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Evaluation of Iron Sucrose and Ferric Carboxymaltose Therapies in Patients with Iron Deficiency Anemia

ORIGINAL INVESTIGATION

Muzaffer Keklik[1], Uğur Kalan[2], Serdal Korkmaz[1], Gülşah Akyol[1], Bilal Aygün[1], Ertuğrul Keklik[3]

ABSTRACT

Objective: Iron deficiency anemia (IDA) affects the quality of life substantially. Recently, different parenteral iron preparations have been used as intravenous iron supplements. The aim of this retrospective study was to assess the efficacy of intravenous ferric carboxymaltose (FCM) and iron sucrose (IS) treatments in patients with IDA.

Materials and Methods: The present study included 180 patients treated with intravenous iron at Kayseri Education and Research Hospital. FCM was administered a maximum of two infusions of 500- or 1000-mg iron. Also, IS was 200 mg administered in up to five infusions in 12 days. In all patients, laboratory evaluations were performed before beginning treatment and 4 weeks after treatment.

Results: An expected increase in hemoglobin (Hb) and transferrin saturation (TS) levels was observed in the two groups. Also, the median ferritin increase was 54.50 ng/mL in the FCM group, whereas it was 28.05 ng/mL in the IS group ($p<0.001$). Likewise, post-treatment ferritin levels increased more significantly in the FCM group than in the IS group (58.15 vs. 29.65 ng/mL, respectively) ($p<0.001$).

Conclusion: Our results show high efficacy and good tolerability of both the treatments. Also, FCM has the advantage of allowing more iron to be administered in fewer infusions and rapid correction of ferritin levels in IDA.

Keywords: Ferric carboxymaltose, intravenous iron, iron sucrose

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[1]Department of Hematology, Kayseri Training and Research Hospital, Kayseri, Turkey

[2]Department of Internal Medicine, Kayseri Training and Research Hospital, Kayseri, Turkey

[3]Department of Physiology, Erciyes University Faculty of Medicine, Kayseri, Turkey

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Correspondence Muzaffer Keklik, Department of Hematology, Kayseri Training and Research Hospital, Kayseri, Turkey
Phone: +90 352 336 88 84
e.mail: muzafferkeklik@yahoo.com

INTRODUCTION

Iron deficiency anemia (IDA) develops as a result of the decrease of the dietary iron absorption (e.g., inflammatory bowel disease (IBD) and gastrointestinal surgery) or the increase of the iron need in the organism or increased iron loss (e.g., during pregnancy/childbirth, heavy uterine bleeding, lactation, or hemodialysis) (1-3). According to literature, the median prevalence of IDA is 36.4% in women (4). High prevalence of IDA has consequences not only on health but also on socioeconomic issues, including decreased work capacity and productivity (5, 6).

Iron treatment has been used for more than 300 years. Oral and parenteral iron products are used in the treatment. Although oral iron treatment is an easy-to-use, inexpensive, and effective alternative, it may cause certain side effects and decrease the compliance of patients to the treatment (7, 8). Regarding these aspects, intravenous (IV) iron treatment is a good alternative available in the market. Primarily, it has the advantage of rapidly increasing hemoglobin (Hb) levels and iron deposits in the body (1, 9, 10). Ferric carboxymaltose (FCM) is a new intravenous iron product with limited data regarding its efficacy (11, 12). Also, after a thorough search of the literature, only few research articles have been found that compared FCM with iron sucrose (IS) (13, 14). In this study, we evaluated the effects of intravenous FCM and IS treatments in patients with IDA.

MATERIALS and METHODS

In this retrospective study, overall data obtained from 180 patients undergoing FCM and IS treatments (n=90 for each) were randomly selected among 300 procedures performed at Kayseri Education and Research Hospital between January 2015 and January 2016. Patients were 18 years and older with IDA and had a history of intolerance to oral iron or an unsatisfactory response to oral iron. The baseline Hb had to be ≤11.0 g/dL, also baseline ferritin level had to be ≤100 or ≤300 ng/mL when transferrin saturation (TS) was ≤30%.

In all patients, the following laboratory evaluations were performed before treatment began: complete blood count (CBC), serum iron level, total iron-binding capacity (TIBC), TS, and serum ferritin level. TS was estimated by using the following formula: serum iron level/TIBC˝100. The treatment regimen was calculated by the Ganzoni formu-

la: Total iron dose=[body weight˝(target Hb-actual Hb)]˝2.4+iron storage depot. Patients with iron treatment or blood transfusions within 4 weeks prior to treatment or history of erythropoietin treatment were excluded. Details of treatment tool were explained to each patient who gave due consent before the procedure. The study approved by the Kayseri Education and Research Hospital Training and Planning Committee (52332816/50- 09.02.2016) and written informed consent was obtained from all individuals.

Ferric carboxymaltose (Ferinject®; Vifor France SA Neuilly-sur-Seine, France) was administered in single, once-weekly infusions of 1000- or 500-mg iron over at least 15 minutes on day 0 and, if needed, on day 7. Also, for patients who received IS (Ferroven®; Santa Farma, Turkey) the drug at a dose of 200 mg of iron was administered over at least 30 minutes on days 0, 3, 6, and 9 and, if needed, on day 12. The adverse effects to drug administration in the groups were recorded.

Statistical Analysis

The variable distribution was evaluated with Shapiro-Wilk test. Regarding the group comparisons, T-test was used for the parameters with normal distribution and Mann-Whitney U test for the parameters without normal distribution. All data were analyzed using the Statistical Packages for the Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA).

RESULTS

The results of 180 treated patients were analyzed (90 data for each group). While there were 75 females and 15 males in the FCM group, there were 82 females and 8 males in the IS group. Baseline clinical and laboratory characteristics of patients are provided in Table 1. Regarding the etiology underlying the IDA, it was found that of the 90 patients in the FCM group, 62 had hypermenorrhea (68.9%), 17 had IBD) or gastrointestine-related condition (18.9%), five had chronic kidney disease (CKD) (6%), four had postpartum anemia (PPA) (4%), and two were pregnant (2%). In the IS group, it was found that of the 90 patients, 60 had hypermenorrhea (67%), 11 had IBD or gastrointestine-related condition (12%), 10 had pregnancy (11%), six had PPA (7%), and three had CKD (3%).

In the analysis, we evaluated the pre- and post-treatment laboratory values between the two groups (Table 2). An expected increase in Hb and TS levels was observed in both the groups, but there were no statistically significant differences between the groups. Post-treatment ferritin levels increased more significantly in the FCM group than in the IS group (58.15 vs. 29.65 ng/mL, respectively) ($p<0.001$). Also, the median ferritin increase was 54.50 ng/mL in the FCM group, whereas it was 28.05 ng/mL in the IS group after 4 weeks ($p<0.001$) (Table 3). After 4 weeks, the mean Hb increase was 4.19 g/dL in the FCM group and 4.04 g/dL in the IS group, and this findings was not statistically significant. Likewise, no significant differences were observed in median TS rate increases.

The groups were compared regarding adverse events during therapy. Both treatment regimens were well tolerated, and most adverse events were mild or moderate. The most common events were nausea (4.4% in the IS group vs. 2.2% for FCM) and hypertension (2.2% vs. 1.1%). No true hypersensitivity reactions were reported. Also, there were no other high-rate adverse events that would cause termination of the treatment.

Table 1. Baseline patients' characteristics

Variables	FCM (n=90)	IC (n=90)
Male/ Female	15/ 75	8/ 82
Age,years[a]	40.39±11.10	39.37±10.06
Etiology of IDA, n (%)		
Hypermenorrhea	62 (68.9)	60 (66.7)
IBD/gastrointestinal related	17 (18.9)	11 (12.2)
CKD	5 (5.6)	3 (3.3)
PPA	4 (4.4)	6 (6.7)
Pregnancy	2 (2.2)	10 (11.1)
Iron intolerance, n (%)		
No	38 (42.2)	41 (45.6)
Yes	52 (57.8)	49 (54.4)
Baseline Hemoglobin (g/L)[a]	86.1±19.1	83.9±13.6
Baseline TS (%)[b]	3.07 (0.54-24.04)	2.52 (0.22-23.53)
Baseline ferritin (ng/mL)[b]	2.40 (1-21)	2.50 (1-27)

FCM: ferric carboxymaltose; IS: iron sucrose; SD: standard deviation; IDA: iron deficiency anemia; IBD: inflammatory bowel disease; CKD: chronic kidney disease; PPA: postpartum anemia; TS: transferrin saturation
[a]Mean±standard deviation [b]Median (range)

Table 2. Pre- and post-treatment laboratory values

Variables	FCM (n=90)	IC (n=90)	p
Hb (g/L)[a]			
Before	86.1±19.1	83.9±13.6	0.364
After	128.1±13.5	124.4±13.2	0.062
TS (%)[b]			
Before	3.07 (0.54-24.04)	2.52 (0.22-23.53)	0.286
After	25.85 (2.27-96.27)	26.16 (2.68-107.91)	0.134
Ferritin (ng/mL)[b]			
Before	2.40 (1-21)	2.50 (1-27)	0.500
After	58.15 (6.8-831.8)	29.65 (2.9-269.5)	<0.001*

Hb: hemoglobin; TS: transferrin saturation
[a]Mean±standard deviation [b]Median (range) *statistically significant

Table 3. Increases in hematological parameters end of the 4 weeks

Variables	FCM (n=90)	IC (n=90)	p
Hb (g/L)[a]	41.9±15.4	40.4±14.7	0.510
TS (%)[b]	20.27 (0.05-94.60)	22.83 (0.19-103.50)	0.361
Ferritin (ng/mL)[b]	54.50 (4.80-428)	28.05 (1-260)	<0.001*

Hb: hemoglobin; TS: transferrin saturation
[a]Mean±standard deviation [b]Median (range) *statistically significant

DISCUSSION

Iron deficiency is one of the world's most common and potentially treatable health problems (5, 15). Treatment for IDA should involve prompt iron replacement plus diagnostic steps directed toward identifying the underlying cause of IDA (16). Oral iron is the first-line treatment for most patients due to its safety and low cost; however, this formulation presents a number of disadvantages, including low absorption of iron, and high incidence of gastrointestinal side effects. Thus, parenteral iron treatment was introduced in clinical practice to overcome limitations and disadvantages related to oral iron. IV iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron supplements. Currently, different IV iron formulations are available. These products are similar in terms of safety profile but differ in the content and frequency of the doses administered (17). Most clinical trials have used IS to evaluate efficacy and safety of IV iron therapy. IS was effective in 50%-91% of patients with IDA depending on the study criteria (18). In clinical practice, IS proved to be an effective and well-tolerated IV iron preparation (19). In contrast, a typical therapeutic course of IS requires 5-10 injections of 100-200 mg doses of each and multiple infusions are required to replenish iron stores. FCM is a new formulation that allows the administration of high doses of iron over a limited time (20). This formulation can be administered in single doses of up to 1000 mg of iron within 15 minutes. The efficacy and tolerability of FCM have been shown in various conditions, including anemia associated with IBD, postpartum phase, CKD, and heavy uterine bleeding (2, 11, 21, 22). Contrastingly, after a thorough literature search, only a few articles comparing FCM with IS treatments have been found. In the Fergicor study, Evstatiev et al. (13) compared the efficacy and safety of FCM with IS in patients with IBD and IDA. They administered 500 or 1000 mg of FCM in up to three infusions or 200 mg of IS in up to 11 infusions, twice weekly. More patients with FCM achieved an Hb response than IS (65.8% vs. 53.6%, respectively). The frequency of adverse events was comparable between the groups. In our study, of the 180 patients, three had IBD and 25 had other gastrointestinal pathologies. We administered the FCM and IS treatments at doses similar to those in the Fergicor study. While the mean Hb and the median increase in TS levels were not statistically significant, the median increase in ferritin level was more significant in the FCM group than in the IS group. In another study, Onken et al. compared the efficacy and cardiovascular safety of FCM and IS in patients with IDA and nondialysis-dependent CKD (14). They administered 750 mg of FMS twice weekly or 200 mg of IS in five infusions in 14 days. More patients in the FCM group achieved an Hb increase ≥1.0 g/dL than in the IS group (48.6% vs. 41.0%, respectively). The mean Hb increase was 1.13 g/dL with FCM and 0.92 g/dL with IS. There was no significant difference between the FCM and IS formulations with respect to the major adverse cardiac events of death, myocardial infarction, or stroke. The most common events were nausea (8.6% with FCM vs. 1.6% with IS), hypertension (4.6% vs. 2.0%), flushing (3.0% vs. 0.1%), dizziness (2.4% vs. 1.2%), and dysgeusia (2.4% vs. 1.2%). In our study, there were eight nondialysis-dependent stage 3 CKD patients. The patients were not using erythropoiesis-stimulating agent, and no significant differences were observed in baseline laboratory values. Adverse events were more common in the IS group compared to the FCM group: nausea (4.4% vs. 2.2%) and hypertension (2.2% vs. 1.1%). There were no significant differences in the adverse event rates between groups.

In another study, Rathod et al. (23) compared the efficacy and safety of FCM, IS, and oral iron treatments in patients with PPA. A statistically significant increase in Hb and serum ferritin levels was observed in all groups, but the increase in the FCM group was significantly higher than the increases in the IS and oral iron groups. The mean increase in Hb level after 2 weeks was 0.8, 2.4, and 3.2 g/dL and after 6 weeks was 2.1, 3.4, and 4.4 g/dL a in the oral iron, IS, and FCM groups, respectively. Moreover, the mean increase in serum ferritin levels after 2 weeks was 2.5, 193.1, and 307.1 ng/mL and after 6 weeks was 14.2, 64, and 106.7 ng/mL in the oral iron, IS, and FCM groups, respectively. In addition, compared to the IS group, adverse events were significantly less frequent in the FCM group. In our study, laboratory evaluations were performed 4 weeks after treatment. The findings and adverse events in the present study were comparable with those in the study by Rathod et al. (23).

In addition, of the 157 female patients, 122 had hypermenorrhea, 12 were pregnant, and 10 had PPA. According to the literature, menstrual bleeding, pregnancy, and PPA are the most common etiological causes of IDA in women (24). In a retrospective study, Pels et al. evaluated the efficacy and safety of FCM in pregnant women with IDA (25). The median Hb level increased from 8.4 g/dL to 10.7 g/dL at the first FCM administration, and no treatment-related adverse events were reported. Our findings in pregnant women were similar to those of the study by Pels et al.

CONCLUSION

Our results indicate that when compared with IS administered in five infusions of 200 mg each, FCM administered in one or two infusions of 500-1000 mg given 1 week apart is a safe and effective alternative for the treatment of IDA. Moreover, FCM appears to provide a better and more rapid correction of serum ferritin levels in patients with IDA than IS. The advantages of FCM should be investigated through prospective and broader analyses.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kayseri Training and Research Hospital (52332816/50- 09.02.2016).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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