



Revisión

Perioperative intravenous iron; an upfront therapy for treating anaemia and reducing transfusion requirements

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Abstract

Perioperative anaemia, with iron deficiency being its leading cause, is a frequent condition among surgical patients, and has been linked to increased postoperative morbidity and mortality, and decreased quality of life. Postoperative anaemia is even more frequent and is mainly caused by perioperative blood loss, aggravated by inflammation-induced blunting of erythropoiesis. Alloge- nic transfusion is commonly used for treating acute perioperative anaemia, but it also increases the rate of morbidity and mortality in surgical and critically ill patients. Thus, overall concerns about adverse effects of both preoperative anaemia and allogeneic transfusion have prompted the review of transfusion practice and the search for safer and more biologically rational treatment options. In this paper, the role of intravenous iron therapy (mostly with iron sucrose and ferric carboxymal- tose), as a safe and efficacious tool for treating anaemia and reducing transfusion requirements in surgical patients, as well as in other medical areas, has been reviewed. From the analysis of published data and despite the lack of high quality evidence in some areas, it seems fair to conclude that perioperative intravenous iron administration, with or without erythropoiesis stimu- lating agents, is safe, results in lower transfusion require- ments and hastens recovery from postoperative anaemia. In addition, some studies have reported decreased rates of postoperative infection and mortality, and shorter length of hospital stay in surgical patients receiving intra- venous iron.

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HIERRO INTRAVENOSO PERIOPERATORIO; UNA OPCIÓN TERAPÉUTICA PARA EL TRATAMIENTO DE LA ANEMIA Y LA REDUCCIÓN DE LOS REQUERIMIENTOS DE TRANSFUSIÓN

Resumen

La anemia perioperatoria, cuya principal causa es la deficiencia de hierro, es frecuente entre pacientes quirúr- gicos y se asocia a un aumento de la morbimortalidad pos- toperatoria y a una disminución de la calidad de vida. La anemia postoperatoria es aún más frecuente y está causada principalmente por la pérdida perioperatoria de sangre, agravada por la reducción de la actividad eritropoyética inducida por la inflamación. La transfusión alogénica es el tratamiento habitual de la anemia aguda perioperatoria, pero también aumenta la tasas de morbimortalidad en pacientes quirúrgicos y críticos. La preocupación por los efectos adversos de la anemia preoperatoria y la transfu- sión alogénica han impulsado la revisión de la práctica transfusional y la búsqueda de opciones de tratamiento más seguras y biológicamente más racionales. En este artículo se revisa el papel de la terapia con hierro intrave- noso (mayoritariamente hierro sacarosa y carboxymal- tosa de hierro), como herramienta segura y eficaz para el tratamiento de la anemia y la reducción de los requeri- mientos transfusionales en el paciente quirúrgico, así como en otras áreas médicas. Del análisis de los datos publicados y a pesar de la falta de evidencia de alta cali- dad en algunas áreas, parece razonable concluir que la administración perioperatoria de hierro intravenoso, con o sin agentes estimuladores de la eritropoyesis, es segura, reduce las necesidades de transfusión y acelera la recupe- ración de la anemia postoperatoria. Además, algunos estudios han encontrado una reducción de las tasas de infección postoperatoria y de mortalidad, así como de la duración de la estancia hospitalaria, en pacientes quirúr- gicos tratados con hierro intravenoso.

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Palabras clave: *Anemia perioperatoria. Transfusión alo- génica. Hierro intravenoso. Seguridad. Eficacia.*

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Abbreviations

ABT: Allogeneic blood transfusion.
ADEs: Adverse drugs events.
BS: Bariatric surgery.
CRC: colorectal cancer.
CHF: Chronic heart failure.
CKD: Chronic kidney disease.
ESAs: Erythropoiesis-stimulating agents.
FCM: Ferric carboxymaltose.
FID: Functional iron deficiency.
Hb: Haemoglobin.
HMWID: High molecular weight iron dextran.
IBD: Inflammatory bowel disease.
ICU: Intensive care unit.
ID: Iron deficiency.
IDA: Iron deficiency anaemia.
IS: Iron sucrose.
IV: Intravenous.
LMWID: Low molecular weight iron dextran.
NATA: Network for the Advancement of Transfusion Alternatives.
NSQIP: National Surgical Quality Improvement Program.
PHF: Pertrochanteric hip fracture.
RCT: Randomised controlled trial.
RES: Reticulo-endothelial system.
rHuEPO: Recombinant human erythropoietin.
SHF: Subcapital hip fracture.
THR: Total hip replacement.
TKR: Total knee replacement.

Introduction

Perioperative anaemia has been linked to increased postoperative morbidity and mortality, and decreased quality of life. Depending on the procedures and the definitions of anaemia, from 11% to 76% of surgical patients may present with preoperative anaemia.¹ Iron deficiency (ID) is the leading cause of anaemia in surgical patients, and results from the interplay of three distinct risk factors: increased iron requirements (e.g., associated with treatment with erythropoiesis-stimulating agents), limited external supply (e.g., *Helicobacter pylori* infection, autoimmune atrophic gastritis, chronic and acute inflammatory diseases, etc) and increased blood loss (e.g., due to phlebotomy or haemorrhage).²

Postoperative anaemia, which may be present in up to 90% of patients undergoing major surgery¹ is mainly caused by perioperative blood loss and may be aggravated by blunting of erythropoiesis by inflammatory responses, especially through decreased iron availability due to hepcidin-induced down-regulation of intestinal absorption and impaired mobilization of iron from body stores.³

Thus, 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 from the macrophages of the reticulo-endothelial system (RES). FID occurs in anaemia of inflammatory diseases because iron is trapped in the RES as a result of increased secretion of hepcidin, a hormone that controls iron release from cells.³ FID may also occur in response to the therapeutic use of 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

Iron deficiency can be investigated using different laboratory tests which fall into two categories: measurements providing evidence of iron depletion in the body (serum iron, transferrin, transferrin saturation, ferritin, soluble transferrin receptors, ferritin index, etc), and measurements reflecting iron deficient red cell production (haemoglobin [Hb], mean corpuscular volume, variability in red cell size, mean corpuscular Hb, percentage of hypochromic red cells, reticulocyte Hb content, etc.). The appropriate combination of these laboratory tests allow for differential diagnosis of anaemia and ID status.³

Anaemia, allogeneic blood transfusion and patient's outcome

Preoperative anaemia is one of the major predictive factors for allogeneic blood transfusion (ABT) related to surgery with moderate to high blood loss.^{4,5} ABT is commonly used to rapidly and effectively restore the Hb levels, avoiding the deleterious effects of severe anaemia, especially when acutely developed or in elderly patients whose compensatory mechanisms have a limited capacity of response. However, though increasingly safer, ABT can never be a risk-free therapy and likely increases the rate of morbidity and mortality in surgical and critically ill patients.⁶

Wu et al.⁷ retrospectively analyzed the National Surgical Quality Improvement Program (NSQIP) database for 239,286 patients older than 65 years of who underwent major non-cardiac surgery in 1997 to 2004 at veteran hospitals nationwide. Intraoperative ABT was associated with a lower 30-day postoperative mortality if there was substantial operative blood loss or low preoperative haematocrit levels (< 24%), whereas ABT was associated with increased mortality risks for those with preoperative haematocrit levels between 30% and 35.9% and < 500 mL of blood loss. In contrast, in another retrospective review of 10,100 patients undergoing general, vascular, or orthopaedic surgery, intraoperative ABT was associated with a higher risk of 30-day mortality and morbidity in patients with severe anaemia (haematocrit < 30%). It is unknown whether this association is due to the adverse effects of ABT or is the result of increased blood loss in the patients receiving blood.⁸

The analysis of a population-based follow-up study in Denmark identified 28,087 primary total hip

replacement (THR) procedures performed from 1999 to 2007. Using a propensity score matching, the authors compared postoperative outcomes of 2,254 transfused and 2,254 non-transfused THR patients, and found that ABT was associated with increased odds of death and pneumonia. Although the odds estimates may partly reflect unmeasured bias due to blood loss, they indicate the need for careful assessment of the risk versus benefit of ABT even in relation to routine THR procedures.⁹

Moreover, in colorectal cancer (CRC) surgery, ABT is also associated with increased rates of cancer recurrence.¹⁰⁻¹² In a meta-analysis, 23 out of 36 studies on 12,127 patients showed a detrimental effect of ABT. Patients randomized to ABT had a higher rate of tumour recurrence than those not transfused with a clustered odds ratio (OR): 1.42 (95% Confidence Interval [CI]:1.20-1.67). However, the authors considered that an effect of other variables, such as the surgical technique, cannot be excluded and that, therefore, a cause and effect relationship between ABT and tumour recurrence cannot be established. Nevertheless, they strongly recommend that is essential to minimize the use of ABT in surgery.¹²

On the other hand, perioperative anaemia in itself has been associated with harmful effects over and above the increased risk imparted by the increased need for ABT. A variety of studies in cardiac¹³⁻¹⁶ and non-cardiac surgery¹⁷⁻¹⁹ have linked anaemia with increased mortality. As for cardiac surgery, in a multi-center cohort study of 3,500 cardiac surgery patients, those with a Hb level of less than 12.5 g/dL (26%) fared worse in regard to cardiovascular outcomes after controlling for confounding variables and propensity score matching.¹⁴ In other studies, preoperative anaemia was associated, not only with an increased risk of ABT,¹⁵ but also with a greater risk for lower survival after coronary artery bypass grafting.¹⁶ Disease severity and co-morbidity have the greatest effect on mortality in anaemic cardiac surgical patients, which may be aggravated by transfusion of stored blood, anaemia being just a consequence of some other disorders such as acute or chronic blood loss, nutritional ID, renal failure, malignancy, or chronic inflammatory disease.

As for patients undergoing non-cardiac surgery, Wu et al.¹⁷ in a cohort of 310,311 elderly patients from the Department of Veterans Affairs hospitals, found a prevalence of preoperative anaemia of 42.9% (haematocrit < 39%), and data analysis demonstrated an increase in postoperative death and cardiac events associated with decreasing haematocrit levels. Musallam et al.¹⁸ also analysed data from a prospective validated outcomes registry for 227,425 patients undergoing major non-cardiac surgery, of whom 69,229 (30.4%) had preoperative anaemia. They found that preoperative anaemia, even to a mild degree, was independently associated with an increased risk of 30-day morbidity and mortality. Finally, Leichtle et al.¹⁹

analysed the NSQIP database for 23,348 patients undergoing elective open and laparoscopic colectomies, using multivariable models, controlling for potential confounders and stratifying on propensity scores. The results of this analysis suggested that the presence of severe, moderate and even mild preoperative anaemia is an independent risk factor for complications and a longer hospital stay.

Thus, overall concerns about adverse effects of both preoperative anaemia and ABT have prompted the review of transfusion practice and the search for a safer and more biologically rational treatment option, such as stimulation of erythropoiesis with intravenous iron, with or without ESAs. Consequently, the first step to be taken in the setting of elective surgery will be the preoperative identification and evaluation of anaemia early enough to implement the appropriate treatment.²⁰

As for iron deficiency anaemia (IDA) caused by poor intake, chronic blood loss, etc, iron absorption is increased and, provided there is no pathology of the gastrointestinal tract, oral iron administration usually leads to correction of the anaemia.³ However, for a person weighing 70 kg with a Hb 8.5 g/dL a body iron deficit of about 1,700 mg could be estimated. Even at the maximum daily iron absorption in the presence of ID (10 mg), nearly 6 months of oral iron replacement regimen would be required to correct the iron deficit in this patient. Such a time frame is unacceptable for most patients who require prompt surgery and preoperative IV iron administration might be considered, as it can allow up to a five-fold erythropoietic response to significant blood-loss anaemia in normal individuals.³

On the other hand, in anaemia of chronic inflammation (e.g., rheumatoid arthritis, Crohn's disease, chronic renal or heart failure, cancer, etc), as well as in that associated with acute inflammation (e.g., trauma, surgery, etc), the utility of oral iron administration is rather limited, since absorption is down-regulated, and the small amount of iron absorbed is directed to the RES, where it is sequestered. Hepcidin, a hepatic acute-phase protein, plays a major role in both processes.² Again, IV iron would be a more effective mode of administration in these situations, although some patients will most probably benefit from addition of ESAs to intravenous iron, as ESAs therapy increases iron mobilization from the RES into the erythroid precursors.^{2,3}

Perioperative intravenous iron therapy

Most 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. However, the structure of iron isomaltoside 1000 is somehow different as the linear oligosaccharide isomaltoside 1,000 allows for the formation of a matrix with interchanging iron and carbohydrate.²¹ Differences in

core size and carbohydrate chemistry determine pharmacological and biologic differences between the different agents, including clearance after injection, iron release *in vitro*, early evidence of iron bioactivity *in vivo*, and maximum tolerated dose and rate of infusion. Among the existing preparations (table I), six different products are available in Europe: iron gluconate (Ferrlecit®), iron sucrose (Venofer®), low molecular weight iron dextran (LMWID, Cosmofer®), ferric carboxymaltose (FCM, Ferinject®), iron isomaltoside 1000 (Monofer®), and ferumoxytol (Rinso®, FeraHeme®), whereas high molecular weight iron dextran (HMWID, Dexferrum®) is only available in USA (See references 21-23 for further details). We will review the role of perioperative IV iron therapy (mostly with iron sucrose and FCM), as a safe and efficacious tool for reducing transfusion requirements.

Anaemia in obstetric and gynaecological surgery

Anaemia due to ID or iron loss is a common condition both during pregnancy and postpartum. During pregnancy, oral iron is the first option for treatment of IDA. However, iron sucrose with or without adjuvant ESAs might be considered for the treatment of gestational IDA resistant to therapy with orally administered iron alone.²⁴

Similarly, oral or IV iron with or without ESAs have shown to be equally useful for the treatment of postpartum anaemia.²⁵ However, Broche et al.²⁶ showed that administration of IV iron sucrose (200-600 mg) was superior to oral iron for treating anaemic puerperae (Hb < 8 g/dL with 48 h of delivery), as it resulted in higher elevation of Hb levels at postpartum day 7 (1.9 g/dL vs. 0.9 g/dL, respectively; $p < 0.01$). Wagström et al.²⁷ reported a mean increment in Hb of 1.8 g/dL after 1 week, and 2.8 g/dL after 2 weeks in patients with Hb values < 8 g/dL within 72 h after who were given a total dose of 450 mg IV iron sucrose. In comparison to IV iron alone, the addition of ESAs did not further increase Hb.²⁷ Similar positive results have been reported for postpartum administration of iron sucrose²⁸⁻³¹ or FCM alone,^{32,33} especially in women undergoing Caesarean section. In contrast, one study showed that IV FCM was just as effective as oral ferrous sulphate in correcting postpartum anaemia.³⁴ Thus, IV iron improves postpartum anaemia and iron status and reduces ABT frequency, whereas additional treatment with ESAs should be reserved for patients with profound postpartum inflammation.²⁴

In gynaecological practice the greatest number of ABT occur at the time of abdominal radical hysterectomy. In the usual circumstance, ABT is prompted by surgical blood loss in a patient. Since many of these patients presented with IDA or ID, due to chronic blood loss, preoperative correction of anaemia emerges as a possible alternative to ABT. In two randomized controlled trials (RCT) including 81 mildly anaemic

women who underwent total hysterectomy, patients who received ESAs once weekly for 3-4 weeks, plus oral iron supplementation had a significantly higher preoperative Hb levels and lower requirements for ABT than those who received only oral iron supplementation.^{35,36} However, as ESAs administration in gynaecological surgery is an *off-label* indication, Díez-Lobo et al.³⁷ investigated the utility of preoperative IV iron in a series of 31 patients with IDA or ID undergoing abdominal hysterectomy who received a mean of 800 mg iron sucrose (500-1,600 mg) over 2-4 weeks preoperatively. A parallel series of 54 matched patients receiving no IV iron serves as control group. Compared to those from the control group, patients from the iron sucrose group presented with higher Hb levels both immediately before surgery (13.3 vs. 11.7 g/dL, for IV iron and control, respectively; $p < 0.05$) and at discharge (12.5 vs. 11.8 g/dL, respectively; $p < 0.05$), despite fewer patients received ABT (0% vs. 29%, respectively; $p < 0.05$). Only minor side effect to iron sucrose were observed (2 phlebitis, 10 pain at the injection site), but they did not result in treatment discontinuation. In addition, data from a phase III RCT in women with heavy uterine bleeding, clearly showed that IV FCM was more efficacious in correcting anaemia and replenishing iron stores at 6 weeks than oral ferrous sulphate.³⁸

On the other hand, the efficacy and safety of treatment with IV iron for postoperative anaemia was prospectively assessed in 52 gynaecological surgery patients (46% abdominal hysterectomy; 21% myomectomy) with Hb levels of less than 10 g/dL, who received 3 x 200 mg doses of IV iron sucrose administered on consecutive days. Fifteen days after the last dose, patients came for a follow-up test and were asked about side effects. After treatment, Hb increased by 2.7 g/dL (95% CI 2.2-3.1; $p < 0.001$), one patient had side effects (pain at the injection site), and no patient received ABT.³⁰

Therefore, the low incidence of serious side effects and the rapid recovery of Hb levels make IV iron a safe, effective option for treating perioperative anaemia in this patient population, and probably to correct persistent fatigue which is the most common complaint of patients following hysterectomy.³⁹

Anaemia in inflammatory bowel disease

Approximately, one third of inflammatory bowel disease (IBD) patients suffer from recurrent anaemia (ranging from 6% to 73%, depending on Hb cut-off for the definition of anaemia; patient selection, IBD phenotype, and year of publication), and the prevalence of ID is even higher (mean prevalence: 45%).⁴⁰ Anaemia is also frequent in patients with ulcerative colitis requiring elective (22%) or urgent (67%) colectomy.⁴¹ Both ID due to blood loss in the intestine, that cannot be matched by duodenal iron absorption,

Table I
Some characteristics of the different intravenous iron formulations

Brand name	Iron gluconate	Iron sucrose	Low molecular weight iron dextran (LMWD)	Ferric carboxymaltose	Iron isomaltoside 1000	High molecular weight iron dextran (HMWD)	Ferumoxyl
	Ferrlecit®	Venofer®	Cosmofer® INFeD®	Ferinject® Injectafer®	Monofer®	Dexferrum®	FeraHeme® Rinso®
Carbohydrate shell	Glucanate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide)	Isomaltoside (linear oligosaccharide)	Dextran (branched polysaccharide)	Polyglucose sorbitol carboxy-methyl-ether
Complex type	Type III Labile and weak	Type II Semi-robust and moderately strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong	Type I Robust and strong
Molecular weight (kD)	289-440	30-60	165	150	150	265	750
Initial distribution volume (L)	6	3.4	3.5	3.5	3.4	3.5	3.16
Plasma half-life (h)	1	6	20	16	20	60	15
Direct iron donation to transferrin (% injected dose)	5-6	4-5	1-2	1-2	<1	1-2	<1
Test dose required	No	Yes/No*	Yes	No	No	Yes	No
Iron content (mg/mL)	12.5	20	50	50	100	50	30
Maximal single dose (mg)	125	200	20 mg/kg	20 mg/kg (max 1,000 mg in one infusion)	20 mg/kg	20 mg/kg	510
Premedication	No	No	No	No	No	TDI only	No
Life-threatening ADE (x 106 doses)	0.9	0.6	3.3	??	??	11.3	??

ADE: Adverse drug event; TDI: Total dose infusion. * Only in some European countries.

creating a negative iron balance, and the inflammatory nature of the disease contribute most to the development of anaemia in IBD, whereas cobalamin or folate deficiency and various other causes of anaemia occur infrequently. Finally, various pharmacologic drugs that are used for the treatment of IBD (e.g., sulfasalazine, azathioprine and 6-mercaptopurine) may interfere with erythropoiesis. Chronic fatigue, a frequent IBD symptom, is commonly caused by anaemia and may debilitate patient as much as abdominal pain or diarrhoea. However, in spite of being a condition having a significant impact on the quality of life of affected patients, anaemia treatment in IBD has been given scant attention.^{40,42}

The efficacy of oral iron therapy in patients with IBD may be hindered by more pronounced gastrointestinal side effects of oral ferrous iron,⁴³ including an increase in clinical disease activity and reduced absorption due to chronic inflammation.⁴⁴ These limitations of oral iron therapy in IBD patients mean that parenteral routes of iron administration must be considered, especially in patients presenting with moderate to severe anaemia (Hb <10 g/dL), severe intestinal disease activity, or using ESAs, and in those scheduled for surgery in less than one month. After the initial resolution of anemia and the repletion of iron stores, patient's haematological and iron parameters should be carefully and periodically monitored, and maintenance iron treatment should be provided as required.⁴⁵

A summary of the main published studies assessing the efficacy of IV iron in anaemic IBD patients is depicted in table II.⁴⁶⁻⁵² Overall, for patients who completed iron treatment, the mean response to the treatment of IBD-associated anaemia (Hb \geq 2 g/dL or normal Hb) was 73.6% with IV iron and 65.1% with oral iron (OR = 1.49; 95% CI 1.02-2.17; $p = 0.02$). However, when the analysis was performed for data extracted from RCT only, the percentage of responses were 72.5% vs. 58.2%, respectively (OR = 1.87; 95% CI 1.13-3.09; $p = 0.0097$). In addition, reviewed data strongly suggest that for patients with IBD, treatment with IV iron is effective, safe, well tolerated (lower rates of treatment discontinuation due to adverse events with IV iron than with oral iron: 1.3% vs. 11.4%; $p = 0.001$), provides a fast Hb increase and a sufficient refill of iron stores, and presents a lower rate of treatment discontinuation than oral iron. The main disadvantage of IV iron sucrose is the need for multiple infusions as the maximum weekly dose should not exceed 600 mg. The availability of stable parenteral iron compounds allowing for higher dose infusion (table I) may greatly facilitate iron replacement therapy in IBD patients (table II). In this regard, an open-label phase III RCT by Evstatiev et al.⁵³ compared the efficacy and safety of a novel fixed-dose FCM regimen with that of individually calculated iron sucrose doses in 485 patients with IBD and IDA. Patients received either FCM in a maximum of 3 infusions of 1,000 or

500 mg iron, or Ganzoni-calculated iron sucrose dosages in up to 11 infusions of 200 mg. By week 12, both treatments improved quality of life scores, but more patients with FCM than with iron sucrose showed full adherence to treatment, achieved a Hb response of 2 g/dL or more (66% vs. 54%, $p = 0.004$), or Hb normalization (73% vs. 62, $p = 0.015$). Repeated measures analysis showed significantly stronger increases in Hb (from week 2 onwards), transferrin saturation, and ferritin (at all time points) in the FCM group. Nevertheless, repletion of iron stores (ferritin > 100 mg/L) at the end of treatment was achieved only for 31% of patients, indicating that iron needs in IBD patients were underestimated.⁵³ In this regard, a retrospective analysis of 88 patients showed that insufficient iron repletion relates to rapid recurrence of IDA within 4 months and consequent re-initiation of iron treatment,⁵⁴ highlighting the need for complete iron repletion and close follow-up in these patients. Data from an ongoing phase III, multi-centre, RCT (NCT00810004) on the efficacy and safety of a standardised maintenance dosage regimen of IV FCM versus placebo in 200 patients with IDA caused by IBD will probably further clarify this issue.

As for children, the safety and efficacy IV iron therapy was retrospectively evaluated in 70 paediatric patients with IBD who received 119 HMWID infusions to replenish total iron deficiency. The average increase in Hb concentration was 2.9 g/dL. The authors concluded that total dose infusion of HMWID, when appropriately used, is a safe and potentially efficacious treatment for children with IBD and IDA who are unresponsive to or noncompliant with oral iron therapy.⁵⁵ However, cited estimated adverse event rates of > 25% should urge clinicians not to use HMWID. Thus, it must be borne in mind that iron dextran has the disadvantage of potentially life-threatening dextran-associated anaphylactic reactions, especially when HMWID is used.²¹⁻²³ Studies on the use of newer IV iron formulation in children with IBD are urgently needed.

Anaemia in hip fracture surgery

As stated above, anaemia is common among patients needing surgery for hip fracture repair, and is the major predictive risk factor for receiving ABT.⁴ Among this elderly population with hip fracture, ABT was not associated with changes in mortality, but was associated with an increased rate of postoperative infection.⁵⁶ As ID is the leading cause of preoperative anaemia in patients sustaining hip fractures, the efficacy of iron therapy for improving Hb and reducing ABT has been tested in several studies. When administered in the postoperative period, the results of several RCTs suggested that the administration of oral iron was no effective in correcting anaemia in patients presenting with hip fracture.⁵⁷⁻⁵⁹ In contrast, Cuenca et al.^{60,61} observed that preoperative administration of 200-300

Table II
 Characteristics of the clinical trials involving IBD patients that compared non-dextran IV iron administration with oral iron or no intervention included in the review

Study year (ref.)	n	Study design	Compound	Baseline Hb (g/dL)	Total dose, mg (Schedule)	Duration (weeks)	Response	DCT
Gasche et al. 2001 ⁴⁵	103	Multicentre, open-label	Iron sucrose	≤ 10.5	1,200 mg (6 x 200 mg)	4	65%	0%
Bodemar et al. 2004 ⁴⁶	59	Retrospective	Iron sucrose	< 12	Mean 1,400 mg (1-2 x 200 mg/week)	8 12	60% 91%	0%
Schröder et al. 2005 ⁴⁶	46	Multicentre randomized open-label	Iron sucrose (22) Ferrous sulfate (24)	< 10.5 ♀ < 11 ♂	Mean 1,418 mg (7 mg/kg + 5 x 200 mg) Mean 5,600 mg (100-200 mg/day)	6	55% 53%	4.5% 20.8%
García-López et al. 2006 ⁴⁷	70	Single centre prospective observational	Iron sucrose	< 10.5*	Mean 920 mg (200-1,800 mg) (200 mg/1-3 times a week)	Mean 5 (1-9)	67%	0%
Kulnigg et al. 2008 ⁴⁸	200	Multicentre randomized open-label	Ferric carboxymaltose (137) Ferrous sulfate (63)	≤ 10	1,000-1,500 mg (1-2 infusion of 500-1,000 mg) 16,800 mg (200 mg/day)	12	77% 68%	1.5% 7.9%
Lindgren et al. 2009 ⁴⁹	91	Multicentre randomized investigator-blinded	Iron sucrose (45) Ferrous sulfate (46)	< 11.5	Mean 1,700 mg (200 mg/1-2 weeks) Mean 38,400 mg (200-400 mg/day)	20	66%	7%
Gisbert et al. 2009 ⁵⁰	100	Multicentre, open-label	Iron sucrose (22) Ferrous sulfate (78)	< 10 > 10	Not reported (2 x 200 mg/week if Hb < 10) (106 mg/day)	26 19,000 mg	77% 89%	0% 5.1%

Response: Hb ≥ 2 g/dL or normal Hb; DCT: discontinuation due to serious adverse events.

* Also those patients with no response or intolerance to oral iron, or with clinical need of quick recovery of anaemia.

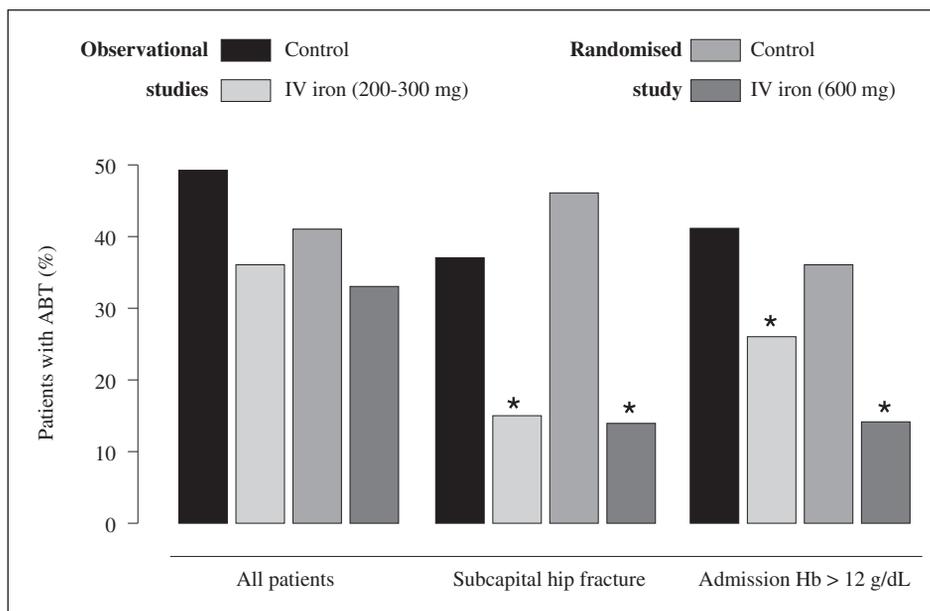


Fig. 1.—Effect of preoperative IV iron sucrose administration on transfusion requirements in patients undergoing surgery for hip fracture repair included in observational^{60,61} and randomised studies⁶². * $p < 0.05$, IV iron vs. control.

mg IV iron sucrose to patients with pertrochanteric (PHF) or subcapital hip fracture (SHF) reduced the percentage of transfused patients, compared to a control group (especially in patients sustaining SFH or with admission Hb > 12 g/dL). These results have been recently confirmed by a RCT of patients sustaining PHF or SHF who received 600 mg iron sucrose preoperatively⁶² (fig. 1). No adverse reactions were observed in patients receiving iron sucrose, but there were lower postoperative infection rate and lower 30-day mortality, plus a trend towards shorter hospital stay.^{60,61} On the other hand, data from patients with admission Hb \leq 12 g/dL suggest that a benefit could be obtained if IV iron sucrose and ESAs (e.g., recombinant human erythropoietin [rHuEPO]) were administered jointly.⁶⁰⁻⁶²

The effects of this combined therapy was explored in a study including patients with PHF or SHF who received 600 mg iron sucrose (plus 40,000 IU rHuEPO, if Hb < 130 g/L) and were managed with a restrictive transfusion protocol (transfusion trigger: Hb < 8 g/dL and/or symptoms of acute anaemia).⁶³ Once again, the treatment resulted in a reduction of both the percentage of transfused patients (70 vs. 24%), the number of transfused units (1.7 ± 1.3 vs. 0.6 ± 1.1), and the postoperative infection rate (31 vs. 13%), when compared with a control group. In addition, there was a trend to lower 30-day mortality, and no adverse reactions to iron sucrose administration were witnessed. However, a subsequent prospective audit at the authors' institution showed a low adhesion to this protocol, as only 81 out of 196 anaemic patients presenting with hip fracture in 2008 received IV iron plus rHuEPO (41%), whereas the remaining 59% received IV iron only.⁶⁴ A detailed data analysis revealed that there were significant differences in perioperative ABT rates between groups (42% vs. 60%, for those with or without rHuEPO, respectively; $p = 0.013$). However, the differ-

ences in ABT rates between groups were significant for PHF (64% vs. 43.5%, respectively; $p = 0.027$), but not for SHF (52.5% vs. 40%, respectively; $p = 0.279$). In addition, Hb levels on postoperative days 7 and 30 were higher among those receiving rHuEPO, who also presented higher Hb levels on postoperative day 30 than on admission (12.7 g/dL vs. 11.9 g/dL, respectively; $p = 0.030$). Administration of rHuEPO did not increase postoperative complications or 30-day mortality rate, and only three mild adverse events due to IV iron administration were witnessed.⁶⁴ Therefore, in anaemic PHF patients managed with perioperative IV iron and restrictive transfusion protocol, preoperative administration of rHuEPO is associated with reduced ABT requirements. However, appropriate training, education and awareness are needed to avoid protocol violations and to limit further exposure to ABT and ABT-related risks.

Elective orthopaedic surgery

Unilateral total knee replacement (TKR) or THR results in a substantial blood loss and 30-50% of these patients receive ABT; this transfusion rate may be even higher among anaemic patients.⁶⁵ Again, ID is one of the most prevalent causes of preoperative anaemia among these patients populations.^{66,67} We assessed the requirements for ABT in 156 consecutive patients undergoing surgery for primary TKR, who received iron ferrous sulphate (256 mg/day; 80 mg of Fe^{2+}), vitamin C (1,000 mg/day) and folic acid (5 mg/day) during the 30-45 days preceding surgery, and who were transfused if Hb < 8 g/dL and/or clinical signs/symptoms of acute anaemia/hypoxemia (Group 2). A previous series of 156 TKR patients served as a control group (Group 1).⁶⁸ Compared to those in Group

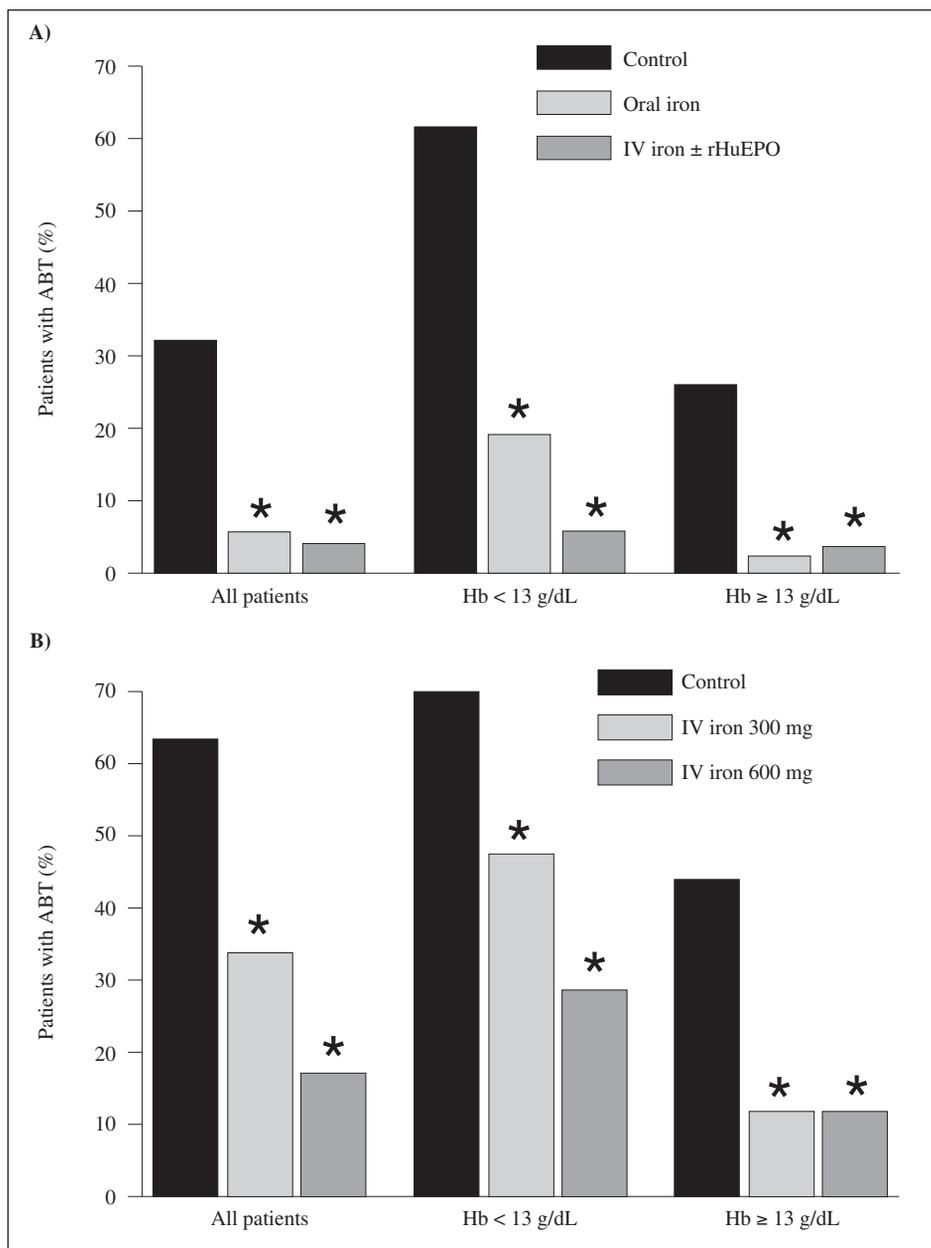


Fig. 2.—Effect of perioperative IV iron administration on transfusion requirements in patients undergoing major orthopaedic surgery. A) Patients undergoing total knee replacement received 200 mg IV iron 48 h before and after surgery or not treatment (control)^{68,76}; patients presenting with Hb < 13 g/dL also received a single 40,000 IU rHuEPO preoperatively. B) Patients undergoing total knee or hip arthroplasty or hip fracture repair received 300 or 600 mg IV iron or no treatment (control) (Unpublished data). * $p < 0.05$, oral iron or IV iron vs. Control.

1, patients in Group 2 presented a lower transfusion rate (5.8% vs. 32%; $p < 0.01$) (fig. 2A), and a lower transfusion index (1.8 vs. 2.2 units per transfused patient; $p < 0.05$). After patient's stratification according to a preoperative Hb above or below 13 g/dL, the differences in transfusion rate remained significant, although 19% of patients from Group 2 still needed ABT if their preoperative Hb < 13 g/dL (fig. 2A). Therefore, this protocol seems to be effective for avoiding ABT in non-anaemic TKR patients, suggesting a widespread underlying depletion of iron stores in this patient population despite a normal Hb,⁶⁹ although in another observational study of patients undergoing TKR or THR, preoperative oral ferrous sulphate therapy administered to non-anemic patients

had no significant benefit on improving preoperative Hb and was associated with a high risk of adverse drug reactions.⁷⁰ In contrast, our data suggests that for anaemic patients another blood saving strategies, such as the administration of IV iron, should be implemented.

Following the recommendations of NATA (Network for the Advancement of Transfusion Alternatives) consensus statement on the role of IV iron for perioperative anaemia management,⁷¹ we evaluated the efficacy of IV iron administration (approx. 1,000 mg; 3-5 weeks prior to surgery) for correction of preoperative anaemia in 160 patients scheduled for major elective surgery (45 colon cancer resections, 52 abdominal hysterectomies, 63 lower limb arthroplasties).⁷² As for

orthopaedic patients, administration of IV iron caused a significant increase of Hb levels (+1.8 g/dL; $p < 0.001$), anaemia was resolved in 83% of patients, overall transfusion rate was only 19%, and no serious adverse effect was witnessed. Similar, although more modest results have been reported for patients with ID or IDA by Theusinger et al.⁷³ and González-Porras et al.⁷⁴ This strategy is also recommended in more recent NATA guidelines on detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient.⁷⁵

However, quite often we do not have such a time frame to investigate anaemia and implement the appropriate treatment. In this regard, we evaluated the effects of perioperative administration of IV iron sucrose (2 x 200 mg, 24 hours before surgery and 24 hours after surgery) plus folic acid and vitamin C until discharge, on transfusion requirements in patients undergoing surgery for TKR and managed with a restrictive transfusion protocol. In addition, patients with preoperative Hb < 13 g/dL received one dose of rHuEPO (40,000 UI, 24 hours before surgery). No adverse effects of iron sucrose or rHuEPO administration were witnessed, and only 4% of patients received ABT overall⁷⁶ (fig. 2A). Interestingly, ABT rate in patients with preoperative Hb < 13 g/dL (9%) was no different from that previously reported for TKR receiving 4 x 40,000 UI rHuEPO plus oral iron (10.8%).⁷⁷ Additionally, at postoperative day 30, only 15% were anaemic, 71% of Hb loss and 92% of preoperative Hb was recovered, and iron stores were increased.⁷⁸ Interestingly, ABT rate in patients with preoperative Hb < 13 g/dL (9%) was no different from that reported with the preoperative administration of rHuEPO at the dosage of 4 x 40,000 IU plus oral iron (10.8%)⁷⁹ or 4 x 10,000 IU plus 4 x 200 mg of iron sucrose (0%).⁷⁴

More recently, Na et al.⁸⁰ randomised 108 iron deficient patients scheduled for bilateral TRK to receive 200 mg of iron sucrose IV and 3000 IU of rHuEPO during the operation and during the postoperative period if the Hb level was around 7-8 g/dL (Group IE) or no treatment (Group C, control). Haemoglobin, ferritin and transferrin saturation levels at 1, 2, and 3 days and at 2 and 6 weeks post-operation were significantly higher in Group IE. Furthermore, the transfusion rate (20.4% vs. 53.7%, $p = 0.011$) and transfusion index (0.2 vs. 0.8 units/patient; $p = 0.005$) were significantly lower in Group IE. Therefore, treatment with IV iron and low-dose rHuEPO in bilateral TKR effectively attenuated anaemia and decreased transfusion requirements in iron-deficient patients. Hence, these short-term protocols seem to reduce ABT and may hasten the recovery from postoperative anaemia in TKR patients, although further studies are needed to ascertain which patients may benefit of extended IV iron and/or rHuEPO administration.

In the postoperative period, the results of several RCTs suggested that the administration of oral iron was no effective in correcting anaemia after orthopaedic

surgery.⁸¹⁻⁸³ However, iron sucrose (3 mg/kg/day) was shown to be a more effective oral iron to restore postoperative Hb levels after spinal surgery in children,⁸⁴ although this positive effect was not seen in adult patients receiving IV iron with or without rHuEPO.⁸⁵ In lower limb arthroplasty surgery, we evaluated the effect of postoperative administration of 300-600 mg of IV iron sucrose or FCM on ABT requirements in 315 patients. Compared to no treatment, postoperative administration of either 600 mg iron sucrose or FCM seems to be safe, and more effective than that of 300 mg iron sucrose to reduce ABT requirements in THR, TKR and HF patients, although the intervention seems to be more efficacious for patients with preoperative Hb ≥ 13 g/dL (fig. 2B) (Unpublished observations). In addition, patients with postoperative Hb < 10 g/dL receiving 300 or 600 mg IV iron showed shorter length of hospital stay, and lower postoperative infection rate.⁸⁶ No adverse reactions to iron administration were witnessed, and FCM had the additional advantage of being given in a rapid single infusion. A RCT to confirm the efficacy of postoperative FCM in TKR patients is currently ongoing (EudraCT 2010-023038-22).

Anaemia in cardiac surgery

Up to 40% of patients scheduled for cardiac surgery presented with preoperative anaemia,^{13,14,87-89} which is associated with an increased risk of perioperative transfusion and postoperative adverse outcome.^{14-16,87-89} A recent study, 210 out of 576 patients (36.5%) undergoing elective cardiac surgery at one institution presented with anaemia, and logistic regression analysis revealed that age, chronic kidney disease (decreased EPO production), and consumption of proton pump inhibitors or histamine H₂ receptor antagonists (reduced iron absorption), and diuretics were independent risk factors for the presence of preoperative anaemia.⁸⁷ A small cohort study of 60 patients found that 45% of them were anaemic preoperatively, 22% had serum iron < 50 g/dL, 42% ferritin < 100 μ g/L, 28% transferrin saturation < 20%, 22% C-reactive protein > 1 mg/dL, and 17% IL-6 > 10 pg/mL (Unpublished observations). Finally, a prospective observational study found that 37 out of 100 patients were diagnosed with ID, which was associated with lower preoperative Hb levels, higher ABT rates and higher score of postoperative physical fatigue.⁸⁹ These data suggest that anaemic patients scheduled for cardiac surgery might benefit from treatment with iron and/or rHuEPO.⁹⁰

In adult patients scheduled for cardiac surgery, preoperative treatment with rHuEPO reduced the risk of exposure to ABT (31% vs. 54%; RR, 0.57; 95% CI, 0.43-0.75; $p < 0.001$), but there was a great variability in total rHuEPO dose and iron supplementation, as well as in outcomes.^{91,92} In valvular cardiac surgery, data for 59 consecutive anaemic patients who was

given rHuEPO 5 x 500 IU/kg/day (4 weekly doses and a fifth dose 48 hours before surgery) plus IV iron sucrose supplementation were compared to those from a control group. Multivariable logistic regression analysis showed that administration of combined therapy was independently associated not only with lower ABT rate, but also with decreased postoperative morbidity and in-hospital mortality, and shorter length of hospital stay.⁹³ Using a similar approach to that described for elective and non-elective orthopaedic surgery,^{63,64,76} two studies have shown that very short term rHuEPO plus IV iron administration (1-4 days before surgery) improved postoperative Hb levels and iron parameters and reducing the requirements for ABT in off-pump coronary revascularization⁹⁴ and valvular heart surgery.⁹⁵ Unfortunately, there are no studies on preoperative IV iron as monotherapy.

In the postoperative period, the administration of oral iron after uncomplicated coronary artery bypass surgery did not help to restore red blood cell mass nor to maintain total body iron stores.⁹⁶ In contrast, postoperative IV iron alone preserved iron stores during recovery from anaemia.^{97,98} Moreover, in one study, the increase in Hb level from postoperative day 4 (nadir) to postoperative day 30 was 1 g/dL higher in patients who received IV iron supplements, with or without rHuEPO, when compared to those who received placebo.⁹⁷

On the other hand, a RCT in patients undergoing cardiac (42%) or orthopaedic surgery concluded that treatment with IV iron alone or in combination with rHuEPO does not appear to accelerate early recovery from postoperative anaemia, although reticulocyte counts and ferritin levels at postoperative day 7 were higher in the combination group and there was a trend towards lower transfusion requirements and better Hb recovery at postoperative day 42.⁸⁵ However, the study was prematurely stopped and the authors did not exclude the possibility that higher doses or different timing of postoperative intravenous iron and rHuEPO may be effective in accelerating correction of postoperative anaemia. Finally, a retrospective study of 863 cardiac surgery patients showed no differences in infection rates between patients receiving IV iron gluconate plus rHuEPO (n = 302) or standard care (i.e., ABT as indicated; n = 561), for correction of postoperative anaemia (OR = 1.03; 95% CI 0.908-1.170)⁹⁹

Anaemia in colorectal cancer

Anaemia is one of the signs of CRC, which may be present in up to 75% of patients, depending of the Hb cut-off and tumour stage.¹⁰⁰⁻¹⁰⁵ A study on 358 patients with CRC showed that one quarter of them had severe anaemia (Hb < 10 g/dL). The multivariate analysis showed that patient's age, tumor site (right colon), and tumor size (large size), but not clinical stage or histological type, were significant factors related to anaemia.¹⁰¹ Similar results were obtained in more

recent study 1,189 Norwegian patients.¹⁰² As for other major surgical procedures, a hematocrit less than 30% has been shown to be an independent risk factor for requiring perioperative ABT in CRC patients.¹⁰³ However, the incidence of a low serum iron level was about twice the frequency of a Hb level < 10 g/dL,^{101,104,105} and the multivariate analysis showed that none of the above mentioned factors were significantly related to ID.^{101,104} Thus, both IDA and ID may be corrected pre-operatively by either oral iron, if time allows, or by the use of IV iron in CRC patients.

Okuyama et al.¹⁰⁶ studied 32 anaemic patients (Hb ≤ 10 g/dL) who received oral iron supplementation (sodium ferrous citrate, 200 mg/day) for at least 2 weeks preoperatively and 84 anaemic patients who did not. Iron supplementation resulted in higher Hb levels immediately before surgery (+1.2 g/dL; p < 0.05), and fewer patients receiving intraoperative ABT (9.4% vs. 27.4%, p < 0.05). However, there were no significant differences in postoperative Hb levels or ABT volumes between the two groups. Lidder et al.¹⁰⁷ conducted a small RCT of oral ferrous sulphate (200 mg/12 h) for a mean of 14 days pre-operatively (12-56 days) versus no iron therapy in patients with IDA or ID scheduled for CRC surgery. Oral iron was found to prevent Hb decrease from recruitment to admission, and to reduce ABT rate (25% vs. 59%, for iron and control, respectively; p = 0.031), although these differences were not significant for patients with IDA. More recently, in a series of 103 patients receiving oral ferrous sulphate (200 mg/12 h) for a median of 39 days pre-operatively (interquartile range = 7-63 days) and no preoperative ABT, Quinn et al.¹⁰⁸ observed that: 1) Fifty-eight (56.3%) patients were anaemic at presentation gaining a mean of 1.7 g/dL (p < 0.001); 2) Right-sided tumours (lower mean Hb at presentation) responded more to oral iron when compared to left-sided tumours (p < 0.017); 3) Increase in Hb was unrelated to pathological stage, but was greater in patients receiving iron for more than 14 days; and 4) The ABT rate for all curative resections was 0.69 units/patient (compared to 1.69 units/patient for an historical cohort).

Edwards et al.¹⁰⁹ conducted a pilot RTC to ascertain whether iron sucrose reduces the likelihood of postoperative ABT in patients undergoing elective CRC resection. Iron sucrose (600 mg; n = 34) or placebo (n = 26) was given IV in two divided doses, at least 24 h apart, 14 days before surgery, and no difference was demonstrated between groups regarding perioperative Hb levels or ABT rates. Therefore, the author concluded that patients undergoing resectional surgery for CRC do not benefit from preoperative administration of IV iron sucrose. However, this study has important limitations that preclude for drawing meaningful conclusions.^{110,111} First, the primary endpoint (on which the sample size was also based) was a change in Hb of 0.5 g/dL, and such a small change is clinically insignificant and unlikely to have an impact on perioperative transfusion requirements. Second, recommendation for

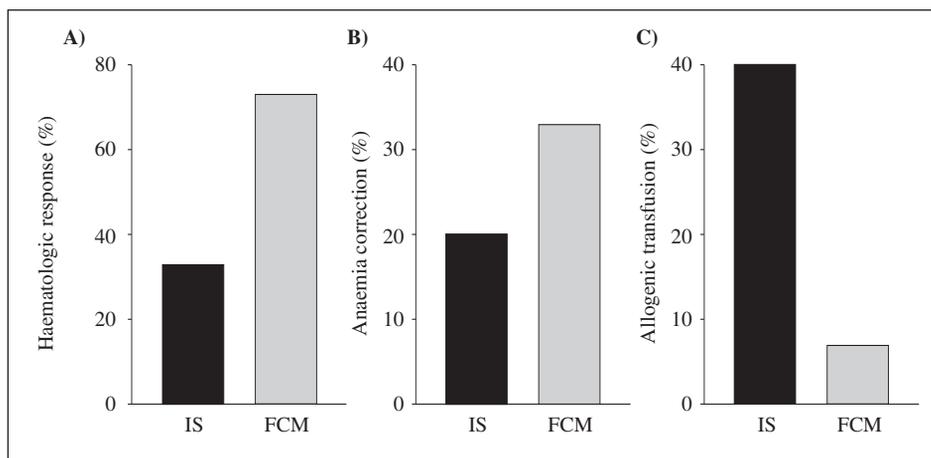


Fig. 3.—Effect of preoperative IV iron sucrose (IS) or ferric carboxymaltose (FCM) administration in patients undergoing colorectal cancer surgery. A. Haematologic response, defined as a Hb increment ≥ 1.5 g/dL or a final Hb ≥ 13 g/dL. B. Anaemia correction, according to WHO definition. C. Transfusion rate⁷². * $p < 0.05$, IV IS vs. IV FCM.

dosing IV iron sucrose is based on the individual patient's body weight and the differential between actual and target Hb values, rather than administration of a fixed dose as used in this study. Third, by recruiting all patients undergoing surgery for CRC, they included non-anaemic patients with no biochemical evidence of iron deficiency. In fact, in this study only nine patients in each group had a Hb level below normal. Therefore, the authors should have restricted the study to anaemic patients and had reduction in perioperative ABT as the primary outcome.

In a comparative study, clinical and laboratory data of 15 anaemic CRC patients receiving preoperative FCM (500-1,000 mg/session) to replenish total iron deficiency were compared with those from previous series of 30 patients receiving preoperative iron sucrose (100-200 mg/session).⁷² In despite of similar total iron deficiency (1,125 mg vs. 1,025 mg) and lower baseline Hb level (9.2 g/dL vs. 10.1 g/dL; $p < 0.05$), patients in the FCM received more iron than those in the iron sucrose group (1,550 mg vs. 1,140 mg; $p < 0.05$), and showed a higher post-treatment Hb increment (+2.5 g/dL vs. +0.9 g/dL; $p < 0.05$). Thus, patients receiving FCM showed better haematologic response, more correction of anaemia and lower perioperative ABT (fig. 3). The "extra" amount of iron administered to the FCM group, which compensated for the ongoing blood loss from recruitment to surgery, might have account for the observed differences.

In another study, 43 CRC patients received preoperative treatment with 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, during 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 g/dL 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 adminis-

tered perioperative ABT (48% vs. 35%; $p = 0.161$). However, the treatment was ineffective in patients with a high transfusion index (> 5 units/patient).¹¹²

Diaz-Espallardo et al.¹¹³ analysed data from 437 patients undergoing CRC surgery in the period 2005-2009. Patients presenting with Hb < 13 g/dl and/or abnormal Fe metabolism (Group A, $n = 242$) received preoperative iron supplementation (178 patients received a mean of 867 mg IV iron sucrose, and 64 oral iron), whereas patients presenting with Hb ≥ 13 g/dl and/or normal Fe metabolism, received no treatment (Group B, $n = 195$). From diagnosis to the day of surgery, Hb increased by 0.6 g/dL in Group A, while it decreased by 0.8 g/dL in Group B ($p < 0.05$). Moreover, from diagnosis to hospital discharge, Hb decreased by 0.4 g/dL in Group A, and by 2.5 g/dL in Group B ($p < 0.05$). This tendency to progressive anaemia observed in both groups, may be secondary to the neoplastic disorder, chemo-radiotherapy treatment, the blood loss due to the tumour and later surgery. However, the differences between groups strongly suggest that iron therapy prevented patients from group A for reaching undesirably low Hb levels. In this regard, it is worth noting that the overall ABT rate was 8.6% (32/244, 13.1% vs. 6/195, 3.1%, for group A and B, respectively; $p = \text{NS}$) and no differences in complications were observed. Regarding postoperative complications after abdominal surgery, it must be borne in mind that infections were reported to be significantly more common in patients with low preoperative serum ferritin compared with patients with normal ferritin; confounders including Hb level were taken into account in the analysis.¹¹⁴ In addition, Zago et al.¹¹⁵ evaluated the usefulness of vitamin and mineral indicators as nutritional markers of general and surgical wound complications in 100 adult patients from programmed surgical procedures of hernia ($n = 41$) or gallbladder lithiasis ($n = 59$), and found lower plasma retinol (a marker of low vitamin A intake) and higher erythrocyte protoporphyrin (an early marker of ID) in patients with complication compared to those without complications. Thus, the authors considered

that these two markers would provide useful tools in evaluating surgical risk since they had been allowed to identify patients who were at risk of suffering postoperative complications.

In contrast, in a retrospective paired case-control study, Titos-Arcos et al.¹¹⁶ observed that postoperative administration of IV iron sucrose (592 ± 445 mg) did not decrease ABT rates (28.8% vs. 30.8%, for case and control, respectively). In addition, for patients not receiving ABT, there were also no differences in Hb concentration decrease between the first postoperative day and hospital discharge (0.88 g/dL vs. 0.82 g/dL, for case and control, respectively).

Therefore, early treatment of anaemic CRC patients enables optimization of preoperative Hb, thus switching them from a high transfusion risk to a low transfusion risk. It is possible that the effectiveness of perioperative iron treatment could be enhanced by concomitant rHuEPO administration. Thus, perioperative treatment with rHuEPO reduced the risk of exposure to ABT (38% vs. 47%; RR, 0.81; 95% CI, 0.61-1.00; $p = 0.054$), in patients with moderate anaemia scheduled for gastrointestinal cancer surgery (mostly colorectal), although a reduction of both the percentage of transfused patients and the number of transfused units was only observed for those receiving rHuEPO plus IV iron. Additionally, the use of IV iron allowed for a significant reduction in the total dose of EPO.¹¹⁷ A recent systematic review and meta-analysis of 4 RCTs found there is insufficient evidence to support the use of rHuEPO in the preoperative and post-operative period for improving anaemia and decreasing ABT, although there was no evidence that rHuEPO increased complications or deaths.¹¹⁸ Therefore, in line with our comments regarding the management of anaemia in IBD patients, future studies of IV iron and/or rHuEPO in CRC surgery should increase the doses and/or the duration of treatment.

Anaemia after kidney transplantation

A European survey of 4,263 adult patients found anaemia in almost 40% of renal transplant recipients.¹¹⁹ In one study the prevalence of anaemia at 6 and 12 months after transplantation was 35% and 25%, respectively, and 60% of patients received at least one ABT.¹²⁰ Post-transplantation anaemia was particularly associated with impaired renal function, although only one third of patients received rHuEPO during the first few months post-transplantation.¹²⁰ The prevalence is even higher in children. As reported in a study of 162 paediatric renal transplantation recipients, almost 85% were anaemic in the first month after transplantation, and almost 65% were anaemic or present ID between 1-6 months and 6 years from transplantation.¹²¹

As for adults, the administration of rHuEPO (100 IU/kg, three times per week) in the immediate post-transplantation period (3 months) seems to have no

relevant clinical impact on the correction of anaemia or reduction of blood transfusion rate, with respect to patients receiving no rHuEPO.¹²² This might be related to the high prevalence of ID or FID during the early weeks after transplantation, as well as among long-term renal transplant recipients. However, iron treatment must be carefully administered and monitored because of the risk of post-transplant erythrocytosis.¹²³

In this regard, Mudge et al.¹²⁴ conducted a RCT of IV iron polymaltose (500 mg single dose) versus oral ferrous sulphate (210 mg elemental iron daily, continuously) in 104 patients with post-transplant anaemia. The median time to resolution of anaemia (Hb > 11 g/dL) was 12 days in the IV group versus 21 days in the oral iron group ($p = 0.32$). There were also no differences in infections (20% vs. 24%, $p = 0.62$), acute rejection (8% vs. 6%, $p = 0.68$), blood transfusions (10% vs. 18%, $p = 0.24$), and severe gastrointestinal side-effects (6% vs. 12%, $p = 0.29$) between the IV iron and the oral iron groups. Therefore, both IV and oral iron were safe and effective in the management of post-transplant anaemia.

Gillespie & Symmons¹²⁵ treated 14 paediatric and young adults ID renal transplant recipients with iron gluconate (100-1,000 mg; 1-50 days), with or without rHuEPO. Data analysis revealed an overall increase in Hb levels (10.1 ± 1.6 g/dL vs. 11.4 ± 2.1 g/dL; $p < 0.01$), but only a weak trend towards an increase in transferrin saturation. In addition there was a trend to higher increase in Hb (2.1 ± 2.0 g/dL vs. 0.6 ± 0.8 g/dL, respectively; $p = 0.087$), but no differences in the number of responders (Hb increase ≥ 1 g/dL; 5 vs. 3, respectively; $p = 0.592$), in patients receiving rHuEPO plus iron when compared to those receiving iron alone. There were 4 incidents in 3 patients receiving iron gluconate 3.4, 5.1 and 6.4 mg/kg (infusion stopped in the later due to hypertension). Thus, IV iron appears to have potential to improve anaemia in young renal transplant recipients, but the paucity of published information on this topic highlights the need for stronger data. Meanwhile, it seems prudent to caution against the use of high dose of iron gluconate (> 3 mg/kg) or total iron repletion treatments in children.

Anaemia in other medical or surgical scenarios

– *Chronic heart failure (CHF)*. There is increasing evidence that anaemia is one of the most relevant comorbid conditions associated with CHF, not only because it is common but also because it is a marker of greater impairment in functional capacity and an independent predictor of mortality and hospitalization among CHF patients.¹²⁶ Correction of anaemia with rHuEPO and oral iron leads to improvement in New York Heart Association status, measured exercise endurance, oxygen use during exercise, renal function and plasma B-type natriuretic peptide levels and reduces the need for hospitalization.¹²⁷⁻¹³¹ However,

both ID and FID may also play a role in the cardio-renal-anaemia syndrome. In this regard, the combined results from 5 RCTs indicate that IV iron therapy is associated with improved quality of life parameters, such as New York Heart Association class and the Minnesota Living With Heart Failure Questionnaire, mean ejection fraction, 6 min walk distance, and iron indices, and with lower rates of hospitalizations due to any cause and lower C-reactive protein levels, whereas no increase in the rate of adverse events was found.¹³²⁻¹³⁶

– *Chronic kidney disease (CKD)*. Nowadays the administration of ESAs with iron supplements, but not ABT, is the standard therapy for the anaemia of CKD, although some patients are still being transfused. On the other hand, the effects of IV iron alone in partially correcting this anaemia were long ago reported. In anaemic non-dialyzed CKD patients, the haematocrit response was more rapid in patients receiving IV iron in combination with low-dose rHuEPO, but 50% of patients with iron alone showed an increase in haematocrit greater than 3%. In addition, 29% of these patients reached the target haematocrit (35%) compared with 40% of those receiving the combination therapy.¹³⁷ Another five studies show that administration of IV iron to CKD patients significantly increased the haematocrit, with 35-40% reaching target haematocrit, in absence of rHuEPO administration.¹³⁸⁻¹⁴² Thus, it is clear that IV iron alone can achieve some correction of anaemia in CKD, possibly sufficient to avoid ABT, but many patients will also require ESAs supplementation to attained target Hb level.

– *Anaemia of cancer*. Patients with cancer may have anaemia with ID or FID as a result of their disease or its treatment. These conditions can lead to an insufficient supply of iron for incorporation into erythrocytes during supportive care with ESAs for chemotherapy. A meta-analysis of 5 studies of cancer patients receiving chemotherapy have shown that intravenous IV iron increases the haematopoietic response to rHuEPO and may reduce ABT requirements with respect to those receiving oral iron or no iron. In addition, the effects on Hb levels and measures of iron metabolism were notably greater with IV iron formulations than with oral iron formulations.¹⁴³ The use of IV iron in this clinical setting seems to be cost-effective as it allows for a reduction of ESA dosage.¹⁴⁴ Moreover, data from 2 studies of patients with gynaecologic cancer receiving chemotherapy and/or radiotherapy showed that the administration of IV iron alone improves Hb levels and reduces ABT rate.^{145,146}

– *Bariatric surgery (BS)*. Obesity-induced chronic inflammation leads to activation of the immune system that causes alterations of iron homeostasis including hypoferraemia, iron-restricted erythropoiesis, and finally mild-to-moderate anaemia.^{147,148} Thus, preoperative anaemia and ID are common among obese patients scheduled for BS.¹⁴⁸ On the other hand, BS is a long-lasting inflammatory stimulus in itself and entails a reduction of the gastric capacity and/or exclusion of

part of the small bowel which impair nutrients absorption, including dietary iron. Chronic gastrointestinal blood loss and iron-losing enteropathy may also contribute to iron deficiency after BS. Iron supplements should be administered to patients after BS, but compliance with oral iron is no good. In addition, once iron deficiency has developed, it may prove refractory to oral treatment. In these situations, IV iron has emerged as a safe and effective alternative for perioperative anaemia management. Monitoring should continue indefinitely even after the initial iron repletion and anaemia resolution, and maintenance IV iron treatment should be provided as required (see ref. 148 for a detailed review).

– *Critically ill patients*. Anaemia is highly frequent among medical and surgical patients admitted to the intensive care unit (ICU) and generally has a multifactorial origin.¹⁴⁹ In order to avoid the deleterious effects of anaemia, 40% of ICU patients receive ABT, and this figure increases up to 70% if the ICU stay is longer than 7 days.^{150,151} However, ABT is associated with a dose-dependent increase in morbidity and mortality.^{150,151} Thus, pharmacological treatment for anaemia in ICU has been assayed.

A large proportion of critically ill patients presented with FID which correlates with the inflammatory status and the length of stay, and some 20% may have absolute ID (SAT < 20; ferritin < 100 and sTfR > 2.3).¹⁵² Since oral supplementation of iron seems to be ineffective in surgical critically ill patients, except for those previously transfused,¹⁵³ these patients might benefit of IV iron therapy for correction of ID or FID, which in turn might help to ameliorate their inflammatory status, although available data are rather scant and inconclusive.¹⁵⁴ In contrast, the administration of rHuEPO plus iron supplements, especially IV iron, improves anaemia and modestly reduces ABT requirements (when there is not a predefined transfusion protocol), although it does not reduce mortality (except for younger patients and those with an admitting diagnose of trauma).¹⁵⁵ To ascertain whether treatment of anaemia in the critically ill with rHuEPO and IV iron might improve outcomes and to optimize drug administration schedules and dosage, further studies with sufficient statistical power and adequate follow-up are needed.

Safety of intravenous iron administration

Although no serious life-threatening adverse drug events (ADEs) has been reported in the different studies reviewed above, both the numbers of patients included in these studies and the follow-up time were not large enough to draw definitive conclusions regarding the safety of IV iron agents in different clinical settings reviewed.

However, according to the analysis of data from Food and Drug Administration US (2001-2003; 30x10⁶ doses), the incidence of life-threatening ADES, mostly

hypersensitivity reactions (2.2 per million doses), and deaths (0.4 per million doses), associated to the use of four IV iron preparations (iron gluconate, iron sucrose, HMWID, and LMWID), is much lower than that associated to the use of ABT (10 and 4 per million units, respectively).^{156,157} An analysis of reported adverse events among patients using IV iron products from October 2009 through June 2010, concluded that iron sucrose and sodium ferric gluconate were associated with much lower rates of serious adverse events and deaths per million units sold than iron dextran or ferumoxytol, which were associated with the highest rates of all reported adverse event classifications.¹⁵⁸ The immunologic basis of allergic hypersensitivity to IV iron agents is not known. Both antibody-mediated and non-antibody-mediated, concentration-dependent mechanisms have been identified in patients after anaphylaxis to iron dextran.¹⁵⁹ HMWID is not commercially available in Europe, the National Comprehensive Cancer Network recommends against the use of Dexferrum, and the Food and Drug Administration US has altered HMWID (Dexferrum[®]) labelling to warn that it is not clinically interchangeable with LMWID (INFeD[®]).^{160,161} On the other hand, most ADEs due acute iron toxicity might be linked to labile, biologically active iron. The risk of inducing the release of labile iron appears to depend on the dose of IV iron, the molecular weight of iron complex, the rate of iron infusion, and the available apotransferrin/transferrin to bind the iron. Many of the ADEs attributed to iron gluconate including flushing, hypotension, nausea, vomiting and diarrhea have been linked with the release of labile iron.^{162,163}

Regarding the newer iron formulations, overall assessment of the benefits and risks of FCM demonstrates a favorable benefit-risk profile. There are, however, some safety concerns (e.g., hypophosphatemia) as well as important missing information (e.g., use in children and pregnant women, or use in hepatic diseases). Should the manufacturer appropriately address these concerns and FCM finally be approved by the Food and Drug Administration US, a widespread use of this IV iron preparation should be expected in the next years.²² The iron isomaltoside 1000 (Monofer[®]) regulatory application includes references to general IV iron documentation, including evidence with iron dextran. The regulatory authorities have therefore placed Monofer[®] in the B03A C06 ATC code, but they recognise the unique properties of Monofer[®], the unique generic name iron isomaltoside 1000 (a non-anaphylactic carbohydrate), and no requirement for a test dose application which is always the case with iron dextran.²¹ Overall, with the exception of HMWID (increased rates of severe side effects and deaths), it seems that the acute safety differences among IV iron products are small when given at the recommended doses, though comparator trials are needed to be certain.

It has long been suggested that patients with iron overload are at increased risk of infection,¹⁶⁴ but no

increased rates of postoperative infection have been observed in the reviewed studies. In addition, a meta-analysis of 6 observational studies (807 patients) revealed that the administration of IV iron to patients undergoing major orthopaedic surgery led to a significant decrease in both transfusion (RR: 0.60; 95% CI: 0.50-0.72; $p < 0.001$) and infection rates (RR: 0.45; 95%CI: 0.32-0.63; $p < 0.001$).¹⁶⁵ As stated above, orthopaedic surgical patients with postoperative Hb < 10 g/dL receiving 300 or 600 mg IV iron showed shorter length of hospital stay, and lower postoperative infection rate.⁸⁶ In contrast, studies of patients undergoing surgical hip fracture repair or abdominal surgery have found an association between low preoperative ferritin levels and increase rates of nosocomial infections.^{115,166} Nevertheless, in despite of the absence of definitive clinical data, it seems sensible to avoid IV iron administration in the setting of acute infection, and to withhold IV iron in patients with pre-treatment ferritin values > 500 ng/mL.²⁰ Nevertheless, the evidence argues for caution, not complacency, in prescribing IV iron.¹⁶⁷

Conclusions

In a recent, rather incomplete review of the topic, the authors concluded that “*in gastrointestinal or trauma surgery there is no evidence to support the routine preoperative treatment with intravenous iron, although it may be beneficial when it is used with erythropoietin. Intravenous iron alone or in combination with EPO in the postoperative period has not been proved useful for rapid correction of anemia, reduction of hospital stay or mortality*”.¹⁶⁸ However, from data reviewed in this article and despite the lack of high quality evidence in some areas, we believe that it is fair to conclude that:

- Perioperative anaemia is a common condition among the patients admitted to the hospital for elective or non-elective surgery.
- Preoperative anaemia is more frequently due to iron deficiency or chronic inflammatory disease, and is one of the major predictive factors for perioperative blood transfusion.
- Postoperative anaemia is mainly caused by perioperative blood loss, and it might be aggravated by inflammation-induced inhibition of erythropoietin secretion and action, and functional iron deficiency that cannot be corrected by the administration of oral iron.
- Perioperative IV iron administration, with or without rHuEPO, to surgical patients is safe, as no treatment side-effects were observed, and resulted in lower transfusion requirements and hastened recovery of postoperative anaemia. In addition, some studies have reported decreased postoperative infection and mortality rates and shorter length of hospital stay in surgical patients receiving IV iron.

Conflict of interest

MM, JC and JAGE have received honoraria for lectures and/or consultancy and travel support from Vifor Pharma (Switzerland), Vifor-Uriach (Spain), and/or PharmaCosmos (Denmark), but not for this review. SGR, EMM and JP have nothing to declare.

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