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Review Article

Intravenous Iron Therapy in Patients Undergoing Cardiovascular Surgery: A Narrative Review

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MANY OF THE RISK factors for iron deficiency, including advancing age and chronic illness, also are present in patients undergoing major surgery. More than one third of patients undergoing major cardiac and noncardiac surgery may be iron deficient before surgery.[1] Furthermore, surgery itself can cause inflammation, activating signaling pathways that lead to iron sequestration, decreased circulating iron, and inhibition of enteral iron absorption. The result is a potentially prolonged state in which essential processes, including erythropoiesis, become iron-restricted.[2]

Oral iron therapy requires prolonged therapy, is often poorly tolerated, and is relatively ineffective. Historically, older intravenous (IV) iron preparations were associated with a high incidence of serious adverse effects, including hypersensitivity reactions.[3] However, newer preparations of IV iron appear to be safer and are effective in increasing erythropoiesis.[4,5] In patients undergoing cardiac surgery, IV iron may decrease postoperative anemia, allogenic red blood cell (RBC) transfusion requirement, and mortality.[6,7]

Preoperative Anemia, Red Blood Cell Transfusion, and Perioperative Outcomes

Preoperative anemia occurs in approximately 1 in 3 patients undergoing major surgery.[8] In patients undergoing cardiac surgery, the prevalence of preoperative anemia may be even higher[9,10] and is an independent risk factor for major cardiac and noncardiac perioperative adverse events including myocardial infarction, stroke, renal failure, and both short- and long-term mortality.[10–12] This also is true for patients undergoing vascular surgery in whom the presence and severity of perioperative anemia are associated with increased morbidity and mortality.[13–15]

The severity of preoperative anemia is a strong predictor of perioperative allogeneic RBC transfusion requirement[2,10,16,17] and is the only known modifiable risk factor for this intervention.[18] Allogeneic RBC transfusion is an independent, dose-dependent, risk factor for prolonged intensive care unit (ICU) and hospital admission and in-hospital mortality.[11,19–21]

Despite this, cardiac surgery remains an extremely common indication for RBC transfusion, accounting for 1 in 5 available units prescribed internationally.[22] The adverse events associated with RBC transfusion in this group of patients include acute lung injury,[23] post-coronary artery bypass graft (CABG) occlusion,[24] ischemia,[25] infection,[3,26–28] acute kidney injury,[23] increased length of hospital stay, higher early and late mortality, and increased hospital costs.[2,25] In those undergoing major vascular surgery, RBC transfusion is associated with up to an 11-fold increase in 30-day mortality and an 8-fold increase in myocardial infarction, independent of baseline characteristics, surgical risks, bleeding, and propensity to receive transfusion.[29,30]

Current guidelines recommend a conservative RBC transfusion strategy, even if this may worsen anemia.[11,19,20,31]

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However, this approach has been challenged.[32] In contrast to critically ill patients, Hovaguimian et al[32] found that patients undergoing cardiovascular procedures appeared to have an increased risk of adverse events, including major adverse cardiac events, acute renal failure, cerebrovascular accidents, and mortality. A recent pivotal randomized controlled trial (RCT),[33] suggests that a conservative RBC transfusion strategy is non-inferior to a more liberal strategy in patients undergoing cardiac surgery.[34]

Perioperative Diagnosis of Iron Deficiency

Iron deficiency may be present prior to surgery or occur perioperatively due to hemorrhage, phlebotomy losses, hemolysis, and inflammation.[11,12,31,35] Despite its many life-sustaining functions, iron is the most prevalent nutritional deficiency globally and accounts for up to half of the worldwide burden of anemia.[36] The main causes of iron deficiency are provided in Table 1. In general terms, iron deficiency can be a consequence of increased iron requirements, decreased exogenous supply, and/or increased losses.[17,37] Multiple causes often coexist, and investigation of the underlying cause(s) is essential.

In otherwise healthy individuals, a full blood count, transferrin saturation, and ferritin concentration generally are sufficient to diagnose iron deficiency. However, ferritin is an acute-phase reactant and elevated concentrations may mask underlying iron deficiency in the presence of acute or chronic inflammation.[35,39–41] For example, a pattern of low serum iron, low transferrin saturation, and high ferritin occurs in more than 75% of patients after major trauma or surgery.[42,43] These changes are mediated primarily by increased secretion of hepcidin, the master regulator of iron metabolism (Fig 1).[44]

Hepcidin inhibits enteral absorption of iron and decreases circulating iron concentration. Persistently elevated hepcidin concentration in response to inflammation can lead to a state of iron-restricted erythropoiesis, in which progressive anemia occurs irrespective of the status of iron stores.[45] Although the concept of functional iron deficiency is well-established and associated with a recognized pattern of iron study results, specific diagnostic criteria have not been agreed on and additional studies are necessary to measure the effect of related treatment algorithms on patient-centered outcomes.[46,47] Suggested diagnostic criteria for the spectrum of deficiencies in iron metabolism are provided in Table 2.

Table 1
Causes of Absolute Iron Deficiency[37,38]

Increased Iron Requirements	Limited Exogenous Supply or Absorption	Increased Loss
Rapid growth (eg, infancy, childhood)	Poor intake/bioavailability of iron and/or ascorbic acid	Iatrogenic • Excessive phlebotomy • Dialysis
Treatment with erythropoiesis-stimulating agents	High gastric pH	Hemorrhage • Surgery • Trauma • Gastrointestinal (eg, malignancy, ulcer, diverticulosis, parasitosis) • Genitourinary (eg, menorrhagia, malignancy, chronic infection) • Pulmonary
	Competition from other metals (eg, copper, lead)	
	Malabsorption	
	Loss or dysfunction of absorptive enterocytes (eg, bowel resection, intrinsic enterocyte defects)	
	Celiac disease	
	Inflammatory bowel disease	

Intravenous Iron

Composition

IV iron consists of a polynuclear iron(III)-hydroxide mineral core surrounded by a carbohydrate ligand that stabilizes the complex and regulates iron release.[52,53] The molecular weight determines the reactivity of each complex. Larger complexes result in more regulated iron release with slower plasma clearance rates and longer elimination half-lives.[53] The characteristics of commonly available IV iron preparations are provided in Table 3.

Potential Benefits

Compared with alternative treatments such as oral iron and allogeneic RBC transfusion, IV iron has been shown to result in net savings in both direct (acquisition and administration costs of treatment) and indirect costs (hospitalization costs).[55–58] In a study by Calvet et al[58] in patients with colorectal cancer and anemia, ferric carboxymaltose reduced length of hospitalization by 2.3 days compared with iron sucrose and by 2.6 days compared with oral iron. This resulted in cost savings of $532 and $300 per patient, respectively. These findings are consistent with those in patients undergoing cardiovascular and orthopedic surgery. Hallward et al[10] found that each 10 g/L increase in hemoglobin (Hb) in patients before cardiac surgery improved the probability of discharge from the ICU and hospital by 4% and 12%, respectively, and costs were reduced further through lower transfusion requirements. Muñoz et al[57] found that postoperative IV iron reduced the allogeneic transfusion rate by 15% and hospitalization by 1.9 days. Additional data are required to establish IV iron therapy as a cost-effective component of patient blood management in the perioperative setting.

With the advent of newer IV iron formulations that allow for the safe and rapid administration of larger single doses of IV iron, consideration should be given to the development and assessment of standardised preoperative blood management pathways. The availability of IV iron currently can pose a barrier to treatment. In a recent survey on perioperative medicine in the United Kingdom,[59] 67.4% of centers that offered perioperative anemia screening had access to IV iron therapy. Within these centers, there were restrictions for use of IV iron only for urgent cases and specific cancers (gastrointestinal or urologic), or IV iron was administered on a

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