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Role of intravenous iron therapy for management of perioperative anaemia: A narrative review

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Highlights

- Iron deficiency is the commonest cause for anaemia in patients undergoing surgeries, and this review summarizes its implications.
- Intravenous iron is a better treatment option for iron deficiency than other iron preparations.
- Body iron metabolism is a complex process, and evidence is conflicting on iron supplementation in surgical patients.
- Intravenous iron replacement, as a part of patient blood management, has shown benefit in perioperative anaemia.

Abstract

Anaemia is a frequent problem in surgical patients, and the commonest cause is iron deficiency. There is no agreement among perioperative clinicians on the utility of intravenous (IV) iron therapy in surgical patients. In this study, publications in Medline, Web of Science, and Embase databases, along with major perioperative guidelines up until 2022 were searched using specific key words, and relevant papers that investigated IV iron therapy in the perioperative settings were screened out. Management of perioperative anaemia is comprehensively discussed in major guidelines. However, the diagnosis and management of iron deficiency is not as straightforward as those for anaemia. Iron metabolism is a complex process. IV iron supplementation remains the treatment choice for perioperative iron deficiency; however, it has limited and conflicting evidence of benefits in surgical patients. IV iron replacement, as a part of patient blood management, has shown benefit in perioperative anaemia.

Keywords: Iron, anaemia, perioperative care, surgery, intravenous

Introduction

Anaemia is a common pathological condition, and its prevalence varies from 30% to 75% across patients undergoing elective surgical interventions [1]. Perioperative anaemia is reported in 54.4% patients prior to cardiac surgeries and in 39% undergoing non cardiac surgeries [2].

Anaemia is defined as reduction of body red cell mass, and the World Health Organization criteria for the diagnosis of anaemia are haemoglobin (Hb) level <12 g/dl for women and Hb level <13 g/dl for men [3]. However, the pathological consequences of anaemia in males and females are equivalent during operative procedures, so the lower Hb threshold in females is debatable. Patients undergoing major surgeries with expected blood loss greater than 500 ml should achieve target Hb level >13 g/dl [4]. Cell oxygenation and optimal cellular metabolism require an adequate level of Hb [5, 6]. Anaemia is associated with poor outcomes perioperatively, including intensive care admission, transfusion requirements, extensive length of stay, and mortality [7, 8]. Anaemia in older patients is associated with further increased risk of perioperative complications [9, 10].

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Table 1. Major guidelines on perioperative anaemia and blood management

Guideline	Recommendation on Perioperative anaemia	Class of recommendation	Level of evidence
National Association of Testing Authorities guidelines 2011 [4].	Elective surgical patients should have an Hb level determination as close to 28 days before the scheduled surgical procedure as possible.	1	C
	Patient's target Hb before elective surgery should be within the normal range (female ≥12 g dl^{-1}, male ≥13 g dl^{-1}), according to the World Health Organization criteria.	2	C
European Society of Anaesthesiology guidelines 2016 [12].	Patients at risk of bleeding should be assessed for anaemia 3 to 8 weeks before surgery.	1	C
American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015 [13].	Preoperative evaluation of a patient to identify risk factors for requiring a blood transfusion or adjuvant therapy includes (1) reviewing previous medical records, (2) conducting a patient or family interview, (3) reviewing existing laboratory test results, and (4) ordering additional laboratory tests when indicated.	3/4	B
Patient Blood Management Australia, module 2 Perioperative. March 2012 [14].	Recommendations for multidisciplinary approach in patient blood management during perioperative period.	1/3/4	C

However, the significance of anaemia and its impact on adverse surgical outcomes are undervalued [11]. Routine preoperative investigations should include measuring blood Hb levels, so that treatments could be initiated timely. **Table 1** summarizes the leading available guidelines for perioperative anaemia investigations [4, 12-14].

Iron deficiency (ID) anaemia

Amongst the causes of anaemia, ID is the leading aetiology across all ages, and it is the commonest nutritional deficiency globally [15]. World Health Organization estimates that ID accounts for approximately 50% of all anaemias [16]. Females in childbearing age are more frequently affected by ID than males. It is a problem in both developed and developing countries [17, 18].

Pathophysiology of ID could be absolute or functional. Low or absent iron stores is defined as absolute ID (in contrast to diminished erythropoiesis). High or normal level of iron stores indicate relative or functional ID [15, 19]. Iron metabolism in human body is a complex process which accounts for the above-mentioned types of ID.

Iron (Fe) is a main element of red blood cell Hb and muscle cell myoglobin. Iron is also an important component in enzymes, DNA, and mitochondria. Iron is stored in the form of ferritin and haemosiderin in liver, bone marrow, and spleen [15, 20, 21]. Adults require about 25 mg of elemental iron for red cell Hb production and cellular metabolism daily. However, the average daily intake of iron is only 1 to 2 mg. Due to the limited iron intake, iron homeostasis is maintained by recycling body iron. Older red blood cells are phagocytosed by macrophages, and iron molecules are taken up as a part of the salvage process. Hepcidin is a small peptide secreted mainly from hepatocytes and is the primary regulator of iron homeostasis. Higher iron concentrations and inflammation up-regulate hepcidin production. Hepcidin binds to the ferroprotein, an iron transporting molecule on cell surfaces, and down-regulates its availability. As a result, iron is no longer released to the plasma. This process leads to functional ID in the context of inflammation [19]. Common causes of ID are summarized in **Table 2** [15, 22, 23].

Diagnosis of ID is not as simple as recognition of an apparent ID anaemia. Red cell indices such as mean cell volume and haematocrit are useful markers for assessment of ID. Low mean cell volume corresponds to microcytosis, and low haematocrit is indicative of hypochromia. Presence of these changes in a blood picture suggests long standing ID. Haemoglobinopathies and nutritional deficiencies could alter interpretation of these results [24, 25]. Nevertheless, an iron study is the most useful test to identify ID (See **Table 3**). The ratio of serum iron to total iron binding capacity is presented as transferrin saturation, and a low transferrin saturation usually indicates ID. Serum ferritin levels reflect total body iron stores, and low ferritin is thus indicative of ID. However, acute and chronic inflammatory conditions can elevate ferritin level as a part of the inflammatory process. Low transferrin saturation in the pres-

Table 2. Common causes of iron deficiency

Causes of iron deficiency		
Absolute iron deficiency	Blood loss	Gastro-intestinal bleed, menstrual loss, worm infestation, regular blood donation, other surgery / trauma
	Lack of iron in diet	Vegans, lack of iron rich food
	Malabsorption	Coeliac / Crohn's disease, H. pylori infection, by-pass surgery / small intestinal resection/ gastrectomy, H2 antagonists / proton pump inhibitors
	Increase demand	Infancy and childhood growth, erythropoiesis stimulation treatment, pregnancy
Functional iron deficiency	Anaemia of chronic disease	Heart failure, obesity, cancer, inflammatory diseases, perioperative response

Table 3. Iron study interpretation

Iron study	Level	Diagnosis
Ferritin	<30 mcg/L	Iron deficiency
Ferritin Transferrin saturation	<100 mcg/L <20% (C-reactive protein >5 mg/L)	Iron deficiency + Anaemia with chronic inflammation
Ferritin Transferrin saturation	>100 mcg/L <20% (C-reactive protein >5 mg/L)	Anaemia with chronic inflammation

ence of elevated ferritin levels is suggestive of anaemia of chronic inflammation [26-28].

Treatment for ID

The first approach to manage ID is to treat the underlying cause (See **Table 2**). This is part of the pre-operative assessment. Oral iron therapy increases haemoglobin and reduces perioperative transfusion requirements [29]. However, dietary therapy and oral iron supplements are less effective, mainly due to low efficacy and intolerance [30]. The next available option to treat ID is parenteral iron therapy. Intramuscular injections are available and effective in improving body iron levels; however, intramuscular iron injections are painful and can cause skin staining [31, 32]. There were reported cases of sarcoma after intramuscular iron treatment, hence it remains a less attractive option [33].

Intravenous (IV) iron therapy

IV iron therapy is a choice for perioperative anaemia. Iron dextran was the first successful IV preparation introduced in 1950s. This is a high molecular weight preparation and associated with significant side effects and high risk of anaphylaxis [34]. There are now many other preparations marketed. **Table 4** summarises available iron preparations with their basic properties [35, 36].

Positive evidence for perioperative use of IV iron therapy

IV iron has many advantages in managing perioperative anaemia. Although initial IV iron preparations were less popular due to high incidence of reactions, newer preparations have improved tolerance [37, 38]. The primary benefit of IV iron therapy is the fast response following a single dose. Therefore, IV iron therapy is currently the best option to manage perioperative ID anaemia.

The severity of anaemia has been shown to have a direct relationship with postoperative complications and mortality [39-41]. Preoperative anaemia is an independent risk factor for receiving postoperative blood transfusions [7, 40]. Allogenic blood transfusion has been shown to be associated with adverse outcomes, such as increased infection rates, cardiac complications, hospital length of stay, and mortality [41-45]. These complications are seen even with a transfusion of one unit of packed red blood cells [46]. At the same time, red cell transfusions are relatively expensive [47, 48]. Comprehensive patient blood management programs that include perioperative iron optimisation protocols have been developed to manage preoperative Hb levels and reduce postoperative anaemia and blood transfusions [49-53]. A Cochrane review on the use of perioperative

Table 4. Intravenous iron preparations

Intravenous iron preparation (Carbohydrate substrate)	Brand name	Half-life (Terminal plasma)	Molecular Wt (kDa)
Iron dextran	INFeD, DexFerrum	27-30 hours	103,000
Iron Carboxymaltose	Ferinject	7-9 hours	150,000
Iron sucrose	Venofer, Ferriecit	5-6 hours	43,300
Iron Isomaltosde	Monofer	20-23 hours	69,000
Ferumoxytol	Feraheme	14 -15 hours	185,000
Iron gluconate	Ferrlecit	1-2 hours	37,500

Table 5. Major guidelines on perioperative iron replacement

Guideline	Recommendation	Level of evidence
Patient Blood Management Australia, module 2 Perioperative. March 2012 [14]. *IV iron is indicated when oral not tolerated or rapid correction is required (surgery in <2 months)	Iron therapy is recommended for cases where there is a risk of perioperative iron deficiency anaemia.	B
	Patients with preoperative anaemia should get iron.	A
	For patient with post-operative anaemia, oral iron is not recommended.	B
American Society of Anesthesiologists Task Force on Perioperative Blood Management 2015 [13].	Use of ESA and iron is indicated in risk of anaemia.	A
European Society of Anaesthesiology guidelines 2016 [12].	Oral iron is for patients with iron deficiency diagnosed 6 to 8 weeks before surgery. IV iron for those cannot not tolerated oral iron or closer to the surgery date.	C

Note: ESA, Erythropoietin Stimulating Agents; IV, intravenous.

iron concluded that administration of preoperative IV or oral iron can accelerate Hb recovery and reduce transfusion requirements [54]. However, IV iron therapy showed many benefits over oral iron therapy in perioperative period. It is the only treatment option for preoperative ID when surgery is imminent within 6-8 weeks [12]. Preoperative IV iron therapy demonstrated improved surgical outcomes such as shorter length of stay and higher Hb concentrations at discharge [55-57]. All major blood management guidelines suggest preoperative iron replacement to improve operative outcomes (See **Table 5**).

IV iron therapy is also a viable treatment choice in cases of ID associated with bowel pathology, such as inflammatory bowel disease or bowel resection with poor oral iron absorption [58]. Oral iron is poorly tolerated in these patients due to production of reactive oxygen compounds, such as superoxides and peroxides, from non-absorbed iron salts. This can precipitate acute flares of bowel inflammation. Furthermore, ongoing inflammation in such conditions may cause functional ID as well [59].

Pregnancy and related surgical procedures are other situations where IV iron therapy demonstrates beneficial effects in optimizing Hb and iron levels. Iron supplements are essential during pregnancy to meet the excess demand. Both oral and IV iron supplements are indicated in pregnancy related anaemia or ID [60]. Most studies demonstrated better outcomes with IV iron replacement after childbirth [61]. Considering transfusion reactions and the cost, IV iron therapy is the preferred choice for acute post childbirth anaemia [62].

Severe ID anaemia is best treated with IV iron therapy in both perioperative and non-operative patients. On most occasions, anaemia is diagnosed in pre-operative investigations. All patients undergoing surgical procedures with significant blood loss require iron studies as a part of their preoperative review. When severe ID anaemia is identified in patients who are awaiting surgical procedures, the only treatment option is IV iron therapy. This was reviewed in multiple studies, and the efficacy and potency of IV iron therapy in severe ID have been reported in the literature [55, 56, 63].

Operative or non-operative management of anaemia in cancer patients is usually treated with erythropoietin stimulating agents. However, many studies reported beneficial effects of

Table 6. Risk factors for adverse events from intravenous iron therapy

Risk factors for adverse reactions	Factors increase severity of reaction
Previous hypersensitivity to Intravenous iron History of other allergies Severe asthma or eczema High iron infusion rate	Male sex Older age 1st trimester pregnancy Excess physical activity Beta blocker/Angiotensin converting enzymes Mastocytosis Systemic inflammatory disease Anxiety or psychological issues

combining erythropoietin stimulating agents with IV iron therapy, which improved response to ESA in these patients [64-66]. In fact, absolute and functional ID can co-exist in cancer patients, and IV iron therapy can promote bioavailability of iron for Hb production [65, 66].

Other cohorts of patients who benefit from IV iron therapy are the those with anaemia secondary to chronic kidney disease (CKD). Chronic inflammation in these patients leads to functional ID, and poor oral intake and gastrointestinal bleeding cause absolute ID. Furthermore, patients undergoing dialysis loss blood in each dialysis circuit, contributing to ID. Patients with CKD are frequently on erythropoietin agents which promotes ID due to increased demand of erythropoiesis [67]. This is the reason for using IV iron with Epo in patients with CKD as recommended in Kidney Disease Improving Global Outcomes guidelines [68]. Patients with CKD who are scheduled to undergo surgical procedures should get their Hb and iron levels optimized prior to any surgical interventions, and IV iron therapy combined with erythropoietin is the best option. Peri-operative correction of Hb and iron demonstrated better surgical outcome in CKD patients [4, 69]. However, the ideal level of Hb concentration to achieve optimal surgical outcomes in patients with CKD is not well defined in the literature [70].

Iron can also be given to patients without ID anaemia. Patients with beliefs that preclude the use of blood products (such as Jehovah's Witnesses) benefit from preoperative IV iron dosing to optimize their red cell mass and minimize need for red cell transfusion [71]. Iron is a cofactor in human enzymes. Patients with heart failure and ID were reported to have improved overall outcomes regarding exercise tolerance and heart failure symptoms after IV iron therapy [72, 73]. Therefore, this is an important aspect of optimizing heart failure management prior to surgical procedures.

Disadvantages of IV iron therapy

Perioperative and non-operative IV iron therapy may cause harm as well, but not frequently. The main disadvantage of IV iron therapy is the risk for adverse drug reactions and allergy. The most reported adverse reactions include dizziness, palpitation, urticaria, itching, flushing, and high blood pressure. These are not common and reported in less than 1% of patients. On the other hand, most of these effects are self-limiting [74, 75]. Severe reactions are rare but could lead to life threatening anaphylaxis. Factors predisposing to adverse reactions to IV iron therapy are summarized in **Table 6** [76, 77]. Patho-physiological basis of those reactions is IgE-mediated immunological response and complement activation related pseudo allergy. These responses are partially secondary to labile free irons in the circulation [77]. Management of these reactions are beyond the scope of this article.

Newer IV iron preparations demonstrate less potential for reactions. Iron dextran has high antigenicity effect [77]. Also, dextran-iron high molecular weight compound releases iron faster, causing more rapid increase in free iron levels (See **Table 4**). A follow-up of side effects after IV iron dextran and IV iron gluconate over 3 years revealed an allergic reaction incidence of 21.5% without a difference between two preparations [78]. But most other studies demonstrated a higher incidence of adverse reactions with old-fashioned IV iron preparations, such as iron dextran compared with newer preparations [79, 80].

Another main disadvantage of IV iron supplementation is the potential risk of precipitating infections. This is a debatable issue, and controversial results are found in literature. Extracellular pathogens utilize free iron for their cellular metabolism. IV iron therapy increases free iron in circulation and promotes pathogen activities. This is demonstrated in some animal studies with worsened pneumonia, shock, lung injury, and mortality observed in IV iron group compared to red blood cell transfusion group [81]. Iron is also recognized

as a growth factor for microbes, and a higher incidence of bacterial infection was reported in patients with haemochromatosis experiencing iron overload [82]. Another hypothesis is that retention of iron in macrophages can impair its function. This will affect cellular immunity and increase risk of microbial growth [83]. Another potential mechanism of increasing infection risk is oxidative stress. Sodium ferric gluconate and iron sucrose are responsible for higher non-transferrin bound iron, which is a marker of oxidative stress compared with iron dextran [84]. Oxidative stress was only noted after iron sucrose compared with iron dextran [85]. However, the significance of non-transferrin bound iron in predicting oxidative stress is controversial. Iron loading also accelerates inflammatory response to lipopolysaccharide and produces more superoxide from mitochondria [86]. On the other hand, clinical evidence of increased incidence of infection following iron infusion is lacking. A study investigating infection rate among patients who received no iron, oral iron, and IV iron revealed no significant increase in infection risk [64].

Iron and risk of cancer progression has been discussed for many years. Iron caries carcinogenic potential in some reports [87]. High free iron levels following IV iron therapy could form hydroxyl radicals, and those reactive molecules facilitate lipid peroxidation and oxidative DNA damage. Eventually, the process could lead to tumour growth and angiogenesis [88]. Increased risk of hepatocellular carcinoma in iron overload conditions, such as hereditary haemochromatosis, is possibly related to cirrhosis at the time of cancer diagnosis. Therefore, the relationship between iron overload and cancer is unclear [89]. At the same time, higher iron stores failed to demonstrate increased cancer risk [90]. It is impossible to conduct randomized prospective trials to prove this for ethics concerns.

Conclusion

Anaemia is a common problem during perioperative period, with ID being its leading cause. Pathogenesis of ID is multifactorial. Iron is the main compound in Hb and a vital element of cell metabolism. Diagnosis of anaemia and ID is part of preoperative assessment due to its adverse effect on surgical outcomes and associated increased need for red cell transfusion. IV iron supplementation is the best available treatment for ID and related anaemia perioperatively. There are multiple benefits of IV iron therapy in treating perioperative anaemia. However, safety concerns related to IV iron therapy may counteract some of its beneficial effects. IV iron therapy, as a part of patient blood management strategy, has shown good evidence of benefit [49]. However, as a therapeutic agent, it failed to demonstrate consistent evidence of benefit in perioperative settings. Large scale randomized studies are required to understand the benefit of IV iron supplementation as a treatment for preoperative anaemia.

References

[1] Shander A, Knight K, Thurer R, et al. Prevalence and outcomes of anemia in surgery: a systematic review of the literature. Am J Med 2004;116 Suppl 7A:58s-69s.

[2] Hans GA, Jones N. Preoperative anaemia. Continuing Education in Anaesthesia Critical Care & Pain 2013;13:71-74.

[3] Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Available at: https://www.who.int/publications/i/item/WHO-NMH-NHD-MNM-11.1

[4] Goodnough LT, Maniatis A, Earnshaw P, et al. Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth 2011;106:13-22.

[5] Ince C, Mik EG. Microcirculatory and mitochondrial hypoxia in sepsis, shock, and resuscitation. J Appl Physiol (1985) 2016;120:226-235.

[6] Shander A, Goodnough LT, Javidroozi M, et al. Iron deficiency anemia--bridging the knowledge and practice gap. Transfus Med Rev 2014;28:156-166.

[7] Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011;378:1396-1407.

[8] Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. Lancet 1996;348:1055-1060.

[9] Bailes BK. Perioperative Care of the Elderly Surgical Patient. AORN J 2000;72:185-207.

[10] Auron M, Castillo MYD. Preoperative anemia optimization: role of iron supplementation. J Xiangya Med 2018;3:37.

[11] Lagoo J, Wilkinson J, Thacker J, et al. Impact of anemia on surgical outcomes: innovative interventions in resource-poor settings. World J Surg 2012;36:2080-2089.

[12] Kozek-Langenecker SA, Ahmed AB, Afshari A, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology: First update 2016. Eur J Anaesthesiol 2017;34:332-395.

[13] American Society of Anesthesiologists Task Force on Perioperative Blood Management. Practice guidelines for perioperative blood management: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Management*. Anesthesiology 2015;122:241-275.
[14] Patient Blood Management Guidelines: Module 2 Perioperative. Available at: https://blood.gov.au/pbm-module-2
[15] Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. Lancet 2016;387:907-916.
[16] Stoltzfus RJ. Iron deficiency: global prevalence and consequences. Food Nutr Bull 2003;24:S99-S103.
[17] Perez-Escamilla R, Bermudez O, Buccini GS, et al. Nutrition disparities and the global burden of malnutrition. BMJ 2018;361:k2252.
[18] Saad RA, Qutob HM. The relationship between anemia and obesity. Expert Rev Hematol 2022;15:911-926.
[19] Busti F, Campostrini N, Martinelli N, et al. Iron deficiency in the elderly population, revisited in the hepcidin era. Front Pharmacol 2014;5:83.
[20] Finch CA, Hegsted M, Kinney TD, et al. Iron metabolism; the pathophysiology of iron storage. Blood 1950;5:983-1008.
[21] Kohgo Y, Ikuta K, Ohtake T, et al. Body iron metabolism and pathophysiology of iron overload. Int J Hematol 2008;88:7-15.
[22] Killip S, Bennett JM, Chambers MD. Iron deficiency anemia. Am Fam Physician 2007;75:671-678.
[23] Camaschella C. Iron-deficiency anemia. N Engl J Med 2015;372:1832-1843.
[24] Guyatt GH, Oxman AD, Ali M, et al. Laboratory diagnosis of iron-deficiency anemia: an overview. J Gen Intern Med 1992;7:145-153.
[25] Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician 2013;87:98-104.
[26] Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol 2005;18:319-332.
[27] Punnonen K, Irjala K, Rajamäki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. Blood 1997;89:1052-1057.
[28] Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233-247.
[29] Lidder PG, Sanders G, Whitehead E, et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial. Ann R Coll Surg Engl 2007;89:418-421.
[30] Petis SM, Lanting BA, Vasarhelyi EM, et al. Is There a Role for Preoperative Iron Supplementation in Patients Preparing for a Total Hip or Total Knee Arthroplasty? J Arthroplasty 2017;32:2688-2693.
[31] Baird IM, Podmore DA. Intramuscular iron therapy in iron-deficiency anaemia. Lancet 1954;267:942-946.
[32] Treatment of iron deficiency anemia in adults. Available at: https://www.uptodate.com/contents/treatment-of-iron-deficiency-anemia-in-adults
[33] Grasso P. Sarcoma after intramuscular iron injection. Br Med J 1973;2:667.
[34] Cançado RD, Muñoz M. Intravenous iron therapy: how far have we come? Rev Bras Hematol Hemoter 2011;33:461-469.
[35] Neiser S, Rentsch D, Dippon U, et al. Physico-chemical properties of the new generation IV iron preparations ferumoxytol, iron isomaltoside 1000 and ferric carboxymaltose. Biometals 2015;28:615-635.
[36] Martin-Malo A, Borchard G, Flühmann B, et al. Differences between intravenous iron products: focus on treatment of iron deficiency in chronic heart failure patients. ESC Heart Fail 2019;6:241-253.
[37] Kumpf VJ. Parenteral iron supplementation. Nutr Clin Pract 1996;11:139-146.
[38] Kumpf VJ. Update on parenteral iron therapy. Nutr Clin Pract 2003;18:318-326.
[39] Beattie WS, Karkouti K, Wijeysundera DN, et al. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. Anesthesiology 2009;110:574-581.
[40] Baron DM, Hochrieser H, Posch M, et al. Preoperative anaemia is associated with poor clinical outcome in non-cardiac surgery patients. Br J Anaesth 2014;113:416-423.
[41] Dunkelgrun M, Hoeks SE, Welten GM, et al. Anemia as an independent predictor of perioperative and long-term cardiovascular outcome in patients scheduled for elective vascular surgery. Am J Cardiol 2008;101:1196-1200.
[42] Acheson AG, Brookes MJ, Spahn DR. Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis. Ann Surg 2012;256:235-244.
[43] Blajchman MA, Vamvakas EC. The continuing risk of transfusion-transmitted infections. N Engl J Med 2006;355:1303-1305.
[44] Goodnough LT. Risks of blood transfusion. Anesthesiol Clin North Am 2005;23:241-252.
[45] Glance LG, Dick AW, Mukamel DB, et al. Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery.

Anesthesiology 2011;114:283-292.
[46] Bernard AC, Davenport DL, Chang PK, et al. Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009;208:931-937.
[47] Toner RW, Pizzi L, Leas B, et al. Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. Appl Health Econ Health Policy 2011;9:29-37.
[48] Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 2010;50:753-765.
[49] Ferraris VA, Davenport DL, Saha SP, et al. Surgical outcomes and transfusion of minimal amounts of blood in the operating room. Arch Surg 2012;147:49-55.
[50] Kotzé A, Carter LA, Scally AJ. Effect of a patient blood management programme on preoperative anaemia, transfusion rate, and outcome after primary hip or knee arthroplasty: a quality improvement cycle. Br J Anaesth 2012;108:943-952.
[51] Spahn DR, Moch H, Hofmann A, et al. Patient blood management: the pragmatic solution for the problems with blood transfusions. Anesthesiology 2008;109:951-953.
[52] Leahy MF, Hofmann A, Towler S, et al. Improved outcomes and reduced costs associated with a health-system-wide patient blood management program: a retrospective observational study in four major adult tertiary-care hospitals. Transfusion 2017;57:1347-1358.
[53] Meybohm P, Herrmann E, Steinbicker AU, et al. Patient Blood Management is Associated With a Substantial Reduction of Red Blood Cell Utilization and Safe for Patient's Outcome: A Prospective, Multicenter Cohort Study With a Noninferiority Design. Ann Surg 2016;264:203-211.
[54] Gurusamy KS, Nagendran M, Broadhurst JF, et al. Iron therapy in anaemic adults without chronic kidney disease. Cochrane Database Syst Rev 2014;2014:Cd010640.
[55] Peters F, Ellermann I, Steinbicker AU. Intravenous Iron for Treatment of Anemia in the 3 Perisurgical Phases: A Review and Analysis of the Current Literature. Anesth Analg 2018;126:1268-1282.
[56] Wilson MJ, Dekker JW, Bruns E, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion 2018;58:795-803.
[57] Heschl M, Gombotz H, Haslinger-Eisterer B, et al. The efficacy of pre-operative preparation with intravenous iron and/or erythropoietin in anaemic patients undergoing orthopaedic surgery: An observational study. Eur J Anaesthesiol 2018;35:289-297.
[58] Muñoz M, Gómez-Ramírez S, García-Erce JA. Intravenous iron in inflammatory bowel disease. World J Gastroenterol 2009;15:4666-4674.
[59] Crichton RR, Danielson BG, Geisser P. Iron therapy with special emphasis on intravenous administration. UNI-MED Verlag. 2008.
[60] Seeho SKM, Morris JM. Intravenous iron use in pregnancy: Ironing out the issues and evidence. Aust N Z J Obstet Gynaecol 2018;58:145-147.
[61] Holm C. Intravenous iron treatment in the puerperium. Dan Med J 2018;65:B5471.
[62] Chua S, Gupta S, Curnow J, et al. Intravenous iron vs blood for acute post-partum anaemia (IIBAPPA): a prospective randomised trial. BMC Pregnancy Childbirth 2017;17:424.
[63] Shin HW, Park JJ, Kim HJ, et al. Efficacy of perioperative intravenous iron therapy for transfusion in orthopedic surgery: A systematic review and meta-analysis. PLoS One 2019;14:e0215427.
[64] Henry DH, Dahl NV, Auerbach M, et al. Intravenous ferric gluconate significantly improves response to epoetin alfa versus oral iron or no iron in anemic patients with cancer receiving chemotherapy. Oncologist 2007;12:231-242.
[65] Bastit L, Vandebroek A, Altintas S, et al. Randomized, multicenter, controlled trial comparing the efficacy and safety of darbepoetin alpha administered every 3 weeks with or without intravenous iron in patients with chemotherapy-induced anemia. J Clin Oncol 2008;26:1611-1618.
[66] Gilreath JA, Stenehjem DD, Rodgers GM. Diagnosis and treatment of cancer-related anemia. Am J Hematol 2014;89:203-212.
[67] Zadrazil J, Horak P. Pathophysiology of anemia in chronic kidney diseases: A review. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2015;159:197-202.
[68] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1-150.
[69] Palevsky PM. Perioperative management of patients with chronic kidney disease or ESRD. Best Pract Res Clin Anaesthesiol 2004;18:129-144.
[70] Shavit L, Hitti S, Silberman S, et al. Preoperative hemoglobin and outcomes in patients with CKD undergoing cardiac surgery. Clin J Am Soc Nephrol 2014;9:1536-1544.

[71] Lawson T, Ralph C. Perioperative Jehovah's Witnesses: a review. Br J Anaesth 2015;115:676-687.

[72] Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2016;18:786-795.

[73] Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. Eur Heart J 2015;36:657-668.

[74] Chertow GM, Mason PD, Vaage-Nilsen O, et al. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006;21:378-382.

[75] Miller HJ, Hu J, Valentine JK, et al. Efficacy and tolerability of intravenous ferric gluconate in the treatment of iron deficiency anemia in patients without kidney disease. Arch Intern Med 2007;167:1327-1328.

[76] Lim W, Afif W, Knowles S, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. Vox Sang 2019;114:363-373.

[77] Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica 2014;99:1671-1676.

[78] Eichbaum Q, Foran S, Dzik S. Is iron gluconate really safer than iron dextran? Blood 2003;101:3756-3757.

[79] Bailie GR, Clark JA, Lane CE, et al. Hypersensitivity reactions and deaths associated with intravenous iron preparations. Nephrol Dial Transplant 2005;20:1443-1449.

[80] Wang C, Graham DJ, Kane RC, et al. Comparative Risk of Anaphylactic Reactions Associated With Intravenous Iron Products. Jama 2015;314:2062-2068.

[81] Suffredini DA, Xu W, Sun J, et al. Parenteral irons versus transfused red blood cells for treatment of anemia during canine experimental bacterial pneumonia. Transfusion 2017;57:2338-2347.

[82] Marx JJ. Iron and infection: competition between host and microbes for a precious element. Best Pract Res Clin Haematol 2002;15:411-426.

[83] Maynor L, Brophy DF. Risk of infection with intravenous iron therapy. Ann Pharmacother 2007;41:1476-1480.

[84] Pai AB, Boyd AV, McQuade CR, et al. Comparison of oxidative stress markers after intravenous administration of iron dextran, sodium ferric gluconate, and iron sucrose in patients undergoing hemodialysis. Pharmacotherapy 2007;27:343-350.

[85] Stefánsson BV, Haraldsson B, Nilsson U. Acute oxidative stress following intravenous iron injection in patients on chronic hemodialysis: a comparison of iron-sucrose and iron-dextran. Nephron Clin Pract 2011;118:c249-c256.

[86] Hoeft K, Bloch DB, Graw JA, et al. Iron Loading Exaggerates the Inflammatory Response to the Toll-like Receptor 4 Ligand Lipopolysaccharide by Altering Mitochondrial Homeostasis. Anesthesiology 2017;127:121-135.

[87] Greenberg G. Sarcoma after intramuscular iron injection. Br Med J 1976;1:1508-1509.

[88] Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrotoxic disease. Cancer Sci 2009;100:9-16.

[89] Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. Gastroenterology 2004;127:S79-S86.

[90] Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. Cancer Epidemiol Biomark Prev 2014;23:12-31.