Original Research Article

Application and correlation of hematological scoring system and serum prolactin levels in early diagnosis of neonatal sepsis – 3 year study

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Abstract

Neonatal septicemia is defined as a bacterial infection documented by a positive blood culture in the first 4 weeks of life. The clinical symptoms and signs are non specific and vague. So it is important to make diagnosis and to start treatment as early as possible to prevent serious morbidity and mortality caused by non-treatment or late treatment of septicemia. This study was conducted for a period of 3 years. 200 neonates under the age of 28 days were studied to find out hematological parameters including sepsis screen, hematological scoring system and serum procalcitonin levels in neonates suspicious of sepsis. We concluded that, though blood culture is a gold standard for the diagnosis of sepsis, combined use of sepsis markers increases the diagnostic accuracy in suspected cases and simultaneously prevents over treatment of clinically suspicious cases.

Key words

Hematological scoring system, Serum prolactin level, Neonatal sepsis.

Introduction

Neonatal sepsis, especially during 1st month of life, is a major cause of morbidity and mortality and is responsible for about 30-50% of total neonatal deaths in developing countries, incidence being 1-8 cases/ 1000 live births, signs and symptoms of which are often vague and non-specific. It is divided into 2 subtypes-early onset and late onset depending upon within 24 hours or after. A positive blood culture is gold standard for diagnosis of sepsis but it is time consuming and has a success rate of only 4%. An early, sensitive and specific laboratory test would be helpful in avoiding unnecessary antibiotic treatment of uninfected patients. Early treatment is possible with the help of certain indirect markers such as leukopenia, toxic granules, immature to total neutrophil ratio and CRP, micro ESR along with PCT which is a recent marker, which is known as the sepsis screen.

Aim

- To assess the utility of hematological scoring system (HSS) of Rodwell, et al. as per **Table – 1** and **Table - 2** for early detection of neonatal sepsis and its correlation to serum prolactin levels (PCT) levels.

Table - 1: Hematological scoring system by Rodwell et al.

Criteria	Abnormality	Score
Total WBC count	<5,000/µl >25,000 at birth >30,000 12-24 h >21,000 Day 2 onwards	1 1
Total PMN count	No mature PMN seen Increased/decreased <1800 or >5400 cells/µl	2 1
Immature PMN count	Increased (>600 cells/µl)	1
I:T PMN Ratio	Increased (>0.12)	1
I:M PMN Ratio	>0.3	1
Degenerative changes in PMN	Toxic granules/ cytoplasmic vacuoles	1
Platelet Count	<150,000/µl	1

(Maximum score is 8, minimum score is 0)

Table - 2: HSS core interpretation.

Score	Interpretation
<2	Sepsis is very unlikely
3 or 4	Sepsis is suspected
>5	Sepsis or infection is very likely

Materials and methods

The study was conducted in Gandhi Medical College, Department of Pediatrics and pathology. 200 neonates suspicious of sepsis were studied in the duration of July 2013 - July 2016, for a period of 3 years below the age of 28 days. The inclusion criteria were neonates admitted to NICU with signs and symptoms of sepsis.

Inclusion criteria

- Neonates with signs of infection.

Exclusion criteria

- Neonates with mother having HIV and Hepatitis B infection and partially treated cases.

Initially after admission, sepsis screen was done. Blood was collected by venipuncture under strict aseptic conditions, in a EDTA vacutainer from suspicious infants. The sample was processed through 5 part coulter cell counter and parameters of Hemoglobin, TLC, RBC count, MCV, Hematocrit and platelet count were noted. The peripheral smear was prepared and stained by the protein Leishman stain. RBC morphology, WBC differential count with specific emphasis on Absolute neutrophil count and Immature neutrophil count was done. Immature neutrophil count to total neutrophil count ratio was taken (I/T), immature neutrophil to mature neutrophil count (I/M) was also taken. Toxic granules were identified. Platelet count and Morphology was noted. C - reactive protein was detected by latex agglutination using span CRT kit. ESR was estimated by standard westergren method.ESR>n 15 mm after 1st or was considered positive. Sample for blood culture was taken in all neonates prior to the administration of antibiotics, under strict aseptic precautions by performing venipuncture 0.5 ml of blood was collected in 5 ml of glucose broth for this and was sent immediately to microbiology department there three subcultures were observed at the intervals of 24,48 and 120 hours if no growth was observed after 5 days, the culture was reported negative .If growth was observed, the material was further analyzed for specific organisms. Common gems obtained work of Gram Negative organisms and staphylococci with characteristics pink colour of E. Coli on Mac conkey medium and different colours of staphylococcus on nutrient Agar. Procalcitonin was determined categorically (<0.5ng/ml-normal, 0.5 to <2 ng/ml, 2 to 10 ng/ml and >10 ng/ml) using semi quantitative PCT-Q kit (BRAHMS diagnostica Berlin, Germany), according to the manufacturer's procedure using 200 microlitre of fresh plasma. The method used was Immune-chromatographic assay.

Hematological scoring system was calculated using the following parameters.

- WBC and platelet count
- Differential count
- nRBC count
- Assessment of neutrophil morphology for degenerative changes like vacuolisation, toxic granules and Dohle bodies.
- Immature neutrophils include promyelocyte, myelocyte, metamyelocyte and band form.

Results

Study was conducted for a Period of 3 years from 2013 July to 2016 July at Gandhi Medical College/ Hospital in department of Pathology and Pediatrics. 200 neonates below the age of 28 days with clinical suspicion of septicemia were included out of which, 112 male babies (50%) were affected with septicemia and 88 female babies (44%) affected indicating male preponderance. Early onset septicemia i.e. within 3 days of birth was found in 144 babies (72%) and late onset sepsis (later than 3 days) was found in 56 babies (28%) of cases, indicating that early onset septicemia was more common than late onset. Babies weighing < 2000 grams per 124 (62%) and those weighing >2000 grams were 76 (38%), indicating that septicemia was more common in low birth weight babies. Preterm babies < 37weeks were 112 (56%) and full term babies were 88 (44%), indicating that preterm babies are more susceptible than full term babies. Early onset septicemia was present in 80 preterm neonates (71.4%), out of 112 babies, term neonates affected were 60 out of 88.77% of low birth weight neonates has early onset septicemia compared to 65% of normal birth weight neonates.

Culture was positive in 116 cases (58%) negative in 84 cases (42%). Organisms isolated were klebsiella in 56 cases (48.2%), staphylococcus aureus in 32 cases (27.6%), acetobacter in 10

cases (17.2%), E. Coli in 4 cases (3.5%), pseudomonas in 4 cases (3.5%).

Culture positivity was seen in only 76 cases (53%) of early onset septicemia, compared to 40 cases (71%) in late onset septicemia, and positivity was observed more in low birth weight babies than normal weight babies and also in late onset septicemia cases. HSS was done in all cases and score was determined. HSS score >5 was seen in 84 cases (72%) of culture positive cases and 4 cases (4%) of culture negative cases. HSS score of 3-4 was seen in 24 cases (21%) of culture positive cases and 28 cases (35%) of culture negative cases. HSS score of 1-2 was seen in 8 cases (7%) of culture positive cases and 26 (62%) of culture negative cases. For score >5, sensitivity is 95%, and specificity was 86%, positive predictive value was 93%, NPV was 61%. P value of the study was 0.0001. Among the Hematological parameters, immature Neutrophils and I:M ratio has highest sensitivity of 82 to 75% each with total WBC count having least sensitivity of all parameters. I:M ratio has highest specificity of 80 to 95% and PPV. C reactive protein was positive in 80 cases out of which culture positive cases 60 (51.8 %) and 20 cases (23.8%) culture negative.

CRP was negative in 120 cases, out of which 56 cases (48.2%) were culture positive and 64 cases (76.2%) culture negative, accounting to sensitivity of 75% and NPV of (76%). ESR was positive in total of 92 cases, out of which 76 were culture positive (65.5%) and 16 were culture negative. ESR was negative in 108 cases, out of which 40 were culture positive (34.5%) and 68 were culture negative (71%) accounting to its sensitivity of 65.5% and specificity of 80.9%, PPV of 82.6%, NPV of 62.3%. Procalcitonin of <2 was found in total of 40 cases out of which 4 were culture positive (3.4%), 36 culture negative (43%). PCT of 2-10 was found in 56 cases of which 20 were culture positive (17.2%) and 36 cases (43%) were culture negative. PCT>10 was found in total of 104 cases, out of which 92 were culture positive (79.4%) and 12 were culture negative (14%). Sensitivity for PCT of value>10, accounted to 79.3% and specificity of 85.71%, PPV 88.5%, NPV 75%, P value was <0.0001.

HSS score was compared to PCT levels and the results were that, HSS score of <2 was found in total of 60 cases, out of which PCT <2 in 32 cases, 2-10 in 16 cases, >10 in 12 cases. HSS score of 3-4 was found in total of 52 cases, out of which PCT was <2 in 8 cases, 2-10 in 32 cases and >10 in 12 cases. HSS score of >5 was found in 88 cases, out of which PCT <2 was not seen in any cases, 2-10 was seen in 8 cases and >10 was seen in 80 cases. Based on these observations, It was predicted that PCT <2 and HSS <2 were seen in 32 cases, in which sepsis was very less likely. PCT >10 and HSS >5, suggested that risk of sepsis was high in 80 cases. By using PCT and HSS, sepsis was very likely in 112 cases (**Photo – 1 to 4, Table – 3, Table - 4**).

Photo – 1: Neutrophilia 40X Leishman Stain.

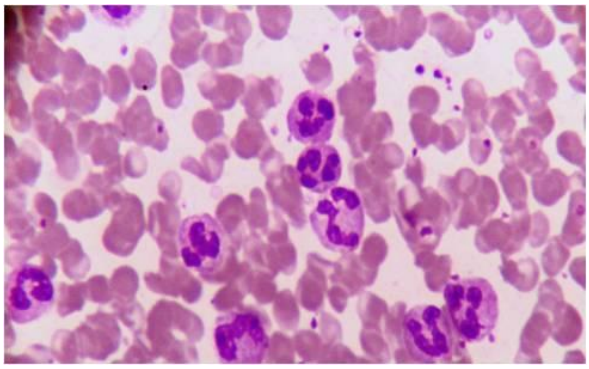

Photo – 2: Degenerative Changes in Neutrophils.

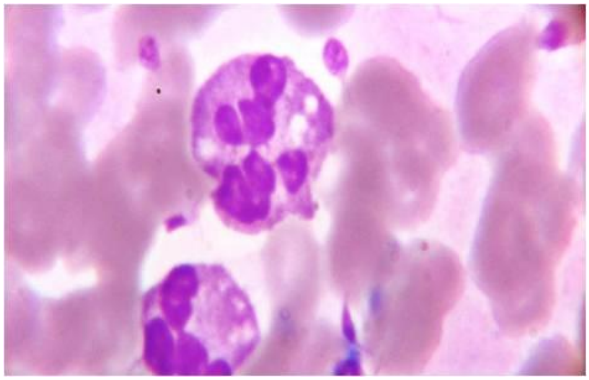

Photo – 3: Immature Neutrophils 40X Leishman Stain.

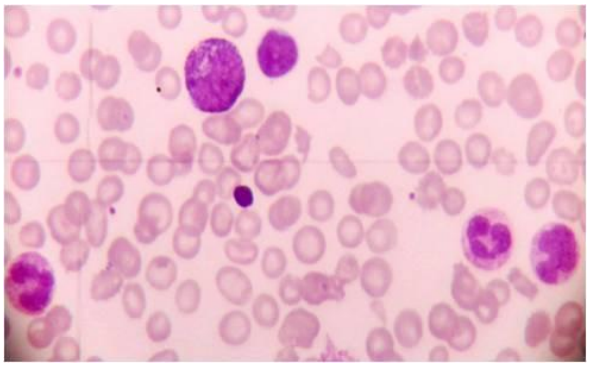

Photo – 4: Thrombocytopenia 40X Leishman Stain.

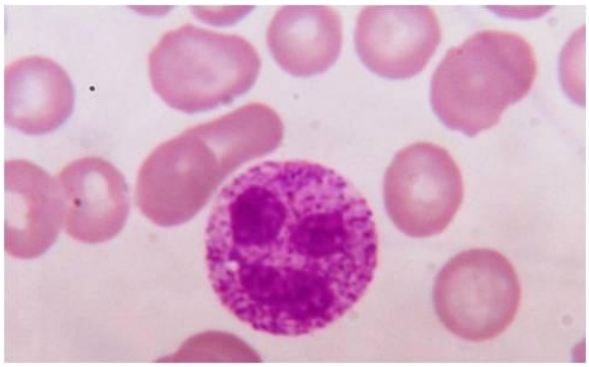

Table – 3: Serum Prolactin level and culture report.

PCT	Culture Positive	Culture Negative	Total
<2	4 (3.4%)	36 (43%)	40
2-10	20 (17.2%)	36 (43%)	56
>10	92 (79.4%)	12 (14%)	104
Total	116	84	200

Table – 4: HSS score and Serum Prolactin level.

HSS Score	PCT			Total
	<2	**2-10**	**>10**	
<2	32	16	12	60
3-4	8	32	12	52
>5	0	8	80	88
Total	40	56	104	200

Discussion

200 neonates below the age of 28 days with clinical suspicion of neonatal septicemia were included in this study. Clinical profile, sepsis screen, HSS on peripheral smear and serum procalcitonin were determined.

In our study, 112 male babies (56%) and 88 female babies (44%) were affected by neonatal septicemia. Nelson [1-3] stated that males have an approximately 2 fold higher incidence of sepsis than females. Preponderance was also seen in several other studies by Piyush Gupta, et al. [3], Somu, et al. [3], Philip, et al. [5], Khatua, et al. [4], Sinha, et al. [6] observed that the male to female ratio was 1.7:1. David Wilson [7] stated that increased incidence of sepsis neonatorum in male infants is probably related to higher incidence of congenital anomalies of urinary tract in males, resulting in primary urinary tract infection and secondary sepsis. Morven S and colleagues [8] observed male to female ratio of 2:1.

They postulated the genetic Origin for these sex differences, because of female possession of 2 X chromosomes in contrast two males who have only one x chromosome early onset septicemia of <3 days was observed in 114 cases in our study (72%) and late onset septicemia of >3 days was seen in 56 cases (28%) concluding that early onset was more common than late onset septicemia. Our findings were consistent with other studies. Gupta, et al. [2] found that 76.4%

of cases occurred in <7 days, that is early onset type. Vesikari, et al. [9] reported early onset in most of the patients with neonatal sepsis. Karen, et al. [16] observed that 70% of cases developed early onset septicemia as was found in our study.

Sucilathangam, et al. [10] observed that out of 50 babies, 28 had normal birth weight, Ari Mulyni, et al. [11] noticed that out of 99 neonates, suspicious of sepsis, 65 neonates had birth weight >2000 grams. However, various other authors observed that onset of sepsis was more common in low birth weight babies. Nellian, et al. [12], Mehrotra, et al. [13], Gupta, et al. [2], Agarwal, et al. [14], Khatua, et al. [4] and Kontouby, et al. [15] observed that low birth weight newborns have higher incidence of neonatal septicemia which was consistent with our study. Nelson [11] stated that the low birth weight was the single most important factor in neonatal septicemia. There was 3-10 fold higher incidence of septicemia in these infant than in normal weight infants. Anand, et al. [17] found that more than 2/3 cases of neonatal sepsis were in low birth weight babies. 112 preterm babies and 88 full term babies were affected by sepsis in our study, concluding that preterm babies were more affected than full term babies by neonatal septicaemia. Ari, et al. [11] in their study,observed that out of 99 neonates suspiciousof sepsi,77 neonates were term babies. Sucilathangam, et al. [10] observed that 28 terms babies out of 50 neonates were affected. However various other studies have shown that sepsis is more common in preterm babies. Anand, et al. [17] observed that 62% preterm babies were affected, Karen, et al. [16] observed that out of 92 babies with neonatal septicemia, 58 were preterm accounting to 52%. Fanaroff, et al. [18], Koutouby, et al. [15], Gupta, et al. [2], Mehrotra, et al. [13] found that preterm babies were more affected than full term babies by neonatal sepsis. Similarly, early onset septicemia was observed in 71.4% of preterm babies in our study, which was consistent with other studies. Clinical manifestations in our study were refusal of feeds (64%), temperature abnormality (45%), jaundice (28%), pallor (20%), convulsions (6%). Several other studies also show variable clinical presentations, but major presentations were common in studies. Kathua, et al. [4], observed that refusal of feeds, lethargy, diarrhoea, temperature abnormality, abdominal distention jaundice and vomitings were the most common presenting features. Agarwal, et al. [14] observed that refusal of feed, slugggish activity, fever, jaundice were common clinic features. Gupta, et al. [2] observed that lethargy, feeding problems, abdominal distension, respiratory distress, hypothermia, Apnoea and irritability were the most common features. Somu, et al. [3] observed that abdominal distention, diarrhoea, refusal of feeds, lethargy, vomitings, pallor were common features. Anand, et al. [17] noted the same symptoms as in our study, concluding that clinical features are non specific and may be indicating stable from those occurring in non infectious conditions during neonatal period. Culture positivity was observed in 58% of cases in our study, which was in concurrence with studies done by Gupta, et al. [2], Sharma, et al. [19], Kathua, et al. [4], Namdeo, et al. [20], Bhatia, et al. [21], Chaturvedi, et al. [22], Sugandi, et al. [23], which observed culture positivity of 33 %, 56%, 59.8%, 50%, 66.7%, 73% and 42.5% respectively. Allthough blood cultures are normally basis for a diagnosis of bacterial infection, the bacteremia phase of the illness may be missed by poor timing of blood collection. Also, before drawing blood the patient may be treated with some parenteral antibiotics by private practitioners. Due to this, blood culture has low sensitivity, We had 116 culture positive cases, out of which, klebsiella was isolated in 48% of cases, staphylococcus aureus in 27.6%, acetobacter in 17.2% pseudomonas in 3.5%, E. coli in 3.5% were the common organisms isolated. Mehrotra, et al. [10] observed that E. coli were the commonest organism isolated. Similar observations were found in studies done by Shah, et al. [24], Nagwa Gad Mohamed, et al. [25], Kari A, et al. [26], pseudomonas, proteus and klebsiella were the other organisms frequently found. Kathua, et al.

[4] observed that klebsiella, E.coli, citrobacter, pseudomonas were the common organisms isolated. Chaturvedi, et al. [22] and Nellian, et al. [19] found that klebsiella, E.coli, pseudomonas were commonly isolated organisms. Wilson, et al. [7] stated that the organisms causing neonatal septicemia vary considerable in different nurseries and at different places. Sepsis screen was done in our study which included HSS on peripheral smear CRP, ESR, Serum Prolactin, in both culture positive and culture negative cases. HSS score of more than 5 was seen in 72% of culture positive cases and 4% of culture negative cases. HSS score of 1-2 was seen in 7% of cases of culture positive cases and 62% of culture negative cases. In our study, for HSS score of more than 5, the sensitivity is 95%, specificity is 86%, PPV is 93%, NPV is 61%. Aparna Narsimha, et al. [27], in there study stated that HSS more than 5 was seen in 10 out of 12 cases of sepsis (83.3%) and HSS less than 5 seen in 2 out of 12 cases (16.6%). Manisha Makkar, et al. [28], found that out of 42 culture positive cases, HSS score more than 5 is seen 35 cases. Our study findings correlated with other studies.

Immature Neutrophil count and immature to mature neutrophil ratio have high sensitivity of 82.75% each, followed by degenerative changes in neutrophils with 75.86% sensitivity. PPV is high for I:M ratio accounting to 85.71%. Unfortunately PPB often abnormal WBC count is poor. This is not surprising as many non-infectious conditions can be associated with an abnormal neonatal WBC count. Thus it may not be helpful in the decision to start antibiotic treatment for an asymptomatic neonate with identifiable sepsis risk factor. But immature neutrophil count and its ratio with total WBC and mature neutrophil ratio as a part of HSS is very much useful as part of initial screening of neonatal sepsis.

In Aparna Narsimha, et al. [27] study total PMN count (89.47%) was highly sensitive followed by immature PMN count (78.94%) in identifying infants with sepsis. The PPV was high for immature to total PMN ratio (88.88%) followed by plated count (85.71%) in Makkar, et al. [28] study, immature neutrophil count had high sensitivity of (96.87%) followed by I:T ratio (93.75%) with total PMN 90%. PPV is highest for I:M ratio with 99.4%.

CRP in our study had sensitivity of (51.7%), specificity of 76% and PPV of 75%. Our findings were consistent with other studies. Hiew, et al. [29] in a study observed CRP sensitivity of 83%, specificity of 41% and PPV of 37%. Rekha, et al. [30] found out that out of 58 cases of proven sepsis, 53 had raised CRP, with a sensitivity of 52% specificity of 61% and PPV of 91%. Singh, et al. [41] observed CRP sensitivity of 80% specificity of 91% and PPV of 92% in there study.

Gupta, et al. [2] observed that this test had 90.9% sensitivity and 96% specificity as a prognostic indicator of neonatal sepsis. Thus these studies along with our study indicate that CRP is a sensitive indicator of neonatal sepsis.

ESR was raised in 76 out of 116 culture positive cases (65.5%) and 16 out of 84 culture negative (19%) cases in our study, giving it a sensitivity of 65.5%, 80.9% specificity and PPV of 82.6%. Most of the studies showed that micro ESR was a reliable early sepsis marker. Parida S, et al. [31] in their study stated that 10 out of 14 sepsis cases showed raised micro ESR (> 8mm). Diwakar, et al. [32] in their study with 32 neonates the culture positive sepsis showed 20 cases with elevated micro ESR. The sensitivity and specificity of micro ESR was 62.5% and 60.9% respectively.

Serum PCT more than 10 is seen in 92 out of 116 culture positive cases (79.4%), 12 out of 84 culture negative cases (14%). PCT less than 2 is seen in 4 out of 116 culture positive cases and 36 out of 84 culture negative cases (43%). Therefore, for value of PCT more than 10, the sensitivity was 79.3%, specificity was 85.71% and PPV was 88.5% and NPV was 75%.

Sucilathangam, et al. [10] in their study, noticed that 64.3% of neonates with sepsis had PCT more than 10. Ibrahim aboud, et al. [33] in their study noticed that serum PCT levels were significantly higher in sepsis cases (14.1 ±18.7 ng/ml) than in the control group (0.38±0.43 ng/ml). In addition, after 7 days of treatment, neonates to had achieved clinical recovery had a significantly lower serum PCT levels (0.26±0.37 ng/ml). At a cutoff value of >0.8 ng/ml, the sensitivity, specificity, PPV and NPV of PCT were 84%, 80%, 86% and 84% respectively.

Koskenvyo, et al. in their study, noticed that all 5 neonates with bacterial sepsis had high PCT levels (>2ng/ml) within 12+4 hr of birth, and 80% of PCT values return to normal by 72+12 hr of birth. In our study, we combined both HSS and PCT levels. There by in 32 cases sepsis was ruled out or very unlikely. It was very likely in 112 cases and sepsis was possible in remaining 56 cases. Therefore combined use of early haematological findings and serum procalcitonin levels enables early diagnosis of sepsis in majority of cases.

Conclusion

Clinical features of neonatal septicemia are non specific and vague and may be clinically indistinguishable from those occurring in noninfectious conditions during neonatal period. Male, preterm and low birth weight babies are more prone for neonatal septicemia. Early onset septicemia is more common than late, of which gram negative septicemia is more common than gram positive one, and is more common in low birth weight neonates.

Sepsis screen has good sensitivity, specificity and positive predictive accuracy. It is a valuable aid in early diagnosis of neonatal septicemia. It is simple, cost effective, less time consuming and easy to perform even at bed side. As an individual test, procalcitonin and HSS have highest sensitivity, specificity and PPV and are sensitive indicators of early neonatal sepsis. Combination of test increase the specificity and positive predictive accuracy thereby help in reducing the morbidity and also unnecessary usage of antibiotics.

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