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EVALUATION OF SEPTIC SCREEN AS A DIAGNOSTIC TOOL FOR NEONATAL SEPSIS IN A TERTIARY HOSPITAL

Neonatology

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KEYWORDS

INTRODUCTION:

Sepsis is the commonest cause of neonatal mortality; responsible for about 30-50% of the total neonatal deaths in developing countries [1,2]. Neonatal sepsis (NNS) is a clinical syndrome characterized by signs and symptoms of infection in the first month of life with or without accompanying bacteremia [3]. It has been reported that approximately 1% neonates die of sepsis related causes and it has been estimated that up to 20% of neonates develop sepsis [2]. The mortality due to sepsis can be prevented with early diagnosis, rational antimicrobial therapy and aggressive supportive care.

National Neonatal Perinatal Database (NNPD, 2002-03) reported neonatal sepsis in 30 per 1000 live births and reported as the commonest causes of neonatal mortality that contributes to 19% of all neonatal deaths [4] The outcome of sepsis largely depends on its early identification. Early diagnosis of NNS has remained a frustrating experience even in the developed countries. Due to the subtle and non-specific signs and symptoms,prompt and correct diagnosis of NNS is difficult. The blood culture is of gold standard for diagnosis but, it is costly and delay of at least 48 hours before preliminary results are received[5]

Early treatment with antibiotics is possible with the help of certain indirect markers such as neutropenia (<1800 cells/ mm3), leucopenia (<5000 cells/mm3), band cells, micro ESR and C-reactive protein (CRP). All these investigations are collectively known as sepsis screen and aids in early diagnosis of neonatal sepsis in absence of negative blood cultures. They together can be used as sepsis screen. Presence of two or more abnormal parameters in case of strong clinical suspicion is considered as positive sepsis screen. The results can be obtained much earlier than blood culture and early medical intervention can be issued. This can be helpful to reduce neonatal mortality and morbidity[6]Newer inflammatory markers such as interleukin-6, interleukin-8, and plasma elastase are highly sensitive and specific to diagnose neonatal sepsis and septic shock, but they require sophisticated and expensive kits [6]. Therefore, impractical for routine clinical work-up in community health delivery systems, particularly in developing countries like India. A simple, quick, inexpensive laboratory test which may assist the diagnosis of sepsis (or its exclusion) would ensure early treatment and prevent unnecessary antibiotic therapy and hence this study was planned.

METHODOLOGY

Study Design: Cross sectional study.

Source of Data: Neonates admitted to our NICU with clinical suspicion of sepsis during ----- to -------

Sample Size: All the babies satisfying the inclusion criteria and admitted during the study period were included in the study. This came up to 195 newborns.

Inclusion Criteria: Neonates (<30 days) admitted to our NICU with clinical suspicion of sepsis.

Exclusion Criteria:

Neonates who received antibiotics before admission.
Neonates who died before work up were complete.
Neonates who underwent surgery.

Data Collection:

Institutional Ethical committee clearance was taken prior to the study and Parental written consent was taken before enrolling newborn to the study. All the babies underwent sepsis screen and blood culture. Blood samples were obtained under strict aseptic precautions from peripheral venepuncture in all neonates within 24 h of admission, before initiation of antibiotic therapy.

Sepsis screen included following tests: Total Leucocyte Count (TLC), absolute Neutrophil Count (ANC), Platelet Count (PC), Immature: Total Neutrophil ratio (I: T ratio), Micro Erythrocyte Sedimentation Rate (mESR), C-reactive protein (CRP) tests.

Sepsis screen was considered positive if any 2 of the following were present [8-12]:

Total Leucocyte Count (TLC) of <5000/cu mm or >20000/cumm

Absolute Neutrophil Count of < 1800/cumm
I/T ratio of > 0.2,
Micro ESR >15mm in 1st hour
Platelet Count of < 150000/cumm
CRP value of >1 mg/L.

Blood culture was performed under strict sterile precautions. A single blood sample (2 ml) was inoculated into the culture bottle. The BacT alert microbial detection system was used for blood culture.

Statistical Analysis

All the study parameters were entered in the excel sheet and were analysed using epi-info software. Descriptive parameters were used for the univariate analysis. Sensitivity, specificity, NPV and PPV of septic screen was compared with culture outcome (gold standard) using a contingency table.

RESULTS

Out of 195 suspected neonatal sepsis patients, 52.3 % (102) were males and 47.7% (93) were females. Thus male babies were more affected by suspected neonatal sepsis than female babies. Among the patients with suspected neonatal sepsis, the most common presenting clinical feature was respiratory distress followed by fever and feeding problems. Among 195 cases there were 103(52.8%) term babies and 92(47.1%) preterm babies. Early onset septicemia was found in 125(64.1) cases and Late onset septicemia was present in 70(35.9%) cases. Birth weight less than 2500 gms (low birth weight) was present in 122(62.5%) cases. Birth weight greater than equal to 2500 gms (normal birth weight) was present in 73(37.4%) cases. In a total of 195 cases 131(67.2%) were inborn and 64(32.8) were outborn.

Characteristic	Number	Percentage
Gestational age		
Preterm	92	47.17
Term	103	52.8
Gender of the baby		
Male	102	52.3
Female	93	47.7
Age at onset of sepsis		
Early onset	125	64.1
Late onset	70	35.9

Place of birth		
Inborn	131	67.2
Outborn	64	32.8
Birth weight categories (kg)		
<1.5	11	5.6
1.5-2.5	111	56.9
>2.5	73	37.4

When considered individually, the sensitivity, specificity, PPV and NPV value of each of septic parameters varies widely. Amongst all sepsis screening parameters CRP had the highest predictive accuracy. As the single parameter CRP per se had the highest sensitivity (79.7%), specificity (75.4%), positive predictive value (73.1%) and the negative predictive value (81.6%). Although, both the CRP and I/T ratio were statistically significant as the sepsis parameters, the predictive accuracy of the screening test increased noticeably when two or more positive parameters were combined together which is sensitivity of 94.3% as illustrated in table 1.

Table 1:

	SENSITIVITY	SPECIFICITY	PPV	NPV	P VALUE
TLC	47.1	91.5	82.3	67.3	<0.001
ANC	48.3	90.5	81.1	67.6	<0.001
CRP	79.7	75.4	73.1	81.6	<0.001
m ESR	67.4	89.6	84.5	76.6	<0.001
I:T	68.5	88.6	83.5	77.0	<0.001
SEPSIS SCREEN	94.3	93.3	92.3	95.1	<0.001

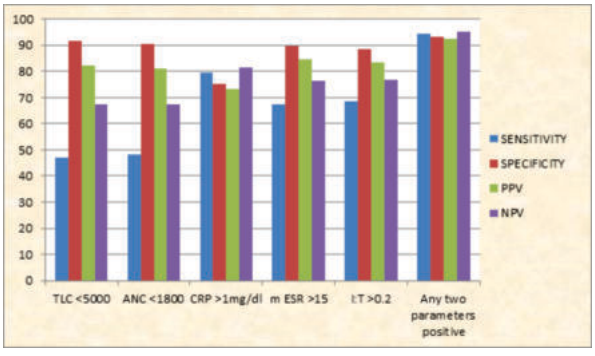

Figure1:

Bacteriologically positive cases were found in 89(45.6%) of the total 195 clinically suspected neonates. Bacteriologically negative but sepsis screen positive cases were found in 7 (7.6%) of the total 195 neonates. Bacteriologically negative, sepsis screen negative but clinical course compatible with sepsis were found in 99 (95%) neonates.

As illustrated in table 2, significant number 84(92.3%) of culture positive cases were positive for two or more septic screen parameters. On contrary, only 5(4.8%) of septic screen negative cases were culture positive. Blood culture negative suspicious sepsis cases, which were positive for septic screen parameters were total 7(7.6%) in number. 99(95.1%) cases were both culture and septic screen negative but had strong clinical suspicion for sepsis.

Table 2:

	BLOOD CULTURE				P Value
Sepsis Screen		+	-	Total	<0.001
	+	84(92.3%)	7(7.6%)	91	
	-	5(4.8%)	99(95.2%)	104	
	Total	89	106	195	

DISCUSSION:

Neonatal sepsis is a clinical syndrome. It is characterized by signs and symptoms of infection with or without bacteremia in the first month of life [7]. The incidence is much higher in the developing world. Early diagnosis and effective treatment is the best way to reduce morbidity and mortality. The delay in diagnosis and initiating therapy are the main reasons for high mortality. Blood culture is still regarded as a gold standard for diagnosis. Different hematologic parameters, multiple inflammatory cytokines and acute phase reactants levels are used in this regard.[8-10]

Of the infected babies, 52.3% were boys and 62.5% were low birth weight. This was possibly due to impaired defense mechanisms and low immunoglobulin G levels in boys and low birth weight neonates [11-13].

Maximum culture positive cases were seen in neonates of age ≤72 hours(i.e,60%) as compared to neonates aged more than 72 hours(i.e,29%). The higher proportion of early onset sepsis cases may be due to the immature immunological responses of the neonates in the first week of life, making them more susceptible to infections in this period

In present study, the percentage of culture positive cases in preterms was 51% and in terms it is 40%. Similar results were seen in other studies. Preterm babies are more susceptible to infections due to inherent deficiencies of both humoral and cellular defense mechanisms. According to Barbara J. Stoll et al[14] the incidence of septicemia increased with the decreased gestational age of the neonates.[14]

Non-infectious disorders may produce haematological changes similar to those seen with infection, thereby compromising the specificity and PPV of the hematological screening tests. However, a combination of hemotological changes and/or a rise in CRP as septic screen, can be used to improve the diagnosis. Previously many authors have tried to find out the credibility of septic screen with blood culture as gold standard to detect neonatal sepsis.

As no single individual haematological parameter is superior in comparison to another in predicting neonatal sepsis, a combination of these parameters in the form of septic screen has been recommended [8-10].

Total Leucocyte Count in response to sepsis, varies widely. Cut off values for normal range is not defined and offers little help in diagnosis. A TLC < 5 × 109/L had a sensitivity of 32% as per Spector *et al*. [15] Whereas, Chandna *et al*. [16] and Liu *et al*. [17] reported sensitivities of 17% and 29% respectively for a TLC < 5 × 109/L. **In the present study TLC < 10 × 109/L had a sensitivity of 47.1, an NPV of 67%, with a PPV of 82%.**

In neonatal sepsis, probably because of utilization at the infection site and adhesion to endothelial cells, neutropenia is a more common finding than neutrophilia [18]. Berger *et al*. recommended a value <4 × 109/L (sensitivity 78%, PPV 25%) to detect early onset sepsis [19]. **In the present study, ANC < 1750/mm3 had a sensitivity of 48% and a PPV of 81% in detection of sepsis**. Neutropenia in newborns can occur in cases of asphyxia, certain inborn errors of metabolism and also in Pregnancy induced hypertension in mother [18]. Therefore, its use as a sole predictor of sepsis is misleading. The variations between the results in different studies may be due to different criteria used, timing of sample, severity of infection, and the age of presentation and the reduced sensitivity of these tests in first week of life.

A 'left shift' of neutrophils happens during sepsis because of immature neutrophils released from marrow which increases the ratio of Immature to Total neutrophils. Manroe *et al*. [20] observed that in healthy neonates, I/T ratio was 0.16 in the first 24 h, which fell to 0.13 by 60 h and remained so until 28 days of age. Christensen *et al*. [21] suggested that neutrophil ratios were often abnormal during neonatal sepsis. **In the present study, I/T ratio > 0.2 had a sensitivity of 68.5%,** while Rodwell *et al*. [22] had a sensitivity of 47% with same cut off. The reported cut-off value of I/T ratio is variable in different studies, possibly due to the inter observer variation in interpretation of peripheral smear [23-24]. Rodwell *et al*. [22] used I/M > 0.30 as a predictor of infection. Unlike ANC, I/T ratio will not increase in cases of neonatal asphyxia. Thus, neutrophil ratios overcome the limitations of neutropenia and give fewer false negative results compared with band count.

Gerdes [24] has recommended normal value of micro-ESR as "day of life +3" corresponding to the 95th percentile value reported by Adler and Denton [25]. It would imply that 95th percentile values for micro-ESR on postnatal days 1, 3, 5 and 7 would be 4mm, 6mm, 8mm and 10 mm, respectively. 10mm has been considered as highest normal range for newborns more than 7 days. In our study, we considered micro ESR more than 15mm in 1st hour as positive. With this cut off, **we had sensitivity of 67%, Specificity of 89%, Positive predictive value of 84% and Negative predictive value of 77%.** Other studies Walliullah *et al*. [26] and Mondal *et al*. [27] found Sensitivity of micro ESR to be 63% and 63.2% respectively.

In the present study, CRP was the single best diagnostic test of the

various indicators of sepsis. Da Silva *et al*. [28] too found the same. Sharma *et al*. [29] observed that CRP had 80% sensitivity and 93% specificity. Chandana *et al*. [16] observed 83% sensitivity but only 42% specificity for CRP. This variation could be because of the different methodologies used to measure CRP and the cut off used.

Sl. No.	Author	Year	Sensitivity	Specificity	PPV	NPV
1	Philip *et al.* [35]	1980	93%	88%	39%	-
2	Chandna *et al.* [15]	1988	88%	23%	51%	-
3	Gerdes *et al.* [30]	2004	100%	83%	27%	100%

Two or more abnormal parameters had a high accuracy in predicting neonatal sepsis. The results in the present study were in accordance with Gerdes et al[24] and Jadhav et al[30] The sensitivity of two or more abnormal parameters was 94.3%, specificity was 93.3%, positive predictive value was 92.3% and negative predictive value was 95.1%. The sepsis screen should be considered as a positive septic screen, If two parameters are abnormal and antibiotic therapy can be started. If there is strong clinical suspicion and sepsis screen is negative, in 12 hours the screen can be repeated. If the screen is negative even after that, then sepsis may not be present.

CONCLUSION:

CRP had highest sensitivity, specificity, positive predictive value and proved to be a sensitive and responsive indicator of neonatal sepsis. The presence of two or more abnormal parameters has more sensitivity than any single abnormal parameter. The combination of tests also yielded statistically significant correlation with blood culture status than individual test. The parameters used in this study are simple, quick and cost effective. This can be useful to reduce neonatal morbidity and mortality.

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