A Study on Clinical and Laboratory Findings in Early Neonatal Sepsis in Tertiary Care Hospital

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Abstract
Introduction: Neonatal sepsis is a clinical syndrome of bacteremia with systemic signs and symptoms of infection within the first 28 days of life. It is caused by the microorganisms or their toxic products in the circulation. It is further classified as early onset (within 72 hrs of life) EOS and late onset (LOS). EOS is more common than LOS in which the EOS causes a mortality rate of 15-40% of total 30-50% of neonatal sepsis.

Materials & Methods: A descriptive study of 200 neonates were included in the study, conducted in King George Hospital, department of pediatrics, Visakhapatnam from January 2018 to July 2018. 100 term and 100 preterm neonates with clinically suspected were selected by using New Ballard score as gestational age assessment, all neonates are evaluated with detailed history of mother and perinatal events and bacteriological profile in these 200 neonates studied by various types of culture and compared with serum samples.

Results: Premature rupture of membranes and meconium stained amniotic fluid are common antenatal complications, Respiratory distress is the most common clinical presentation seen in 52% of cases with preterm significance. CRP is the rapid diagnostic test has high sensitivity in both preterm and term neonates.

Introduction
In India, neonatal sepsis is the single most important cause of neonatal deaths, accounting for over half of them. Maternal factors, fetal factors and interventions include feeding techniques are responsible for neonatal sepsis. Low socio-economic state, contaminated, unclean delivery leading to maternal infection and premature and low birth weight delivery and poor postnatal follow-up are the common causes for neonatal sepsis. The high frequency of infection in the new born is due to the immaturity of the immune system at birth and more in pre-term baby and decreased transplacental transfer of immunoglobulins in a pre-term delivery.
Early initiation of appropriate antibiotic therapy is necessary for successful treatment, but early diagnosis of neonatal bacterial infections is difficult because clinical signs are non-specific and may initially be subtle (1,2). Positive blood cultures still remain the gold standard for the diagnosis of sepsis but many times, the culture may be negative. C-reactive protein is an excellent marker for established neonatal bacterial infection which is economical, fast and reliable.
Aims and Objectives
1. To know common microorganisms in our tertiary care center.
2. To correlate the C-reactive protein levels with blood culture.

Materials and Methods
Study design: A descriptive study of 200 cases of clinically suspected neonatal sepsis. Study contains two groups:

a) 100 term neonates.
b) 100 pre-term neonates.

Study period: January 2018 – august 2018
Inclusion criteria: Neonates with clinically suspected early onset sepsis
Exclusion criteria
a) Neonates who received antibiotic before admission
b) Neonates with major congenital malformations
c) Mother with history of antibiotic usage during labour

Methodology
This study was conducted at the department of Pediatrics, King George College and General Hospital, Visakhapatnam, during the period between January 2018-August 2018. Gestational age assessment was done for all neonates using modified New Ballard score, who got admitted to NICU, at our King George Hospital and 100 term and 100 pre-term neonates with clinically suspected neonatal sepsis were selected as the subjects for the present study to compare with each other. These neonates included both those born at our King George Hospital and those who were born outside our hospital and referred here for management of suspected early onset neonatal sepsis.

During admission all these selected neonates were evaluated with detailed history of their mothers and perinatal events including maternal factors that predisposed Bacteriological profiles in these 200 neonates were studied by blood culture, CSF culture, urine culture and they were compared with serum CRP levels. Blood cultures were done in all neonates where as other cultures were done only in selected neonates depending on the clinical picture. The clinical presentations of sepsis between preterm and term babies were noted and compared.

Investigations
All the babies were subjected to detailed septic screening workup.
1. Haemoglobin level was estimated in all cases.
2. Total and differentiated WBC counts were done in all cases and 5000-20,000/cumm was taken as normal range.
3. Platelet count was done in all neonates and count <1 lakh/cumm was taken as significantly abnormal.
4. Peripheral blood smear and neutrophilic count was done in all neonates.
5. Serum C-reactive protein(CRP) levels were estimated by Turbilatex a quantitative immune turbidometry assay, a latex agglutination test, which has high sensitivity and give results in few seconds. CRP was done in all cases and more than 1 mg/L was considered as positive. CRP levels were correlated with other clinical and lab parameters.
6. Blood culture was done using brain heart infusion broth media. Blood was drawn for culture in all cases under standard precaution, before starting antibiotics in the NICU. The culture was taken from peripheral line under standard precautions. Smears and cultures from superficial infection sites like skin pustules were taken appropriately as required.
7. Urine culture was done in some specific cases depending on clinical picture.
8. CSF examination and culture was done in cases with suspected meningitis.
9. Radiological evaluations such as chest X-ray, X-ray abdomen, ultra sound abdomen etc were done in relevance.
10. Smears and cultures from superficial infection sites like skin pustules were taken appropriately as required.
11. Urine culture was done in some specific cases depending on clinical picture.
12. CSF examination and culture was done in cases with suspected meningitis.
13. Radiological evaluations such as chest X-ray, X-ray abdomen, ultra sound abdomen etc were done in relevance

**Statistical Methods**

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented on Mean±SD (min-max) and results on categorical measurements were presented in Number (%). Significance was assessed at 5% level of significance. Student “t” test has been used to find the significance of study parameters on continuous scale between two groups. Fisher Exact test has been used to find the significance of study parameters on categorical scale between two groups. 95% confidence interval has been computed to find the significant features. Confidence interval with lower limit more than 50% was associated with statistical significance. Diagnostic statistics viz. Sensitivity, Specificity, PPV, NPV and Accuracy have been computed to find the correlation of CRP and blood cultures.

**Results**

Out of 200 neonates with sepsis 104 were born at our King George Hospital and 96 were born outside this hospital and referred here for management. Out of 200 neonates with sepsis 90 were born normal vaginal delivery, 24 were born by assisted vaginal delivery and 86 were born by LSCS.

Out of 200 neonates with sepsis males were 132 and females were 68 with male to female ratio 1.9:1. Out of 200 neonates with sepsis antenatal complications were present in 82 among which PROM is accounted for 36% and meconium stained amniotic fluid accounted for 24%.

| Chief complaint            | Term | Pre-term | Total |
|----------------------------|------|----------|-------|
| Respiratory distress       | 42   | 60       | 102   |
| Refusal of feeds           | 36   | 26       | 62    |
| Jaundice                   | 14   | 16       | 30    |
| Vomiting                   | 10   | 16       | 26    |
| Lethargy                   | 10   | 20       | 30    |
| Irritability               | 8    | 4        | 12    |
| Convulsions                | 8    | 6        | 14    |
| Cyanosis                   | 0    | 16       | 16    |
| Fever                      | 2    | 2        | 4     |

Among 200 neonates with sepsis respiratory distress was the chief complaint accounting for 51%. Refusal of feeds was the chief complaint in 31%. There was no statistical significance for any of the presenting complaints except cyanosis between term and preterm neonates.

Respiratory distress was the most frequent clinical sign observed. Respiratory distress was more common among preterm neonates than term neonates with statistically significant difference. 200 neonates with sepsis only 38 neonates had significant total WBC count to predict sepsis. Out of these 38 neonates preterm neonates were only 10 in number suggesting that in preterm neonates total WBC count is less sensitive for predicting sepsis. Neutropenia is observed in 30 cases out of them 22 are preterm and 8 are term neonates. This show neutrophil count is less sensitive in predicting neonatal sepsis.

Early onset sepsis isolated in blood culture in my study

| Organism                                  | No. of cases |
|-------------------------------------------|--------------|
| Escherichia coli                          | 16           |
| Staphylococcus aureus                     | 11           |
| Klebsiella pneumonia                      | 12           |
| Coagulase negative staphylococcus aureus  | 5            |
| (CONS)                                    |              |
| Beta haemolytic streptococci              | 4            |
| Pseudomonas aureginosa                    | 5            |
| Acinetobacterspp                          | 4            |
| Candida albicans                          | 3            |
| Total                                     | 60           |
Most commonly positive (86%) test followed by significant total leucocyte count positivity (16%) and thrombocytopenia (11%) with wide range of difference. Total leucocyte count positivity is significantly more in term neonates compared to preterm neonates (14% Vs 5%) with p<0.003. In 200 clinical neonatal sepsis cases considering culture positivity as gold standard of sepsis and CRP positivity in culture negative cases as false positive and CRP positive in culture positive cases as true positive cases the following observations were made:

The 53% of false positive cases which determine the presence of sepsis in culture negative cases is significant. This indicates the need of CRP in the diagnosis of sepsis. The false positive cases are little more in term neonates, indicating the CRP is significantly well produced in term septic neonates compared to preterm. The six cases of false negative are positive for CSF culture in which two cases are term and remaining is preterm.

The sensitivity of CRP in correlation to Blood culture and all culture is 90.90 and 91.66 respectively. This is satisfactory for CRP. The NPV of CRP is 78.57 and 78.57 in compare to blood culture and all culture respectively.

**Discussion**

Infection in neonates continues to be a public health problem with significant morbidity and mortality. Timely diagnosis is vital to prevent serious complications in neonates. In an investigation carried out by (licona et al 2016), at Santa Barbara integrated hospital, a prevalence of 60.60% of early neonatal sepsis is found among outpatient diagnoses.

The diagnoses of early onset neonatal sepsis continues to be a challenge, since clinical manifestations are variable and at the same time nonspecific of infection. The study tries to understand clinical profile and role of CRP in early onset neonatal sepsis, most common organisms isolated and their sensitivity patterns at our tertiary care centre. Hence, 100 term and 100 preterm neonates who are meeting the criteria for this study are selected from NICU at King George Hospital, Visakhapatnam.

In this present study neonatal sepsis is more common in male gender (66% vs 34%) with reported male to female ratio of 1.9:1 .this ratio is comparable to study by Jain NK et al , 2003 in which the ratio was 1.78:1. Respiratory distress is the most frequent presenting complaint which constituted 51% of the total presenting complaints .Studies by Jain NK et al , 2003  and also Eman M. Rabieshehab EL-Din et al 2015almost similar frequency (42%) and (46.7%) respectively , of this complaint was found. Following to respiratory distress, refusal of feeds, jaundice and lethargy are the common presenting complaints observed in the present study. Fever and diarrhoea were found in some studies but which are the least frequent presenting complaints in our study. Respiratory distress is more common in preterm neonates when compare dto term neonates even though not statistically not significant (p=0.07).

Cyanosis is observed in 8 preterm neonates but none in term neonates with statistically significant difference of occurrence between them ( p=0.003). Respiratory distress is the most frequent sign observed in the present study which is present in 52% of cases. More than this it is more common in preterm neonates accounting for 64% compared to 40% in term neonates which is statistically significant (p value 0.018). This data is almost similar to that observed in studies by Sidra Younis et al 2015, Al Zwaini EJ et al 2009 and Borna H and Borna S et al 2005, Cyanosis, icterus and abdominal distension are the next frequent signs with almost similar frequency. Skin rash is noticed in 5% of cases,36% of the cases have Hb (haemoglobin) <15 g% and 7 cases have Hb of < 10%. majority of the cases have Hb> 15 gm% and mean Hb of all neonates is 15.01±3.370. 81% of neonates have total leukocyte count in normal range only 19% have total leukocyte count suggestive of sepsis, showing the poor sensitivity of it in diagnosis of neonatal sepsis. The p value of number of preterm and number of term cases having normal total leukocyte count is 0.158.
Platelet count is in normal range in 89% of cases and only 11% of cases have counts suggestive of sepsis when cut of value of platelet count was taken as 1 lakh showing the poor sensitivity in diagnosis of sepsis. In the present study, CRP value of > 1mg/dl is considered positive. The CRP is positive in 88% of cases, and 12% of cases have value <1 mg/dl. This observation is almost close to that observed in study by Ahmed Z et al, 2005. CRP is not a specific test for sepsis, and different studies have mentioned wide range of specificity, and it is depend on the method of test done and CRP is raised in many conditions, hence specificity is not considered in this study. The CRP can be equally considered for diagnosis of neonatal sepsis in both term and preterm as p value is 0.226. The blood culture is done in all neonates, out of them 60 cases (34.09%) had positive blood culture. This percentage of positive blood culture is closely similar to that observed in study by E.J. Alzwaini et al, 2009. There is no statistically significant difference of blood culture positivity between term and preterm cases (p value 0.101). The 34.09% of positive blood culture is not sufficient for diagnosis of sepsis as this is very low. Hence rapid diagnostic tools are necessary in diagnosis of sepsis. In this present study Gram negative organisms are the most common pathogen (58.6%) isolated in blood cultures. Among Gram negative organisms, E.coli is most common (26.6%), in both term and preterm neonates. This finding is closely similar to that observed in studies by Jain NK, et al 2003. Klebsiella and Staphylococcus aureus are the next common pathogens isolated.

Conclusions and Summary

- Neonatal sepsis has vague signs and symptoms, so high index of suspicion is needed for an early diagnosis and management.
- Neonatal sepsis is more common in male neonates.
- Early onset sepsis is more common than late onset sepsis
- Among antenatal complications leading to neonatal sepsis premature rupture of membranes and meconium stained amniotic fluid are more common.
- Respiratory distress is the most common clinical presentation of neonatal sepsis. This is much more common in preterm neonates with statistical significance.
- Majority of neonatal sepsis cases have normal range of total leukocyte count. Hence it has very low sensitivity for predicting neonatal sepsis.
- Majority of neonatal sepsis have normal platelet counts.
- Almost all neonatal sepsis cases which are blood culture positive have positive CRP values.
- Bacteriological profile of neonatal sepsis is predominated by gram negative organisms among which E.coli is most common and is sensitive for piperacillin-tazobactam and meropenem at our centre. S.aureus is the most common gram positive organism isolated.
- Majority of neonatal sepsis cases have positive CRP values
- CRP as the rapid diagnostic test has high sensitivity in diagnosis of neonatal sepsis, both in term and preterm neonates.

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