

On the relevance of outpatient intravenous iron therapy for anemia management

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Iron is an essential micronutrient, as it is required for an adequate erythropoietic function, oxidative metabolism and cellular immune response. In the human body, iron metabolism pathways include absorption from food, distribution to target cells, storage and recycling.⁽¹⁾ Dietary iron is found as heme (10%) and non-heme (ionic, 90%) forms; absorption occurs at the apical surface of duodenal enterocytes via different, tightly regulated, mechanisms with absorption balancing losses (1-2 mg/day) as no active iron excretory mechanisms exist. Dietary non-heme iron primarily exists in an oxidized (Fe^{3+}) form that is not bioavailable and must first be reduced to the Fe^{2+} form by a ferrireductase enzyme, that uses vitamin C as a coenzyme, before being transported across the intestinal epithelium by the divalent metal transporter 1 (DMT1). Heme iron is transported into the enterocyte by a putative heme carrier protein 1 and metabolized by heme oxygenase to release Fe^{2+} , which enters a common pathway with dietary non-heme iron before it leaves the enterocyte. Iron is exported by ferroportin 1 (the only putative iron exporter) across the basolateral membrane of the enterocyte into the circulation (absorbed iron) where it binds to transferrin and is transported to sites of use and storage. Transferrin-bound iron enters target cells – mainly erythroid cells, but also immune, muscle and liver cells – through a process of receptor-mediated endocytosis.

Erythrocytes contain up to 65-70% of body iron. Senescent erythrocytes undergo phagocytosis by macrophages of the reticuloendothelial system, heme is metabolized by heme-oxygenase and the released iron stored as ferritin. Iron will later be exported from macrophages to transferrin, a process accomplished primarily by ferroportin 1, the same iron-export protein expressed in the duodenal enterocyte and in ceruloplasmin. The amount of iron required for a daily production of 300 billion red blood cells (20-30 mg) is provided mostly by macrophage iron recycling. Thus, this internal turnover of iron is essential to meet the requirements of erythropoiesis.

Hepcidin, synthesized by hepatocytes in response to low iron levels, inflammation, hypoxia and erythropoiesis, is the main iron homeostasis regulatory hormone. Hepcidin binds ferroportin on enterocytes, macrophages and hepatocytes triggering its internalization and lysosomal degradation. Therefore, increased hepcidin secretion may lead to iron deficiency (ID) and anemia.⁽¹⁾

As stated above, under physiological conditions, there is a balance between iron absorption and iron losses in the human body. Thus, ID and iron deficiency anemia (IDA) may result from the interplay of three distinct risk factors: increased iron requirements, limited external supply and increased blood loss.⁽²⁾ ID can be either absolute or functional. In absolute ID, iron stores are depleted; in functional ID (FID), iron stores, although replete, cannot be mobilized as fast as necessary from the macrophages of the reticuloendothelial system to the bone marrow (treatment with erythropoiesis stimulating agents and inflammation are the most common causes of FID). In chronic inflammation, the excess of hepcidin decreases iron absorption and prevents iron recycling, resulting in hypoferrremia and iron restricted erythropoiesis, in despite of normal iron stores, and finally anemia of chronic disease (ACD), which can further evolve to ACD plus true ID (ACD + ID).

Investigation of ID in the clinical practice mostly relies on laboratory tests which fall

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into two categories: measurements providing evidence of iron depletion in the body and measurements reflecting iron deficient red cell production.⁽²⁾ The appropriate combination of laboratory tests, together with clinical signs and symptoms, will help to establish a correct diagnosis of anemia and ID status. In the absence of inflammation (e.g., serum concentrations of C-reactive protein < 0.5 mg/dL), true ID can be defined by a ferritin level < 15-30 ng/mL. In the presence of inflammation, true ID could be defined by a ferritin concentration < 100 ng/mL and a transferrin saturation (TSAT) < 20%, whereas FID is generally defined by a ferritin concentration > 100 ng/mL and a TSAT < 20%. Patients should be considered to suffer from IDA when they present with low Hb (men < 13 g/dL, women < 12 g/dL), TSAT < 20% and ferritin < 30 ng/mL, but no signs of inflammation (mean corpuscular hemoglobin rather than mean corpuscular volume became this is the most important red cell marker for detecting ID in circulating red blood cells).

Patients should be considered to suffer from ACD, also called anemia of inflammation, when they have: anemia, evidence of chronic inflammation, and TSAT < 20%, but normal or increased serum ferritin concentration (> 100 ng/mL). ACD, as well as FID, is frequent among patients with inflammatory disease without apparent blood losses (e.g. rheumatoid arthritis, renal failure or chronic hepatitis). ACD may evolve to ACD + ID which is characterized by low transferrin saturation (TSAT < 20%), and low serum ferritin concentrations. This type of anemia is more frequent in patients with inflammatory diseases and chronic blood losses (e.g. inflammatory bowel disease, hemodialysis).

For intermediate serum ferritin concentration (30-100 ng/mL), a serum transferrin receptor (sTfR)/log ferritin ratio < 1 indicates FID and sTfR/log ferritin ratio > 2 indicates true ID. In addition, there are several important hematologic indices that may also help in the diagnosis of ID in ACD (e.g., reticulocyte Hb content [CHR] or hypochromic red blood cells [HYPO]), but unfortunately they are only available in specific hematology analyzers.

Oral iron supplementation is adequate for treating ID in most clinical conditions. In the absence of inflammation or significant ongoing blood loss, the administration of oral iron can correct anemia, provided significant doses can be tolerated. However, although conventional wisdom "says" that up to 200 mg of elemental iron per day is required to correct IDA, this is incorrect and lower doses (50-100 mg) can also be efficacious.⁽²⁾

Intravenous (IV) iron supplementation is another treatment option for ID (intramuscular administration is no longer recommended). Seven different products are principally used in clinical practice: iron gluconate, iron sucrose, high-molecular-weight iron dextran (HMWID), low-molecular-weight iron dextran (LMWID), ferric carboxymaltose, iron isomaltoside 1000 and ferumoxytol. Their efficacy to treat anemia is directly related to the amount of iron administered, although differences in core size and carbohydrate chemistry determine pharmacological and biological differences between the different iron complexes. This efficacy has been consistently proved in a variety of

clinical settings, including nephrology, oncology, cardiology, digestive tract diseases, obstetrics and gynecology, rheumatology, and more recently surgery.⁽³⁾ With such evidence available, one would think that IV iron would be widely used in these clinical settings. Yet, with the exception of chronic kidney disease, it can be estimated that treatment with IV iron is considered in less than 5% of patients who would clearly benefit from receiving it. The reason for this resistance to use IV iron may be that there exists a generalized fear of anaphylactic reactions and deaths based on reports of poorly characterized, infrequent reactions, when in fact the overwhelming majority of serious events occur when HMWID is used.⁽⁴⁾ Therefore, with the exception of HMWID (increased rates of severe side effects and deaths), the acute safety differences among the IV iron products are small and clinically irrelevant when given at the recommended doses (and, more importantly, smaller than those associated with red cell transfusions), though comparator trials are needed to be certain.

Usually, intravenous (IV) iron was indicated in situations such as intolerance, contraindication or inadequate response to oral iron (e.g., inflammation, erythropoiesis stimulating agent administration). The study by Cançado et al.⁽⁵⁾ published in this issue of *Revista Brasileira de Hematologia e Hemoterapia* clearly exemplifies these indications for IV iron replacement. They evaluated the efficacy and safety of IV iron sucrose (IS, 200 mg/week, until anemia correction or replenishment of calculated ID; 515 infusions) for the treatment of 86 adult patients with IDA, intolerance or no effect of oral iron therapy. IS administration led to an average increase of hemoglobin levels of 3.5 g/dL (≥ 2 g/dL in 86% of patients) and an anemia correction rate of 67%, while ferritin levels increased by 87 ng/mL and no moderate or serious adverse drug reactions were witnessed. These data add to the concept that modern IV iron formulations are a safe and effective alternative for anemia management, as they present several advantages over oral supplementation. The administration of IV iron allows up to a five-fold erythropoietic response to significant blood-loss anemia in normal individuals, hemoglobin starts rising in a few days, the percentage of responding patients is higher and iron stores are increased. In addition, as oral iron therapy is time-consuming, these data should also drive a broader use of IV iron supplementation in other clinical scenarios, such as in anemic patients presenting with short time to surgery, especially in those with severe anemia, significant ongoing bleeding and/or high perioperative blood loss.

In this regard, the efficacy of intravenous IS administration (1000 ± 400 mg/patient over 3-5 weeks) for correction of preoperative anemia in 84 patients who were scheduled for major elective surgery (30 colon cancer resections, 33 abdominal hysterectomies, 21 lower limb arthroplasties) has been recently evaluated.⁽⁶⁾ Administration of IV iron caused a significant increase of hemoglobin levels (2.0 ± 1.6 g/dL) and anemia was resolved in 59% of patients. No life-threatening adverse effect was witnessed, and overall transfusion rate was only 24%. However, the main disadvantage of IS was the need for multiple infusions

as the maximum weekly dose should not exceed 600 mg (200 mg IV, 1-3 times/week). Additional data from another 76 anemic surgical patients receiving preoperative ferric carboxymaltose (FCM, 500-1000 mg per session) showed a similar hemoglobin increment (2.1 ± 1.4 g/dL). However, compared with patients receiving IS, those with FCM attained iron replenishment more frequently (82% vs. 62%, respectively) with fewer treatment sessions, showed higher final hemoglobin levels with a trend towards a higher rate of anemia correction (79% vs. 59%, respectively), and received allogeneic blood transfusion less frequently (9% vs. 24%).⁽⁶⁾

All together, despite their limitations (e.g. the use of a historical comparator group, or the lack of a control group receiving either placebo or oral iron), data from these studies support the efficacy and safety of IV iron supplementation in ambulatory ID patients for whom oral iron is not adequate. The availability of stable parenteral iron compounds, such as FCM, allowing for higher dose infusion without the need for a test dose may greatly facilitate iron replacement therapy in these ID patient populations, as they increase patient convenience (such as the time spent at the hospital including treatment and waiting time and travel for continuous treatments can be reduced considerably) and lower costs

(such as nursing and medical time and cost of administration).

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