ORIGINAL ARTICLE

Validity of C-Reactive protein in neonatal sepsis

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ABSTRACT

Aim: To evaluate the validity of C-Reactive Protein(CRP) in neonatal sepsis keeping blood culture as gold standard.
Study design: It is a cross sectional study of newborns with suspected sepsis.
Place and duration: The study was conducted in Newborn Intensive Care Unit, Department of Paediatrics Rangers Teaching Hospital, Lahore, from 1st November 2018 to 30th October 2019.
Methodology It was a cross sectional study of newborns with suspected sepsis. The study was conducted in Newborn Intensive Care Unit, Department of Paediatrics, Rangers Teaching Hospital, Lahore, from 1st November 2018 to 30th October 2019. 60 neonates (0-30 days of age) with clinical signs and symptoms suggestive of infection with positive blood culture were included in the study. CRP as a screening test was performed along with blood culture. Blood culture was considered as a gold standard. All neonates with clinical signs and symptoms suggestive of infection with positive blood culture were included in the study. Neonates who had already received antibiotic treatment for the same disease or during the same admission were excluded. After explaining the procedure and obtaining consent from the parents, neonates presenting with clinical suspicion of infection and culture proven sepsis were included in the study.
Results: In this study, a total of 60 neonates were studied, 36 patients were culture positive. Of these 21 were CRP positive also (Table 1). 10 neonates with positive CRP were culture negative. 15 subjects were culture positive with negative CRP. 14 neonates were both culture negative and CRP negative. Among the 36 patients with culture proven sepsis, 20(55%) were males while 16(44.44%) were females. 25 subjects (69.44%) were less than 5 days old. Mean age of onset was 4 days (range 1-25 days).
Conclusion: We concluded that the sensitivity, specificity, positive and negative predictive values as calculated in this study are not high enough to make it a good screening test. Considering the high morbidity and mortality associated with it, clinical criteria along with other hematological parameters and diagnostic markers along with CRP should be considered in evaluating a neonate for sepsis.
Keywords: C-reactive protein, Neonates, Neonatal Sepsis.

INTRODUCTION

The incidence of neonatal sepsis is 1-21 newborns out of 1000 live births with mortality rates as high as 30-69%[1]. It is a common cause of morbidity and mortality amongst the neonates. Exact diagnosis based on clinical signs and symptoms, is difficult as these are nonspecific[1,2]. Traditional methods like blood culture do not give a rapid diagnosis. Therefore, to lessen the morbidity and mortality associated with it, early diagnosis is important. Early diagnosis is largely based on the measurement of serum concentration of different mediators of systemic inflammation, as well as on a group of proteins[3]. Among these, C-reactive protein (CRP) has been the most extensively used and investigated so far. The sensitivity and specificity of CRP for neonatal sepsis keeping blood culture as gold standard in one study was 66.6% and 48.27 percent respectively[4] .C-reactive protein (CRP) is an acute phase protein synthesized in the liver in response to inflammatory cytokines. Its level may rise upto 1000 fold during an acute phase response[3,4]. It's short half life (19 hours) means level should fall rapidly after elimination of the source. There is generally a delay of upto 24 hours between onset of symptoms and a rise in CRP. A level 6mg/L has been shown to be the cut off to indicate sepsis.

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There is a link between the level of elevation of CRP and the risk of sepsis[4]. Serial CRP has been shown to be more useful than a single measured CRP.

In diagnostic evaluation of neonates with suspected infection[2] certain risk factors are involved in neonatal sepsis. These are prematurity, low birth weight, premature rupture of membranes, maternal infection, invasive medical procedures and prolonged hospital stay. Important clinical findings associated with neonatal sepsis are reluctance to feed poor reflexes temperature instability, respiratory distress, Jaundice, irritability, abdominal distention and unexplained apnea or cyanotic spells. These finding along with a rise in CRP are mainly used as criteria for treating a suspected case of neonatal sepsis. As CRP levels rapidly falls after elimination of infection, it enables earlier discontinuation of antibiotics[5]. In patients with inadequate initial antibiotic therapy, serum CRP levels increase further during the second day of treatment, indicating the need for the replacement of initial antibiotics[5]. Discontinuation of antibiotic treatment is also primarily based on return of normal CRP levels[6]. The aim of my study is to find out validity of CRP in neonatal sepsis, thus treating the infection at its earliest reducing there by the high mortality and morbidity associated with it. C reactive protein (CRP) is a native protein synthesized in the liver[7].

MATERIAL AND METHODS

It was a cross sectional study of newborns with suspected sepsis. The study was conducted in Newborn Intensive Care Unit, Department of Paediatrics, Rangers Teaching Hospital, Lahore, from 1st November 2018 to 30th October 2019. 60 neonates (0-30 days of age) with clinical signs and symptoms suggestive of infection with positive blood culture were included in the study. CRP as a screening test was performed along with blood culture. Blood culture was considered as a gold standard. All neonates with clinical signs and symptoms suggestive of infection with positive blood culture were included in the study. Neonates who had already received antibiotic treatment for the same disease or during the same admission were excluded. After explaining the procedure and obtaining consent from the parents, neonates presenting with clinical suspicion of infection and culture proven sepsis were included in the study. A detailed history about the mode of delivery, antenatal and post natal risk factors were noted. A printed proforma containing a comprehensive record was filled in each case. Blood Culture, Complete Blood Picture and CRP at 0 and 72 hours were performed.

RESULTS

In this study, a total of 60 neonates were studied, 36 patients were culture positive. Of these 21 were CRP positive also (Table 1). 10 neonates with positive CRP were culture negative. 15 subjects were culture positive with negative CRP. 14 neonates were both culture negative and CRP negative. Among the 36 patients with culture proven sepsis, 20(55%) were males while 16(44.44 %) were females (Fig. 1). 25 subjects (69.44%) were less than 5 days old. Mean age of onset was 4 days (range 1-25 days) (Table 2).

CRP as screening test: Positive CRP was found in 21 neonates of culture positive cases and in 10 (45.83%) of culture negative cases. Sensitivity of the test was calculated as 58.33%. Specificity was 56.52% while positive predictive value and negative predictive value was 67.74 and 48.27% (Table 3). Serial estimation of CRP: In 21 cases of positive CRP with culture proven sepsis, 17(80%) had a fall in CRP values at 72 hrs. 3 had a rise in CRP level at 72 hours and their condition deteriorated clinically.

Figure 1: Percent of Gender distribution in the study

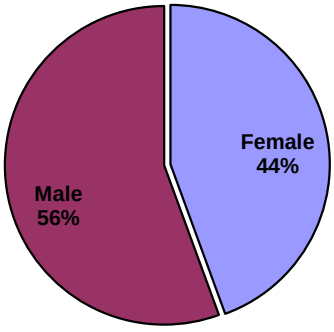

Table 1: Total percentage of blood culture positive neonates out of 60 studied

Blood Culture Result	n	%age
Positive	36	60
Negative	24	40

Table 2: Age distribution of blood culture positive cases

Age (days)	n	%age
< 5	25	69.44
> 5	11	30.56

Table 3: CRP as a screening test

Perinatal risk factors	Clinical risk factors
Sensitivity	58.33%
Specificity	56.52%
Positive Predictive Value	67.74%
Negative Predictive Value	48.27%

DISCUSSION

Neonatal sepsis is the major and common cause of morbidity and mortality. The incidence is much higher in the developing world. Early diagnosis and effective treatment is the best way to lessen the mortality and morbidity associated. The delay in diagnosis and initiating therapy are the main reasons for high mortality. Blood culture is still regarded as a gold standard for diagnosis. Different hematologic parameters, multiple inflammatory cytokines and acute phase reactants levels are oftenly used in this regard. Among the various tests CRP role in neonatal sepsis has been vastly studied.

In this study, validity of CRP in the diagnosis of sepsis was studied. 60 cases of neonatal sepsis were confirmed on blood culture and clinically diagnosed, were evaluated. 36 out of 60 i.e 60% were culture proven sepsis. Most of the patients evaluated had the known risk factors and clinical features associated with sepsis. Initial CRP level was followed by a repeat level at 72 hours of admission. Blood culture was performed in each case. According to the study conducted, CRP had the sensitivity and specificity of 58.33% and 56.52% respectively. The test had a positive predictive value of 67.74% and 48.27%. In a similar study conducted by Mustafa S and colleagues.[4] Sensitivity, specificity, positive and negative predictive value were 60%, 78.94%, 60% and 31.57% respectively.

It was stated in a study by Benitz and colleagues[8] that the sensitivity of the test is only 40% if performed at presentation. There is generally a delay of upto 24 hours between the onset of symptoms of infection and a rise in serum CRP. The sensitivity is increased upto 90% if performed 24 hours later. The same was observed in a study by Mather NJ and colleagues[9] showing a sensitivity rise from 22% to 61% with increasing time after admission.

Wagle S and Colleagues.[10] studied the role of CRP in sepsis in very immature babies and documented that the sensitivity/specificity of CRP on Day 1 was 62% and 87.7% increasing upto 70.2 and 97% on Day 2. Chan DK and colleagues[11] gave similar result at a cutoff CRP level of 7mg/L. The sensitivity, specificity, negative and positive predictive values were 56%, 72%, 71% and 57%. In our study CRP was found positive in 58% of culture negative cases, while it was negative in 41% of culture proven sepsis. In 3 culture proven cases, CRP was found positive at 0 hours and its level raised at 72 hours detection inspite

of empirical antibiotic treatment. Clinically the condition of neonates also deteriorated, end result was fulminant sepsis in two cases.

Keeping in view the mortality associated with neonatal sepsis, treatment is often initiated on suspicion of sepsis. In this study CRP was found positive in 10 infants in culture negative cases. This could be due to the administration of intrapartum antibiotics, influencing the result of culture. These neonates cannot be excluded from the study because fatal infection has been reported in the presence of a negative blood culture[4]. Similarly infants with intrapartum risk factors and clinical features of sepsis were also included. Raised CRP levels are found in 50-90% of neonates from six hours of onset of bacteremia. Raised levels are not specific for bacterial infection[12]. Other conditions in which CRP levels are raised are asphyxia, shock[13,14]. Intraventricular hemorrhage, surgery and meconium aspiration. This observation rules out the role of CRP as the only indicator of sepsis. Latex agglutination slide test was used for the detection of CRP in the study. It is an easy to perform, economical and readily available method. Other technique available is the quantitative radioimmuno diffusion technique. It is more specific but costly and time consuming.

As per results of the study, CRP cannot be regarded as a good screening test for early diagnosis of sepsis but can be made part of a scoring system. Hematologic parameters along with clinical criteria should also be included in this scoring system. This would decrease the indiscriminate use of antibiotic on one hand and lesser the delay in initiation of therapy on the other.

CONCLUSION

We concluded that the sensitivity, specificity, positive and negative predictive values as calculated in this study are not high enough to make it a good screening test. Considering the high morbidity and mortality associated with it, clinical criteria along with other hematological parameters and diagnostic markers along with CRP should be considered in evaluating a neonate for sepsis. CRP levels also increases in a variety of conditions in the initial hours of life. Its validity can be increased if it is performed after 24 hours. It should be repeated serially to access the severity of disease and its response to treatment. In the study, CRP continued to rise in cases of severe sepsis. Initial empiric antibiotics were replaced. The response to treatment was judged by its level returning to normal

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