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DOI: https://doi.org/10.1111/j.1423-0410.2007.01014.x

Manuscript for Vox Sanguinis

(revised version)

EFFICACY AND SAFETY OF INTRAVENOUS IRON THERAPY AS AN ALTERNATIVE/ADJUNCT TO ALLOGENEIC BLOOD TRANSFUSION

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Abstract

Anaemia is common in medical, surgical and critically ill patients, mostly due to absolute or functional iron deficiency (e.g.chronic blood loss or chronic inflammatory states respectively). Other causes are less frequent. Its presence is predictive for perioperative blood transfusion. Postoperative anaemia is mainly caused by blood loss, and may be aggravated by inflammation-induced inhibition of erythropoietin and functional iron deficiency (not correctable by the administration of oral iron). All these mechanisms may be involved in the anaemia of the critically ill. Intravenous iron administration seems to be safe, with few severe side-effects, and may hasten recovery from anaemia and reduce transfusion requirements. All the same, many indications given for IV iron are not supported by much evidence, which must be borne in mind when making decisions for a particular patient. Thus we need large, randomized controlled trials on the safety and efficacy of IV iron for the treatment of anaemia in various clinical settings.

1. INTRODUCTION

Iron metabolism is tightly regulated. The enterocyte absorbs haem-iron and inorganic iron via the apical membrane and releases it to the blood through its baso-lateral membrane by means of ferroportin [1]. Iron storage in the liver and macrophages is mostly in the form of ferritin. Transferrin effects iron transport from absorption and storage sites to the bone marrow, and makes iron available for incorporation into haemoglobin (Hb) (Figure 1) [1].

Under physiological conditions, there is a balance between iron absorption, transport, and storage in the human body. But iron deficiency (ID) and iron deficiency anaemia (IDA) are common in medical, surgical, and critically ill patients, and result from the interplay of three distinct risk factors: increased iron requirements, limited external supply, and blood loss (Table 1) [2]. Iron deficiency can be either absolute or functional. In absolute ID, the iron stores are depleted; in functional iron deficiency (FID), iron stores, although replete, cannot be mobilized as fast as necessary from the macrophages of the reticulo-endothelial system (RES) to the bone marrow. FID occurs in the anaemia of inflammatory diseases because iron is trapped in the RES as a result of increased secretion of hepcidin, a hormone that controls ferroportin activity in releasing iron from cells (Figure 1) [1,2]. FID may also occur in therapy with erythropoiesis-stimulating agents (ESAs), such as epoetin or darbopoetin, which place a

significant demand on iron stores that may surpass the iron-release capacity of the RES [3]. Thus, laboratory tests for ID fall into two categories: measurements of body iron depletion, and those reflecting iron-deficient red cell production (Table 2) [4].The appropriate combination of these tests will help to establish a correct diagnosis of anaemia and iron deficiency status [5].

Allogeneic blood transfusion (ABT) rapidly and effectively restores the haemoglobin (Hb) levels. This may avert the deleterious effects of severe anaemia, especially when acute or in elderly patients with impaired cardio-respiratory compensatory mechanisms. But ABT, though safer than it was, is not risk-free. It reflects the current state of health of society, and new illnesses and infections influence blood safety unpredictably [6]. Thus, concerns for the reduction of ABT-related risks have prompted the review of transfusion practices, and the search for a safer and more biologically rational treatment of anaemia (i.e., pharmacological treatment). This should also hasten recovery of a patent's functional capacity.

In IDA (resulting from inadequate intake, chronic blood loss, etc), iron absorption is increased and, provided there is no pathology of the gastrointestinal tract, oral iron administration is usually effective to correct anaemia.. By contrast, anaemia can occur in chronic inflammation (e.g., rheumatoid arthritis, Crohn's disease, chronic renal or heart failure, or cancer), and in acute processes (e.g., trauma or surgery) associated with ID. In those cases the utility of oral iron may be limited, since absorption is down-regulated, and the small amount of iron absorbed is sequestered in the RES. Hepcidin an hepatic acute-phase protein, plays a major role in both processes through its effects on ferroportin expression and activity (Figure 1) [1,5]. Intravenous (IV) iron may be a more effective mode of administration in these situations, as well as in cases of intolerance or contraindication to oral iron, treatment with ESAs, imminent surgery, or severe anaemia. In this review we will focus on the efficacy and safety of intravenous iron administration as an alternative or adjunct to ABT for the treatment of anaemic patients in different clinical contexts.

2. INTRAVENOUS IRON AGENTS

2.1 Structure, biochemistry, and pharmacokinetic properties

All IV iron agents are colloids with spheroidal iron-carbohydrate nanoparticles. Each particle consists of an iron-oxyhydroxide core (Fe [III]) and a carbohydrate shell that stabilizes the iron-oxyhydroxide core. Three different products are used in clinical practice: iron dextran (73 – 265 kDa), iron gluconate (38 kDa), and iron sucrose (43 kDa) [9,10], and differences in core size and carbohydrate chemistry

determine pharmacological and biological differences between the different agents. This includes clearance after injection, iron release *in vitro*, early evidence of iron bioactivity *in vivo*, and maximum tolerated dose and rate of infusion [7,8] (Table 3).

After IV injection, iron-carbohydrate agents mix with plasma, then enter the RES directly from the intravascular fluid compartment. Resident phagocytes of the liver, spleen, and bone marrow remove iron agent from the circulating plasma. Within phagocytes, iron is released from the iron-carbohydrate compound into a low molecular weight iron pool. Low molecular weight iron is either incorporated by ferritin into intracellular iron stores, or leaves the cell to bind with the extracellular iron-binding protein transferrin [11]. A small fraction, however, likely bypasses the intracellular steps and donates iron directly to transferrin in plasma (Table 3) [8]. Transferrin binds to receptors on the surface of erythroid precursors, and the resulting internalization of the iron-transferrin-receptor complex supplies iron for Hb synthesis and maturation of the red cell [11].

The precise cellular events by which RES phagocytes take up carbohydrate compounds and thereby clear them from plasma are not clear, although it seems to be a saturable process and to depend on molecular weight [11]. In contrast, the rate of transfer of iron from RES into circulating red cells seems to depend on the severity of ID, the rate of erythropoiesis, or circulating factors that influence those disorders (e.g., hepcidin). It is more rapid and more complete with ID than with cancer or inflammation [11]. In addition, given the same iron loading dose, experimental animals show higher RES iron levels after iron dextran than after ferric gluconate and iron sucrose, suggesting that the rate of metabolism and utilization of IV iron may be lower for agents with higher molecular weights [11].

2.2 Adverse side effects.

A. Allergic and anaphylactic reactions. The stability of the dextran complex allows administration of high single doses (“total dose therapy”). However, these iron complexes may cause dextran-induced anaphylactic reactions in some patients receiving iron dextran [12]. In contrast, iron gluconate is labile, with fast degradation kinetics, and can cause acute adverse reactions related to labile iron release. Non-transferrin-bound labile iron may induce acute endothelial cell injury and a transient capillary leak syndrome (nausea, hypotension, tachycardia, chest pain, dyspnoea due to lung oedema, and oedema of the hands and feet) that should not be misread as anaphylaxis [7]. To avoid these side effects, the maximum recommended single dose is 125 mg and the administration of total dose is not recommended. Finally, with iron sucrose, if the infusion is too fast (above 4 mg Fe^{3+}/min) or the single

total iron dose too high (above 7 mg Fe^{3+}/kg), labile iron toxicity might occur [7]. Single doses of up to 300 mg are safe, and the maximal recommended dosage is 600 mg/week [12]. Overall, iron sucrose is currently considered the safest IV iron preparation [9,10].

Although no serious life-threatening adverse events have been reported in the studies reviewed in this paper, the numbers of patients included are not large enough to draw conclusions about the safety of IV iron agents in different clinical settings. Therefore, this section will focus on adverse drug events (ADEs) associated with parenteral iron in chronic kidney disease (CKD) patients.

The United States Food and Drug Administration (FDA) reported adjusted-rate adverse drug events (ADEs) per 100 mg dose of four formulations of intravenous iron during 2001–2003. These included higher and lower molecular weight iron dextran, sodium ferric gluconate complex, and iron sucrose. In these data, the total parenteral iron-related ADEs were 1141 amongst approximately 30 million doses given (about 38 ADEs per million), with 11 deaths (7 iron dextran, 3 iron gluconate, 1 iron sucrose) [13]. Relative to lower molecular weight iron dextran, total and life-threatening ADEs were significantly more frequent among recipients of higher molecular weight iron dextran and less so with sodium ferric gluconate complex and iron sucrose. The absolute rates of life-threatening ADEs were 0.6, 0.9, 3.3 and 11.3 per 10^6 doses for iron sucrose, sodium ferric gluconate complex, lower molecular weight iron dextran, and higher molecular weight iron dextran, respectively, whereas absolute rates of death were 0.11, 0.25, 0.75, and 0.78 per 10^6 doses, respectively. Therefore, the rates of intravenous iron-related ADEs reported to the FDA are extremely low and life-threatening and other ADEs appear to be lower with the use of non-dextran iron formulations [13].

B. Infection and iron. Current information on the relationship between IV iron and infection, and between IV iron and oxidative stress deserves special consideration. Elemental iron is an essential growth factor for bacteria with many species expressing iron transport proteins that compete with transferrin, and patients with iron overload seem to be at increased risk of infection [14]. In contrast, in the peritoneal dialysis population, patients receiving IV iron had no increased risk of peritonitis compared with those who did not [15]. In addition, a study of 988 dialysis patients found increased risk of bacteraemia (RR 0.7 for each 1g/dL less of Hb) in the presence of anaemia [16]. Nevertheless, despite the lack of definitive clinical data, it seems sensible to avoid giving intravenous iron in acute infection.

C. Oxidant damage and iron. Biologically active iron, which all IV iron agents release, also plays a role in inflammation, oxidant stress and the propensity for accelerated atherosclerosis. Persistent oxidative stress in CKD patients promotes inflammation and, in turn, atherogenesis and increased cardiovascular morbidity and mortality. However,

available evidence relating IV iron administration to atherogenesis is indirect, and there is little evidence that IV iron adversely affects survival in patients with dyalisis-dependent CKD. Nevertheless, the evidence argues for caution, not complacency, in prescribing IV iron (7).

D. Iron overload. If iron status is not followed closely, patients receiving IV iron may develop iron overload. In short, markers of risk, stores, and efficacy all prompt a single conclusion: IV iron is associated with evidence of increased risk and excessive tissue iron stores in patients with a serum ferritin >600 ng/mL and a lack of therapeutic efficacy in the patient with a serum ferritin >500 ng/mL. The evidence supports withholding IV iron in patients with pre-treatment ferritin values >500 ng/mL [7]. However, in CKD patients, administered iron accumulates preferentially in the macrophages of the RES, including the Kupffer cells of the liver. Therefore, the deleterious effects of the overload are of lesser significance compared with idiopathic haemochromatosis, where iron accumulation occurs primarily in parenchymal cells [12].

3. INTRAVENOUS IRON THERAPY IN NON-SURGICAL PATIENTS

3.1 Pregnancy and post-partum

Anaemia due to iron deficiency or iron loss is common during and after pregnancy [17]. Bayoumeu et al [18], in a random, prospective, open study, compared intravenous iron sucrose with oral iron sulfate in 50 patients with haemoglobin between 8 and 10 g/dL and ferritin <50 ng/mL. On day 30, no differences in Hb increase were observed between groups, though ferritin levels were higher in the IV group both on day 30 and at delivery. In contrast, Al et al (19) in a randomized open-label study in 90 patients with similar Hb (8 -10.5 g/dL) but lower ferritin value (<13 ng/mL) found that iron sucrose increased Hb and restored iron stores faster than oral iron during the first month of treatment. Similar results occurred in a non-randomized prospective study where 111 pregnant women with IDA (ferritin <20 ng/mL) were sequentially assigned to IV or oral iron [20]. Overall, between 1992 and 2005, more than 500 pregnant women with IDA were treated at the Zurich Obstetrics Clinic (mean iron sucrose total dose,1000 mg) without serious adverse events. The mean increase in Hb was 2 g/dL [17]. From

the results of these studies, iron sucrose appears to be a treatment without serious side effects for the correction of pregnancy anaemia and iron stores depletion.

In postpartum anaemia, Breymann *et al* [21] randomised 40 patients (Hb = 86 ± 11 g/L) to receive iron sucrose, or oral iron alone, daily for 4 days beginning 48-72 h postpartum, and found that both regimens were of equal efficacy in both rate and degree of Hb recovery in the postpartum period. In contrast, two more recent studies found IV iron sucrose to be better than oral iron for treating anaemic postpartum mothers [22,23]. But Bhandal *et al* [22] gave iron only to those patients with proven ID anaemia, whereas Breyman *et al* [21] excluded those with antepartum anaemia. Thus, oral and IV iron appear to be equivalent except perhaps in particular circumstances. Additional treatment with rHuEPO should be reserved for those patients with profound postpartum inflammation (e.g., anaemic patients after Caesarean section) [24].

3.2 Inflammatory bowel disease

About a third of patients with inflammatory bowel disease (IBD) suffer from recurrent anaemia, which significantly affects their quality of life. In IBD, blood loss in the intestine overwhelms duodenal iron absorption, resulting in negative iron balance and ID, and combines with anaemia of chronic inflammatory disease. These contribute most to the development of IBD anaemia. Cobalamin or folate deficiency and various other causes of anaemia, such as haemolysis, occur less often [25].

In these patients, IBD-specific factors may hinder the efficacy of oral iron therapy. Among them are gastrointestinal side effects of oral ferrous iron (release of activated hydroxyl radicals) or iron absorption reduced by inflammation [26].These limitations of oral iron therapy in IBD mean that we must consider parenteral routes. In a study of IBD patients with poor response or intolerance to oral iron, the administration of iron sucrose (200 mg once or twice weekly to replenish total iron deficiency) resulted in a positive response (Hb increment 2 g/dL or correction of anaemia) in 60% of patients within 8 weeks and in 90% within 12 weeks [27]. However, a randomized, controlled, open-label, multicenter trial in 46 patients with anemia and transferrin saturation 20% and/or serum ferritin concentrations 20 ng/mL, found no differences in Hb increment within 6 weeks between patients receiving iron sucrose or iron sulfate. But they did build up iron stores (ferritin in the range of 200 ng/mL after six weeks) [28]. In addition, five patients (20.8%) receiving iron sulfate had to discontinue the study drug because of intractable gastrointestinal reactions, whereas only one patient (4.5%) on iron sucrose had to withdraw because of side effects [28]. In another randomized study, oral ferrous

fumarate, but not intravenous iron sucrose, increased clinical disease activity in IBD patients, whereas intravenous iron sucrose increased intravascular oxidative stress [29]. Thus, despite equal short-term efficacy and tolerability, iron sucrose seems better tolerated by the gastrointestinal tract. But we need further research on when best to start treatment, target Hb and ferritin levels, and the effects of intravenous iron on the clinical course of IBD.

3.3 Congestive heart failure

Anaemia correlates with chronic heart failure (CHF), not only because it is common but also because it indicates greater impairment in functional capacity, and independently predicts mortality and hospitalization in CHF patients [30]. The causes of anaemia in CHF patients are probably many. A vicious cycle may exist between heart failure, anaemia and CKD, the "cardio-renal-anaemia" syndrome [30]. In anaemic CHF patients, correction of anaemia with rHuEPO and oral iron (increase in Hb from 10.4 ± 0.6 to 12.4 ± 0.8 g/dL; $p<0.01$) leads to improvement in New York Heart Association status, exercise endurance, oxygen use during exercise, renal function, and plasma B-type natriuretic peptide levels. It also reduces the need for hospitalization [31]. Both ID and FID may also play a role in the cardio-renal-anaemia syndrome. Bolger *et al.* [32] found that iron sucrose increases Hb levels (11.2 ± 0.7 vs. 12.6 ± 1.2; $p<0.001$), reduces symptoms, and improves exercise capacity in anaemic patients with CHF. In addition, they found no adverse events relating to drug administration or during follow-up. Other randomized trials, such the IRON-HF [33], could indicate the best Hb level at which to start treatment, the target Hb, which patients might benefit from IV iron alone, or when IV iron should be supplemented with rHuEPO.

3.4 Chronic kidney disease

Nowadays, the administration of ESAs with iron supplements, but not ABT, is standard therapy for the anaemia of CKD, although some patients still receive transfusions. On the other hand, IV iron alone partially corrects this anaemia. In anaemic non-dialyzed CKD patients, the haematocrit response is more rapid in patients receiving IV iron with low-dose rHuEPO, but 50% of patients with iron alone had greater than 3% increase in haematocrit. In addition, 29% of these patients reached the target haematocrit (35%) compared with 40% of those receiving the combination therapy [34]. Administration of IV iron to CKD patients significantly increases the haematocrit, with 35-40% of them reaching target haematocrit without rHuEPO [35,36]. So IV iron alone can correct anaemia in CKD, possibly enough to avoid ABT, but many patients will also need ESA supplementation to attain the target Hb level.

3.5 Anaemia of cancer

Patients with cancer may have anaemia with ID or FID as a result of their disease or its treatment. Supportive care with ESAs in these conditions can lead to an insufficient supply of iron for incorporation into erythrocytes. In cancer patients receiving chemotherapy, IV iron dextran or ferric gluconate increases the haematopoietic response to rHuEPO compared with patients receiving oral iron or no iron (70%, 40%, and 35%, respectively) [37,38]. The effects on Hb levels (2.4, 1.5 and 1.2 g/dL, respectively) and measures of iron metabolism were notably greater with IV iron formulations than with oral. However, the FDA recently issued an alert giving new safety information for erythropoiesis-stimulating agents (ESAs: darbepoetin alfa, epoetin alfa). Analysis of four new studies in patients with cancer found more serious and life-threatening side effects and even death with ESAs. Use of these agents to achieve a target hemoglobin of 12 g/dL or greater in cancer patients: 1) shortened the time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy; 2) shortened overall survival and increased mortality from disease progression in patients with metastatic breast cancer receiving chemotherapy; 3) increased the risk of death in patients with active malignant disease not under treatment with chemotherapy or radiation. These research studies were evaluating an unapproved dosing regimen, a patient population for which ESAs are not approved, or a new unapproved ESA [39]. Thus, the role of ESAs is increasingly uncertain in the treatment of the anaemia of cancer.

4. INTRAVENOUS IRON THERAPY IN SURGICAL PATIENTS

Perioperative anaemia is linked to increased postoperative morbidity and mortality, and decreased quality of life [40]. Preoperative anaemia, which is one of the major predictive factors for ABT in surgeries with moderate to high blood loss [6], may be present in one-third to one-half of them due to ID, chronic inflammation, or both [3,5]. Deficiency of folic acid and/or vitamin B12 is also frequent, especially in the older population [3,5]. Although oral iron supplementation should be preferred, it is time-consuming and, for some surgical patients with severe preoperative anaemia, IV administration might be considered.

In contrast, postoperative anaemia occurs in up to 90% of patients [40]. Operative blood loss is the main cause, and may be aggravated by inadequate erythropoiesis due to inflammation, especially with decreased iron availability [41]. These alterations in iron metabolism also apply to critically ill and to trauma patients [42]. In normal persons with significant blood-loss anaemia, intravenous iron can allow

up to a five-fold erythropoietic response [3]. However, patients with perioperative inflammatory anaemia probably benefit most from the combination of rHuEPO and intravenous iron, as rHuEPO increases iron mobilization from the RES into RBC precursors [3].

4.1 Non-elective Orthopaedic Surgery.

Three non-randomized studies evaluated iron sucrose for the treatment of acute anaemia in pertrochanteric (PHF) and subcapital (SHF) hip fracture patients, and found no adverse reactions to iron administration in any of them [43-45]. In the first two, there was a trend towards a lower transfusion rate (-13%), lower 30-day mortality (-11%) and shorter hospital stay (-2 days) in 75 patients (55 PHF, 20 SHF) receiving 200-300 mg iron sucrose preoperatively (significant for SHF patients) when compared with a historical control group (159 patients: 102 PHF, 57 SHF) [43,44]. In a subsequent study, perioperative administration of 600 mg iron sucrose (plus 40,000 IU rHuEPO subcutaneously if Hb <13 g/dL upon admission) (n=83), together with a restrictive transfusion protocol (transfusion trigger: Hb <8 g/dL and/or symptoms of acute anaemia), also resulted in a reduction of the percentage of transfused patients (24% vs. 71%, respectively; $p<0.05$) when compared with a parallel control group from another surgical unit in the same institution (n=41) [45]. In addition, there was a trend towards reduced 30-day mortality (7% vs. 15%, respectively) [45].

4.2 Elective Orthopaedic Surgery

In a recent study, 27 consecutive patients scheduled to undergo major orthopaedic surgery were given preoperative IV iron infusions (600-1200 mg over 2-3 weeks) because of intolerance to oral iron administration, poor intestinal absorption, chronic inflammatory anaemia, or functional iron deficit [46]. Twenty patients received preoperative IV iron plus rHuEPO and 7 received only IV iron (rHuEPO therapy being ruled out because of cardiovascular or thromboembolic disease, or because they had pure iron deficiency). There were no differences in preoperative Hb increase (+1.7 g/dL) or postoperative transfusion rate between groups [46]. Although no comparison was made with oral iron, these data suggest that IV iron therapy may improve the preoperative haemoglobin in this patient population, whereas rHuEPO should be reserved for those not responding to IV iron.

A more recent study gave immediate perioperative iron sucrose (2 x 200 mg, days 0 and +2) plus one dose of rHuEPO (40,000 IU subcutaneously on day 0, only for patients with preoperative Hb < 13 g/dL) to 311 patients undergoing surgery for total knee replacement (TKR) under a restrictive transfusion protocol. Again, they found no adverse effects of iron sucrose or rHuEPO administration,

and only 4% of the patients received ABT [47]. Interestingly, the ABT rate in patients with preoperative Hb < 13 g/dL (9%) was no different from that reported with the administration of 4 x 40,000 IU rHuEPO (10.8%) [48]. In addition, FDA warned that the preliminary results of a 681 patient, multi-center, randomized, open-label study of rHuEPO (4 x 40,000 IU) compared with standard-of- care orthopaedic surgery showed that the frequency of deep venous thrombosis in patients treated with rHuEPO was more than twice that of patients who received only blood conservation care (4.7% vs. 2.1%, respectively) [39].

For postoperative anaemia, the administration of oral iron after orthopaedic surgery does not appear to be worthwhile [49-51]. However, iron sucrose (3 mg/kg/day) is more effective in restoring postoperative Hb after spinal surgery in children than historical controls receiving oral iron [52], and postoperative iron sucrose reduced the requirements for ABT in hip arthroplasty [53]. On the other hand, Karkouti et al [54] conducted a double-blinded, placebo-controlled randomized study of 31 adult patients without preoperative anemia (13 cardiac surgery, 18 orthopaedic) whose Hb was 7 to 9 g/dL on the first postoperative day (POD 1). Patients were assigned to one of three groups: control, IV iron alone (200 mg of iron sucrose on POD 1, 2, and 3), or IV iron with rHuEPO (600 U/kg on POD 1 and 3). There were no differences in Hb at one or six weeks after surgery, although reticulocyte counts were higher on POD-7 in the combination group. The authors concluded that early postoperative treatment with IV iron alone or in combination with rHuEPO does not appear to accelerate early recovery from postoperative anemia. However, this study has several limitations, including the small number of patients recruited relative to the number of patients screened (which limits generalizing the results), the inclusion of cardiac and orthopedic surgical patients (whose postoperative inflammatory reactions differ in intensity and duration), and the lack of parameters of baseline iron status. In addition, the authors recognized that this study cannot exclude the possibility that higher doses or different timing of postoperative IV iron and rHuEPO might accelerate the correction of postoperative anaemia [54].

In this regard, one report found that 71% of Hb loss and 92% of preoperative Hb was recovered by postoperative day 30 in TKR patients receiving perioperative intravenous iron (2 x 200 mg, days 0 and +2) with (n=19) or without EPO (n=129), and only 15% of them remained anaemic [55]. This Hb reconstitution was attained without a reduction of iron stores. On the other hand, a similar Hb reconstitution (80%) was found using oral iron or no treatment, but this was at postoperative day 56

and associated with significant reduction of ferritin levels in patients that were not transfused [56]. Hence, perioperative IV iron may hasten the recovery from postoperative anaemia and preserve iron stores in TKR patients, especially those with preoperative ferritin <100 ng/mL [55]. We offer a tentative algorithm of perioperative iron administration in patients undergoing major orthopaedic surgery (figure 2).

4.3 Cardiac surgery

In the postoperative period after uncomplicated coronary artery bypass surgery, oral iron neither restored red blood cell mass nor maintained total body iron stores [57]. In contrast, postoperative intravenous iron preserved iron stores during recovery from anaemia [59]. Moreover, the increase in Hb level from postoperative day 4 (nadir) to postoperative day 30 was 1 g/dL higher in patients who received intravenous iron supplements, with or without rHuEPO, compared with those who received placebo [58]. However, as mentioned above, the study by Karkouti et al. did not find any benefit of postoperative IV iron and rHuEPO in cardiac surgery [54]. Finally, a retrospective study of 863 cardiac surgery patients showed no differences in infection rates between patients receiving intravenous iron plus rHuEPO (n=302) or ABT (n=561), as indicated, for the correction of postoperative anaemia [59]. Adult cardiac surgery patients who received EPO had fewer ABT exposures (60/195, 31% *vs.* 56/104, 54%)(RR, 0.57; 95% CI, 0.43-0.75; $P < 0.001$), but the total rHuEPO dose varied greatly. Evidence is lacking that IV iron is better than oral iron in supporting rHuEPO treatment in cardiac surgery [60].

4.4 Colorectal cancer

Iron deficiency and anaemia are frequent in colorectal cancer (CRC) patients. Significant risk factors for anaemia include patient's age, tumour site (right colon), and tumour size (large), but not clinical stage or histological type. Thus, both IDA and ID might be therapeutic targets in CRC patients.
Oral iron supplementation (sodium ferrous citrate, 200 mg/day) to CRC patients resulted in higher Hb levels immediately before surgery, and fewer patients receiving intraoperative ABT (9.4% *vs.* 27.4%, P<0.05), when compared with a control group [61]. But there were no significant differences in postoperative Hb levels or transfusion volumes between the two groups [61]. In another study, 43 colorectal cancer patients received preoperative oral iron if Hb > 14 g/dL and iron deficiency; iron sucrose (200 mg/week) if Hb 10-14 g/dL; or iron sucrose (200 mg twice a week) if Hb < 10 g/dL, for 2-3 weeks. Seventeen of these patients also received postoperative iron sucrose (200 mg on days 0, 2, and 4). A retrospective series of patients not receiving iron was used as a control group (n = 66).

Despite a lower baseline Hb (12.3 *vs.* 11.5 g/dL; $P < 0.05$), iron therapy reduced the transfusion index (4.0 *vs.* 1.3 unit/patient; $P < 0.05$) and the percentage of patients who received preoperative ABT (33% *vs.* 9%; $P<0.05$), but not the percentage of patients administered perioperative ABT (48% *vs.* 35%; $P=0.161$). However, the treatment was ineffective in patients with a high transfusion index (> 5 units/patient) [62].

The effectiveness of perioperative intravenous iron can be enhanced by concomitant rHuEPO administration. Thus, perioperative treatment with rHuEPO alone reduced the risk of exposure to ABT in patients with moderate anaemia scheduled for CRC surgery (38% *vs.* 47%; RR, 0.81; 95% CI, 0.61-1.00; $P = 0.054$), whereas a reduction of both the percentage of transfused patients and the number of transfused units was observed only in those receiving both rHuEPO and intravenous iron. Additionally, the use of intravenous iron allowed for a significant reduction in the total dose of rHuEPO [62]. Nevertheless, even when this is a short term therapy, we should take into account the above-mentioned uncertain role of rHuEPO on cancer patients' outcome.

4.5 Gynaecological surgery

In gynaecological practice, most blood transfusions occur at the time of radical surgery. Many patients already have IDA or ID, from chronic blood loss, so preoperative correction of anaemia emerges as a possible alternative to ABT. In two randomized controlled studies of 81 healthy, mildly anaemic women who underwent total hysterectomy, patients who received rHuEPO once weekly for 3-4 weeks with oral iron had higher preoperative Hb levels and less need of ABT than those who received only oral iron [63,64]. But in one of these studies, the authors found that in most cases of myoma iron alone seemed as efficacious as iron plus rHuEPO in correcting anaemia preoperatively [63]. Another study evaluated the efficacy and safety of treatment with intravenous iron for postoperative anaemia in 52 gynaecological surgery patients (46% abdominal hysterectomy; 21% myomectomy) with Hb levels less than 10 g/dL, who received three 200 mg doses of IV iron sucrose on consecutive days. Fifteen days after the last dose, Hb was increased by 2.7 g/dL (95% CI 2.2-3.1; $p<0.001$), only one patient had side effects (pain at the injection site), and no patient received ABT [65]. Therefore, the low incidence of serious side effects and the rapid recovery of Hb levels make iron sucrose a safe, effective drug for treating perioperative anaemia in this patient population.

5. CRITICALLY ILL PATIENTS

More than a third of ICU patients have FID, a condition that cannot be corrected with oral iron supplements [42,66]. Patients with FID have longer episodes of systemic inflammatory response syndrome (SIRS) and longer ICU stays than those without FID [66]. In contrast, critically ill patients with anaemia treated with IV iron sucrose (20 mg/day) experienced an improvement of SIRS (reduction of C-reactive protein levels) and a trend to reduced transfusion and mortality rates, compared with those in a control group who only received folic acid [67]. In a recent study, the number of RBC units transfused and the percentage of transfused patients were lower in ICU patients receiving IV iron sucrose (100 mg three times a week) and subcutaneous rHuEPO (40,000 units once a week or three times a week) than in patients receiving iron sucrose alone, although there were no differences in morbidity or mortality rates among the three groups [68] (Table 4). This protocol resulted in both a lower transfusion rate and a net increase in Hb levels, when compared with data reported by Corwin *et al*. [69] (Table 4). Thus, the administration of intravenous iron to critically ill patients seems to be safe and effective in improving the dose-dependent response to rHuEPO. But it is not yet clear whether the administration of rHuEPO to ICU patients gives a better outcome. This indicates that patient selection is important, and better rHuEPO and intravenous iron titrations are needed to improve morbidity, mortality and cost-effectiveness.

6. CONCLUSIONS.

Anaemia is common in patients admitted to hospital medico-surgical departments, and in the critically ill. It is most often due to absolute ID or FID (Table 1). In contrast, postoperative anaemia is mainly caused by perioperative blood loss, and might be aggravated by inflammation-induced depression of erythropoiesis. All these mechanisms may affect the anaemia of the critically ill.

We should take note of patients who might receive perioperative transfusions on the basis RBC mass, transfusion trigger, and expected blood loss (e.g., using Mercuriali's algorithm) [70]. Therefore, whenever clinically feasible, patients undergoing elective surgery with a high risk of postoperative anaemia should have tests for Hb [71] and iron status (serum iron, ferritin, and transferrin saturation index) at least 30 days before the scheduled surgical procedure. For patients older than 60 years, vitamin B12 and folic acid should also be measured [72]. Unexplained anaemia should always be considered secondary to some other process and, therefore, elective surgery should be deferred pending diagnosis [71].

Administration of IV iron, with or without EPO, to medical and surgical patients seems to be safe, as very few severe side-effects have been observed. It may result in lower transfusion requirements, shorter length of hospital stay, and hastened recovery from anaemia. However, many of the recommendations given for IV iron are not supported by much evidence (Table 5) and this must be borne in mind when making decisions for a particular patient. Because of this, we need more large, randomized controlled trials on the safety, efficacy and cost-effectiveness of IV iron for treating anaemia in the clinical settings reviewed.

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Table 1. Main causes of iron deficiency

A. Increased Demands
• Growth during infancy and childhood • Treatment with erythropoiesis-stimulating agents
B. Increased Losses
• Phlebotomy Blood donation Dialysis (particularly haemodialysis) • Haemorrhage Surgery Trauma Gastrointestinal bleeding Genitourinary bleeding Respiratory tract bleeding
C. Insufficient Intake
• Malnutrition • Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid • Malabsorption Gastric resection *Helycobacter pylori* infection Malabsorption syndromes (Crohn's disease and celiac disease) • Drug interference (gastric antiacid agents and antisecretory drugs)

Table 2. Main laboratory tests for the diagnosis of iron deficiency.

A. Measurements providing evidence of iron depletion in the body
• Serum iron • Transferrin • Total iron binding capacity (TIBC) • Transferrin saturation • Ferritin (Ft) • Soluble transferrin receptors (sTfR) • Ratio of sTfR to serum Ft (sTfR/log Ft)
B. Measurements reflecting iron deficient red cell production
• Hb • Mean corpuscular volume (MCV) • Variability in red cell size (RDW) • Mean corpuscular Hb (MCH) • Percentage of hypochromic red cells • Reticulocyte Hb content

Table 3. Some **chemical and pharmacokinetics** characteristics of the different intravenous iron formulations.

	Iron dextran (HMW)	**Iron dextran (LMW)**	**Iron gluconate**	**Iron sucrose**
Molecular weight (kD)	265	73	38	43
Particle diameter (nm)	30 ± 10	----	3 ± 1	7 ± 4
Initial distribution volume (L)	3.5	3.5	6	3.4
Plasma half-life (h)	60	30	1	6
Direct iron donation to transferrin (% injected dose)	1-2	1-2	5-6	4-5
Labile iron release	-	-	+++	± (1)
Maximal single dose (mg)	Total dose	Total dose	125	300

HMW, high molecular weight; LMW, low molecular weight; ADE, adverse drug events

(1) If the infusion speed >4 mg Fe^{3+}/min or dose >7 mg Fe^{3+}/kg

Table 4. Effectiveness of rHuEPO and intravenous iron in critically ill patients

	Corwin, 2002 [1]		**Georgopoulos, 2005** [2]		
	Control	rHuEPO	Control	rHuEPO-1	rHuEPO-2
Patients (n)	652	650	48	51	49
Transfusion (%)	60.8	50.5*	59.3	37.3*	26.5*
Transfused units	1963	1590*	138	33*	23*
Transfusion index (U per patient)	3.0 ± 5.4	2.4 ± 4.8	2.8 ± 3.9	0.6 ± 1.0*	0.5 ± 0.9
Baseline Hb (g/dL)	10 ± 1.2	10 ± 1.2	9.2 ± 1.3	9.3 ± 1.2	9.2 ± 0.9
Observed ΔHb (g/dL)	0.9 ± 0.9	1.3 ± 2.0*	0.7 ± 1.5	1.4 ± 1.7*	2.2 ± 2.2*
Net ΔHb (g/dL)[3]	– 2.1	– 1.1	– 2.1	+ 0.8	+ 1.7
Mortality	18.4	17.1	14.6	9.8	20.4

[1] rHuEPO 40,000 IU once a week, oral iron (IV iron if intolerance to oral iron or development of iron deficiency), transfusion threshold Hb <9 g/dL.

[2] rHuEPO 40,000 IU once a week (rHuEPO-1) or three times a week (rHuEPO-2), intravenous iron sucrose 100 mg three times a week, transfusion threshold Hb <7 g/dL.

[3] Net ΔHb (g/dL) = Observed ΔHb (g/dL) - Transfusion index (U per patient); assuming that 1 packed red cell unit increases Hb concentration by 1 g/dL.

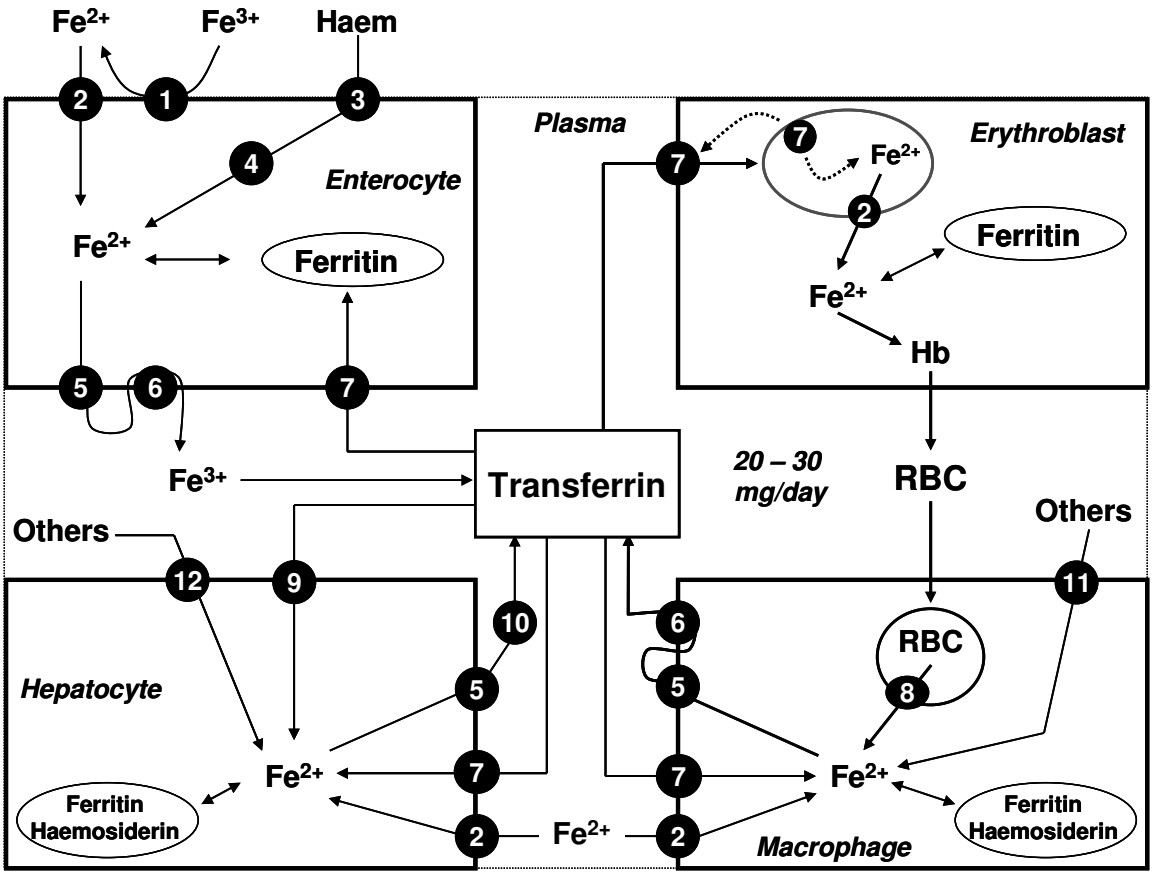
* P<0.05

Table 5. Grade of recommendation of intravenous iron therapy for treating anaemia and/or avoid allogeneic transfusion medico-surgical patients, according to modified Delphi methodology (75).

Clinical Setting	Recommendation
A. Medical patients	
• Pregnancy and post-partum	**C**
• Inflammatory bowel disease	**C**
• Congestive heart failure	**D**
• Rheumatoid arthritis	**D**
• Chronic kidney disease	**B**
• Anaemia of cancer	**C**
B. Surgical patients	
• Non-elective orthopaedic surgery	**D**
• Elective orthopaedic surgery	**D**
• Cardiac surgery	**E**
• Colo-rectal cancer surgery	**E**
• Gynaecological surgery	**D**
C. Critically ill patients	**D**

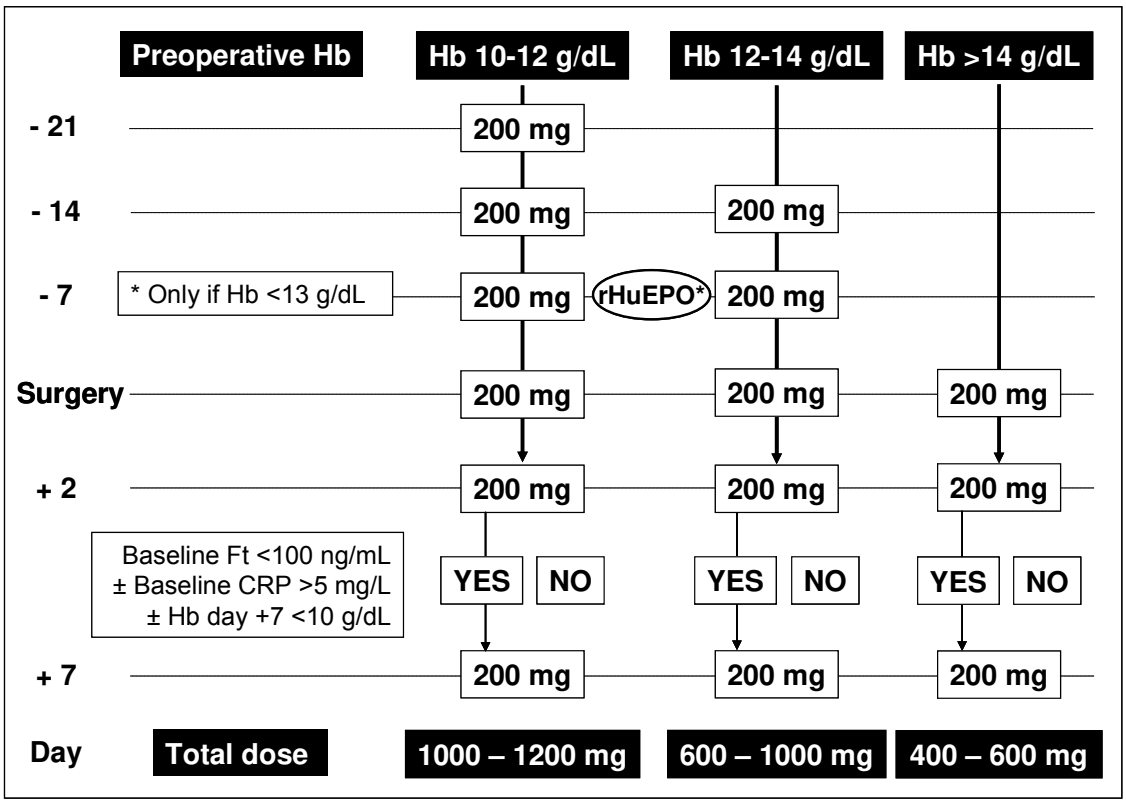
Grades of recommendation: A, supported by at least 2 studies of level 1 (RTCs with large sample populations, clear objectives and low or a very low risk of bias, or well-conducted meta-analyses or systematic reviews); B, supported by 1 study of level I; C, supported by studies of level II (RTCs with small sample populations, clear objectives and moderate risk of bias); D, supported by studies of level III (Observational studies with contemporary controls); E, supported by studies of level IV (Observational studies with historical controls) or V (Non-analytic studies, e.g. case reports, case series. Expert opinion)

Figure 1. Main pathways of iron absorption, distribution and storage in humans.



Keys. 1. Ferrireductase; 2. Divalent metal transporter (DMT-1); 3. Haem receptor; 4. Haem hydroxilase; 5. Ferroportin (Fpn1); 6. Haefastin; 7. Transferrin receptor-1 (TfR1); 8. Natural resistance macrophage protein (Nramp-2); 9. Transferrin receptor-2 (TfR2); 10. Ceruloplasmin; 11. Others: bacteria, lactoferrin, Hb-haptoglobin, Haem-haemopexin, etc. 12. Others: Hb, haem, ferritin.

Figure 2. A tentative algorithm for the use of intravenous iron sucrose in a 70 kg patient scheduled for major orthopaedic surgery with an expected haemoglobin drop of 4 g/dL



Total iron dose (mg) = Total iron deficiency (TID) + Surgical iron loss (SIL)
TID = [Target Hb (g/dL) – Actual Hb (g/dL)] x Weight (kg) x 2.4; where target Hb is 14 g/dL and 2.4 is a factor (Hb iron content x blood volume x 1000)
SIL = expected Hb drop (g/dL) x 165; assuming that 165 mg of iron are needed to raise Hb by 1 g/dL.
Day, perioperative day (- preoperative, + postoperative); Ft, ferritin; CRP, C-reactive protein.