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Review article

Intravenous iron

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A B S T R A C T

Parenteral iron is a useful and safe therapeutic measure to treat anaemia, and is a proven clinical alternative to blood transfusion. This review article summarises the main characteristics of the different formulations of parenteral iron, their advantages, indications, dosages, and adverse effects. Moreover, we analyse some of the most important published articles on parenteral iron therapy in general surgery and other surgical specialties, as well as providing information about new formulations that will soon be available.

Hierro intravenoso

R E S U M E N

El hierro intravenoso representa una medida terapéutica eficaz y segura para corregir la anemia, y constituye una alternativa respecto a la transfusión sanguínea clínicamente demostrada. El presente artículo de revisión resume las principales características de los distintos preparados de hierro parenteral, sus ventajas, indicaciones, dosificación y efectos adversos. Asimismo, se analizan algunos de los principales estudios publicados sobre ferroterapia parenteral en cirugía general y especialidades quirúrgicas afines, y se avanzan algunos datos sobre las nuevas formulaciones próximamente disponibles.

Introduction

Anaemia is one of the most frequent diseases in the general population (with a prevalence of 17% to 63% in the population older than 64 years) and is especially common (from 5% to 80%) in surgery patients.[1-7] Aside from the perioperatory blood losses, iron deficiency and anaemia of chronic disease (ACD) are the most frequent causes of anaemia in surgery patients, and its treatment requires a multidisciplinary approach, where the intravenous iron therapy plays an essential role, primarily as an effective therapeutic alternative to allogenic blood transfusions (which is an expensive, scarce resource

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that is associated with important complications and adverse events).[3,8,9] The use of parenteral iron was cautiously used starting in the second half of the twentieth century based on the studies by Goetsch et al (1946), Nissim (1947), and Baird and Podmore (1954).[10,11] The progressive improvements in the safety profile and in the rates of adverse events, together with its clinical efficacy, made the generalisation of its use possible as a therapeutic tool in transfusional medicine.[12] The first intravenous iron sucrose preparation was commercialised in Spain in 2002 (Venofer®, Vifor Int./Grupo J. Uriach S.A.), which made it possible to cover a pharmacological area that was lacking in those clinical situations where oral iron was not effective, insufficient, or contraindicated.[13] To today's date, only one intramuscular iron preparation was available (iron sorbitol), an intravenous formula only accessible as a foreign medication (iron gluconate) and a iron dextran formula whose use was abandoned due to the elevated risk of anaphylactic reactions.

Table 1 – Indications for intravenous iron

- Intolerance or incompliance with oral iron therapy
- Partial or absent response to oral iron therapy
- Poor intestinal absorption
  - IBD
  - Previous gastrointestinal surgery
- Peptic ulcer
- Active bleeding
- Postoperatory privation of oral diet
- Perioperatory anaemia
- Auto-transfusion programs
- FDI
- ESA
- Anaemia in nephrology patient
- Anaemia associated with neoplasias or chemotherapy
- Anaemia during pregnancy or during postpartum
- Anaemia and heart failurea
- Cardio-renal anaemia syndromea
- Restless legs syndromea

ESA indicates erythropoiesis stimulating agents; FDI, functional deficit of iron; IBD, inflammatory bowel disease.
[a]Scarce clinical experience or contradictory results available.

Advantages and indication for intravenous iron

Several randomised clinical trials (RCT) have demonstrated a faster and longer erythropoietic response with parenteral iron than with oral supplements.[2,14] Globally, intravenous iron is superior regarding efficacy, tolerance, predictable effects, and faster improvement in the quality of life of the patients when compared with oral iron supplements.[2] Likewise, the administration of parenteral iron enables a faster functional recovery and reduces the risk of repeated hospital admissions.[15] The intravenous preparations solved problems of intolerance, poor absorption, slowness of effects, and abandonment of the treatment associated with oral iron.[16] In addition, the functional deficit of iron (FDI)—associated with CDA—cannot be effectively corrected with oral iron (due to the inhibition of the intestinal absorption and of the macrophage liberation of iron), but it responds favourably to the administration of intravenous iron.[1,15] The current possible indications of intravenous iron are reflected in Table 1.[1,13,16-22]

Formulations of intravenous iron: types and mechanisms of action

There are different formulations of intravenous iron in the market, with differences in their physical and biochemical characteristics (molecular weight, complex stability, degradation kinetics), safety profile (acute toxicity, risk of anaphylaxis), and dosage (maximum dose, need for test dose, infusion time, possibility of intravenous injection).[2] The available preparations are high molecular weight iron dextran, low molecular weight iron dextran, iron gluconate, iron sucrose, and ferric carboxymaltose (Table 2).[2,12,23] In Spain, only Venofer®, Feriv®, Iron Sucrose Normon® and Cosmofer® (low molecular weight iron dextran) are currently commercialised. New preparations of parenteral iron, such as Ferumoxytol (AMAG Pharmaceuticals)—nanoparticles of iron oxide—or Iron-HES—a colloidal suspension of iron oxyhydroxide covered with hydroxyethyl starch—have demonstrated their efficacy and safety in various RCT (phase

Table 2 – Preparations of parenteral iron

Molecule	Commercial name	Laboratory
Iron dextran (high mw)	Dexferrum®	American Regent Laboratories Inc.
Iron dextran (low mw)	INFeD®	Watson Pharma Inc.
	Cosmofer®	Pharmacosmos A/S
Iron gluconate	Ferrlecit®	Watson Pharma Inc.
Iron sucrose	Venofer®	Vifor Int./Grupo J.Uriach S.A.
	Feriv®	GES Genéricos Españoles
	Normon®	Laboratorios Normon S.A.[a]
Ferric carboxymaltose	Ferinject®	Vifor Int.[a]
	Injectafer®	American Regent Laboratories Inc.

mw indicates molecular weight.
[a]To be commercialised in Spain soon.

III) in patients with chronic kidney disease and anaemia.[24-26] All of the intravenous iron preparations are formed by a central nucleus (core) of elemental iron covered by a glycidic layer that stabilises the complex and slows down the liberation of iron. The different preparations have different iron nucleus sizes and the identity and density of the carbohydrate layer are different also.[12,27] The molecular weight of the complex, which reflects the size of the nucleus and its cover, determines its degradation velocity, and this then conditions the dose to be administered and the velocity of infusion.[26-28] An excessive dose of intravenous iron could cause an accelerated liberation of the elemental iron of the complex and over-saturate the uniting capacity of the plasmatic transferrin, with possible anaphylactic reactions due to the excess of "free iron."[26,27,29] After its intravenous administration (by injection or infusion), the iron-carbohydrate complexes mix with the plasma and the macrophages of the reticuloendothelial system (RES) of the spleen, the liver and the bone marrow phagocytise them by means of the surface recipient, transporter of divalent metals or DMT1.[26] Inside of the phagocyte, the iron is freed from the complex with 2 possible routes: incorporation to the intracellular deposit (attached to the ferritin) or plasmatic liberation at a variable speed to attach itself to the transferring, to be available for erythropoiesis.[12,15] The liver clears the carbohydrates. The rate of the transfer of plasma is faster and more complete in the case of iron deficiency than in situations of FDI. In certain intravenous iron preparations, such as the sucrose iron, a small fraction of the product (from 4% to 15%) passes directly to the plasmatic transferring, which is then rapidly available for erythropoiesis.[14,23,30-32] The iron sucrose (iron hydroxide in sucrose, plasmatic half-life of 5 to 6 hours), due to its molecular weight (34-60 kDa) and its high hydro-solubility, it possesses a fast tissue diffusion and an elevated bioavailability, which makes it especially effective in donating iron directly to the medullar erythroid precursors.[20]

Dosage of intravenous iron

Intravenous iron has a rapid bioavailability for erythropoiesis and it accelerates the recovery of anaemia.[33] The estimated increase of haemoglobin is approximately 1 g/dL for every 150 to 200 mg of intravenous iron administered. Its erythropoietic effects is manifested from the 7th to the 10th day of treatment, and a positive response is achieved (increase of haemoglobin ≥2 g/dL) in 2 to 4 weeks.[2,34] The administration of intravenous iron reaches maximum plasmatic concentration of iron in 10 minutes, the incorporation of iron in bone marrow in less than an hour and a use rate for the erythropoiesis of 59% to 99% in 4 weeks (iron sucrose).[29,35,36] The dose of iron needed to correct the deficit, with the objective to re-establish the haemoglobin concentration and refill the biological deposits, should be calculated in an individual manner (mg of elemental iron) depending on the weight of the patient and the plasmatic concentration of haemoglobin using the classic formula of Ganzoni: iron deficit (mg) = weight (kg)×["target" haemoglobin (g/dL)—current haemoglobin (g/dL)]×2.4+500.[31-33,37] The fast liberation of the administered iron limits the maximum dose that can be given in one single administration.[23] However, there is little data on the optimal and safest dosage, with multiple administration regimens published (doses of 20 to 500 mg, single or repeated, by injection or infusion).[23,38-41] Thus, Chandler et al tested the dose safety of 200 mg and of 300 mg of iron sucrose infused in 250 mL of saline solution in 2 hours, in 189 nephrology patients.[23] Bisbe et al tested the efficacy of the preoperatory administration of 200 mg of iron sucrose diluted in 200 mL of saline solution in 30 minutes, one to 3 times per week, in 27 patients that were candidates for major orthopaedic surgery.[1] One of the most used regimens consists of 100 to 200 mg per dose, with a maximum of 600 mg/week, diluted in 100 to 250 mL of saline solution and infused in 20 to 30 minutes.[40,42] There is clinical evidence with intravenous iron at high doses and even in single-doses (total dose infusion), with variable doses of 1000 to 3750 mg, which would allow for a lower number of doses and greatly simplify its administration, with few associated adverse events.[17,19,33,38,39,43-45] Blaustein et al tested the safety and efficacy of a regimen of 2 doses of 500 mg of iron sucrose diluted in 250 mL of saline solution in 3 hours, in 2 consecutive days, in a prospective study in 107 nephrology patients, with significant increases in the values of the transferrin saturation index (TSI) and ferritin and a rate of adverse events due to the treatment of 1.8%.[39] Schröder et al tested the safety of one single maximum dose of 500 mg of iron sucrose infused in 250 mL of saline solution in 3.5 hours in 31 patients with iron deficiency anaemia from digestive causes, with an adverse event rate of 6.5% (all mild and transitory).[38] Some studies have used slower infusion rates to try to reduce the rates of adverse events.[23,39]

Adverse effects of intravenous iron

The secondary effects classically described regarding the parenteral iron preparations are headaches, rashes or itchiness, chest pain, lower back pain, metallic taste in mouth, joint pain, shaking, nausea and vomiting, diarrhoea, epigastralgia, peripheral oedemas, hypotension, bradycardia, proteinuria and other anaphylactoid reactions (attributed to the presence of free iron) or anaphylactic reactions (only described with iron dextran).[32,46] Some experimental studies and animal models indicate that an excessive treatment with parenteral iron could generate cytotoxicity, oxidative stress, neutrophil dysfunction and even, promote the atherosclerosis.[41,46,47] Globally, the prevalence of severe adverse events associated to intravenous iron is very low, around 2.2-5 cases/million doses (estimated mortality of 0.3 to 0.4 cases/million), lower than that described with the use of allogenic blood transfusions, where the prevalence of severe adverse events is greater than 10 cases/million doses (mortality of 4 cases/million).[8,15,48] The new intravenous iron preparations produce less adverse events (<0.5%) than their predecessors (like the high molecular weight iron dextran, which is currently obsolete due to the potential risk of anaphylactic reactions mediated by antibodies and mortality), and currently they represent very effective and

safe preparations.[12,15,41,48-51] Currently, iron sucrose is considered as the most safe parenteral iron formulation, followed by iron gluconate.[50] The use of intravenous iron is contraindicated in anaemias with totally complete iron deposits, indications of iron overload and during the first trimester of pregnancy. In spite of the fact that no study in humans has demonstrated a significant increase in the risk of infections (or neoplasic progression) with the administration of intravenous iron, caution should be used in cases of acute or chronic infections.[12,41,46,52] Treatment should be stopped during episodes of bacteraemia. In patients with active chronic infections, the potential risks and benefits should be considered, as well as the relevance of the associated ACD (which can only be countered with parenteral iron therapy). During the administration of parenteral iron, a slight and transitory increase is relatively common of the values of alanine-transaminase (less than 10% of cases) or of the aspartate transaminase, gamma-glutamyl transpeptidase, and lactate dehydrogenase (less than 1%). According to the technical sheet of certain preparations, the elevation of the transaminases 3 times above the normal values is a contraindication for its administration. Although parenteral iron could contribute to the hepato-cellular damage in patients with the hepatitis C virus (HCV), certain studies confirm that the controlled administration (specifically, in patients with HCV in haemodialysis) represents an effective and safe measure to correct anaemia.[53,54] Finally, the administration of parenteral iron should be avoided in patients with liver failure where the iron overload is a triggering factor, such as the haemochromatosis or the porphyria cutanea tarda.

Studies on intravenous iron

A large number of studies have demonstrated the clinical efficacy of intravenous iron in terms of recovering rates of haemoglobin, reducing perioperatory allogenic blood transfusions, reducing postoperatory infections and complications, hospital stay and mortality.[1,3,8,13-15,30,34,55-59] Likewise, the use of intravenous iron, associated or not to ESA (erythropoiesis stimulating agents), is especially effective in the treatment of preoperatory anaemia in patients that are candidates for scheduled surgery, included in auto-transfusion programs.[1,13,27,60] Various series confirm the role of intravenous iron, associated or not to ESA; as an indispensable part of the treatment of anaemia in cancer patients, nephrology patients and patients in chemotherapy treatment, with significant improvements in the haemoglobin concentrations, allogenic blood transfusion rates, haematopoietic response, adverse events and quality of life.[12,30,32,61-66] The majority of the studies published on intravenous iron-therapy analyse similar evaluation criteria: the number and proportion of patients that reach the "target" concentrations of haemoglobin (usually of 14 to 15 g/dL or 11 to 12 g/dL in nephrology patients and in oncology patients), TSI (≥20% or to 50%) and ferritin (≥100 µg/L); the number and the proportion of patients that present a positive erythropoietic response (increase of haemoglobin ≥2 g/dL) and the average time needed to reach it; the maximum peaks of haemoglobin, ferritin and TSI and the times needed to reach them; the number and proportion of patients that need perioperatory allogenic blood transfusions and the transfusion index, as well as the percentage of abandonments and mild secondary effects compared with severe secondary effects.[19,37,55] To monitor the response to the administration of intravenous iron, haemograms and seried iron-kinetic determinations should be requested.

Studies with intravenous iron in General Surgery

Multiple studies have tested the efficacy of intravenous iron, associated or not to ESA, in the correction of pre and postoperatory anaemia in patients that are candidates for gastro-intestinal surgery.[13,58,60] The study by Kosmadakis et al (RCT, n=63 cases) demonstrated the efficacy of the daily administration of intravenous iron sucrose (100 mg/day) and of subcutaneous alpha epoetin (300 U/kg/day) during 14 perioperatory days (7 days before and 7 days after the intervention) in patients that were candidates for gastro-intestinal oncologic surgery (79% colorectal and 21% gastric), with significant improvements in the concentrations of haemoglobin pre and postoperatory, decreases in the need of intraoperatory allogenic blood transfusions (29% in the treatment group compared to 59% in the control group, *P*=.02) and postoperatory allogenic blood transfusions (3% compared to 28%, *P*=.001), reduction of the postoperatory complications (13% compared to 41%, *P*=.02), hospital stay (10 days compared to 13 days, *P*=.02) and greater survival after one year (81% compared to 59%, *P*=.04).[58] Braga et al demonstrated the efficacy of the preoperatory combination of intravenous iron gluconate (125 mg/day during 15 days) and rHuEPO (*recombinant human erythropoietin*) (400 U/kg, divided in 4 doses every 4 days) in terms of the increase of the preoperatory haemoglobin value (average increase of 2.2 g/dL) in 20 patients with gastrointestinal neoplasia and candidates for elective surgery.[67] Tsuji et al (RCT, n=10 cases) demonstrated the efficacy of the daily perioperatory combination (from the 7th day before surgery until the 14th day after surgery) of rHuEPO (200 U/kg/day) and intravenous iron (40 mg/day) to prevent postoperatory anaemia and in the reduction of allogenic blood transfusions after gastrectomies for gastric neoplasias.[59]

Studies with intravenous iron in other medical and surgical specialties

Since 1998, parenteral iron has become a part of the standard treatment of patients with chronic kidney disease in haemodialysis.[18,62] Various studies have demonstrated the superiority of parenteral iron compared with orally-administered iron in patients in regimens of kidney substitution treatment (haemodialysis and continuous peritoneal dialysis) or in a pre-dialysis state, with significant increases in haemoglobin concentrations, ferritin, TSI and the rate of reduction of the needed doses of rHuEPO.[32,49,68-70] The safety of iron sucrose has also been confirmed in this group of patients in various trials.[24,51,66,71] Various studies have confirmed the safety and efficacy of parenteral iron in

the treatment of iron deficiency anaemia during pregnancy.[57] This way, Al-Momen et al demonstrated that the daily administration of 200 mg of iron sucrose was superior in terms of haemoglobin concentrations reached (12.8 g/dL compared to 11 g/dL), values of ferritin and rapidness of action (maximum haemoglobin concentration reached in 6.9 weeks compared to 14.9 weeks) in comparison with a standard regimen of oral ferrous sulphate.[72] Perewusnyk et al documented the safety profile of iron sucrose (rate of adverse events of 0.36%) in anaemia associated with pregnancy.[57] Van Wyck et al demonstrated in a RCT with 352 patients, a faster, more effective and better tolerated response with intravenous ferric carboxymaltose (maximum dose of 1000 mg/week) compared with oral ferrous sulphate (325 mg/8 hours) in the treatment of postpartum anaemia.[55] The studies by Breymann et al and Seid et al confirmed in many RCT, with 349 and 291 cases, respectively, the efficacy, safety and tolerance of the ferric carboxymaltose (maximum of 1000mg/week) compared with oral ferrous sulphate in the treatment of postpartum anaemia, which shortens the response time and improves digestive tolerance.[56,73] Likewise, various studies confirm the safety and efficacy of iron sucrose to correct iron deficiency anaemia in the paediatric population.[74] Gasche et al evaluated the efficacy of the periodical administration of intravenous iron (iron sucrose, 200 mg/dose) in a clinical trial, alone or combined with ESA, for treatment of anaemia from Crohn's disease that does not respond to oral iron. The majority of the patients (75% in the group without rHuEPO and 95% in the group that received rHuEPO) responded satisfactorily to parenteral iron; the increase in haemoglobin was associated with positive changes in the quality of life scales and indexes of the activity of disease. The authors concluded that iron sucrose is the choice treatment in patients that do not respond to or that do not tolerate oral iron therapy and where the coadministration of ESA carries out a secondary role.[75] Gasche et al demonstrated in another multi-centre study the efficacy of iron sucrose (total average dose of 1.2 g) in 103 cases of severe anaemia associated to the inflammatory bowel disease (IBD), with a satisfactory response in 65% and a partial response in 35%.[76] The retrospective study by Bodemar et al confirmed the efficacy and safety of iron sucrose in 61 patients affected with IBD and anaemia and with previous intolerance to oral iron therapy (32 patients with Chron's disease and 29 patients with ulcerative colitis); the response rate was satisfactory in 91% after 12 weeks.[77] Kulnigg et al, in a multi-centre RCT confirmed the efficacy and safety of intravenous ferric carboxymaltose compared with oral iron in 200 cases of iron deficiency anaemia associated with IBD (average deficit of 1405 mg in the parenteral iron group). The regimen used was ferric carboxymaltose (1000 mg/week) compared to oral ferrous sulphate (200 mg/day); the results of the study showed an average increase of the rates of haemoglobin and safety profile that were similar, but with greater rapidness of action and an increase in the values of ferritin in the parenteral iron group.[37] The perioperatory administration of intravenous iron (with or without associated ESA) has demonstrated a reduction of the allogenic blood transfusions and postoperatory complications, especially concerning infections, in orthopaedic surgery in various studies.[14,34,42,78-80] Likewise, the combination of iron therapy and ESA increases the efficacy of the self-donating blood programs in Trauma and Orthopaedics and Gynaecology.[81] The anaemia related with neoplasias, associated with a decrease in the quality of life and worse prognosis, needs a multi-modal treatment in many occasions (ESA, oral iron, parenteral iron, allogenic blood transfusions, etc).[18] The multi-centre study by Auerbach et al (RCT, n=157 patients affected by anaemia related with chemotherapy in treatment with ESA) demonstrated the superiority of the co-treatment with intravenous iron (iron dextran) compared to oral iron and the absence of iron therapy in terms of erythropoietic response (68% with parenteral iron compared to 36% with oral iron and 25% without iron therapy) and improvements in the quality of life of the patients.[32,65] A study by Pedrazzoli et al on 149 patients affected by anaemia from chemotherapy confirmed the efficacy of the combination of parenteral iron (iron gluconate 125 mg/week) and darbepoetin alpha in terms of haematopoietic response.[63] A multi-centre RCT on 396 neoplasic patients with anaemia confirmed the superiority of the combination of parenteral iron and darbepoetin over the isolated use of darbepoetin (haematopoetic response in 86% compared to 73% in the control group, *P*=.01, and need for allogenic blood transfusions of 9% compared to 20%, *P*=.005).[82]

Ferric carboxymaltose

Ferric carboxymaltose (FCM) is anew iso-osmolar preparation of trivalent parenteral iron (50 mg of ferric iron/mL) designed for rapid administration in large doses, which reduces the need for multiple infusions, with an optimal safety and tolerance profile.[37,55] It is especially useful in patients with iron deficiency anaemia with intolerance to oral iron or in patients that need a rapid reposition of iron deposits (the commercialisation of this molecule will soon be started in Spain by the name Ferinject®, Vifor Int./Grupo J.Uriach S.A.).[56] The FCM can be administered in doses up to 1000 mg/week at an infusion velocity much higher than other parenteral iron preparations: as an intravenous injection of up to 200 mg/day (maximum: 3 administrations per week) or by a maximum infusion of 1000 mg/week (300 to 400 mg diluted in 100 mL of saline solution at 0.9% in 6 minutes or 500 to 1000 mg diluted in 250 mL of saline solution in 15 minutes).[37,38,55] Due to its safety profile and fast administration (it does not require an initial test dose), it is useful not only in patients admitted to the hospital, but also in outpatient patients.[56] After its administration, maximum concentrations of iron in plasma are reached in approximately one hour (plasmatic half—life of 7 to 12 hours) and the RES of the spleen, liver and bone marrow capture it rapidly. Tomography studies by the emission of positrons and radio-marked iron have demonstrated that the red blood cells use from 61% to 99% of the FCM administered; these values increase in cases of iron deficiency. Different studies on postpartum anaemia, uterine bleeding, patients in haemodialysis or anaemia in IBD have confirmed the efficacy and safety of the FCM, as the haemoglobin rates quickly increase and the biological

deposits of iron are quickly refilled with few secondary effects in a much faster way than with the administration of oral iron.[37,55,56,73] The FCM provides important advantages compared to other available intravenous iron preparations, and thus it will represent a valuable therapeutic tool in the treatment of anaemia.

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