IRON SUPPLEMENTATION FOR PERIOPERATIVE ANAEMIA IN PATIENT BLOOD MANAGEMENT

*Manuel Muñoz,[1] Susana Gómez-Ramírez,[2] Arturo Campos[3]

1. Perioperative Transfusion Medicine, School of Medicine, University of Málaga, Málaga, Spain
2. Department of Internal Medicine, University Hospital Virgen de la Victoria, Málaga, Spain
3. Department of Hematology and Clinical Laboratory, University Hospital Virgen de la Victoria, Málaga, Spain
*Correspondence to mmunoz@uma.es

ABSTRACT

In patients undergoing major surgical procedures, preoperative anaemia and perioperative allogeneic blood transfusion (ABT) have been linked to increased postoperative morbidity and mortality, as well as longer hospital stays. A multidisciplinary, multimodal, individualised strategy - collectively termed patient blood management - used to minimise or eliminate ABT is indicated to improve outcomes. This new standard of care relies on detection and treatment of perioperative anaemia (Pillar 1) and reduction of surgical blood loss and perioperative coagulopathy (Pillar 2) to harness and optimise physiological tolerance of anaemia (Pillar 3), thus allowing the use of restrictive transfusion criteria. Normalisation of preoperative hemoglobin levels is a World Heath Organization recommendation. Iron repletion should be routinely ordered when indicated. Preoperative oral iron is time-consuming and poorly tolerated with low adherence in published trials. Postoperative oral iron has been proven to be inefficacious and is no longer recommended. Preoperative and perioperative intravenous iron, with or without erythropoiesis stimulating agents, is safe and effective at reducing ABT rate and hastening the recovery from postoperative anaemia. Intravenous iron does not seem to increase the risk for postoperative thromboembolism, infection, or mortality. Newer intravenous iron formulations demonstrate potentially much lower immunogenic activity, allow complete replacement dosing in 15 to 60 minutes, markedly facilitating care, and may be cost-effective in many clinical settings.

Keywords: Anaemia, surgery, transfusion, intravenous iron, erythropoiesis stimulating agents, patient blood management.

INTRODUCTION

Major surgical procedures (e.g. orthopaedic, cardiac, gynaecological, cancer resection, etc.) may result in a significant postoperative decline in hemoglobin (Hb) levels. As a result, a significant proportion of patients received at least one unit of allogeneic blood for treating acute postoperative anaemia. Evidence of the clinical and economic disadvantages of allogeneic blood transfusion (ABT) has prompted recommendations for its restrictive use,[1,2] and a growing interest in multidisciplinary, multimodal, individualised strategies, collectively termed patient blood management (PBM), aimed to minimise ABT with the ultimate goal of improving patient outcomes,[3] which has been endorsed by the 63rd World Health Assembly.[4]

This new standard of care, which relies on the detection and treatment of perioperative anaemia (Pillar 1) and the reduction of surgical blood loss and perioperative coagulopathy (Pillar 2) to harness and optimise physiological tolerance of anaemia (Pillar 3); thus, allowing restrictive use of ABT, is now being established for elective surgery in several European countries.[3]

In this paper, we will review the diagnosis and treatment options for perioperative anaemia, with a special emphasis on the role of intravenous (IV) iron. The recommendations on the use of a particular therapeutic option will be given in accordance with the updated Seville Document (SD update) on alternatives to ABT and NATA (Network for Advancement of Transfusion Alternatives) consensus statements.[1,5,6] All of the recommendations were formulated according to GRADE methodology, taking into account efficacy, safety, and target patient populations.[7-9]

DIAGNOSIS OF PREOPERATIVE ANAEMIA

Preoperative anaemia is a major, independent, predictive factor for the need of perioperative ABT. Moreover, preoperative anaemia in itself has been linked to increased postoperative morbidity and mortality.[10-12] Therefore, patients scheduled for major surgery should have a full blood cell count (including reticulocyte counts) and iron status (serum iron, ferritin, and transferrin saturation) test, preferably 30 days before the scheduled surgical procedure to allow the implementation of appropriate treatment, if available.[5,6,13] Preoperative hematinic deficiencies without anaemia should also be treated. The diagnosis of an unexpected anaemia should be considered an indication for rescheduling surgery until the evaluation is completed.[6]

Transferrin saturation (TSAT) is a measure of iron in transport, and values of <20% indicate decreased iron availability for the bone marrow (and also the need for parenteral iron in the setting of anaemia treated with erythropoiesis stimulating agents [ESAs]). When used with either the ferritin concentration or red blood cell (RBC)/reticulocyte variables, %TSAT may be useful in the diagnosis of functional iron deficiency (FID).[13,14] Serum ferritin assay is essential for evaluating iron stores (1 μg/L serum ferritin corresponds to 8 mg stored iron). However, it might be accurate when low levels are found but not with high levels since ferritin is also an acute phase reactant.

As for surgical patients, values <30 μg/L indicate absent iron stores (iron deficiency anaemia [IDA]).[13] Importantly, the cause of iron deficiency (ID) should be investigated, and this may include upper and lower gastro-intestinal investigations, screening for coeliac disease and Helicobacter pylori colonisation, and/or genito-urinary blood loss evaluation, depending on the patient's age and gender.[13,14] In the presence of inflammation, TSAT <20% and serum ferritin >100 μg/L are suggestive of iron sequestration (anaemia of chronic disease [ACD]), whereas ferritin values <100 μg/L are associated with a high likelihood of iron deficiency (ACD+ID) and a potentially good response to IV iron (Figure 1).

The percentage of hypochromic red cells (%HRC >5) and reticulocyte Hb content (CHr <27 pg) are the best-established variables for the identification of iron sequestration.[14] Mean cell volume (MCV) and mean cell Hb (MCH) values are useful at diagnosis and in assessing trends over periods of weeks or months (treatment follow-up), whereas red cell distribution width (RDW) differentiates IDA from other microcytic anaemias. Zinc protoporphyrin (ZPP) in circulating red cells is increased in conditions that limit iron supply to the erythroid marrow or stimulate porphyrin synthesis. However, due to lack of specificity and low sensitivity to acute iron changes, ZPP may be used to monitor response to therapy, but not as a sole diagnostic test.[14] The soluble transferrin receptor (sTfR) assay is relatively expensive and not widely available, but it may have a role, either alone or in combination with the ferritin assay, if automated measures such as %HRC or CHr are unavailable. The utility of serum hepcidin measurement as a diagnostic tool is currently uncertain, but it could be helpful in identifying IDA or ACD with ID when reduced hepcidin levels are detected, whereas high hepcidin levels would predict unresponsiveness to oral iron.

When anaemia in surgical patients cannot be explained by acute blood loss, IDA, ACD, or ACD+ID, it is important to consider other causes that would demand specific treatment. In these cases, further testing should include B_{12} (especially for those aged >60 years), lactate dehydrogenase, and serum creatinine in order to exclude other nutritional deficiencies, hemolysis, or renal disease. If malabsorption or severe malnutrition, a red cell folate may also be useful.[13,15,16] An easy-to-follow algorithm, which allows for detection and classification of most cases of anaemia and implementation of appropriate therapy in surgical patients, is depicted in Figure 1.
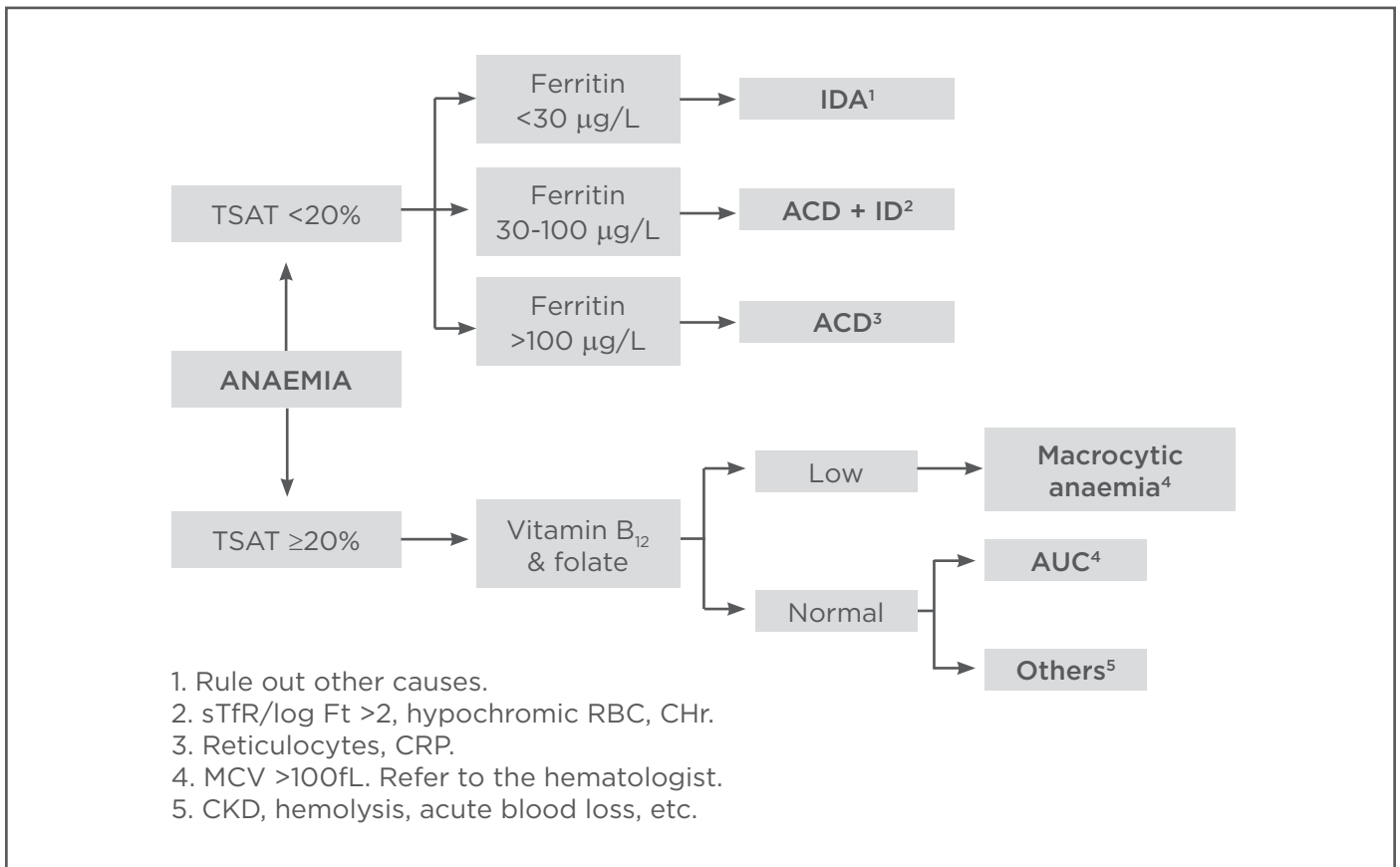
Figure 1: An algorithm for anaemia diagnosis in surgical patients.

IDA: iron deficiency anaemia; TSAT: transferrin saturation; ACD: anaemia of chronic disease; ID: iron deficiency; AUC: anaemia of unknown cause; sTfR: serum transferrin receptor; Ft: ferritin; RBC: red blood cell; CHr: reticulocyte hemoglobin; CRP: C-reactive protein; MCV: mean corpuscular volume; CKD: chronic kidney disease.

MANAGEMENT OF PERIOPERATIVE ANAEMIA

Iron Therapy

Efficacy

Whenever there is enough time and no contraindications, oral iron supplementation should be attempted for IDA treatment (Grade 2B).[1] In patients scheduled for orthopaedic procedures or colon cancer resection, ferrous salts (100-200 mg/d; 2-4 weeks) improved Hb levels, reduced transfusion rates, and, in some cases, the length of hospital stay,[17-21] while others did not.[22] Postoperative oral iron did not hasten the correction of anaemia or reduce the transfusion rate, but was associated with a high rate of adverse effects,[23-29] and is therefore not recommended (Grade -1B).[1] Newer oral iron formulations, such as heme iron polypeptide or liposomal iron, seem to offer advantages over the traditional iron salts even in the context of inflammation, although more studies are needed.[30-33]

If there is poor absorption or poor tolerance of oral iron, or an accelerated response to treatment is required, preoperative IV iron supplementation could be considered. Several IV iron formulations are currently available (Table 1). An IV iron course, starting 3-4 weeks prior to the scheduled procedure, is suggested (Grade 2B)[1] as it increases reticulocyte counts and Hb levels (or corrected anaemia), and may result in reduced ABT requirements.[34-40] IV iron formulations are clearly superior to oral iron in replenishing iron stores. Should this timeframe not be available, short-term perioperative IV iron - with or without ESAs - may be administered, as they have been shown to be efficacious at reducing ABT rate (Grade 2B).[1,5,41-43]

Table 1: Some characteristics of the different intravenous iron formulations.

	Iron gluconate	Iron sucrose	HMWID	LMWID	Ferric carboxymaltose	Iron isomaltoside 1000	Ferumoxytol
Brand name	Ferrlecit®	Venofer®	Dexferrum®	Cosmofer® INFeD®	Ferinject® Injectafer®	Monofer®	Rienso® FeraHeme®
Carbohydrate shell	Gluconate (monosaccharide)	Sucrose (disaccharide)	Dextran (branched polysaccharide)	Dextran (branched polysaccharide)	Carboxymaltose (branched polysaccharide)	Isomaltoside (linear oligosaccharide)	Polyglucose sorbitol carboxymethylether (branched polysaccharide)
Molecular weight (kD)	289-440	30-60	265	165	150	150	750
Plasma half-life (hours)	1	6	60	20	16	20	15
Direct iron donation to transferrin (% injected dose)	5-6	4-5	1-2	1-2	1-2	<1	<1
Iron content (mg/mL)	12.5	20	50	50	50	100	30
Maximal single dose (mg)	125	200-300	20 mg/kg	20 mg/kg	20 mg/kg (max 1000 mg in one infusion)	20 mg/kg	510
Premedication	No	No	TDI only	No	No	No	No
Life-threatening ADE (x106 doses)	0.9	0.6	11.3	3.3	??	??	??

HMWID: high molecular weight iron dextran; LMWID: low molecular weight iron dextran; TDI: total dose infusion; ADE: adverse drug event.

Similarly, IV iron therapy is recommended for treating moderate-to-severe anaemia in postpartum (Grade 1B)[44-50] and inflammatory bowel disease (Grade 1B),[16,51,52] as well as an adjuvant to ESAs at correcting chemotherapy-induced anaemia (Grade 1A).[53-57] In addition, the use of IV iron has emerged as a viable alternative to allogeneic blood transfusions and a valuable tool to face restrictions on ESAs in cancer patients (Grade 2B).[58-61] In contrast, intramuscular (IM) iron administration is no longer recommended.

Safety

Although no serious IV iron-related adverse effects have been described, the number of surgical patients enrolled in the studies analysed is insufficient to draw definitive conclusions, especially in regards to the infrequent severe anaphylactic-type reactions. Future low risk of bias, adequately powered, prospective efficacy and safety trials in various surgical settings would be required to make evidence-based conclusions.[62]

However, data from the chronic kidney disease (CKD) study indicate that the frequency of severe adverse effects and deaths is extremely low except for high molecular weight iron dextran,[63] and significantly lower than the frequency with ABT.[64] More recently, using clinical data from 117,050 patients of a large US dialysis provider merged with data from Medicare's End-Stage Renal Disease programme, Brookhart et al.[65] estimated the effects of iron dosing patterns during repeated 1-month exposure periods on risks of mortality and infection-related hospitalisations during the subsequent 3 months. In 776,203 exposure/follow-up pairs, they observed that maintenance dosing did not associate with increased risks for adverse outcomes, compared with no iron.

Iron dextran complexes may cause well-known dextran-induced antibody-mediated anaphylactic reactions, which are significantly more frequent with those of higher molecular weight (not available in Europe) (Table 1). However, it must be remembered that all IV preparations have been reported to cause anaphylactoid reactions, which are characterised by nausea, hypotension, tachycardia, chest pain, dyspnoea (lung oedema), and bilateral oedema of the hands and feet, and they should not be misread as anaphylaxis.[66] These anaphylactoid reactions are mostly due to transferrin oversaturation and are, therefore, less frequent with the newer, more stable IV iron formulations (Table 1). As with other nanomedicines, complement activation-related pseudoallergy (CARPA), a mechanistic term for infusion or anaphylactoid reactions, could also be observed.

As of 28th June 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of IV exceed their risks (favourable benefit-risk profile), when appropriately prescribed and dosed, and adequate measures are taken to minimise the risk of allergic reactions.[67] To improve patient safety, CHMP has issued clear recommendations for healthcare professionals, including:

• IV iron medicines should only be administered when staff trained to evaluate and manage anaphylactic and anaphylactoid reactions are immediately available as well as resuscitation facilities.

• A test dose is no longer recommended, as there are data indicating that allergic reactions may still occur in patients who have not reacted to a test dose.

• In the case of hypersensitivity reactions, healthcare professionals should immediately stop the iron administration and consider appropriate treatment for the hypersensitivity reaction.

• Patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an IV iron medicine.

• IV iron-containing products are contraindicated in patients with hypersensitivity to a specific active substance or excipients, or other parenteral iron products.

• The risk of hypersensitivity is increased in patients with known allergies or immune or inflammatory conditions and in patients with a history of severe asthma, eczema, or other atopic allergy.

• IV iron products should not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the potential serious risks to the foetus such as anoxia and foetal distress.

• All prescribers should inform patients of the risk and seriousness of a hypersensitivity reaction and the importance of seeking medical attention if a reaction occurs.

With regards to the risk of infection, a recent meta-analysis concluded that: "Compared with oral iron and no iron, IV iron effectively increased Hb concentration and reduced RBC transfusions in various settings, but it was also associated with increased risk of infection."[68] However, infection was not a predefined endpoint in many pooled studies, a dose-response association between iron and risk of infection was not detected, further undermining the causal relationship, and rates of mortality, and other serious adverse events were not statistically significantly higher with IV iron. In contrast, when diagnosis of infection was clinically made using pre-established criteria and confirmed by laboratory, microbiologic, or radiologic evidence, no impact of IV iron on the infection rate was detected in large series of orthopaedic or cardiac surgeries.[41-43]

Practicalities and costs

Iron needs should always be calculated on an individual basis to avoid both infra and supra-dosage. The use of newer IV iron formulations (e.g. iron isomaltoside 1,000 or ferric carboxymaltose), which allow the administration of larger single doses (≥1,000 mg) will facilitate a more accurate iron replacement therapy in surgical patients. In addition, these newer IV iron formulations are safer and more convenient both for the patient (e.g. less venous punctures, less time out from work, etc.) and the health system (e.g. less visits to day hospital, less ambulance transfers, etc.).[16] These advantages may clearly out-balance their higher acquisition costs and make them cost-effective, suggesting that novel IV iron formulations are a valuable tool for the efficient and cost-effective treatment of iron deficiency in various therapeutic areas, including surgery.[38,43]

ESAs

Efficacy

In Europe, ESA administration is only indicated for reducing ABT rate in patients with moderate anaemia (Hb between 10 and 13 g/dL) scheduled for elective orthopaedic surgery who are expected to have moderate blood losses[69,70] (Grade 1A). ESA administration is also approved for those included in an autologous blood predonation programme and scheduled for procedures usually requiring three or more units of packed red cells (Grade 1C). The minimum effective dose of ESA in these indications is presently unknown.[71] Off-label use of ESA is suggested in patients undergoing cardiac surgery[72-74] or gastrointestinal cancer resection[75] (Grade 2B), and is not recommended in critically ill patients who do not have a previous indication (Grade -1A).[1,76]

Current European guidelines for anaemia management in CKD patients suggest using ESA therapy to generally maintain CKD patients with Hb values ranging between 10 and 12 g/dL, individualising the value in this target range according to the possible comorbidities of the patients. Hb values >13 g/dL should not be intentionally aimed for during ESA therapy in this setting.[77] However, no specific recommendations were issued for CKD patients undergoing major surgery.

Safety

Various government agencies (US FDA, EMA) have issued alerts on the association between the use of recombinant human erythropoietin and an increased risk of thromboembolic events and mortality in patients receiving long-term treatment for anaemia associated with chronic renal failure[77] or cancer chemotherapy,[54-56] as well as in patients undergoing orthopaedic surgery without thromboembolic prophylaxis.[78] It is important to stress that administration of IV iron alone will never result in supra-physiological Hb levels and thrombocytosis, leading to increased risk of thromboembolic complications, as could be the case with high ESA doses. In surgical patients, it would be, therefore, advisable to adjust ESA dose individually, ensure iron supply to the bone marrow (administering adjuvant iron, preferably IV), and provide adequate pharmacological thromboembolic prophylaxis.[1]

Restrictive Use of Allogeneic Blood Transfusion

After major surgery, perioperative blood loss and postoperative blunted erythropoiesis, due to surgery-induced inflammation, may lead to severe postoperative anaemia, especially in those presenting with low preoperative Hb. In this context, ABT continues to be the most frequently used treatment for acute intra and postoperative anaemia, although its quick and effective increase in Hb levels is transitory, there is a lack of evidence regarding its efficacy for increasing tissue oxygen

consumption or reducing tissue oxygen debt in selected patients, and it is associated with poorer outcomes. Subsequently, ABT should be used restrictively and judiciously in patients for whom pharmacological options are not available or cannot be implemented (e.g. acute severe anaemia with hemodynamic instability).

Accordingly, in making a transfusion decision in euvolaemic, non-bleeding patients: 1) the risk of anaemia and the risks and benefits of red cell transfusion should be carefully balanced for each individual patient; 2) the so-called 'liberal' transfusion protocols (pre-transfusion Hb concentration >9-10 g/dL) should be generally avoided; 3) should ABT be deemed necessary, single unit transfusions are desirable; and 4) patients should be reassessed between transfusions to determine the remaining transfusion needs.[79]

Efficacy

The use of patient-based restrictive transfusion criteria reduces both the frequency and volume of ABT (and, consequently, ABT-related risks) and should be the cornerstone of any PBM. In most surgical patients, ABT could be considered for maintaining Hb concentrations between 7-9 g/dL (Grade 1A); for those with cardiac and/or central nervous system dysfunction, ABT could be considered for patients with symptoms or Hb level of 8 g/dL or less, and given for maintaining Hb concentrations between 8-10 g/dL (Grade 1A).[1,2,79] Nevertheless, whenever possible, avoidance of ABT is preferable.[80]

Safety

Following the seminal Transfusion Requirements in the Critical Care trial,[81] a number of studies have demonstrated that restrictive transfusion triggers reduced transfusion rates and did not increase morbidity or mortality rates or the length of hospital stay in a variety of clinical settings, and could even be beneficial in some aspects.[79,80] However, its effects in high-risk groups need to be tested in further large clinical trials.[82,83] Meanwhile, for patients presenting with acute myocardial infarction, unstable angina, or other organ dysfunctions (heart failure, respiratory insufficiency, sepsis, etc.) it seems sensible to adopt a less restrictive transfusion protocol aimed at maintaining higher hemoglobin levels, although more studies are needed.[84-86]

AUTHORS' PERSPECTIVE

From the analysis of the reviewed evidence and the recommendations issued in several consensus documents, it seems fair to conclude that:

1. Preoperative anaemia should be detected, classified, and treated prior to elective procedures. For non-elective procedures, anaemia should be detected, classified, and treated as soon as possible. Whenever possible, pharmacological treatment should be preferred, whereas ABT should be restricted to those with severe anaemia and/or poor physiological reserve.

2. In elective procedures, preoperative IV iron replacement seems to be safe, results in lower transfusion requirements, and hastens recovery from postoperative anaemia. The use of newer IV iron formulations (ferric carboxymaltose or iron isomaltoside-1000) may facilitate iron replacement and offer additional benefits for both the patient and the health system.

3. If there is no contraindication, the preoperative use of ESAs seems to be justified, especially in those whose anaemia has an inflammatory component, although the minimal effective dose is presently unknown. An adequate iron supply should be ensured when using ESAs.

4. As they are inexpensive and non-toxic treatments, preoperative supplementation with folic acid (5 mg/day, oral) and vitamin B_{12} (1 mg, IM) could be considered to prevent functional or absolute deficiency during anaemia correction, especially if their levels are not routinely measured and/or in patients older than 60 years.

5. In non-elective procedures, the current evidence (mostly in hip fracture) broadly supports the use of IV iron or IV iron plus ESAs in reducing transfusion rates and improving outcome. Therefore, the acceptable safety profile and the ability to be administered without delaying surgery further support its clinical use.

6. Finally, the aim of performing major surgical procedures without the use of ABT and without placing the patient at risk of complications may be better accomplished by combining several blood conservation strategies into a defined PBM algorithm.

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