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Efficacy of Intravenous Iron Therapy in Female Patients with Iron Deficiency Anemia

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Abstract: In this study, it was aimed to show the efficacy of intravenous (IV) ferric carboxymaltose treatment for iron deficiency anemia (IDA), which is a public health problem due to its high prevalence in the world and in Türkiye. Since it is the first study in the region, its importance is increasing even more. Eighty female diagnosed with IDA and treated with IV iron carboxymaltose, who applied to Siirt Training and Research Hospital Internal Diseases Polyclinics between June 2018 and September 2019, were included in the study. Biochemical data before and after treatment from the data recorded in the system of the patients who signed the consent form of Siirt University Research Hospital were included in the study retrospectively. After treatment, hemoglobin (HGB), hematocrit (HTC), mean cell volume (MCV), ferritin, iron and B12 values increased statistically ($p<0.05$). In addition, platelet (PLT), total iron binding capacity (TIBC) and folate values were statistically significantly lower ($p<0.05$). Additionally, platelet (PLT), total iron binding capacity (TIBC) and folate values were statistically significantly lower ($p<0.05$). The study is important in terms of revealing the female IDA profile in the region and showing the positive results of IV iron therapy data. It is thought that the study can be a guide in finding solutions to irrational drug use, prolongation of the treatment period and high expenditures while creating IDA treatment protocols.

Demir Eksikliği Anemili Kadın Hastalarda İntravenöz Demir Tedavisinin Etkinliği

Anahtar Kelimeler
Demir eksikliği anemisi,
Demir replasmanı,
İntravenoz karboksimaltoz,
Serum TIBC,
Serum folat

Öz: Bu çalışmada, dünyada ve Türkiye'de prevalansının yüksek olması nedeniyle bir halk sağlığı sorunu olan demir eksikliği anemisinde (DEA) intravenöz (İV) ferrik karboksimaltoz tedavisinin etkinliğinin gösterilmesi amaçlandı. Bölgedeki ilk çalışma olması nedeniyle önemi daha da artmaktadır. Haziran 2018-Eylül 2019 tarihleri arasında Siirt Eğitim ve Araştırma Hastanesi İç Hastalıkları Polikliniği'ne başvuran, DEA tanılı ve İV demir karboksimaltoz tedavisi uygulanan 80 kadın çalışmaya dahil edildi. Siirt Üniversitesi Araştırma Hastanesi onam formunu imzalayan hastaların sisteme kaydedilmiş verilerinden tedavi öncesi ve sonrası biyokimyasal verileri retrospektif olarak çalışmaya dahil edildi. Tedavi sonrası hemoglobin (HGB), hematokrit (HTC), ortalama hücre hacmi (MCV), ferritin, demir ve B12 değerlerinde istatistiksel olarak artış görüldü ($p<0.05$). Ayrıca trombosit (PLT), toplam demir bağlama kapasitesi (TIBC) ve folat değerleri istatistiksel olarak anlamlı derecede düşüktü ($p<0.05$). Çalışma bölgedeki kadın DEA profilini ortaya koyması ve İV demir tedavisi verilerinin olumlu sonuçlarını göstermesi açısından önemlidir. Çalışmanın DEA tedavi protokolleri oluşturulurken akılcı olmayan ilaç kullanımına, tedavi süresinin uzamasına ve yüksek tedavi harcamalarına çözüm bulunmasına yol gösterici olabileceği düşünülmektedir.

1. INTRODUCTION

Iron deficiency anemia (IDA) is the most common type of anemia among the types of anemia, which is common in the world and especially in underdeveloped countries. Although IDA is seen in almost all age groups, it is more common especially in women of childbearing age [1-3]. In studies conducted in different age groups, IDA was found to be at the level of 30-78% in Türkiye [4]. It is defined as a public health problem because it is frequently seen in the world and in Türkiye. Iron replacement therapy is administered to patients with IDA in two ways, orally and parenterally. Today, the major treatment method is oral iron administration [5]. However, due to factors such as the observation of gastrointestinal side effects and long-term use in oral iron treatment, the treatment is limited due to patient incompatibility. For these reasons, there is increasing interest in parenteral iron therapy (as it provides a larger and faster source of iron) [6,7]. According to the definition of the World Health Organization, anemia is expressed as a hemoglobin (Hb) value below 13 g dL^{-1} in men over the age of 15, 12 g dL^{-1} in women over the age of 15 and non-pregnant women, and below 11 g dL^{-1} in pregnant women [8]. The first diagnosis to be considered in the differential diagnosis of the patient with anemia is IDA. In addition to low ferritin and iron levels in the serum, increased total iron binding capacity, erythrocyte protoporphyrin, and transferrin-binding receptors are indicators of IDA. Serum ferritin is the strongest test for IDA marker. It is suggested that the diagnostic cut-off value of IDA is in the range of 12-15 mg L^{-1} [9,10]. The main causes of IDA are inadequate dietary intake (severe malnutrition), blood losses (traumatic hemorrhages, hemoptysis, hematemesis, hematuria, melena, menorrhagia, pregnancy-birth, unrecognized hemorrhages, etc.), decreased iron absorption (H. pylori infection, atrophic gastritis, bariatric surgery, etc.) and hereditary mutations (SLC11A2 mutation, TMPRSS mutation, etc.). The treatment of patients with IDA should be arranged by considering the etiological reasons listed above [11,12,13]. Ferric carboxymaltose (Ferinject™) is a new IV iron complex with a very low risk of anaphylaxis, hypersensitivity, non-dextran and does not require a test dose [14,15]. A single dose infusion of up to 1000 mg of this IV iron complex can be performed in as little as 15-30 minutes [14,15,16]. Ferric carboxymaltose treatment is preferred because it eliminates the gastrointestinal side effects of oral therapy, shortens hospital stay and reduces cost. Ferric carboxymaltose is superior to other parenteral treatments due to its physical osmolarity and neutral pH level, and single dose administration in a short period of time [17,18].

The fact that there are no IDA studies in the literature in Siirt, which is one of the provinces with high fertility, and the idea of showing the effectiveness (effects and side effects) of IV ferric carboxymaltose constitutes the original value of our study. In this study, we aimed to show the effects of ferric carboxymaltose, which is one of the IV iron treatments, since the IDA profile is not found in the literature in Siirt.

2. MATERIAL AND METHOD

2.1. Participants

While creating the experimental group of this study; Non-Interventional Clinical Research Ethics Committee approval was received for the use of the data in the hospital registry system of the participants who signed the Siirt University Hospital consent form (dated 2020/01.03. and numbered). The study was conducted in accordance with the Declaration of Helsinki. Female patients (80 patients aged 18 to 60 years) who applied to the Siirt Training and Research Hospital Internal Medicine Polyclinics between June 2018 and September 2019 and were found to have IDA were included and the effects of IV iron carboxymaltose treatment were examined. Demographic data of the patients obtained retrospectively, pre- and post-treatment hemogram, iron and ferritin results were included in the study. Patients who underwent erythrocyte replacement were excluded from the study.

2.2. Analyses of Samples

In our study, female patients with anemia who applied to Siirt Training and Research Hospital Internal Medicine Polyclinics were retrospectively identified. Among these patients, those with active vaginal bleeding, gastrointestinal (GI) bleeding, hemoptysis, and hematuria were excluded from the study. By examining the hospital records, eligible patients who received iron carboxy maltose replacement (1000 mg 150 cc in 0.9% physiological saline intravenously over 30 minutes) were identified and included in the study. The records in the biochemistry laboratory of our hospital were evaluated for the patients who had 5-8 cc of venous blood collected in 1 EDTA hemogram tube and 2 gel biochemistry tubes in the polyclinic blood collection department before and after the replacement. Hemogram, iron, ferritin and B12 values taken after 4-6 weeks in the patient records were used for analysis. Hemoglobin, hematocrit, ferritin, iron and B12 values measured before and after iron carboxymaltose replacement are recorded in the hospital system. In the biochemistry laboratory of our hospital, hemogram was studied with the "Roche Diagnostic XN-1000" brand device. In our biochemistry laboratory, iron, ferritin and B12 were studied with the "Beckman Coulter DXC-800" brand device.

2.3. Statistical Analysis

After taking the average of the measurements, the normality of the distributions in terms of continuous variables was determined by the Shapiro-Wilk test. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 24.0, and p value of <0.05 was considered statistically significant. Paired T test was used to compare the data between pre-treatment and post-treatment.

3. RESULTS

The symptoms observed in 80 female patients who participated in our study are given in Table 1.

Table 1. Symptoms observed in patients.

Symptoms (N=80)	Yes N (%)	No N (%)
Headache/dizziness	5.0	95.0
Hypersensitivity	1.3	98.7
Dyspnea	2.5	97.5
GIS Symptoms	6.3	93.7
Myalgia	2.5	97.5
Hypotension/hypertension	0.0	100.0
Skin rash	2.5	97.5
Palpitation	1.3	98.7

The mean, minimum and maximum values of HGB and HTC changes (increase rates) in patients are summarized in Table 2.

Table 2. The mean, min. and max. values of HGB and HTC in patients who participating in the study.

Descriptive statistics (N=80)	Mean	Min.	Max.
Age (years)	32	18	60
Control period (days)	30	18	50
HGB increase amount (g dL-1)	2.85	0.7	6.1
HTC increase amount (%)	7.6	1.1	16.8

HGB: hemoglobin; HTC: hematocrit, Mean: average, Min: minimum, Max: maximum

3.1.Comparison of Values Before and After Treatment

While there was no significant difference between WBC values as observed in Table 3 in terms of values before and after treatment, a statistically significant increase was found in HGB, HTC, MCV, ferritin, iron and B12 values after treatment ($p<0.05$). In addition, it was determined that there was a statistically significant decrease in platelet, total iron binding capacity and folate values ($p<0.05$).

Table 3. Distribution of hematological parameters (iron status markers) in patients before and after treatment.

N=80	Before treatment (Mean±SD)	After treatment (Mean±SD)	P
WBC ($x10^9$ L^{-1})	6.91 ± 1.71	6.89 ± 1.56	0.907
HGB (g dL^{-1})	9.4 ± 1.28	12.41 ± 1.13	<0.001*
HTC (%)	31.42 ± 3.39	39.3 ± 3.1	<0.001*
PLT ($x10^9$ L^{-1})	311.93 ± 90.26	259.96 ± 74.5	<0.001*
MCV (fL)	71.81 ± 8.9	82.01 ± 6.4	<0.001*
Ferritin (ng mL^{-1})	3.85 ± 1.94	156.74 ±104.75	<0.001*
Serum iron (µg dL^{-1})	16.56 ± 7.84	75.91 ± 25.24	<0.001*
TIBC (µg dL^{-1})	455.91 ± 55.8	232.61 ± 57.23	<0.001*
B12 (pg mL^{-1})	314.65 ± 78.58	368.7 ± 193.72	0.008*
Folate (ng mL^{-1})	9.1 ± 3.42	8.27 ± 3.61	0.010*

*Significance level was accepted as <0.05 for Paired T test. WBC: white blood cells, HGB: hemoglobin, HTC: hematocrit, PLT: platelet, MCV: mean corpuscular volume, TIBC: total iron binding capacity, Mean: mean, SD: standard deviation.

4. DISCUSSION AND CONCLUSION

Among the types of anemia, IDA is the most common and most treatable. Although the primary treatment method is oral iron administration [5], treatment is limited due to gastrointestinal side effects, long-term use and patient incompatibility. For such reasons, the trend towards parenteral iron therapy, which can provide faster iron supply, is increasing day by day [6,7]. However, we can encounter the diversity of IDA tables in Türkiye due to regional dietary patterns and economic factors. Siirt DEA table, which emerged with our study and has not been encountered in the literature before, may draw attention to this difference. In this study, it was found that HGB, HTC, MCV, ferritin, iron and B12 values after IV iron carboxymaltose administration were statistically significantly higher than the pre-treatment data ($p<0.001$) (Table 3).

Iron sucrose, iron dextran, sodium ferrous gluconate can be used as IV preparations in patients with IDA. The use of these preparations is restricted due to long infusion times (sodium ferrous gluconate), increased hypersensitivity reactions (iron dextran), and multiple use of low doses to replenish iron stores [19]. Iron dextran can cause life-threatening anaphylactic reaction, hypersensitivity, myalgia, arthralgia, fever etc. undesirable effects are encountered.

In the meta-analysis about the safety of intravenous iron therapy; It was determined that no increase in risk in terms of mortality and infection and no serious side effects were observed in the treatment, and it is suggested that fever, arthralgia and myalgia improved [20]. Ferric carboxymaltose, which has physical osmolarity and neutral pH, is claimed to be superior to other parenteral treatments [17,18]. According to our study results, the absence of any significant finding in terms of side effects (symptoms such as headache, hypersensitivity, dyspnea, gastrointestinal system symptoms, myalgia, hypertension/hypotension, skin rash and palpitations) supports the superior aspects of the application.

The World Health Organization (WHO) claims that anemia plays a direct or indirect role in 40% of maternal deaths [21]. In addition, moderate bleeding can be fatal in anemic pregnant women [22]. It has been reported that the clinically administered ferric carboxymaltose treatment in pregnant women is effective [23,24]. In this study, it was revealed that the data obtained from women with IDA in Siirt (Table 3) support the literature. In addition, the fact that the fertility rate in Siirt is higher than that of Türkiye further increases the importance of these data.

In a study, it was reported that IDA reduces maternal tolerance to peripartum blood loss, the risk of hemorrhagic shock and cardiovascular insufficiency increases, and wound healing is impaired [25]. It is suggested that an increase of 1 g dL^{-1} in the hemogram can significantly reduce maternal mortality [26]. In our study, an increase of 2.85 g dL^{-1} and 7.6% was observed for the hemogram parameters HGB and HTC, respectively (Table 2). Although there were no pregnant women in our study group, this increase in our findings gains importance because women are prone to anemia and have the potential for pregnancy. When we look at the findings of IDA in the Turkish population in a study conducted in Türkiye, it was revealed that the mean value of TIBC in women was 352 ± 64 µg dL^{-1} [27], and in the findings of our study, this value was 455.91 ± 55.8 µg dL^{-}

^{1} before treatment (Table 3). Thus, it can be said that new and more comprehensive studies are needed to investigate the reasons for the higher IDA profile in Siirt compared to Türkiye. The reasons for this situation may be factors such as nutritional habits, socioeconomic status and environmental conditions. A study conducted in Jordan found that iron deficiency anemia is caused by many factors, and that these factors, such as heavy menstrual periods in women and low consumption of red meat, are associated with the severity of anemia. When the study data were examined, it was seen that the values of HGB 8.47 g dL^{-1}, MCV 66.4 fL, Platelet 333.5 $x10^{9}$ L^{-1} and serum ferritin 6.67 ng mL^{-1} in patients with IDA coincided with the pre-replacement values of the patients with IDA in our study. In this case, it can be said that iron deficiency anemia and socioeconomic levels may be related [28]. In addition, IV iron carboxymaltose treatment reduced the TIBC from 455.91 ± 55.8 µg dL^{-1} to 232.61 ± 57.23 µg dL^{-1}, which is considered normal in a shorter time ($p<0.001$) (Table 3). When platelet levels are examined, it is seen that Siirt findings(311.93±90.26 109 L-1) are above the Türkiye average (237±76 10^{9} L-1). It was determined that this value decreased to levels such as 259.96±74 10^{9} L-1 with the treatment performed in Siirt ($p<0.001$) (Table 3). In this study, a statistically significant increase was found after the administration in terms of vitamin B12 as a result of IV iron carboxymaltose treatment. Although the statistically significant increase in vitamin B12 value draws attention to the positive results of the applied treatment, the high level of folate and vitamin B12 deficiency in general suggests that it may be caused by unbalanced nutritional habits. In 2021, Kefeli et al. vitamin B12 deficiency was detected in their study. The study suggests that there is a statistically significant relationship ($p=0.06$) between red meat consumption and vitamin B12, and that as red meat consumption increases, vitamin B12 deficiency decreases [29]. Similar to the above study, it is thought that the B12 deficiency in the data in our study may be due to the low socioeconomic status of Siirt province.

As a result, it was determined that ferric carboxymaltose administration, which is one of the IV iron treatments, is more reliable in terms of side effects and its effectiveness is higher. In addition, the patient's faster recovery compared to oral administration was one of the important results of this study. We think that the research with the data obtained as a result of ferric carboxymaltose treatment, which is one of the intravenous iron treatments, can contribute to the literature and guide clinicians who regulate the treatment of IDA. This study can create new approaches to increase the awareness of physicians and to create solutions for irrational drug use, prolongation of treatment, harm to patients, and high treatment expenditures while creating treatment protocols for IDA.

Conflict Statement

The authors declare that there is no conflict of interest for the study.

Ethical Approval/Patient Consent

Before starting the study, approval was obtained from Siirt University Non-Interventional Clinical Research Ethics Committee (dated 2020/01.03. and numbered). The data of the patients who signed the Siirt University Research Hospital consent form were used for the research.

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