RED CELL DISTRIBUTION WIDTH AS A MARKER FOR EARLY ONSET NEONATAL SEPSIS – A CROSS SECTIONAL STUDY

Pediatrics

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ABSTRACT

Neonatal sepsis is a major cause of mortality, morbidity worldwide. A number of biochemical markers have been tested for accurate diagnosis of sepsis in the shortest time. Hence, this study was carried out to investigate the potential role of Red cell Distribution Width (RDW) as a marker of early onset neonatal sepsis. This hospital-based cross-sectional study was conducted in 144 Neonates born to high risk mothers for developing early neonatal sepsis. Data was analyzed for correlation between all explanatory variables and sepsis.10.4% (n=15) of the study population had positive blood cultures. The mean RDW was 21.13 ± 1.56 in sepsis group whereas 13.57 ± 2.41 in neonates without sepsis. This difference between two groups was statistically significant (p <0.001) revealing RDW as risk factor for neonatal sepsis (p = 0.014) RDW is an independent predictor of neonatal sepsis.

KEYWORDS

neonatal sepsis, RDW, markers of neonatal sepsis

INTRODUCTION:

In developing countries, one of the major causes of neonatal mortality is sepsis.[1] It is one of the most common reasons for admission to neonatal intensive care units in developing countries. Neonatal Sepsis is an invasive infection occurring within the first 28 days of life. Early onset neonatal sepsis (EONS) occurs within the first 72 hours of life and is defined as bacterial infection confirmed by blood orcerebrospinal fluid cultures.[2, 3]IMR (Infant Mortality Rate) of india was 33 in 2017 according to the recently published government data.[4]The NMR (Neonatal Mortality Rate) has declined from 44 per 1000 live births in 2000 to 28 per 1000 live births in 2013.[5]About three-fourths of total neonatal deaths occur in the first week of life.[1,5]The first 24 h account for more than one-third (36.9%) of the deaths that occur in the entire neonatal period.[1]The projected rates for Early NMR for 2020 was 18 per 1000 live births.[5] The high level and slow decline in early NMR in india is also reflected by its high and stagnant perinatal mortality rate.[5]Early onset neonatal sepsis (EONS) remains a major cause for neonatal mortality and morbidity. Infants with EONS usually present with respiratory distress and pneumonia. The case fatality in EONS ranges from 16.7% to 19.4%.[6] In United states, the case fatality ratio of EONS is 24.4%.[2] Hence early diagnosis is of utmost importance. But earlydiagnosisof EONS still remains a challenge. The present study was carried out with the objective to investigate Red cell Distribution Width (RDW) asa marker of early onset neonatal sepsis (EONS).Thegold standard for detecting bacterial sepsis isblood culture, but its positivity ranges from as lowas 8 % to 73% in the diagnosis of potentialneonatal sepsis and it has limitation of 24 to 48hour assay time.[7-9]Various hematological markers include clinical and laboratory findings (totalWBC counts, absolute number of neutrophils,immature/total neutrophil ratio) and acute phasereactants (CRP and procalcitonin) in differentcombinations have been used for early identification of neonatal sepsis.[8, 10, 11]Blood culture which isgold standard for diagnosis of neonatal sepsis not only takes time, but it is also complicated, with alow yield.[2,12]A number ofbiochemical markers have been tested for accuratediagnosis of sepsis in the shortest time.[13]RDW indicates heterogeneity of erythrocyte volume in circulationand routinely it is reported as a component of CBC without incurringadditional cost. RDW is calculated by dividing standard deviation ofred blood cell (RBC) volume by mean corpuscular volume (MCV) andmultiplying the product by 100. Hence, this study was carried out to investigate the potential role of Red cell Distribution Width (RDW) as a marker of early onset neonatal sepsis.

MATERIALS AND METHODS:

Place of study: Department of paediatrics , Tertiary care centre
Type of study: cross sectional study
Sampling methods: convenient sampling
Sample size and collection: Hospital

144 neonates born to high risk group for developing early neonatal sepsis Were identified. CBC, Blood group , CRP Was done for these neonates. Follow up and clinical correlation of Blood reports will be done

Inclusion criteria:

Term neonates(> 37 weeks of gestation), late preterm neonates(gestational age- 34weeks to36 weeks + 6 days)with risk factors for developing Neonatal sepsis

Exclusion criteria:

Early Preterm neonates (< 34 weeks of gestation), neonates with congenital malformations

Any specific score:

The correlation between Red cell distribution width (RDW) and sepsis(Positive CRP and Blood culture) Was made to identify the variance of Red cell distribution width with positive CRP and positive blood culture sensitivity

Risk factors for developing neonatal sepsis were as follows :
- Premature rupture of membranes
- Prolonged rupture of membranes > 18 hours
- Maternal fever
- Chorioamnionitis
- Foul smelling liquor
- Urinary tract infection
- Multiple vaginal examinations

STATISTICAL METHODS:

Sepsis was considered as primary outcome variable / variables. Gender, Gestational Age in Weeks, Birth weight in kg, Maternal Age at Delivery, RDW, Haemoglobin (Gm%), Packed Cell Volume (%), White Blood Cells(T/Mm3), Platelets(T/Mm3), CRP Dilution and Blood Culture were considered as primary explanatory variable.

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables.

Univariate Binary logistic regression analysis was performed to test the association between the explanatory variables and study group. Unadjusted Odds ratio along with 95% CI is presented. Variables with statistical significance in univariate analysis were used to compute multivariate regression analysis. Adjusted odds ratio along with their 95% CI is presented.

P value < 0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis. [14]

RESULTS:

A total of 144 subjects were included in the final analysis.

Table 1: Descriptive analysis of Demographic and anthropometric variables in study population (N=144)

Parameter	Summary
Gender	
Male	75 (52.08%)
Female	69 (47.92%)
Gestational Age in Weeks	
< 37 weeks	21 (14.58%)
≥ 37 weeks	123 (85.42%)
Birth weight in kg (Mean ± SD)	2.67 ± 0.44
Maternal Age at Delivery (Mean ± SD)	24.99 ± 2.98
RDW (Mean ± SD)	14.35 ± 3.29
Haemoglobin (Gm%) (Mean ± SD)	17.05 ± 2.64
Packed Cell Volume (%) (Mean ± SD)	53.48 ± 50.21
White Blood Cells(T/Mm3) (Mean ± SD)	77.13 ± 765.58
Platelets(T/Mm3) (Mean ± SD)	239 ± 76.48
CRP Dilution	
Positive	35 (24.31%)
Negative	109 (75.69%)
Blood Culture (N=143)	
Positive	15 (10.49%)
Negative	128 (89.51%)
Sepsis	
Yes	15 (10.42%)
No	129 (89.58%)

Among the study population, 75 (52.08%) participants were male and 69 (47.92%) participants were female. Among the study population 21 (14.58%) participants gestational age was less than 37 weeks and remaining 123 (85.42%) participants gestational age was more than or equal 37 weeks. The mean of birth weight(kgs) was 2.67 ± 0.44, it was 24.99 ± 2.98 in maternal delivery age, it was 14.35 ± 3.29 in RDW, it was 17.05 ± 2.64 in haemoglobin (Gm%), it was 53.48 ± 50.21 in packed cell volume (%), it was 77.13 ± 765.58 in white blood cells (T/Mm3) and it was 239 ± 76.48 in platelets(T/Mm3). Among the study population 35 (24.31%) participants had positive CRP dilution. Out of 143 participants in study population 15 (10.49%) participants had positive blood culture. Among the study population 15 (10.42%) participants had Sepsis (table 1)

Table 2: Uni variate binary logistic regression analysis of parameters on sepsis in study population (n = 144)

Parameter	Un adjusted odds ratio	95%CI Lower	95%CI Upper	p value
Gender (baseline=female)				
Male	1.058	0.362	3.088	0.918
Gestational Age in Weeks (baseline=≥ 37 weeks)				
< 37 weeks	0.891	0.186	4.265	0.885
Birth weight in kg	0.195	0.044	0.871	0.032
Maternal Age at Delivery	0.865	0.711	1.052	0.147
RDW	4.961	1.811	13.588	0.002
Haemoglobin (Gm%)	1.332	1.050	1.689	0.018
Packed Cell Volume (%)	1.000	0.989	1.011	0.996
White Blood Cells(T/Mm3)	1.103	1.019	1.194	0.015
Platelets(T/Mm3)	0.999	0.992	1.006	0.702
CRP Dilution (baseline=negative)				
Positive	1211606076.415	0.000	0.000	0.996
Blood culture (baseline=negative)				
Positive				

During univariate binary logistic regression analysis, the factors which have shown statistically significant association were birth weight in kg, RDW, haemoglobin (gm%), white blood cells(t/mm3).

Table 3: Multi variate binary logistic regression analysis of influencing Parameters on sepsis in study population (N=144)

Parameter	Un adjusted odds ratio	95%CI Lower	95%CI Upper	p value
Birth weight in kg	0.320	0.005	19.269	0.586
RDW	18.347	1.797	187.278	0.014
Haemoglobin (Gm%)	1.027	0.675	1.562	0.900
White Blood Cells(T/Mm3)	0.788	0.622	0.999	0.049

During multivariate binary logistic regression analysis, after controlling for potential confounding variables, the factors which have shown statistically significant association were presence of sepsis.

After confounding for the effect of potential confounding factors the odds of sepsis was 0.320 times higher among others with birth weight(kgs) (95% CI 0.005 to 19.268) (P value 0.586).After confounding for the effect of potential confounding factors the odds of F sepsis GR was 18.347 times higher among others with RDW (95% CI 1.797 to 187.278) (P value 0.014).After confounding for the effect of potential confounding factors the odds of sepsis was 1.027 times higher among others with haemoglobin (95% CI 0.675 to 1.562) (P value 0.900).After confounding for the effect of potential confounding factors the odds of sepsis was 0.788 times higher among others with white blood cells (95% CI 0.622 to 0.999) (P value 0.049). (table 3)

Table 4: Comparison of mean of RDW between sepsis(N=144)

Parameter	Sepsis (Mean± SD) Yes (N=15)	No (N=129)	P value
RDW	21.13 ± 1.56	13.57 ± 2.41	<0.001

The mean of RDW was 21.13 ± 1.56 in sepsis, the difference between two groups was statistically significant (p value <0.001) (table 4)

DISCUSSION:
RDW is estimated from CBC which does notincur additional cost. RDW is a low-priced arithmetical index and is part of a standardcomplete blood count. RDW is quickly obtained, and also does notrequire additional costs and easily can be provided.

Higher RDW values indicate increase in variations of RBC volume. RDW is mainly used for the differential diagnosis of microcytic anemia.[7]

Neonatal sepsis is a major cause of mortality in the developing countries. Red cell distribution width (RDW) is a readily available pragmatic means to predict outcomes of various comorbidities in adults and children, without causing any additional blood loss. However, its utility in neonates remains unexplored. This study was done on 144 neonates to evaluate the association of RDW with neonatal sepsis and its role as a predictive marker for mortality.The baseline characteristics of our study were comparable with that of Singh M et al[11] and Jajoo M et al.[15]10.4% (n=15) of the neonates had neonatal sepsis during admission. JajooM et al[15]in their study observed that the Incidence of EONS was 18/1000 admission. 52.1% of the study subjects were malesin our study but this difference between proportion of males and females with sepsis was not different.A higher incidence of sepsis has been suggested among male neonates, possibly based on the "male disadvantage hypothesis". Males neonates are more sensitive to adverse perinatal and postnatal environmental conditions, and are more likely to be born preterm and with a lower birth weight, both of which increase the risk of neonatal sepsis.[16, 17] 85.42% of neonates had gestational age of ≥ 37 weeks in our study and it was comparable to that observed by Singh M et al.[11] The mean birth weight was 2.67 ± 0.44 kg in our study and similarly Singh M et al[11] in their study observed a mean birth weight of 2.74 kg in cases and 2.67 kg in controls while JajooM et al[15] in their study observed the mean birth weight at admission was 2016 ± 724.04 g. This difference could be due to the difference in the inclusion and exclusion criteria and the sample population. The mean maternal age at delivery in our study was 24.99 ± 2.98 years and similarly Singh M et al[11] in their study observed a mean maternal age of 26 years while JajooM et al[15] in their study observed a mean age of 23 years.

The mean RDW was 21.13 ± 1.56 in sepsis group compared to 13.57 ± 2.41 in neonates without sepsis. This difference between two groups was statistically significant (p <0.001) in this study.Singh M et al[11] in their study also observed that Mean RDW levels was significantly higher (p<0.001) in EONS (21.31 ± 3.08 %) as compared to healthy controls (16.23 ± 1.16%). Ellahony DM et al[18] in their study also observed that RDW was significantly elevated in infants with septic shock compared with those having severe sepsis and those with sepsis (P < 0.0001). In the study by Martin SL et al[19], RDW levels were significantly higher among the neonatal sepsis cases (19.90%) as compared to the controls (18.90%) with a p value of < .001 and RDW was significantly higher amongst the nonsurvivors than survivors (p < .003). In their study, Kaplan-Meier curve showed that septic neonates having RDW values ≥20% had significantly increased mortality (p <

.02) with a hazard ratio of 0.5.[19] Singh M et al[11] in their study observed that the area under the ROC curve for RDW was 0.988 (0.973 –1.000), which indicated that RDW was a good predictor of EONS (p<0.001). The Critical cut off point was found to be 18.55 using Youden's index with a sensitivity of 94.55% and specificity of 96.36% for diagnosis of EONS. The statistically significant risk factors for neonatal sepsis by univariate analysis in our study were Birth weight (p = 0.032), RDW (p = 0.002), Hb (p = 0.018), WBC count (p = 0.015). But multivariate analysis revealed RDW as the only statistically significantly risk factor for neonatal sepsis (p = 0.014). Male sex (OR: 1.3, 95% CI: 1.02, 1.68), out born neonates (OR: 5.5, 95% CI: 2.39, 12.49), need for artificial ventilation (OR: 5.61; 95% CI:8.21, 41.18), gestational age <37 weeks (OR: 2.05; 95% CI:1.40, 2.99) and premature rupture of membranes (OR:11.14, 95% CI: 5.54, 22.38) emerged as risk factors for neonatal sepsis in the study by Murthy S et al.[20] Maternal factors such as premature delivery (gestational age <37 weeks) and PROM have also been implicated as significant risk factors in a meta-analysis on neonatal EOS (OR: 2.3, 95% CI: 1, 5.4; I^2 = 93.4%; aOR: 4.9, 95% CI: 1.9, 12.8).[21] Maternal colonization/infection, prolonged rupture of membranes >18 hours significantly increase the risk of early-onset neonatal infections.[21] Neonates are at a high risk of EOS, which can occur as a result of a direct transmission of the maternal colonizers (e.g. bacteria in the maternal vaginal tract) to the newborns during delivery**.**

Neonatal Sepsis is an invasive infection occurring within the first 28 days of life. Despite advances in perinatal & neonatal care, neonatal sepsis is still a significant cause of mortality & morbidity. RDW was observably higher in new-born with EONS. It is a hematological index estimated within the standard CBC profile and can be easily and rapidly estimated without additional cost.

This study was limited by the fact that it was only a cross sectional study and hence causal relationship could not be determined. The lack of statistical significance of many of the differences between the study groups may be attributed to smaller sample size. The generalizability of the study findings are limited, as the study has been conducted in a single centre. There is a need for large-scale multicentric studies on the subject, to enhance the quality of available evidence on the Indian population. Till such quality evidence is awaited, it is difficult to make any strong clinical practice recommendations.

CONCLUSION:
RDW is an independent statistically significant predictor of neonatal sepsis.

High RDW is associated with neonatal sepsis. RDW measurement is a cheap, rapid, easily accessible and universally available marker for rapid identification of early onset neonatal sepsis. Larger prospective studies are required to further confirm this evidence.

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