and accurate diagnostic tool for spotting sepsis in premature babies. In our investigation, we also discovered that CRP is a useful marker of neonatal sepsis because its qualitative state aids in both diagnosing the condition and determining the patient's course of treatment. (Jin Charadze et al., 2006)

Treatment is frequently started on the suspicion of sepsis because of the death rate linked to newborn sepsis. In 20 infants in this investigation with culture-negative instances, CRP was found to be positive. This might be because intrapartum antibiotics were given, which affected the culture's outcome. Since fatal infections have been documented in the context of negative blood cultures, these newborns cannot be excluded from the study. Similarly, babies with clinical signs of sepsis and intrapartum risk factors (oxytocin-assisted labor, epidural anesthesia, maternal fever, and meconium-stained liquor) were also included. 50–90% of newborns had elevated CRP levels within six hours of the bacteremia starting. Elevated levels are not exclusive to infections caused by bacteria. CRP levels can also rise in the following circumstances: meconium aspiration, hypoxia, shock, intraventricular hemorrhage, and surgery. (Pepys, 1981)

In the study, CRP was found using the latex agglutination slide test. This approach is affordable, simple to use, and easily accessible. The quantitative radioimmuno diffusion approach is an additional method. Although more expensive and time-consuming, it is more precise. The study's findings indicate that while CRP is not an effective screening test for early sepsis diagnosis, it can be included in a scoring system. This grading method ought to incorporate hematologic markers in addition to clinical criteria. This would, on the one hand, lessen the indiscriminate use of antibiotics and, on the other, shorten the time it takes to start medication. In their work, Manucha and colleagues discussed the value of a grading system. The Rodwell et al. grading system was assessed by them. Ahmed Z and associates assessed the function of CRP in conjunction with hematological indicators as a diagnostic marker. (Ahmed et al., 2005) (Manucha et al., 2002)

Based on the findings of our investigation and all of these studies, a panel of experts can develop a score system for the identification of newborn sepsis. Other affordable, easy-to-perform assays should be included in the scoring system in addition to CRP to facilitate the early diagnosis of newborn sepsis.

CONCLUSIONS

While CRP estimation is useful in the diagnosis of newborn sepsis, it is not a reliable enough test to be used as the sole marker. This study's computed values for sensitivity, specificity, positive, and negative predictive values are insufficient to qualify the test as a good screening tool. When assessing a neonate for sepsis, clinical criteria, additional hematological measures, diagnostic markers, and serial CRP should all be taken into account because to the high morbidity and mortality that are linked with it.

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