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RESEARCH ARTICLE

# Is an Additional Dose of Intravenous Ferric Carboxymaltose Useful in the Treatment of Iron Deficiency Anemia?

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## Abstract

**Objectives:** Even though a single high dose administration of intravenous ferric carboxymaltose (FC) is supposed to be effective, it is unknown whether the second dose of FC given one week after the initial dose provides additional benefits. The aim of the present study was to investigate whether two doses of intravenous ferric carboxymaltose is more effective than a single dose of intravenous FC for replenishing iron stores and correction of anemia in patients with iron deficiency.

**Methods:** This retrospective study was performed on medical records of a total of 516 patients treated with FC in the hematology department of a tertiary care center between 2016 and 2018. Patients were allocated into two groups: Group I (n = 367) had received a single dose (1000 mg) of FC, while Group II (n = 149) had two doses of 1000 mg of FC repeated with a one-week interval. Etiologies of anemia, baseline descriptives as well as hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), ferritin and transferrin saturation (TS) before and after treatment were compared between 2 groups.

**Results:** The increases in levels of Hb ($p < 0.001$), Hct ($p < 0.001$), MCV ($p < 0.001$), ferritin ($p = 0.012$) and TS ($p = 0.007$) after intravenous FC treatment were more effective in Group II. Pre-treatment levels of Hb, Hct, MCV, and ferritin significantly influence the response to FC treatment, whereas TS values before treatment do not have a remarkable impact on therapeutic response. The second dose of FC was quite useful to fulfill the iron stores and achieve Hb, Hct and ferritin levels four weeks after treatment.

**Conclusions:** Our results demonstrated that two doses of intravenous FC provide a more rapid and more effective treatment regimen for iron deficiency anemia compared to a single dose.

## Keywords

Anemia, Iron deficiency, Treatment, Intravenous, Ferric carboxymaltose, Ferinject®

## Introduction

Anemia is defined as a hemoglobin (Hb) concentration less than 13.0 g/dl for men and less than 12.0 g/dl for women who are not pregnant [1]. Iron deficiency anemia (IDA) may affect people of all ages, while some populations like elderly and women at childbearing period are at higher risk. The prevalence of anemia has been reported as high as 11% for elderly population [1,2]. The high prevalence of IDA not only has health-related impacts but also it brings about socio-economical results such as loss of productivity and work capacity are remarkable [2,3].

Iron treatment can be given as oral and parenteral forms. Even though it is an easy, cheap and effective option, oral iron treatment is not fully devoid of side effects which may interfere with the compliance of the patient [3,4]. Taking these adverse reactions into account, intravenous iron treatment can constitute a good option and may help to alleviate symptoms over the short term [4]. Ferric carboxymaltose (FC) is a relatively new intravenous iron product approved in many countries for the intravenous treatment of iron deficiency. It can be infused as a single high dose (1,000 mg) in a short interval such as 15 minutes. In clinical trials, FC was associated with rapid hematopoietic improve-

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ment by increasing hemoglobin levels, refurnishing iron stores (i.e., changes in ferritin levels), and increasing available iron for erythropoiesis (i.e., raise in transferrin saturation) [5,6]. Ferric carboxymaltose (Ferinject®) has been reported to improve the functional class and exercise capacity in patients with chronic heart failure and iron deficiency [7]. FC can be administered as a single 750 mg dose via a slow IV push injection over 7.5 minutes or as an IV infusion over at least 15 minutes [8]. The second dose is administered at least seven days later for a recommended cumulative dose of 1500 mg iron [9]. Use of high doses reduces the number of infusions, enabling the possibility of cost reductions compared to multiple administrations [10-13]. Even though a single high dose administration of intravenous FC is supposed to be effective, it is unknown whether the second dose of FC given one week after the initial dose provides additional benefits.

The purpose of the present study was to compare the efficacies of 2 doses and a single dose of FC treatment regimens regarding the improvement of Hb and Hct levels and restoration of iron stores in patients with IDA.

## Materials and Methods

### Study design

The study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board.

This retrospective study was performed using the data derived from the medical files of 516 iron deficiency anemia patients treated in the outpatient clinic of the hematology department in our tertiary care center between 2016 and 2018.

Baseline descriptive (age, gender), and etiology for iron deficiency anemia were noted. Hemoglobin (Hb), hematocrit (Hct) and ferritin levels, mean corpuscular volume (MCV), and transferrin saturation (TS) were recorded before and after intravenous FC (*Ferinject®, Vifor France SA Neuilly-sur-Seine, France*). Patients were allocated into two groups according to the dose of intravenous FC: Group I (n = 367) had received a single dose of FC (1000 mg); whereas Group II (n = 149) had two doses of 1000 mg of FC and the second dose was administered one week after the initial dose. The drug was introduced as an intravenous infusion for 15 minutes. The hematopoietic responses were assessed on the 4$^{th}$ week (between 3$^{rd}$ to 5$^{th}$ weeks) after the administration of FC.

The two distinct criteria for hematopoietic responses to FC were ≥ 2 g/dl or ≥ 3 g/dl increase in the initial Hb levels. Two groups were compared regarding baseline descriptive, the aforementioned hematologic parameters and hematopoietic response rates to FC.

All cases were ≥ 18 years of age with a history of intolerance or poor hematopoietic response to oral iron. They routinely had undergone laboratory analysis for complete blood count, TS and serum ferritin levels.

Patients with IV iron replacement or a history of blood transfusion in the preceding four weeks before FC were excluded from the study. Other exclusion criteria were cardiac, hepatic or respiratory diseases, history of allergy to FC and anemia due to other causes else than iron deficiency.

### Statistical analysis

The categorical variables were summarized with frequency and percentage. Continuous variables were summarized with mean ± SD or median (range: minimum-maximum), where appropriate. The two groups were compared for different characteristics with different statistical testing procedures. The categorical variables were assessed using chi-square tests. The normally distributed continuous variables were analyzed with t-tests. Mann-Whitney U test was used for the analysis of non-normal continuous variables. In addition to univariate comparisons, a multivariate analysis using logistic regression was conducted to assess the effect of treatment on two different end-points (the first criterion was ≥ 2 g/dl increase from initial Hb level; the second criterion was ≥ 3 g/dl increase from initial Hb level) after adjustment for baseline characteristics. The odds ratios (OR) and their 95% confidence intervals (CI) were estimated for different groups, as well as other characteristics of the patients.

## Results

A univariate analysis was implemented for comparison of 2 groups (Table 1). The average age of patients in Group II was significantly older than that of Group I (p = 0.041). The hematopoietic response to intravenous FC treatment was significantly more favorable in Group II which received two doses with an interval of 1 week. Concerning the first criterion of hematopoietic response indicating an increase of ≥ 2 g/dl in Hb level, Group II displayed a better outcome than Group I (79.9% vs. 62.5%; p < 0.001). Similarly, Group II exhibited a better hematopoietic response to FC treatment regarding the second criterion, which defined hematopoietic response as an increase of 3 g/dl in Hb level (54.4% vs. 44.2%; p = 0.047). There were no differences between 2 groups regarding other characteristics such as etiology of iron deficiency anemia, gender distribution, and frequencies of side effects (Table 1). There were only a few side effects such as urticaria (n = 4), myalgia (n = 4), nausea and vomiting (n = 4), fever (n = 2), abdominal pain (n = 1) and arthralgia (n = 1) in this series.

Table 2 demonstrates a comparison of 2 groups regarding Hb, Hct, MCV, ferritin and TS values before and after treatment. Accordingly, Group II had lower values for Hb (p = 0.010), Hct (p = 0.022), ferritin (p = 0.016) and TS (p = 0.002) before FC treatment. After FC

**Table 1:** Comparison of baseline descriptives, side effects and treatment responses in both groups.

| Characteristics | Group I (n = 367) | Group II (n = 149) | p-value |
|---|---|---|---|
| Age | 44 (17-88) | 48 (22-84) | ***0.041**** |
| Male gender | 61 (22.8%) | 23 (15.4%) | 0.071 |
| Etiology | | | 0.742 |
| Pregnancy | 5 (1.9%) | 5 (3.4%) | |
| GIS | 125 (46.8%) | 62 (41.6%) | |
| GUS | 40 (15.0%) | 28 (18.8%) | |
| Malignancy | 16 (6.0%) | 9 (6.0%) | |
| Nutritional | 10 (3.7%) | 8 (5.4%) | |
| Poor oral intake | 1 (0.4%) | 0 (0) | |
| Other | 70 (26.2%) | 37 (34.8%) | |
| Chronic renal failure | 62 (23.2%) | 30 (20.1%) | 0.467 |
| Bariatric surgery | 13 (4.9%) | 10 (6.7%) | 0.430 |
| Side effects | 13 (4.9%) | 4 (2.7%) | 0.281 |
| Hemoglobin increase ≥ 2 g/dl | 167 (62.5%) | 119 (79.9%) | ***< 0.001**** |
| Hemoglobin increase ≥ 3 g/dl | 118 (44.2%) | 81 (54.4%) | ***0.047**** |

(Hint: Data expressed as median (min-max) and n (%); *: statistically significant at $p < 0.05$); (GIS: gastrointestinal system; GUS: genitourinary system).

**Table 2:** Serum levels of hemoglobin, hematocrit and ferritin, mean corpuscular volume and transferrin saturation in both groups.

| | Group I (n = 367) | Group II (n = 149) | p-value |
|---|---|---|---|
| Pre-treatment hemoglobin (g/dl) | 9.33 ± 1.35 | 8.98 ± 1.28 | ***0.010**** |
| Pre-treatment hematocrit (%) | 31.13 ± 3.85 | 30.25 ± 3.56 | ***0.022**** |
| Pre-treatment MCV (fl) | 73.78 ± 10.10 | 71.93 ± 9.01 | 0.064 |
| Pre-treatment ferritin (ng/mL) | 4.50 (1.20-25.10) | 4.00 (1.00-25.00) | ***0.016**** |
| Pre-treatment transferrin saturation (%) | 7.00 (1.00-18.00) | 6.00 (1.00-15.00) | ***0.002**** |
| Post-treatment hemoglobin (g/dl) | 11.97 ± 1.36 | 12.31 ± 1.35 | ***0.016**** |
| Post-treatment hematocrit (%) | 38.2 ± 4.01 | 39.2 ± 4.07 | ***0.016**** |
| Post-treatment MCV (fl) | 82.62 ± 7.06 | 83.7 ± 6.54 | 0.125 |
| Post-treatment ferritin (ng/mL) | 94.55 (24.30-69.90) | 115.40 (26.70-42.00) | ***0.024**** |
| Post-treatment transferrin saturation (%) | 22.50 (5.00-60.0) | 24.00 (5.00-59.00) | 0.163 |
| Time for evaluation of treatment response | 4.00 (3.00-6.00) | 4.00 (3.00-6.00) | 0.065 |

(Hint: Data expressed as mean ± SD or median (min-max); *: statistically significant at $p < 0.05$); (MCV: mean corpuscular volume).

**Table 3:** Differences in hemoglobin, hematocrit, mean corpuscular volume, ferritin and transferrin saturation after treatment in both groups.

| | Group I (n = 367) | Group II (n = 149) | p-value |
|---|---|---|---|
| Hemoglobin (g/dl) | 2.64 ± 1.60 | 3.32 ± 1.49 | ***< 0.001**** |
| Hematocrit (%) | 7.07 ± 4.35 | 8.95 ± 4.08 | ***< 0.001**** |
| MCV (fl) | 8.84 ± 6.40 | 11.76 ± 6.91 | ***< 0.001**** |
| Ferritin (ng/mL) | 86.40 (17.10-54.90) | 110.50 (13.90-240.10) | ***0.012**** |
| TS (%) | 15.00 (-6.00-57.00) | 18.00 (-6.00-55.00) | ***0.007**** |

(Hint: The difference of after treatment-before treatment expressed as mean ± SD or median (min-max);
*: statistically significant at $p < 0.05$); (MCV: mean corpuscular volume; TS: transferrin saturation).

treatment, levels of Hb ($p = 0.016$), Hct ($p = 0.016$), and ferritin ($p = 0.024$) were higher in Group II.

As shown in Table 3, increases in levels of Hb ($p < 0.001$), Hct ($p < 0.001$), MCV ($p < 0.001$), ferritin ($p = 0.012$) and TS ($p = 0.007$) after intravenous FC treatment were more noteworthy in Group II. This finding is particularly important since pre-treatment values for all these variables were lower in Group II. It can be speculated that the second dose of FC was quite useful to replete iron stores and achieve more acceptable Hb, Hct and ferritin levels four weeks after treatment.

**Table 4:** Analysis of factors prone to influence two different types of treatment response ( ≥ 2 g/dl vs. ≥ 3 g/dl increase in hemoglobin levels).

| | Hemoglobin difference > 2 | | Hemoglobin difference > 3 | |
|---|---|---|---|---|
| | **OR (95% CI)** | **p-value** | **OR (95% CI)** | **p-value** |
| Age | 0.98 (0.96, 1.00) | 0.094 | 1.00 (0.98, 1.02) | 0.772 |
| Male gender | 1.29 (0.66, 2.51) | 0.463 | 1.82 (0.89, 3.72) | 0.101 |
| Total dose | 1.95 (1.1, 3.46) | ***0.022**** | 1.24 (0.74, 2.08) | 0.410 |
| Etiology[a] | | | | |
| Pregnancy | - | - | | |
| GIS | 0.28 (0.03, 3.06) | 0.297 | 1.27 (0.29, 5.57) | 0.748 |
| GUS | 0.24 (0.02, 2.8) | 0.257 | 1.81 (0.38, 8.53) | 0.453 |
| Malignancy | 0.74 (0.06, 10.04) | 0.823 | 2.36 (0.43, 12.91) | 0.323 |
| Nutritional | 0.51 (0.03, 8.06) | 0.629 | 3.61 (0.56, 23.22) | 0.177 |
| Other | 0.27 (0.02, 3.04) | 0.290 | 3.13 (0.68, 14.41) | 0.143 |
| Chronic renal failure | 0.84 (0.39, 1.81) | 0.656 | 0.53 (0.24, 1.19) | 0.126 |
| Bariatric surgery | 0.66 (0.20, 2.13) | 0.483 | 0.27 (0.08, 0.88) | ***0.030**** |
| Pre-treatment Hb (g/dl) | 0.17 (0.08, 0.35) | ***< 0.001**** | 0.22 (0.12, 0.44) | ***< 0.001**** |
| Pre-treatment Hct (%) | 1.46 (1.17, 1.83) | ***0.001**** | 1.43 (1.16, 1.76) | ***0.001**** |
| Pre-treatment MCV (fl) | 0.99 (0.95, 1.03) | 0.616 | 0.93 (0.90, 0.97) | ***0.001**** |
| Pre-treatment ferritin (ng/mL) | 0.89 (0.84, 0.94) | ***< 0.001**** | 0.93 (0.87, 0.98) | ***0.008**** |
| Pre-treatment TS (%) | 1.01 (0.93, 1.09) | 0.861 | 1 (0.93, 1.08) | 0.965 |

(Hint: CI: confidence interval, OR: Odds ratio, [a]Reference group: pregnancy); (GIS: gastrointestinal system; GUS: genitourinary system; Hb: hemoglobin; Hct: hematocrit; MCV: mean corpuscular volume; TS: transferrin saturation).

Logistic regression was administered as a multivariate analysis to evaluate the impacts of variables on two different criteria for hematopoietic responses. The aim of the multivariate analysis was to compare the success rates of two groups after elimination of the influences of other parameters. As seen in Table 4, the therapeutic success rate in Group II concerning the first criterion (≥ 2 g/dl increase in Hb levels) was 1.95 times higher than that in Group I (p = 0.022). However, no difference was detected regarding the therapeutic success rate between 2 groups regarding the second criterion (≥ 3 g/dl increase in Hb levels) (p = 0.410). Interestingly, patients who had undergone bariatric surgery were 73% less likely to display hematopoietic response to treatment concerning second criterion (≥ 3 g/dl increase in Hb levels) (p = 0.030).

Pre-treatment levels of Hb, Hct, and ferritin, significantly influence the hematopoietic response to FC treatment regarding both criteria. Pretreatment MCV levels are likely to affect the hematopoietic response with respect to the second criterion only (≥ 3 g/dl increase in Hb levels). On the other hand, TS values before treatment do not have a remarkable impact on the hematopoietic response (Table 4).

## Discussion

The aim of the present study was to investigate whether administration of a second dose of intravenous FC provides additional benefit in the treatment of IDA patients. Our results imply that the second dose of FC given one week after the initial dose was beneficial to increase Hb and Hct levels and to replete iron stores in IDA patients. No additional adverse reactions or significant side effects were observed due to the second dose of FC.

Iron deficiency is the most frequent form of nutritional deficiency, and approximately one-sixth of the total population in developed countries is affected. It is linked with increased vulnerability to infections, fatigue, decreased work capacity and diminished quality of life. Furthermore, IDA is associated with increased morbidity and mortality [14]. The first-line treatment for iron deficiency anemia is oral iron supplementation; however, oral iron treatment has certain disadvantages like drug interactions, gastrointestinal side effects, and malabsorption. These undesired effects may decrease the compliance to oral iron supplementation and decrease the efficacy of treatment. Intravenous iron formulations like FC may solve these problems and may be more suitable for IDA patients [5]. Intravenous iron treatment is a more effective and better-tolerated mode of treatment which improves the quality of life better than the oral iron supplements.

Today, FC has been approved for use in more than 50 countries. Following its approval in Europe, more than 1 million patients were treated with FC. In 2013, the FDA approved FC for the indication of intravenous treatment of IDA in adults intolerant to oral iron or who have had an unsatisfactory response to oral iron as well as in adults who have nondialysis-dependent chronic

kidney disease [15]. There are various formulations for intravenous iron treatment. Although the safety profiles are similar, the content and the dosage may differ. FC is a relatively new formula that permits the introduction of high doses of iron within a restricted time course. The efficacy and tolerability of FC have been well-documented [16].

In the relevant literature, FC was found to be linked with a quick improvement of hematopoietic parameters via increasing hemoglobin levels, refilling iron stores (as reflected ferritin levels), and amplifying the available iron for erythropoiesis (as reflected an increase in TS). The administration of FC was also well-tolerated by patients, with most drug-related adverse events considered to be mild to moderate in severity [17]. Our results were consistent with this data, and in both groups, we observed the remarkable and rapid correction of hematological parameters.

Regarding the dose adjustment for FC, a single dose is supposed not to exceed 1,000 mg of iron (up to a maximum of 15 mg/kg if given by intravenous injection and up to a maximum of 20 mg/kg when introduced by intravenous infusion), and 1,000 mg of iron should not be employed more frequently than once a week [18].

Reported drug-related adverse events to include a headache, dizziness, nausea, abdominal pain, constipation, diarrhea, rash and injection-site reactions [5]. In parallel to recent publications on this topic, FC was well tolerated by our patients, and the few adverse reactions detected in our series were temporary. The administration of intravenous FC in a single or two dose fashion allows reduction of time for completion of treatment and diminishes the likelihood of failure to achieve the full course of treatment.

In the present study, patients with a lower baseline Hb value who received IV iron therapy had a greater increase in Hb from baseline than did patients with a higher baseline Hb value. An important finding was that patients with more severe anemia exhibited a more clear and obvious response to the FC treatment administered at two doses with a one-week interval. This is in conjunction with literature indicating that efficacy of FC treatment was more effective in patients with lower baseline Hb values [19]. This may reflect the body's demand to achieve physiologic homeostasis. Similar analysis could not be conducted on the oral iron group because the number of patients was too small to be conclusive.

Intravenous iron treatment has been linked with oxidative stress. At therapeutic doses, FC must not elicit a lipid peroxidative reaction in the parenchyma since iron derived from FC is mainly accumulated in the reticuloendothelial system [20]. Molecular changes, pharmacodynamic drug interactions and long-term effects of intravenous iron treatment must be studied in further trials. In this context, oxidative stress and pro-inflammatory alterations leading to cardiovascular system disorders attributed to the intravenous infusion of iron must be investigated carefully. Even though FC is approved for the management of IDA, it may be useful for anemia associated with chronic diseases in which there is a functional defect for iron needed for red blood cell production [21].

Despite the clear beneficial effect of the second dose of FC, the cumulative dose of FC needed to restore Hb levels and refill the iron stores must be planned separately for every patient on an individualized basis. Even though no serious adverse reactions were encountered in this series, attention must be paid not to exceed the optimal dose. Our results imply that the use of FC may potentially diminish the costs linked with the administration of intravenous iron preparations. On the other hand, pharmacoeconomic analyses should be carried out to document the cost/benefit aspect and to guide the decision for the use of FC in routine clinical practice instead of other currently available agents [22]. The doses administered in this study were selected based on non-clinical, repeated dose, no observed adverse effect level (NOAEL) data together with preliminary safety data on single FC doses of up to 1000 mg iron in humans [23]. In a study of patients with IDA secondary to gastrointestinal disorders, total serum iron levels were determined above normal values for six hours after 15 minutes of FC infusion; however, after 4-7 days, returned to the values at the beginning of treatment [24]. When subsequent doses of FC were administered, total serum iron levels followed a similar pattern.

The main limitation of our study is the retrospective design, and this compromises the conclusions that can be drawn. Retrospective studies are vulnerable to bias in the selection of patients, and this bias may skew the results. Future studies may be necessary to allow for generalization of our data to other populations. Other limitations include patient population consistent of only adults, impacts of social, environmental and ethnic factors, data confined to the experience of a single institution and lack of long-term results. Finally, the possible occurrence of hypophosphatemia and inflammation was not taken into account in the present study and the levels of proinflammatory interleukins or serum isoprostane that might indicate increased inflammation or oxidative stress were not measured.

## Conclusion

In conclusion, our results demonstrated that FC administered at two doses one week apart from each other is superior to a single dose regimen in the treatment of iron deficiency anemia. This regimen may allow a better and more rapid restoration of Hb and Hct levels as well as refilling the iron stores in the body. A better understanding of the safety, immunological

aspects and long-term outcomes of FC treatment warrants implementation of further multi-centric, prospective, controlled trials on larger series.

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