COMPARATIVE STUDY OF SERUM PROCALCITONIN (PCT) AND C-REACTIVE PROTEIN (CRP) LEVELS IN NEONATAL SEPSIS

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ABSTRACT

Objectives

To assess the Procalcitonin levels in neonatal sepsis and to compare the procalcitonin with CRP in neonatal sepsis

Methods

This cross sectional study was conducted on 50 neonates who were admitted in NICU, clinical features of neo-natal sepsis with maternal risk factors were recorded at greater accuracy. Laboratory factors inclusion with Blood culture, C - reactive protein, Procalcitonin and other investigations for sepsis were performed on subjective basis.

Results

PCT levels was raised in significantly (p<0.01) higher number of study cases (80.0%) as compared to CRP which was positive in 58%. The sensitivity, specificity and positive predictive value (PPV) of PCT for detecting sepsis was 93.00%, 50.00%, 78.26 % respectively as compared to CRP (p<0.01) with fewer or lesser sensitivity, specificity, PPV as 50.00%, 33.33% and 31.00% respectively (p<0.01) . The CRP positive and PCT positives were 65% significantly associated (p<0.01) with risk factors. Total 90% of Culture positive neonates were showed to be increased level of PCT. The PCT was a significantly better (p<0.01) in early diagnostic marker for intitutive event of sepsis.

Conclusions

PCT is the better indicator of sepsis , could be able to yield better results and reliable marker than CRP in the early diagnosis of neonatal sepsis .

KEYWORDS : Neonatal Sepsis, CRP, Procalcitonin

INTRODUCTION

The sepsis is the commonest cause of neonatal mortality and is responsible for 30-50% of total neonatal deaths each year in developing countries. It is estimated that up to 20% of neonates develop sepsis and approximately 1% die of sepsis related causes. The term neonatal sepsis, refers to systemic infection of neonates including septicemia, pneumonia, meningitis, arthritis, osteomyelitis, and urinary tract infection. As per National Neonatal Perinatal Database (NNPD) 2002-2003, the incidence of systemic infection is 3% among intramural babies in tertiary care institutions in India, with septicemia being present in three fourth of the cases and pneumonia in one third of neonates. Infection is the primary cause of mortality in 18.6% of intramural neonates in which Klebsiella pneumoniae is the most frequent bacterial isolate (32.5%), followed by Staphylococcus aureus (13.6%). Sepsis is a major cause of morbidity and mortality in the neonatal period. Neonatal sepsis is classified...
depending on the hours of presentation into early onset: within first 72 hours of life Late onset; occurring after 72 hours of life. Early onset neonatal sepsis is often due to organism present in the maternal vaginal flora. Mortality in this condition is much higher than in late onset sepsis. Early diagnosis and prompt antimicrobial therapy is necessary for managing this condition. Infection in early neonatal period is one of the important factors responsible for high perinatal mortality and morbidity in developing countries. Early manifestations of neonatal septicemia are vague and nonspecific. There are various predisposing factors that lead to an increased neonatal susceptibility to infection. These include maternal history of: 1 Low birth weight (<2500gms) or preterm baby, Febrile illness in the mother within 2 weeks prior to delivery, Foul smelling and/or meconium stained liquor amnii, Prolonged rupture of membrane (>24 hours), More than 3 vaginal examinations during labor, Prolonged and difficult delivery with instrumentation, Perinatal asphyxia (Apgar score <4 at 1 minute of age) or difficult resuscitation, Neonates with presence of foul smelling liquor or three of above mentioned risk factors should be considered to have EOS & treated with antibiotics. Presence of ≥2 risk factors should be investigated with sepsis screen and treated accordingly. Hence early detection of sepsis by history, clinical, laboratory investigation is very useful to reduce the neonatal morbidity and mortality. The late onset Late onset sepsis usually presents after 72 hours of age. The source of infection is either nosocomial or community acquired and neonates usually present with septicemia, pneumonia or meningitis. LOS is a slow, progressive focal involvement with features similar to early onset sepsis except that meningitis is more frequent. Mortality is 10% to 20%. Risk factors for development of LOS includes viz., NICU admission, Poor hygiene, Low birth weight (LBW), Poor cord care, bottle feeding, Invasive procedure, Superficial infection (pyoderma, umbilical sepsis), prelacteal feeding, Ventilation, Aspiration of feeds. Investigations-direct markers of sepsis: The following investigation done at study period, blood culture and Gram staining, Lumbar puncture, Suprapubic specimen of urine and chest X-Ray; Indirect markers - Abnormal value TLC < 5000/mm3, ANC < as per Manroo chart for term1 and Mouzinho’s chart for very LBL (VLBW) infants12 Immature/ total neutrophil > 0.2, Micro-ESR > 15mm in 1st hr and CRP > 1mg/dl. All neonates suspected to have sepsis should have a septic screen to corroborate the diagnosis. Acute phase Reactants are done; C - reactive protein and procalcitonin. Newer diagnostic tests for diagnosis of neonatal sepsis is carried out (cell surface markers, Granulocyte colony stimulating factor, Cytokines, Molecular genetics and Mol cell proteomics). Early detection of neonatal sepsis is difficult because the first sign of this disease may be minimal and are similar to those of various non infectious process, and definitive blood cultures results are not immediately available. Furthermore, the results of recent studies have underlined the concern about the culture negative clinical sepsis, particularly in the setting of increasing use of maternal antibiotics. The availability of laboratory tests to accurately and more rapidly identify septic neonates than is done by isolation of microorganisms from body fluid specimens would therefore be considerable value in improving the outcome of this challenging clinical problem and in minimizing unnecessary treatment of uninfected NICU patient. Several indicators have been evaluated for the diagnosis of neonatal sepsis and have included various leukocyte indices and acute phase protein reactant levels. However the inability of any single laboratory test to date to provide rapid, reliable and early identification of infected neonates has led to a search for other diagnostic markers. Delay in the institution of antimicrobial therapy is fraught with dangers of several complications and increase in mortality. Isolation of the infecting organism from blood provides the definitive diagnosis and is considered as the “gold standard” The present study aims to assess the procalcitonin levels in neonatal sepsis and to compare procalcitonin with CRP levels in neonatal sepsis
MATERIALS AND METHODS

A Cross Sectional observational study conducted at Vani Vilas hospital & Bowring and Lady Curzon hospitals attached to BMC & RI during 2013-14. The term Neona tes with clinical features of neonatal sepsis with maternal risk factors, admitted to our hospital. A total 50 neonates who were admitted to the NICU with signs which is suggestive of sepsis. History and clinical examination using a systematically designed proforma. The relevant laboratory examination like CBC, blood culture, chest X-ray, CRP, procalcitonin and CSF analysis in relevant cases. All patients meet inclusion and exclusion criteria, Inclusion; term neonates with Clinical features of sepsis like feed intolerance, lethargy, temperature instability, apnea, respiratory distress, poor perfusion, seizures, bradycardia, tachypnea, abdominal distention and vomiting and Maternal risk factors such as fever, prolonged rupture of amniotic membranes > 24hours. Exclusion criteria; pre-term babies, those who have received antibiotics, diabetic mothers, hyaline membrane disease and with history of birth asphyxia. Univariate statistical model was employed to test the hypothesis.

RESULTS

The hospital based Cross-Sectional study of term neonates with clinical features of neo-natal sepsis with maternal risk factors, admitted to Vani Vilas hospital & Bowring and Lady Curzon hospitals attached to BMC & RI. The results revealed that most of the neonates were seen in LOS group. Total 40% of the cases were seen EOS and 60% cases were seen in LOS group. The mean age in EOS and LOS was 2.05 and 7.27 days respectively. Gender distribution comprises males were 70% are females were 30% with insignificant ratio 2.3:1 p>0.01. The Casual component of male is predominance as compared to females because due to gene located on the sex - chromosome involved in the function of the thymus and synthesis of immunoglobulins. Neonates in EOS explicitly affected weight of LBW and LOS (maximum affected in normal weight-42%) p >0.01. However the total count was found to be normal in maximum number (66%) of neonates for both groups p<0.01.

![Figure 1: Bar Diagram Showing Distribution Based on Total Count in Neonatal Sepsis](image)

In the present study most of neonatcces were expressed normal differential count followed by lymphocytosis (32.0%), neutrophilia (23.0%), neutropenia (2.0%) for both groups p>0.01. although LP +ve was seen in 16% cases of study group p>0.01.

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Table 1: Distribution Based on CRP Levels in Neonatal Sepsis

<table>
<thead>
<tr>
<th>Group</th>
<th>CRP Levels</th>
<th>Total</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP +ve</td>
<td>CRP -ve</td>
<td></td>
</tr>
<tr>
<td>EOS</td>
<td>09</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>45.0%</td>
<td>55.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>LOS</td>
<td>20</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>66.7%</td>
<td>33.3%</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

The CRP positive was seen 58% in study group as could found to be statistically significant difference p<0.01 as compared with rest of the group, the Sensitivity=10/20 x 100=50% Specificity=10/30 x 100=33.33%, Positive predictive value (PPV)=09/29x 100=31%, Negative predictive value (NPV)=10/21x 100=47.6% Table 1

Table 2: Gender Wise Distribution Based on Procalcitonin Levels in Neonatal Sepsis

<table>
<thead>
<tr>
<th>Gender</th>
<th>Procalcitonin Levels</th>
<th>Total</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Sepsis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>06-17.1%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4-26.7%</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10-20.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Where as PCT inclusively elevated 80% in study group p<0.01 . Procalcitonin with >10ng/ml (fatal outcome) levels and 2-10 ng/ml(organ dysfunction) was 44% and 26% recorded with good Sensitivity=33/36 x 100=93%; specificity=7/14 x 100=50%; positive predictive value (PPV)=36/46 x 100=78.26%;negative predictive value (NPV)=4/4x 100=100%.Blood Culture Sensitivity was positive in 40% of the cases in study group. LOS 46.6% of cases were seen as compared with EOS 30% P<0.01.In present study, blood culture sensitivity was 50% p<0.01, klebsiella was 10% p<0.01 of MRSA was 10% p<0.01 of Pseudomonas respectively Table 2.

Figure 2: Distribution Based on Organism Found in Blood Culture Sensitivity in Neonatal Sepsis

Table 3: Comparison of CRP with Differential Count

<table>
<thead>
<tr>
<th>Group</th>
<th>Status</th>
<th>Differential Count</th>
<th>Total</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Lymphocytosis</td>
<td>Lymphopenia</td>
<td>Neutrophilia</td>
</tr>
<tr>
<td>EOS</td>
<td>CRP +ve</td>
<td>63.6%</td>
<td>0%</td>
<td>9.1%</td>
</tr>
<tr>
<td></td>
<td>CRP -ve</td>
<td>40.0%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>LOS</td>
<td>CRP +ve</td>
<td>37.0%</td>
<td>7%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>CRP -ve</td>
<td>66.7%</td>
<td>16.7%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>
In the present study, Neonatal sepsis with CRP +ve has 34% normal Neutrophil count. count in Neonatal sepsis. In the present study, Correlation of EOS and LOS group with CRP +ve and chest X-ray positive findings has 9.1% and 20% respectively.

Figure 3: Bar Diagram Showing Distribution Based on Comparison of CRP with Differential

Figure 4: Bar Diagram Showing Distribution Based on Comparison of CRP and Blood Culture in Neonatal Sepsis
DISCUSSIONS

The neonatal septicemia is a leading cause of mortality and morbidity in neonates. Early diagnosis of neonatal septicemia helps the clinician in instituting antibiotic therapy at the earliest, thereby reducing the mortality rates in the neonates. The positive blood culture is the only definitive method of confirming a case of septicemia. Culture and sensitivity tests requires a minimum period of 48 hours which is a precious time in making decisions in the treatment of sepsis in newborns. The readily achievable complete blood count and the leukocyte differential assays have a relatively poor specificity for diagnosing sepsis. Therefore, the need persists for improved diagnostic indicators of neonatal sepsis.

There is no single reliable test for the early definite diagnosis of neonatal sepsis, and therefore, there is a continuing search for a new infection marker. The C-reactive protein has been the most analyzed parameter for the detection of bacterial infections for years. Procalcitonin (PCT) has been proposed as a marker of bacterial sepsis. The advantage of PCT as compared to C-reactive protein is that the increase of the further in bacterial infection and its restoration to normal is more rapid. The purpose of study, to assess the procalcitonin levels in neonatal sepsis, and to compare procalcitonin with CRP levels in neonatal sepsis. Our study, LOS group were 60% than in EOS constituted 40% which is comparable with Naher BS et al\textsuperscript{52} 15-50% for EOS and 12-20% for LOS. Mean age among the neonates into EOS & LOS group is 0.759 & 4.540
Comparative Study of Serum Procalcitonin (PCT) and C-Reactive Protein (CRP) Levels in Neonatal Sepsis

respectively with a p <0.001. Comparable to Neeraj kumar et al\textsuperscript{28} study mean age of presentation in early onset of sepsis was 1.68±0.83 days.

The sepsis is more common in males (70%) p<0.01 , which was found to be consistent with all findings put forth by Tallur \textit{et al} (68%) \textsuperscript{42}, Neeraj Kumar \textit{et al} (59%)\textsuperscript{28}. It may be linked to the x-linked immunoregulatory gene making male neonates more susceptible to infection \textsuperscript{43}. This is also probably due to the attitude of the parents who seek medical services more for their male babies than females. sepsis were more seen in the normal weight babies(68%) followed by LBW(32%) p<0.01. Another backdrop of low neutrophil count was 02% p<0.01 triggered for the present hypothesis and it was found to be more sensitive than WBC counts (p<0.01)\textsuperscript{.} Xanthou \textit{et al} opied that predictive value (PPV 74.52) of high WBC is poor amongst and dynamic value declined upto 30% of neonates with proven sepsis have expressed normal value\textsuperscript{44}. However, the result indicates that 66% of neonates had normal WBC count in culture proven cases and found to be statistically significant (p<0.01). The reason for this high false negative result might be due to time interval between the onset of bacteremia and sampling (p<0.01) \textsuperscript{45}. The WBC count was found to be the most specific of all tests but least sensitive p<0.01 (Specificity 85.26%, PPV 76.81%). The chest X-ray findings are found in 14% of Neonatal sepsis followed by significant results correlate in Lumbar puncture findings 15% and 16.7% in EOS and LOS group respectively ( p <0.01) respectively. Many authors has documented the static figures of blood culture and asper their results findings it was found to be statistically significant and positively correlate with our present study hypothesis Guha \textit{et al} \textsuperscript{41}(2003) 42%, Mondal \textit{et al}\textsuperscript{38} (2012) N=62, 61.3%; R.S. Jawal \textit{et al}\textsuperscript{37} (2014) N=50 35.86% and Rahul kamble \textit{et al}\textsuperscript{10} (2015) N=198 40%. In our study, the percentage of positive blood culture was 40% this was comparable with the above studies had high yield of positive results. The sensitivity and specificity for CRP levels are 50% and 33.33% respectively and found to be statistically significant (p<0.01) this study is comparable to P.Kite \textit{et al} (61.8%) p<0.01. The similar findings dealt by I.M.Singh \textit{et al} \textsuperscript{49}, P.Kite \textit{et al}\textsuperscript{50}, Berger \textit{et al}\textsuperscript{51}. We found that 93% sensitivity, 50% specificity for procalcitonin as a marker for the early diagnosis of neonatal sepsis. Also, the results of study by Khoshdel \textit{et al} (2008) in Iran (Shahrekord) showed that 87.5% sensitivity, 87.4% specificity of PCT level for neonatal sepsis\textsuperscript{23}. In all other studies like Boo \textit{et al}\textsuperscript{24}, Minoo \textit{et al}\textsuperscript{25} and Suclidathangam G \textit{et al}\textsuperscript{26} sensitivity for PCT is comparable whereas specificity is comparable with Minoo \textit{et al}\textsuperscript{25}.The study is nearly seems to be express the positive predictive value is 78.6% and negative predictive value is 75% in PCT level. However we also found that 80% Procalcitonin, 58% CRP and 40% of blood culture positive which was comparable to Neeraj Kumar \textit{et al} \textsuperscript{28} study of 87.5% PCT, 55.2% CRP and 37.9% of blood culture positive. In Naher BS \textit{et al}\textsuperscript{52} study less number of culture proven sepsis may be due to late arrival, sample collection after giving antibiotic and faultly technique in collection procedure. The correlation of Procalcitonin levels with its outcome in EOS and LOS group with PCT Levels of >10ng/ml has 100% and 90% mortality respectively. P value in LOS has statistical significant (p<0.01). Similarly, Brunkhorst \textit{et al} \textsuperscript{47} (98%), have even demonstrated that very high PCT values are related to septic shock and death with considering a bad prognostic values greater than10ng/dl. A study in Denmark by Jensen JU \textit{et al} \textsuperscript{48} (92%) that patients with septic process present less mortality risk with PCT levels less than 1mg/dl, and increments in this value of more than, 1mg/dl per day are associated with an increment in mortality.
CONCLUSIONS

Summing of all the findings the present study concludes that, the Serum PCT is used as a good tool for the early diagnosis of neonatal sepsis. If it is widely used the cost will fallon euphoratically. The findings of the study would helps to pediatric clinicians for taking accurate decision for early diagnosis at the larger extent. An important limitation of the study is CRP Levels were not been estimated by Latex agglutination test with serial titers level.

REFERENCES


