Review Article

Preoperative anemia optimization: role of iron supplementation

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Abstract: The presence of anemia in the surgical patient is highly prevalent and is associated with adverse clinical outcomes in the perioperative period. One of the three pillars of perioperative blood management is the optimization of the red blood cell mass. However, the use of allogeneic blood transfusions for anemia optimization is associated with increased risk of adverse clinical outcomes as well as increase healthcare financial costs. Therefore, the optimization of anemia has been shifted toward preference for a non-transfusional approach. Efforts aimed to mitigate the risk of allogeneic blood transfusion in anemic surgical patients by means of hematinic and nutrient supplementation are pursued to enhance perioperative outcomes. Iron deficiency is the most commonly associated etiology of anemia in surgical patients, and depending on the total body iron deposits as well as its bioavailability, it can be divided in absolute and relative iron deficiency. In both types of iron deficiency, the supplementation with parenteral iron is an effective and safe therapy to optimize the preoperative hemoglobin values, mitigating the risk of allogeneic blood transfusion by means of raising the postoperative hemoglobin nadir and avoiding reaching the transfusional threshold. There are multiple parenteral iron preparations, and its safety has been well validated.

Keywords: Intravenous iron; parenteral iron; iron; blood transfusion; preoperative; anemia

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Introduction

Mitigating the risk of adverse effects in the perioperative period, along with enhanced patient outcomes, is the mainstay of perioperative medicine. Among the most relevant elements that impact the perioperative morbidity is severe anemia. Preoperative anemia carries a reported prevalence of up to 75% of patients and it is the single most important risk factor for intraoperative blood transfusion (1,2).

The tree pillars of perioperative blood management include optimization of hemoglobin and hematocrit, decrease blood losses, and enhancement of patients' physiologic tolerance to anemia (3).

Aiming to decrease the risk of transfusing blood is paramount and this can be achieved by optimizing the preoperative hemoglobin levels in addition to optimizing hemostasis. Investigation of the source of anemia must be pursued, generally after the surgical period. In this manuscript we'll focus exclusively on preoperative hemoglobin optimization with parenteral iron supplementation.

Physiologic considerations

Anemia plays a significant role in oxygen delivery, given that the arterial content of Oxygen (CaO_2) is defined by the product of the arterial oxygen saturation (SaO_2%) and the result of the product of the hemoglobin level (g/dL) by oxygen-carrying capacity of hemoglobin (which is 1.34 mL/g),

as determined by the formula:

CaO_2 (mL/dL) = [SaO_2 × 1.34 × (Hb)] + (0.0031 × PaO_2)

The last part of the equation is the product of the PaO_2 (mmHg) by the solubility of oxygen in plasma at 37 ℃ [mL/(dL·mmHg], but given its small value is often not taking into account.

The product of CaO_2 by cardiac output is what determines the oxygen delivery (DO_2). Therefore, the body has compensatory adaptive mechanisms to anemia such as reticulocytosis as well as increasing the cardiac output. Other mechanisms include oxyhemoglobin dissociation curve shift to the right with consequent enhanced release of oxygen at the tissue level, which is achieved by the increased synthesis of 2,3-diphosphoglycerate (2,3-DPG) as well as the increased release of carbon dioxide into the blood (Bohr effect) (4-6).

The actionable clinical elements of the above principles in preoperative anemia optimization is aiming to rise the preoperative hemoglobin values in anticipation to surgical blood loss and avoid the hemoglobin nadir reaching the transfusion threshold values. An accessible way to enhance hematopoiesis is assessment and optimization of substrate (hematinic) levels (7).

Therefore, in order to be able to optimize hemoglobin values preoperatively, laboratory measurement of serum levels of the different hematinic substrates should be assessed: iron, total iron binding capacity (TIBC), percentage of transferrin saturation and ferritin levels; in patients older than 60 years old measurement of vitamin B12 is recommended. In addition, assessment of reticulocytosis allows having a baseline to be followed up as a measure of response to treatment (8).

A relevant consideration is the understanding of iron metabolism and bioavailability for effective erythropoiesis. Iron deficiency can be considered absolute (true depletion of iron stores) or functional (where iron stores are adequate, however, the hematopoietic effect is inadequate due to lack of bioavailable iron at the erythroid marrow). Functional iron deficiency is quite common especially in patients with anemia of chronic disease, which encompasses active inflammation, malignancy and infectious processes. The two tests that allow a better assessment of this anemia are the percentage of hypochromic red cells (%HRC) and the reticulocyte hemoglobin content (CHr). Also, the differentiation of combined absolute and functional iron deficiency can be done by the measurement of soluble transferrin receptor levels (sTfR). However, the availability of these tests is quite limited, in addition to its associated elevated cost (9).

Recognizing the presence of functional iron deficiency is relevant from the therapeutic perspective, as it can be optimized with parenteral iron as will discuss subsequently (10).

Prognostic implications of preoperative anemia

Preoperative anemia is associated with increased postoperative morbidity and mortality as well as risk of allogeneic blood transfusions, and this has been demonstrated in orthopedic surgery (7).

A study of 310,311 elderly veterans aiming to identify the cardiovascular morbidity of preoperative anemia demonstrated that every percentage-point decrease in preoperative hematocrit value below 39% was associated with a 1.6% (95% CI: 1.1–2.2%) increased 30-day postoperative mortality (7). The prevalence of preoperative anemia was of 40% in a retrospective study of 8,000 patients undergoing non-cardiac surgery; this was associated with a five-fold increase in 90-day postoperative mortality (11).

The prevalence of preoperative anemia in a prospective validated outcomes registry of 227,425 patients was 30.44%. Patients with anemia (defined as Hct <39% for men and <36% for women) had a higher postoperative mortality at 30 days (OR 1.42, 95% CI: 1.31–1.54) and also a higher postoperative morbidity at 30 days (OR 1.35, 95% CI: 1.30–1.40). (12)

In a study of 1,534 patients undergoing major elective orthopedic surgery the prevalence of anemia increased from 14.1% preoperatively to 85.8% postoperatively. Mean Hb decrease was 1.9 g/dL in patients with preoperative anemia and 3.0 g/dL in non-anemic patients. Transfusional needs occurred in 14.8% of patients with preoperative anemia *vs.* 2.8% of non-anemic patients. Postoperative complications occurred in higher proportion among patients with preoperative anemia *vs.* non-anemic patients (36.9% *vs.* 22.2%; P=0.009) (13).

Several retrospective analyses of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) have shown a prominent prevalence of anemia in different surgical populations. A review of 15,761 surgical patients with inflammatory bowel disease demonstrated that half of the population (49.8%) were anemic upon presentation to surgery (14).

Also, a review of 24,473 adult patients undergoing elective spinal surgery showed a 24% prevalence of anemia, which was associated, independently of its severity, with increased duration of hospitalization as well as worse

surgical outcomes (15).

The above data showcases the importance of hemoglobin level optimization preoperatively. Aiming to correct anemia preoperatively has the intent to decrease the associated morbi-mortality in addition to the utilization of blood products which also carry intrinsically associated increased morbi-mortality.

Pharmacologic optimization of preoperative anemia: iron

Rationale for preoperative iron supplementation

Iron deficiency is often the most common cause of anemia in the surgical population as can be ascertained by a large variety of studies including different surgical populations.

In orthopedic surgery, the prevalence of anemia in patients presenting for elective surgery ranges from one third to one half of the cases, and often the cause of anemia is iron deficiency (16-18).

A retrospective analysis of 3,342 patients undergoing major elective surgery (orthopedic in 1,286, cardiac in 691, colorectal cancer resection in 735, radical prostatectomy in 362, gynecological in 203 and resection of liver metastases in 122) showed an overall prevalence of anemia of 36%, from which 62% had absolute iron deficiency (19).

In colorectal surgery, 70% of patients have iron deficiency anemia associated with blood loss (20). In a recent study of 339 patients with colon cancer, the prevalence of iron deficiency was 48.1% (21).

Recently, it has been reported that morbid obese patients undergoing bariatric surgery have preoperative iron deficiency in 30–35% of patients (22-24).

The above studies support the assessment of anemia prior to large elective surgery (e.g., orthopedic, colorectal, oncological, spine, etc.) and consider that in cases with potential risk for large blood losses and to assess iron levels and provide iron repletion.

Why parenteral iron?

The enteral administration of iron generally provides suboptimal bioactive iron supplementation to support erythropoiesis in situations of significant ongoing iron deficit, such as perioperative blood loss. As stated previously, iron deficiency can be absolute or functional. Absolute deficiency occurs in situations of chronic blood loss as well as poor supplementation (either from dietary restrictions or from malabsorption) (10). Common causes that impair enteral absorption of iron include active comorbid conditions such as bacterial overgrowth, chronic GI bleeding, platelet dysfunction (chronic kidney disease, CKD), use of anti-platelet agents, frequent phlebotomies, proteinuria (transferrin losses) and increased iron utilization (use of EPO in CKD). Use of antacids impairs iron absorption as well. In addition, an increasingly recognized factor that also affects the GI iron absorption is celiac disease (25,26). In addition, in the USA there is a growing population of patients undergoing metabolic (bariatric) gastric bypass surgery which predisposes to lifetime suboptimal iron absorption (22-24).

A prospective, observational cohort study of 87 patients undergoing hip or knee arthroplasty showed no improvement in hemoglobin values after receiving for 3 weeks preoperatively oral ferrous sulfate 300 mg 3 times daily; however, there was increased incidence of adverse effects such as constipation (33.3%), heartburn (13.8%), and abdominal pain (12.6%) (27).

In a cohort of patients undergoing colorectal surgery for colon cancer, intravenous iron provided higher increase in hemoglobin values than oral iron (28).

The clinical superiority of intravenous iron in the preoperative setting has been demonstrated by multiple studies in surgical patients (including cardiac, gynecologic, orthopedic and colorectal surgery); however, most studies are observational studies with few randomized controlled trials; the protocols included oral and parenteral iron as well concomitant EPO (29-31). Recently, a systematic review of 13 studies totaling 4,959 patients demonstrated that preoperative anemia optimization using blood management programs in patients undergoing hip arthroplasty was beneficial; the protocols including oral and intravenous iron as well as EPO (32).

A study of 60 patients comparing IV iron versus usual care in patients undergoing major abdominal surgery demonstrated a 60% decrease in allogeneic blood transfusion, as well as higher hemoglobin concentration at 4 weeks, as well as it was associated with a decrease in the length of stay (33).

Most studies and clinical approaches for anemia optimization are focused on the preoperative setting. To address the role of anemia optimization in the postoperative setting, a prospective, randomized, controlled study of postoperative major surgical patients evaluated the degree of anemia and iron deficiency on the postoperative day

one and compared the outcomes of administering one gram of ferric carboxymaltose *vs.* standard care. At 4 weeks it demonstrated improved hemoglobin concentration, improved iron stores and substantial decreased transfusion rate compared with the standard of care group (34).

Results of a current ongoing trial (PREVENTT: preoperative intravenous iron to treat anemia in major surgery) should be published soon. This study is comparing IV ferric carboxymaltose (1 gram) *vs.* placebo for a period of 10 to 42 days preoperatively for major abdominal surgery. In addition to the decrease in transfusional efforts, other outcomes will be length of stay and costs of care (35).

In medical, non-surgical setting, besides the optimization of anemia in renal patients on dialysis, another area where parenteral iron has proven to be effective is in patients with chronic heart failure with low ejection fraction, where the administration of parenteral iron is associated with improvement in both exercise capacity and quality of life (36).

However, iron deficiency can also be functional, where the iron stores are presumably normal yet with poor bioavailability of the same to the erythroid marrow. This occurs in settings of increased inflammation, such as autoimmune inflammatory diseases, malignancy, or chronic infectious processes; in these settings there is increased hepcidin production, which is a protein that impairs the iron bioavailability. In this setting it has been demonstrated that the use of parenteral iron overcomes the effect of hepcidin, allowing enhanced iron bioavailability to the erythroid marrow and allowing enhanced hematopoiesis (9).

In addition, a strong consideration for the utilization of parenteral iron is the cost when comparing with blood utilization. One gram of either ferric gluconate or iron sucrose cost approximately $500 US dlls (37,38); one unit of blood (which contains approximately 250 mg iron) costs $761 ± 294 US dlls, so the administration of 4 units (1 gram of iron) rises up the cost to $3,044 US dlls per gram of iron compared with $500 US dlls of the iron preparations. The cost of packed red blood cells includes the blood bank management, skilled nursing care and ancillary services (39).

The clinical effectiveness in anemia optimization, in addition to decrease not only the inherent risk of blood transfusion, but it's associated concomitant cost, makes intravenous iron an excellent treatment alternative for preoperative anemia optimization, especially in bloodless surgery protocols for patients who refuse blood transfusions.

Safety of parenteral iron therapy

Intravenous iron therapy has been closely scrutinized for risks and adverse events (40-42). A retrospective review of 688,183 IV iron preparations (including iron dextran, gluconate, sucrose, or ferumoxytol) recipients found a total of 274 anaphylaxis episodes with the first exposure to IV iron. The anaphylaxis risk at first IV iron exposure was: (I) dextran iron: 68 per 100,000 persons; (II) non-dextran iron preparations: 24 per 100,000 persons.

The cumulative anaphylaxis after administration of 1 gram of iron dextran over a 12 weeks period was 82 per 100,000 persons (95% CI: 70.5–93.1) while the risk with iron sucrose was 21 per 100,000 persons (95% CI: 15.3–26.4) (42).

Iron dextran complexes have been proved to cause anaphylactic reactions, which occur more frequently (3-fold) with high molecular weight iron dextran than with low molecular weight iron dextran. The prevalence of these reactions appears to be the same regardless of whether the patient receives a low-dose (100 mg) or a high dose (500–1,000 mg) (43).

Safety aspects of parenteral iron (iron dextran, ferric gluconate, and iron saccharate) in patients with end-stage renal disease have been scrutinized (44). Ferric gluconate was approved for use in the United States in February 1999 as an intravenous iron preparation in renal dialysis patients limiting the dose to 125 mg over a 1-hour infusion at each administration (45). A double-blind, placebo-controlled study of 2,534 hemodialysis patients found a very low incidence of adverse effects (less than 5%) in patients receiving ferric gluconate; and among those who had adverse reactions (hypotension, rash, and chest or abdominal pain), had no increase in tryptase levels, a marker of mast cell degranulation which should be increased in true anaphylaxis (46).

Iron sucrose has a low reported reaction rate in open label studies with demonstrated effectiveness in anemia treatment in dialysis patients (47); the authors recommended optimizing iron stores (serum ferritin 200–400 μg/L and transferrin saturation above 25–35% prior to using EPO. Iron sucrose was well tolerated in 665 hemodialysis patients including 80 patients (12%) considered intolerant to iron dextran (48). Iron sucrose is administered in intravenous push doses up to 200 mg over 2 to 5 min with a good safety profile (49).

Ferric carboxymaltose and ferumoxytol are newer

alternatives for parenteral iron therapy and are FDA approved and available at the US (50-53). Ferric carboxymaltose has shown a strong safety profile and has the advantage that 1 gram can be administered in a single doseas it is used in other countries; however, the FDA has approved it only for 750 mg at a time (54). The safety profile of ferumoxytol has been scrutinized by the FDA recently due to higher risk of anaphylaxis (52,53).

A recent randomized double-blind trial compared ferric carboxymaltose versus ferumoxytol. The efficacy in hematopoiesis was similar between both (change in hemoglobin of approximately 1.5 g/dL at 5 weeks) and no anaphylaxis reactions were seen. However, ferric carboxymaltose was associated with hypophosphatemia (38.7%) *vs.* 0.4% for ferumoxytol (55).

Iron isomaltoside 1000 is a novel preparation that has not been associated with anaphylaxis and can allow rapid administration of a full 1,000 mg elemental iron dose in a single dose. Yet it is still only approved to use in Europe (56).

Despite lack of compelling evidence to support it, the use of parenteral iron is avoided in patients with severe infections; this is based on the hypothesis that elemental iron is an essential growth factor for bacteria that expresses iron transport proteins that compete with transferrin (57). Given the lack of strong clinical evidence to support this risk, patients who benefit from parenteral iron supplementation ought to receive it with careful monitoring of iron levels (57,58).

Another potential adverse effect of intravenous iron therapy is a clinical syndrome of acute iron toxicity (nausea, facial reddening, and hypotension) that has been described with rapid infusion of ferric gluconate (125 mg within 30 minutes). Therefore, the recommendation is to administer ferric gluconate in a longer infusion of no less than 1 hour (59). Also, the half-life of ferric gluconate and iron sucrose is of 1 hour and 8 hours, respectively, which allows a safe administration as frequently as every 24 hours (60).

The recommended parenteral administration of iron is always intravenous. Intramuscular administration of iron is discouraged due to its lack of superiority over intravenous therapy, painful administration, skin discoloration and risk for development of gluteal sarcomas (61).

Current recommendations for preoperative parenteral iron use

The preoperative optimization of anemia aims to decrease the utilization of allogeneic blood along with the associated adverse outcomes and cost.

The iron deficit can be calculated by the Ganzoni's formula which takes into account that 1 gram of hemoglobin contains 3.3 mg of elemental iron (62). However, for practical reasons, the iron deficit is not usually calculated; it is a common practice to supplement 1,000 mg of elemental iron preoperatively to supplement both the deficit and the postoperative loss. On average, an administration of an IV iron dose of 1,000 mg raises the hemoglobin by approximately 2.0 g/dL, resolve the anemia in up to 58% of cases, decreased the transfusion rate by 66% and the infection rate by 55% (63,64).

A recent study demonstrated that although the administration of 1,000 mg is the routine practice, it may not be sufficient to replete the patient's body iron deficit; the authors suggest a higher total dose of 1,500 mg (65).

The Network for Advancement of Transfusion Alternatives (NATA), a European organization focused on blood management, proposes using preoperative IV iron in patients with ferritin <100 ng/mL; transferrin saturation <20%, or expected blood loss >1,500 mL. The cutoff limit to avoid further IV iron administration is when ferritin levels are above 300 ng/mL and transferrin saturation is above 50%, or when there is acute infection (7,64). The updated 2006 KDOQI guidelines recommended to maintain in hemodialysis patients a transferrin saturation (TSAT) >20% and a ferritin between 200 ng/mL and less than 500 ng/mL (66). The 2012 KDIGO guidelines supports to maintain a TSAT >30% and ferritin >500 ng/mL (67). The most recent international consensus statement for perioperative anemia and iron deficiency management also recommend the use of parenteral iron for TSAT <20% and ferritin <100 ng/mL. However, the authors state that if there is sufficient time (6 to 8 weeks) to allow for anemia optimization, and the patients have no contraindications, oral iron therapy can be attempted; the recommendation for oral therapy is low dose iron dosing of 40 to 60 mg of iron daily, or 80 to 100 mg every other day; the rationale for this is that high dose of enteral iron has been associated with increased hepcidin release (68).

There are variable protocols for preoperative administration of iron formulations for anemia optimization; ideally the iron replacement should initiate with sufficient time to allow for effective erythropoiesis—3 to 4 weeks prior to surgery—targeting a total dose of 1 gram. The Anemia Working Group in Spain has a nice algorithm where iron sucrose is administered at a dose of 200 mg IV every week starting 3–4 days before surgery, and administers a dose in the day of surgery and additional postoperative doses depending of the hemoglobin level (63).

International protocols use formulations that allow the administration of a single dose of intravenous iron, such as isomaltoside 1000, which allows a single dose of 1,000 mg (56). Other formulation like ferric carboxymaltose can also be administered in a single 1,000 mg dosing as is used in Europe; however, in the United States the recommended single dose is 750 mg and if a second dose is given to achieve a total 1,500 mg dosing, it should be separated by 7 days (54).

At our institution, the main source of referrals for preoperative anemia are orthopedic patients undergoing elective joint replacement; subsequently are patients undergoing gynecological surgery; less frequently are colorectal surgery patients. Our protocol differs between the outpatient and inpatient setting given the pharmacy logistics; in the outpatient setting, we use iron sucrose at a dose of 300 mg intravenous push over 5 minutes every other day for a total of 3 doses (900 mg) or 5 doses (1 gram). A repeat hemoglobin and reticulocyte count can be reassessed 1 week to 10 days after last dose; usually this protocol allows for an increase in hemoglobin of approximately 2 g/dL. In the inpatient setting we use ferric gluconate 125 mg IV over 1 hour every day to every other day for a total of 8 doses (1 gram) (69). The patients' primary care physician must be notified about the iron supplementation and should be advised to pursue further evaluation of the underlying cause of iron deficiency once the patient has recovered from surgery: e.g., endoscopic studies, celiac panel, duodenal biopsy, etc. (69).

Conclusions

The presence of anemia in the surgical patient is associated with adverse clinical outcomes; the most common hematinic deficiency associated with preoperative anemia is iron deficiency. The use of parenteral iron has been demonstrated as a safe alternative to optimize anemia preoperatively with the aim to mitigate the risk of allogeneic blood transfusion.

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