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Ferric carboxymaltose versus ferrous glycine sulfate for treatment of iron deficiency anemia and their effect on vitamin B12 and folic acid: A retrospective study

Demir eksikliği anemisinin tedavisinde ferrik karboksimaltoz ile demir glisin sülfatın karşılaştırılması ve bu iki ajanın B12 vitamini ve folik asit üzerine etkisi: Retrospektif bir çalışma

Mustafa Genco Erdem[1]

Abstract

Aim Anemia is a major public health problem, affecting about one-third of the world's population, and is most commonly caused by iron deficiency. Iron deficiency anemia requires oral or intravenous iron replacement therapy. The purpose of this study was to assess the change in several hematological parameters, vitamin B12, and folic acid from baseline to the first month of follow-up following therapy with oral ferrous glycine sulfate or intravenous ferric carboxymaltose.

Methods: All patients who received oral ferrous glycine sulfate or intravenous ferric carboxymaltose for the treatment of iron deficiency anemia between January 1, 2016, and December 31, 2018, were included in the trial. Along with age and gender information, values of hemoglobin, ferritin, transferrin saturation, mean corpuscular volume, vitamin B12, and folic acid were derived from patients' records at the beginning of treatment and first month follow-up.

Results: Laboratory values obtained after treatment showed statistically significant improvement in both groups (intra group, $p<0.001$). When the percentage of change between groups was compared: Percentage-based increases in hemoglobin, mean corpuscular volume, transferrin saturation and ferritin values were significantly higher in the ferric carboxymaltose group ($p<0.001$). The percentage decrease in vitamin B12 and folic acid values was higher in the ferric carboxymaltose group ($p=0.005$ and $p=0.01$, respectively) when compared with oral ferrous glycine sulfate group.

Conclusions: According to the findings of our study, iron deficiency anemia can be treated very successfully using ferric carboxymaltose; however, it should be remembered that concurrent supplementation of elements such vitamin B12 and folic acid is necessary for the appropriate progression of erythropoiesis.

Keywords: Ferric carboxymaltose, ferritin, folic acid, iron, iron deficiency anemia, vitamin B12.

Öz

Amaç: Dünya nüfusunun yaklaşık üçte birini etkilemesiyle önemli bir halk sağlığı sorunu olan anemi, en sık demir eksikliğinden kaynaklanır. Demir eksikliği anemisi, oral veya intravenöz demir replasman tedavisi gerektirir. Bu çalışmanın amacı, oral demir glisin sülfat veya intravenöz ferrik karboksimaltoz tedavileri altında başlangıçtan birinci ay takibine kadar çeşitli hematolojik parametrelerin, vitamin B12 ve folik asidin değişimini incelemektir.

Yöntemler: Çalışma, 1 Ocak 2016 ve 31 Aralık 2018 tarihleri arasında oral ferröz glisin sülfat veya iv ferrik karboksimaltoz ile demir eksikliği anemisi nedeniyle tedavi edilen tüm hastaları içermiştir. Hastaların dosyalarından elde edilen yaş ve cinsiyet verilerinin yanısıra, tedavi başlangıcında ve tedaviden sonraki birinci ay kontrollerinde alınan hemoglobin, transferrin satürasyonu, ferritin, ortalama korpüsküler hacim, vitamin B12 ve folik asit değerleri kayıt edildi.

Bulgular: Tedavi sonrasında elde edilen laboratuvar değerleri her iki grupta da istatistiksel olarak anlamlı iyileşme göstermiştir (grup içi, $p<0,001$). Gruplar arasındaki değişim yüzdesi karşılaştırıldığında: Hemoglobin, ortalama korpusküler hacim, transferrin satürasyonu ve ferritin değerlerindeki yüzde bazlı artışlar ferrik karboksimaltoz grubunda anlamlı olarak daha yüksekti ($p<0,001$). B12 vitamini ve folik asit değerlerindeki yüzde düşüş, oral demir glisin sülfat grubuyla karşılaştırıldığında ferrik karboksimaltoz grubunda daha yüksekti (sırasıyla $p=0,005$ ve $p=0,001$).

Sonuç: Çalışmamızın bulgularına göre, demir eksikliği anemisi, ferrik karboksimaltoz kullanılarak başarılı bir şekilde tedavi edilebilir; ancak, eritropoezin uygun gelişimi için B12 vitamini ve folik asit gibi faktörlerin eş zamanlı takviyesinin gerekli olduğu unutulmamalıdır.

Anahtar Kelimeler: Ferrik karboksimaltoz, ferritin, folik asit, demir, demir eksikliği anemisi, vitamin B12.

[1] **Beykent University, Faculty of Medicine, Dept of Internal Medicine, Istanbul, Turkey.**

MGE: 0000-0002-7783-8130

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Sorumlu yazar / Corresponding author:

Mustafa Genco Erdem

Beykent Üniversitesi, Avalon Kampüsü, Beylikdüzü, İstanbul, Türkiye.

e-mail: m.gencoerdem@gmail.com

Tel/Phone: 0 555 634 10 37

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Introduction

Iron deficiency anemia (IDA) is a common condition that affects people of all ages. The World Health Organization (WHO) defined anemia as a hemoglobin (Hb) concentration of less than 13 g/dL for men and less than 12 g/dL for non-pregnant women [1].

The global prevalence of anemia was found to be 32.9% in 2010 [1]. Iron deficiency is the leading cause of anemia [2]. The treatment of IDA can be divided into two groups: oral and intravenous iron replacement therapies. Oral iron replacement therapy is cost-effective, but it requires daily usage for up to 6 months and has side effects including constipation and abdominal pain. In contrast, intravenous (iv) iron preparations, particularly ferric carboxymaltose, are expensive but restore iron stores after one or two infusions (lasting around 20 minutes) [3-5]. The low side-effect profile of ferric carboxymaltose treatment and its rapid results have made it the first choice, especially in countries with high incomes. Yet, there is no definitive guideline about which agent should be the first choice in treatment.

In erythropoiesis, erythroblasts need folic acid and vitamin B12 (Vit B12) during differentiation [6,7]; in the absence of these two factors, megaloblastic anemia is known to occur due to ineffective erythropoiesis [8,9]. Although many studies have compared the efficacy of oral versus intravenous iron replacement in patients with iron deficiency anemia [10-12], very few have examined the changes in additional factors such as Vit B12 and folic acid concurrently with intravenous ferric carboxymaltose.

The purpose of this study was to compare several hematological parameters at baseline and one month after therapy with oral ferrous glycine sulfate (Ferro Sanol Duodenal®, Turkey) and intravenous ferric carboxymaltose (Ferinject®, Germany). In addition, we designed this study to assess the effects of intravenous ferric carboxymaltose on other erythropoiesis-related factors like Vit B12 and folic acid.

Material and methods

Study

In this single-center retrospective study, from January 1, 2016, to December 31, 2018, all adult patients treated for IDA at the internal medicine outpatient clinic were consecutively included. The patients' medical records were reviewed for one month since the time of inclusion. Demographic and clinical data were collected by hospitals information system. The study protocol was approved by Medicalpark Fatih Hospital's institutional review board (approval number: 2021 – 1 – 10). All of the procedures were in accordance with the World Medical Association Helsinki Declaration of 1964 and later versions. The written consent could not be taken due to the retrospective design of the study.

Patients

WHO defines anemia as Hb 13 g/dL in men and 12 g/dL in women; IDA is defined as transferrin saturation <20% and ferritin <25 ng/mL in anemic patients [1,13]. Inclusion criteria were as follows: age >18 years, having been treated for IDA, having first month follow-up one. Exclusion criteria included pregnancy, having active inflammatory bowel diseae, macrocytic anemias (folic acid or Vit B12 deficiency) or any other chronic disease (an infection, a rheumatic or malignant disease), incomplete medical records or incomplete follow-up.

Patients' demographics (age, gender), type of medication, and the results of the hematological parameters [Hb (g/dl), mean corpuscular volume (MCV) (fL), transferrin saturation (TS) (%), ferritin (ng/mL), Vit B12 (pg/mL), and folic acid (ng/mL)] were recorded.

Eligible patients were divided into two groups depending on the iron therapy at the time of enrollment. Subjects on ferrous glycine sulfate received a daily dose of 567.7 mg given orally for one month. Subjects on ferric carboxymaltose therapy received a single dose of a single dose of 1000 mg, in a slow intravenous infusion over 20 min. Following the first infusion of ferric carboxymaltose or ferrous glycine sulfate prescription, none of the patients in ferric carboxymaltose group received oral iron therapy and none in ferrous glycine sulfate group received intravenous iron treatments during the follow-up.

The data was compared between oral ferrous glycine sulfate group and intravenous ferric carboxymaltose group. The primary endpoint of the study was the change in Hb, MCV, TS, and ferritin from the beginning of the study to the first month of intragroup follow-up; and the secondary outcome was the change of Vit B12 and folic acid among the groups.

Statistical Analysis

Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). The normality of continuous variables was investigated by Shapiro-Wilk's test. Descriptive statistics were presented using mean and standard deviation for normally distributed variables and median (and minimum-maximum) for the non-normally distributed variables. Non-parametric statistical methods were used for values with skewed distribution. For the comparison of two non-normally distributed independent groups, Mann Whitney U test was used. For the comparison of two non-normally distributed dependent groups, Wilcoxon Signed Rank test was used. The comparison of categorical variables was performed by using the Chi-Square test. Statistical significance was accepted when the two-sided p value was lower than 0.05.

Results

A total of 333 patients were included in the study. The ferrous glycine sulfate group included 186 patients and the ferric carboxymaltose group included 147 patients. The flow chart of the study is shown in Figure 1.

Table 1 shows the demographics of 333 patients included in the study. There were no statistical differences between groups according to age and gender distribution values (p=0.072, p=0.947, respectively).

Table 1. Demographic characteristics of the study groups.

	Ferrous glycine sulfate Group	Ferric carboxymaltose Group	p
Gender †			0.072[1]
Female	93 (50)	88 (59.9)	
Male	93 (50)	59 (40.1)	
Age (years) ‡	43 (18-70)	40 (18-78)	0.947[2]

†: n (%), ‡: median (min-max), [1]: Chi-Square test, [2]: Mann Whitney U test.

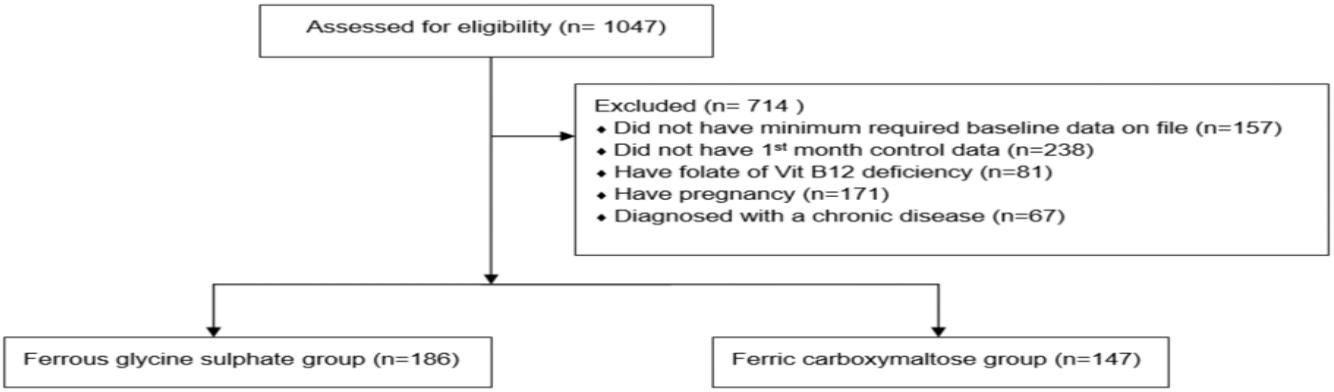

Figure 1. Flowchart of the study.

There was no significant difference between the groups regarding baseline Hb and TS values (p=0.100, p=0.850, respectively) (Table 2).

Table 2.

	Ferrous glycine sulfate group	Ferric carboxymaltose group	$p^{1/3}$
Hemoglobin-baseline (g/dL)	8.9 (8-11)	8.9 (8-10)	0.100[1]
Hemoglobin-first month (g/dL)	10.1 (9-12.7)	11.4 (9.7-13.5)	<0.001[1]
Difference	1.2 (0.4-1.8)	2.5 (1.3-3.5)	<0.001[3]
Δ % change	13.8 (4.6-22.2)	27.9 (14.4-42.7)	<0.001[3]
p^2	<0.001	<0.001	
MCV-baseline (fL)	74 (65-79)	72 (65-79)	0.002[1]
MCV-first month (fL)	79 (69-89)	83 (73-93)	<0.001[1]
Difference	5.5 (-2-15)	11(8-14)	<0.001[3]
Δ % change	7.6 ((-2.6)-23.1)	15.8 (10.3-21.5)	<0.001[3]
p^2	<0.001	<0.001	
TS-baseline (%)	0.1 (0.01-0.2)	0.1 (0.01-0.2)	0.850[1]
TS-first month (%)	0.2 (0.06-0.3)	0.3 (0.2-0.5)	<0.001[1]
Difference	0.1 (0.1-0.2)	0.2 (0.2-0.4)	<0.001[3]
Δ % change	100 (29.4-1400)	250 (79-2800)	<0.001[3]
p^2	<0.001	<0.001	
Ferritin-baseline (ng/mL)	9 (1-15)	7 (1-15)	<0.001[1]
Ferritin-first month (ng/mL)	36 (7-60)	209(155-261)	<0.001[1]
Difference	28 (5-48)	201 (148-260)	<0.001[3]
Δ % change	323.6 (64.3-4200)	2950 (1233.3-26000)	<0.001[3]
p^2	<0.001	<0.001	
Vit B12-baseline (pg/mL)	290 (199-324)	267 (210-320)	<0.001[1]
Vit B12-first month (pg/mL)	267 (181-306)	231 (198-288)	<0.001[1]
Difference	-22 (-30-(-10)	-29 (-111-75)	0.018[3]
Δ % change	-7.47 ((-11.4)-(-3.2))	-11 ((-35.7)-35.2)	0.005[3]
p^2	<0.001	<0.001	
Folic acid-baseline (ng/mL)	7 (5-10)	7.7 (4.5-11)	0.006[1]
Folic acid-first month (ng/mL)	5.8 (4.3-7.8)	5.7 (3.2-10)	0.947[1]
Difference	-1.3 (-5.6-2.8)	-1.7 (-3.2-1.1)	0.009[3]
Δ % change	-18.2 ((-56)-56)	-23.1 ((-47.6)-23.4)	0.010[3]
p^2	<0.001	<0.001	

All values were represented by median (min-max).
p^1 :Intergroup comparison, Mann Whitney U test, p^2: intragroup comparison, Wilcoxon Signed Rank Test, p^3: other comparions, Mann Whitney U test.
MCV: mean corpuscular colume, TS: transferrin saturation, Vit B12: vitamin B12.

Significant differences were detected in terms of baseline MCV, ferritin, Vit B12, and folic acid. Median MCV, ferritin, and Vit B12 baseline values were significantly higher in ferrous glycine sulfate group than in ferric carboxymaltose group (p=0.002, p<0.001, p<0.001, respectively). The median folic acid baseline value was significantly lower in ferrous glycine sulfate group compared to ferric carboxymaltose group (p=0.006).

Significant improvements were detected in both groups (intra-group) in terms of laboratory values obtained after treatment (p<0.001). There were significant differences between the groups (inter-group numerical) except for folic acid in median laboratory values at the end of the first month. For subjects receiving oral ferrous glycine sulfate, Hb increased from baseline of 8.9 (8-11) to 10.1 (9-12.7) g/dL at first month follow-up (p<0.001). For subjects receiving ferric carboxymaltose, Hb increased from baseline of 8.9 (8-10) to 11.4 (9.7-13.5) g/dL at at first month follow-up; (p<0.001). MCV, TS, and ferritin values were significantly higher in ferric carboxymaltose compared to ferrous glycine sulfate group (p<0.001).

At baseline Vit B12 value in ferric carboxymaltose group was significantly lower than ferrous glycine sulfate group (p<0.001); conversely the baseline folic acid value was significantly lower in ferrous glycine sulfate group (p=0.006). When we compare the first month follow-up values: There was no significant difference in folic acid value between groups (p=0.947); but Vit B12 value was significanty lower in ferric carboxymaltose group (p<0.001).

When the delta percentage change between groups (inter-group %) is compared: The delta percentage change increase in Hb, MCV, TS, and ferritin values were significantly higher in ferric carboxymaltose group than in ferrous glycine sulfate group (p<0.001). The delta percentage change decrease in Vit B12 and folic acid values were higher in ferric carboxymaltose group than in ferrous glycine sulfate group (p=0.005, p=0.010, respectively).

Discussion

In our study, Hb increase was more significant in ferric carboxymaltose patients than in ferrous glycine sulfate patients. Furthermore, as can be seen by ferritin and TS value increases, replenishment of iron stores was significantly greater in the iv ferric carboxymaltose group than in the oral ferrous glycine sulfate group. These numeric and percentage based increases in the first month, consistent with previous studies, are promising for patients who need rapid correction of anemia and have difficulty using oral iron preparations due to gastrointestinal disturbances.

Treatment of IDA can be challenging due to side effects of chosen drug or compliance of patient to the length of the treatment. Oral iron has a history of non-compliance and is linked

to more frequent adverse events; in contrast, older IV iron treatments carried their own risks and were not consistently demonstrated to be superior to oral iron in randomized controlled trials. Fortunately, this perception started to shift as ferric carboxymaltose became more widely used [10-13]. The low compliance with oral iron treatments due to the gastrointestinal discomfort they cause may be one of the obvious factors influencing our study's primary outcome. Due to the retrospective nature of our study, we were unable to investigate the patients' adherence to oral medicine and anticipate how low treatment compliance would affect the results.

When oral iron therapy is given, the patient is usually reassessed two to four weeks after initiation; the hemoglobin level is checked, the tolerability of oral iron is reviewed. With intravenous iron, we usually see patients four to eight weeks after the iron is given. Four weeks should be the minimum interval because after iv iron is given, there is a significant fluctuation in blood iron parameters such as iron, TS and ferritin [14-16]. We did our follow-up at the end of first month because 4 weeks is the intersection cluster for monitoring both oral and iv iron treatment efficacy.

In one of the few studies in which iv ferric carboxymaltose did not produce a more significant Hb increase than oral iron therapy, Bager et al. [17] conducted a study in 64 upper gastrointestinal bleeding patients, which showed no significant difference in Hb increase between oral ferrous glycine sulfate and iv ferric carboxymaltose. This may be because the participants in Bager's study had baseline hemoglobin levels that were higher than those in the current investigation (mean Hb at baseline was, respectively, 10.1 and 9.7 g/dL in the oral and iv iron groups). Still, the restoration of iron depots was faster by iv ferric carboxymaltose than oral ferrous glycine sulfate. In many other studies, ferric carboxymaltose treatment outperformed oral iron treatment in terms of Hb level increase and correction time. In REPAIR-IDA study performed by Onken JE et al. [18], patients with chronic kidney disease and IDA were randomly assigned to receive a total dose of 1500 mg ferric carboxymaltose in 1 week or 200mg iron sucrose in up to five infusions in 2 weeks. Increases in Hb, ferritin, and TS values were superior for patients receiving ferric carboxymaltose compared with patients receiving iron sucrose. In another study, Lichtensten et al. [19] conducted a study that they pooled data from four other studies; they took 191 patients treated for IDA with ferric carboxymaltose; in this study improvements in Hb, TS, and ferritin values were significantly greater ($p=0.001$) than patients receiving oral iron therapies. Ferrer-Barceló et al. [20] performed a prospective study of 61 patients with acute gastrointestinal bleeding who were treated with iv ferric carboxymaltose or oral ferrous glycine sulfate; ferric carboxymaltose provided a significant Hb, TS, and ferritin increase and was better tolerated than oral ferrous glycine sulfate. Finally, in 2021, Cirillo et al. [21] conducted a retrospective, monocentric, observational study reviewing 349 non-dialysis-dependent chronic kidney disease patients. 239 patients were treated with a single dose of iv ferric carboxymaltose and 110 with one or two daily dose of 325 mg oral ferrous glycine sulfate. They reported that iv ferric carboxymaltose treatment in non-dialysis-dependent chronic kidney disease patients results in better replenishment of iron stores when compared to oral ferrous glycine sulfate.

In the light of all these and new studies, iv iron carboxymaltose therapy has begin become the first choice of treatment in more and more patients since it fills iron stores faster, has a low side effect profile and high treatment compliance compared to oral iron replacement therapy [22-24].

We also evaluated baseline and first month follow-up Vit B12 and folic acid blood levels in this study. After one month from the first day of therapy, both factors have been decreased. When we compare groups, there was no significant difference in folic acid values but Vit B12 value in iv ferric carboxymaltose group was significantly decreased compared to oral ferrous glycine sulfate group. Additionally, when we examined the percentages between the two groups at the first month follow-up, we found that the levels of folic acid and vitamin B12 in the IV ferric carboxymaltose group were significantly lower than those in the oral ferrous glycine sulfate group.

This result occurred because erythroblasts require Vit B12 and folic acid to proliferate during their differentiation [6]. Vit B12 is used as a cofactor during the synthesis of tetrahydrofolic acid. Tetrahydrofolic acid is used during the synthesis of deoxythymidine monophosphate; in the end, deoxythymidine monophosphate is required for DNA synthesis in erythropoiesis [25]. Therefore, after we restored the iron depots, erythropoiesis began to work. Consequently, Vit B12 and folic acid were utilized at a rate proportional to erythropoiesis. This process explained the decline in folic acid and vitamin B12.

Only two studies in the literature examined these two factors' baseline values during iv ferric carboxymaltose treatment, and just one of them included first month follow-up values. Venturini et al. [26] analyzed 106 patients with IDA on admission to a cardiac rehabilitation unit after cardiac surgery. They treated patients with iv ferric carboxymaltose or oral sucrosomial iron. Unfortunately, they could only reach the baseline Vit B12 and folic acid levels before the treatment; obtained data show that folic acid deficiency is quite frequent after cardiac surgery, detected in 60.4% of patients; meanwhile, only 6.6% of this group had Vit B12 deficiency. In the other study, contrary to our findings, Huguet et al. [27] found no significant change in Vit B12 and folic acid values compared to the baseline value after one month of a single 500mg ferric carboxymaltose dose in iron deficiency patients without anemia. The main reason for reaching this result can be that patients in the study did not have anemia; also the relatively low amount of iv ferric carboxymaltose used can be considered as another reason.

As a result, if Vit B12 and folic acid levels are not controlled before therapy, this decline may result in a deficit of these two vitamins and diminish the efficiency of the treatment. Furthermore, low levels of Vit B12 and folic acid can even lead to severe neurological deficits in the long run. Therefore, supplementing Vit B12 and folic acid at the beginning of ferric carboxymaltose treatment may be a simple, effective, inexpensive solution to prevent adverse events.

Being a single-center and a retrospective study can be cited as the limitations of this study. We think that prospective studies with more patients will make new contributions to the literature.

In conclusion, our study's results indicate that ferric carboxymaltose treatment is very effective for restoring iron depots in IDA, it should be kept in mind that concomitant, adequate supplementation of factors such as Vit B12 and folic acid is essential for the proper progression of erythropoiesis.

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