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Original Research Article

Correlation between C - Reactive Protein and Blood Culture in Neonatal Sepsis at a Tertiary Care Centre in Western Nepal

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ABSTRACT:

Introduction: Neonatal sepsis is a serious problem which needs to be addressed for a better outcome of the neonates. This study was conducted to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of C-Reactive Protein (CRP) in neonates with sepsis in comparison with blood culture. **Methods:** This cross-sectional study was carried out in clinically suspected neonates with sepsis in a tertiary hospital. Association between C-reactive protein and blood culture positivity in neonatal sepsis was studied. **Results:** Out of 245 patients admitted with clinical suspicion of sepsis, 104 (42.45%, 95% CI: 36.18-48.90%) were blood culture proven sepsis. CRP was reactive in 92 cases (88.5%, 95% CI: 80.71 % - 93.89%) of blood culture proven sepsis. Gram negative organisms were predominant, 58 (57.55%) seen from the isolates of blood culture while gram positive organisms were found to be 46 (43.23%). Early onset sepsis was seen in 194 (79.18%) cases, while late onset sepsis accounted for 51(20.82%).The sensitivity and specificity of CRP in the diagnosis of neonatal sepsis was 88.5% and 46.1% respectively with positive predictive value of 54.8% and negative predictive value of 84.1% and diagnostic accuracy of 64.1%. **Conclusion:** Neonatal sepsis is still an important cause of hospital admission in the neonatal intensive care unit of our hospital. This study highlights the high sensitivity and negative predictive value but lower specificity and positive predictive value of CRP in relation to blood culture. The present study depicts a significant correlation between culture positivity and CRP.

Keywords: Blood culture, C - reactive protein, Neonatal intensive care unit, Neonatal sepsis

INTRODUCTION

After prematurity and intra-partum complications, neonatal sepsis is the third leading cause of neonatal mortality, accounting for 42% of early and 13% of overall neonatal mortality.[1] A Nepalese study has reported the prevalence of neonatal sepsis to be 20.3%.[2]

Diagnosing neonatal sepsis can become challenging as it resembles other conditions like congenital pneumonia, meconium aspiration syndrome, congestive heart failure and respiratory distress syndrome. Despite being gold standard method to diagnose neonatal sepsis, blood culture is time consuming, requires well equipped laboratory and above all large amount of blood needs to be drawn from neonates.[3] The yield of blood culture is between 30-70%, hence some neonates go undetected.

C-reactive protein (CRP) is a helpful marker for the diagnosis of sepsis used in addition to blood culture.[4] Various studies have shown that raised CRP has high sensitivity, specificity, positive and negative predictive values for neonatal sepsis. [5,6] This study was conducted to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of CRP in neonates with sepsis in comparison with blood culture. It also aimed to study the association of CRP with blood culture results in the evaluation of neonatal sepsis.

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METHODS:

This observational, cross-sectional study was conducted in the neonatal intensive care unit (NICU) and special care baby unit (SCBU) of Lumbini Medical College and Teaching Hospital (LMCTH), Nepal. Data collection was done for a period of one month from 15 April 2019 to 15 May 2019. During this period, the files of all the neonates admitted to NICU and SCBU from March 2017 to February 2019 with the diagnosis of neonatal sepsis were revisited from the record section. Ethical approval was taken from the Institutional Review Committee (IRC-LMC014-A/019).

All the outborn and inborn neonates, admitted to the NICU and SCBU during the study period with suspected neonatal sepsis and weighing > 1500 grams were included in the study. Neonates who had undergone recent surgical interventions (< two weeks) and those with congenital anomalies rendering them easily susceptible to infections such as cystic fibrosis, Down's syndrome, tracheo-esophageal fistula etc. were excluded.

Data on all the relevant investigation reports like complete blood count, CRP, peripheral blood smear, chest X-ray and blood cultures were noted. Obstetric risk factors and/or clinical features of sepsis such as apnoea, respiratory distress, feeding intolerance and shock were noted.

All the information including birth weight, gestational age at the time of delivery, sex, mode and place of delivery, clinical signs and symptoms, NICU stay, blood culture isolates, and outcome of the patients were retrieved from the manual search of case files from Medical Record Department (MRD). Sepsis was diagnosed based on clinical suspicion and laboratory values such as leucocytosis (>11,000 cells/mm3), leucopenia (<5000 cells/mm3), band cells and toxic granules in peripheral blood smear and positive CRP (>10mg/dl) and positive blood culture.[7] Neonates were classified as having early onset sepsis or late-onset sepsis according to age cut-off of 72 hours of life.

Taking the prevalence of 62%and sensitivity of 90.32% [8], the sample size was calculated using the formula

$$n \geq \frac{(Z_{1-\alpha/2})^2 \times \text{Sens}\,(1-\text{Sens})}{d^2 \times \text{Prevalence}}$$

Where,

Z=1.96 at 95% confidence interval.

P=prevalence, 62%

d= Margin of sampling error tolerated, 0.05

Sens=Sensitivity

α = alpha (0.05)

The minimum calculated sample size was 223.06.

Data were entered in an Excel spreadsheet and analysed using Statistical Package for Social Sciences (SPSS™) version 16. All the qualitative variables and level of CRP were described by using mean ± standard deviation. The sensitivity, specificity, PPV and NPV were calculated for CRP in comparison to blood culture. The association between different variables and clinical outcome was examined using the Pearson Chi-square (X^2) test. A p value < 0.05 was considered to be statistically significant.

RESULTS:

During the study period, a total of 547 neonates were admitted to the NICU and SCBU. Out of these, 245 neonates fulfilling the inclusion criteria were enrolled into the study. Blood culture was positive in 104 neonates (42.45%, 95% CI: 36.18-48.90%) and culture was negative in 141 (57.55%, 95% CI: 49.9-62.6%). Most of the newborns presented with early onset sepsis (n=194, 79.18%), of which 69 (35.57%) cases were culture positive. There were no cases of polymicrobial sepsis, i.e. more than one organism isolated per episode. CRP was reactive in 92 cases (88.5%, 95% CI: 80.71 % - 93.89%) of blood culture proven sepsis.

Table 1. Demographic parameters of the neonates enrolled in the study (N=245)

Variables		Frequency (%)
Sex	Male	150 (61.22%)
	Female	95 (38.78%)
Place of delivery	Inborn	171 (69.80%)
	Outborn	74 (30.20%)
Onset of sepsis	Early onset	194 (79.18%)
	Late onset	51 (20.82%)
Mode of delivery	Normal delivery	164 (66.94%)
	Caesarean section	72 (29.39%)
	Instrumental delivery	9 (3.67%)
Risk factors for sepsis	Perinatal asphyxia	36 (14.70%)
	Meconium	37 (15.10%)
	Maternal fever	27 (11.02%)
	PROM*	39 (15.92%)
	Chorioamnionitis	06 (2.45%)
	Undetermined	100 (40.81%)

*PROM: Pre-labour Rupture of Membrane

Table 1 presents the demographic details of the neonates. The mean weight of the neonates was 2.9±0.68 kg. The mean age at time of presentation was 3.79±6.04 days.

Gram negative organisms accounted for 58 (55.77%) cases of the culture proven sepsis, of which most were due to Enterococcus and Klebsiella. Gram positive organisms isolated constituted 46 (44.23%) cases as shown in table 2.

Table 2. Association of organisms with the onset of sepsis.

Organisms	Early onset sepsis (69 blood culture positive)	Late onset sepsis (35 blood culture positive)
Coagulase negative staphylococcus	12 (17.39 %)	7 (20%)
Staphylococcus aureus	9 (13.04 %)	10 (28.57%)
Alpha hemolytic streptococcus	5 (7.25%)	0 (0%)
Enterococcus	9 (13.04 %)	5 (14.29%)
Klebsiella	10 (14.49%)	4 (11.43%)
Pseudomonas	8 (11.60%)	3 (8.58%)
Acinobacter	8 (11.60%)	2 (5.71%)
E. coli	5 (7.25%)	2 (5.71%)
Salmonella typhi	2 (2.89%)	0 (00%)
Staphylococcus epidermidis	1 (1.45%)	2 (5.71%)

Table 3 shows the association of CRP with the blood culture results of the study population. There is a statistically significant association between CRP reactivity and growth in blood culture, with a p value of <0.001(X^2 =33.173, df=1) (Table 3).

Table 3. Association between CRP and blood culture status (N=245)

CRP	Blood culture (n, %)		p value
	Growth	No growth	
Reactive	92 (54.76%)	76 (45.27%)	p<0.001
Non-Reactive	12 (15.6%)	65 (84.4%)	

In this study, CRP showed 88.5% sensitivity, 46.1% specificity, 54.8% PPV, 84.4% NPV and diagnostic accuracy of 64.1% for diagnosis of culture positive neonatal sepsis.

DISCUSSION:

Neonatal sepsis constitutes one of the important causes of NICU admissions. The gold standard for diagnosis, blood culture is costly and preliminary results are delayed. This study was done to compare and evaluate CRP with blood culture results.

The proportion of blood culture proven sepsis in our study (42.45%) was comparable to the study done by Thakur et al. (42%) and Rawat A et al.[8,9] Other studies have reported similar prevalence. [10,11] In contrast, a study done by Galhotra et al. [12] showed a prevalence of only 7.7%. This might be due to highly sensitive bacteria which responded to the antibiotics. Other studies from Nepal showed a prevalence of 32% and 48%.[13] This high prevalence which is similar to our results may be due to the increasing trend of antibiotic resistance.

Early onset sepsis accounted for 79.18% of the neonatal sepsis in this study. This is in agreement to a study by Thapa B et al. which showed a prevalence of 91.4%.[14] The male preponderance (61.2%) in our study may be linked to the X-linked immunoregulatory gene factor which contributes to the host's susceptibility to infections in male.[15] This can be compared to another study conducted at Kanti Children Hospital in Nepal in which males (69%) were more affected than females (31%).[15]

Chorioamnionitis was present in 5(4.85%) of culture proven sepsis in this study which is higher than that reported by Radis et al. (0.7%).[16] This high incidence in our study may be due to the high rate of maternal fever (11.02%).

Our study revealed predominant bacterial isolates to be gram negative organisms (57.77%), which is similar to a study done by Mendoza-Palomar N et al.[17] Some other studies, on the other hand, showed a predominance of gram positive organisms from the bacterial isolates.[18] This may be due to the fact that the bacteria causing neonatal sepsis continue to change with place and time.[19]

In this study, perinatal asphyxia, meconium stained amniotic fluid, maternal fever and prelabour rupture of membranes were the common risk factors associated with neonatal sepsis. This is in concordance to other studies which may be attributed to the immature immune system.[20]

We found 88.5% sensitivity and 46.1% specificity of CRP in relation to blood culture positivity. These results are comparable to a study done by Bhatia et al. which showed 81.25% sensitivity and 42.86% specificity.[10] El-Sonbaty et al. showed a sensitivity of 91%.[21] Several studies have reported that the sensitivity of CRP for

identifying neonatal infection ranges from 63% to 95%, and specificity from 40% to 97%.[5,22]

Our study showed that there is association between CRP reactivity and culture positivity. CRP was elevated in 88.5% of cases which is similar to a study done by Lim et al.[23] which showed reactive CRP in 84.2% of blood culture positive cases. Hisamuddin et al. found only 76.92% sensitivity and 53.49% specificity of CRP in ruling out sepsis. [5] Saeed et al. also found similar results about CRP sensitivity and specificity.[24]

In our study, PPV and NPV for CRP were 54.8% and 84.4% respectively which is similar to a study by Saboohi et al. which showed 91.3% NPV. [25]

There were certain limitations of our study. In case of outborn neonates, there was paucity of information regarding the mode of delivery, rupture of membranes, maternal infection or illness in the peripartum period available. Lack of standardization also contributed to as one of the limiting factors.

CONCLUSION:

Neonatal sepsis is an important indication of admission to the neonatal intensive care unit of our hospital. A high index of suspicion is required for its diagnosis especially in the presence of risk factors and non-specific clinical features.There was predominance of gram negative organisms from the bacterial isolates in our study. This study highlighted the high sensitivity and negative predictive value but lower specificity and positive predictive value of CRP in relation to blood culture. CRP can therefore be employed as a good test for screening of neonatal sepsis.

Conflict of Interest:

The authors declare that no competing interest exits.

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