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RESEARCH ARTICLE

EVALUATION OF NEONATAL SEPTICAEMIA USING HEMATOLOGICAL PARANTELERS

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ABSTRACT

Neonatal septicemia was one of the major factors contributing to the high perinatal and neonatal mortality and morbidity. The definite diagnosis of septicemia was made by a positive blood culture which required a minimum period of 48-72 hours and yielded a positive result in 30-70% of cases. Hence there was a critical need for laboratory tests that aid in the rapid diagnosis of neonatal sepsis. We studied the Rodwell's hematological parameters including the various changes seen in the peripheral smears of 110 neonates clinically suspicious of having sepsis. Out of 110 infants, 23(20.9%) cases with proven sepsis, 30(27.2%) cases with probable sepsis and 57(48.18%) cases were on safer side. 74.5% infants had early onset neonatal sepsis and 25.45% infants had late onset. 60.8% preterm infants were more prone. Nucleated Red blood cells values were higher in sepsis and significantly seen in 78.2% of early onset neonatal sepsis cases in proven sepsis and 50% in probable sepsis. The advantage of study was that these can be done rapidly even in small hospitals, allowing prompt treatment to neonates with sepsis and minimizing therapy. It can be good predictors of short term neonatal outcome and carries diagnostic and prognostic value.

INTRODUCTION

Systemic infection in the newborn is the commonest cause of neonatal mortality. Data from National Neonatal Perinatal Database 2000, incidence of neonatal sepsis has been reported to be 38 per 1000 intramural live births in tertiary care institutions. *Klebsiella pneumonia* commonest causing organism followed by *Staphylococcus aureus* and *Pseudomonas* in India (Aggarwal R *et al*, 2001).Clinical features of sepsis are nonspecific in neonates and a high index of suspicion is required for early diagnosis. Although blood culture is the "**Gold Standard**" for the diagnosis of sepsis, reports are available after 48-72 hrs and they may be affected by intrapartum antibiotic administration to the mother (Chandna A *et al*, 1988). The definite diagnosis of septicemia is made by a positive blood culture, which requires a minimum period of 48-72hrs and yields positive result in 30-40% of cases. In order to diagnose septicemia early, several rapid diagnostic tests have been described recently. These can be performed rapidly in an hour or two and antibiotics can then be used judiciously, thereby reducing the incidence of drug resistance and improving the survival rate of septicemia (Chandna A *et al*, 1988). *Xanthou M (1970, 1972)* reported that neonates who had life threatening (or fatal) infections became neutropenic prior to death and studied ill preterm and term babies and those who died with bacterial infection were seen to have neutropenia, a 'left shift' and toxic granulation in neutrophils. *Rod well RR et al (1988)* enrolled 287 neonates in a study, who had predisposing perinatal factors or clinical suspicion of sepsis. Hematologic finding and published complete blood cell count criteria were evaluated as screening tests. A hematological scoring system was formulated that assigned a score of 1 for each of seven findings, namely abnormal leucocyte count, abnormal total neutrophil count, elevated band cell, elevated immature to mature neutrophil ratio (I:T); elevated immature to mature neutrophil ratio(I:M), decreased platelet count and degenerative changes in neutrophils. They found that higher the score, the greater was the likelihood of sepsis. *Ghosh S. et al (2001)* studied the hematologic profiles of 103 new born infants according to the scoring system of Rodwell's *et al* for the early detection of sepsis in high risk infants. They found it to be a simple, quick and cost effective tool which could provide a guideline to decisions regarding antibiotic therapy. *Dulay et al (2008)* studied neonatal hematological indices and assessedsepsis categorization in all 68 neonates. Laboratory criteria were based on modification of the criteria of Rodwell *et al*. He found that Early-Onset Neonatal Sepsis (EONS) and WBC count and absolute neutrophil count (ANC) were not significant. In contrast, the associations with absolute band count (ABC), hematocrit, hemoglobin, bandemia, lymphocytes and I/T ratio continued to remain significant. *Shirazi et al (2010)* studied 138 neonates with suspected sepsis.

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They evaluated the usefulness of white blood cell count and C-reactive protein as an early indicator of neonatal septicemia. The advantage of hematological scoring system (HSS) is that it is easy to perform and applicable to all infants, including those who have received antibiotics. *Narasimha A, Harendra kumar (2011)*analysed 50 peripheral blood smears of newborns for neonatal sepsis using HSS of Rodwell *et al*. criteria. They found that an abnormal immature to total neutrophil ratio (I: T), followed by an abnormal immature to mature neutrophil ratio (I: M), were most sensitive indicators in the diagnosis of neonatal sepsis. The hematological scoring system (HSS) is a simple, quick, cost effective screening tool for early diagnosis of neonatal sepsis.

MATERIALS AND METHODS

The present study is a prospective analysis of the hematological profile of 110 neonates admitted to the neonatal intensive care unit at our college. Infant with predisposing perinatal risk factors or if there was clinical suspicion of sepsis were included in this study. A detailed clinical history of each patient was recorded. Neonates were divided into 3 groups mainly,

Group 1 (Proven sepsis): neonates with sepsis (with positive blood culture)
Group 2 (Probable sepsis): neonates with probable infection (with strong clinical history and negative blood culture)
Group 3 **(**No sepsis): normal neonates (with minimal h/o or signs of sepsis).

The blood samples were collected in non-siliconized vaccutainer tubes with tripotassium EDTA as an anticoagulant. Peripheral blood smears were prepared within 1–2 hr of venipuncture, stained with Leishman stain and examined under oil immersion light microscopy at a final magnification of ×1000. The sepsis work up included blood culture and routine blood counts along with the hematologic score. Total leucocyte count was obtained using multichannel automated cell counter—MINDRAY model BC1000 with standard calibration and corrected for nucleated red blood cells. Differential counts were performed on Leishman stained smears and about 100 cells were counted. The peripheral blood smears of all newborns from birth up to 1 week were analyzed for early diagnosis of neonatal sepsis using the hematological scoring system of Rodwell *et al*. The HSS assigns a score of one for each of the seven criteria found to be significantly associated with sepsis (Table 1) with one exception. An abnormal total count is assigned a score of 2 instead of 1, if no mature polymorphs are seen on the peripheral smear to compensate for the low I:M ratio. Sensitivity, specificity, positive and negative predictive values were evaluated for each of the seven criteria of HSS.

Table 1 Hematological scoring system

Criteria	Abnormality	Score
Total WBC count	≤5,000/µl	1
	≥25,000 at birth	1
	≥30,000—12-24hrs	
	≥21,000—day2 onwards	
Total PMN count	No mature PMN seen	2
	Increased/ decreased	1
Immature PMN count	Increased	1
I:T PMN ratio	Increased	1
I:M PMN ratio	≥0.3	1
Degenerative changes in PMN	Toxic granules/cytoplasmic vacuoles	1
Platelet count	≤150,000/µl	1

The normal values are according to Manore *et al*:
Total PMN count- 1800-5400
Immature PMN count – 600
Immature: Total PMN ratio- 0.12
Immature: Mature PMN ratio- ≥0.3

Immature neutrophils include promyelocyte, myelocyte, metamyelocyte and band forms. A band cell was defined as a neutrophil in which, the nucleus was invented by more than half, but in which the isthmus between the lobes was wide enough to reveal two distant margins with nuclear material between. The polymorph nuclear leucocytes were also examined for degenerative morphological changes such as toxic granulation, toxic vacuolization and Dohle bodies. The hematological findings were analyzed according to the hematological scoring system of Rodwell *et al*.

C-reactive protein levels were also recorded. This test was done in the immunology laboratory by immune turbidimetric method using MISPA-I analyser. For culture 2ml blood in 20 ml glucose broth were taken before administering any antibiotic and sent to Microbiology department immediately. Subcultures were observed after 24-48 & 120 hours. If growth was observed, material was further analyzed for isolation of organism & antibiotic sensitivity. If no growth was observed after 5 days, culture was reported negative.

Inclusion Criteria

All clinically suspected cases of neonatal sepsis included in the study.

Exclusion Criteria

Neonates of mothers with pregnancy induced hypertension, diabetes and neonates with history of asphyxia and congenital anomalies were excluded by a detailed perinatal history and clinical examination.

Table 2 Interpretation of hematological scoring system

Score	Sepsis
≤2	Sepsis is unlikely
3 or 4	Sepsis is possible
≥5	Sepsis or infection is very likely

Statistical Analysis

The data collected was statistically analyzed, to find out the performance of the test individually and as a scoring system under the following parameters. Sensitivity, Specificity, Positive predictive value, Negative predictive value, Chi-square test, and Contingency coefficient *and* P value < 0.05 was considered as significant.

RESULTS

The present study was conducted on 110 neonates who clinically presented with symptoms of sepsis. Based on clinical findings and laboratory data infants were classified into three categories.

Proven sepsis(23/110cases): The diagnosis of sepsis was made when there were positive findings on blood culture.

Probable sepsis(30/110***):***Infants were classified as having probable infection when blood cultures were negative but there was a strong clinical history indicating infection. Certain high risk factors such as prolonged rupture of membranes,

me-conium aspiration, prolong labour and maternal fevers were noted in these neonates. The infants presented with clinical features such as respiratory distress and grunting, apnea, lethargy, poor feeding/sucking, abdominal distension and shock.

No sepsis (57/110):This group consisted of neonates with negative blood culture, who finally presented with feature of suspected sepsis or with associated risk factors. On further investigation they were found to be suffering from other disorders such as hyaline membrane disease, transient tachypnea of the new born and hypoglycemia. The study had males 72(65.5%) as well as females 38(34.5%). We had 71(64.5%) term infants and 39(35.4%) pre-term infants with the age ranging from 24 h to 7 days.

Neonatal sepsis was divided into 2 groups according to the onset of symptoms.

1. Early onset sepsis: usually presents within the first 72hrs of life.
2. Late onset sepsis: usually presents after 72hrs.

The Neonates in the present study were classified accordingly

Table 3 Neonatal sepsis group

Type of onset	No of neonates	Percent(%)
Late	28	25.5
Early	82	74.5

Many of the neonates presented with more than one symptom. The commonest form of presentation was respiratory distress (82%) and lethargy/poor feeding (59%).

Table 4 Hematological scores of neonates of present study

Infection status	Proven sepsis(n=23)	Probable sepsis(n=30)	No sepsis(n=57)
≥1	0	0	25
≥2	0	1	24
≥3	1	2	5
≥4	3	10	2
≥5	10	13	1
≥6	9	4	0

higher in sepsis and significantly seen in 78.2% of early onset neonatal sepsis cases in proven sepsis and 50% in probable sepsis.

DISCUSSION

Neonatal sepsis, sepsis neonatorum and neonatal septicemia are terms that are used to describe the systemic response to infection in the newborn infant(Narasimha A *et al*, 2011). Sepsis is the commonest cause of neonatal mortality. It is responsible for about 30-50% of the total neonatal deaths in developing countries. It is estimated that upto 20% of neonates develop sepsis and approximately 1% die of sepsis related causes (Shankar MJ *et al*, 2008). Infants are deficient in their inherent protective mechanisms, humoral and cellular immunity (Khatua SP *et al*, 1986).In the preterm VLBW infant, though all molecular and cellular elements necessary for adequate host defense are present, their number/capacity or function is reduced (newborn's immune naivety*)* accounting for decreased magnitude of immune response. This immune naivety is made worse by sepsis. Unless this is adequately addressed in the management package along with killing of the pathogens it is unlikely that mortality rates from sepsis will come down (Haque KN *et al*, 2010).

The definite diagnosis of septicemia is made by a positive blood culture which requires a minimum period of 48-72hrs and yields positive result in 30-40% ofcases (Chandna A *et al*, 1988).An early and accurate etiological diagnosis is not always easy, especially since the disease may start with minimal or non-specific symptoms. Delayed treatment until clinical recognition of signs and symptoms of sepsis entails risk of preventable mortality, not withstanding the fact that presumptive antibiotic therapy may result in overtreatment (Kumhar GD *et al*, 2002).The unnecessary use of stronger antibiotics for minor infections and for prophylaxis should be discouraged (Monga K *et al*, 1986).

In order to diagnose septicemia early, several rapid diagnostic tests have been described, which are easily performed and have

Table 5 Performance of individual hematological findings and CRP levels in 23 infants with sepsis from 110 evaluations in the first month of life.

Hematological findings	Sensitivity (%)	Specificity (%)	Positive prediction value (%)	Negative prediction value (%)
↑ or ↓ WBC	45	94	82	66
↑ or ↓ Total PMNs	78	87	80	67
↑Immature PMNs	65	87	49	90
↑ I:T ratio	91	79	78	51
↑ I:M ratio	94	97	94	97
Degenerative changes	53	89	68	82
Platelet <150 x 10^3/µL	48	93	54	68
CRP levels	82	70	54	91

Immature: Mature PMN ratio (94%) was highly sensitive followed by Immature: Total PMN count (91%) in identifying infants with sepsis. Total leucocyte count (TLC) (94%) followed by platelet counts (75%) were highly specific tests helpful in diagnosing sepsis. The positive predictive value was high for Immature: Mature PMN ratio (94%) followed by Total WBC counts (82%) which were helpful in identifying infants who really had sepsis. Negative predictive value was high in Immature: Mature PMN ratio (97%) along with degenerative changes (82%) which indicated that the infants did not have any evidence of sepsis. Nucleated Red blood cells values were the benefit of quick availability of reports. In our study considering all four parameters i.e.: sensitivity, specificity, positive predictive value and negative predictive value, I:M ratio and I:T ratio were the most reliable tests for diagnosing sepsis. Degenerative changes in neutrophils were not found to be a very sensitive indicator of sepsis. Thrombocytopenia was consistently associated with poor prognosis.

These findings were in comparison with other studies (Rodwell *et al*, Philip AGS *et al*, Deorari AK *et al*, Narasimha A *et al*). The higher the score, the greater was

the likelihood of sepsis. A score ≤2 suggests that sepsis was unlikely.

Hematologic scoring system (HSS) can improve the efficiency of the complete blood count as a screening test for sepsis and permits an objective assessment of hematological changes (Rodwell RL *et al*, 1988).

The HSS is simpler, quick, cost effective and readily available tool in the early diagnosis of neonatal sepsis and could provide a guideline to decision regarding antibiotic therapy (Rodwell *et al*, Ghosh S *et al*).The higher the score, the greater the certainty that sepsis is present. Therefore it simplifies the interpretation of hematological profiles.

Tripathi *et al* (2010) stated that cytokines released in sepsis have an important role in stimulating nucleated RBC production independent of hypoxia. She has concluded in her study that there is significantly elevated NRBCs demonstrated in early onset sepsis and increased NRBC count immediately after birth could be an interesting marker of early onset neonatal sepsis in absence of hypoxia.

Dulay *et al* (2008) have studied the NRBC count of neonates with early onset neonatal sepsis was significantly higher independent of gestational age at birth, erythropoietin (EPO) or hypoxia.

Though there are several methods for rapid detection of microorganisms in blood cultures of newborn infants using automated blood culture system, DNA probe and fluorometric detection systems (Narasimha A *et al*, 2011), still HSS can be employed as a useful test to distinguish the infected from the not infected infants. It has high sensitivity and specificity, the certainty of sepsis being present with higher scores.

CONCLUSION

HSS is a simple, quick, cost effective tool which can be used as a screening test for early diagnosis of neonatal sepsis. It may aid the clinicians in identifying sepsis and to institute proper antibiotic therapy. Unnecessary exposure of infants to antibiotic therapy can thus be avoided.

Elevated nucleated RBCs values in peripheral blood are significantly associated with an increased risk of early onset newborn sepsis and could be an interesting marker of early onset neonatal sepsis in absence of hypoxia.

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