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REVIEW

Does pumping iron bring gains? A review of the role of intravenous iron in perioperative blood management

GRN Robinson, A Breedt, CON Oghenetega, S Chetty

Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa
Corresponding author, email: *chiomao@sun.ac.za*

In recent years, there has been an increased focus on practices that decrease the need for perioperative blood transfusions. Intravenous (IV) iron therapy has globally been instituted as part of perioperative care protocols to potentially decrease the need for blood transfusions in surgical patients who are anaemic or at risk for significant blood loss during the perioperative period. Recommendations for its use are now highlighted to largely have been based on expert opinion as trials investigating the perioperative use of IV iron had been scarce. The PREVENTT trial, published in 2020, was a large multicentre randomised controlled trial (RCT) that provided evidence that does not support routine perioperative IV iron therapy as this intervention was not shown to decrease the need for blood transfusions, or improve morbidity or mortality, despite its associated increase in haemoglobin (Hb) compared to controls. Various aspects of the PREVENTT trial, however, can be criticised, which places into question its validity to impact practice. There is evidence that certain surgical populations may derive more benefit from IV iron therapy than others, with evidence of reduced risk for blood transfusions in orthopaedic populations. The timing of IV iron therapy may also influence its effectiveness with postoperative administration potentially deriving more benefit than preoperative use. It has become evident that there is a need for further studies and higher quality of evidence in these areas.

Keywords: intravenous iron therapy, patient blood therapy, perioperative management

Introduction

Perioperative blood management (PBM) is a bundle of care practices encompassing all the key practice points for administering blood products to a patient presenting for major surgery with the risk of significant blood loss (> 500 ml in adults).[1] PBM should be activated at the moment the decision is made for surgery and implemented until the patient has made a full recovery. PBM encompasses three main pillars in its multimodal approach, and this review relates to the first, optimising disorders causing anaemia (see Table I).[1] Globally, routine use of preoperative intravenous (IV) iron therapy has been widely adopted to increase preoperative haemoglobin (Hb) and reduce the risk of blood transfusion. Currently, there is a paucity in robust evidence supporting this practice.

Methodology for literature review

Between 1 August and 9 December 2021, an initial broad electronic search was conducted to identify journal articles which addressed the use of IV iron to treat anaemia in the perioperative setting and to better identify important search keywords. A secondary, more detailed search was then conducted on two electronic databases, including MEDLINE and the Cochrane database for controlled trials, using the following keywords: "anaemia", "haemoglobin", "intravenous", "iron", "surgery", "infection", and "transfusion" in various combinations. Inclusion criteria included peer-reviewed journal articles with a preference for systematic reviews and meta-analysis or large-scale studies, although each article of interest was reviewed regardless of sample size or study type. Each article considered was screened by one of the authors for relevance for inclusion. Exclusion criteria for this review included studies not written in the English language and studies not performed on adult humans. A total of 82 articles were screened, and 61 articles were excluded due to irrelevance to the search topic. Other reasons for excluding articles include that studies were already included in a systematic review/meta-analysis already included in the review, studies that did not use IV iron to treat anaemia, and studies that did not focus on participants during the perioperative period. The publication types of the 21 articles included for the review were systematic reviews and/or meta-analysis, randomised control trials and observational studies, including cohort and case-control studies.

Perioperative anaemia

Anaemia is defined by the World Health Organization (WHO) as a Hb level of less than 13 g/dl in males, 12 g/dl in non-pregnant females and 11 g/dl in pregnant females. A recent international consensus statement on the perioperative management of anaemia and iron deficiency challenged this definition of anaemia as being insufficient, specifically in non-pregnant females, as they have comparably lower circulating blood volumes compared to males, while experiencing similar amounts of blood loss during surgery, leading to a higher proportional blood volume loss and higher transfusion rates. This expert panel recommended that a Hb of < 13 g/dl be used for both sexes to define anaemia in the perioperative setting.[1]

Anaemia is associated with increased morbidity and mortality and is an independent risk factor for allogenic blood transfusion (ABT). Perioperative anaemia is also relatively common in patients presenting for major surgery. Up to a third of patients are identified with anaemia during preoperative screening and

Table I: A breakdown of perioperative blood management[1]

	First pillar: Optimise red cell mass	**Second pillar:** Minimise blood loss and bleeding	**Third pillar:** Harness and optimise the physiological reserve of anaemia
Preoperative	• Check for anaemia at least 4–6 weeks before planned surgery. • Determine the underlying disorder(s) producing anaemia. • Treat low iron storage, iron deficiency, folate and vitamin B12 deficiency, and chronic illness anaemia. • Consider erythropoiesis stimulating therapy if nutritional causes have been ruled out or treated.	• Identify and manage bleeding risk. • Manage iatrogenic blood loss including reduced phlebotomy. • Plan and rehearse procedure. • Review medication list for antiplatelet/ anticoagulant therapy.	• Evaluate and improve the patient's physiological reserve and risk factors (e.g. cardiac and pulmonary function). • Contrast the estimated blood loss with the patient's acceptable blood loss. • Create a patient-specific management plan that makes use of relevant blood conservation strategies to reduce blood loss, increase red cell mass, and manage anaemia.
Intraoperative	• Time surgery with haematological optimisation of red cell mass.	• Meticulous haemostasis and surgical techniques. • Blood-sparing surgical devices including cell salvage. • Anaesthetic blood conserving strategies (e.g. central neuraxial blockade, patient positioning, goal-directed fluid therapy). • Autologous blood transfusion. • Maintain normothermia. • Pharmacological/haemostatic agents, including antifibrinolytics.	• Optimise cardiac output. • Optimise ventilation and oxygenation.
Postoperative	• Optimise erythropoiesis. • Be aware of drug interactions that can worsen anaemia: ◦ Proton pump inhibitors ◦ Anticoagulants ◦ Nonsteroidal anti-inflammatories	• Closely monitor and manage postoperative bleeding. • Avoid subsequent bleeding. • Maintain normothermia/rapid warming (unless hypothermia is particularly indicated). • Autologous blood donation. • Reduce iatrogenic blood loss. • Management of haemostasis and anticoagulation. • Prevent upper gastrointestinal haemorrhage. • Avoid infections or treat these as soon as possible. • Be careful of medication's side effects.	• Maximise oxygen delivery. • Minimise oxygen consumption. • Avoid infections or treat these as soon as possible. • Use evidence-based transfusion triggers tailored to individual patient requirements.

up to 75% of these cases have iron deficiency as a contributing factor.[1-3]

ABT has many potential harms and complications, such as allosensitisation, allergic reactions, circulatory overload, and transfusion-associated acute lung injury. It is also associated with an increased risk of perioperative infections, cardiac ischaemic events, and mortality. Logically, optimising Hb levels and erythropoiesis perioperatively should reduce the need for ABT and improve patient outcome.[4]

Iron deficiency anaemia

Iron deficiency occurs in approximately two billion people worldwide and remains the most common form of anaemia affecting patients having major surgery (See Table II).[3] Serum ferritin levels remain the standard for diagnosing iron deficiency anaemia. Iron deficiency can be divided into three stages:

1. Inadequate iron stores: This is represented by a low-normal serum ferritin level (30–100 ng/l) and a normal Hb but represents insufficient iron stores to support the increased

Table II: Causes of iron deficiency anaemia[1]

Increased demand	**Decreased supply**	**Increased losses**
Period of growth (childhood and adolescence)	Poor oral intake or iron/ascorbic acid deficient diet	Haemorrhage
Use of erythropoiesis-stimulating agents	Malabsorption • Gastric or small bowel resection • H. pylori infection • Malabsorption syndromes (e.g. pancreatic exocrine insufficiency, short bowel syndrome, inflammatory bowel disease)	Phlebotomy • Blood donation • Haemodialysis
	Drug interactions (gastric antacids)	

erythropoiesis required for a decrease in Hb (i.e. a patient with a serum ferritin level < 100 ng/l may not be able to recover from a drop in Hb of 3–4 g/dl while maintaining normal iron stores).

2. True iron deficiency: This is represented by a low serum ferritin level (< 30 ng/l) but a normal Hb.
3. Iron deficiency anaemia: This is the combination of iron deficiency with a low Hb.

IV iron therapy

Iron supplementation remains the sole treatment for iron deficiency and can be administered orally or intravenously. Oral administration in the perioperative setting has many drawbacks including the prolonged period needed to see an increase in serum ferritin levels and Hb (six – eight weeks) and the high incidence of gastrointestinal side effects such as abdominal pain, constipation and diarrhoea. This can contribute to a high treatment non-adherence of up to 40%. Patients presenting for gastrointestinal surgery may have reduced intestinal absorption of iron due to the nature of their disease process.[1,5] The indications for IV iron therapy include:[6]

- Intolerance to, or reduced effectiveness of oral iron replacement
- Faster response time needed (i.e. in preparation for surgery)
- Excessive, ongoing blood loss
- Gastrointestinal malabsorption of iron
- Treatment of anaemia of chronic kidney disease in conjunction with erythropoiesis stimulating agents

Table III lists various major risk and adverse events associated with IV iron therapy.

Table III: Major risks and adverse events associated with IV iron therapy[1,7]

Anaphylaxis (rare) • Increased risk with: ◦ High molecular weight dextrans as carrier molecule ◦ Faster infusion rate ◦ History of severe asthma/atopy/allergies ◦ Severe cardiorespiratory disease ◦ Pregnancy
Pseudo allergy (1:200 patients) • Due to complement immune system activation and includes arthralgia, myalgia and flushing
Infection risk • Theoretically because free iron is a pro-oxidant and a micronutrient for bacterial growth in vitro

More recently, there is evidence to support that newer formulations of IV iron therapy are safe for use. A 2021 meta-analysis of preoperative IV iron therapy before major surgery found no increased risk of adverse events compared to controls (relative risk (RR) 1.13; 95% CI 0.78–1.65; $p = 0.52$), and an international consensus statement on the perioperative management of iron deficiency anaemia released in 2017, stated that with the administration of preoperative IV iron the benefits outweighed the risks.[1,3]

The role of IV iron therapy in the risk of perioperative infection is a controversial topic, and current guidelines recommend against the use of IV iron therapy when there is evidence of an active patient infection. The evidence regarding the risk of perioperative infection following IV iron therapy is heterogenous: a 2021 meta-analysis of ten randomised controlled trials (RCTs), which included a total of 1 039 patients, concluded that IV iron therapy was not associated with an increased risk of postoperative infection, although only five of the ten reviewed RCTs reported on postoperative infection, and only two of these provided comparative infection rates between IV iron therapy and controls. Another meta-analysis on case-controlled studies looking at IV iron therapy in an orthopaedic population, found that there was a 33% decrease in infections in the IV iron therapy group compared to the control group (RR 0.67; 95% CI 0.49 to -0.91; $I^2 = 15\%$; $p = 0.01$).[1,3,7] In addition to this, increased Hb preoperatively should decrease the risk for ABT, which is also an independent risk factor for perioperative infection.

These findings are disputed by a more recent meta-analysis, which looked at 154 RCTs and over 32 000 patients, which concluded that there was moderate quality evidence to support that IV iron was associated with an increased risk of infection compared to oral iron or control (RR 1.16; 95% CI 1.03–1.29; $I^2 = 36\%$).[8] This review analysed studies from both medical and surgical populations, with no specific focus on perioperative IV iron therapy. The increased incidence of infection may be attributed to the fact that a large number of studies looked at IV iron therapy in patients with chronic kidney disease. These patients are immunosuppressed and, therefore, at a higher risk for infections.

IV iron formulations

There are many different IV formulations of iron available, and these differences generally relate to the different types of carbohydrate shell used to form a compound with the free iron molecule. These shells prevent immediate release of free iron into the circulation, which can cause severe toxic reactions. Initial preparations of IV iron used high molecular weight dextran as the carrier molecule. These preparations were associated with an elevated risk of anaphylactic reactions and their use has mostly been discontinued in favour of newer formulations, including the less anaphylactogenic low molecular weight dextrans and sugar-based carriers such as iron sucrose (Venofer®) and ferric carboxymaltose (Injectafer®). Newer formulations allow for faster infusions of higher iron concentrations with lower risk of allergic reactions. Only iron sucrose (Venofer®) and low molecular weight iron dextran (CosmoFer®) are currently available in South Africa.[1,6]

There have been multiple RCTs comparing various different formulations of IV iron therapy, and no significant difference in Hb increase or adverse events have been noted between the different IV iron therapy groups.[9-11]

Current evidence for use of IV iron therapy perioperatively

The use of IV iron therapy globally is increasing, due to a combination of availability of safer, more efficacious drug formulations, as well as the increasing awareness of PBM principles. Until recently, substantial literature that guided clinical practice included a 2008 consensus review on IV iron therapy, which did not recommend routine use of IV iron therapy based on sparse available evidence, and a 2014 meta-analysis on IV iron therapy use in gastrointestinal surgery based on only two RCTs reaching a similar conclusion.[12,13] In 2020, the journal *Lancet* published one of the first multicentre RCTs that investigated preoperative IV iron therapy in a large sample group. The PREVENTT trial was performed in 46 centres in the United Kingdom and compared IV iron therapy to a control group for the treatment of anaemia before major abdominal surgery. The 487 participants received either a single dose of ferric carboxymaltose or a placebo 10–42 days prior to surgery; and the primary outcomes assessed were the risk of blood transfusion, the number of units of blood transfused, and 30-day mortality. The secondary outcomes investigated were change in Hb postoperatively, total length of stay (LOS), re-admission at eight weeks/six months post-surgery, and health-related quality of life. While the study concluded that there was a significant increase in postoperative Hb in the IV iron therapy group, there was no significant difference between IV iron therapy and control with reference to the risk for blood transfusion and no effect on mortality.[14]

The PREVENTT study has raised doubt on the efficacy of IV iron therapy and the role of this therapeutic intervention in PBM since its publication. However, on review of the trial, there are limitations to be noted. The study was likely to be underpowered considering that they did not achieve the calculated sample size of 500 patients and that the rate of blood transfusion in the placebo group (28%) was significantly less than the anticipated rate of 40%. Another limitation is that the study specifically looked at elective open abdominal surgery, while not looking for potential benefits in other surgical groups. Additionally, the efficacy of using a single dose of IV iron therapy within a limited space of time preoperatively can be questioned as it may not have been a sufficient dose or window period to allow the full effects of IV iron therapy, as only 21% of participants' anaemia was fully corrected prior to surgery.

The eligibility criteria for the study could also be criticised. Although participants did have anaemia as per the WHO criteria, only 17% had a Hb value of less than 10 g/dl. Abnormal iron studies were also not an inclusion criterion, meaning that many of these patients only had mild anaemia and may have had anaemia from a cause other than iron deficiency, which may explain the lack of treatment effect shown by the study. Finally, the timing of dosing of IV iron therapy was restricted to the preoperative period, with no investigation into its role when given postoperatively.[15,16] These study limitations, therefore, raise concerns for the clinician on how much this study should influence clinical practice.

Evidence for IV iron therapy in different surgical populations

Abdominal surgery

The available evidence for major abdominal surgery is in keeping with the findings of the PREVENTT trial, with a 2021 systematic review of nine studies concluding that while there was a significant increase in Hb in the IV iron therapy groups, this did not equate to a significantly lower incidence of blood transfusion compared to control groups.[2]

When looking at quality of life as an outcome, a trial on IV iron in colorectal cancer-associated anaemia (IVICA) found that quality of life components increased significantly up to three months post-surgery in patients who received IV iron therapy compared to oral iron or placebo. This is most likely related to the reduction in symptoms of anaemia such as fatigue, lethargy, and dyspnoea.[5]

Cardiac surgery

A 2020 meta-analysis on IV iron therapy in cardiac surgery, which reviewed both observational studies and RCTs, noted that there was a significant benefit in mortality (RR 0.39; 95% CI 0.23–0.65; $p < 0.001$), risk of transfusion (RR 0.81; 95% CI 0.7–0.94; $p = 0.005$; $I^2 = 10\%$) and reduction in number of units transfused (MD -1.22; 95% CI -1.85 to -0.60; $p < 0.001$, $I^2 = 0\%$). It must, however, be noted that the significant results from the observational studies analysed were low-moderate quality evidence and that these results were not replicated in the RCTs included in the review. A subsequent large single-centre RCT of 200 patients undergoing complex cardiac surgery also found that while IV iron therapy was associated with a significant increase in postoperative Hb (11.6 ± 1.5 g/dl vs 10.9 ± 1.4; $p < 0.001$), there was no difference in transfusion rates (60.4% vs 57.2%) and no observed mortality benefit.[4,17]

Orthopaedic surgery

The evidence for use of IV iron therapy in the orthopaedic population appears to show more benefit compared to other surgical populations. A 2019 meta-analysis on IV iron therapy in orthopaedic surgery concluded that IV iron therapy reduced the risk of transfusion by 31% (RR 0.69; $p = 0.0002$) with a minor reduction in number of units transfused by 0.34 units/person ($p = 0.0007$). These results were mirrored by another meta-analysis of acute major non-cardiac surgery, of which 77% of the studies reviewed were orthopaedic in origin, noting a significant mortality reduction of 4.6% compared to controls. However, the quality of evidence for both these studies was low to moderate, with the benefit only being observed in observational studies, while not being reproduced in a subgroup analysis of RCTs included.[7,18]

Obstetrics

Despite anaemia being a prevalent concern in the obstetric population, there is no current available studies assessing the effect of IV iron therapy on the reduction of blood transfusion in the obstetric patient population. A 2018 meta-analysis by Govindappagari et al.[19] compared IV iron therapy to oral iron supplementation, and outcomes were directed to an increase in Hb as the primary outcome. Hb levels were found to be higher at four weeks with IV iron therapy compared to the oral supplementation (MD 1.2 g/dL; 95% CI 1.0–1.3; $p < 0.001$).[19]

Evidence for IV iron therapy in the acute emergency surgery setting

Much of the literature concerning perioperative IV iron therapy concerns its use in elective surgery, with very few studies looking at its potential benefit in the acute emergency setting. A meta-analysis on acute emergency surgery looked at three RCTs, two focused on hip fracture surgery and one on kidney transplants. The study concluded that IV iron therapy in all three RCTs had no significant benefit in decreasing transfusion rates (RR 0.9; 95% CI 0.73–1.11; $p = 0.46$; $I^2 = 0\%$), increasing Hb concentration (MD -0.32; 95% CI -3.28–2.64; $I^2 = 37\%$) and had no mortality benefit; the two RCTs on hip fracture surgery also found no significant benefit of IV iron therapy on length of stay.[20]

Timing of administration of IV iron therapy in the perioperative setting: pre- or postoperative?

The PREVENTT trial looked at IV iron therapy administration preoperatively, and since this study was published, there has been a meta-analysis on preoperative iron therapy in a variety of different surgical populations. Ten RCTs were analysed in this review, which concluded that preoperative iron supplementation decreases ABT by up to 16% (RR between the study groups: 0.84; 95% CI = 0.71–0.99; $p = 0.04$) and increased Hb levels by approximately 1 g/dl (MD between groups: 7.15 g/L; 95% CI 2.26–12.04; $p = 0.004$) or 0.715 g/dl compared to controls. However, if patients were transfused, it did not result in less units of blood being used. These differences were observed in both oral iron and IV iron therapy groups, with no difference noted between the two.[3]

Another meta-analysis looking at orthopaedic surgery compared studies administering IV iron therapy preoperatively vs postoperatively and found that IV iron therapy was associated with a significant decrease in ABT by 31%, but this difference was only noted in the groups who received IV iron therapy postoperatively, with no association with pre- or perioperative administration. This difference was also only observed in the observational studies reviewed, with no difference noted in the included RCTs.[7]

The most optimal timing for administration of IV iron therapy is not clear based on the available evidence, but there may be more of a role for it in the postoperative setting, where decreased gastrointestinal tolerance may limit the effectiveness of oral iron therapy.

Cost-effectiveness of IV iron therapy compared to ABT

All the studies reviewed have primarily focused on patient-related outcomes, while one also needs to consider limited financial and blood resources, especially in the setting of a developing country such as South Africa, considering whether IV iron therapy has a potential financial benefit over ABT.

A comparative trial of costs of IV iron therapy vs ABT by Bhandari published in 2011,[21] found that at all doses, IV iron therapy resulted in a net saving over ABT, with the savings increasing when newer formulations such as ferric carboxymaltose were used.

In South Africa, the current per unit cost price of Venofer® and CosmoFer® at the time of publishing of this article according to the South African National Department of Health's medicine price registry is R204.95 and R168.67, respectively. This equates to an approximate total cost for an average single treatment regimen for a 70 kg adult of R2 448.00 for Venofer® and R4 032.00 for CosmoFer®. Comparing this to the costs of ABT, the South African National Blood Service state patient pricelist for 2023–2024 indicates the cost of an adult red cell concentrate (RCC) at R2 379.35 per unit with an additional cost of R1 058.69 for a transfusion crossmatch. This equates to an average direct cost saving of approximately R990.00 when comparing a single treatment regimen of Venofer® with a single unit transfusion of RCC.[22]

Aside from the direct costs of ABT, one must consider the many other costs associated with the care of an anaemic surgical patient. One of the secondary outcomes of the PREVENTT trial was the rate of re-admission at eight weeks post-surgery, and the authors noted that there was a significant decrease in re-admissions (9% reduction) in the IV iron therapy group compared to the control group. Richards et al.[14] compared the different formulations of IV iron therapy and found a statistically significant decrease in length of stay of 2.3 days with ferric carboxymaltose, which equated to an approximate saving of R9 000 per patient.

Conclusion

The current evidence for the use of IV iron therapy is not convincing that it positively changes patient outcomes, or even that it decreases patient exposure to allogenic blood products. The therapy does, at the very least, not produce worse outcomes compared to blood transfusion. Despite this underwhelming evidence base, there still may be benefits to be elicited, as higher quality evidence is still needed, with larger scale RCTs still lacking on many aspects of the subject. Despite all the conflicting evidence, international guidelines still recommend the use of IV iron therapy for correction of iron deficiency anaemia prior to surgery, specifically when there is no/limited response to oral iron, or if surgery is planned in less than six weeks.[1] Whether IV iron therapy has a role in the developing world, where direct

healthcare costs need to be balanced with a rapid turnover of hospital beds, still needs to be unpacked.

Conflict of interest

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Declaration

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ORCID

GRN Robinson https://orcid.org/0000-0003-1059-1249
A Breedt https://orcid.org/0000-0002-5242-3684
CON Oghenetega https://orcid.org/0000-0001-8863-2894
S Chetty https://orcid.org/0000-0002-9878-5488

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