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Frequency of Raised C - Reactive Protein in the Diagnosis of Clinically Suspected Neonatal Sepsis

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ABSTRACT

Introduction: Despite increasing knowledge of pathophysiology and modern therapeutic approaches, the mortality and morbidity associated with Neonatal sepsis remains alarmingly high. Its clinical features are non-specific and can be confused with many other diseases. This study is done to find out some rapid and reliable diagnostic tool in early detection of neonatal sepsis, thereby allowing prompt management and treatment of suspected cases. **Objective:** To determine the frequency of raised C - reactive protein in the diagnosis of suspected neonatal sepsis. **Study design:** Cross sectional survey. **Setting:** neonatal unit of pediatric medicine department of Chaudhry Rehmat Ali Memorial Trust Hospital Lahore, Pakistan. **Duration of study:** Six months from 01-10-2012 to 31-03-2013. **Sample size:** The calculated sample size is 140 cases. **Sampling technique:** Non probability purposive sampling. **Data collection procedure:** Data was collected by taking the history and physical examination of cases admitted in neonatal unit. C reactive protein was checked at bedside through quick read commercially available kits. Data was analyzed through SPSS version 12 and entered in Proforma. **Results:** Majority of neonates in our study population; 66 among 84(79.4%) with early onset sepsis (with in first 3 days of life) and 48 among 56 (85.7%) with late onset sepsis (4 to 28 days) has raised C reactive level for i - e ≥6 mg%. **Conclusion:** CRP is a readily available, inexpensive, reliable and highly sensitive marker in detection of neonatal sepsis.

Keywords: C- reactive protein, neonatal sepsis, septicemia, early onset sepsis, late onset sepsis.

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INTRODUCTION

Neonatal sepsis is the leading cause of admissions in neonatal units[1,2]. In the developed world, 10% of the infants have infection in their first month of life[3]. It is three times more common in the developing world like Pakistan mainly due to poor antenatal care, home deliveries and poor sterilization in labor rooms[4]. Term male infants have found to have higher incidence of sepsis as compared to female term infants[3]. Around 5 million neonates die each year among which 20% die due to neonatal sepsis and most of these deaths occur in Asia and Africa[5]. Neonatal sepsis has vast spectrum of etiologies and clinical manifestations. Neonates with sepsis may have non-specific signs and symptoms with focal signs of infection like fever, hypotension, apnea, respiratory distress, grunting, lethargy, irritability, seizures, feeding intolerance, abdominal distention, jaundice, purpura and bleeding issues[3].

Although serious efforts have been done to device clinical criteria for the diagnosis of neonatal sepsis and other serious infections in children[6–8], but still the clinical signs mimics so much with other causes that definite diagnosis could not be made with confidence. Therefore a lot of diagnostic tools are available for the diagnosis[9–11]. A definite diagnosis is usually based on culture of blood, urine and CSF. However culture report is not available before 24-48 hours. It is wise to start the antibiotics before the result of culture reports, if the clinical suspicion of neonatal sepsis is very high. Still, significant number of patients may have negative blood culture, and require other investigations for supporting the suspicion of diagnosis and managing accordingly[3,9].

Serum concentrations of many acute phase reactants rise with onset of infection. These can be used in the diagnosis of bacterial sepsis including C-reactive protein, multiple leukocyte activation markers like IL-6, IL-8, TNF-alpha and Procalcitonin[9,12,13]. C reactive protein is a non-specific acute phase protein that rises in response to inflammatory process. Sufficient evidence exists to support the use of C-reactive protein measurement in conjunctions with others established diagnostic tests, such as total and differential leukocytes count and blood culture to establish or exclude the diagnosis of sepsis in full term or near term infants[14–18]. Risk factors for neonatal sepsis like rupture of membranes for > 18 hours, labor for more than 12 hours and maternal fever are associated with early rise in CRP level. So measurement of CRP level can help as early as at birth[19]. C reactive protein has the highest sensitivity of 85.7%, frequency of 80.5% and specificity of 95%[14]. CRP levels rise with onset of infection and decreases with subsiding infection. So, treatment of neonatal sepsis can also be guided by CRP levels. Antimicrobial therapy can be stopped when CRP value returns back to normal[20,21]. Pakistan, where most of the parents belong to low socioeconomic status, cannot afford the high cost of specialized tests and empirical antibiotic treatment. CRP can be used as a tool for early and cost effective diagnosis of neonatal sepsis, thereby ensuring prompt treatment and decreased mortality and morbidity.

Objective

To determine the frequency of raised C - reactive protein in the diagnosis of suspected neonatal sepsis.

METHODOLOGY

Study design: Cross sectional survey

Setting: Neonatal unit of pediatric medicine department of Chaudhry Rehmat Ali Memorial Trust Hospital Lahore, Pakistan.

Duration of study: Six months from 01-10-2012 to 31-03-2013.

Sample size: The calculated sample size is 140 cases, with 6% margin of error,95% confidence level taking percentage of raised C-reactive protein in clinically suspected cases of neonatal sepsis up to 80.5%

Sampling technique: Non probability purposive sampling

Inclusion criteria:

- Both genders
- Gestational age between 33-42 weeks
- Clinical signs of neonatal sepsis as explained in operational definition

Exclusion criteria:

- Babies with congenital malformations detected on clinical examination
- Lab evidence of inborn error of metabolism
- History of birth asphyxia
- Hemolytic jaundice on the basis of laboratory and clinical evaluation
- Patient already on antibiotics
- Meconium aspiration syndrome diagnosed on clinical grounds

Data collection procedure

One hundred and forty cases with suspicion of neonatal sepsis admitted in neonatal unit of Chaudhry Rehmat Hospital from OPD, obstetrical unit and referred from other hospitals were included in the study. Demographic information including name, age, gender, address, and contact numbers were recorded. An informed consent was obtained from their parents for including them in the study and using their data in research. They were ensured that there is no risk involved to the babies. Information regarding the antenatal, natal and post-natal events was obtained. Detailed history about the presenting complaints and detailed physical examination was done. Blood sample for C-reactive protein was collected at the time of initial evaluation before giving antibiotics. Quantitative C-reactive protein value was tested through quick read C-reactive protein(QR-CRP) commercially available kits at bed site. Value of > 6 mg /dl was taken as raised as per kit manual. All the information was recorded in predesigned Performa.

Data analysis:

All the collected information was entered and analyzed using SPSS version12.0. The quantitative variables were presented by calculating mean and standard deviation. The qualitative variables like gender or positive cases of raised C-reactive protein were presented by calculating frequency and percentage.

RESULTS

In this study a total of 140 cases of neonatal sepsis suspected on clinical grounds were included. There were 84 (60%) male babies and 56 (40%)female babies (Table 1).

Refusal to feed was the most common (65%) presenting complaint. Other complaints were respiratory distress (46%), lethargy (50%), fits

(20%), vomiting (18%), irritability (30%), diarrhea (15%), jaundice (15%), bleeding diathesis (12%) and fever in 40% patients (Table 2).

Table 1: Gender distribution of neonates with suspected sepsis.

Gender	Number	Percentage
Male	84	60%
Female	56	40%

Temperature instability (51%) was the most common sign followed by poor sucking (45%) tachycardia (20%) hypotension (15%) poor perfusion (30%) cyanosis (5%) bradycardia (9%) grunting (5%) apnea (5%) and abdominal distention (3%).

Table 2: common clinical presentations (symptoms) in babies with Sepsis

Clinical presentation	No. of patients	Percentage %
Refusal to feed	91	65
Respiratory distress	65	46
Lethargy	70	50
Seizures	28	20
Vomiting	25	18
Irritability	42	30
Jaundice	21	15
Bleeding	17	12
Fever	56	40

Among total of 140 babies, C-reactive protein was positive in 81.4%. Majority of neonates in our study population 66 among 84(78.5%) with early onset sepsis (within three days of life) and 48 among 56 babies (85.7%) with late onset sepsis (between 4 to 28 days) had raised C-reactive protein level i-e > 6mg (Table 3).

Table 3: Distribution of raised C reactive protein in cases of Early onset sepsis(EOS) and Late onset sepsis (LOS)

Cases	Number	Raised CRP	Percentage
EOS	84	66	78.5%
LOS	56	48	85.7%
Total	140	114	81.4%

Mean age±SD at the time of presentation was 6.92±1.66 days. Majority of the babies 84 (60%) presented in three days after birth (early onset neonatal sepsis) while 56 (40%) presented between 4 to 28 days (late onset neonatal sepsis) (Table 4).

Table no 4: distribution of clinically suspected cases of neonatal sepsis with age.

Age	Number	Percentage
< 3 days	84	60%
4- 28 days	56	40%

The mean weight ±SD was 2.9± 0.319kg. In our study group 104 babies (74%) were delivered through spontaneous vaginal delivery(SVD)and 36 babies (26%) through caesarian section (figure 1). Most of these 78 babies (56%) were born at home while 32 babies (23%) were delivered at public hospital and 30 babies (21%) in private hospital (figure 2).

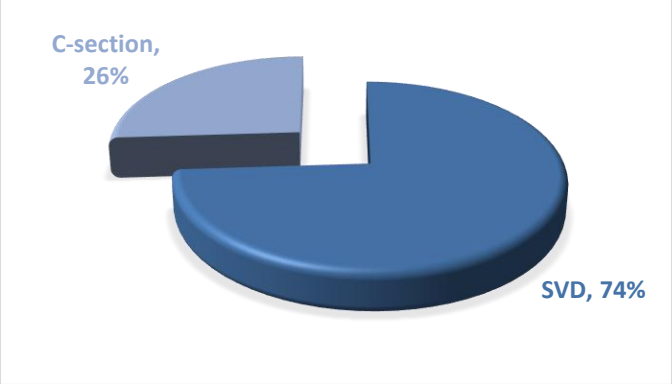

Figure 1: Distribution of neonatal sepsis based on mode of delivery

SVD= Spontaneous Vaginal Delivery, C-Section= Cesarean section

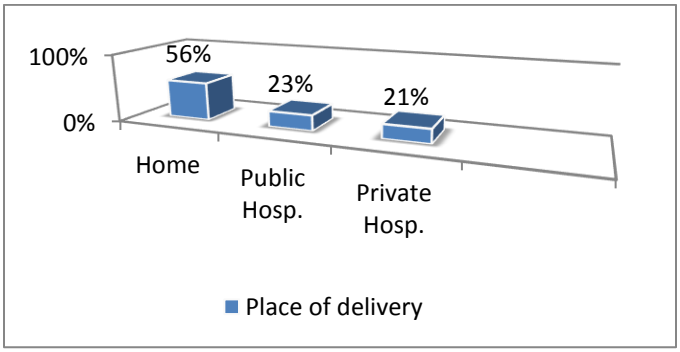

Figure 2: Distribution of neonates with suspected neonatal sepsis according to place of birth

DISCUSSION

World Health Organization estimates that 6.3 million children died in 2013 in their first 5 years of life and among these 51.8% died because of infectious causes.[22] Above recorded deaths were less as compared to previous data of 2010 where the death below 5 years of age were 7.6 million, and 64 % were attributed to infectious causes.[23] Most of these deaths are occurring in the developing countries, despite the fact that the neonatal mortality in the developing countries is generally unreported.[24] Neonatal septicemia is responsible for 30-50% of neonatal deaths in developing countries.[1]There are many acute phase reactants including C-reactive protein, IL-8,IL-6, tumor necrotic factor-alpha and procalcitonin which rise with the onset of neonatal sepsis and can be used as a diagnostic marker. These markers are frequently being used for early detection of neonatal sepsis.[25–27]In the current study, the diagnosis was based on clinical grounds and supported by raised CRP. Babies up to 7 days of life were entertained as early onset sepsis and from 8 to 28 days as cases of late onset sepsis. The mean age ±SD at the time of admission was 6.9±1.6 days. Majority of neonates (60%) presented within 7 days after birth (early onset neonatal sepsis). The results in this study regarding age are comparable with another study done by many researchers. [26–30]Gender distribution revealed male preponderance (60%) than female (40%). There may be two reasons. First, male sex carries a higher risk for sepsis as compared to females.[3]Second, parents of our country are more concerned for their boys and bring them earlier to the hospital. In this study, the frequency of raised CRP in clinically suspected cases of neonatal sepsis was found 81.4%.These results are comparable to the results of study done by Arif et al, which showed frequency of 75%.[31]A meta-analysis of more than 1100 cases of neonatal sepsis from USA has documented the frequency of raised CRP 92.95% and 85.0% for proven and suspected cases.[32] These results are also similar to the results of our study for probable sepsis. A study conducted in Bangladesh has documented 55% frequency of CRP[2] which is far below our results. Benitz long ago has mentioned that CRP frequency is higher for diagnosing late infections than early infection.[32] These results are supporting our observations; CRP is raised in 85% cases of LOS while in 79% of EOS in our study. CRP estimation has now an established value as a marker of neonatal sepsis and many workers have concurred upon its utility in diagnosis and monitoring of treatment of neonatal sepsis.[14–16,21,33,34]

Many studies have been done on other laboratory tests. Detection of cytokines is one the tests with high sensitivity,IL-1,IL-6,and IL-8 are sensitive parameters for diagnosis of neonatal sepsis.[9]Procalcitonin has been researched in many studies as a potential marker and is also a valuable marker for determining shock severity.[2,29,30,35–37] The contradictions between the results of CRP in different studies are probably due to different testing methods, time of sampling and various sample selection. CRP is a cheaper and more accessible and because of having high sensitivity, we can decide whether to start the treatment or not.

Limitation of Study: Blood culture is the gold standard for diagnosis of neonatal sepsis, which is not done in this study. Therefore negative and positive predictive values, sensitivity and specificity of CRP in the study were not calculated. This invites for further studies comparing blood cultures, CRP and other novel makers for early detection and finding a more specific and sensitive marker for diagnosis and prompt treatment of neonatal sepsis.

CONCLUSION

It is concluded from this study that neonatal sepsis has nonspecific signs and symptoms. Index of suspicion should be very high while managing a sick neonate. CRP is a readily available, inexpensive, reliable and highly sensitive marker of neonatal sepsis. It should be done in every case of suspected neonatal sepsis at the earliest possible to diagnose sepsis earlier as the culture reports takes longer to be available and the sensitivity of cultures is not optimal. Early intervention with empirical antibiotic therapy in suspected cases of neonatal sepsis with raised CRP level helps to treat this life threatening condition and prevent its complications.

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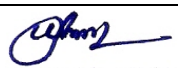
Dr. Muhammad Usman	Data collection & Results interpretation, Statistical evaluation	
Prof. Dr. Naveed Jabbar	Technical Review	
Dr. Khurrum Shahnawaz	Data collection & writing results