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NEONATAL SEPSIS;

DIAGNOSTIC ACCURACY OF C-REACTIVE PROTEIN (CRP) IN THE DIAGNOSIS OF NEONATAL SEPSIS.

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ABSTRACT… Objectives: To determine the diagnostic accuracy of C-reactive protein in the diagnosis of neonatal sepsis keeping blood cultures as gold standard. **Study Design:** Descriptive cross-sectional study. **Setting:** Pediatric Unit of Lady Reading Hospital Peshawar Pakistan. **Duration:** Six months from 09-06-2012 to 08-12-2012. **Methodology:** Total of 196 patients meeting the required inclusion criteria with clinical suspicion of sepsis. Those neonates were subjected to investigations. C.R.P. was tested using the Quantitative method according to the instructions provided with the kit. By keeping blood culture as gold standard, patients with both positive and negative cultures were taken and the results compared to the results of C.R.P. in these subjects being positive or negative. **Results:** Among the 196, majority of the neonates included were less than a week old having a mean age of 4.5 days. There were 57 (29%) females and 139 (71%) males, with male to female ratio of 2.4:1. Blood cultures were positive in 85 (43%) and negative in 111 (57%) cases, while C.R.P. was positive in 95 (48%) and negative in 101 (52%) cases. Sensitivity, specificity, and positive and predictive values of C-reactive protein were calculated using formulas, and they turned out to be 77.6%, 73.8%, 69.4%, and 81.2% respectively with accuracy being 0.41%. **Conclusion:** An accurate and timely diagnosis of early onset neonatal sepsis remains challenging to the clinician as well as laboratory. Physicians can prevent unnecessary antibiotic use by performing the qualitative estimation CRP as a single, rapid and inexpensive test with a negative predictive value of 81.2%.

Key words: Blood Culture, C-reactive Protein, Diagnostic Accuracy, Neonatal Sepsis.

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INTRODUCTION

Infections are the leading cause of morbidity among neonates, and neonatal sepsis keeps raising the red flags remaining a major contributor to their morbidity and mortality.[1]The problem of neonatal sepsis is prevalent worldwide. Every year around 30 million neonates develop infections and 1-2 million of these neonates die.[2] In developing countries mortality from neonatal sepsis is 10.4%, higher than that in the developed countries having an incidence of 0.69 deaths/1000 live births.[3] The statistical data from Pakistan is largely unavailable but according Indian National neonatal perinatal database, the incidence of neonatal sepsis per 1000 live births is 30 with an overall neonatal death rate of 30-50% in the developing countries. The problem of such high sepsis related mortality in neonates can be minimized by adopting aggressive approach towards this disease.[4]

Neonatal sepsis causes a systemic inflammatory response with some non-specific signs and symptoms or focal signs of infection. It carries potentially fatal complications affecting major organ systems including cerebral edema or thrombosis, adrenal hemorrhages, bone marrow dysfunction and disseminated intravascular coagulation.[4] It has a high fatality rate if not treated properly. Thus with non-specific initial presentation, a high index of suspicion must always be kept for early diagnosis and favorable outcome.[5]

Performing blood culture and sensitivity test is always a gold standard in the diagnosis of neonatal sepsis.[4] Culture reports have shown that organisms like *Escherichia coli, klebsiella*

pneumonia, *Staphylococcus aureus*, *S. pneumonia* and some group B streptococci are common pathogens involved with some gram negatives predominance.[6] Unfortunately blood culture and sensitivity test takes 48-72 hours to get the results, and investigators have developed a panel of some simple, rapid and inexpensive tests to be able to confirm neonatal sepsis accurately than blood culture alone.[7]

To diagnose a serious and life threatening yet treatable illness, such as neonatal sepsis, a rapid diagnostic test with maximal sensitivity and negative predictive value is always desirable. A few hematological parameters (HP) have been a subject of debate. The frequently used parameters are increase or decrease in leukocyte count, with sensitivity of 35% and specificity of 77%, increase or decrease in total neutrophil count, with sensitivity of 35% and specificity of 74%, reduced platelet count with sensitivity of 61% and specificity of 82% and C-reactive protein with sensitivity and specificity of 23% and 84% respectively with overall prevalence of neonatal sepsis of 34.8%.[7]

Currently other diagnostic markers are also being evaluated those include procalcitonin[8], acute phase reactants, bacterial genomes and inflammatory cytokines[9], and CD 64 neutrophil cell surface marker.[10]

The present study was performed to find the diagnostic accuracy of C-reactive protein estimation in neonatal sepsis, keeping blood cultures as gold standard. The rationale behind this study is that C.R.P. is simple and easily interpretable parameter. The results can be easily and quickly comprehended and clinically correlated. This study shows significant sensitivity and specificity of CRP in diagnosing neonatal sepsis and may be recommended as a routine diagnostic test for neonatal sepsis. CRP is relatively rapid and cost effective as compared to blood cultures which take longer time, and are expensive for the patients.

METHODOLOGY

This study was done in Pediatric Unit, Medical Teaching Institution LRH Peshawar, Pakistan for six months from 09-06-2012 to 08-12-2012. A total of 196 neonates with drowsiness, reluctance to feed, hypothermia (<35°C), fits or breathing difficulty, neonates of mothers who had high grade fever and or foul smelling discharge at the time of delivery of either gender were included in the study with suspicion of sepsis clinically. Neonates who had received oral or parenteral antibiotic therapy, whose mothers had narcotic analgesics during labor and those with congenital heart disease, were excluded from our study.

Prior approval of the study was taken from hospital ethical and research board. All neonates meeting the inclusion criteria (reluctance to feed, hypothermia, drowsiness, fits or breathing difficulties) were included in the study through O.P.D. or labor room. All the guardians of neonates were properly explained the purpose of our study and the data usage, and their informed written consent was obtained before the study.

Demographic information i.e. name, gender and age were recorded and a thorough clinical history and detailed physical examination was done. Some required baseline investigations were performed in all included neonates. Under strict aseptic technique 10 cc of blood was obtained from all neonates and was sent to hospital laboratory to detect neonatal sepsis on the basis of C.R.P. and later blood cultures were performed to confirm the presence of neonatal sepsis. All the laboratory investigations were done under supervision of single expert pathologist having minimum of five years of experience.

All procedures and interventions were performed under the principles of medical ethics and codes of conduct, and none was harmful to the neonates. The above mentioned information were all recorded in a pre-designed proforma.

Laboratory data was recorded and then analyzed through SPSS version 21 using study variables of age, gender, CRP, neonatal sepsis and blood culture report. Mean + standard deviation, frequencies and percentages were calculated. Sensitivity, Specificity, PPV and NPV were

calculated taking blood cultures as gold standard.

RESULTS

Majority of neonates included in this study were below one week of age with a mean of 4.5 days (Table-I).

Of the study subjects, there were 57 females and 139 males, the percentage being 29% and 71% respectively and male to female ratio was 2.4:1(Table-II)

Among them, blood culture revealed sepsis in 85 (43%) cases and was negative in 111 (57%) of neonates with a clinical suspicion of sepsis. Out of 196 neonates, CRP was positive in 95 (48%) and negative in 101 (52%) included neonates. (Table-III).

From those with negative blood culture, CRP was negative in 82 cases (73.8%), being True Negative and C.R.P. was positive in 29 cases (26.1%), being False Positive. (Table-V).

The sensitivity, specificity and predictive values positive as well as negative of C-reactive protein were obtained according to formulas, and they turned out to be 77.6%, 73.8%, 69.4%, 81.2% respectively as shown (Table-V) diagnostic accuracy of CRP being 75%.

Majority of the cultured pathogens were gram negative. The most common was *E. coli* followed by *klebsiella pneumoniae*. *S. aureus* and *S. Epidermidis* were the commonest organisms respectively among gram positive pathogens.

Age in days	Frequency	Minimum	Maximum	Mean	Std. Deviation
0-29	196	1.00	17.00	4.5714	3.80283

Table-I. Baby age

Gender	Frequency	Percentage
Female	57	29.1
Male	139	70.9
Total	196	100.0

Table-II. Gender of babies

	Blood Culture		CRP	
	Frequency	Percentage	Frequency	Percentage
Positive	111	57	95	48
Negative	85	43	101	52
Total	196	100	196	100

Table-III. Blood culture and CRP

	Blood Culture		
CRP	Positive	Negative	Total
Positive	66	29	95
Negative	19	82	101
Total	85	111	196

Table-IV. CRP and blood culture correlation

Sensitivity	(a / a + c) x100	77.6%
Specificity	(d / b + d) x 100	73.8%
P.P.V.	(a / a + b) x100	69.4%
N.P.V.	(d / c + d) x100	81.2%
Accuracy of C.R.P.	(d + a) / overall patients	75 %

Table-V. Sensitivity, Specificity, P.P.V, N.P.V. and Diagnostic Accuracy of C.R.P.

DISCUSSION

Worldwide, around 4 million neonates die annually due to different morbidities as estimated by the World Health Organization.[11] In the developing countries, neonatal infections cause almost 1.6 million mortalities yearly where sepsis and meningitis are the main cause for most of these deaths.[12] Newborns have a weak immune system which render them prone to infections. Furthermore, newborns mostly deteriorate rapidly after infections and any failure or delay in their treatment may cause significant mortality and morbidity, hence necessitates an efficient diagnosis for the clinicians which is rather challenging.[13]

Traditionally, diagnosing neonatal sepsis includes some hematological investigations including CRP. Sensitivity and the diagnostic ability of these hematological parameters vary widely in the literature. Since, a challenging part in the management neonatal sepsis is an accurate and timely diagnosis for the clinicians, a test with quick turnaround time and high sensitivity allowing accurate diagnosis is desirable for proper treatment. Usually a reasonable specificity of a test is always needed to safely quit antibiotics therapy in non- infected neonates.[13]

Major problem in diagnosis of neonatal sepsis for a clinician is the identification of infected and non-infected infants, because of its nonspecific clinical presentation in this age group.[5]

This study evaluates the usefulness of CRP as a disease marker in neonatal septicemia. CRP is a simple and easy to perform test, and the results are readily available to the clinicians taking blood culture as gold standard. In our study CRP was analyzed by qualitative method using a cut off level of 5mg/dl.

The study was done on 196 full term neonates. Majority of the subjects studied were less than a week old with a mean of 4.5 days similar to a mean age of 4 days given by Khurshid et al.[14]

There were 139 males and 57 females in this study, the percentage being 71% and 29% respectively, which was closer to 65% males and 35% females in a study by West et al.[15] Male to female ratio is 2.4:1, while the ratio varies from 1:1to a few showing a malepredominance,.[16] The reason may be that male preponderance in neonatal septicemia is associated with the X-linked immune regulatory gene factor contributing to the host's susceptibility to infections in males.[5]

Out of 196 study subjects, blood cultures were positive in 43% and negative in 57%. This is similar to 43% positivity given by West et al.[15] and closer to 42% culture positive cases in a study conducted by Khurshid et al.[14] The number percent of culture positive cases in this study were however higher than 34.7% by Shirazi H et al[7] and 28% by Zeeshan et al.[17] In another study by Sriram R,[5] 58 out of 115 cases were culture positive, with 50.4% and 57 were negative with 49.6%.

In our study, 111 neonates had signs and symptoms of sepsis but lacked microbiologic proof. Culture negative cases pose a diagnostic and therapeutic dilemma and could not be ignored because fatal sepsis have been reported.[18] This study showed CRP to be positive in 48% cases, higher than 39% positivity of Shirazi H et al[7] and it was negative in 52% of cases.

Among neonates with proven sepsis, having positive blood culture, C.R.P. was positive in 77.6%, these being True Positive and C.R.P. was negative in 22.3%, designated as False Negative. Khurshid et al.[14] has documented positive CRP in 66.66 % of culture positive while it was negative in 33.33% of culture proven sepsis. West et al[15] demonstrated 74% positive CRP in neonates with positive blood culture while 26.0% had negative CRP.

We did not distinguish between the culture yield of neonates by segregating them in groups of early and late onset sepsis. As has been done by Kumar et al[16] hence analyzing the utility of CRP on the basis of onset in the sepsis as well.

The sensitivity of 77.6 %, specificity of 73.8% and a higher negative predictive value of 81.2 %, in

our study, implies that around three quarters of suspected neonates will be diagnosed correctly by CRP estimation. This means, that one out of every four neonates with sepsis have a possibility a false negative result. This value is higher for making a decision not to start empirical antibiotic therapy for a suspected septic neonate, particularly when CRP is estimated keeping blood culture gold standard, and its positivity may represent only a proportion these subjects.[19] Particularly, if a neonate is given antibiotics before presenting to the clinician as is common in our setup or if mother is given antibiotics intra-partum. A negative CRP test in neonates without clinical feature is helpful in making decision to discontinue antibiotics, thus facilitating early discharge with significant reduction in complications and cost of treatment.[20]

Our study shows that neonates with suspected sepsis, having negative blood culture results, C.R.P. was negative in 73.8%, being true negative and C.R.P. was positive in 26.1%, being False Positive. Similarly West et al,[15] showed that among neonates with suspected sepsis, 46.7% were positive and 53.3% were negative for CRP test giving the sensitivity, specificity and predictive values (positive and negative) of 74.0%, 74.1%, 68.4% and 79.0%, respectively.

While in the study done by Khurshid et al.[14] the sensitivity of CRP was 95.2%, specificity 85.3%, positive predictive value 80.6%, and negative predictive value was 96.5% and overall accuracy given by them was 96.5% in proven sepsis.

Similarly Ahmad et al.[17] demonstrated a bit higher values, that CRP was positive in 85.7% of proven sepsis and 80.5% probable sepsis and had a specificity of 95%. And in another study by Nakamura et al.[21] the specificity of CRP was 85% while the sensitivity was 72% in patients with sepsis. While Shirazi H et al[7]reported the sensitivity of CRP as low as 23% and there was not a good correlation with the sepsis.

The reported CRP sensitivity in bacterial infection is varied in the literature ranging from 47 to 100 percent. The differences in the reports of this parameter shown in different studies seems to be due to the variations in their diagnostic criteria, the duration of infection and different CRP estimation methods used.[5]

In positive blood culture cases in our study majority of the isolates were gram negative organisms, E. coli being the commonest organism, followed by klebsiella pneumoniae and among the gram positive organisms Staph aureus is the commonest organism followed by staph epidermidis. Similar to our study, data from Pakistan reveal that S. aureus, Klebsiella, and E. coli are the common organisms isolated in neonatal units at Karachi and Peshawar.[22] However, correlation of CRP positivity with respect to the type of organism isolated was not analyzed in our study.

CRP has moderate sensitivity and specificity and with diagnostic accuracy of 75% it can reliably predict the sepsis in patients who are awaiting blood culture results. With a high negative predictive value of 81.2% it can reliably exclude the neonatal sepsis and guide antibiotic therapy preventing unnecessary treatment. However, when combined with other parameters like total leukocyte count, neutrophil count, platelet count, ESR the diagnostic utility of CRP can be considerably enhanced. Performing serial determinations of CRP levels can also improve the diagnostic value as CRP levels take a few hours to reach maximum levels but we were unable to do so due to poor resources and financial constraints. To improve the accuracy of this test, a large data set with a large sample size is needed, where more neonates could be registered from multiple centers.

Thus, CRP shown to be an accurate indicator of sepsis. In countries like Pakistan, all neonates with a suspicion of infection must be screened with this test, and it can help us to predict the neonatal sepsis reliably and early.

CONCLUSIONS

The C-reactive protein is an accurate indicator of neonatal sepsis. An early and accurate diagnosis of neonatal sepsis is always challenging for the

clinician, and estimation of CRP through laboratory has been thoroughly evaluated in several studies. The qualitative estimation of CRP is a quick, simple and less expensive method to diagnosis; moreover, the results are readily available. With moderate sensitivity and specificity of 77.6% and 73.8% respectively and diagnostic accuracy of 75% it can reliably predict the neonatal sepsis in cases of clinical suspicion. The high NPV of 81.1% can help to exclude the sepsis and prevent unnecessary antibiotic therapy. The C - reactive protein can therefore be used to initiate treatment till the availability of blood culture results.

The C-reactive protein estimation is a simplified invaluable method in the management of infections in neonates of the resource poor health facilities where blood culture may not be possible. In countries like Pakistan, all neonates with suspected sepsis should be screened with this test, and it can help us to predict the neonatal sepsis reliably and early.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Mohsin Hayat	Methodology, result, Discussion and references.	
3	Hina Parvez	Helped in data collection, analysis and manuscript writing.	
4	Ihsan Ullah	Data analysis, review as pathologist proof reading and final correction.	
5	Zia ur Rehman	Abstract, discussion and conslusion.	