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Diagnostic Efficacy of Nucleated Red Blood Cells in Neonatal Sepsis at A Tertiary Care Hospital

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Abstract

Background: The most common cause of neonatal mortality in the developing countries is neonatal sepsis. Neonates with sepsis show excess Nucleated RBC (NRBC's) in peripheral blood, which correlates with adverse outcome. Newer studies reveal that elevated NRBCs levels in neonatal sepsis help in predicting an adverse neonatal outcome and thus can improve the care by prioritizing them.

Material and Method: All newborns, delivered in Chirayu Medical college and hospital and out born babies fulfilling the inclusion criteria were included in the study. Study design was cross sectional study. The study included the neonates with clinical suspicion of sepsis at birth, within 72 hours and history of infection was present in the mother. Data of the neonates with clinical suspicion of sepsis admitted to the NICU were collected. A thin blood film was prepared and air dried. The slide was flooded with stain. On peripheral smear nRBCs were counted per 100 WBCs, immature granulocytes, toxic granules in neutrophils, platelet counts and B:N ratio were noted. A P-value less than 0.05 was taken to be statistically significant.

Result and Discussion: The mean NRBC in culture positive cases was 19.73, in clinical sepsis it was 13.17 and 6.42 in no sepsis group and the difference was found to be statistically significant. In our NRBC score of >10/100WBC in our study was 87.1%. In this present study the sensitivity of NRBC in identifying sepsis was 78.5%, its specificity was 59.25%, positive predictive value was 71.25% and negative predictive value was 76.23%.

Conclusion: Estimation of NRBC on day 1 in suspected neonatal sepsis can predict sepsis earlier. The difference of NRBC count in sepsis and no sepsis group was found to be significant. NRBC can be an early marker of sepsis along with the septic screen, that is cost effective, rapid, simple tool for early diagnosis and intervention. NRBC count can be helpful in assessing prognosis of sepsis and response to therapy. It can be a better predictor of mortality in neonatal sepsis.

Keywords: Neonates; NRBC; Sepsis; Peripheral smear; Early diagnosis

Introduction

The most common cause of neonatal mortality in the developing countries is neonatal sepsis [1]. Most of these deaths occur at home even before getting the required medical attention. Neonatal deaths continue to be a global health concern and account for 40% of all death in children less than 5 years of age [2].

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A lot of effort needs to be put to bring down the neonatal mortality from levels as high as 40 to 60 per 1000 live births and to achieve Millennium Development Goal for child survival (Goal 4 - to reduce child mortality by two-thirds between 1990 and 2015) [3]. Neonatal mortality in their first month of life is at an average global rate of 17 deaths per 1000 live births in 2022 (UNICEF) [4]. In India, the average Neonatal Mortality Rate is 19 per 1000 live births (The World Bank 2021) [5].

Majority of the estimated 2.3 million neonatal deaths occur in low and middle income countries.

Compared to the term neonates, sepsis in preterm neonates is up to 1000-folds more common and is associated with higher mortality rates and lifelong neurodevelopmental disability [6].

Unfortunately, the sensitivity and specificity of these traditional sepsis diagnostic markers are limited, as they frequently show an elevated response to other neonatal disorders such as meconium aspiration, prolonged rupture of the membrane and hypoxia. The isolation of pathogenic bacteria in blood cultures is necessary for the final diagnosis of sepsis, although this process is slow to act and affects the start of antibiotic therapy [7].

There is a persistent search for a test which is rapid, fundamental and cost effective that can be done in the early new born period, which can bring a significant impact in the improving neonatal health care. Neonates with sepsis show excess Nucleated RBC (NRBC's) in peripheral blood, which correlates with adverse outcome [8,9].

Newer studies reveal that elevated NRBCs levels in neonatal sepsis help in predicting an adverse neonatal outcome and thus can improve the care by prioritizing them. Sepsis is associated with an inappropriate immune response and on account of increased cytokine release, is accompanied by an increased nucleated red blood cell (NRBC) production [10]. Specifically, interleukin-6 (IL-6) is involved [11]. This implies that the foetal inflammatory response and foetal distress have distinct roles in NRBC production and/or release in the peripheral circulation.

Nucleated RBCs are in the peripheral blood of normal infants up to the fifth day of life. At birth, 3-10 NRBCs per 100 WBC are present [12,13]. Mean value of NRBCs in the first few hours of life in healthy term newborns is about 500 NRBCs/mm3, and a value above 1000 NRBCs/mm3 can be considered elevated. Expressed differently, 0–10 NRBCs/100 WBCs are typical, and values above 10 NRBCs/100 WBC are considered elevated [14].

If increased level of nucleated RBCs is noted at an early stage, early empirical antibiotic can resort to higher antibiotics therapy or other intensive management to prevent poor outcome can be sought. There are limited studies evaluating the role of nucleated RBCs in neonatal sepsis and hence this study has been undertaken.

Materials and Methods

The study was conducted in the Department of Paediatrics, Chirayu Medical College and Hospital, Bhopal, Madhya Pradesh, India, after approval by ethics committee. All newborns, delivered in Chirayu Medical college and hospital and out born babies fulfilling the inclusion criteria were included in the study to be done over a period of 18 months from August 2022 to February 2024. Study design was cross sectional study.

Using expected incidence of neonatal sepsis as 70 per 1000 live births (According to National Library of medicine 2022), At 5% precision and 95% confidence level sample size calculated as 101 [15].

$$N = (1.96)^2 \times P\ (1 - P) \div d^2$$

Where,

P = Prevalence (From previous studies, P=0.07)

d = Allowable error (5 – 20% of P)

The study included the neonates with clinical suspicion of sepsis at birth, within 72 hours and history of infection was present in the mother.

Data of the neonates with clinical suspicion of sepsis admitted to the NICU were collected. Clinical, perinatal history and demographic data like age, sex, gestational age -preterm/full term, weight and manner of delivery were noted.

Procedure of Leishman's stain – A thin blood film was prepared and air dried. The slide was flooded with stain. After 2 minutes double the volume distilled water was added and stained for 5-7 minutes. The slide was washed with buffered water and kept upright for drying.

On peripheral smear nRBCs were counted per 100 WBCs, immature granulocytes, toxic granules in neutrophils, platelet counts and B:N ratio were noted.

Analysis and statistical aspects- Mean and Standard Deviations were calculated from the data obtained. The data were analysed using one-way ANOVA with Fisher's LSD multiple comparison tests or t-test using Graph Pad Prism 7 software for sensitivity, specificity and positive predictive value (PPV) and negative predictive values (NPV) of haematological parameters and NRBCs. A P-value less than 0.05 was taken to be statistically significant.

Result and Discussion

Total 101 babies were taken of which 37.62% were negative for both blood culture and sepsis screen were labelled as **Suspected sepsis**, 31.68% were positive for sepsis screen

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but negative for blood culture labelled as **Clinical sepsis**, where as 30.69% were positive for blood culture labelled as **Proven sepsis** (Table 1-5).

Table 1: Final diagnosis of study participants.

Diagnosis	Number	%
Clinical Sepsis (C)	32	31.68
Proven Sepsis (P)	31	30.69
Suspected sepsis/no sepsis	38	37.62
Total	**101**	**100.0**

Table 2: Correlation of NRBC with Positive blood culture.

Parameter	Blood Culture (+Ve) (n = 31)	Blood Culture (-Ve) (n = 70)	Total= 101
NRBC's			
>10/100WBC's	25 (80.64%)	38(54.28%)	63 (62.37%)
<10/100WBC's	06 (19.36%)	32(45.71%)	38 (37.62%)

Of the total cases, nucleated RBC were positive in 55 (54.45%) cases and negative in 46 (45.54%) cases.

Table 3: Distribution of Nucleated RBC among study subjects.

Range	NRBC >10/100WBC (+Ve) (n=55)	NRBC <10/100WBC (-Ve) (n=46)
10-20	44 (80%)	00
21-30	10(18.18%)	00
>30	01(1.81%)	00

Table 4: Mean value of NRBC in study groups.

Final Diagnosis	Mean Value
Culture positive sepsis/ Clinical sepsis	13.17
Proven sepsis	19.73
Suspected sepsis	6.42

Table 5: Comparison of Nucleated RBC Vs Sepsis.

Nucleated RBC	Sepsis (C+P) (n=63)	Suspected Sepsis (n=38)	Total n=101	P value
Positive	51 (80.95%)	12 (31.57%	63	P = 0.0001
Negative	12 (19.05%)	26 (68.43%)	38	

In this study 63 cases had increased number of NRBC from normal range. 51(80.95%) cases fall in sepsis group (clinical and culture proven sepsis) whereas 12 (19.05%) cases showed no sepsis. Difference between sepsis and non-sepsis group is more and p value is significant.

Discussion

All the 101 babies were subjected to these investigations along with blood culture. Positive blood culture was taken as gold standard for the confirmation of diagnosis of neonatal sepsis. The diagnostic value of these tests was analyzed against blood culture individually and in combinations.

The mean NRBC in **culture positive** cases was 19.73, in **clinical sepsis** it was 13.17 and 6.42 in **no sepsis** group and the difference was found to be statistically significant. In our NRBC score of >10/100WBC in our study was 87.1% similar result was found in a study done by Rathi R et al. [16], 47 cases out of 56 neonates with proven sepsis had a NRBC score 83.9%.

In this present study the sensitivity of NRBC in identifying sepsis was 78.5%, its specificity was 59.25%, positive predictive value was 71.25% and negative predictive value was 76.23%. Almost similar observation was found in a study done by Rathi R, Kapoor A et al. [16] sensitivity of nRBCs was found to be 86.15%, specificity of 51.06%, positive predictive value 54.9% and negative predictive value of 84.21%.

Conclusion

A total of 101 neonates were enrolled. The blood culture positivity was 30.69% in our study, that was significant.

NRBC can be an early marker of sepsis along with the septic screen, that is cost effective, rapid, simple tool for early diagnosis and intervention. NRBC count can be helpful in assessing prognosis of sepsis and response to therapy. It can be a better predictor of mortality in neonatal sepsis.

Strength

Presence of NRBC in Peripheral smear is easy affordable quick readily available feasible tools to predict neonatal sepsis and their prognosis. This test can be used in peripheral setup with minimum infrastructure and facility as it is easy cost effective with no expertise needed especially useful in rural areas that can improve neonatal outcome.

Limitations of the Study:

Micro-ESR was not done as a part of sepsis screening due to non-availability of the test.

Recommendations

In future, further studies are needed to evaluate the usefulness of nucleated RBC as a good predictor of Neonatal sepsis, using large sample sizes. Nucleated RBC can be used as a prognostic marker for adverse neonatal outcome.

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