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Original Article

Pathology Section

Sepscore- An Improved Armament in the Diagnosis of Neonatal Sepsis

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ABSTRACT

Introduction: Neonatal sepsis is the third most frequent cause of neonatal mortality. Early diagnosis and treatment are very crucial for successful outcome. Blood culture, which is the gold standard for diagnosis, will not be available early for appropriate management. Haematological Sepsis Scoring (HSS) is a rapid, low-cost sensitive lab tool for diagnosing neonatal sepsis. Modification of HSS (Sepscore) done by removal of repetitive parameters and addition of Nucleated Red Blood Cells (nRBC) which are elevated in sepsis, have higher specificity.

Aim: To compare the diagnostic utility of the modified HSS (Sepscore) with Rodwell's HSS.

Materials and Methods: The prospective analytical study was conducted over 18 months in a tertiary care hospital in South India blood samples of 350 neonates admitted to Neonatal Intensive Care Unit (NICU) with signs of sepsis were evaluated by HSS and Sepscore. The sensitivity, specificity, predictive values and likelihood ratios of Sepscore and cut-off value of the Sepscore using the Receiver Operating Characteristic (ROC) curve for diagnosis of neonatal sepsis was determined.

Results: A total of 146 (41.7%) of 350 had neonatal sepsis and rest served as controls. A total of 188 (53.7%) of the subjects were preterm. The cut-off was determined as three for both HSS and Sepscore. The sensitivity and specificity of HSS were 71% and 54% whereas that of Sepscore was 68% and 61%, respectively. The diagnostic ability of Sepscore was found to be significantly higher than that of HSS (p=0.0094).

Conclusion: According to the observation of the present study sepscore has a higher specificity and marginally lower sensitivity compared to the HSS in neonatal sepsis.

Keywords: Blood culture, Haematological score, Neonate

INTRODUCTION

Neonatal sepsis is a clinical syndrome characterised by systemic signs and symptoms of infection and is accompanied by bacteraemia in the first month of life. The incidence of neonatal sepsis is inversely proportional to gestation at birth due to the poorly developed immune system [1]. Incidence of neonatal sepsis ranges from 1-10 per 1000 live births worldwide [2,3]. According to the data by World Health Organisation (WHO), neonatal sepsis is the third most frequent cause of neonatal mortality [4]. Co-existing conditions often complicate the diagnosis resulting in delayed treatment. Neonatal sepsis accounts for one-third of neonatal mortality [5].

The conventional gold standard for the diagnosis of neonatal sepsis is blood culture. The results are generally obtained after 48 hours and the yield is universally low. Early diagnosis and initiation of treatment is the key determinant of reduction in mortality and morbidity in neonatal sepsis. Delayed diagnosis and treatment due to clinical uncertainty can be mitigated with the help of lab investigation with high specificity. Hence, waiting for blood culture results to commence appropriate treatment can be detrimental. Serial measurements of a neonate's blood counts can provide diagnostically useful and perhaps indispensable information by acting as indirect evidence of sepsis in culture awaited or culture-negative cases with strong clinical suspicion of sepsis. Haematological parameters such as leukocyte count, differential count, immature cell count, and platelet count individually are highly sensitive in predicting neonatal sepsis. However, the specificity of each individual parameter alone is quite low to be clinically useful. Hence, a combination of these parameters was studied and validated as HSS by Rodwell RL et al., [6,7]. Many of the parameters counted in HSS stems from the same pathological mechanism and hence are repetitive. Despite this limitation, HSS has shown to be useful tool in diagnosis of neonatal sepsis [8]. Current advances in neonatal sepsis have shown that elevated nucleated RBCs are direct response to mediators of inflammation in newborns with early onset sepsis [9]. Incorporation of this parameter and removal of repetitive parameters from HSS resulted in modification of the HSS termed as 'Sepscore' which has shown increased diagnostic specificity in a pilot study [10].

Clinical suspicion of neonatal sepsis is highly sensitive tool and needs to be supported by more specific tool to avoid over treatment and antibiotic resistance. This score was developed and studied to precisely address this issue. Incorporating various haematological parameters which are individually shown to be useful in diagnosis of neonatal sepsis and avoiding repetitive parameter has been the novelty of this score.

The main objective of this study was to estimate the diagnostic ability of Sepscore in neonatal sepsis and compare it with HSS.

MATERIALS AND METHODS

The prospective analytical study was conducted between August 2018 to February 2020 over the period of 18 months in a tertiary care hospital in South India. Institutional Ethical Board approved in the present study without need for any special consent (JSSMC/PG/5900/2016-17). Sample size was calculated on the basis of hospital incidence of neonatal sepsis of 28% and sensitivity based on pilot study [10] which was 68% at the cut-off value of 3 Sepsocre. Considering these values, precision of 10%, and confidence interval of 95%. Total 350 samples were taken for this study. Diagnostic ability of HSS and Sepscore were compared in this study [7,10]. The components of both the scoring systems and their weightage are given in [Table/Fig-1].

Parameters	Values	HSS	Sepscore
TLC (cells/cmm)	<5000	1	2
	>25000 (at birth)	1	1
	>30000 (12-24 h)	1	1
	>21000 (day 2 onwards)	1	1
	Normal	0	0

TNC	No neutrophils	2	2
	Increased/Decreased	1	1
	Normal	0	0
Immature neutrophils	Increased	1	1
	Not increased	0	0
I:T ratio	>0.2	1	1
	<0.2	0	0
I:M ratio	>0.3	1	0
	<0.3	0	0
Degenerative changes	Present	1	2
	Absent	0	0
Platelet count (per microlitre)	<150000	1	1
	>150000	0	0
NRBC	>5%	0	1
	<5%	0	0

[Table/Fig-1]: Components and weightage of HSS and Sepscore.
HSS: Haematological sepsis score; TLC: Total leucocyte count; TNC: Total neutrophil count; I:T: Immature to total; I:M: Immature to mature; NRBC: Nucleated RBC

Inclusion criteria: Babies less than 28 days of age with clinical signs of sepsis and systemic inflammatory response syndrome admitted to NICU were included as cases.

Controls: Babies who were asymptomatic but had their blood counts done for other reasons were taken as controls.

Exclusion criteria: Babies with multi-organ dysfunction, on steroids and bone marrow suppressant medications, were excluded from the study.

Study Procedure

One mL of Ethylenediamine Tetraacetic Acid (EDTA) anti-coagulated samples was analysed on Sysmex XN-1000. A complete haemogram was performed and total White Blood Cells (WBC) count, absolute neutrophil count, platelet count, and nucleated RBC count were recorded. Peripheral smears were stained by Leishman stain and reported by one senior pathologist. The Immature: Total (I:T) and Immature: Mature (I:M) ratio was calculated. Degenerative changes and toxic granules were noted. Blood for culture was obtained under aseptic technique in all the study subjects.

STATISTICAL ANALYSIS

Data was compiled in Microsoft excel and analysed using Analyse-it V 4.3 software. Medians were compared using Mann-whitney U test. Proportions were compared using Chi-square test. Diagnostic ability of both the scoring system was reported as sensitivity, specificity, positive predictive value, and negative predictive value. The diagnostic ability of the two scores was compared using the McNamara test and ROC curve was constructed for obtaining optimal cut-off value.

RESULTS

A total of 350 subjects were recruited, out of which 146 (41.7%) fulfilled the clinical criteria of neonatal sepsis-sepsis group. A total of 204 (58.3%) did not have sepsis but had their blood counts for various other reasons. These babies constituted control group. All relevant data were collected from both neonatal case records and Laboratory Information Services. Both Rodwell HSS and Sepscore were computed.

Overall, 61% subjects were males. 63% neonates in the sepsis group and 59.3% in the control group were males. This difference was not statistically significant with a p-value of 0.489.

Overall, the median (Interquartile Range-IQR) gestation was 36 (32-37) weeks Median (IQR) in sepsis group it was 37 (33.9-38) weeks and in control group 35.5 (32-37) weeks. The difference was statistically significant (p-value=0.013). Median (IQR) age at sampling of was 5 (1-11) days in the sepsis group and 4 (1-8.6) days in the control group. This difference was not statistically significant with a p-value of 0.88. The birth weight of all the subjects ranged between 750 grams and 4200 grams with a median (IQR) of 2250 (1640-2721) grams. Median (IQR) birth weight in the sepsis group was 2365 (1715-2761) grams and that in control group was 2200 (1600-2711) grams. The difference was not statistically significant with a p-value of 0.28.

Among all the study subjects, 53.7% were preterm babies. Forty seven percent of babies in sepsis group and 59% in the control group were premature. This difference was statistically significant (p-value=0.023). Twenty four out of 146 (16.4%) cases were proved sepsis. Blood culture was positive in 17, five had UTI, two had meningitis. The most common organism isolated was the Klebsiella Species (52%) followed by E.coli (18%). The diagnostic ability of the scoring system at the various cut-off scores is depicted in [Table/Fig-2]. At a cut-off score of 3, Rodwell Sepsis Score showed a sensitivity of 0.79 and specificity of 0.39.

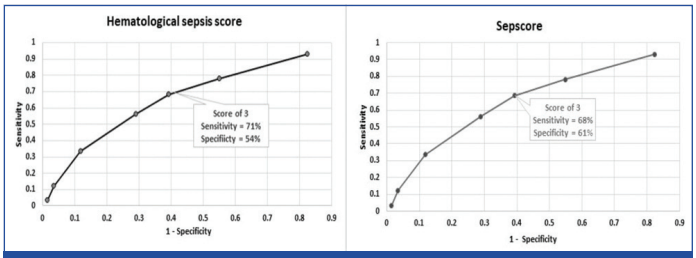
Haematological sepsis score			HSS score of 3			
Cut-off	Sensitivity	Specificity		Sepsis	Control	Total
1	0.94	0.14	HSS=/>3	104	94	198
2	0.87	0.33	HSS=/<2	42	110	152
3	0.71	0.54	Total	146	204	350
4	0.60	0.66				
5	0.40	0.80	PPV	0.53	LR+	1.54
6	0.16	0.96	NPV	0.54	LR-	0.53
7	0.02	1.00				
Sepscore			**Sepscore of 3**			
Cut-off	Sensitivity	Specificity		Sepsis	Control	Total
1	0.93	0.18	Sepscore=/>3	100	80	180
2	0.78	0.45	Sepscore=/<2	46	124	170
3	0.68	0.61	Total	146	204	350
4	0.56	0.71				
5	0.34	0.88	PPV	0.56	LR+	1.75
6	0.12	0.97	NPV	0.73	LR-	0.53
7	0.03	0.99				

[Table/Fig-2]: Comparison of diagnostic ability of both the scores at various cut-off values.
LR: Likelyhood ratio; PPV: Positive predictive value; NPV: Negative predictive value; HSS: Haematologic sepsis score

At the same cut-off value, the sensitivity and specificity of Sepscore were 0.68 and 0.61, respectively. [Table/Fig-3] depicts the various diagnostic ability parameters at a cut-off score of 3 for both HSS and Sepscore. The two scoring systems were compared using the McNamara test [Table/Fig-4]. The proportional difference between HSS and Sepscore is 0.171 and the 95% confidence interval was 0.102 to 0.239. The difference in the diagnostic ability was statistically significant (p-value of <0.0001).

Test	Sensitivity	Specificity	PPV	NPV	LR+	LR-
HSS	0.79	0.39	0.48	0.72	1.29	0.53
Sepscore	0.68	0.61	0.56	0.73	1.75	0.53

[Table/Fig-3]: Diagnostic parameters of HSS and Sepscore at the cut-off value of 3.
McNamara test. p-value=0.0094
LR: Likely hood ratio; PPV: Positive predictive value; NPV: Negative predictive value; HSS: Haematologic sepsis score



[Table/Fig-4]: ROC curve for both HSS and Sepscore.

A total of 135 (92%) out of 146 neonates in the sepsis group, improved on treatment. Five (3.4%) of them died and 6 (4.1%) were discharged against medical advice. None of the babies in control group died.

DISCUSSION

Neonatal septicaemia is characterised by clinical signs and symptoms accompanied by bacteraemia [11]. Early diagnosis of neonatal septicaemia is still a challenge. Though blood culture is the gold standard for diagnosing bacteraemia, it is time-consuming and has a wide range of yield (0-60%) [12]. In the present study, culture positivity was in 16.4% with Klebsiella Pneumonia being the commonest pathogen isolated followed by E.coli. This is similar to other studies on neonatal sepsis in the developing world [12,13].

Statistically significant difference in gestational age and birth weight between sepsis and control group in the present study is because, controls were not matched with cases. This was due to the ethical issues involved if controls were matched with cases. The controls who had lab investigations for reasons other than sepsis such as evaluation of neonatal hyperbilirubinaemia, protocol work up for maternal infection etc. Many other authors have reported the distribution of gender, birth weight, and gestation like index study population [11,14,15]. Neonatologists often encounter a challenge to diagnose septicaemia, in babies who present with soft clinical signs. Timely diagnosis can be aided by removing the clinical uncertainty using lab indicators. For the early diagnosis of septicaemia, several rapid diagnostic tests have been in vogue. These can be performed rapidly in an hour or two, enabling judicious but early usage of the antibiotics, thereby, reducing the incidence of drug resistance and improve the survival rate. For early diagnosis of neonatal sepsis, a HSS of Rodwell is in usage till date. The main shortcoming of this score is its lower specificity. Clinical suspicion by in itself is a sensitive tool for diagnosis of neonatal sepsis. Combining this with another sensitive tool will not improve the confidence of the clinician in diagnosis of sepsis. Instead, addition of a specific tool would do.

The observation of the present study was that, the popular HSS had several parameters that are derived from the same pathogenic path and hence appeared to be repetitive for e.g., IT and IM ratio and increased band count. All of these parameter stem from the same mechanism and hence are not contributory when combined together. Recent studies suggested that, nRBCs count in the peripheral blood of neonates with early-onset sepsis was significantly higher, independent of gestational age at birth, Erythropoietin (EPO) level, or hypoxia and it was correlated to proinflammatory cytokines like interleukin 6 [16].

A pilot study was conducted by modifying the HSS. The changes were adding of nRBCs and removal of repetitive parameters like I:M ratio and increased band count. Other changes included increased weightage for degenerative changes and leukopenia. This modification which is renamed as 'Sepscore' improved the specificity [10]. This study has validated the same showing an improvement in the specificity of over 20%.

Limitation(s)

In the present study, existing criteria in the hospital neonatal unit for diagnosis of sepsis was considered. However, recently procalcitonin has been shown to be quite specific for diagnosis bacterial sepsis. No procalcitonin was done in the index patients.

CONCLUSION(S)

Sepscore can be determined by the easily available haematological parameters from most of the modern analyser. This does not need any new addition of equipment or technology. By expanding the parameter base and recalibrating the weightage given for each parameter along with removal of duplication, results in improved specificity of the score. In this study, overall diagnostic ability is greatly improved with modified HSS or Sepscore in making a definitive diagnosis of neonatal sepsis in a suspected baby.

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