Research Article

Early diagnosis and evaluation of neonatal septicemia by hematological scoring system

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ABSTRACT

Background: Neonatal septicemia is a major health problem. Morbidity and mortality in the neonatal period are mostly due to neonatal septicemia. **Objective:** The present study was undertaken to highlight the importance of hematological scoring system (HSS) in the early diagnosis and evaluation of neonatal septicemia and to correlate these hematological parameters with blood culture and C-reactive protein. **Materials and Methods:** This study was prospective and was done over the period of 1 year including 100 clinically suspected neonatal septicemia cases admitted in neonatal intensive care unit. Hematological parameters were measured in all cases. Culture positivity was taken as the criterion for definitive diagnosis. Specificity, sensitivity, positive predictive value, negative predictive value, and *P* value were calculated for each hematological parameter. **Results:** Of 100 clinically suspected neonates with sepsis studied, 19% were culture positive, 63.2% were male, 84.2% were term neonates, and 84.2% were low birth weight neonates (<2.5 kg). Early onset septicemia was more common (73.6%). In neonates who were delivered by spontaneous vaginal delivery (73.7%), septicemia was more common and also in neonates who were delivered in the hospital (84.2%). *Klebsiella pneumoniae* was the most common organism isolated (36.8%). By comparison of Rodwell's HSS with blood culture results, it was found that the presence of likelihood of sepsis with score ≥3 was 59.25 % and with score ≥5 was 100%. With score ≤2, the likelihood of sepsis was absent (95.9%). **Conclusion:** HSS is useful for distinguishing the infected infants from non-infected infants. It is also useful to provide an effective guideline for making decisions regarding the proper use of antibiotics for early treatment.

KEY WORDS: Hematological scoring system; Neonatal septicemia; Early diagnosis; Evaluation

INTRODUCTION

Neonatal sepsis is the most important cause of mortality and morbidity, especially, among low birth weight and preterm babies in developing countries. Neonatal septicemia can be defined as generalized bacterial infection in infants during the 1st month of life. The incidence of naonatal sepsis is around 30 per 1000 live births according to pooled hospital data based on National Neonatal Perinatal Database(NNPD).[1] Clinical features of infection in neonates are very non-specific and may be different at different age, so, for early diagnosis, higher index of suspicion is required by the pediatricians.[2]

Clinical diagnosis of neonatal septicemia is a difficult task. The early signs and symptoms are non-specific, but treatment has to be started immediately, as an outcome of septicemia in neonate largely depends on its early identification.[3] Pediatricians need a screening blood test by which they can predict the bacterial infection with confidence for the ill newborn and can give early treatment.

Although blood culture was considered as the gold standard to diagnose septicemia, the technique takes more time at least 48 h, and for doing the test, well-equipped laboratory

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is required which is not available in most of the hospitals. Therefore, the test which is cheaper and can be easily performed is needed. The test which is ideal for the diagnosis of neonatal sepsis should have maximum specificity and sensitivity. Although this marker is specific and sensitive, it is time consuming, expensive, and not practically applied for every clinically suspected infant.[4]

Pediatricians give antibiotics to the septic newborns empirically to prevent deterioration because diagnosis by culture takes more time. Nowadays, antibiotics are used prophylactically, so there are problems such as development of drug resistance, cost of unnecessary drug treatment, and drug toxicity. Thus, early diagnosis of neonatal septicemia is important; for that reason, this study was done.

Rodwell *et al*. developed a hematological scoring system (HSS) based on the white blood cell (WBC) count, degenerative changes in neutrophils, total and immature neutrophil counts and ratios, and thrombocytopenia. In that, sensitivity was 96% and negative predictive value (NPV) was 99%. He concluded that the HSS should improve the diagnostic accuracy so it can be used as a screening test for sepsis and could make interpretation of test easy and simple.[5]

There is an increased use of antibiotics due to the inability of early diagnosis of neonatal sepsis. Thus, laboratory tests that can help the clinician to diagnose neonatal sepsis have a considerable relevance.[6,7] The early diagnosis of neonatal sepsis is a challenge for pediatricians and pathologists. The present study is conducted to see the role of HSS (Rodwell's HSS) in early diagnosis of neonatal septicemia. This is a simple and cost-effective test which can be done quickly before giving antibiotic therapy to the neonate. By this test, the clinicians can identify sepsis and can prescribe proper antibiotic therapy to the infected neonates. Hence, unnecessary exposure of neonates to antibiotics can thus be prevented. The advantage of HSS is that it is very simple, easy to perform, cheaper and can be applied to all neonates, including neonates who have taken antibiotic therapy.[4]

MATERIALS AND METHODS

A prospective study was done during a period of January 2014–December 2015 after getting ethical clearance. Samples were collected from 100 cases who were clinically suspected and admitted in the neonatal intensive care unit (NICU) of the civil hospital. All the newborns in the age group of 0–28 days with clinical features suggestive of septicemia (fever, not taking feed, respiratory distress, low birth weight, convulsion, poor cry, and meconium stained liquor) were included in the study. Newborns with >28 days of life, neonates whose mothers had pregnancy-induced hypertension, and neonates with asphyxia were excluded from the study.

Table 1: Rodwell's hematological scoring system

Criteria	Abnormality	Score
Total WBC count	≤5,000/mm^3	1
	≥25,000, 30,000, and 21,000/mm^3 at birth, 12–24 h, and day 2 onward, respectively	1
Total PMN count	1800–5400/mm^3	0
	Increased or decreased	1
	No mature PMN seen	2
Immature PMN count	600	0
	Increased	1
I: T PMN ratio	0.120	0
	Increased	1
I: M PMN ratio	<0.3	0
	≥0.3	1
Degenerative changes in PMN	Toxic granules/cytoplasmic vacuoles	1
Platelet count	<150,000/mm^3	1

WBC count: White blood cell count, PMN: Polymorphonuclear cells (neutrophils), I: T PMN ratio: Immature-to-total neutrophil ratio, I: M PMN ratio: Immature-to-mature neutrophil ratio

Table 2: Scoring system interpretation

Score	Interpretation
≤2	Sepsis is very unlikely
3– 4	Sepsis is suspected
≥5	Sepsis or infection is more likely

Score ≤2 was interpreted as unlikely of sepsis; scores 3–4: Possibility of sepsis and≥5 infection or sepsis is more likely. Obtained minimum scoring is 0 and maximum scoring 8

Neonates who were presented within first 7 days of life were defined as early onset neonatal septicemia and neonates who were presented within 7-28 days of life were defined as late onset septicemia.

Blood samples of these neonates collected by the pediatrician in vacutainer tubes with EDTA as an anticoagulant under complete aseptic condition sent to laboratory were taken to study the hematological parameters.

Hemoglobin, platelet count, and uncorrected WBC count were measured using Micro-60 automated hematology analyzer-3 part after running quality control of low, normal, and high values for accurate results. Peripheral blood smears were prepared within 2 h of receiving sample and stained with Giemsa stain.

The smears were examined under microscope for the Rodwell's HSS which includes the following findings: Corrected leukocyte count, neutrophil count polymorphonuclear cells (PMN), immature PMN count*, immature-to-total (PMN ratio I:T), immature-to-mature (PNM ratio I:M), and degenerative changes in neutrophils**

(differential counts were done on Giemsa stained smears by counting 100 cells).

Immature PMN include promyelocyte, myelocyte, metamyelocyte, and band forms. In band cell, nucleus is indented by more than one-half, with central band between two lobes.

**In degenerative changes, vacuolization, toxic granulations, [Figure 2] degenerated neutrophils, and Dohle bodies were included [Figure 3].

HSS reserves a 1 score for each of seven findings which are significantly associated with sepsis: Abnormal total leukocyte count (TLC), abnormal total PMN count, elevated immature PMN count >600, elevated immature-to-total (I:T) PMN ratio >0.120, and immature-to-mature (I:M) PMN ratio ≥0.3, platelet count ≤150,000/mm which is thrombocytopenia and pronounced degenerative changes or toxic granulations in PMNs. If no mature PMN is observed on the peripheral smear, total PMN count assigns score 2 instead of 1.

Blood culture and C-reactive protein (CRP) results of the same patient were compared with the hematological parameters. Culture positivity was taken as the criterion for definitive diagnosis.

Statistics

For each parameter, sensitivity, specificity, and positive and NPV were calculated. For different parameters, *P* value was also calculated. Compilation of data and statistical analysis were done with the use of SPSS software. The research work got approval by the ethical committee of our medical college.

RESULTS

Of the 100 clinically suspected septicemia cases studied, 19 (19%) were culture positive and 81 (81%) were culture negative. 55 were males and 45 were females. Septicemia was more common in male neonates in 12 cases(63.2%) compared to female neonates in 7 cases (36.8%)among the 19 culture positive cases. Male neonates were commonly infected compared to female neonates with a ratio of 1.7:1. Among the culture-positive cases, majority neonates were less than 1 week old that is 90 (90%). 3.3 days was the mean age of the neonates in the study. Early onset septicemia was more common, seen in 14 (73.68%) cases, than late-onset septicemia seen in 5 (26.32%) cases among the culture-positive cases. In the study population, mean birth weight was 2.46 kg. Septicemia proven by culture was more common among 16 (84.2%) of term neonates, 16 (84.2%) of low birth weight neonates, 14 (73.7%) neonates with spontaneous vaginal delivery, and 16 (84.2%) of the hospital born neonates.

Majority of the blood culture isolates were Gram-negative organisms, in which the most common isolate was *Klebsiella pneumoniae* in 36.84% of the 19 culture-positive cases, followed by *Methicillin-resistant Staphylococcus aureus* (21.05%), *Enterococcus* (15.8%), *Escherichia coli* (10.52%), *S. aureus* (5.2%), *Pseudomonas aeruginosa* (5.2%), and *Acinetobacter baumannii* (5.2%).

Table 3 shows that, with increasing score, sensitivity and NPV were decreased, whereas specificity and positive predictive value were increased.

Table 3: Comparison of sensitivity, specificity, positive predictive value, and NPV of hematological Score

Hematological score	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	NPV (%)
≥1	100	6.1	20	100
≥2	100	50.6	32.2	100
≥3	84.21	86.4	43.24	95.89
≥4	31.57	86.41	75	85.86
≥5	10.52	100	100	82.65

NPV: Negative predictive value

Table 4: Comparison of sensitivity, specificity, positive predictive value, and NPV of each hematological parameter

Hematological parameters	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	NPV (%)
Total WBC count	10.53	86.42	15.38	80.46
Total PMN count	57.89	45.68	20	82.22
Immature PMN count	78.94	66.67	35.71	93.10
I: T PMN ratio	36.84	96.29	70	86.67
I: M PMN ratio	15.79	98.76	75	83.33
Degenerative changes in PMN	31.58	95.06	60	85.56
Platelet count	73.68	53.09	26.92	89.58

WBC: White blood cell count, PMN: Polymorphonuclear cells (neutrophils), I: T PMN ratio: Immature: Total neutrophil ratio, I: M PMN ratio: Immature: Mature neutrophil ratio

Table 4 shows that, among the all hematological parameters studied, immature neutrophil count showed the highest sensitivity (78.94%) and NPV (93.10%). I: M PMN ratio (98.76%), I: T PMN ratio (96.29%), and degenerative changes in neutrophil (95.06%) showed high specificity.

Association of total immature PMN count, I: T PMN ratio, immature-to-mature PMN ratio, and degenerative changes in PMN with culture results was found to be highly statistically significant ($P = 0.01$). Association between platelet count and blood culture results was found to be statistically significant ($P = <0.05$).

By comparison of Rodwell's HSS with blood culture results, it was found that the likelihood of sepsis with score ≥3 was 59.25 % and score ≥5 was 100%. With score ≤2 the likelihood of sepsis was absent 95.9% (Table 5).

By comparison of Rodwell's HSS with CRP, it was found that association was highly statistically significant ($P < 0.01$) (Table 6).

DISCUSSION

In the present study, it was found that cases of neonatal sepsis were more common in early neonatal period (1–7 days) (73.68%) than in late neonatal period (7–28 days) (26.32%). In neonatal sepsis there is a male predomonance with male female ratio.1.7:1. Cases of neonatal sepsis were more common in term neonates (37–42 weeks) (84.2%) than preterm neonates (<37 weeks) (15.8%), in neonates with low birth weight (<2.5 kg) (84.2%) than neonates with normal birth weight (≥2.5 kg) (15.8%), in neonates who were delivered by spontaneous vaginal delivery (73.7%) than neonates delivered by caesarean section, and in the neonates who were delivered at the hospital. (84.21%). Neonatal sepsis by Gram-negative infection was more common, and the most common organism isolated was *K. pneumoniae* (36.84%). Among the all hematological parameters studied and compared to blood culture results, immature PMN count showed highest sensitivity (78.94%) and negative predictive value (93.10%). Immature-to-mature PMN ratio (98.76%), immature-to-total PMN ratio (96.29%) and degenerative changes in PMN (95.06%) showed high specificity. Association of total immature PMN count, immature-to-total PMN ratio, immature-to-mature PMN ratio, and degenerative changes in PMN with culture results were found to be highly statistically significant ($P < 0.01$). Association between platelet count and blood culture results was found to be statistically significant ($P <0.05$). Association of TLC and total neutrophil count with blood culture results was turned out to be statistically not significant. By comparison of Rodwell's HSS with blood culture results, it was found that 59.25 % shows likelihood of sepsis with score ≥3 and 100% shows score ≥5. Likelihood that sepsis was absent was 95.9% with score ≤2. By comparison of Rodwell's HSS with CRP, it was found that association was not statistically significant ($P >0.05$).

Table 5: Combined hematological score in comparison with blood culture results

Hematological score	Culture positive (%)	Culture negative (%)	Total (%)
Score 0–2	3 (4.1)	70 (95.9)	73 (100)
Score 3–4	14 (56)	11 (44)	25 (100)
Score ≥5	2 (100)	0	2 (100)
Total	19	81	100

Table 6: Hematological score in comparison with CRP value

Hematological score	CRP value		Total
	>6 mg/L	<6 mg/L	
0	3	2	5
1	12	24	36
2	9	23	32
3	14	5	19
4	6	0	6
5	2	0	2
6	0	0	0
Total	46	54	100

CRP: C-reactive protein

The factors regulating globulin synthesis are present on the X-chromosome. In male, only one X-chromosome is present; hence, he is less protected than females. Hence, sepsis is more common in male than in female. Low birth weight neonates get low IgG from mother, so they are more susceptible to infection.[8] The early onset sepsis was more common than late-onset sepsis because of infection after rupture of membrane or through infected birth canal or during resuscitation of newborn baby.

Neonatal septicemia was more common in vaginally delivered neonates than neonates delivered by cesarian section may be due to the surface colonization of neonate with the microbial flora of the birth canal during vaginal delivery. Among the hospital born neonates, septicemia was common, mostly due to hospital-acquired infection. Clinical use of Total leukocyte count(TLC) in diagnosis of neonatal septicemia is not significant because of wide variation in values due to variation in blood sampling time,the severity of infection and reduced sensitivity of this test after the first week of life. The sensitivity of TLC 10.53%,specificity 86.42%,PPV 15.38% and NPV 80.46%,were consistent with other studies Makkar *et al*[9],Khair *et al*[10] and Gerdes.[11]

Sepsis due to neutropenia is more common than neutrophilia. Neutropenia in the newborn is mostly due to secondary infection, but there are other causes such as congenital

neutropenia, isoimmune neutropenia, and neutropenia due to inborn error of metabolism.

In this study, total PMN leukocyte count 1800–5400 cells/mm^3 had a sensitivity of 57.89%, specificity of 45.68%, PPV of 20%, and NPV of 82.22%. Similar results were observed by various studies Makkar *et al*.,[9] Sriram.[12] In the present study, the total PMN count was associated with low positive predictive value and low specificity. Therefore, it cannot be used as an only predictor of sepsis. In patients with bacterial infection, immature neutrophil counts (band form) [Figure 1] are increased.[13] In the present study, immature PMN count with cutoff value >600 cells/mm3 had sensitivity of 78.94%, specificity of 66.67%, PPV of 35.71% and NPV of 93.10%. Similar result was observed by the studies of Makkar *et al*.[9] except positive predictive value. In the present study, I/T ratio >0.120 had a sensitivity, specificity, PPV, and NPV of 36.84%, 96.29%, 70%, and 86.67%, respectively. The sensitivity of I/M ratio (>0.3) was 15.79%, specificity of 98.76%, PPV of 75%, and NPV of 83.33%. For decreasing the inappropriate use of antibiotics in cases, tests must have a reasonably high specificity and better predictive value. Thrombocytopenia was frequently associated with poor prognosis in sepsis. In the present study, thrombocytopenia was a good predictor of neonatal septicemia because in early neonates the platelet counts are significantly low and increase after this period.[12] This is thought to be due to platelet destruction and sequestration is increased due to infections, and platelet production is decreased due to damage of megakaryocytes.[14] In the present study, thrombocytopenia had sensitivity of 73.68%, specificity of 53.09%, PPV of 26.92%, and NPV of 89.58%. Hence, thrombocytopenia could be used as an early but nonspecific marker for diagnosis of sepsis. Similar results were observed by Sriram study.[12]

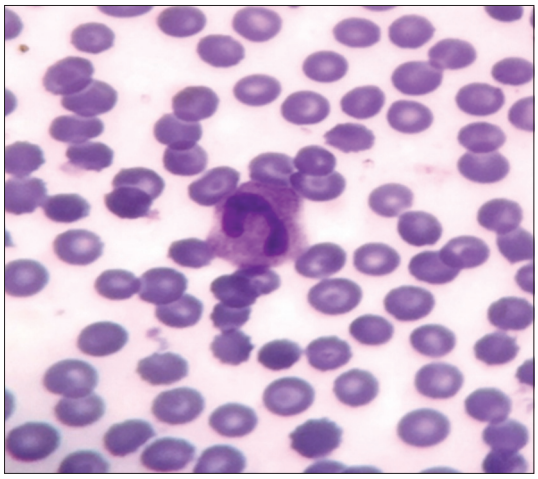

Figure 1: ×100 peripheral smear cells showing immature neutrophil

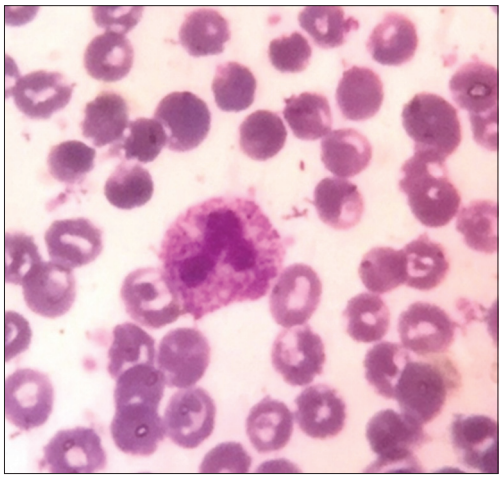

Figure 2: ×100 peripheral smear showing toxic granules in neutrophil-degenerative changes in neutrophil

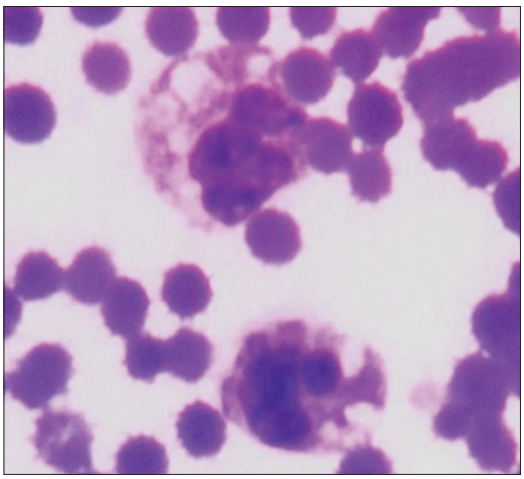

Figure 3: ×100 peripheral smear cells showing cytoplasmic vacuolization-degenerative changes in neutrophil

CONCLUSION

Single individual hematological parameter is not useful in predicting neonatal sepsis, so HSS by a combination of hematological parameters such as total leukocyte count, total neutrophil count, immature-to-total neutrophil ratio, immature-to-mature neutrophil ratio, degenerative changes in neutrophils, and platelet count is considered as an important system for early diagnosis of neonatal sepsis. Although blood culture is the definitive test for sepsis, it is time consuming and results are obtained at least after 48–72 h. Sample for blood culture must be collected before treatment by antibiotics. CRP is also a better test with high sensitivity, but it has a low specificity and a special kit is needed for the test, which may not be available at primary health-care centers. Hence, a quick, simple, cost-effective, and easy test is the need for early diagnosis of neonatal septicemia. It was concluded that Rodwell's HSS is a useful test for distinguishing the septic infants from aseptic infants. This is simple and cost-effective test which can be done quickly before giving antibiotic therapy to the neonate with high sensitivity and specificity for the early diagnosis of neonatal sepsis and can also be used in the neonates who have already received antibiotics before evaluation. HSS (score >4) may guide to make decisions for judicious use of antibiotic treatment which can save the life of neonate and early cure. It may also useful in decreasing mortality, decreasing the hospital

stay and minimizing the risk of resistance due to misuse of antibiotics and side effects, and reducing the cost of treatment.

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