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Umbilical Cord Blood Red Cell Distribution Width as a Predictor of Neonatal Hyperbilirubinemia

Neonatal Hiperbilirubineminin Prediktörü Olarak Umblikal Kord Kanı Kırmızı Hücre Dağılım Genişliği

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ÖZ

Amaç: Yenidoğanların doğum sonrası erken taburcu edilmesi, çoğunlukla neonatal hiperbilirubinemi nedeniyle hastaneye yeniden yatış riskine yol açar. Bu nedenle hiperbilirubinemi gelişme riski yüksek olan yenidoğanların erken teşhisi önemlidir. Bu çalışmada, hiperbilirubinemi gelişme riski yüksek olan yenidoğanları belirlemek için kord kanı kırmızı hücre dağılım genişliği (RDW) düzeylerinin kullanılıp kullanılamayacağını değerlendirmeyi amaçladık.

Gereç ve yöntemler: Ocak-Haziran 2017 tarihleri arasında Ordu Üniversitesi Eğitim ve Araştırma hastanesinde doğan, kord kanı örneği alınan tüm term bebeklerin verileri geriye dönük olarak incelendi. Kord kanı RDW, kord kanı bilirubin, yenidoğan/anne kan grupları ve direkt Coombs testi (DCT) sonuçları analiz edildi. Postnatal ilk 48 saatte fototerapi ihtiyacı nedeniyle yenidoğan yoğun bakım ünitemizde yatırılanların bilirubin düzeyleri kaydedildi.

Bulgular: Çalışmaya toplam 175 yenidoğan dahil edildi. 58 yenidoğana postnatal ilk 48 saatte fototerapi verildi. Hiperbilirubinemili yenidoğanlarda ortalama kord kanı RDW düzeyleri kontrollere gore anlamlı derecede yüksekti (18±1.6'ya karşı 16.4±1.0, p<0.001). Hiperbilirubinemi gelişme riskini öngörmek için kord kanı RDW düzeyinin cut off değeri 17.1, duyarlılığı %70.7, özgüllüğü %88 bulundu. DCT pozitif olan yenidoğanların hemoglobin değerleri daha düşük, kord kanı RDW ve bilirubin düzeyleri daha yüksekti (p<0.05). Kord kanı RDW ve kord kanı bilirubin değerleri arasında pozitif yönde güçlü bir korelasyon tespit edildi (p<0,001, r: 0.476). Çoklu regresyon analizinde kord kanı RDW, bilirubin düzeyi ve DCT pozitifliğinin fototerapi gereksinimi için bağımsız birer risk faktörü olduğu bulundu.

Sonuç: Kord kanı RDW hiperbilirubinemi geliştirme riski taşıyan yenidoğanların erken belirlenmesinde yararlı bir belirteç olabilir.

Anahtar kelimeler: RDW; kırmızı hücre dağılım genişliği; umblikal kord kanı bilirubin, yenidoğan, hiperbilirubinemi, hemolitik hastalık

ABSTRACT

Aim: Early postnatal discharge of newborns leads to the risk of hospital readmission, mostly due to neonatal hyperbilirubinemia. Therefore, early identification of newborns at risk of hyperbilirubinemia is important. In this study, we aimed to evaluate whether the cord blood red cell distribution width (RDW) levels could be used to identify newborns at risk of developing hyperbilirubinemia.

Material and methods: The data of all term newborns born in Ordu University Training and Research Hospital between January and June 2017 whose cord blood samples were examined were reviewed retrospectively. Cord blood RDW, cord blood bilirubin, newborn/mother's blood groups and direct Coombs'test (DCT) results were analyzed. Serum total/direct bilirubin levels of those hospitalized in our neonatal intensive care unit due to the need for phototherapy treatment during the first 48 hours postnatally were recorded.

Results: A total 175 newborns were included. Phototherapy was required 58 newborns in the first 48 hours postnatally. The mean cord blood RDW levels among newborns with hyperbilirubinemia was significantly higher compared to controls (18±1.6 vs. 16.4±1.0, p<0.001). The cut-off value of cord blood RDW to predict the occurrence of significant hyperbilirubinemia was 17.1 with a sensitivity of 70.7 % and specificity of 88 %. Newborns with positive DCT had lower hemoglobin values and higher cord blood RDW and bilirubin levels (p<0.05). There was a strong positive correlation between cord blood RDW and bilirubin values in newborns (p<0.001, r: 0.476). Multiple regression analysis showed that cord blood RDW, bilirubin level and DCT positivity were found to be an independent risk factor for phototherapy requirement.

Conclusion: Cord blood RDW may be a useful marker in the early identification of newborns at risk of developing hyperbilirubinemia.

Keywords: RDW; red cell distribution width; umbilical cord blood bilirubin; newborn; hyperbilirubinemia; hemolytic disease

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INTRODUCTION

Neonatal hyperbilirubinemia is the most common cause of admission to hospital within the first week of life (1). Due to the high hospital occupancy rates and economic reasons in our country, the mother-baby couple can be discharged early (2). This situation may cause delays in early diagnosis and treatment of severe hyperbilirubinemia (2).

Neonatal hyperbilirubinemia is a multifactorial disease (3). Any disease that causes an increase in bilirubin production and/or decreases conjugation can lead to neonatal hyperbilirubinemia (3). However, the most common cause of neonatal hyperbilirubinemia is isoimmune hemolytic disease caused by blood group incompatibility between mother and fetus. Transport of maternal immunoglobulin G antibodies to the placenta in hemolytic diseases causes severe anemia and hyperbilirubinemia with hemolysis of fetal and neonatal red blood cells (4). Therefore, severe hyperbilirubinemia may occur in the first days of life. However, to predict which newborns will develop severe hyperbilirubinemia, a biomarker approved at birth has not yet been revealed.

Red cell distribution width (RDW) is a numerical measure that describes the heterogeneity of circulating red blood cell volume and a parameter that is routinely reported as part of a complete blood count (5). It has been shown that RDW levels in adults vary according to kidney, heart and respiratory problems, anemia, hypoxic conditions, malignancy, inflammation and oxidative stress (6,7). However, there are only a few studies about RDW levels for determining the risk of specific conditions in newborns (8-11). It has been reported that RDW reference values in newborns are higher than children and adults (8). It has been shown that RDW values range between 15-20% within the first 2 weeks of life, with the highest values being in the anemic newborns with prenatal hemorrhage or hemolysis (12). Increased RDW indicates impaired erythropoiesis and abnormal red blood cell survival (6). RDW is expected to increase in newborns with immune hemolytic anemia. Also, studies have shown that oxidative stress can trigger hyperbilirubinemia by directly damaging erythrocytes (7,13). In this study, our aim is to determine whether cord blood RDW level can be used in the early detection of newborns at high risk of developing hyperbilirubinemia.

MATERIALS AND METHODS

This study was conducted by retrospective analysis of the medical records of newborns born at Ordu University Faculty of Medicine between January 1st 2017 and June 31th 2017. The cases were divided into 2 groups according to the need for phototherapy treatment. Newborns who were treated with phototherapy were included in the study group. Healthy newborns who did not need phototherapy were also included in the control group. In addition, the newborns in the study group were also divided into two groups according to DCT positivity. Newborns with gestational week ≤35 weeks, birth weight ≤2500gr, newborns with intrauterine growth retardation (IUGR), sepsis, asphyxia, congenital malformation, chromosomal anomaly and congenital heart disease were excluded from the study.

Due to our hospital policy, complete blood count, bilirubin levels, blood group and DCT are routinely studied from umbilical cord blood. Demographic features, cord blood test results (RDW, Hemoglobin (Hb), Hematocrit (Htc), mean corpuscular volume (MCV), cord bilirubin (UCB), blood group and DCT) were recorded. Phototherapy indications were determined according to total bilirubin levels exceeding threshold bilirubin values on the charts described by the American Academy of Pediatrics (14). The presence of hemolysis was considered in cases with positive DCT in the presence of increased UCB, decreased Hb level and hyperbilirubinemia. Newborns with cord Hb values<13 g/dL were classified as anemic (15). Demographic features, cord blood RDW, Hb, Htc, MCV, and UCB values were compared between groups.

Receiver operating characteristic (ROC) analysis was performed to determine the sensitivity, specificity, negative predictive value and positive predictive value of cord blood RDW for predicting the need for phototherapy. Multivariate regression analysis was carried out to evaluate the risk factors (cord blood RDW, UCB, DCT positivity, Rh incompatibility, ABO incompatibility, mode of delivery and gender) in predicting the need for phototherapy.

Hematological parameters (Hb, Htc, MCV, RDW levels) were measured by an automated analyzer (Abbott Cell-Dyn 3700 Hematology Analyzer, Abbott Diagnostics, USA). All modern automated blood cell counters report the RDW as the coefficient of variation of red blood cell (RBC) volume, which is computed by dividing the standard deviation of RBC volume by MCV and multiplying this quantity by 100. The obtained samples were studied by hemagglutination and antiglobulin antibody assay

for blood type and Rh determination and gel centrifugation/colon agglutination method for DCT via DiaMED-ID Micro Typing System® (Diamed, Morat, Switzerland). UCB measurements were performed in the biochemistry laboratory. Total serum bilirubin levels were determined with heel stick (capillary) samples using bedside BR 5000N Apel bilirubinometer. The study was approved by the Ordu University Institutional Ethics Committee (Approval No:2017/51).

Statistical analyses

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA). Data were given as mean, standard deviation, minimum, maximum, and percent. The categorical data were analyzed by Fisher's exact test and Chi-square test. The variables were evaluated after controlling for normality and homogeneity of variance preconditions. Normally distributed variables were compared with Student t test, and non-normally distributed variables with Mann-Whitney U tests. Correlation analysis was performed with Spearman test. The prognostic ability of RDW for phototherapy was assessed using the are under the ROC curve (Fig.1). Accuracy was assessed in terms of sensitivity, specificity, negative predictive value and positive predictive value for RDW cut-points. The logistic regression analysis was used to predict phototherapy requirement from potential independent variables. Results were evaluated at a 95% confidence interval, and the p-value of <0.05 was considered significant.

RESULTS

During the study period, a total of 175 newborns (study group n=58, control group n=117) were born in our hospital. Any statistically significant difference was not found between two groups in terms of gestational week, birth weight, gender and mode of delivery. The characteristic features of the study and control groups were shown in Table 1.

Table 1. The characteristics of the study and control groups

Variables	Phototherapy (+) (n=58)	Phototherapy (-) (n=117)	P- value
Gestational age (week)*	39.1±0.9	39.2±1.0	0.404
Birth weight (g)*	3296.6±358.1	3274.4±358.1	0.582
Male (n, %)**	33 (56.9%)	62 (53%)	0.625
C/S (n, %)**	38 (65.5%)	49 (41.9%)	**0.003**
RDW (%)*	18±1.6	16.4±1.0	**<0.001**
UCB(mg/dl)*	2.5±0.1	1.7±0.4	**<0.001**
Hb (gr/dl)*	15.0±2.3	16±1.5	**<0.001**
Htc (%)*	43.9±6.8	48.6±4.5	**<0.001**
MCV(fL)***	106.7±6.1	107.9±4.5	0.193

Abbreviations: RDW: Red cell distribution width, UCB: Umbilical cord blood bilirubin, Hb: Hemoglobin, Htc: hematocrit, MCV: Mean corpuscular volüme.

Data are presented as mean, standard deviation or n (%).

*Statistical analysis was performed by Mann-Whitney U test

** Statistical analysis was performed by Chi-square test

***Statistical analysis was performed by Student t test

Of cases, the blood type was A in 91(52%), B in 27(15.4%), O in 49 (28%), and AB in 8 (4.6%). ABO incompatibility was determined in 21.7% of cases (n: 38) (31 newborns with the blood type of A, and 7 newborns with the blood type of B). Rh incompatibility, ABO+Rh incompatibility was detected in 21(12%) and 2 cases (1.1%), respectively. The result of DCT was positive in 35 cases. Any newborns did not require exchange transfusion.

The cord blood RDW, UCB values of newborns in the study group were significantly higher, and Hb and Htc values were lower compared to the control group (p<0.05) (Table 1). Also, the newborns with positive DCT group had higher RDW values than those with negative DCT (p: 0.002) (Table 2).

Table 2. Comparison of laboratory values of newborns received phototherapy classified according to DCT

Values	DCT positive (n:35)	DCT negative (n:26)	P- value
RDW (%)*	18.6±1.6	17.4±1.4	**0.002**
UCB(mg/dl)*	2.6±0.1	12.3±0.6	0.611
Hb (gr/dl)**	14.1±2.3	16.1±1.8	**<0.001**
Htc (%)**	41.2±6.7	47.2±5.4	**<0.001**
MCV(fL)**	107.4±4	106.0±6.7	0.380
IVIG treatment (n,%)	2 (6.3%)	NA	**<0.001**
Postnatal , age at admission (hours)*	22.9±13.5	51±24.3	**<0.001**

Abbreviations: RDW: Red cell distribution width, UCB: Umbilical cord blood bilirubin, Hb: Hemoglobin, Htc: Hematocrit, MCV: Mean corpuscular volüme.

Data are presented as mean, standard deviation or n (%).

* Statistical analysis was performed by Mann-Whitney U test.

**Statistical analysis was performed by Student t test.

The correlation was found between cord blood RDW and UCB values (p<0.001, r: 0.476). Thirteen (40.6%) of the newborns with DCT positivity were found to be anemic. The mean RDW values of newborns with and without anemia were found as 19.1±1.9 and 17.7±1, respectively (p=0.004).

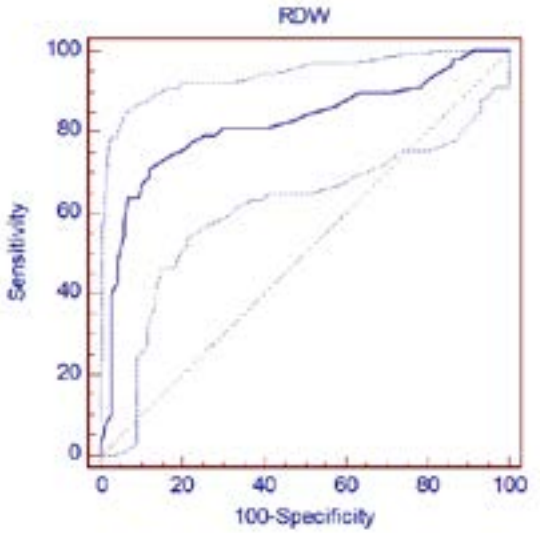
Multivariate regression analysis for whole group demonstrated that cord blood RDW (odds ratio[OR] 2.24, 95% confidence interval [CI]1.52 - 3.30, P < 0.05), UCB level (OR 6.53, 95% CI 2.71-15.72, p< 0.05) and DCT positivity (OR 12.58, 95% CI 3.42 – 46.36, p < 0.05) were found to be an independent risk factor for increased risk of phototherapy requirement.

The area under the ROC curve of cord blood RDW for phototherapy treatment was 0.82±0.04 (p<0.001, 95% CI 0.75-0.87) (Figure 1). When cutoff value for RDW regarding prediction of significant hyperbilirubinemia was considered as 17.1; sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were found to be 70.7%, 88%, 74.5% and 85.9%, respectively.

Figure caption:

Figure 1.ROC analysis for RDW in determining the possibility of phototherapy in the whole group.

Figure 1.ROC analysis for RDW in determining the possibility of phototherapy in the whole group. (RDW: Red cell distribution width)



DISCUSSION

In this study, we showed that cord blood RDW values were higher among newborns with hyperbilirubinemia who required phototherapy compared to the healthy controls. Therefore, we suggest that cord blood RDW values could be used in in the early diagnosis of newborns with hyperbilirubinemia. To the best of our knowledge, this is the first study evaluating cord blood RDW values among newborns with hyperbilirubinemia who required phototherapy.

Neonatal hyperbilirubinemia can be observed in 60% of term newborns and 80% of preterm newborns (3). Therefore, early determination of bilirubin levels is important. To date, many studies such as serum bilirubin, transcutaneous bilirubin, ambient carbon monoxide and UCB measurement have been carried out to identify newborns at high risk of developing hyperbilirubinemia in the early postnatal period (16-20). Serum bilirubin measurement before discharge is the gold standard method, but it is an invasive procedure (16) Although transcutaneous bilirubin measurement is painless and easy to perform as an alternative method, interpretation of transcutaneous bilirubin according to serum bilirubin nomograms is not recommended (17). Ambient carbon monoxide measurement is not an effective method and cannot be used routinely (18). Numerous studies have been conducted on UCB values, but the results could not be standardized because of different cut-off values of UCB in each of these studies (19,20). This situation requires repeated bilirubin measurements to determine the risk and causes many invasive procedures. Therefore, we aimed to determine the reliability

of cord blood RDW measurement, which is a rapid and easy method to detect newborns with hyperbilirubinemia in the early postnatal period.

The normal ranges of RDW values in newborns were determined (5,8). Tonbul et al. reported that RDW values were higher in preterm (gestational week≤ 34) newborns compared to term newborns (8). Studies have shown an inverse relationship between gestational age and RDW (5). Grafoli et al. reported that the highest RDW values were in preterm newborns, followed by IUGR and term newborns, respectively (9). Therefore, newborns with a gestational age of <35 weeks and/or with IUGR were not included in our study.

Data on the association of RDW and neonatal morbidity are limited. Studies have reported a relationship between RDW and mortality in diseases such as PDA, BPD and sepsis (9-11). To our knowledge, our study is the first study on RDW and neonatal hyperbilirubinemia. Evaluation of cord blood RDW as a predictive value in newborns with neonatal hyperbilirubinemia is an innovative idea. The presence of ABO and/or RH incompatibility leads to immune hemolysis of neonatal erythrocytes and degradation of red blood cells causes an increase in total serum bilirubin concentration (20). Iron released during hemolysis of red blood cell is considered as one of the major factor for enhanced reactive oxygen species production (21). Some of studies have reported that the increase of total serum bilirubin level is associated with an increase of oxidative stress (22,23). Oxidative stress may damage erythrocytes directly. It has been reported that oxidative stress increases the fragility of red blood cells, decreases the rate of erythroid maturation and decreases erythrocyte lifespan (7). It has been suggested that induction of heme oxygenase occurs as a response to oxidant stress (24). Therefore, oxidative stress indirectly increases RDW levels. In our study, cord blood RDW values were higher in newborns with hyperbilirubinemia requiring phototherapy in both blood group incompatibility and non-blood incompatibility groups compared to the control group. This situation can be related to oxidative stress. We think that cord blood RDW measurement is an independent risk factor for hyperbilirubinemia independent of DCT positivity.

Studies have proposed that RDW values are found to be higher in anemic newborns, which could be due to in utero hemolysis (5,12). Prolonged hemolysis can lead to severe anemia, which stimulates fetal erythropoiesis in the liver, spleen, bone marrow and extra medullary organs. In our study, Hb values were lower in newborns with positive DCT and RDW levels were higher in anemic newborns than the others. High RDW levels of the anemic newborns shows that erythropoiesis had been activated secondary to hemolysis. Qurtom et al. and Bessman et al. recommended the use of RDW values to classify anemia (12,25). Christensen et al. reported that high RDW values in newborns are a remarkable sign of anisocytosis and this may associate with impaired erythropoiesis and erythrocyte degradation (5). Since hemolysis is the etiology of hyperbilirubinemia, a correlation between cord blood RDW and bilirubin levels is expected. It has been revealed in our study that there is a correlation between cord blood RDW and UCB values. We think that the increased RDW values in the cord blood may be an indicator of the increased bilirubin levels in the newborn. Our data suggest that newborns with a cord blood RDW of less than 17.1 are at low risk of severe hyperbilirubinemia. Cord blood RDW may be a useful marker in the early identification of newborns at risk of developing hyperbilirubinemia. Thus, it may be possible to identify newborns at risk of significant hyperbilirubinemia and therapeutic intervention may be initiate earlier.

Our study has limitations. First, our study was single-centered and the low number of cases. Second, the reticulocyte measurement could not be assessed.

CONCLUSION

In this study was demonstrated that cord blood RDW may be a useful marker in the early identification of newborns at risk of developing hyperbilirubinemia. Randomized controlled studies with more participants are required to provide additional data, enabling us to confirm these results.

Conflict of interest:

The authors have declared that they have no conflicts of interest relevant to this article.

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