Fluctuating Course of Red Cell Distribution Width in Treatment of Iron Deficiency Anemia and Its Clinical Relevance

Demir Eksikliği Anemisi Tedavisinde RDW’nin Dalgalı Seyri ve Klinik Önemi

ABSTRACT

Background: Red cell distribution width (RDW) is a routine parameter of blood count. The use of this parameter is generally restricted to the differential diagnosis of microcytic anemia. However, there is insufficient published data on the course of RDW in the treatment of iron deficiency anemia and on its clinical importance. Therefore, this study investigated the course of RDW in the treatment of iron deficiency anemia and its association with increased hemoglobin values.

Methods: One hundred five patients diagnosed with iron deficiency anemia were enrolled in this study.

Results: The mean hemoglobin values of patients at diagnosis and at 1, 2 and 3 months after initiation of treatment were 9.2±1.5, 11.7±1.0, 12.7±0.8, and 13.1±0.8 g/dL, respectively. The mean RDW values of patients at diagnosis and 1, 2 and 3 months after initiation of treatment were 18.4±2.6, 26.4±6.5, 17.8±4.3, and 14.7±1.7%, respectively. Between baseline and 1 month of treatment there was a significant increase in RDW values (p<0.0001), and between 1, 2 and 3 months there was a significant decrease in RDW values (p<0.0001). Regression analysis revealed a linear correlation between the increase in RDW at month 1 and increase in hemoglobin level at months 1, 2 and 3 (p<0.0001, r=0.461; p<0.0001, r=0.51; p<0.0001, r=0.472, respectively).

Conclusion: We suggest that an increase in RDW may be used to predict the response to iron treatment.

Key words: RDW, iron deficiency anemia, iron therapy, increase in RDW

ÖZET

Giriş: RDW, kan sayımının rutin bir parametresidir. Bu parametreün kullanım genel olarak mikrositer anemilerin ayırıcı tansıyalı kastıdır. Bununla birlikte literatürde demir eksikliği anemisinin tedavisinde RDW’ın seyri ve klinik önemiyle ilgili yetene kadar bilgi bulunmamaktadır. Bundan dolayı bu çalışmada RDW’ın demir eksikliği anemisinin tedavisindeki seyri ve hemoglobin artış ile ilişkisinin araştırılması amaçlanmıştır.

Metod: Demir eksikliği anemisi tanı konulan 105 hasta bu çalışmaya alınmıştır. Bu parametrein kullanım genel olarak mikrositer anemilerin ayırıcı tansıyalı kastıdır. Bununla birlikte literatürde demir eksikliği anemisinin tedavisindeki seyri ve hemoglobin artış ile ilişkisinin araştırılması amaçlanmıştır.

Bulgular: Tanı anında ve tedavi başlandıktan sonra 1. ve 3. ayda ortalamalı hemoglobin değerleri sırasıyla 9.2±1.5, 11.7±1.0, 12.7±0.8 ve 13.1±0.8 g/dL, RDW değerleri sırasıyla %18.4±2.6, %26.4±6.5, %17.8±4.3 ve %14.7±1.7 bulundu. Tanı anında ve 1. ayda RDW değerleri arasında istatistiksel olarak belirgin artış (p<0.0001), 1. ve 3. ayda RDW değerleri arasında belirgin azalma (p<0.0001) tespit edildi. Regresyon analizinde 1. ayda RDW artış ile 1. ve 3. ayarda hemoglobin artışları arasındaki doğrusal bir bağıntı olduğu görüldü (sirasıyla p<0.0001, r=0.461; p<0.0001, r=0.51; p<0.0001, r=0.472).

Sonuç: Bu çalışmamın sonuçlarına göre, RDW’ de meydana gelen artışın demir tedavisi yanıtını öngördürmek için kullanılabileceğini düşüneceğiz.

Anahtar kelimeler: RDW, demir eksikliği anemisi, demir tedavisi, RDW artış.
INTRODUCTION

Red cell distribution width (RDW) is a relatively new routine parameter. It is evaluated using a fully automated hematology analyzer and part of the complete blood count (CBC). The RDW represents the coefficient of variation of the red blood cell volume distribution and can be considered as an index of heterogeneity, equivalent to anisocytosis observed in the peripheral blood smear. The use of this parameter is generally restricted to the differential diagnosis of iron deficiency anemia (IDA) and thalassemia traits. An increased RDW value indicates anisocytosis and is observed in IDA. However, there is insufficient published data on the course of RDW in the treatment of iron deficiency anemia and its clinical importance. Therefore, this study investigated the course of RDW in the treatment of iron deficiency anemia and its association with increased hemoglobin values.

METHODS

Study Population
This study was a retrospective, cross-sectional, single-center study. Patient selection was laboratory based and independent from etiology. A total of 105 patients diagnosed with isolated iron deficiency anemia between November 2012 and November 2013 were enrolled. Subjects with the other anemia types like thalassemia or folate/vitamin B12 deficiency, chronic disease anemia were excluded from the study.

Laboratory Studies
Complete blood counts, serum iron, serum unsaturated iron binding capacity (UIBC), and serum ferritin levels were determined at diagnosis and response to therapy at 1, 2, and 3 months after initiation of oral iron treatment (80–160 mg elemental iron equivalent to 270–540 mg ferrous sulfate/day) was evaluated with measurement of serum ferritin level. IDA was defined according to the World Health Organization criteria as hemoglobin <12 g/dL in females and <13 g/dL in males, and serum ferritin <15 ng/mL.

Serum iron and UIBC were measured by the ferrozine method (Roche Diagnostics GmbH, Mannheim, Germany), and serum ferritin was measured by an immunoturbidimetric method (Roche Diagnostics), analyzed using a Cobas e 601 immunoassay analyzer. Complete blood counts of all patients were performed using a Coulter LH 750 hematological analyzer (Beckman-Coulter, Brea, CA, USA).

Statistical Analysis
Patient characteristics were examined using descriptive statistics. Continuous variables were reported as means ± SD, and categorical variables as percentages. Mean values were compared using Student’s t-test and one-way analysis of variance (ANOVA). Standard linear regression using the Enter method was used for multivariate analysis of independent variables. Variables with significant P values (p<0.05) and marginally nonsignificant P values (p<0.1) in univariate analysis were included in the multivariate analysis. All reported P values were two-tailed and SPSS 17.0 for Windows statistical software (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS
The study totaled 105 patients including 102 (97.1%) females and 3 (2.9%) males. The mean age was 38.4±12.3 years. Patient data at diagnosis and after initiation of iron treatment are shown in Table 1. The changes in patient hemoglobin and RDW values associated with iron treatment are shown in Figure 1a and 1b, respectively.

Table 1. Patient data at diagnosis and after iron treatment.

|                  | Baseline | Month 1 | Month 2 | Month 3 |
|------------------|----------|---------|---------|---------|
| WBC (x10³/µL)   | 7.0±2.1  | 6.7±1.6 | 7.1±2.0 | 7.3±1.9 |
| RBC (x10¹²/L)   | 4.3±0.44 | 4.78±0.41| 4.78±0.4 | 4.8±0.39 |
| Hb (g/dL)       | 9.2±1.5  | 11.7±1.0| 12.7±0.8| 13.1±0.8 |
| Hct (%)         | 29.8±4.2 | 36.9±2.6| 38.5±2.6| 39.4±2.4 |
| MCV (fL)        | 89±8.6   | 77.5±6.1| 81.7±5.1| 83.9±3.7 |
| RDW (%)         | 18.4±2.6 | 26.4±6.5| 17.8±4.3| 14.7±1.7 |
| PLT (x10³/µL)   | 324±107  | 282±74  | 277±73  | 271±62  |
| Serum Iron (µg/dL) | 21±10    | -       | -       | -       |
| Serum UIBC (µg/dL)| 431±58   | -       | -       | -       |
| Serum Ferritin (ng/mL) | 5±3     | 29±32   | 36±23   | 38±15   |

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Hct, haematocrit; MCV, mean corpuscular volume; RDW, red cell distribution width; PLT, platelet; UIBC, unsaturated iron binding capacity.
Figure 1a. Hemoglobin values of patients at diagnosis and at 1, 2 and 3 months after initiation of treatment.

Figure 1b. RDW values of patients at diagnosis and at 1, 2 and 3 months after initiation of treatment.

The mean hemoglobin values of patients at diagnosis and at 1, 2 and 3 months after initiation of treatment were 9.2±1.5, 11.7±1.0, 12.7±0.8, and 13.1±0.8 g/dL, respectively. Between the baseline (at diagnosis) and 1, 2 and 3 months after initiation of treatment, hemoglobin values increased significantly (p<0.0001).

The mean RDW values of patients at diagnosis and 1, 2 and 3 months after initiation of treatment, hemoglobin values increased significantly (p<0.0001).

From baseline, the increase in RDW at 1 month after initiation of treatment (RDW1-RDWbaseline/ RDWbaselineX100) and the increase in hemoglobin level at 1, 2 and 3 months after initiation of treatment are shown in Table 2.

| Table 2. The increases in RDW and hemoglobin after initiation of treatment. |
|-------------------------|-------------------|-------------------|-------------------|
|                         | Month 1           | Month 2           | Month 3           |
| Increase in RDW (%)     | 43±23.9           | -                | -                |
| Increase in Hb (g/dL)   | 2.5±1.3           | 3.4±1.5          | 3.9±1.8          |

Hb, hemoglobin; RDW, red cell distribution width.

Patients were separated into three groups according to the increase in RDW at 1 month after initiation of iron treatment (<25%, 25–50% and >50%). The increase in hemoglobin level of each group at 1, 2 and 3 months after initiation of treatment are shown in Table 3 and Figure 2.

Table 3. The increase in hemoglobin level after iron treatment according to the increase in RDW.

| Increase in RDW <25% (n=29) | Increase in RDW 25–50% (n=36) | Increase in RDW >50% (n=40) | p     |
|-----------------------------|--------------------------------|----------------------------|-------|
| Increase in Hb at month 1 (g/dL) | 1.8±1.3                  | 2.4±1.3               | 3.1±1.0 | <0.0001 |
| Increase in Hb at month 2 (g/dL) | 2.6±1.6                  | 3.2±1.6               | 4.3±0.9 | <0.0001 |
| Increase in Hb at month 3 (g/dL) | 3.0±2.1                  | 3.6±1.6               | 4.9±1.4 | <0.0001 |

Hb, hemoglobin; RDW, red cell distribution width.

Regression analysis revealed a linear correlation between the increase in RDW at month 1 and increase in hemoglobin level at months 1, 2 and 3 (p<0.0001, r=0.461; p<0.0001, r=0.51; p<0.0001, r=0.472, respectively; Figure 3).
DISCUSSION

RDW is utilized by clinicians in the diagnosis of IDA and differential diagnosis of microcytic anemia. RDW is a measure of anisocytosis; it is increased in IDA and is normal or slightly increased in β thalassemia traits.5 Aulakh et al.2 demonstrated a significant increase in mean RDW among children with iron deficiency anemia (18.37±2.22%) compared to non-iron deficiency anemia (16.55±1.51%). Uchida6 reported mean RDW values of 12.7±0.7% in normal individuals, 13.2±0.8% in prelatent deficiency and 15.6±1.7% in iron deficiency anemia. Sensitivities of 77.1% for diagnosis of iron deficiency anemia, 49.2% for iron deficiency anemia and latent deficiency, and a specificity of 90.6% were reported. Vishwanath et al.7 reported sensitivity of 92.1% and specificity of 90.9% using RDW for detection of iron deficiency. Cesana et al.8 used the RDW index for differential diagnosis of microcytic anemia, and demonstrated correct β thalassemia trait diagnoses in 94.4% and 86.7% of first validation samples, respectively, and IDA correct diagnoses in 86.2% and 90.9% of first and validation samples, respectively.

At present, there is insufficient data regarding the course of RDW after iron treatment. Aslan et al.4 reported an increase in RDW values 5–7 days after initiation of iron treatment, rising until week 4 before beginning to decline. Vishwanath et al.7 also reported that RDW showed significant improvement after iron therapy. We also found a significant increase in mean RDW at 1 month after initiation of iron treatment, followed by a decrease. We think that new producing normocytic erythrocytes after initiation of iron treatment increase RDW values in comparison to the baseline, and when normocytic erythrocytes become predominant in the following months, RDW values decrease slowly. In contrast to our study, Aslan et al.4 used the increase in RDW for differential diagnosis of IDA and α/β thalassemia traits. However, we have additionally identified a linear correlation between increase in RDW and the overall hemoglobin response.

Several biomarkers have been used by researchers to predict the response to iron therapy. Chuang et al.9 used reticulocyte hemoglobin content (CHr) and reticulocytes in a high-fluorescence intensity region (HFR) for early prediction of response to intravenous iron supplementation, and demonstrated that changes in CHr and HFR at 2–4 weeks are superior to the conventional erythrocyte and iron metabolism indices. Brugnara et al.10 suggested that reticulocyte indices might allow real-time evaluation of iron deficient erythropoiesis and the effectiveness of iron replacement therapy. Bhandari et al.11 reported that measurement of estimated red blood cell ferritin and CHr might facilitate identification of patients with functional iron deficiency and allow for more accurate monitoring of the response to intravenous iron therapy. Urrechaga et al.12 suggested that red blood cell size factor (RSf) and low hemoglobin density (LHD%) may be reliable parameters for evaluation of iron metabolism status.

Although a new biomarker, the change in RDW after initiation of iron treatment can help to predict treatment response and avoid the need for more expensive laboratory tests. Similar to the reticulocyte indices, we propose that the increase of RDW in IDA can also be used to predict the treatment response. In addition, the changes in RDW after initiation of iron treatment should be investigated by prospective studies, and may be used in place of reticulocyte indices in clinics where reticulocyte indices cannot be used.

Cost-effectiveness is one of the crucial principles in family medicine due to limited resources. RDW is a laboratory parameter which is already tested within the complete blood count. So RDW change may be used as a predictor of response to therapy in iron deficiency anemia in primary care setting without the need for additional cost. The physicians should be aware of the value of this inexpensive and reliable parameter.
Despite its contribution to the literature, our study has some limitations. The retrospective nature of the study design restricted us, therefore we could not detect earlier changes in RDW. We were also unable to evaluate the RDW response in comparison to other reticulocyte indices.

CONCLUSION

This is the first report of a correlation between the increase in RDW at 1 month of iron treatment and the overall hemoglobin response. Based on these data, we suggest that an increase in RDW may be used to predict the response to iron treatment.

Conflict of interest

The authors declare no conflicts of interest.

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