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Correlation of C-Reactive Protein, Low Total Leucocyte Count and Platelet Count with Blood Culture in Neonates With Sepsis

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Abstract

Background: Neonatal sepsis is characterized by systemic signs and symptoms of generalised bacterial infection in the first four weeks of life. Early recognition and diagnosis of neonatal sepsis remains a challenge because of the variable and nonspecific clinical presentation. A combination of haematological and biochemical tests may provide a more rapid diagnosis of sepsis than blood culture which takes at least 24 to 48 hours for the results. Objectives: To study the correlation of parameters of sepsis screen with blood culture in neonates with clinical sepsis and or having significant risk factors for sepsis and To study the outcome of neonatal sepsis was our secondary aim. **Material & Methods:** The descriptive prospective study with cross sectional design was conducted on 100 neonates admitted with signs and symptoms of sepsis in the nursery ward and NICU of paediatric department of Bebe Nanki Hospital, GMC, Amritsar. Sepsis screen and blood culture (gold standard for neonatal sepsis diagnosis) and other relevant investigations were sent under strict aseptic conditions and treatment was started. S.CRP levels >1mg/dl, total leukocyte count < 5000 cells/cumm, platelets count < 1.5 lakhs/ µL were taken as positive significant (P <0.005) markers for neonatal sepsis. The data was tabulated and subjected to statistical analysis. **Results:** Positive CRP (>1mg/dl) were found to be highly significant (p<0.0001), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 93.33%,16.00%,76.92%,44.44% and 74.00% respectively. TLC <5000 were found to be significant (p<0.0001), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 65.33%,44.00%,77.78 %,29.73% and 60.00% respectively. Platelet count < 1.5 lakhs/ µL was found to be significant (p<0.0091), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 68.00%, 16.00%,70.83%,14.29% and 55.00% respectively. **Conclusions:** In developing countries like India, where blood culture investigations are limited, altered haematological parameters such as CRP, TLC, and Platelets counts can serve as quick, simple, economical methods to diagnose neonatal sepsis. Further studies with larger sample size are required to substantiate the results.

Keywords:- Neonatal Sepsis, CRP, TLC and Platelet Count

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INTRODUCTION

Neonatal sepsis refers to a clinical syndrome characterized by systemic signs and symptoms due to generalised bacterial infection with a positive blood culture in the first four weeks of life.[1] It develops in approximately 22/1000 live births with a case mortality of between 11% and 19% for those affected.[2] Because of their inherent vulnerability to infections and the invasive treatments to which they are subjected, neonates are vulnerable to sepsis. This is especially true for neonates delivered prematurely or with a low birth weight. Malnutrition, poor socioeconomic status, unhygienic delivery settings, lack of medical infrastructure, and various community-based traditional and cultural practises are all factors that contribute to greater rates of neonatal sepsis in developing countries. Achieving an accurate and timely diagnosis of neonatal sepsis continues to be a challenge for paediatricians.[3]

Neonatal sepsis may be classified according to the time of onset of the disease into early onset sepsis (EOS) and late onset sepsis (LOS). Early onset sepsis presents within the first 72 hours and late onset sepsis presents after 72 hours of age. EOS is caused by microorganisms from the maternal genital tract before or at the time of birth and LOS occurs due to bacteria acquired after delivery (nosocomial or community sources).[4,5]

Newborn with sign and symptoms of sepsis are screened for infection by sepsis screen which includes- Total leukocyte count (TLC), Immature/Total cell ratio (I/T ratio), Absolute neutrophil count (ANC), micro-Erythrocyte sedimentation rate (m-ESR) and C reactive protein (CRP). If any two of the above parameters are positive or significant, the sepsis screen is said to be positive as per NNF guidelines.[6] Definitive diagnosis of neonatal sepsis is based on positive blood or cerebrospinal fluid (CSF) culture, which both take at least 24 to 48 hours and are often falsely negative. The successful treatment and outcome of bacterial infections in neonates depend on the early initiation of appropriate antibiotic therapy.[7]

Early recognition and diagnosis of neonatal sepsis remains a challenge because of the variable and nonspecific clinical presentation. A combination of haematological and biochemical tests may provide a more rapid diagnosis of sepsis than the conventional microbiological methods which are time consuming. Hence, this study was planned to determine the correlation of blood culture with C-reactive protein, platelet count and total leucocyte count in neonatal sepsis as described in methodology.

MATERIAL AND METHODS

This descriptive prospective study with cross sectional design was conducted in the nursery ward and NICU of paediatric department of Bebe Nanki Hospital, GMC, Amritsar in collaboration with department of microbiology of the institute. One hundred neonates admitted to neonatal wing of paediatric department of GMC, Amritsar with signs and symptoms of clinical sepsis{8} or presence of significant predisposing factors for development of sepsis were included after getting written Informed consent from parents or guardian and after approval from the institutional ethical committee,GMC, Amritsar.[8]

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Neonates with Congenital anomalies of GI system, e.g. tracheoesophageal fistula, malrotation of the gut or respiratory system, e.g. Lobar agenesis or cardiovascular system, e.g. TGA, complex heart diseases or central nervous system e.g. microcephaly, anencephaly, other neural tube defects etc, Inborn errors of metabolism, Neonate who received antibiotic before admission or those who have not given consent were excluded.

Proper history of mother and neonate as regards symptoms and signs of clinical sepsis/significant predisposing factors for sepsis were taken and detailed examination of neonate was done as per pre-structured proforma. Sepsis screen (TLC, DLC, platelet count, PBF, Absolute neutrophil count, I/T ratio) and blood culture (The gold standard for neonatal sepsis) of all patients along with other relevant investigations (like Hb,urine culture sensitivity, lumber puncture,and chest x-ray) were sent under strict aseptic conditions and treatment was started.

Blood sample in EDTA vial was sent for Hb, TLC, DLC, platelet count, PBF, Absolute neutrophil count, I/T ratio. Blood sample (2 ml) was collected and sent for quantitative S.CRP levels which were measured by nephalometry in the lab. S.CRP levels >1mg/dl were considered to be positive for sepsis. Total leukocyte count < 5000 cells/cumm and Platelets count < 1.5 lakhs/µL were considered positive for sepsis.[6]

Blood culture method: 1 mL sample of blood was put in blood culture bottle containing 5-10 mL of culture media following all standard precautions and protocol. All blood cultures were observed for at least 72 hours before they were reported as sterile. Drug sensitivity testing was also done.

The collected data was tabulated and subjected to statistical analyses, performed using IBM SPSS Statistics for Windows, Version 25.0. Results were presented as Frequency (Percentage). Inferential statistics like Chi-square test/Fischer Exact test and Independent t test were applied. P value <0.05 was taken as statistically significant to meet the objective of the study.

RESULTS

The present study showed predominance of male neonates. Out of 100 neonates, 61% were males and 39% were females. The mean maternal age was 24.91 ± 3.62 years. 56% cases had maternal age between 20-25 years, followed by 35% cases with age between 25-30 years. There were 4% cases each in age group below 20 years and between 30-35 years. Only 1% case had age above 35 years. The study population consisted of neonates whose mothers were primigravida in 57% cases and in remaining 43% cases, mothers were multigravida. 61% neonates were born through normal vaginal delivery (NVD) and 39% cases through lower segment Caesarean section (LSCS) delivery.
Seventy five (75%) of septic neonates were positive on blood culture and 25 (25%) cases were negative. Out of 75 cases with positive blood culture, Klebsiella 18 (24%) was the most common organism isolated, Pseudomonas in 14(18.7%) and Acinetobacter in 13(17.3%), E.coli, CONS, Staph Aureus, Enterococcus and MRSA were present in 11(14.7%), 9(12%),7(9.3%),2 (2.7%) and 1(1.3%) cases with positive blood culture respectively.

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Table 1:

Blood Culture	Number	Percentage
Positive	75	75%
Negative	25	25%
Micro-Organism	Number	Percentage
Klebsiella	18	24%
Pseudomonas	14	18.7%
Acinetobacter	13	17.3%
E. Coli	11	14.7%
CONS (Coagulase Negative Staphylococci)	9	12%
Staph Aureus	7	9.3%
Enterococcus	2	2.7%
MRSA	1	1.3%
Total	75	100%

Sixty (60%) cases in the present study were of Early Onset Sepsis. The remaining forty(40%) cases were of late onset type. Out of 60 cases with early onset sepsis, 50 (83.3%) were blood culture positive and 10 (16.7%) were blood culture negative. Out of 40 cases with late onset sepsis, 25 (62.5%) were blood culture positive and 15 (37.5%) were blood culture negative.

Table 2:

Type of Neonat Al Sepsis	Blood Culture Positive (N=75)		Blood Culture Negative (N=25)		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
EOS (early onset Sepsis)	50	83.3%	10	16.7%	60	60%
LOS (Lateonset Sepsis)	25	62.5%	15	37.5%	40	40%

Positive CRP ((quatitative) >1mg/dl) were found to be highly significant in the study (p<0.0001), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 93.33%,16.00%,76.92%,44.44% and 74.00% respectively.

Table 3:

Parameter		Total		Blood Culture Positive (N=75)		Blood Culture Negative (N=25)		P-Value
		Number	Percentage	Number	Percentage	Number	Percentage	
CRP (mg/L)	Positive	91	91%	70	76.9%	21	23.1%	<0.000 1
	Negative	9	9%	5	55.6%	4	44.4%	0.6442

Parameter	Sensitivity	Specificity	PPV	NPV	Accuracy
CRP (>1 mg/dl)	93.33%	16.00%	76.92%	44.44%	74.00%

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TLC <5000 were found to be significant in the study (p<0.05), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 65.33%, 44.00%, 77.78%, 29.73% and 60.00% respectively.

Table 4:

Parameter		Total		Blood culture positive (n=75)		Blood culture negative (n=25)		P-value
		Number	Percentage	Number	Percentage	Number	Percentage	
TLC (cells/cumm)	<5000	63	63%	49	77.8%	14	22.2%	<0.0001
	5000-20000	22	22%	14	63.6%	8	36.4%	0.0745
	>20000	15	15%	12	80.0%	3	20.0%	0.0012

Parameter	Sensitivity	Specificity	PPV	NPV	Accuracy
TLC (<5000 cells/cumm	65.33%	44.00%	77.78%	29.73%	60.00%

Platelet count below 1.5 lakhs/ µL was found to be significant (p<0.05), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 68.00%, 16.00%,70.83%,14.29% and 55.00% respectively.

Table 5:

Parameter		Total		Blood culture positive (n=75)		Blood culture negative (n=25)		P-Value
		Number	Percentage	Number	Percentage	Number	Percentage	
Platelet count (lakhs/ µL)	<1.5	72	72%	51	70.8%	21	29.2%	0.0091
	>1.5	28	28%	24	85.7%	4	14.3%	0.0281

Parameter	Sensitivity	Specificity	PPV	NPV	Accuracy
Platelet Count (< 1.5lakhs/µL)	68.00%	16.00%	70.83%	14.29%	55.00%

Out of the 100 cases of neonatal sepsis,86 (86%) cases were discharged,9 (9%) expired, 4(4%) took leave against medical advice and 1(1%) were referred for further management.

Table 6:

Outcome	Number	Percentage
Discharged	86	86%
Lama	4	4%
Referred	1	1%
Expired	9	9%

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DISCUSSION

The present study had 50 (83.3%) with early-onset sepsis which is similar to findings of Sriram R and Garg A et al.[9,10] Prevalence of blood culture proven neonatal sepsis was 75% and this is comparable to study done by Patel U et al,[11] who found it to be 70.73% in their study. This was higher than studies done by Chako B et al,[12] (41.7%), Roy I et al,[13] (47.5%), Ahmed Z et al,[14] (28%), Manucha V et al,[15] (14%) and Ugochukwu EF16 (10.7%). The low blood culture positivity in some studies might be due to the low amount of blood drawn or possibility of infection with anaerobes or presence of fastidious organisms. Klebsiella pneumoniae is found to be most common organism of neonatal sepsis in developing countries as shown by studies of Ahmed Z et al,[14] and Manucha V et al.[15] This is similar to the findings of our study. The reason for isolation of different predominant organism in different studies may be because of different geographic location and replacement of one organism or a group of organisms with another organism or group of organism.[16]

Sixty three (63%) neonates had TLC below 5000 cells/cumm, twenty two (22%) neonates had TLC between 5000 to 20,000 cells/cumm and fifteen(15%) neonates had TLC greater than 20,000 cells/cumm. Among those with TLC below 5000 cells/cumm, 49 (77.8%) cases had positive blood culture and 14 (14%) cases had negative blood culture. This was found to be highly statistically significant ($p<0.0001$) Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 65.33%, 44.00%, 77.78 %, 29.73% and 60.00% respectively. Anwer SK et al,[17] documented a high specificity (93.1%) and a low sensitivity (14.3%) for TLC. Neonates who are not infected may also demonstrate abnormal TLC related to the stress of delivery thus, Manucha V et al,[15] concluded that TLC is of little clinical use in the diagnosis of neonatal infection because of the wide variations in values and the overlap between normal and abnormal values.[18,19,20]

CRP is a non-specific, acute-phase protein that rises in response to inflammatory processes. Ninety one (91%) cases were found to be CRP positive in our study, this is comparable to the findings of Monga N et al,[21] and Goswami Y et al.[22] Out of 91 neonates who had positive CRP in our study 70(76.9%) were blood culture positive and 21 (23.1%) were blood culture negative. The number of neonates with positive blood culture was significantly higher as compared to neonates with negative blood culture ($p<0.05$) positive CRP (>1mg/dl) were found to behighly significant ($p<0.0001$), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 93.33%, 16.00%, 76.92%, 44.44% and 74.00% respectively. Ahmed Z et al,[14] reported the sensitivity, specificity, PPV and NPV of CRP as: 85.5%, 95.0%, 82.7% and 95.9% respectively while Shabbir et al,[23] has reported that CRP had 74% sensitivity and 76% specificity. The marked difference of results among studies evaluating C-reactive protein as useful marker, can be explained by non-availability of universally acceptable definition of neonatal sepsis, difference in reference range values and environmental influence on the results in different setups. A negative CRP, however can be more useful in making the decision to discontinue antibiotics especially if the neonate has no clinical feature of sepsis. Khashabi J et al,[24] in 2004 also demonstrated that CRP can be

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a useful guide in making a decision to discontinue antibiotic therapy, thus facilitating early discharge, significantly reduced cost, complications of treatment, misuse of antibiotics and family anxiety.

Seventy two (72%) neonates had platelets counts < 1.5 lakhs/ µL were 51(70.8%) cases had positive blood culture this was found to be highly statistically significant (p < 0.0091) and 21(29.2%) were blood culture negative. Platelet count < 1.5 lakhs/ µL was found to be significant (p<0.05), Sensitivity, Specificity, PPV, NPV and Diagnostic accuracy were 68.00%, 16.00%,70.83%, 14.29% and 55.00% respectively. Arabdin N et al,[25] out of 170 neonates, 104 of neonates mean age of 12.12±8.88 days. The majority of the babies 73 (42.9%) were in the age group of 0-7 days. Most of the neonates 72 (42.4%) were born via normal vaginal delivery (NVD). Of the neonates, 117 (68.82%) presented with fever, and 105 (61.76%) were reluctant to feed. Furthermore, 65.29% of the neonates had thrombocytopenia, of which 34 (20%) had mild, 43 (25.3%) had moderate, and 34 (20%) had severe thrombocytopenia. In neonates with positive blood culture, the platelet level was low (p<0.001).

CONCLUSIONS

The study focuses on neonatal sepsis risk factors and the significance of haematological markers in the diagnosis of neonatal sepsis. In developing countries like India, where facilities to blood culture is limited, newborns with altered haematological parameters such as CRP, TLC, and Platelets count, as well as clinical signs and symptoms, should be regularly monitored and considered in sepsis diagnosis and thus treating them appropriately to prevent morbidity and mortality. These can serve as quick, simple, economical methods to diagnose neonatal sepsis in developing countries. This will also help to minimize the duration of antibiotic treatment which can prevent neonates from the microorganisms with emerging antibiotic resistance.

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