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Efficacy and safety of intravenous ferric carboxymaltose in iron deficiency anemia; Real-life data from Turkey, a single center experience

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Abstract

The most common reason of anemia is iron deficiency. Oral iron preparations are the first and most preferred method of treatment of iron deficiency anemia (IDA). In cases where Hb levels need to be increased rapidly, intravenous iron treatment gives more favorable results. Ferric carboxymaltose (FCM) is the most recent formulation developed to reduce the problem of anaphylaxis and has reached a very wide usage rate in a short time. In this study, we wanted to show the efficacy and safety of this treatment in patients diagnosed with IDA and treated with FCM in our clinic. In this study, 103 patients older than 18 years old who were diagnosed with IDA and treated with FCM, in our clinic, between January 2020 and December 2020 were included in the study. A total of 103 patients were evaluated. In the tests performed one month and two months after FCM use, an increase was seen as the following; the median of hemoglobin (Hb) level was 2.6 and 3.7 gr/dL, the median of hematocrit (Hct) level was 6% and 10%, the median of transferrin saturation (TS) was 17% and 18%, and the median of ferritin level was 85 and 48 ng/mL, respectively. When the Hb, Hct, TS and ferritin values were compared basal and after FCM treatment, statistically significant increase was found ($p<0.05$). Various side effects occurred as the following; allergic reaction in the form of itching in three of the patients (2.9%), bone and joint pain in two of the patients (1.9%), nausea in two of the patients (1.9%), dizziness in one of the patients (0.9%), and headache in three of the patients (2.9%). None of the patients complained about anaphylactic reaction, vomiting, constipation, diarrhea or abdominal pain. FCM is an effective and safe drug in iron deficiency anemia.

Keywords: Iron deficiency anemia, hemoglobin, ferritin, ferric carboxymaltose

Introduction

Anemia is the most frequent disease finding in various diseases worldwide [1]. The most common reason of anemia is iron deficiency and is mostly seen due to chronic blood loss, nutritional deficiency, and iron malabsorption from the gastrointestinal system [2,3]. In addition, functional iron deficiency is also seen in chronic kidney failure, autoimmune diseases, and cancers [4]. Iron deficiency causes weakness, fatigue, decrease in workforce capacity due to decrease in effort capacity, and deterioration in quality of life [5]. Therefore, it is a condition that must be treated. Oral iron preparations are the first and most preferred method of treatment of iron deficiency anemia (IDA) [6]. However, gastrointestinal (GI) side effects such as patient incompatibility, GI malabsorption, diarrhea or constipation, and interactions with other drugs reduce the effectiveness of oral iron treatment [3,6,7]. In cases where the hemoglobin (Hb) level is very low (ie Hb<10g/dL), long-term oral treatment may be required and this may reduce patient compliance. In cases such as heart failure, preoperative period, where Hb levels and iron stores need to be increased rapidly, and especially in patients with GI malabsorption, intravenous (IV) iron treatment gives more favorable results [8]. IV iron formulation used for this purpose are iron dextran, ferric gluconate, iron sucrose and ferric carboxymaltose (FCM) [9]. The use of iron dextran has been limited due to its anaphylactic side effects [10]. FCM is the most recent formulation developed to reduce the problem of anaphylaxis and has reached a very wide usage rate in a short time [11].

In this study, we wanted to show the efficacy and safety of this treatment in patients diagnosed with IDA and treated with FCM in our clinic.

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Material and Methods

In this study, 103 patients older than 18 years old who were diagnosed with IDA and treated with FCM, in our clinic, between January 2020 and December 2020 were included in the study. Patients' age, gender, Hb, hematocrit (Hct), transferrin saturation (TS), ferritin levels and side effects measured at the time of diagnosis, and one month and two months after FCM treatment were recorded retrospectively from the patients' files. TS was calculated with the formula "serum iron/total iron binding capacity x 100". Iron requirement for patients was calculated with the formula "total iron dose = kg x 2,4 x (target Hb-patient Hb) + 500". The treatment of patients with an iron requirement of up to 1000 mg was administered at once, and patients with iron requirement with more than 1000 mg, 1000 mg were administered on the first day and 500 mg one week later. A maximum of 1500 mg FCM was administered to the patients.

Statistical Analysis: Mean, standard deviation, median, minimum, maximum value frequency and percentage were used for descriptive statistics. The distribution of variables was checked with kolmogorov-simirnov test. Wilcoxon test were used for the repeated measurement analysis. SPSS 27.0 was used for statistical analyses.

Ethics

This study was approved by the Bezmialem Vakıf University Ethics Commitee without Intervention (Date: 19.01.2021, Number: 01/2) and was performed compatibility by all principles of the Helsinki Declaration.

Results

Of the 103 patients included in the study, 89 (86.4%) were female and 14 (13.6%) were male. The median age of the patients was 45 (range: 19-92). Pre-treatment basal Hb level median was 9.4 (range: 5.8-11.9) gr/dL, Hct median was 31 (range: 20-38) %, TS median was 6 (range: 2-24)%, ferritin level median was 3 (range: 1-20) ng/mL. In the evaluation one month after FCM infusion; Hb median became 12 (range: 9.5-14) gr/dL, Hct median became 37 (range: 27-47) %, TS median became 23 (range: 12-56)%, ferritin median became 88 (range: 26-621) ng/mL. The following levels were detected in the laboratory findings two months after FCM treatment; Hb median 13.1 (range: 11.3-14.5) gr/dL, Hct median 41 (range: 34-48) %, TS median 24 (range: 13-45)%, ferritin median 51(range: 11-225) ng/mL. In the tests performed one month and two months after FCM use, an increase was seen as the following; the median of hemoglobin (Hb) level was 2.6 and 3.7 gr/dL, the median of hematocrit (Hct) level was 6% and 10%, the median of transferrin saturation (TS) was 17% and 18%, and the median of ferritin level was 85 and 48 ng/mL, respectively. When the baseline levels of the examinations performed one and two months after FCM treatment compared, statistically significant increases were found in Hb (figure 1), Hct (figure 2), TS (figure 3), and ferritin (figure 4) ($p<0.05$) (table 2). When the first- and second-month laboratory findings after treatment were compared, a statistically significant increase was observed in the levels of Hb, Hct, TS, and ferritin (figures 1, 2, 3, 4, respectively) ($p<0.05$) (table 2). Various side effects occurred as the following; allergic reaction in the form of itching in three of the patients (2.9%), bone and joint pain in two of the patients (1.9%), nausea in two of the patients (1.9%), dizziness in one of the patients (0.9%), and headache in three of the patients (2.9%). None of the patients complained about anaphylactic reaction, vomiting, constipation, diarrhea or abdominal pain (table 3).

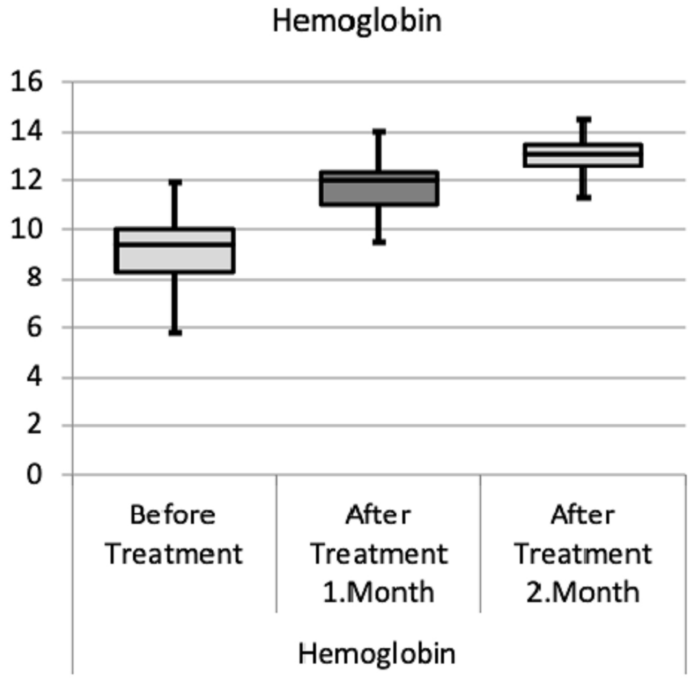

Figure 1. Hemoglobin values increase before and after one and two months of FCM treatment

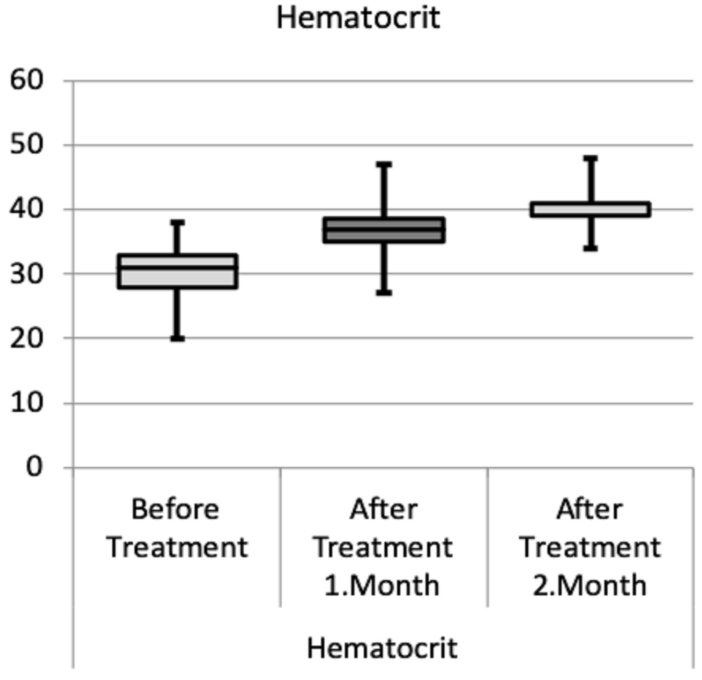

Figure 2. Hematocrit values increase before and after one and two months of FCM treatment

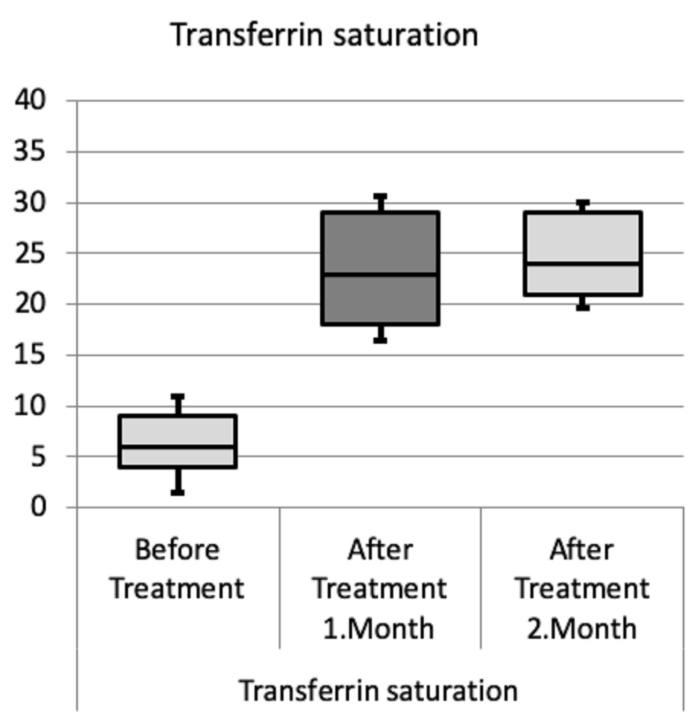

Figure 3. Transferrin saturation values increase before and after one and two months of FCM treatment

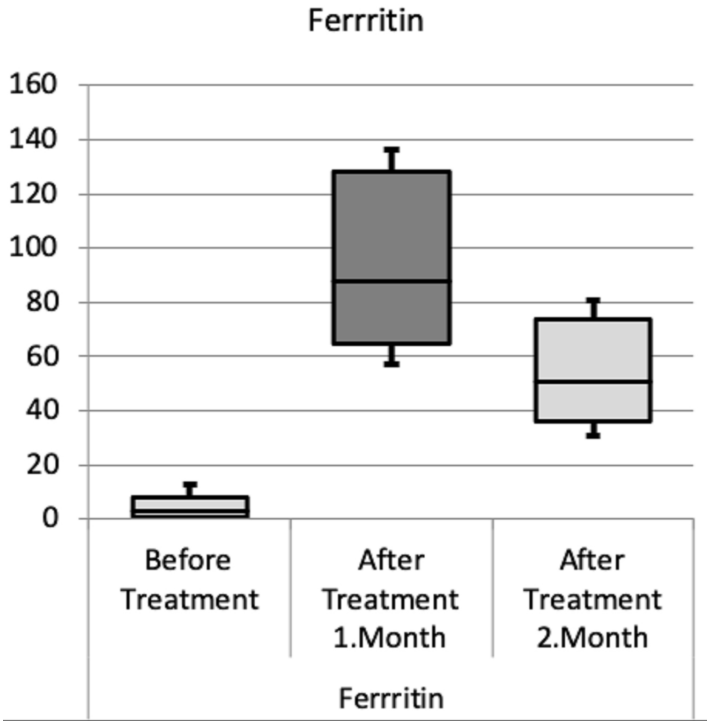

Figure 4. Ferritin values increase before and after one and two months of FCM treatment

Table 1. Baseline characteristics of patients

		Min-Max			Median	Mean±sd/n-%		
Age	11.0	-	92.0		45.0	47.3	±	15.7
Gender	Female					89		86.4%
	Male					14		13.6%
Hemoglobin	5.8	-	11.9		9.4	9.2	±	1.4
Hematocrit	20.0	-	38.0		31.0	30.3	±	4.0
Transferrin saturation	2.0	-	24.0		6.0	6.5	±	4.0
Ferrritin	1.0	-	20.0		3.0	5.0	±	4.3

Table 2. Hemoglobin, hematocrit, transferrin saturation and ferritin levels after ferric carboxymaltose treatment

	Min-Max			Median	Mean±sd			p*		p‡	
Hemoglobin											
Before Treatment	5.8	-	11.9	9.4	9.2	±	1.4				
One month later after treatment	9.5	-	14.0	12.0	11.7	±	0.9	0.000	w		
Two months later after treatment	11.3	-	14.5	13.1	13.1	±	0.7	0.000	w	0.000	w
Hematocrit											
Before Treatment	20.0	-	38.0	31.0	30.3	±	4.0				
One month later after treatment	.27.0	-	47.0	37.0	36.7	±	2.9	0.000	w		
Two months later after treatment	34.0	-	48.0	41.0	40.4	±	2.3	0.000	w	0.000	w
Transferrin saturation											
Before Treatment	2.0	-	24.0	6.0	6.5	±	4.0				
One month later after treatment	12.0	-	56.0	23.0	24.9	±	8.9	0.000	w		
Two months later after treatment	13.0	-	45.0	24.0	25.0	±	6.2	0.000	w	0.000	w
Ferrritin											
Before Treatment	1.0	-	20.0	3.0	5.0	±	4.3				
One month later after treatment	29.0	-	621.0	88.0	115.8	±	94.3	0,000	w		
Two months later after treatment	11.0	-	225.0	51.0	58.8	±	33.3	0,000	w	0,000	w

w Wilcoxon test
p* Difference with before treatmennt / p ‡ Difference with previous measurement

Table 3. Post-treatment side effects

Pruritus	-	100	97.1%
	+	3	2.9%
Bone pain and arthralgia	-	100	98.1%
	+	2	1.9%
Headache	-	101	97.1%
	+	3	2.9%
Nausea		101	98.1%
		2	1,9%
Dizziness		102	99.1%
		1	0.9%
Abdominal pain		0	0%
Vomiting		0	0%
Constipation		0	0%
Diarrhea		0	0%
Anaflaxia		0	0%

Discussion

TIron deficiency is the most common reason for anemia worldwide [2]. Oral iron preparations are the most preferred method in IDA [6]. However, treatment incompatibilities, iron-drug interactions, gastrointestinal side effects and ongoing blood loss due to reasons such as hypermenorrhea, gastrointestinal system malignancies, angiodysplasia decrease the effectiveness of oral iron treatment [3,12,13]. Therefore, intravenous iron therapy is more preferred in these patients. The frequency of use of FCM, which has a low incidence of side effects and has been shown to be effective in various studies, has recently increased [14-19].

Breyman et al. compared the efficacy of FCM with oral ferrous sulfate (FS) in pregnant women with IDA [14]. In this study, a significant improvement in Hb levels from baseline was obtained in the FCM arm at week 6 (Hb: 1.75 ± 1.18 g/dL versus 1.32 ± 1.54 g/dL) [14]. Again, in this study, the time taken for pregnant women treated with FCM to reach Hb ≥ 11.0g/dL was shorter than FS (3,4 vs 4.3 weeks) [14]. Nunes et al. conducted a study that found a significant difference of ≥ 3 g/dL in Hb increase in patients with IDA [16]. In the study conducted by Ikuta et al., the average change from the baseline level to the highest Hb level (95% Cl) observed was 3.31 g/dL [18]. Again, in this study, the average Hb reached a maximum level [13.19 g/dL (95% Cl 12.82.13.55)], at the sixth week after FCM administration; later on, it stayed in the same level until the 12th week [18]. Our results were consisted with the results obtained in these studies. In our study, in the tests performed one month and two months after FCM use, an increase was seen as the following; the median of Hb level was 2.6 and 3.7 gr/dL, the median of Hct level was 6% and 10%, the median of TS was 17% and 18%, and the median of ferritin level was 85 and 48 ng/mL, respectively (table 2).

In our study, side effect incidence of FCM was found to be low. None of the side effects required the treatment to be discontinued. In our study, the following complaints were made; allergic reaction in the form of itching in three of the patients (2.9%), bone and joint pain in two of the patients (1.9%), headache in three of the patients (2.9%), dizziness in one of the patients (0.9%), and nausea in two of the patients (1.9%). None of the patients complained about anaphylactic reaction, vomiting, constipation, diarrhea or abdominal pain.

In the comparative study of FCM and FS conducted by Breyman et al.; neurological side effects such as headache, dizziness and dysgeusia were seen in 6% of the FCM arm, and 1% in the FS arm. However, GI side effects such as nausea, vomiting, abdominal pain, constipation, dyspepsia were observed with a rate of 2% in the FCM arm, but were seen with a rate of 13% in the FS arm [14]. In our study, the rate of neurological side effects was similar, but no GI side effects other than nausea (1.9%) were seen.

Lichtenstein et al. found treatment-related total side effects as 11.9% with FCM, 3% with oral iron, and 26.2% with other IV iron formulations. However, the striking point in this study was that the number of patients was 101 in the FCM arm, 25 in the oral iron arm, and 61 in the other IV iron arm [15]. The low number of patients in the oral iron arm may also affect the rate of side effects. In this study, two (2%) patients had arthralgia, one (1%) patient had itchiness, six (6%) patients had GI side effects in the FCM arm, but no neurological side effects were reported [15]. In our study, two (1.9%) patients has GI side effects in the form of nausea, four (3.8%) patients had neurological side effects such as headache and dizziness, and three (2.9%) patients has itchiness. In the study of Lichtenstein et al. although two (2%) patients had GI bleeding and one patient died in the FCM arm, one (1.6%) patient had GI bleeding in the oral iron arm. No death has been reported. However, coronary artery disease was seen in one (1.6%) patient in the oral iron group [15]. Whereas in our study, no serious adverse reactions were observed.

In the study of FCM and iron dextran (ID) conducted by Hussain et al [20]; while GI side effects such as nausea, vomiting, diarrhea was seen with the rate of 29.3% in the FCM arm, the rate was 17.9% in the ID arm. This ratio was higher in the FCM arm but was not statistically significant (p value: 0.099). Also, in this study, while side effects such as headache and dizziness were 19.5% in the FCM arm, it was 21.8% in the ID arm, and this ratio was not statistically significant (p value: 0.845). In this study, hypophosphatemia was observed in 8.5% of the patients in the FCM arm, while it was not observed in the ID arm. This

ratio was found to be statistically significant (p value: 0.014) [20]. Neurological and GI side effects of FCM were found to be lower in our study than the study conducted by Hussain et al. The limitation of our study was that the phosphorus level was not measured after FCM treatment. In the study conducted by Ikuta et al., 5.1% of the patients had urticaria, and 20.5% had GI side effects with FCM [18]. In our study, while none of the patients had urticaria, two (1.9%) patients had GI (nausea).

In a study comparing FCM and IV ferric gluconate in hemodialysis patients, conducted by Rognoni et al., it was shown that it provides cost savings [21].

The advantages of our study are that iron deficiency anemia is seen very often. The limitations of our study are that it is single-centered and cannot be compared with the group receiving oral iron therapy.

Conclusion

Oral iron treatments will be insufficient, especially in cardiological problems with coronary artery disease and heart failure where severe IDA (i.e. Hb<10) and rapid Hb elevation is desired, and in patients with hypermenorrhea or recurrent GI bleeding. Hence, in these cases, the use of FCM with proven effectiveness and low incidence of side effects should be considered. Moreover, increase of Hb in a short time with FCM will both improve the quality of life and reduce the labor loss.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was approved by the Bezmialem Vakıf University Ethics Committee without Intervention.Date: 19.01.2021, Number: 01/21.

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