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Role of Sepsis Screen Tests in Predicting Neonatal Septicemia

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A B S T R A C T

Early diagnosis of neonatal sepsis continues to pose a problem to the clinician caring for newborns. Blood culture has been considered the gold standard for confirmation of diagnosis. An array of sepsis screen tests are now available for early diagnosis of neonatal sepsis. To study the role of sepsis screen tests in early diagnosis of neonatal sepsis. Blood cultures and sepsis screen tests were carried out on 200 neonates. The identification of the causative organism was carried out by standard identification tests. Sepsis screen was carried out with C-reactive Protein, I/T ratio, Total leucocyte count, Absolute neutrophils count, Out of 200 neonates studied with clinical features of sepsis, 128 (64%) were blood culture positive. Among Sepsis screen tests, CRP was the most sensitive test (89.84%) with a specificity of 76.39%. I/T ratio, TLC and ANC showed sensitivity 76.56%, 44.53%, 32.81% and specificity 59.72%.76.39%, 81.94% respectively. Sepsis screen tests may help and can be used as an adjunct in the diagnosis. They are also useful in early detection of neonatal sepsis and can be used as prognostic indicators; thus helping to start early treatment with appropriate antibiotics.

Introduction

Neonatal septicemia is a great masquerader and can present with very nonspecific manifestations pertaining to any system of the body (Jajoo *et al.,* 2015). The incidence of neonatal sepsis in India is approximately 30/1000 live births (Misra *et al.*, 2013). More than half of neonates admitted to neonatal intensive care units (NICUs) carry a diagnosis of "suspected sepsis" and these infants account for up to 25% of NICU days in some units (Jajoo *et al.*, 2015). According to World Health Organization (WHO) estimates, there are about 5 million neonatal deaths a year, of which neonatal sepsis is the major cause. (Shrestha *et al.*, 2007).

Early diagnosis of neonatal septicemia is a difficult task as the early signs of sepsis may be subtle, non-specific and different at different gestational ages and difficult to diagnose clinically (Aparna Narasimha and Harendra Kumar, 2011). There is no laboratory test with 100% sensitivity and specificity. Blood culture and sepsis screen are two most important diagnostic investigations. Blood culture has been considered the gold standard for confirmation of diagnosis but the results are available only after 48-72 hours.

Moreover, in many cases blood culture fails to detect the causative organism (Mondal *et al.*, 2012).

Neonatal sepsis is associated with the high mortality and serious morbidity so it is extremely important to make an early diagnosis of sepsis and prompt institution of empirical antimicrobial therapy. Hence, high index of suspicion is necessary for early diagnosis of sepsis. Test with a very high sensitivity and negative predictive value approaching 100% is desirable for diagnosis. However as no such tests are available; a battery of sepsis screen tests like CRP (C-reactive protein), TLC (Total leucocyte count), ANC (Absolute Neutrophil count), I/T ratio (Immature to Total neutrophil ratio) and m-ESR (micro- erythrocyte sedimentation rate), may help in the diagnosis (Misra *et al.*, 2013; Shatin, 2004). Studies have shown that septic screen tests are simple, quick, and cost- effective tools in the early diagnosis of neonatal sepsis. When these were studied together as combination of tests, it had proved that they increased both sensitivity and specificity. They are also useful early predictors of neonatal septicemia and also they are prognostic indicators; thus helping to initiate early treatment with appropriate antibiotics (Bhalodia *et al.*, 2017). The present study was conducted to know the role of sepsis screen tests in the diagnosis of neonatal sepsis.

The main aim and objectives includes to study the role of sepsis screen tests in early diagnosis of neonatal sepsis.

Materials and Methods

Source of Data

The present study; "Role of sepsis screen tests in predicting neonatal septicemia" was carried out in Department of Microbiology, Mysore Medical College & Research Institute, Mysore over a period of one year from 1st Jan 2014 – 31st Dec 2014.

Method of collection of data

Sample size: 200 clinically suspected cases of neonatal sepsis.

Inclusion criteria: Neonates admitted with signs and symptoms of sepsis.

Exclusion criteria: Neonates with no clinical evidence of sepsis.

Collection of samples and processing

After obtaining informed consent from parents/guardian, 1-5 ml blood was collected aseptically from neonates with suspected sepsis. 1-2 ml blood was inoculated into 5-10ml brain heart infusion broth and remaining blood into two different vials for different hematological and immunological tests. Broth was incubated at 37°C (Jajoo *et al.*, 2015, Rajendraprasad *et al.*, 2013). After 6-18 hours of incubation first subcultures were performed by aseptically removing a few drops of the well-mixed medium and inoculating onto blood agar, chocolate agar and MacConkey agar plate. The blood agar and MacConkey agar plates were incubated aerobically at 37ºC. Chocolate agar plate was incubated in 5 to 10% carbon dioxide jar at 35^{O}C for 48 hours. Growth was further processed and identified according to standard protocols. If no growth was detected then further subculture were performed on 2nd, 3rd and 7th day of incubation. Again growth was processed and identified as mentioned above (Forbes *et al.*, 2014; Shrestha *et al.*, 2007).

Sepsis screen tests

A battery of sepsis screen tests like CRP, TLC, Absolute Neutrophil Count, I/T ratio were carried out on the blood samples of all

the neonates.

C-reactive protein was tested by Latex agglutination test using Bio-Scan kit. CRP ≥ 0.6 mg/dl was considered significant.

I/ T ratio: It was calculated by examining peripheral blood smears stained with Giemsa stain. Blood smear was examined for immature neutrophils i.e., band forms, myelocytes and metamyelocytes. Immature neutrophils (band forms + myelocytes + metamyelocytes) to total neutrophil ratio were calculated. I/T neutrophil ratio greater than 0.2 was considered significant for neonatal sepsis

Total leucocyte count was estimated by using Sysmex automated analyser, which works on the principle of flow cytometry and counter verified by the pathologist. WBC count < 5000 / cmm were considered positive for septicemia. Absolute Nutrophil count was also estimated similarly. A count <1800/cmm were considered significant for sepsis (Kocabaş *et al.,* 2007; Nayak *et al.,* Misra *et al.,* 2013).

Results and Discussion

The present study was carried out in the Department of Microbiology, Mysore Medical College and Research Institute, Mysore from January 2014 - December 2014. The observations made from the study are shown in tables 1–5.

Of 200 neonates studied, 126 were males, 74 were females and 128 (64%) were blood culture positive.

Early diagnosis and treatment of neonatal sepsis is crucial for a favourable outcome. Blood culture is the gold standard in diagnosis of neonatal septicemia; which is positive in only 50-80% at best. A battery of sepsis screen tests may help and can be used as an adjunct in the diagnosis. Isolation of an organism from a sterile site is optimal for definitive diagnosis but it is not always possible to isolate a causative pathogen. Invasive infections can also occur in seemingly asymptomatic neonates (Shane and Stoll, 2014). In order to improve the outcome associated with neonatal sepsis, it is necessary for a diagnostic test to be rapid and sensitive to decrease delay in treatment. At the same time in order to avoid unnecessary exposure to antibiotics and invasive procedures, a test with higher specificity is needed. (Shah and Padbury, 2014) Sepsis screen tests may help in the diagnosis.

Sensitivity and specificity of CRP in our study is comparable with study conducted by Chauhan (Setal *et al.,* 2012). Study conducted by Santhosh Kumar Mondal *et al.,* reported 84% sensitivity and 65% specificity. (Mondal *et al.,* 2012) Study conducted by Misra *et al.,* showed 90.70% sensitivity and 37.50% specificity (Misra *et al.,* 2013). CRP can be considered as a “specific” but “late” marker of neonatal infection.

Serial CRP measurements may also be helpful in monitoring the response to treatment in infected neonates and thus may help clinicians guide the duration of antibiotic therapy. If the CRP levels remain persistently normal, it correlates strongly with the absence of infection thereby guiding safe discontinuation of antibiotic therapy (Shah and Padbury, 2014).

I/T ratio >0.2 was considered as significant for neonatal sepsis. The maximum normal value is 0.16 during the first 24 hrs, 0.14 by 48 hours and 0.13 by 60 hours and it remains until 5 days of age. Thereafter the maximum normal I/T ratio is 0.12 until the end of the first month. (Alison Bedford Russel David Isaacs) Ratio of ≥0.2 suggests bacterial infection (Barbara and Andi).

Table.1 Correlation of CRP with blood culture

CRP	BLOOD CULTURE				TOTAL
	POSITIVE		NEGATIVE		
	N	%	n	%	
Positive	115	89.84	17	23.61	132
Negative	13	10.15	55	76.38	68
TOTAL	128	100	72	100	200
	P value =0.000				

CRP ≥0.6 mg/dl was taken as positive, among blood culture positive cases 115 (89.84%) were CRP positive.

Table.2 Correlation of I/T ratio with blood culture

I/T RATIO	BLOOD CULTURE				TOTAL
	POSITIVE		NEGATIVE		
	N	%	n	%	
<0.2	30	23.43	43	59.72	73
>0.2	98	76.56	29	40.27	127
TOTAL	128	100	72	100	200
	P value =0.000				

Among blood culture positive cases, I/T ratio >0.2 is present in 98(76.56%) cases.

Table.3 Correlation of TLC with blood culture

TLC	CULTURE				TOTAL
	POSITIVE		NEGATIVE		
	n	%	n	%	
<5000	57	44.53	17	23.61	74
5000.01 – 20000	63	49.21	52	72.22	115
>20000	8	6.25	3	4.16	11
Total	128	100	72	100	200
	P value = 0.007				

In Blood culture positive cases, WBC count <5000/cmm was present in 57 (44.53%) cases.

Table.4 Correlation of ANC with blood culture

ANC	BLOOD CULTURE				TOTAL
	POSITIVE		NEGATIVE		
	N	%	n	%	
<1800	42	32.81	13	18.05	55
>1800	86	67.18	59	81.94	145
TOTAL	128	100	72	100	200
	P value =0.025				

In blood culture positive cases, Absolute neutrophil count (ANC) <1800/cmm was present in 42 (32.81%) cases.

Table.5 Sensitivity and specificity of various sepsis screen tests in detecting Sepsis

SEPSIS SCREEN TESTS	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
CRP	89.84	76.39	87.12	80.88
I/T ratio	76.56	59.72	77.16	58.90
TLC	44.53	76.39	77.02	43.65
ANC	32.81	81.94	76.36	40.69

However, the I: T ratio can be affected by various noninfectious processes like labor, prolonged induction with oxytocin, and even prolonged crying. Factors such as maternal hypertension or perinatal asphyxia may cause neutropenia or an elevated I/T ratio. Our study showed sensitivity of about 76.56% and specificity 59.72% with PPV 77.16% which is comparable with study conducted by Misra *et al.,* Study by Arijit Majumdar *et al.,* showed 100% sensitivity n 5% specificity (Majumdar *et al.,* 2013). Study by Aparna Narasimha *et al.,* showed 63.15% sensitivity and 75% specificity (Aparna Narasimha and Harendra Kumar, 2011). I/T ratio may be useful in diagnosing and monitoring infection.

A total leukocyte count of <5000 is significant for sepsis and can be used to infer the diagnosis of neonatal sepsis. Many infected newborns may have higher counts. Our study showed specificity of about 76% with high PPV which is comparable with study conducted by Aparna Narasimha *et al.,* Study conducted Chauhan *et al.,* Reported sensitivity of 30.77% and specificity of 63.15% (Setal *et al.,* 2012). Reported sensitivity of low leukocyte count is only 29%, but specificity can be as high as 91%. Severe bacterial sepsis may also demonstrate an increase in TLC due to rise in mature and immature neutrophils. This could possibly be due to release of various growth factors and cytokines viz. G- CSF, GM- CSF, IL- 3, IL- 6; which stimulate bone marrow. Although CBC (complete blood count) has a poor predictive value, serial normal values can be used to enhance the prediction that bacterial sepsis is not present. However; leucopenia was a better predictor of septicemia as compared to leukocytosis as it has higher specificity (Shah and Padbury, 2014; Misra *et al.,* 2013).

Absolute neutrophil count <1800/cmm was considered significant for sepsis. In present study sensitivity, specificity, PPV, NPV were 32.81%, 81.94%, 76.36%, 40.69% respectively and it is comparable with study done by Misra *et al.,* where in sensitivity, specificity, PPV is 20%, 87.5%, 75% respectively (Misra *et al.,* 2013). The ANC in babies born small for gestational age are lower than those born at weight appropriate for gestational age and may take up to 2 weeks of age to normalise (Alison Bedford Russel David Isaacs)

In summary sepsis screen should be done in all neonates suspected to have sepsis to corroborate the diagnosis. Among septic screen tests, WBC, ANC and I/T ratio have significant limitations in the diagnosis of neonatal sepsis because of their low sensitivity. In our study CRP was the most sensitive test (89.84%) with a specificity of 76.39%. Sensitivity and specificity of the individual tests may not justify their individual use in newborn infants. Sepsis screen is considered positive if two of the tests are positive. If the screen is negative but clinical suspicion persists it should be repeated within 12 hours. Presence of two abnormal parameters in screen is associated with sensitivity 93-100%, specificity 83%, positive and negative predictive value of 27% and 100%respectively in detecting sepsis.[19] Hence sepsis screen can be used as a predictor of sepsis to initiate therapy that can be modified based on blood culture reports. Early diagnosis of neonatal sepsis continues to pose a problem to the clinician caring for newborns. Battery of sepsis screen

tests may help and can be used as an adjunct in the diagnosis. Sepsis screen tests are simple, quick, and cost- effective tools in the early diagnosis of neonatal sepsis and can be used as prognostic indicators; thus helping to start early treatment with appropriate antibiotics.

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