

C-reactive protein and thrombocytopenia as essential early indicators: Subtle approach to neonatal sepsis

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ABSTRACT

Introduction: Early diagnosis of neonatal sepsis is very essential part of newborn care to prevent mortality and decrease morbidity in newborns. **Aim:** The aim of this study is to correlate an increase in C-reactive protein (CRP) titre and a decrease in platelet count with an increased incidence of neonatal septicemia, for an effective subtle approach in neonatal septicemia. **Materials and Methods:** A retrospective study was conducted in the neonatal intensive care unit (NICU) of a tertiary care hospital from Jan 2022 to July 2023. Neonates admitted to the NICU with suspected sepsis were screened for sepsis. Screening was done by taking blood culture samples before administration of antibiotics, serum samples for CRP and blood samples for platelet count. **Result:** A total of 270 newborns with suspected sepsis were included in the study. Blood culture positivity was seen in 27.7 (27/75) cases. About 32.9% (89/270) of the neonates with suspected sepsis and 61.3% (46/75) neonates with confirmed sepsis had raised CRP; 32.2% (87/270) neonates with suspected sepsis and 64% (48/75) with confirmed sepsis had decreased platelet count. Both an increase in CRP and a decrease in platelets were seen in 61.3% (46/75) of confirmed cases. **Conclusion:** In our study, both raised CRP and decreased platelet count were seen in around 60% of confirmed cases of sepsis. So, CRP titre and platelet count can be used as early, rapid diagnostic markers for confirmed sepsis.

Keywords: C-reactive protein, neonate, sepsis, thrombocytopenia

Introduction

Neonatal sepsis (NS) is a serious blood bacterial infection in children of 28 days or younger, manifested by systemic signs and symptoms of infection.^[1] Early-onset neonatal sepsis (EOS) has been defined based on the age at onset, with bacteraemia or bacterial meningitis occurring at ≤ 72 h in infants hospitalized in the neonatal intensive care unit (NICU). Late-onset sepsis (LOS) is sepsis occurring after 72 h in NICU infants and 7 days of life in term infants, has been variably defined as occurring up to the age of <90

or 120 days, and may be caused by vertically or horizontally acquired pathogens.^[2,3]

Newborn infants are susceptible to infections due to low innate and acquired immunity. NS may have diverse and nonspecific symptoms and signs and a delay in the diagnosis and commencement of treatment results in high morbidity and mortality rates. The case fatality rate of sepsis among neonates ranges between 25% to 65% in India.^[4]

Prompt diagnosis is required to reduce neonatal mortality. Though blood culture remains the gold standard in not only identifying the infection but also giving vital information regarding antibiotic sensitivity, it takes 48–72 h to detect the organism. However, its accuracy has been questioned because of spurious positive results due to contamination and negative blood cultures in fatal generalized bacterial infections. The yield

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of a positive blood culture ranges from 8 to 73%, as shown in various studies.^[5]

Therefore other haematological tests are required for early diagnosis and prompt action to reduce mortality among newborns. In recent years, various inflammatory markers like interleukin and haptoglobins have been evaluated for early diagnosis but they are expensive and time-consuming. Hence various cheap but reliable laboratory tests have been evaluated for the diagnosis of systemic infection in neonates.^[6]

The complete blood count (CBC) with various neutrophil parameters and C-reactive protein (CRP) are the most frequently used.^[7]

The present study is aimed to evaluate the role of various blood parameters like platelet count and CRP, as an early indicator of neonatal septicemia because these are simple, bedside tests, on the basis of which antibiotic therapy can be started in the neonate.

Materials and Methods

This study was conducted in the Department of Microbiology of NCR Institute of Medical Sciences Meerut from January 2022 to July 2023 to screen for early neonatal septicemia in the NICU for early prompt antimicrobial therapy and prevention. A total of 270 newborns of either sex, with suspected sepsis, were included in the study. Prematurity and very low birth weights are also important risk factors. Suspected sepsis early symptoms may include irritability, lethargy, or poor feeding. Others are respiratory distress, fever, hypothermia or hypotension with poor perfusion and shock. Diagnosis may also be suspected on the basis of laboratory findings, which may reveal hyperglycemia or hypoglycemia, acidosis or hyperbilirubinemia.^[8]

Maternal factors that put neonates at risk of EOS include group B Streptococcus status, the presence of chorioamnionitis, and infant prematurity or prolonged rupture of membranes.^[9]

For LOS consider the long-term use of invasive interventions, such as mechanical ventilation and intravascular catheterisation, the failure of early enteral feeding with breast milk, a prolonged duration of parenteral nutrition, hospitalisation, surgery and underlying respiratory and cardiovascular diseases.^[10]

Both term and preterm neonates irrespective of the birth weight were included in the study. Neonates with prior antibiotic administration were excluded from the study. Newborns admitted to the NICU were screened for NS. Blood samples were taken for CRP estimation by nephelometry and for platelet count by automated blood counter and microscopic slide method. Also, blood samples were taken before antibiotic administration for blood culture by conventional method.

In the laboratory, a CRP level ≤ 5 mg/L was considered within the normal range. The range for CRP can be classified into three

groups: low (CRP ≤ 10 mg/L), intermediate (CRP 11–100 mg/L) and high (CRP > 100 mg/L).^[11]

Thrombocytopenia, defined as a platelet count below $150 \times 10^9/L$, is a frequent problem in NICUs. Thrombocytopenia was defined as a platelet count below $150 \times 10^9/L$ and was classified as mild ($101-149 \times 10^9/L$), moderate ($51-100 \times 10^9/L$), severe ($21-50 \times 10^9/L$) or very severe ($\leq 20 \times 10^9/L$).^[12]

Blood culture that came positive was subcultured on 5% human blood agar and nutrient agar. Further isolation and antibiotic susceptibility were performed using the disc diffusion method.

Statistical analysis

Statistical analysis was done with the help of the Statistical Package for the Social Sciences (SPSS) version. Descriptive statistics was used to infer results. Positive predictive value (PPV), negative predictive value, sensitivity and specificity were used to analyse the result. Chi-square was also used for analysis.

Results

Blood culture positivity was seen in 75 out of 270 cases (27.7%); 48 out of 75 cases were EOS and 28 out of 75 were LOS. The most common organism isolated from blood culture was *Klebsiella pneumoniae*. Out of 270 newborns, 168 (62.2%) were males and 102 (37.8%) were females. Others were *Escherichia coli*, *Pseudomonas* spp., *Acinetobacter* spp., *Staphylococcus aureus*, *coagulase-negative Staphylococcus* spp., *Enterococcus* spp., *Candida* spp. [Figure 1].

Raised CRP was seen in 89 newborns out of 270 (32.96%). 50 out of 75 cases of confirmed sepsis had raised CRP. The positive predictive value (PPV) of CRP estimation in confirmed sepsis was 56.2%. Also, the sensitivity of CRP in predicting confirmed sepsis is 66.6% [Table 1].

A decrease in platelet count is seen in 87 out of 270 cases (32.22%); 56 newborns with confirmed sepsis had a decrease in platelet

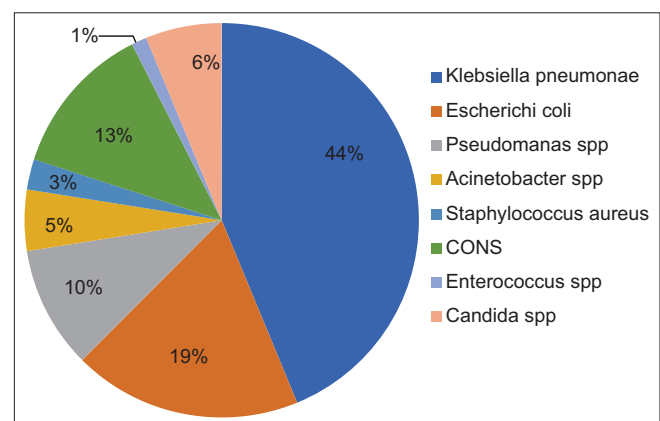


Figure 1: Percentage of various bacterial isolates isolated from blood culture

count. PPV of thrombocytopenia in confirmed sepsis is 64.3% [Table 2].

Both an increase in CRP and a decrease in platelets are seen in 46 culture-positive cases out of 75. The sensitivity of increased CRP and decreased platelet count in culture-positive sepsis is 61.33%. Also, the negative predictive value of CRP and platelet count is 89.6% [Tables 3 and 4].

On analysis, it was found that there is no statistical difference between both EOS and LOS with increased CRP and platelet count. Almost the same number of cases in EOS and LOS had raised CRP and decreased platelet count [Table 5].

Discussion

Out of 270 newborns, 168 (62.2%) were male babies and 102 (37.8%) were female babies. Male babies contributed 62.2% of the study population. This is in accordance with the study of Fanaroff *et al.* who found that the incidence of sepsis is considerably higher in male newborns than female.^[13]

Out of 270 babies with suspected sepsis; blood culture positivity was seen in 75 newborns. The culture positivity rate in our study

was 27.7%. This was in correlation with Manikandan *et al.* whose blood culture positivity was 42.51%.^[14] Similarly, Arshad *et al.*^[15] reported that 25% of cases of NS had positive blood cultures.

Also, the role of high CRP titre in predicting culture-positive sepsis was also analyzed. In our study, it was observed that the sensitivity of raised CRP in predicting confirmed sepsis is 66.6%. The sensitivity of CRP in our study was slightly less than that of Manikandan *et al.* whose sensitivity of CRP was 96.59%.^[14] Our sensitivity was in accordance with Grzywna *et al.*, which showed sensitivity of CRP at 66%.^[16]

In addition, the role of thrombocytopenia in predicting culture-positive sepsis was also analysed. In our study, the sensitivity of a decrease in platelets in confirmed sepsis was 74.6%. This was in accordance with Shirazi *et al.*, who also reported a sensitivity of 61%.^[17] Anwer *et al.* showed sensitivity of thrombocytopenia in the early prediction of sepsis is 52.38%.^[18]

The role of both increase in CRP and thrombocytopenia in predicting confirmed sepsis was also analyzed. It was found that the PPV in our study was 46%. The sensitivity of both raised CRP and decrease in platelets was 61.3%. This was in accordance with Anwer *et al.* in which the PPV was 53.33%.^[18]

Each test used in this study had different specificity, sensitivity and positive predictive accuracy. It has demonstrated that a combination of tests increases the sensitivity, specificity and positive predictive accuracy compared with a single test for the diagnosis of NS.^[19-21]

According to our study, the role of individual haematological tests like CRP and platelet count can be used as the sole indicator of infection, because the sensitivity and specificity of the haematological test for diagnosing sepsis are more compared to blood culture positivity. Culture positivity rate was 27.7% compared to 61% of confirmed sepsis with raised CRP and thrombocytopenia both in early diagnosis of NS.

Evaluation of increased CRP and thrombocytopenia also correlated with EOS and LOS. However, no statistically significant data could be revealed. There was no correlation between EOS and LOS with various haematological markers like CRP and platelet.

So, according to our study, simple haematological tests like CRP titres and platelet count can be used as early, rapid diagnostic markers for confirmed sepsis. Blood culture and sensitivity take

	Culture positive	Culture negative	Total
Raised CRP	50	39	89
Normal CRP	25	156	181
Total	75	204	270

	Culture positive	Culture negative	Total
Thrombocytopenia	56	31	87
Normal platelet	19	164	183
Total	75	195	270

	Culture positive	Culture negative	Total
Increase CRP, decrease platelet	46	54	100
Normal CRP, normal platelet	29	141	170
Total	75	195	270

Haematological test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Increase in CRP	66.6	76.47	56.4	86.1
Thrombocytopenia	74.6	84.1	64.3	89.6
Both increase in CRP and decrease in platelet	61.3	72.3	46.0	89.6

Table 5: Evaluation of increased CRP and thrombocytopenia with EOS and LOS

	Culture positive	Increase CRP, decrease platelet	P
EOS	38	23	0.018
LOS	37	23	0.017
Total	75	46	

$P \leq 0.001$ is considered statistically significant

48–72 h to yield the organism grown and give a sensitivity pattern. Also, a lot of infrastructure is required to give sensitivity report. But blood parameters like total leukocyte count, CRP and platelet count are simple bedside tests yielding reports within a single day on the basis of which empirical antibiotic therapy can be initiated immediately within hours of suspected sepsis, therefore decreasing early neonatal deaths. Also, these tests can be done by simple methods like microscopy and latex agglutination tests without the requirement of bulky, expensive machines.

Conclusion

Blood culture is the gold standard for diagnosing NS. However, blood culture is time-consuming and can take up to 72 h to provide a definitive report. Therefore other haematological tests are required for early diagnosis and prompt action to reduce mortality among newborns. CRP and platelet count can be used as an early indicator of NS.

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Conflicts of interest

There are no conflicts of interest.

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