ORIGINAL ARTICLE

Utility of Hematological Parameters in Detection of Neonatal Sepsis

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Abstract:

Background: Sepsis in neonates may be difficult to differentiate from other conditions because the clinical signs are non specific. The hematological response to inflammation in neonates includes many changes in the form of an abnormal total count, morphological changes, thrombocytopenia and various inflammatory markers in serum. *Aim and Objectives*: To assess the importance of hematological profile in early diagnosis of neonatal sepsis and to calculate the sensitivity, specificity and predictive values of individual hematological tests and various test combinations. *Material and Methods*: It was a prospective study including 128 neonates, out of which 65 were cases (31 proven septic and 34 probable cases; blood culture being the gold standard) while rest 63 were controls. They were evaluated for sepsis using hematological scoring system (HSS) and c-reactive protein (CRP). Parameters used in score were Immature: Total polymorphonuclear cell (I:T) and Immature: Mature polymorphonuclear cell (I:M) ratio, Total White blood cell (WBC) count, Total Polymorphonuclear (PMN) cell count, Immature Polymorphonuclear cell count, Platelet count and degenerative changes observed in neutrophils. *Results*: Blood culture was positive in 31 cases. Preterm infants and low birth infants were more prone to sepsis. I: T ratio, total PMN count, I:M ratio and Immature PMN count were found to have high sensitivity while degenerative changes in PMN was found to be highly specific test for sepsis along with total WBC count. Applying χ^2 test, the association of sepsis was found to be significant with I:T ratio, I:M ratio, Immature PMN count, Total WBC count, Platelet count and positive CRP test. As the Hematological score increased from 1 to 6, sensitivity and negative predictive value decreased and vice-a-versa happened with specificity and positive predictive value. *Conclusion*: HSS has high sensitivity and specificity, the certainty of sepsis being present with higher scores and using combination of various parameters. Hence, it may aid the clinicians in identifying sepsis and to start proper and timely antibiotic therapy.

Keywords: Neonatal Sepsis, Hematological Score System, Rural Set Up

Introduction:

The WHO estimates that perinatal deaths are responsible for most of the childhood mortality below the age of 5 years in developing countries like India [1] and neonatal infections are one of the most common cause of such perinatal mortality [2, 3]. According to National Neonatal Perinatal Database (NNPD 2002-03), in India, the incidence of neonatal sepsis is 30 per 1000 live births [4]. Neonatal septicemia is a clinical syndrome characterized by some signs and symptoms accompanied by bacteremia in the 1st month of life [5]. Group B Streptococcal (GBS) disease is most important cause in Europe and North America, but there is preponderance of gram negative organisms in tropical and developing countries [6]. In India, according to NNDP (2002-03) the most frequent cause is *Klebsiella pneumoniae* followed by *Staphylococcus aureus* [7]. The initial warning signs and symptoms of sepsis are often non specific [8], subtle and different for different gestational ages [9] which makes it difficult to establish an early clinical diagnosis, as well as it is rapidly progressive to

death. Hence, it is critical to make a timely diagnosis when it can be treated. Blood Culture is considered the "Gold Standard" for its diagnosis, but it has certain shortcomings like it is time consuming (requires a minimum of 48-72 hours), has low yield of positive results (8-73%), may show false positive results due to contamination and negative blood cultures in fatal generalized bacterial infections [10] and is not readily available in rural health care centers. In recent years, some highly sensitive and specific inflammatory markers e.g. ELISA, haptoglobins, interleukins, counter immunoelectrophoresis etc. have been evaluated for diagnosis [11], but they are sophisticated and expensive, so impractical for developing countries like India. Hence, the need is for a cheap, easily performed, quick and reliable test. Such are the Complete Blood Count (CBC) with various neutrophil parameters and C-reactive protein (CRP) that is most frequently used [12]. These are cost-effective, simple bed side tests which can be done within a short time before putting the neonate on empirical antibiotic therapy that may result in overtreatment and development of antibiotic resistance and also overburden the underprivileged parents with its high cost [13]. This cross-sectional study was undertaken to evaluate their usefulness as indicators for early diagnosis of neonatal sepsis in a developing country like India with significant health burden.

Material and Methods:

This was a hospital based case control study conducted over a period of two months from April to June 2014. A total of 128 neonates were enrolled out of whom 65 neonates admitted in NICU with clinical suspicion of sepsis (based on clinical features and/or risk factors) were studied and 63 normal neonates from immunization clinic were studied for comparison. The major clinical features were feeding problems, lethargy, respiratory distress, irritability, convulsions, abdominal distention, recurrent attacks of apnea

or cyanotic spells, vomiting, poor cry and tachypnoea and major perinatal risk factors were prematurity, low birth weight, birth asphyxia, home delivery, caesarean section and meconium aspiration. So, the study population (n=128) was categorized as follows:

Group 1 (proven sepsis; n=31) - with clinical suspicion of sepsis and positive blood culture.

Group 2 (probable sepsis; n=34) - with clinical suspicion of sepsis but negative blood culture.

Group 3 (control; n=63) - without any clinical suspicion of sepsis and with negative blood culture.

Exclusion Criteria for both groups were contaminated cultures, prior antibiotic exposure, major congenital abnormality, inborn errors of metabolism and hemolytic jaundice. The research work was approved by Institutional Ethics Committee and informed consent was also obtained from parents of all neonates.

Under complete aseptic conditions, 3 ml of blood sample was obtained by peripheral venipuncture. One ml of the samples was collected in tripotassium ethylene diamine tetra-acetic acid containing non-siliconized vaccutainer tubes. Sepsis work-up involved complete blood counts along with hematological scores, CRP values and blood culture with antibiotic sensitivity. Peripheral blood smears were prepared from the sample itself immediately and stained with Leishman stain. Differential counts were performed on these smears by counting at least 200 cells. Immature neutrophils included promyelocyte, myelocyte, metamyelocyte and band forms [6]. Degenerative morphologic changes in neutrophils were graded on 0 to + 4 scale according to Zipursky *et al* [14] on the basis of different degrees of toxic granulation. Total leukocyte count and platelet count readings were obtained by LH 750 Beckman and Coulter five part automated cell counter. Immature to Total

Neutrophil (I: T) ratio and immature to mature (I: M) ratio were calculated manually. The hematological findings were analyzed according to Hematological Scoring System (HSS) of Rodwell, *et al* [15] using the reference values of Manroe *et al* [12]. The HSS (Table 1 and 2) assigns a score of 1 to each of the seven criteria. The total score varies from 0 to 8. However, an abnormal total PMN count is assigned a score of 2 if no mature polymorphs are seen on peripheral smear to compensate for low I: M ratio. If the total score is ≤2, sepsis is very unlikely and if the score is ≥5 sepsis is considered to be very likely.

Statistical Analysis:

Sensitivity, specificity and positive and negative predictive values were evaluated for each of the seven criteria of HSS and of the combinations using standard statistical methods. $P<0.05$ was considered as significant statistical difference. Comparison was made using Chi square. The statistical analyses were performed using SPSS version 11 for windows.

Results:

Amongst the cases, there were 34 males (52.3%) and 31 females (47.7%), with Male: Female ratio of 1.1:1. Maximum number (32; 49.2%) of patients belonged to the age group 4-28 days. Most of the cases of sepsis were preterm (41; 63%) and low birth weight (56;86.2%) neonates. Maximum cases (40%) belonged to low birth weight group of 1.5 to <2.5 kg.

Out of the total 31 blood culture positive cases, gram negative infection was found in 19 (61.2%) cases whereas in 12 (38.8%) cases, the underlying etiology was infection by gram positive organisms (Table 2).

Table 1: Hematologic Scoring System [15]

Criterion	Abnormality	Score
I:T ratio>0.2[*]	Increase	1
Total PMN Count[*]	Increase/Decrease /No mature PMN seen	1 2
I:M ratio	≥0.3	1
Immature PMN Count[*]	Increase	1
Total WBC Count	Increase/Decrease (≤5,000/mm^3 or ≥25,000, 30,000 and 21,000/mm^3 at birth, 12-24 hr. and day 2 onwards, respectively)	1
Degenerative changes in PMN[**]	≥3+	1
Platelet Count	≤1,50,000/mm^3	1

I: T=Abnormal immature to total neutrophil ratio; I:M=Abnormal immature to mature neutrophil ratio; PMN=Polymorph nuclear; WBC=White blood cell [*]Normal Values as defined by reference ranges of Manroe, et al.[**]Quantified on scale of 0 to +4 according to classification of Zipursky, et al Total PMN Count: 7,800-14,500/mm^3 (<72 h),750-4,500/mm^3 (>72 h)Immature PMN Count: 500-1,450/mm^3 (<72 h) 500/mm^3 (>72 h)

Table 2: Bacteriological Profile in the Blood Culture Positive (Proven Sepsis) Cases (N=31)

Bacteria detected in blood culture	Number of cases (%)
Gram negative organism	
Klebsiella pneumoniae	2 (6.4%)
Pseudomonas aeruginosa	5 (16.1%)
Citrobacter spp.	7 (22.6%)
Acinetobacter spp.	2 (6.4%)
E. coli	1 (3.2%)
Enterobacter spp.	2 (6.4%)
Total	**19 (61.2%)**
Gram positive organism	
Staphylococcus aureus	4 (12.9%)
Coagulase negative *Staphylococci*	7 (22.6%)
Enterococcus spp.	1 (3.2%)
Total	**12 (38.8%)**

Amongst the hematological parameters, I:T ratio and I:M ratio was >.2 in 22 (71%) of proven cases. Total PMN count was also abnormal along with increased immature PMN counts whereas total WBC count was normal in most cases. Interestingly, degenerative changes with grade ≥3 were not observed in any of the controls or proven cases while it was present in only 2 cases of probable sepsis. Platelet count was also decreased in 28 (58.1%) out of 31 proven cases. Further, in both proven and probable cases, there was not much difference in number of cases with positive and negative CRP values. Applying x^2 test, the association of sepsis was found to be significant with I:T ratio, I:M ratio, Immature PMN count, Total WBC count, Platelet count and positive CRP test. No significant association of sepsis was observed with Total PMN count and degenerative changes in PMN (Table 4). On comparative analysis of tests used in proven sepsis population,

I: T ratio, I:M ratio and Immature PMN count were found to have high sensitivity while total WBC count was found to be highly specific test for sepsis along with total WBC count. Maximum positive predictive value was found to be of Total WBC count followed by I:T and I:M ratio, while almost all the parameters of HSS had high negative predictive values (Table 5).

On analyzing the hematological scores of various groups, in the proven cases all had score ≥1 while 14 (45.2%) cases had score ≥5. In probable cases, 33 patients (97%) scored ≥1 and only 9 (26.5%) scored ≥5. Amongst control cases, none scored ≥5, only 4 (6.3%) scored ≥3. Although 48 (76.2%) had score of ≥1. The association of increasing scores was found to be significant with septic cases (Table 6). The hematological scores in 31 sepsis proven cases were compared and it was found that score of ≥6 had 100% specificity and PPV while score ≥2 had very high NPV and sensitivity. As the

score increased from 1 to 6, sensitivity and NPV decreased and vice-a-versa happened with specificity and PPV i.e. the value increased with increase in score reaching 100% score of 6 (Table 7).

When only one parameter of abnormal (either increased or decreased) TLC was used to detect the cases, its specificity was found to be 78% and a NPV of 89.4%. But when the number of parameter was increased by adding I: T ratio, the specificity increased to 94.8%. The specificity was found to increase further (reaching 97.9%) by using three parameters of HS i.e. TLC, I:T ratio and platelet count along with a PPV of 80% for the test combination. If HS of more than 3 was combined with CRP positivity the specificity was found to be 84.5% and NPV 85.4% (Table 8). The results show that using the various parameters of HS in combination increased the specificity and PPV significantly.

Table 3: Results of Various Tests Obtained in Each Study Group

Tests	Control (n=63)	Probable sepsis (n=34)	Proven Sepsis (n=31)	χ^2 test		
				χ^2	Df	P value
I:T ratio				58.042	2	<0.0001
>0.2	1(1.6%)	20(58.8%)	22(71%)			
≤0.2	62(98.4%)	14(41.2%)	9(29%)			
Total PMN count				4.334	4	0.181
Increased	16(25.4%)	13(38.2%)	13(41.9%)			
Decreased	26(41.3%)	14(41.2%)	12(38.7%)			
Normal	21(33.3%)	7(20.6%)	6(19.4%)			
I:M ratio				58.042	2	<0.0001
≥0.3	1(1.6%)	20(58.8%)	22(71%)			
<0.3	62(98.4%)	14(41.2%)	9(29%)			
Immature PMN Count				17.081	2	<0.002
Increased	16(25.4%)	18(52.9%)	21(67.7%)			
Normal	47(74.6%)	16(47.1%)	10(32.3%)			
Total WBC Count				30.55	4	<0.0001
Increased	0(0%)	7(20.6%)	6(19.4%)			
Decreased	1(1.6%)	5(14.7%)	8(25.8%)			
Normal	62(98.4%)	22(64.7%)	17(54.8%)			
Degenerative changes in PMN				5.617	2	0.0603
≥3+	0(0%)	2(5.9%)	0(0%)			
≤2+	63(100%)	32(94.1%)	31(100%)			
Platelet Count				14.794	2	0.0006
Normal	51(81%)	24(70.6%)	13(41.9%)			
Decreased	12(19%)	10(29.4%)	18(58.1%)			
CRP				25.464	2	<0.0001
Positive (≥6μg/ml)	5(7.9%)	15(44.1%)	16(61.6%)			
Negative	58(92.1%)	19(55.9%)	15(48.4%)			

Table 4: Comparative Analysis of Tests Used in Proven Sepsis Population (N=31)

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
I: T ratio	71%	78.40%	51.20%	89.40%
Total PMN Count	80.60%	28.90%	26.60%	82.40%
I: M ratio	71%	78.40%	51.20%	89.40%
Immature PMN Count	67.70%	64.90%	38.20%	86.30%
Total WBC Count	45.20%	86.60%	51.90%	83.20%
Degenerative changes in PMN	0%	97.90%	0%	75.40%
Platelet Count	58.10%	77.30%	45%	85.20%
CRP	51.60%	79.40%	44.40%	83.70%

Table 5: Analysis of Hematological Scores Obtained in Each Study Group

Score	Control (n=63)	Probable Sepsis (n=34)	Proven Sepsis (n=31)	χ^2	P value
≥1	48(76.2%)	33(97.0%)	31(100%)	4.625	0.099
≥2	20(31.7%)	28(82.4%)	30(96.8%)	2.154	0.3406
≥3	4(6.3%)	24(70.6%)	26(83.9%)	16.444	0.0003
≥4	1(1.6%)	16(47.1%)	20(64.5%)	16.27	0.0003
≥5	0(0%)	9(26.5%)	14(45.2%)	0.696	0.4042
≥6	0(0%)	0(0%)	1(3.2%)	NA	NA

χ^2= 49.505; Df= 10; P value <0.0001

Table 6: Comparative Analysis of Hematological Scores in Sepsis Proven Population (N=31)

Score / Test combination	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥1	100%	16.50%	27.70%	100%
≥2	96.80%	50.50%	38.50%	98%
≥3	83.90%	71.10%	48.10%	93.20%
≥4	64.50%	82.50%	54.10%	87.90%
≥5	45.20%	90.70%	60.90%	83.80%
≥6	3.20%	100%	100%	75.80%
TLC	71%	78.40%	51.20%	89.40%
TLC + I:T ratio	38.70%	94.80%	70.60%	82.90%
TLC + I:T ratio + Platelet Count	25.80%	97.90%	80%	80.50%
HS ≥3 + CRP	54.30%	84.50%	53.10%	85.40%

Discussion:

In developing countries like India, risk of neonatal sepsis is increased because of less number of institutional deliveries, poor level of hygiene and postnatal follow-up. Aggarwal *et al* reported that sepsis was the commonest cause of neonatal mortality and was responsible for 30-50% of the total neonatal deaths each year in developing countries. The incidence of neonatal sepsis was reported to be 38 per 1,000 live births in tertiary care institutions [16].

The major problem in neonatal infection is not only identification of the infected infant but also of identifying the non-infected infant. Early as well as correct diagnosis is a difficult task but can be made, to an extent, based on clinical suspicion and laboratory tests.

Out of 65 cases, 41 (63%) were preterm and 56 (86.2%) were low birth weight. Our findings are similar to those by Shirazi *et al*, Khair *et al*, Makkar *et al* and Khurshid *et al* [13, 17-19]. The inability of neonates to completely muster the minimum inflammatory response makes them more susceptible to bacterial invasion of the blood stream than older children and adults and the risks are even higher in preterm infants [20]. As in studies by Patel *et al* [21] and Mondal *et al* [22], in our study also gram negative organisms were commoner than gram positive organisms as the causative agents.

On evaluating the parameters of HS, the association of sepsis was found to be significant ($p < 0.05$) with I: T ratio, I: M ratio, Immature PMN count, Total WBC count and thrombocytopenia as also in other studies [17, 18, 23]. Whereas, degenerative changes observed in neutrophils and total PMN count were nonsignificant findings, which is supported by various studies [17,18] while Mondal *et al* [22] described degenerative

changes to be one of the most reliable indicator. Although, despite no significant association of degenerative changes in our study, it was found to have high specificity (97.9%) i.e. they are never seen in healthy babies. Khair *et al*, in his study discussed that Total WBC count, PMN count, immature PMN were not useful in detection of septicemia [17]. Association of CRP value with sepsis was also calculated as significant which is similar to other studies [19, 21].

Total PMN count was found to have maximum sensitivity (80.6%) amongst various parameters followed by I: T and I: M ratio (71%) to detect sepsis. This finding is supported by Khurshid *et al* [19]. Degenerative changes (97.9%) followed by Total WBC count (86.6%) had maximum specificity. Highest positive predictive value was observed for Total WBC count (51.9%) followed closely by I: T and I: M ratio (51.2% each). Study by Makkar *et al* support our findings while thrombocytopenia had maximum positive predictive value in study by Majumdar *et al* [18,23] I:T and I:M ratio also had highest negative predictive value (89.4%) followed by Immature PMN count (86.3%) and thrombocytopenia (85.2%) in the present study, similar observations were made by other authors [17,18, 23].

A score of more than 3 was present in 26 out of 31 proven cases and 24 out of 34 probable cases. This association of increased score with sepsis was found to be significant. Also score more than 5 was highly specific (90.7%) and had a high positive predictive value of 60.9%. This significant association has also been documented by other authors [17, 18, 20, 24]. As in various studies maximum numbers of cases were detected by combining HS ≥3 and CRP positivity, increasing the sensitivity [22, 24-26]. As found in our study, the increase in the number of parameters used in combination significantly increased the specificity and positive predictive value. A combination of Total WBC count, I:T ratio and thrombocytopenia was found to have a high specificity of 97.9% and positive predictive value of 80%.negative predictive value was highest for a single test of Total WBC count (89.4%) followed by HS ≥3 and CRP positivity (85.4%). These results were consistent with other studies [17, 19]. Siegel recommends an elevated I:T ratio to identify infected infants and indicates that further tests are of no value, our study suggests that a combination of various tests is more reliable to diagnose sepsis [27]. In our study, it is also shown that individual tests can become positive in normal neonates and various non-infective conditions, conversely septicemia can sometimes be observed with normal findings.

Conclusion:

The association of sepsis was found to be significant (p<0.05) with I: T ratio, I: M ratio, Immature PMN count, Total WBC count and thrombocytopenia. Association of CRP positivity with sepsis was also calculated as significant. Combining HS≥3 with CRP positivity also increased sensitivity significantly. The increase in the number of various hematological parameters used in combination significantly increased the specificity and positive predictive value. Combination of Total WBC count, I: T ratio and thrombocytopenia has high specificity (97.9%) and positive predictive value (80%).

HSS has high sensitivity and specificity, the certainty of sepsis being present with higher scores and using combination of various parameters. Hence, it may aid the clinicians in identifying sepsis and to start proper and timely antibiotic therapy. However, it is equally important to further simplify and standardize the interpretation of this test globally.

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