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AN OVERVIEW OF BENEFITS AND SIDE EFFECTS OF CARBOXYMALTOSE INJECTION

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Abstract

Iron deficiency is widespread in many medical problems. Ferric carboxymaltose is a new stable iron preparation that can be given in single infusions over short time intervals. Between July and October 2022, a narrative literature review was conducted for published RCTs on the usage of ferric carboxymaltose and its benefits and drawbacks. All intravenous iron preparations now available appear to be safe and effective, although ferric carboxymaltose appears to provide a better and faster.

Keywords*: carboxymaltose, Iron deficiency.*

INTRODUCTION

Iron deficiency (ID) is the most common nutritional condition worldwide, affecting the majority of preschool children and pregnant women in developing countries and at least 30-40% in developed countries [1, 2]. This syndrome is also common in a variety of therapeutic domains, particularly in individuals with chronic disease (such as inflammatory bowel disease and chronic kidney disease). Chronic blood loss, decreased dietary intake, decreased intestinal absorption, or poor utilisation of endogenous iron due to chronic inflammation can all lead to ID [3]. Fatigue, vulnerability to stress, lack of attention, and underperformance are common symptoms of ID. In addition to being the most frequent cause of anaemia worldwide, ID is associated with an increased risk of infections [3]. The WHO defines anaemia as haemoglobin (Hb) levels of 12 g/dl in non-pregnant women and 13 g/dl in men [2,4]. Iron deficiency anaemia (IDA) affects 2-5% of adult men and postmenopausal women in developed nations and is a leading cause of hospitalization, morbidity, and quality-of-life impairment [4].

Treatment for anaemic patients should include immediate iron supplementation as well as diagnostic efforts aimed at determining the underlying cause of IDA [5]. Non-anemic people with low blood ferritin concentrations and tiredness symptoms may benefit from iron therapy as well [6]. Oral iron supplementation is typically the first line of treatment for iron deficiency; however, intravenous iron may be better suited for patients who are unable to tolerate oral iron intake due to gastrointestinal side effects or whose chronic iron loss exceeds the replacement rate achievable with oral therapy [7]. Parenteral iron formulations are also used when there is a requirement for rapid iron administration, such as during pregnancy or after trauma, or when blood transfusions should be avoided [8]. The earliest iron intravenous preparations were linked to acute toxicity caused by free iron release. Nowadays, all parenteral medicines are designed so that each iron particle is surrounded by a carbohydrate molecule, allowing for gradual

iron release and limiting toxicity. High or low molecular weight iron dextran, ferric gluconate, iron sucrose, and, more recently, ferric carboxymaltose are currently used in intravenous iron formulations [9]. DISCUSSION: Every day, the body absorbs and excretes roughly 1-2 mg of iron in a state of homeostasis. Duodenal enterocytes absorb a little amount of dietary iron every day (1-2 mg out of an average daily intake of 18 mg) [10]. Iron is found in two types in the diet: ferrous iron and ferric iron. The ferrous iron transporter, which is found on the apical brush boundary of primarily duodenal enterocytes, aids in ferrous iron absorption. The most important iron in the diet is ferric iron, which is converted to ferrous iron by iron reductase, which is produced by the brush border of the duodenal enterocyte. Iron circulates in the blood coupled to transferrin and travels to the bone marrow, where it is converted into hemoglobin in erythroid precursors and mature red blood cells (RBCs) in two-thirds. Muscles use about 10-15% of it in the form of myoglobin and other tissues. The liver (1000 mg) and reticuloendothelial macrophages (600 mg) store the majority of iron [10]. These macrophages provide useful iron to tissues by digesting hemoglobin in old red cells and unloading iron onto transferrin for transport to tissues.

Iron homeostasis is carefully controlled by iron absorption in the duodenum, which is regulated by hepcidin, an acute phase protein with antimicrobial activity [11]. Hepcidin levels vary depending on the amount of iron in the body. The hepcidin gene (hepcidin antimicrobial peptide or HAMP) is expressed mostly in the liver, but also in macrophages, adipose tissue, small and large intestine mucosa, muscles, the heart, and the lungs [12]. Hepcidin interacts to ferroportin, a basolateral iron efflux transporter that in turn binds to janus kinase 2 (JAK2). When ferroportin binds to and activates JAK-2, it causes ferroportin to be phosphorylated [13]. Ferroportin cell surface expression modulates the transfer of intracellular iron into plasma. Thus, via modifying ferroportin, hepcidin operates as a master regulator of iron absorption. In a sense, extra iron raises hepcidin levels, which reduces iron absorption by duodenocytes. However, as an acute phase reactant, hepcidin can rise in the presence of active inflammation, thereby limiting duodenocyte iron absorption at a time when the body wants more iron. As a result, hepcidin was found to be a better predictor of treatment response than anemia severity in a trial of patients taking oral iron replacement [13]. Complete blood count (CBC) and iron profile (serum iron (SI), serum ferritin (SF), transferrin saturation (TS%), and total iron binding capacity (TIBC)) are laboratory markers used to diagnose IDA. These parameters are assessed, and treatment is started as a result. Furthermore, in the early stages of IDA, these laboratory values may not aid in diagnosis [14,15].The absence of stainable iron in bone marrow is another definitive approach for diagnosing IDA. However, because it is painful and intrusive, it is only employed as a last resort [16]. Adequate iron replacement therapy, management of the source of IDA, and maintenance of normal iron levels can all help to reverse IDA. The first-line therapy is oral iron supplementation of 200 mg twice or thrice daily [17]. If oral therapy fails, parenteral therapy becomes the treatment of choice [18]. Parenteral iron replenishment is faster than oral iron replenishment and is well tolerated during pregnancy [19]. IS and iron dextran are the most often utilized parenteral preparations [20]. Recently, the Food and Drug Administration approved a new innovative iron formulation ferric carboxymaltose (FCM), which is proven to be more effective at replenishing iron stores. It minimizes the dosing frequency, which is a major disadvantage of parenteral preparations, and there are few drug-related side effects [21]. Almost every organ system need iron to function properly. It is necessary for oxygen transport, mitochondrial activity and synthesis, and protein breakdown in the body. ID therefore impairs not just tissue oxygen transport but also proliferation, differentiation, immunological function, and energy metabolism [22]. It also has an impact on T-cell and macrophage activity, as well as reticulendothelial function. However, it is critical to remember that, in the early stages, ID

can contribute to a variety of signs and symptoms in the absence of anemia. The symptoms are also affected by the severity of the anemia and its rapid development. ID can manifest as nonspecific symptoms such as fatigue, weakness, exercise intolerance, and poor attention, which frequently go unrecognized. Patients only discover these symptoms are related to ID when they improve following treatment. Pica, glossitis, koilonychia, and baldness may occur in ID patients with or without anemia. It can impair children's attention span, school performance, and growth [23]. Other symptoms such as nausea, motility difficulties, hypothermia, pallor of skin, exertional dyspnea, tachycardia, palpitations, danger of heart failure, cardiac hypertrophy, menstruation issues, and loss of libido commonly appear later in the disease's progression when anemia with low hemoglobin has set in. It can limit work capacity by interfering with oxygen delivery to tissues [24]. IDA has a considerable influence on physical function and mental health, as evidenced by poor mental quality of life comparable to depression and poor physical quality of life comparable to myocardial infarction [25]. Thus, it is critical to screen for ID in patients who arrive with more generalized, nonspecific symptoms, particularly in the presence of chronic GI disorders.

Intravenous iron replacement:

Iron carbohydrate compounds are used to deliver intravenous iron [26]. It is made up of a mineral core surrounded by a carbohydrate shell. The carbohydrate shell's function is to stabilize the complex and limit the possibility of hypersensitivity reactions. Complexes are taken up by reticuloendothelial macrophages after administration. The stability of the complex varies amongst intravenous iron formulations. TABLE 1 lists all formulations approved for use in the United States by the Food and Drug Administration (FDA).

TABLE 1. Intravenous iron formulations.

Intravenous iron agent	FDA-approved indication
Iron dextran	Treatment of patients with iron deficiency when oral administration is unsatisfactory or impossible
Sodium ferric gluconate	Treatment of IDA in adult and pediatric patients (⩾6 years of age) with CKD receiving hemodialysis who are receiving supplemental epoetin therapy
Iron sucrose	Treatment of IDA in adult and pediatric patients at least 2 years of age with CKD
Ferumoxytol	Treatment of IDA in adult patients with CKD
Ferric carboxymaltose	Treatment of IDA in adult patients: who have intolerance to oral iron or have had unsatisfactory response to oral iron who have nondialysis-dependent CKD

FCM is a new dextran-free intravenous iron composed of a ferric hydroxide core supported by a carbohydrate shell [27]. This allows for the controlled transport of iron to reticuloendothelial system cells, as well as the subsequent delivery of iron-binding proteins. FCM is useful in the treatment of IDA because it delivers a substantial dosage of iron in a short period of time. It can offer up to 1500 mg of iron in just two 750 mg doses administered at least a week apart. FCM can be given as an intravenous infusion over 15 minutes or as a gradual push over at least 7.5 minutes. It does not require a test dose, but patients must be monitored for signs and symptoms of hypersensitivity for at least 30 minutes before and after administration. When compared to oral iron and other intravenous iron preparations, FCM is demonstrated to be noninferior, with comparable or higher efficacy. The safety profile has also been studied in a number of clinical trials for various indications. For 12 weeks, individuals with IDA secondary to IBD were followed in a trial that compared FCM to oral iron sulfate in terms of safety and noninferiority [28]. In both groups, the median increase in hemoglobin was

comparable. In the first four weeks, the response (defined as a rise in hemoglobin >2 g/dl) was larger in the intravenous iron group, demonstrating that the correction is faster with intravenous iron. Furthermore, oral iron was discontinued more frequently due to adverse effects (iron sulfate 7.9% vs. FCM 1.5%). FCM also adequately replenished iron reserves, as evidenced by a median rise in ferritin. A randomized controlled multicenter trial comparing the efficacy and safety of FCM with iron sucrose in patients with IBD and IDA [29] discovered that 65.8% of the FCM group had a better response, with a hemoglobin rise of at least 2 g/dl versus 53.6% of the iron sucrose group (p = 0.004). The two groups had comparable drug-related adverse effects. In this study, FCM was proven to be a better intravenous iron formulation with higher efficacy and a better safety profile. The initial ferric carboxymaltose dose in this study was based on results from the randomized controlled FERGI- cor trial [21], in which all patients received at least 500 mg ferric carboxymaltose. This simplified ferric carboxymaltose-based dosing regimen outperformed the Ganzoni-calculated iron sucrose dose regimen in terms of efficacy and compliance [30].

Although comparison research on efficacy are uncommon, there is information on adverse effects. In a clinical trial of patients with chronic kidney disease who were not receiving hemodialysis, a lower proportion of ferric carboxymaltose recipients than iron sucrose recipients encountered at least one drugrelated adverse event (5 vs. 10.2%: p value not disclosed). However, there were no statistically significant differences between the groups in terms of any drug acceptability measures [32]. An summary summarizing ten studies with 12,000 patients treated with ferric carboxymaltose [33] summarized the tolerance and safety profile of ferric carboxymaltose. This summary found that 15.3% of ferric carboxymaltose recipients and 26.1% of oral ferrous sulfate recipients experienced at least one drug-related adverse event. Headache, the most commonly reported adverse event associated with ferric carboxymaltose, occurred in!3% of patients in both treatment groups, which is comparable with our study, in which only 1 patient (1.2%) complained about head aches following therapy. Rash and local injection site reactions were more common in ferric carboxymaltose patients, but gastrointestinal side effects (especially constipation and nausea) were more common in ferrous sulfate recipients across the trials [30]. The FERGI- cor trial data [31] show that hyperferritinemia and transitory hypophosphatemia may be an additional adverse effect of ferric carboxymaltose therapy. Beigel and colleagues investigated the efficacy and safety of FCM in 250 patients with IBD [33]. In the therapy group, 83.1% of patients had blood iron levels less than 60 g/dl, 90.4% had ferritin levels greater than 100 ng/ml, and 66.7% had anemia. After treatment, 74.7% of patients had iron concentrations better than 60 g/dl, 61.6% had ferritin concentrations greater than 100 ng/ml, and 90.7% had anemia improvement. The most commonly reported adverse event was a temporary rise in liver enzymes. Within an 8-month study period, Evstatiev and colleagues conducted another multicenter experiment to assess the time to recurrence of anemia in IBD patients [34]. Anemia recurred in 26.7% of FCM individuals and 39.4% of placebo subjects. The FCM group had a longer time to anemia recurrence (hazard ratio 0.62; 95% confidence interval 0.38-1.00; p = 0.049). The two groups had comparable adverse occurrences, including serious adverse events. As a result, the authors found that FCM, when compared to placebo, avoided anemia recurrence in IBD patients.

Adverse reactions Nausea, hypertension, flushing, hypophosphatemia, and dizziness are the most common adverse effects (2%). In clinical trials, the proportion of significant allergic events observed with FCM was 0.1%. The pathophysiology of these reactions is unknown, however they are likely to be due to free iron release [34]. With novel iron formulations such as FCM, the incidence of hypersensitivity reactions and lifethreatening consequences is significantly decreased; however, patients must still be monitored for any infusion-related events [35,36]. In around

1.5% of patients, other allergy symptoms such as rash, itching, urticaria, wheezing, and hypotension have been described. Another disadvantage of intravenous iron therapy is the requirement for additional healthcare personnel or an infusion center for intravenous iron access and treatment, as well as the increased expense. However, as a more effective and speedier treatment alternative, cost effectiveness may match or exceed oral replacement therapy, particularly in a specific patient cohort [37]. CONCLUSION: IDA can cause a variety of signs and symptoms, including poor physical and mental health. As a result, identifying ID is critical because these symptoms can appear even in the early stages of deficiency before anemia develops. Early treatment can alleviate symptoms while the underlying cause of IDA is identified and treated to prevent recurrence. Although oral iron supplementation is a low-cost option for treating mild anemia and those who can tolerate potential GI side effects, intravenous iron may be an appropriate first-line therapy in many patients with GI disease, including those with IBD and those with hemoglobin levels less than 10 g/dl. FCM provides a therapeutic alternative with the greatest iron found in a single intravenous formulation, the capacity to replenish iron stores more quickly and completely, and a reduced side-effect profile.

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