

TREATMENT OF ANEMIA AND IMPROVEMENT OF QUALITY OF LIFE AMONG PATIENTS WITH CROHN'S DISEASE: experience using ferric carboxymaltose

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ABSTRACT - Objectives - Anemia is the most common hematological alteration in patients with Crohn's disease, and is frequently related to intestinal inflammatory activity. Its cause is multifactorial and mostly associated with absolute iron deficiency (iron deficiency anemia) and/or functional iron deficiency (inflammation anemia or anemia of chronic disease). It may also be identified through other causes, such as folic acid or vitamin B12 deficiency and secondary to adverse effects from medications (salicylic derivatives and immunosuppressive drugs). In the present study, patients with active Crohn's disease and anemia were evaluated and treated with intravenous ferric carboxymaltose. We discuss the therapeutic schemes (doses), safety, results and improvement of quality of life. **Methods** - In the present prospective study, 10 consecutive patients with Crohn's disease, with moderate to severe activity, with anemia (Hb: 6.7 to 10 g/dL), who were attended between March 2014 and March 2015, were evaluated. Six (60%) were men and four were women, all with moderate or severe anemia (hemoglobin <10 g/dL). They were treated with a maximum of three intravenous infusions of 1000 mg of ferric carboxymaltose, of at least 15 minutes in duration. It was also sought to correlate the inflammatory Crohn's disease activity degree (measured using the Crohn's Disease Activity Index, CDAI) and C-reactive protein level with the severity of anemia. The primary outcome was an increase in Hb of ≥ 2 g/dL and the secondary outcome was the normalization of anemia (Hb ≥ 12 g/dL for women and ≥ 13 g/dL for men) and the improvement in quality of life seen 12 weeks after the last application of carboxymaltose. **Results** - Among the 10 patients studied, parenteral iron supplementation was administered in three cases during hospitalization and the others received this on an outpatient basis. The total iron dose ranged from 1,000 to 2,000 mg, with an average of 1,650 mg. Crohn's disease activity measured using CDAI and C-reactive protein correlated with the intensity of anemia. An increase of 2 g/dL occurred in eight (80%) patients after 12 weeks and normalization of anemia was found in seven (70%) patients. Improvements in quality-of-life scores were found for all (100%) patients after 12 weeks. Carboxymaltose was well tolerated. Three patients presented adverse reactions (two with nausea and one with headache) of mild intensity. **Conclusions** - Anemia is a frequent complication for Crohn's disease patients. Intravenous iron therapy has been recommended for Crohn's disease patients, because for these patients, oral iron absorption is very limited. This is because of the inflammatory state and "blocking" of iron entry into enterocytes through hepcidin action on ferroportin, along with the elevated rates of gastrointestinal adverse events that compromise adherence to treatment and possibly aggravate the intestinal inflammatory state. The degree of Crohn's disease activity, as measured using CDAI and C-reactive protein, correlates with the severity of anemia. Carboxymaltose is a safe drug, which can be administered in high doses (up to 1,000 mg per application per week) and corrects anemia and iron stocks over a short period of time, with consequent improvement in quality of life.

HEADINGS - Iron-deficiency anemia. Crohn disease. Intravenous injections. Iron. Quality of life.

INTRODUCTION

Anemia is one of the main systemic manifestations associated with Crohn's disease (CD), with prevalence rates of the order of 6% to 73%⁽¹³⁾. This wide variation results from various factors: hemoglobin cutoff levels, patients studied (hospitalized or outpatients), presence or absence of active disease and whether the patient is already under adequate treatment for the underlying disease (immunosuppressive and/or biological drugs), among others. Anemia, just like malnutrition, is a

frequent complication in CD that negatively affects patients' quality of life. Therefore, it should always be investigated when diagnosing inflammatory bowel disease, and when present, treated early⁽⁵⁾.

The etiology of anemia relating to CD is multifactorial, but iron deficiency is the most common cause, present in 80% to 90% of patients⁽²⁴⁾. This iron deficiency anemia is consequent to chronic bleeding from the digestive tract, dietary restrictions, poor intestinal absorption and myelotoxic drug use that alters erythropoiesis. Furthermore, anemia may result

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from chronic inflammatory processes (inflammation anemia or anemia of chronic disease anemia) in which alterations to iron metabolism, erythropoiesis and red blood cell survival are found, caused by pro-inflammatory mediators such as: tumor necrosis factor alpha (TNF-alpha), interleukins (IL-1, IL-6 and IL-10) and interferon delta (INF-delta). These mediators of inflammation stimulate hepcidin synthesis, thereby reducing serum iron levels and interfering in erythropoiesis and iron absorption and metabolism. TNF-alpha inhibits the production of erythroid progenitors (BFU-E), decreases intestinal absorption and blocks iron output from macrophages and monocytes. In conclusion, in situations of anemia of chronic disease, functional iron deficiency occurs such that despite the abundance of iron in the organism, it remains "stuck" inside phagocytes (macrophages and monocytes), and unavailable for erythropoiesis^(12, 18). Anemia of inflammation (anemia of chronic disease) may be related to iron deficiency, in patients with inflammatory bowel disease. Other causes can also be present in cases of CD-related anemia, such as: vitamin deficiency (folic acid and vitamin B12), use of myelotoxic medications (sulfasalazine, azathioprine and 6-mercaptopurine) and hemolytic and autoimmune anemia, among others⁽⁷⁾. Patients with active CD are generally associated with greater severity of anemia, and adequate treatment of the inflammatory process together with iron supplementation parenterally are fundamental stages for therapeutic success^(3, 8, 21). Diagnosing anemia in patients with intestinal inflammatory disease should be done through the following tests: hemogram (Hb, VCM and CHCM), transferrin saturation, serum ferritin and C-reactive protein. Other tests may be necessary (assays on folic acid, vitamin B12, haptoglobin, creatinine, reticulocytes, serum hepcidin and soluble transferrin receptor (sTfR), and the ratio between sTfR and ferritin), which must be requested in cases with diagnostic difficulty or when the initial therapy is unsuccessful. To evaluate inflammatory activity in CD cases, there are clinical parameters (CDAI – Crohn's Disease Activity Index and Harvey-Bradshaw index), laboratory parameters (VHS, C-reactive protein and fecal calprotectin) and endoscopic parameters (colonoscopy). The treatment consists of intravenous iron supplementation, and an adequate response is defined as an increase in hemoglobin level of at least two points after an interval of 2 to 4 weeks. Bergamaschi et al. observed that patients with inflammatory bowel disease who responded well to biological therapy presented early improvement of their anemia. They reported that there were significant improvements in Hb levels and CDAI, 14 days after the first application of anti-TNF.

In the present study, on 10 patients with Crohn's disease and anemia, we aimed to classify the degree of CD activity measured using CDAI and C-reactive protein assays, in relation to the severity of anemia. All of the patients were medicated with ferric carboxymaltose, at an average dose of 1,650 mg of iron (range: 1,500 to 2,000) and were reevaluated 12 weeks after the last application. As the primary outcome, it was sought to evaluate increases in Hb of at least 2 g/dL; and as the secondary outcome, the normalization of anemia and improvement in quality-of-life score.

METHODS

A prospective analysis was performed on 10 consecutive patients with Crohn's disease who presented severe anemia (Hb <10 g/dL), according to the definition set by the World Health Organization. These patients were subjected to iron supplementation parenterally, with ferric carboxymaltose. All of the patients signed an informed consent statement and the study was approved by the Hospital's Ethics Committee. Three patients received intravenous carboxymaltose (FC) during hospitalization and seven were treated as outpatients. To diagnose iron deficiency anemia, the following laboratory tests were performed: complete blood count, serum iron, total iron binding capacity and serum ferritin. The transferrin saturation index (TSI) was calculated using the formula: (iron/total iron binding capacity) x 10. The diagnosis of iron deficiency anemia was defined as Hb <12 g/dL for women and <13 g/dL for men; TSI <20%; and serum ferritin <30 ng/mL. The diagnosis of anemia of chronic disease was defined as Hb <12 g/dL for women and <13 g/dL for men; and TSI <20%, regardless of the value of serum ferritin, as long as it was <300 ng/mL, generally associated with an increase in C-reactive protein.

All the patients with CD were evaluated and the degree of clinical activity was determined based on the Crohn's disease activity index (CDAI), which was correlated with the C-reactive protein laboratory assay⁽⁴⁾. The clinical and laboratory tests were performed 1 to 2 weeks prior to intravenous iron treatment, and were repeated 12 weeks after the last infusion. It is important to note that none of the patients participating in this study presented abscesses, sepsis, intestinal stenosis or other conditions (neoplasia, blood disease or chronic kidney failure) that might have interfered with erythropoiesis. All the patients received ferric carboxymaltose intravenously, with an average dose of 1650 mg (range: 1,500 to 2,000), from which the iron replacement dose was calculated according to the table below (Table 1).

Ferric carboxymaltose was administered intravenously, diluted in 250 mL of sterile sodium chloride solution at 0.9% m/V, and was infused over a 15-minute period.

In order to study quality-of-life after FC treatment, the Inflammatory Bowel Disease Questionnaire (IBDQ) was used. This questionnaire was used because it presents good reproducibility and reflects important alterations to the state of health of patients with inflammatory bowel disease, thus making it fully usable for investigating the impact and efficiency of therapeutic measures^(9, 10). The IBDQ was applied

TABLE 1. Table used to determine cumulative iron dose that needed to be replaced using ferric carboxymaltose. The dose was calculated based on body weight and hemoglobin level

Hemoglobin	Body weight from 35 to 70 kg	Weight above 70 kg
<10 g/dL	1,500 mg	2,000 mg
≥10 g/dL	1,000 mg	1,500 mg

during the 48 hours prior to parenteral iron supplementation, and was then repeated after three months. After these 12 weeks, the participants were reevaluated to analyze the primary outcome, i.e. whether the respondents presented an increase in Hb of two or more points, in comparison with the previous levels. For the secondary outcome, it was sought to evaluate whether anemia had become normalized: for women, Hb ≥ 12 g/dL and for men, Hb ≥ 13 g/dL; serum ferritin > 100 ng/mL; and transferrin saturation: 20% to 40%, at week 12. Also in relation to the secondary outcome, the patients were evaluated in relation to changes in quality of life, from before to after ferric carboxymaltose infusion. The patients were reevaluated every two weeks, with the objective of analyzing the clinical and laboratory response and adverse events.

RESULTS

All ten patients (6 males and 4 females), of average age 37.5 years (range: 20 to 67 years of age) received the programmed FC infusions. Patients with higher C-reactive protein and higher CDAI presented greater severity of anemia with lower Hb and TSI levels. The demographic data, disease activity indexes and laboratory results from the patients are presented in Table 2. FC was well tolerated: only three patients presented adverse reactions (two with nausea and one with headache), of mild intensity with spontaneous improvement, without the need for intervention or suspension of the treatment.

All the patients presented active disease, with CDAI of more than 150 points, and were being treated (seven with immunosuppressants, six with biological agents and three with sulfasalazine). All the patients presented severe anemia (Hb < 10 g/dL), unrelated to disease duration. The degree of CD activity and C-reactive protein level correlated with the severity of the anemia. Patients who responded to drug treatment for CD, with clinical improvement and a decrease in the modified CDAI, responded better to iron therapy.

This correlated with the C-reactive protein data. No correlation was observed between the locations of CD lesions (small or large intestine) and the degree of anemia.

After intravenous infusion of FC, eight patients achieved Hb elevation by at least 2 points and anemia normalization occurred in seven patients (70%). In relation to the quality-of-life evaluation using IBDQ, there was a surprisingly good improvement in all domains, 12 weeks after the treatment. The average score among the patients before iron supplementation was 145.5, and this increased to 178.1, thus indicating that there had been a substantial improvement in quality of life, in the four domains (intestinal, systemic, social and emotional symptoms). In all patients there was an increase in IBDQ score.

All the statistical analyses were performed using Excel 2007 for Windows. The data and the variables before and after infusion of ferric carboxymaltose are presented in Table 2. All the numerical variables were compared using the paired Student's *t* test, in which differences were considered significant when the *P* value was lower than 0.05 ($P < 0.05$).

DISCUSSION

Anemia in Crohn's disease patients is a common systemic manifestation that is generally caused by iron deficiency and chronic inflammatory processes. In the presence of active disease, the levels of pro-inflammatory cytokines increase, thereby altering erythropoiesis and aggravating the anemic condition. Although anemia is related to CD activity and the hematocrit level is part of the CDAI criteria for defining active disease, the erythrocyte data are not taken into consideration and have been undervalued at the time of making the diagnosis.

In the present study, the degree of activity of this disease was associated with lower levels of hemoglobin, and this has also been reported by other studies^(3, 21). The three patients who required hospitalization due to clinical worsening presented CDAI greater than 250 (253, 269 and 305) and all

TABLE 2. Clinical and laboratory data on patients with Crohn's disease before and after treatment with intravenous iron supplementation

Hemoglobin (g/dL)	Before: 9.1 +/- 1.2	After: 12.3 +/- 1.8	<i>P</i> < 0.001
Ferritin (mcg/L)	115 +/- 87	49 +/- 38	<i>P</i> < 0.02
Transferrin saturation index (%)	9 +/- 6	21 +/- 12	<i>P</i> < 0.005
VHS (mm/h)	42 +/- 22	14 +/- 11	<i>P</i> < 0.001
C-reactive protein (mg/dL)	15.21 +/- 6.27	3.60 +/- 2.11	<i>P</i> < 0.001
CDAI score	219 +/- 83	101 +/- 37	<i>P</i> < 0.007
IBDQ score	145.5 (97 to 177.8)	178.1 (151.9 to 193.3)	<i>P</i> < 0.01

IBDQ: Inflammatory Bowel Disease Questionnaire.

of them had Hb levels lower than 8.5 g/dL. In cases of active disease, there are also large increases in acute-phase protein levels, especially C-reactive protein, as found in the present study. These were correlated with anemia levels and also with CDAI. This was expected, since active inflammation in CD patients leads to decreased iron absorption and increased urinary hepcidin excretion⁽²¹⁾. However, no relationship between disease duration and hemoglobin levels was found, which was also reported by Bergamaschi et al. These authors observed higher levels of anemia at the time of making the diagnosis, with a decrease over their 4 years of follow-up. No correlation was found between the locations involved in the gastrointestinal tract and the hemoglobin levels. Half of the patients had ileocecal involvement (three with jejunal-ileal lesions), three presented colic and perineal region involvement and two presented small intestine involvement. No relationship was found with the degree of anemia. Since iron is absorbed in the duodenum and folates in the duodenum and jejunum, in cases with involvement of the upper third of the small intestine, deficient absorption of these nutrients is to be expected^(11, 19).

In the present study, only three patients presented jejunal-ileal involvement, and no higher degree of anemia was found in this group, possibly due to the size of the sample. In pediatric patients with Crohn's disease, involvement of the upper gastrointestinal tract occurs in approximately 30% to 40%, unlike in adults, among whom this occurs in 0.5% to 4% of the cases^(16, 20).

Iron deficiency anemia is recognized through the presence of low levels of serum iron, transferrin saturation (<20%) and ferritin (<30 mcg/L), and was found in five patients of our series. The presence of low hemoglobin levels in CD patients with clinical and biochemical evidence of inflammatory process (elevated CDAI and C-reactive protein), in association with increased serum ferritin (>100 mcg/L) and low transferrin saturation (<20%), are characteristics of anemia of chronic disease, which was found in three of our patients. If serum ferritin values are between 30 and 100 mcg/L and transferrin saturation is lower than 20%, there is a combination of anemia of chronic disease and iron deficiency anemia, and this was present in two of our patients. Treatment can be started in all patients with hemoglobin below normal values, and its objective is to normalize Hb levels, replace iron stocks and, obviously, improve the quality of life. It is important to note that physicians tolerate low hemoglobin levels better than patients do, i.e. they do not give much value to many frequent complaints from anemia patients, in which they aim to justify symptoms (asthenia, weakness, dizziness, nausea, flatulency, etc) as always coming from an underlying disease and not being a consequence of hemoglobin deficit. The guidelines recommend that treatment with oral iron supplementation should be started when hemoglobin levels are above 10 g/dL. Among patients with intolerance or lack of response to oral iron, or when hemoglobin levels are below 10 g/dL, use of intravenous iron is indicated. All of the patients in the present study presented Hb <10 g/dL and were treated with parenteral iron, using

ferric carboxymaltose. The patients received FC at an average dosage of 1,650 mg of iron (range: 1,000 to 2,000 mg), with a maximum of three infusions. FC is an intravenous iron preparation that can be administered at high doses in one simple application, of up to 1,000 mg of iron in 15 minutes, without the need for a test dose. It has been recommended for treatment of iron deficiency in various situations, such as: inflammatory bowel diseases, postpartum, uterine bleeding, post-bariatric surgery, orthopedic operations, chronic kidney failure and cardiac failure, among others, with good results, good efficiency and few side effects^(1, 14, 15, 22, 23). FC was well tolerated by our patients, and only three adverse events were observed, all of mild intensity and transitory, comprising two cases of headaches and one of nausea. The safety of FC treatment has been shown by other authors, who reported that the most common side effects are hyperferritinemia and transitory hyperphosphatemia, which was not observed in the present study⁽⁶⁾. FC administration increased the Hb rate by more than 2 g/dL in 8/10 patients (80%), 12 weeks after treatment. In relation to the secondary outcome, normalization of hemoglobin levels (Hb >12 g/dL in women and Hb >13 g/dL in men) was found in 7/10 (70%) and normalization of transferrin saturation (20% to 50%) was found in 6/10 (60%). The evaluation of quality of life using the IBDQ score, which was performed before and after intravenous iron administration, showed improvement in all domains after ferric carboxymaltose therapy. Gasche et al. showed that parenteral iron administration is more effective than oral administration, besides providing greater improvement in quality of life⁽⁸⁾. Other studies have confirmed that improvements in quality of life and in cognitive functions occur with increases in hemoglobin levels⁽²⁵⁾.

These patients have been monitored through both clinical and laboratory tests every 3 months, with the objective of avoiding recurrence of iron deficiency. Besides prevention of anemia recurrence, it is of great importance to avoid iron overload, which may occur when ferritin levels are over 500 mcg/L and transferrin saturation is over 50%⁽⁸⁾. Iron overload not only is toxic but also can affect and worsen the inflammatory status, thereby increasing intestinal mucosa permeability, activating NF- κ B and recruiting neutrophils^(2, 17).

CONCLUSION

In conclusion, the present study showed that the degree of CD activity measured through CDAI and C-reactive protein shows good correlation with the severity of anemia. Treatment of anemia in CD patients by means of ferric carboxymaltose is safe and corrects hemoglobin levels and iron stocks over a short period of time, with consequent improvement in quality of life.

Authors' contributions

Sobrado CW: protocol/project development, data collection and management. All authors contributed significantly to the analysis, literature review and writing of the final submitted version, and share responsibility for the contents of this paper.

Sobrado CW, Cançado RD, Sobrado LF, Frugis MO, Sobrado MF. Tratamento da anemia e melhora da qualidade de vida em portadores de doença de Crohn: experiência com carboximaltose férrica. *Arq Gastroenterol.* 2015;52(4):xxx.

RESUMO - Objetivos - Anemia é a alteração hematológica mais comum em portadores de doença de Crohn, estando frequentemente relacionada à atividade inflamatória intestinal. Sua causa é multifatorial, está associada na maioria das vezes com deficiência absoluta de ferro (anemia ferropriva) e/ou deficiência funcional de ferro (anemia da inflamação ou anemia de doença crônica), podendo também ser identificadas outras causas como deficiência de ácido fólico ou vitamina B₁₂ e secundária a efeitos adversos de medicamentos (derivados salicílicos e imunossupressores). Neste trabalho, avaliamos portadores de doença de Crohn em atividade com anemia que foram tratados com carboximaltose férrica endovenosa, e discutimos os esquemas terapêuticos (doses), a segurança e os resultados, assim como a melhora da qualidade de vida. **Métodos** - Neste estudo prospectivo, avaliamos 10 consecutivos pacientes portadores de doença de Crohn de moderada a grave atividade com anemia (Hb: 6,7 a 10 g/dL) que foram atendidos no período de março de 2014 a março de 2015. Eram seis (60%) do sexo masculino e quatro do sexo feminino, todos com anemia moderada ou grave (hemoglobina <10g/dL), tratados com no máximo três infusões de 1000 mg de carboximaltose férrica por via endovenosa em, pelo menos, 15 minutos. Procurou-se também correlacionar o grau de atividade inflamatória da doença de Crohn (mensuração realizada com o IADC-índice de atividade da doença de Crohn) e dosagem da proteína C reativa com a gravidade da anemia. O desfecho primário foi aumento da Hb de ≥ 2 g/dL e desfecho secundário a normalização da anemia (Hb ≥ 12 g/dL para mulheres e ≥ 13 g/dL para homens) e melhora na qualidade de vida após 12 semanas da aplicação da última dose de carboximaltose férrica. **Resultados** - Dos 10 pacientes estudados, em 3 a suplementação parenteral de ferro foi realizada durante internação hospitalar, o restante em regime ambulatorial. A dose total de ferro administrada variou de 1.000 a 2.000 mg, sendo a média de 1.650 mg. A atividade da doença de Crohn mensurada pelo IADC e pelo PCR se correlacionou com a intensidade da anemia. O aumento de 2 g/dL ocorreu em oito (80%) pacientes após 12 semanas e a normalização da anemia foi observada em sete (70%). Melhora do escore de qualidade de vida foi observada em todos (100%) após 12 semanas. A carboximaltose férrica foi bem tolerada, três pacientes apresentaram reações adversas (2 – náusea e 1 – cefaléia) de leve intensidade. **Conclusões** - Anemia é uma complicação frequente em portadores de doença de Crohn. A terapia com ferro por via endovenosa tem sido a recomendada em portadores de doença de Crohn, pois nestes pacientes a absorção do ferro oral é bastante limitada devido ao estado inflamatório e “bloqueio” da entrada de ferro nos enterócitos por ação da hepcidina sobre a ferroportina, além das elevadas taxas de eventos adversos gastrointestinais que comprometem a adesão ao tratamento e podem agravar o estado inflamatório intestinal. O grau de atividade da doença de Crohn mensurado pelo IADC e PCR se correlaciona com a severidade da anemia. A carboximaltose férrica é uma droga segura, pode ser administrada em altas doses (até 1.000 mg por aplicação por semana), corrige a anemia e os estoques de ferro em curto espaço de tempo, com consequente melhora da qualidade de vida.

DESCRITORES - Anemia ferropriva. Doença de Crohn. Injeções intravenosas. Ferro. Qualidade de vida.

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