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Relationship between Early-Onset Neonatal Sepsis and Red Blood Cell Distribution Width (RDW)

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Abstract

Background: Comparative studies have shown the correlation between sepsis, septic shock and red blood cell distribution width (RDW) in the adult population. There is limited information about the association between RDW and neonatal sepsis.

Aims: In this study we purpose to compare RDW in healthy new-born and those with early-onset neonatal sepsis (EONS) and to investigate the potential role of RDW in the diagnosis of EONS.

Study design: The type of this study is prospective cohort study.

Methods: Study population consisted of term and near-term new-born delivered by spontaneous vaginal births. EONS (n=43) and control (n=45) groups were compared for RDW, complete blood cell count (CBC), and C-reactive protein (CRP) levels.

Results: In new-born in the EONS group significantly higher levels of white blood cell (WBC) (19.60 ± 6.30 10^3/mm^3 *vs.* 15.48 ± 5.46 10^3/mm^3; p=0.002), RDW (22.35 ± 5.27% *vs.* 15.33 ± 1.87%; p<0.001) and CRP (21.2 ± 19.06 mg/L *vs.* 2.71 ± 0.76 mg/L; p<0.001). A significant and positive correlation was detected between RDW and serum CRP (r=0.26; p=0.01) levels. According linear regression model CRP (β=0.42; p<0.001), RDW (β=0.529; p<0.001) and WBC (β=0.171; p=0.011) were associated with EONS.

Conclusion: RDW was observably higher in term and near-term new-borns with EONS. Besides we detected significant correlations between RDW and CRP in the EONS. RDW can be used with CRP for the diagnosis of EONS.

Keywords: C-reactive protein; Early-Onset Neonatal Sepsis (EONS); Inflammation; Newborn; Red blood cell distribution width

Abbreviations: CBC: Complete Blood Cell Count; CRP: C-Reactive Protein; EONS: Early-Onset Neonatal Sepsis; IL-6: Interleukin-6; LOS: Late-Onset Sepsis; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; MCV: Mean Corpuscular Volume; RBC: Red Blood Cell; RDW: 4 Red Blood Cell Distribution Width; TNF-α: Tumour Necrosis Factor-Alfa; VLBW: Very-Low-Birth Weight; WBC: White Blood Cell

Introduction

EONS has been defined as bacterial infection confirmed by blood or cerebrospinal fluid cultures performed within the first 4 days of life [1]. The incidence of EONS was previously reported as 3-4 cases in 1000 live births. Although its incidence has been currently decreased thanks to advances in obstetric and neonatal care and intrapartum prophylactic antibiotic use to prevent development of perinatal Group B streptococcal infection, it is still an important problem of the new-born [2-4]. Inability of the susceptibility tests performed on culture media which are accepted as gold standard for the diagnosis of EONS, to rule out neonatal sepsis because of lack of bacterial growth despite isolation of the causative bacterial agent [5,6], in addition to limited specificity, sensitivity and reliability of diagnostic markers including WBC parameters (total WBC counts, absolute number of neutrophils, immature/total neutrophil ratio) and acute phase reactants (CRP and procalcitonin) have led to the development of scoring systems which use clinical and laboratory findings in combination for the diagnosis of EONS [6-10].

RDW indicates heterogeneity of erythrocyte volume in circulation and routinely it is reported as a component of CBC without incurring additional cost. RDW is calculated by dividing standard deviation of red blood cell (RBC) volume by mean corpuscular volume (MCV) and multiplying the product by 100. Higher RDW values indicate increase

in variations of RBC volume. It is mainly used for the differential diagnosis of microcytic anemia [11,12].

Current studies have detected an association between RDW with pulmonary embolism, pneumonia, sepsis and acute myocardial infarction and RDW has been correlated with the prognosis in adult patients with acute myocardial infarction [12-16]. Though the mechanism of increased RDW is not known, higher RDW levels demonstrate its association with inflammatory processes. In studies performed, it has been detected that markers of inflammation including RDW-associated interleukin-6 (IL-6), tumour necrosis factor-alfa (TNF-α) and proinflammatory cytokines suppress maturation process of RBC and increase their half-lives with resultant rise in RDW levels [12,17]. Inflammatory response has an important role in the pathophysiology of sepsis; however, limited information is available about the association between RDW and EONS [18]. Therefore, in this study, we compared RDW levels in healthy new-born and those with EONS in order to investigate the potential place of RDW in the EONS and applicability of RDW in the diagnosis of EONS in addition to CRP which is one of the inflammatory markers.

Material and Methods

Study design

This prospective cohort study was approved by the local Institutional Review Board. Written informed consent was obtained from all parents and the investigators complied with the ethical principles stated in the Helsinki Declaration of the World Health Organization in all stages of the study. The study was performed in the Department of Children's Health and Diseases of Manisa Merkez Efendi Government Hospital. Summary of the study protocol was explained by one of the investigators to the parents of the new-born using easily understandable terms and the parents were requested to participate in the study. Study population consisted of term and near-term new-born delivered by spontaneous vaginal births. Age and body weight-matched new-born in the EONS and the control groups were included none of the pregnant women underwent pharmacological induction or received antibiotherapy within 48 h before the deliveries. Physical examination of all new-born was performed by the same researcher (HC). All new-born were of Caucasian origin.

Early-onset neonatal sepsis group

Among new-born hospitalized in the neonatal intensive care unit, the patients with symptoms suggesting neonatal sepsis including decrease in sucking activity, vomiting, changes in body temperature (fever/hypothermia single axillary temperature reading of >38.5°C or <36.0°C, or two consecutive temperature readings of 38.1°C or higher), jaundice, sclerema, hypotonia, convulsion, tachypnea, cyanosis, bradycardia, hypotension and impaired peripheral perfusion were evaluated according to Tölner scoring system criteria so as to diagnose neonatal sepsis as early as possible [8].

The diagnosis of EONS was made according to the presence of the following parameters on clinical, laboratory, or culture screen: (1) Clinical signs consistent with infection based on the Töllner score; (2) Detection of higher CRP (≥10 mg/L) values using nephelometry method; (3) Culture-positivity detected in blood, urine and cerebrospinal fluid samples or signs of pneumonia on chest X-ray [9].

Clinical parameters used in the Tölner scoring system include discoloration of skin, disordered peripheral circulation, hypotonia, bradycardia, apnea, respiratory distress, hepatomegaly, abdominal distension, abnormal laboratory parameters (left-shift in WBC counts, thrombocytopenia) and metabolic acidosis. According to this scoring system, for each parameter one point is assigned. Hence, patients with clinical sepsis (≥10 pts), suspicion of sepsis (5-10 pts) and normal (≤5 pts) new-born were categorized [8].

Term and near-term neonates were diagnosed with suspected clinical sepsis based on a Töllner score of ≥10 or a Töllner score of 5–10 but with the presence of one or more of the following factors associated with an increased risk of infection: maternal fever (≥38°C), prolonged rupture of membranes >18 h and clinical chorioamnionitis [9,19,20]. Inclusion criteria were positive clinical signs of sepsis and/or a history of factors associated with a raised risk of infection. Besides, the criteria included neonates with negative body fluid cultures who met all of the following criteria: Clinical signs of sepsis and/or radiographic findings consistent with pneumonia, a positive sepsis screen, and certain historical and clinical factors associated with a raised risk of infection [9]. Patients with established diagnosis of EONS were included in the patient group and following withdrawal of blood samples, treatment of sepsis was initiated.

Control group

New-born who had not any associated health problems and symptoms of clinical sepsis as determined among infants controlled during routine postnatal visits performed before discharge from the hospital or those brought to the outpatient clinics for neonatal screening program were included in the control group. New-born delivered before 36. gestational week or very-low-birth (<2500 g) infants, those older than 4 days and infants with perinatal asphyxia, meconium aspiration syndrome, congenital malformations, congenital infections associated with the TORCH complex, metabolic disease, Rh or ABO isoimmunisation or those delivered by Cesarian section were excluded from the study. Besides, new-born of the parents who refused to give their written consent was not enrolled in the study.

Laboratory analyses

Peripheral blood samples of the study participants in the patient and the control groups were drawn during their first hospital visits and CBC, CRP and blood typing were determined. After establishment of the diagnosis of sepsis, peripheral smear tests were performed, blood gases were determined and blood cultures were obtained in the EONS group. CBC was calculated by the automated haematology analyser XE-1200 (Sysmex, Japan). The interrun coefficient of variation of the RDW assay was found to be <1 percent. Serum CRP concentrations were measured using nephelometry technique and an appropriate kit (Mindray, People's Republic of China). Blood gas analyses were performed in Radiometer device ABL 900 flex sensor cassette and solution package. Blood culture was studied using Bactec method (bioMerieux kit).

Statistical analyses

Parametric data were presented as mean ± standard deviation and non-parametric data were presented as median. Demographic and laboratory characteristics of the newborns with and without EONS were compared using independent samples t-test. The relation of RDW and CRP with other demographic and laboratory characteristics was evaluated by Pearson's correlation analysis. A multiple linear regression model was established with independent variables that can

affect the level of EONS. All analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and statistical significance was defined as $p<0.05$.

Results

Forty-three new-born with the diagnosis of EONS and 45 healthy new-born were analyzed prospectively. Baseline demographic characteristics and laboratory data of the study population are shown in Table 1. In the EONS group, culture-positivity rate was detected as 41, 86 percent. No death occurred in EONS and control groups. Any significant intergroup difference was not detected regarding postnatal and gestational age, birth weight, RBC, hemoglobin, MCV, mean Corpuscular hemoglobin (MCH), mean Corpuscular hemoglobin concentration values (MCHC) ($p>0.05$). Maternal age was significantly higher in the early-onset neonatal sepsis group (28.78 ± 6.25 years *vs.* 26.29 ± 5.17 years; $p=0.049$). In new-born in the EONS group significantly higher levels of WBC (19.60 ± 6.30 $10^3/mm^3$ *vs.* 15.48 ± 5.46 $10^3/mm^3$; $p=0.002$), RDW (22.35 ± 5.27% vs 15.33 ± 1.87%; $p<0.001$) and CRP (21.2 ± 19.06 mg/L *vs.* 2.71 ± 0.76 mg/L; $p<0.001$), while platelet counts were significantly lower (226.09 ± 71.79 × $10^3/mm^3$ *vs.* 291.56 ± 70.99 × $10^3/mm^3$; $p<0.001$).

	Control group (n=45)	EONS group (n=43)	p Value
Postnatal age (days)	1.87 ± 0.92	1.98 ± 0.9	0.575
Gestational age (weeks)	39.18 ± 0.96	38.91 ± 1.62	0.345
Birth weight (gr.)	3300.3 ± 470.14	3193.7 ± 401.34	0.255
Maternal age (years)	26.29 ± 5.17	28.78 ± 6.25	0.049
CRP (mg/L)	2.71 ± 0.76	21.2 ± 19.06	<0.001
WBC ($10^3/mm^3$)	15.48 ± 5.46	19.60 ± 6.30	0.002
RBC (million/mm^3)	4.62 ± 0.31	4.53 ± 0.33	0.173
Hemoglobin (g/dL)	12.91 ± 1.12	12.55 ± 1.23	0.126
MCV (fL)	85.62 ± 6	82.59 ± 10.12	0.09
Platelet count ($10^3/mm^3$)	291.56 ± 70.99	226.09 ± 71.79	<0.001
MCH (pg)	35.47 ± 2.51	35.17 ± 1.8	0.519
MCHC (gr/dL)	33.97 ± 1.31	33.63 ± 1.54	0.264
RDW (%)	15.33 ± 1.87	22.35 ± 5.27	<0.001

Table 1: Baseline demographic characteristics and laboratory data of the study population.

Results of the Pearson's correlation analysis which examined the correlations between RDW, serum CRP and WBC values of new-born and some clinical and laboratory variables are shown in Table 2. A significant and positive correlation was detected between RDW and maternal age ($r=0.264$; $p=0.014$), while a significant and negative correlation was noted between RBC ($r=-0.214$; $p=0.045$) and platelet counts ($r=-0.36$; $p<0.001$). Also a significant and positive correlation was found between CRP levels and RDW ($r=0.26$; $p=0.01$), while a significant and negative correlation was disclosed platelet counts ($r=-0.23$; $p=0.03$) and MCHC ($r=-0.245$; $p=0.02$) levels. However, between WBC counts and maternal age ($r=0.223$; $p=0.037$) a significant and positive correlation was detected, while a significant and negative correlation was noted between postnatal infant age ($r=-0.212$; $p=0.049$), mean corpuscular hemoglobin (MCH) ($r=-0.218$; $p=0.042$) and mean corpuscular hemoglobin concentration (MCHC) ($r=-0.215$; $p=0.044$) levels.

		RDW	CRP	WBC
Postnatal age (days)	r	0.04	-0.77	-0.21
	p	0.75	0.48	0.049*
Gestational age (weeks)	r	-0.13	-0.44	0.22
	p	0.23	0.69	0.037*
Birth weight (grams)	r	-0.1	-0.53	0.17
	p	0.35	0.63	0.11
Maternal age (years)	r	0.264*	0.03	0.07
	p	0.014*	0.77	0.52
CRP (mg/L)	r	0.258*	Not applicable	0.15
	p	0.015*		0.22
WBC ($10^3/mm^3$)	r	0.19	0.15	Not applicable
	p	0.08	0.16	
RBC (million/mm^3)	r	-0.21	-0.2	-0.97
	p	0.045*	0.07	0.37
Hemoglobin (g/dL)	r	-0.13	-0.13	-0.08
	p	0.22	0.21	0.94
MCV (fL)	r	-0.11	-0.14	0.04

	p	0.33	0.21	0.72
Platelet (10^3/mm^3)	r	-0.36	-0.23	0.07
	p	<0.001*	0.03*	0.52
MCH (pg)	r	-0.29	-0.13	-0.22
	p	<0.80	0.22	0.042*
MCHC (g/dL)	r	-0.19	-0.25	-0.22
	p	0.07	0.02*	0.044*
RDW (%)	r	Not applicable	0.26	0.19
	p		0.01*	0.08

Table 2: Evaluation of the relation between RDW and CRP and other parameters using Pearson's correlation analysis.

Results of linear regression analysis are shown in Table 3. A linear regression model was constructed to investigate the place of RDW and other inflammatory markers including CRP and WBC levels in EONS. In this model EONS was accepted as a dependent and RDW, CRP and WBC as independent variables (adjusted R2=0.645; p<0.001). According to this model CRP (β=0.42; p<0.001), RDW (β=0.529; p<0.001) and WBC (β=0.171; p=0.011) were associated with EONS.

	Standard Error	β	p
(Constant)	0.139	-	<0.001
CRP	0.002	0.42	<0.001
RDW	0.006	0.529	<0.001
WBC	0.005	0.171	0.01
Multiple regression analysis was used. A p value of <0.05 was considered significant.			

Table 3: Linear regression model on the effects of CRP, RDW and WBC on EONS by using multiple linear regression analysis method.

Discussion

In this study, we found increased RDW values in term and near-term infants with EONS. RDW is estimated from CBC which does not incur additional cost. This investigation is the first study in the literature which compared EONS in term and near-term new-born, with RDW values.

RDW is a low-priced arithmetical index and is part of a standard complete blood count. RDW is quickly obtained, and also does not require additional costs and easily can be provided. Comparative studies investigating the correlations between sepsis, septic shock and RDW have been more frequently performed with adult population. In a study performed among patients admitted to the emergency department with diagnosis of sepsis/septic shock, higher mortality rates were found in patients with higher RDW values both at admission and in those demonstrated marked increases in their RDW values at 72 h of their hospitalization relative to the baseline. The authors reported that the combination of baseline RDW value and percent increases in RDW values might be a promising independent prognostic factor in patients with severe sepsis or septic shock [13]. In another study performed in 566 adult patients, RDW was indicated as a potentially independent prognostic factor for 28 day-mortality in patients with sepsis and septic shock [12].

In a study which investigated reference ranges of RDW for new-born, the authors detected lower limits and upper limits of normal at birth, for term and late-preterm infants as 15.5% and 20%, respectively. However, in premature infants, upper limit of RDW was higher (23%) [21]. In our study, mean (± SD) value of RDW (15.33 ± 1.87%) measured within 4 days of the postnatal period was similar to the lower limit of normal reference range of term and late-term infants in the above-mentioned study. Contrary to the above-mentioned study, since new-born with Rh or ABO isoimmunization which might cause hemolysis and hence affect RDW and those with a history of C/S delivery and disease states which might affect inflammation factors were not included in our study, our RDW values may be lower than those of the study cited above.

Limited number of studies has compared some clinical conditions in new-born and RDW values. In a retrospective study, mean (± SD) RDW values measured within the first 3 days after birth, were 15.65 ± 1.18% in full-term new-born, 17.7 ± 2.06% in preterm; and 17.45 ± 1.81% in cases with intrauterine growth retardation. A negative correlation was observed between RDW and gestational age (r=-0.51; p<0.001). In premature infants who had higher RDW values within the first 3 days of their life-time, increased rates of mortality (p<0.0001) and late-onset sepsis (LOS) (p<0.005) were found and the authors indicated the need for further studies to reveal the value of RDW as potential risk indicator in new-born with critical diseases [22]. In our study, mean (±SD) RDW value (15.33 ± 1.87%) estimated in the control group within the first postnatal 5 days was comparable to the mean (±SD) RDW value (15.65 ± 1.18%) of term and near-term infants determined within the first 3 postnatal days of the cited study. In their study LOS had been more frequently seen in premature infants with higher RDW values detected within the first 3 postnatal days. In our study, in term and near-term new-born with EONS, RDW values were higher when compared with those of the control group (p<0.001) (Table 1).

In another study where RDW indices were evaluated in 46 very-low-birth weight (VLBW) infants (birth weight <1000 g) with early sepsis, 16 (35%) infants had died during the evaluation period. When the patients were divided into 3 groups as for RDW indices, mortality rates did not change among RDW groups and also a significant correlation was not found between RDW indices and IL-6 and CRP levels of the patients. The authors suggested that RDW did not predict mortality in VLBW infants [18]. However in our study, in term and near-term new-borns with EONS, RDW indices were higher than those of the control group (p<0.001) (Table 1). Besides in our study, a significant correlation was detected between RDW indices and serum CRP levels (Table 2). Also, significant effects of both CRP and RDW on EONS were revealed (Table 3). Their study was performed on premature infants and ours on term and near-term new-born which might be the reason for differences between the outcomes of their and our studies Since premature infant population is a heterogeneous group because of the presence of respiratory distress syndrome, use of mechanical ventilators and surfactant therapy and also patent ductus arteriosus and intraventricular hemorrhage which might trigger inflammatory processes effective on RDW indices, it may be difficult to compare the correlations between sepsis and RDW indices in prematurity [22].

The main limitation of our study was relatively scarce number of new-born included in the study. Secondly, we did not analyse the levels of IL-6 and TNF-α and other markers of inflammation which involve in the diagnosis and pathogenesis of sepsis and their correlations with RDW. Finally, we made only a single evaluation of parameters in the patient group, which prevented us from determining variations in RDW indices with patients' changing clinical manifestations associated with antibiotherapies and other treatments applied. Consequently, the place of RDW in response to treatments applied could not be revealed.

In conclusion, RDW indices which were estimated from CBC were observably higher in term and near-term new-born with EONS. Besides we detected strong correlations between RDW and CRP in the EONS. RDW and CRP can be used in combination for the diagnosis of EONS. Further studies investigating the correlations between RDW and EONS are needed.

Disclosure Statement

The authors declare no conflict of interest.

Compliance with Ethical Standards

The authors declare no conflict of interest. This study was approved by the local Institutional Review Board. Research involving human participants. Written informed consent was obtained from all parents included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions

H.C., Ö.Y. and M.T. designed the study; H.C. and Ö.Y. collected and analyzed data; H.C. and Ö.Y. wrote the manuscript; H.C., Ö.Y., M.T., P.Ö.Ö., M.K. and Y.B. gave technical support and conceptual advice. All authors read and approved the final manuscript.

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