

# World Journal of *Clinical Cases*

*World J Clin Cases* 2023 April 26; 11(12): 2582-2854



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: *Ying-Yi Yuan*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jin-Lei Wang*.

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Thrice Monthly

**EDITORS-IN-CHIEF**

Bao-Gan Peng, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati, Ja Hyeon Ku

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

**PUBLICATION DATE**

April 26, 2023

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Observational Study

**Ferric carboxymaltose for anemia in Crohn's disease patients at a tertiary center: A retrospective observational cohort study**

Natália Souza Nunes Siqueira, Livia Bitencourt Pascoal, Bruno Lima Rodrigues, Marina Moreira de Castro, Alan Sidnei Corrêa Martins, Dante Orsetti Silva Araújo, Luis Eduardo Miani Gomes, Michel Gardere Camargo, Maria de Lourdes Setsuko Ayrizono, Raquel Franco Leal

**Specialty type:** Medicine, research and experimental

**Provenance and peer review:** Unsolicited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0  
Grade B (Very good): B  
Grade C (Good): C  
Grade D (Fair): 0  
Grade E (Poor): 0

**P-Reviewer:** Rodrigo L, Spain; Rosati A, Italy

**Received:** December 28, 2022

**Peer-review started:** December 28, 2022

**First decision:** February 15, 2023

**Revised:** February 20, 2023

**Accepted:** March 23, 2023

**Article in press:** March 23, 2023

**Published online:** April 26, 2023



Natália Souza Nunes Siqueira, Livia Bitencourt Pascoal, Bruno Lima Rodrigues, Marina Moreira de Castro, Alan Sidnei Corrêa Martins, Dante Orsetti Silva Araújo, Luis Eduardo Miani Gomes, Michel Gardere Camargo, Maria de Lourdes Setsuko Ayrizono, Raquel Franco Leal, Inflammatory Bowel Disease Research Laboratory, Gastrocenter, Colorectal Surgery Unit, School of Medical Sciences, University of Campinas (Unicamp), Campinas 13083-878, São Paulo, Brazil

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**Abstract****BACKGROUND**

Although the gastrointestinal tract is the most affected by Crohn's disease (CD), the condition triggers other consequent manifestations, and iron deficiency anemia (IDA) is one of the most common. Intravenous (IV) iron replacement is currently available through several drugs, such as ferric hydroxide sucrose and ferric carboxymaltose (FCM). However, the clinical management of these conditions can be challenging.

**AIM**

To elucidate the drug's effectiveness, the present study analyzed, through medical records, the clinical and epidemiological data of a cohort of patients with active CD who received IV FCM for the IDA treatment.

**METHODS**

This retrospective observational study included 25 patients with active CD, severe anemia, and refractory to previous conventional treatments. Patients were evaluated two times: During the last treatment with ferric hydroxide sucrose and treatment with FCM.

**RESULTS**

After treatment with FCM, parameters of IDA assessment significantly improved, serum hemoglobin (Hb) levels increased in 93% of patients ( $P < 0.0001$ ), and in

44%, there was an increase of  $\geq 2$  g/dL in a single application. In addition, 86% of the patients showed an increase in serum iron ( $P < 0.0001$ ) and ferritin ( $P = 0.0008$ ) and 50% in transferrin saturation ( $P = 0.01$ ). The serum iron levels at baseline showed a negative association with the ileal and colonic CD and use of biologics and a positive association with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The values of Hb and hematocrit after ferric hydroxide sucrose treatment remained similar to those found before treatment.

### CONCLUSION

This study demonstrated that FCM is an important therapeutic strategy for treating IDA in CD patients, achieving satisfactory results in refractory cases.

**Key Words:** Ferric carboxymaltose; Iron deficiency anemia; Crohn's disease; Inflammatory bowel disease; Anemia; Clinical management

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**Core Tip:** In this observational cohort study, treatment with a single dose of ferric carboxymaltose demonstrated a significant improvement in the hematological parameters evaluated for the treatment of iron deficiency anemia in Crohn's disease patients at a tertiary center of a developing country. These results may contribute to guiding clinical treatment of this condition, mainly in cases of refractoriness to ferric hydroxide sucrose.

**Citation:** Siqueira NSN, Pascoal LB, Rodrigues BL, de Castro MM, Martins ASC, Araújo DOS, Gomes LEM, Camargo MG, Ayrizono MLS, Leal RF. Ferric carboxymaltose for anemia in Crohn's disease patients at a tertiary center: A retrospective observational cohort study. *World J Clin Cases* 2023; 11(12): 2740-2752

**URL:** <https://www.wjgnet.com/2307-8960/full/v11/i12/2740.htm>

**DOI:** <https://dx.doi.org/10.12998/wjcc.v11.i12.2740>

## INTRODUCTION

Crohn's disease (CD) is an inflammatory bowel disease (IBD) characterized by a chronic inflammatory disorder of the gastrointestinal tract[1,2]. Although the gastrointestinal tract is the most affected section in CD, the affection may occur under other manifestations[3,4], such as anemia, among the most common in IBD[5-7]. This condition is commonly defined by the World Health Organization (WHO) as when hemoglobin (Hb) is below average values (less than 12 g/dL in women and 13 g/dL in men)[8]. Its prevalence varies widely, depending on the evaluated CD patients (hospitalized or outpatients).

Iron deficiency anemia (IDA) is usually determined by a negative balance in serum iron levels, where more iron is lost than is consumed in the diet[9]. In CD patients, chronic blood loss from the ulcerated intestinal mucosa associated with diarrhea, decreased iron intake due to dietary restriction, and deficiency in transluminal iron absorption during disease activity plays an important role in causing iron deficiency[10]. Erythropoiesis and iron metabolism may also be affected by increased serum hepcidin levels in high systemic inflammation, impairing dietary iron absorption and resulting in low serum iron levels[11].

Treatment of IDA aims to increase levels of Hb, serum ferritin (s-ferritin), and transferrin saturation (TSAT) levels above the lower threshold of normal to restore iron stocks to prevent recurrent anemia and not just to restore the short-term hematopoietic state[10]. Oral iron supplementation is usually the first choice for treatment, but intestinal absorption in CD patients can be compromised by the activity of the inflammatory process, which limits the effectiveness of treatment[3,12]. In addition, unabsorbed iron results in increased clinical activity in IBD patients due to gastrointestinal side effects, decreasing treatment adherence[13,14]. On the other hand, administering intravenous (IV) iron has helped in the correction of IDA of these patients and the maintenance of iron stocks in a faster and more prolonged response to treatment. Moreover, IV iron administration avoids gastrointestinal side effects, positively influencing treatment adherence and consequently improving quality of life[15,16].

Currently, IV iron replacement for treating IDA is available through several drugs distinguished by their complex chemistry, such as iron hydroxide sucrose and iron dextran[17]. Recent pharmacology progress has led ferric carboxymaltose (FCM) to correct the IDA through its pharmacokinetic characteristics[18,19]. FCM has a robust molecular structure containing stable iron in the form of a non-dextran iron complex with an iron hydroxide core (III) with a carbohydrate ligand. The structure is similar to ferritin's, allowing for iron absorption without releasing free iron in the body. Therefore, administration

can be performed in high doses (with a maximum dose of up to 1000 mg) in a safe and clinically well-tolerated manner[20,21]. Given the above, this study was designed to evaluate the effectiveness of FCM in treating IDA in CD patients in a tertiary center in Brazil, where IBD has become increasingly frequent, mainly in the last two decades[22].

## MATERIALS AND METHODS

### **Study design and Study population**

In this observational retrospective cohort study, 25 patients with active CD who were followed at the IBD Unit of the Clinical Hospital of the University of Campinas (Unicamp) were included sequentially from October 2014 to November 2021. The patient's clinical information was evaluated through outpatient database electronic records. Disease activity was determined by the CD Activity Index (CDAI), CD Endoscopic Index of Severity (CDEIS), magnetic resonance imaging enterography, and clinical and laboratory exams.

All patients presented severe anemia (Hb  $\leq$  10 g/dL and hematocrit  $<$  41% for men and  $<$  36% for women), according to the WHO[8], and they were refractory to previous conventional treatments. Iron deficiency was determined by TSAT  $<$  20%, ferritin  $\leq$  100 ng/mL, and serum iron  $<$  60  $\mu$ g/dL.

Clinical characteristics and laboratory results were collected twice from the patient's past clinical history: During the previous treatment with ferric hydroxide sucrose (a subgroup of the total cohort) and the therapy with FCM.

### **Analysis of the treatment effect after ferric carboxymaltose and ferric hydroxide sucrose**

All laboratory parameters were evaluated before and after treatment with a single IV administration of FCM (500 mg) and after treatment with IV ferric hydroxide sucrose to elucidate the effectiveness of medication in this group of patients. The primary analysis parameters for anemia correction were Hb  $\geq$  12 g/dL in women and  $\geq$  13 g/dL in men or an increase of Hb  $\geq$  1 g/dL. Secondary analyses included increased serum levels of iron, s-ferritin, and TSAT.

### **Statistical analysis**

All results are reported as the median  $\pm$  SEM. The D'Agostino & Pearson and Shapiro-Wilk tests were used to investigate whether the data followed a normal *Gaussian* distribution ( $P > 0.1$ ). The data were analyzed using Person's  $\chi^2$  and paired *t*-test, Wilcoxon matched pair test or Mann-Whitney Test. Data were analyzed using GraphPad Prism<sup>®</sup> 8, with a critical *P*-value of 5%. Finally, univariate and multiple regression analyses using generalized linear models were performed to investigate the association of the hematological parameters with the clinical and demographic characteristics of the patients. For this performance, the significant variables or the ones that adjusted other variables  $< 0.20$  were maintained in multiple models, and data were analyzed using Stata<sup>®</sup> 14, with a critical value of 5%.

## RESULTS

### **Patient characteristics and clinical outcomes**

The clinical and demographic characteristics of the entire cohort are reported in [Table 1](#). A total of 25 CD patients were included in the study, 12 males (48%) and 13 females (52%), with a median age of 37 (20-67) years. The median duration of CD was 144 (6-312) mo. According to the Montreal classification, one patient was diagnosed before the age of 16 years (A1, 4%), 22 patients between 17 and 40 years (A2, 88%), and 2 patients over 40 years old (A3, 8%). Five patients had terminal ileal location (L1, 20%), 4 colonic location (L2, 16%), and 16 ileal and colonic locations (L3, 64%). Regarding the behavior of CD, 8 patients had a non-penetrating pattern (B1, 32%), 13 had stenosing disease (B2, 52%), and the remaining 4 patients had a penetrating disease (B3, 16%). Eleven patients had the concomitant perianal disease (44%), and 20 underwent previous surgeries because of CD complications, such as abscesses, stenosis, and fistula.

Almost all recruited patients were under biological therapy (23 patients, 92%), and 14 were using immunosuppressive therapy (56%). Regarding the treatment of IDA, all patients had previously used other medications, and 10 (40%) had a history of blood transfusion because of severe anemia.

Of the total patients, a subgroup of 16 used ferric hydroxide sucrose previously for the treatment of IDA; 9 males (56.3%) and 7 females (43.7%), with a median age of 37 (25-67) years. The median duration of CD was 144 (24-312) mo and, according to the Montreal classification, one patient was diagnosed before the age of 16 years (A1, 6.25%), 14 patients between 17 and 40 years (A2, 87.5%), and one patient over 40 years old (A3, 6.25%). Four patients had ileal location (L1, 25%), 3 colonic location (L2, 18.7%), and 9 ileal and colonic location (L3, 56.3%). Regarding the CD behavior, 4 patients had a non-penetrating pattern (B1, 25%), 8 stenotic disease (B2, 50%), and the remaining 4 patients had penetrating disease (B3, 25%). Eight patients had concomitant perianal disease (50%), and 15 had undergone

**Table 1** Demographic and clinical characteristics of the patients included in the study

Variables	Ferric carboxymaltose	Iron sucrose	P value
Sex (M/F)	12/13	9/7	0.606 <sup>a</sup>
Age (yr)	37 (20-67)	37 (25-67)	0.989 <sup>b</sup>
Disease duration (mo)	144 (6-312)	144 (24-312)	0.718 <sup>b</sup>
Age at the diagnostic A1/A2/A3 <sup>1</sup>	1/22/2	1/14/1	0.931 <sup>a</sup>
Disease location L1/L2/L3/L4 <sup>1</sup>	5/4/16/0	4/3/9/0	0.882 <sup>a</sup>
Behavior B1/B2/B3 <sup>1</sup>	8/13/4	4/8/4	0.750 <sup>a</sup>
Perianal disease (yes/no)	11/14	8/8	0.707 <sup>a</sup>
Prior Surgery (yes/no)	20/05	15/1	0.224 <sup>a</sup>
Biologic therapy (yes/no)	23/2	15/1	0.962 <sup>a</sup>
Immunosuppressive therapy (yes/no)	14/11	13/3	0.242 <sup>a</sup>
Previous blood transfusion (yes/no)	10/15	8/8	0.529 <sup>a</sup>

<sup>1</sup>Montreal classification.

<sup>a</sup>Pearson's  $\chi^2$  test.

<sup>b</sup>Unpaired *t*-test (Mann Whitney) with  $P < 0.05$ .

Numerical variables are described in median (minimum and maximum), and the categorical variables in absolute frequency.  $n = 25$ . CD: Crohn's disease; M: Male; F: Female.

previous surgeries for CD complications.

All recruited patients with a history of ferric hydroxide sucrose injection for the ADF treatment were under treatment for CD: 15 patients were under biological therapy (93.7%), and 13 were under immunosuppressive therapy (81.3%). Eight patients (50%) of this subgroup needed a blood transfusion because of severe anemia.

### Disease activity

Patients with CD who received iron replacement therapy with FCM had their disease activity determined by nuclear magnetic resonance (presence of ulcers, mucosal enhancement of contrast, or alteration of mesentery associated with the affected intestinal area), colonoscopy with median CDEIS of 16.9 (5.6-26) and/or fecal calprotectin 1000 (104-1000)  $\mu\text{g/g}$  at baseline.

The median CDAI at baseline was 303.5 (128-537.6), and at the end of treatment, it decreased in most patients (61%), 235.8 (13.5-470), but without statistical significance ( $P = 0.21$ ). Regarding other inflammatory biomarkers, most patients included in the study (64%) had serum C-reactive protein (CRP) levels  $> 3$  mg/L (reference value lower than 3 mg/L), with a median of 5.91 (0.16-114) mg/L; and the ERS median was 30 (3-120) mm/h.

### Evaluation of laboratory parameters before and after treatment with ferric carboxymaltose

Hb levels increased in 93% of patients after treatment with FCM. The median Hb concentration increased from 8.5 g/dL (5.8-10) to 10.1g/dL (7.8-13.7) ( $P < 0.0001$ ) (Figure 1A). In addition, correction of anemia and/or Hb increase  $\geq 1$  g/dL was achieved in 84% of patients with just one dose of medication. Eleven patients (44%) had an increase in Hb  $\geq 2$  g/dL. Hematocrit values were within normal parameters in 16% of patients after treatment with FCM, and there was a significant increase in 88% of patients with a median concentration from 27.8% (19.7-32.29) to 33% (25.9-42.8) ( $P < 0.0001$ ) (Figure 1B, Table 2).

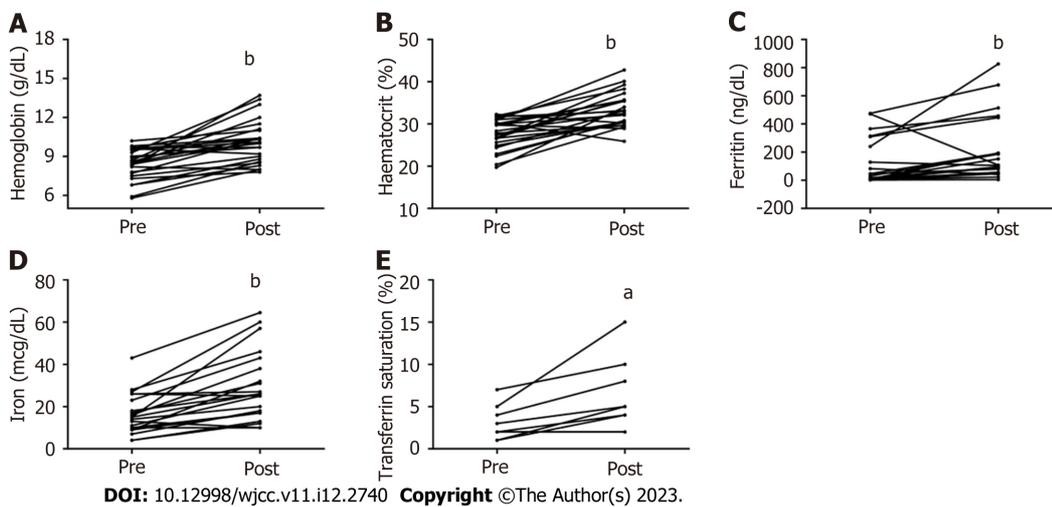
Moreover, serum iron levels increased in 18 patients (86%) after FCM injection. The median serum iron improved from 15  $\mu\text{g/dL}$  (4-43) up to 26  $\mu\text{g/dL}$  (10-64.52), demonstrating the satisfactory effect of the medication in only one application ( $P < 0.0001$ ) (Figure 1C). Ferritin increased in 86% of patients after FCM: 23.79 ng/mL (0.5-475.4) at baseline and 100.38 ng/mL (4.26-826.1) after treatment, 77% of patients showed normalization of this parameter after treatment ( $P = 0.0008$ ) (Figure 1D). Concerning the TAST, it increased under treatment with FCM, from 3.5 at the beginning of treatment (1-21) up to 9 (2-26.3) after injection ( $P = 0.01$ ) (Figure 1E, Table 2).

After a single application with iron carboxymaltose, all patients had an increase in mean corpuscular volume levels, and most reached normalization in the parameter (59%) after treatment ( $P = 0.05$ ) (Table 2). No statistical significance was found regarding the levels of Mean Corpuscular Hemoglobin, Mean Corpuscular Hemoglobin Concentration, and platelets analyzed after treatment (Table 2).

**Table 2** Evaluation of the laboratory parameters in the patients who received ferric carboxymaltose

Variables	Pre-therapy	Post-therapy	P value
Hemoglobin (mg/dL)	8.5 (5.8-10)	10.1 (7.8-13.7)	< 0.0001
Haematocrit (%)	27.8 (19.7-32.29)	33 (25.9-42.8)	< 0.0001
Ferritin (ng/dL)	23.79 (0.5-475.4)	100.38 (4.26-826.1)	0.0008
Iron (mcg/dL)	15 (4-43)	26 (10-64.52)	< 0.0001
STAT (mcg/dL)	3.5 (1-21)	9 (2-26.3)	0.01
MCV (fL)	74.6 (57.8-92.9)	80.8 (64.4-97.8)	0.05
HCM (pg)	22.3 (14.4-37.2)	23.6 (18.5-30.7)	0.15
MCHC (g/dL)	30.1 (24.9-38.8)	30.65 (26.4-33.9)	0.48
Platelets ( $\times 10^3/\mu\text{L}$ )	410 (200-888)	321 (201-708)	0.19

Numerical variables are described in the median (minimum and maximum).  $n = 25$ . Unpaired  $t$ -test (Mann Whitney) with  $P < 0.05$ . MCV: Mean Corpuscular Volume; HCM: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; STAT: Transferrin saturation.



**Figure 1** Hematological variables at baseline and after ferric carboxymaltose treatment. A: Median of hemoglobin; B: Hematocrit; C: Ferritin; D: Serum iron; E: Transferrin saturation.  $n = 25$ . Paired  $t$ -test with <sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.001$ .

Concerning the hematimetric parameters and profile of iron, ferritin, and STAT, we analyzed the associations with the clinical variables under investigation. As observed in Table 3, although all patients included in the study had baseline serum iron levels below the normal range, the baseline serum iron levels were negatively associated with patients with an ileal and colonic CD (L3) who took biologics, but positively associated with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The highest level of ferritin after the application of FCM occurred in patients who presented colonic location (L2) and fistulizing phenotype (B3). The baseline serum STAT levels were associated with patients with stenosing (B2) and fistulizing (B3) phenotypes and perianal disease (Table 3).

**Results of previous ferric hydroxide sucrose injections in this cohort**

Finally, the study aimed to assess the effects of FCM in CD patients, taking into account the previous treatment of ferric hydroxide sucrose in these patients. For this analysis, a subgroup of patients from the total cohort was included, and Hb and hematocrit levels were obtained from the medical charts. The median duration of the treatment with ferric hydroxide sucrose was 5.5 mo (1-30), and the number of applications was 12 (4-32).

The median Hb concentration increased from 8.9 g/dL (6.5-11.8) to 9.7 g/dL (7.5-13.2), and the median hematocrit levels increased from 30.4 (22.2-37.8) to 34.54 (24.8-39.29) after treatment with ferric hydroxide sucrose. However, with no statistically significant difference ( $P < 0.05$ ), this cohort comprises refractory patients to traditional iron replacement as expected. When these patients were treated with FCM, we observed increased Hb ( $P = 0.0005$ ) and hematocrit ( $P = 0.0001$ ) compared to the values

**Table 3 Multiple linear regression analysis of clinical and demographic characteristics associated with serum iron, ferritin, and transferrin saturation in Crohn's disease patients**

Variables	$\beta$ value	95%CI	P value
Serum iron levels at baseline			
Age at the diagnostic <sup>1</sup>			
A3	50.119	(15.778, 84.459)	0.004
Disease location <sup>1</sup>			
L3	-16.328	(-30.601, -2.055)	0.025
Behavior <sup>1</sup>			
B2	18.357	(4.711, 32.002)	0.008
B3	21.961	(2.931, 40.992)	0.024
Biologic therapy			
Yes	-27.271	(-53.623, -0.919)	0.043
Serum ferritin levels after FCM injection			
Disease location <sup>1</sup>			
L2	348.460	(56.087, 640.833)	0.019
Behavior <sup>1</sup>			
B3	335.922	(57.389,614.454)	0.018
STAT at baseline			
Behavior <sup>1</sup>			
B2	8.033	(1.974, 14.091)	0.009
B3	13.866	(5.762, 21.971)	0.001
Perianal disease			
Yes	10.5	(3.907, 17.092)	0.002

<sup>1</sup>Montreal classification.

Analysis of multiple linear regression with  $P < 0.05$ .  $n = 25$ . FCM: Ferric carboxymaltose; STAT: Transferrin saturation.

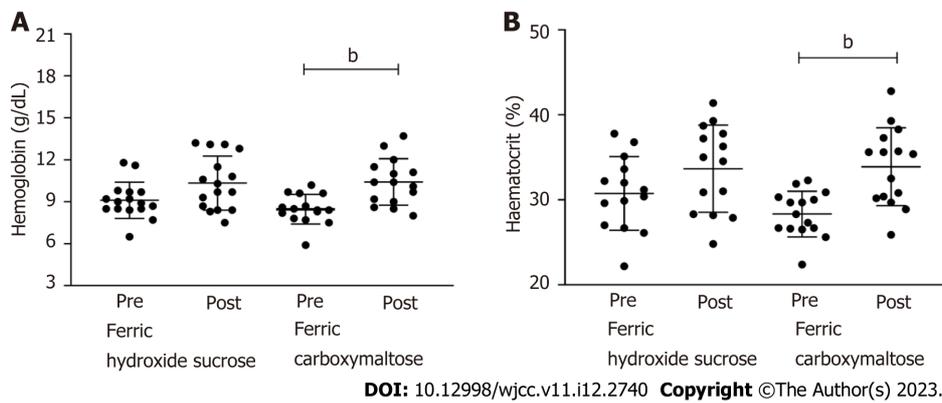
obtained before treatment. (Figure 2A and B)

## DISCUSSION

IDA is the most frequent clinical condition in CD patients. Usually, it is accompanied by the clinical and endoscopic activity of the disease, but at other times it can be the first manifestation that precedes the intestinal and abdominal symptoms and is one of the main causes of fatigue and poor quality of life. Our data demonstrated a significant improvement in Hb, iron, ferritin, and TAST levels after treatment with FCM. Although these findings have been previously proven in a few studies[10,20], our data showed significant improvement in the hematological parameters with a single dose of the medication.

Our results from the clinical practice confirmed the findings obtained by Sobrado *et al*[23], who evaluated FCM for the treatment of anemia in CD patients at a Brazilian center[23]. Although they performed a quite similar study, we included a larger number of patients treated at a tertiary center in selective and strictly defined disease activity criteria (endoscopic and/or radiological imaging). Furthermore, we compared the effects of FCM with previous ferric hydroxide sucrose treatment.

CD patients are at greater risk of developing anemia, especially with active disease[24,25]. To analyze the safety and efficacy of FCM for the anemia treatment of IBD patients, Stein *et al*[10] performed a prospective study. However, not only patients with severe CD activity were included, but also patients in remission, and the disease activity was based on rather unspecific criteria such as serum CRP, CDAI for patients diagnosed with CD, and Colitis Activity Index for patients with ulcerative colitis[11]. All patients in our study had severe disease activity determined by more specific criteria. 40% of our patients had severe activity determined by magnetic resonance enterography. The other 60% had CD activity determined by colonoscopy and fecal calprotectin. Furthermore, the median baseline CD



**Figure 2** Hematological variables at baseline and after the treatment with ferric carboxymaltose and ferric hydroxide sucrose. A: The median of hemoglobin; B: Hematocrit.  $n = 16$ . Paired  $t$ -test with  $^bP < 0.001$ .

activity assessed by the CDAI was 303.5, and CRP levels had a median of 5.91 before treatment with FCM.

Usually, assistant physicians who take care of these chronic patients neglect the importance of IDA and accept it as a consequence of CD, so they proceed without having an established protocol based on gathering information and assessing alternative resolutions that could assist the decision-making and treatment in their clinical practice. Coe *et al*[9] performed a retrospective study and concluded that gastroenterologists should consider treating patients with IBD and IDA with IV iron as it is safe and effective[9]. Our study confirms that IV medication has proved to be an important therapeutic strategy, which can help quickly and safely in the treatment of IDA when prescribed by physicians accompanying this group of patients. A suggested approach to managing patients with CD and IDA is illustrated in Figure 3.

It is important to point out that although other studies have resulted in an increase in Hb levels of  $\geq 2$  g/dL, the assessment was not done with just a single dose of medication[10,20,23]. Our study showed that 44% of patients had an increase of  $\geq 2$  g/dL with a single dose of 50 mg/mL, which demonstrates that FCM can be an important therapeutic strategy when a significant increase in parameters is needed in a short period of follow-up, either to relieve symptoms or to prepare CD patients for surgical procedures and post-surgical recovering.

Iron and ferritin serum levels increased in 86% of patients, and TAST levels increased by 50% after treatment. This early response is in agreement with previous studies that performed this assessment. However, these studies evaluated a complete response between 4 to 8 wk of treatment. Our data point to this response in most patients 15 d after treatment[20,26].

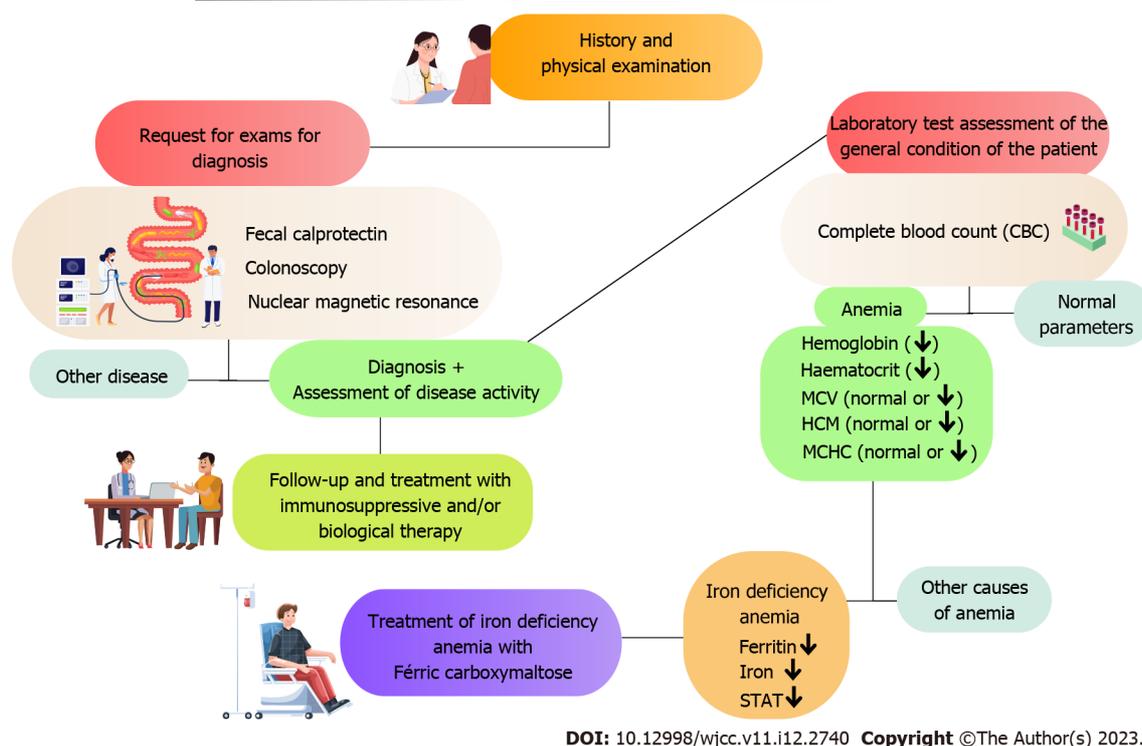
The effect of biological therapy on anemia in patients with IBD is seldom discussed in the literature. Demonstrated evidence showed a significantly improving in anemia in patients using biological therapy for other chronic inflammatory diseases such as arthritis and ankylosing spondylitis[27]. Due to chronic inflammation, anemia is usually characterized as anemia of chronic disease (ACD) in these conditions. However, although ACD is associated with IBD, the most prominent impact is due to iron deficiency, and patients have recurrent anemia even after treatment with immunomodulators[28].

A recent pediatric study showed no statistical difference in Hb levels between IBD patients who responded or did not respond to anti-Tumor necrosis factor treatment[29]. A study of adult patients with IBD demonstrated that although biological therapy had significant beneficial effects on disease activity, the research found no significant change in the prevalence of anemia. Furthermore, one-fifth of patients without anemia at baseline developed anemia after one year of therapy[30]. Our results are in agreement with these recent studies. We demonstrated that although patients had iron levels below normal at baseline, the use of biological therapy had a negative correlation with baseline serum iron levels, indicating that these patients had more severe anemia.

A study evaluating anemia in Korean patients with IBD found no significant association between patients' clinical characteristics and anemia[31]. Bergamaschi *et al*[32], in 2010, did not relate anemia in CD to the location or behavior of the disease[32]. In 2020, a study analyzed the prevalence and risk factors of anemia and iron deficiency in patients with IBD in Brazil and concluded that patients with the penetrating disease phenotype in CD were associated with a lower risk of anemia[33]. Our study demonstrates that patients with an ileal and colonic location correlate negatively with basal serum iron levels, demonstrating more severe anemia. Patients with stenosing and fistulizing phenotypes positively correlated with baseline serum iron levels and TAST.

We also compared treatment effects with FCM and previous treatment with ferric hydroxide sucrose. We observed no statistical difference in Hb and hematocrit levels after treatment with ferric hydroxide sucrose, while those levels showed a significant increase with a single dose of FCM. Although other studies evaluated the efficacy of the two medications[9,34], our study compared the efficacy of the

## Clinical management for patients with Crohn's disease and iron deficiency anemia



**Figure 3 Suggested clinical management to the patient with Crohn's disease and iron deficiency anemia.** MCV: Mean corpuscular volume; HCM: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; STAT: Transferrin saturation.

treatment in the same group of patients, demonstrating that FCM is an important therapeutic strategy in refractory patients who received ferric hydroxide sucrose.

The present study reported a median of 12 applications (4-35) with previous treatment with ferric hydroxide sucrose. However, when the same patients were treated with FCM, a single infusion guaranteed a significant increase in the hematological parameters. Evstatiev *et al*[34] reported in their study treatment with 1 to 3 infusions of FCM, while the ferric hydroxide sucrose treatment lasted 11 infusions[34]. Onken *et al*[35] also showed a similar result; patients treated with ferric sucrose received an average of 5 infusions, while patients treated with FCM underwent two infusions[35].

Thus, CD patients can be exposed to fewer interventions since FCM has better efficacy with a significant increase in hematological parameters, as well as iron, ferritin, and TAST levels with usually a single dose. The consequence is a decreased number of patients' visits to hospitals or private clinics, contributing to the quality of life and emotional well-being.

Currently, the value of an ampoule of FCM (+/- R\$ 641.90 - Brazilian currency) is approximately 10 times more expensive than an ampoule of ferric hydroxide sucrose (+/- R\$ 64.70 - Brazilian currency), which restricts patient adherence to treatment since this medication is not available by the Unified Health System through State Public Pharmacies in Brazil. However, studies indicate that as a final result of the treatment, FCM has a lower cost when compared to ferric sucrose. Vicente *et al*[36] concluded that the overall cost of FCM treatment is significantly advantageous compared to ferric hydroxide sucrose, such as the relatively lower number of infusions of FCM and the quick increase of serum Hb levels after iron replacement[36].

Toblli and Di Gennaro[24] in 2015, evaluated the economic impact of oral iron replacement treatment *vs* FCM in patients with chronic kidney disease. As a result, the study demonstrated that the cumulative cost during the 6 mo study period with FCM was United States \$ 3.070 per patient, whereas compared to oral iron administration over the same period, the cost was US \$ 17.670. The study also found that using FCM to treat IDA resulted in savings of US \$ 14.600 (82.6%) per patient[24].

Another study published in 2021 by Aksan *et al*[37] analyzed and compared the cost-effectiveness of IV and oral iron treatment in patients with IDA associated with IBD and concluded that FCM is designed to be the most cost-effective IV iron therapy in Switzerland and with better clinical response to treatment[37]. Basha *et al*[25] in 2021 evaluated the efficacy and cost-effectiveness of FCM *vs.* iron sucrose. The retrospective study assessed patients who were followed up for 12 mo in a tertiary center, and as a result, although the cost of the medication FCM is 6.5 times higher than iron sucrose, at the end of the period, the treatment with FCM has a lower cost in bed or nursing[25]. Table 4 shows the main characteristics differentiating FCM from iron sucrose[38,39].

**Table 4** Main features of ferric carboxymaltose versus iron hydroxide sucrose

	<b>Ferric carboxymaltose[38]</b>	<b>Iron hydroxide sucrose[39]</b>
Concentration	Up to 20 mL corresponding to 1000 mg of iron	10 mL corresponding to 200 mg of iron
Dosage	1 time a week	1 to 3 times a week (depending on hemoglobin level)
Infusion time	Up to 200 mg of iron - there is no established administration time from 200 mg to 500 mg of iron - the rate of 100 mg per minute above 500 mg up to 1000 mg of iron -66 mg per min	Up to 200 mg of iron - 6.6 mg per min, 300 mg of iron - 3.3 mg per min, 400 mg - 2.6 mg per min, 500 mg - 2.3 mg per min
Molecule	Stable iron is in the form of a complex of non-dextran iron with a polynuclear ferric hydroxide core with a carbohydrate linker. Because of the high stability of the complex, there is only a small amount of weakly bound iron (also called free iron). The structure of the nucleus is similar to that of ferritin, so the complex is intended to provide a controlled supply of usable iron for ferric transport and storage of proteins in the body	Trivalent form as a macromolecular colloidal complex of ferric hydroxide saccharate. The polynuclear ferric hydroxide core is superficially surrounded by a large number of non-covalently linked sucrose molecules, resulting in a complex whose molecular mass is approximately 43 kDa
Pharmacokinetics	After administration of a single dose of iron carboxymaltose of 100 to 1000 mg of iron in patients with anemia, peak serum iron concentrations were between 37 and 333 mcg per mL	After the injection of 100mg of iron in healthy individuals, the maximum plasma concentration, on average, of 538 µmol per L, 10 min after the injection
Volume of distribution	The volume of distribution of the central compartment corresponds to the plasma volume (approximately 3 L). It is retained mainly in the reticuloendothelial system of the bone marrow, liver, and spleen. The average residence time varied between 11 and 17 h	The central compartment volume of distribution correlates well with serum volume (approximately 3 L). The volume of distribution at a steady state was about 8 L, which indicates the low distribution of iron in body fluids
Half-life	7 and 12 h	6 h
Route of administration	Intravenous injectable solution	Intravenous injectable solution

The literature demonstrates the effectiveness of FCM in many diseases. Several studies have shown the important role that medication performs in cardiovascular diseases[40,41]. However, in the gastrointestinal tract, few studies have analyzed the effectiveness of FCM, especially in CD. Thus, our study contributed to a greater understanding of medication use in this disease, helping clinical practice.

The limitations of our study lay in the retrospective character of the research, as data collected through electronic medical records or outpatient databases may be scarce. As described above, we could only analyze the serum levels of Hb and hematocrit in comparing the two medications. Another limitation is that the study evaluated a small number of patients despite being larger than other Brazilian studies. In addition, it was neither possible to correlate the degree of CD activity through the CDAI, CRP, and erythrocyte sedimentation rate values with the severity of anemia nor to determine if the increase of the hematological parameters after FCM treatment correlates with an improvement in quality of life assessed by validated questionnaires, such as IBD Questionnaire[29].

## CONCLUSION

From the analysis performed in this retrospective study, a better understanding of the effects of FCM in the treatment of IDA in CD patients has emerged. The study also showed that FCM is an important therapeutic strategy, as it achieves superior results compared to the administration of iron hydroxide sucrose in patients with refractory IDA. However, there are still many gaps to be addressed in future studies about the molecular mechanism of IDA in CD. We do not yet know if IV iron replacement, besides improving the patient's quality of life and well-being, can affect the activity of the disease and help the patient to enter clinical and endoscopic remission. Our findings support FCM as an important therapeutic strategy to treat anemia and improve CD patients' clinical status.

## ARTICLE HIGHLIGHTS

### Research background

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract, and anemia is one of the clinical manifestations. Iron deficiency anemia (IDA) in CD is due to chronic blood loss from the ulcerated intestinal mucosa associated with diarrhea, decreased iron intake due to dietary restriction, and/or deficiency in transluminal iron absorption during the disease activity. Currently, intravenous (IV) iron replacement is the best option for the treatment of IDA in CD. Recent pharmacology progress has led ferric carboxymaltose (FCM) to correct the IDA through its pharmacokinetic characteristics.

**Research motivation**

The administration of FCM can be performed in high doses safely and well-tolerated. Given that, this study was designed to evaluate the effectiveness of FCM in the treatment of IDA in CD patients in a tertiary center in Brazil, where inflammatory bowel disease has become increasingly frequent. This clinical approach can make the quality of life of CD patients better.

**Research objectives**

The objective of this study was to analyze, through medical records, the clinical and epidemiological data of a cohort of patients with active CD who received IV FCM in the treatment of IDA to elucidate the effectiveness of the drug and compare it to iron hydroxide sucrose treatment.

**Research methods**

It is a retrospective, observational study, which included 25 patients with active CD, severe anemia, and refractory to previous conventional treatments. Patients were evaluated two times: During previous treatment with ferric hydroxide sucrose and treatment with FCM. Epidemiological and clinical data were analyzed, besides hematimetric parameters.

**Research results**

The parameters of IDA assessment significantly improve after treatment with FCM. Serum hemoglobin (Hb) levels increased in 93% of patients, and in 44%, there was an increase of  $\geq 2$  g/dL in a single application. Moreover, 86% of the patients showed increased serum iron and ferritin and 50% in transferrin saturation. The serum iron levels at baseline showed a negative association with the ileal and colonic CD and use of biologics and a positive association with patients who developed CD later in life after the age of 40 (A3) and with a stenosing (B2) and fistulizing (B3) phenotype. The Hb and hematocrit values after ferric hydroxide sucrose treatment remained similar to those found before treatment.

**Research conclusions**

FCM is an important therapeutic strategy for treating IDA in CD patients, achieving satisfactory results in refractory cases.

**Research perspectives**

The study showed that FCM is an important therapeutic strategy to treat IDA in CD patients. However, there are still many gaps to be addressed in future studies about the molecular mechanism of IDA in CD. We do not yet know if IV iron replacement, besides improving the patient's quality of life and well-being, can affect the activity of the disease and help the patient to enter clinical and endoscopic remission. Our findings support FCM as an important therapeutic strategy to treat anemia and improve the clinical status of CD patients.

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**ACKNOWLEDGEMENTS**

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We thank Professor Torriani T for revising the English version of our manuscript and Professor Azevedo AT for revising the statistical methods of this study.

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**FOOTNOTES**

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**Author contributions:** Siqueira NSN, Castro MM, Martins ASC, and Araújo DOS were responsible for collecting the data; Siqueira NSN, Pascoal LB, Castro MM, and Gomes LEM plotted and analyzed the data; Siqueira NSN, Leal RF, Pascoal LB, and Castro MM contributed to interpreting the results; Leal RF conceived the study and performed the final revision of the manuscript; All authors contributed to the writing and revised the manuscript; All authors read and approved the final manuscript.

**Supported by** the National Council for Scientific and Technological Development (CNPq), No. 302557/2021-0 (to Leal RF), the Brazilian Coordination for the Improvement of Higher Education Personnel [CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), Brazil], No. 001 (to Siqueira NSN), and the São Paulo Research Foundation (FAPESP), No. 2021/02997-9 (to D.O.S.A.).

**Institutional review board statement:** The study was approved by the University of Campinas Ethics Committee, No. CAAE:56915516.6.0000.5404.

**Informed consent statement:** Patients were informed, but written consent was waived due to the retrospective methodology of the study. All efforts were made to ensure data confidentiality, as required by the Ethics Committee. This study was performed in accordance with the Declaration of Helsinki, good clinical practice, and applicable

regulatory requirements.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** The data used to support the findings of this study are included within the article. No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement checklist of items, and the manuscript was prepared and revised according to the STROBE Statement checklist of items.

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**S-Editor:** Li L

**L-Editor:** A

**P-Editor:** Zhang YL

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