Safety of Oral and Intravenous Iron

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Abstract

As the adverse effects of iron deficiency are better recognized, the use of oral and intravenous iron has increased dramatically. Oral iron is often poorly tolerated, with up to 70% or more of patients noting gastrointestinal issues; this may affect adherence to therapy. In addition, many patients will not respond to oral iron due to their underlying illness. Intravenous iron is being used more frequently to replete iron stores. True anaphylaxis is very rare, but complement-mediated infusion reactions may be seen in up to 1 in every 200 patients. Previous concerns about intravenous iron increasing the risk of infection or cardiovascular disease are unfounded.

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Indications for Iron Replacement

Over the past few years, the indications for iron replacement have increased as evidence has grown to demonstrate that iron deficiency can have deleterious effects beyond anemia. For example, 2 studies have shown that oral iron replacement can improve symptoms of fatigue in nonanemic women who have ferritin levels <50 ng/dL [1, 2]. Aggressive iron replacement has been shown to be beneficial in heart failure patients even with ferritin levels up to 300 ng/dL [3]. The recent PIVOTAL trial demonstrated that aggressive intravenous iron replacement in dialysis patients – up to ferritin levels of 700 ng/dL or iron saturation of 45% – was associated with a 23% reduction in erythropoietin dosing and a trend toward lower mortality [4]. The adverse effects of iron deficiency in pregnancy and the benefits of iron replacement for both mother and child in this setting are now better understood [5].

Introduction

One of the most common conditions that physicians treat is iron deficiency anemia. While there are many exciting new findings in the understanding and treatment of iron deficiency, physicians' treatment practices may be based on old and out-of-date understanding and information, especially with regard to the safety of oral and intravenous iron therapy. This review will consider the risks of currently available iron therapies.

Risks of Oral Iron

For many patients, oral iron is the first line of therapy. Many products are available to treat iron deficiency, ranging from ferrous iron compounds such as ferrous sulfate to ferric ones such as ferric polymaltose complex. Although the ferric compounds are perhaps better tolerated than ferrous compounds, studies have shown these to be inferior to ferrous compounds in effectiveness of iron replacement in many patient groups [6].

Although iron is thought to be safe enough to be available over the counter, its use is associated with many problems [7]. Up to 30–70% of patients will have complaints of gastrointestinal upset. While constipation is classic, many patients also report diarrhea. Dyspepsia is common, especially when pills are taken on an empty stomach. In a meta-analysis of gastrointestinal issues with oral iron by Tolkien et al. [8], constipation was reported in 12% of patients, diarrhea in 8%, and nausea in 11%. This study also showed that gastrointestinal side effects of oral compounds are twice those of placebo controls in clinical trials and three times those when intravenous iron is the control. These complications often lead to premature discontinuation of oral iron therapy.

Oral iron has also been associated with gastrointestinal mucosal injury. Endoscopy has revealed mucosal iron deposition in 16% of patients taking oral iron [9]. Most of these patients also have coexisting gastritis or even esophageal erosions. In patients with preexisting gastrointestinal issues, the use of oral iron may exacerbate these problems due to these toxic mucosal effects.

Recent studies have shown that iron plays a role in promoting an adverse gut microbiome. Use of oral iron in laboratory animals can exacerbate preexisting bowel inflammation [10, 11]. Studies in children show a shift toward promotion of growth of pathogenic organisms (such as *Escherichia coli*) at the expense of beneficial species such as bifidobacteria and lactobacilli [12, 13]. This shift has been associated with increased bowel inflammation. A shift toward a pathogenic microbiome has also been seen in patients with inflammatory bowel disease with use of oral iron [14].

In pregnant women at risk for malaria, concern has been raised about oral iron increasing the risk for this infection [15]. Iron is crucial for supporting growth of pathogenic organisms such as malaria, and early studies suggested that iron supplementation may increase the risk of this infection. This fear of increased infection was laid to rest by 2 randomized trials that showed no increased risk of malarial infection with antenatal oral iron [16, 17].

Finally, in many situations, the use of oral iron is unlikely to be of benefit, and its use needlessly exposes the patient to side effects. In those with inflammatory bowel disease, oral iron is often ineffective due to lack of iron absorption from diseased bowel, inability to compensate for gastrointestinal blood loss, and inflammation causing higher levels of hepcidin, thereby blocking iron absorption. In addition, as noted above, oral iron may exacerbate bowel inflammation and adversely affect the micro-

biome. In patients with mildly active inflammatory bowel disease, oral iron is associated with decreased quality of life [18]. Patients who have undergone bariatric surgery have an incidence of iron deficiency as high as 50%, with a meta-analysis showing 23% [19]. Oral iron is often ineffective in these patients because of the limited small bowel available for iron absorption and intolerance to the pills. Pregnant patients very often cannot tolerate iron pills due to nausea, vomiting, and constipation [5].

Risk Mitigation

One simple step to improve tolerance to oral iron is to decrease the dose, as many of these side effects may be dose related. In a study comparing oral dosing of 15 versus 50 versus 150 mg elemental iron daily, gastrointestinal effects were more common in the higher-dose iron group [20]. For many patients, 1 pill a day at most should suffice to increase iron stores; after an initial dose of oral iron, serum hepcidin levels rise and then block further iron absorption for over 24 h [21]. There is an intriguing study showing that iron administered every other day may have increased absorption over daily use, and this may be an option for patients who cannot tolerate daily iron [22]. Decreasing the dose of elemental iron can also help. For example, ferrous sulfate has ~60 mg of elemental iron while ferrous gluconate has ~30 mg. Many patients will have improved gastrointestinal tolerance by taking iron with food and, in fact, taking iron with meat protein can increase absorption of iron [23]. The administration of vitamin C with iron can block the negative effect of calcium and fiber on iron absorption [24]. Only tea and coffee should be excluded around the time of iron pill ingestion as they inhibit iron absorption [25]. Avoiding acid suppression with proton pump inhibitors may also help [26]. However, if a patient is having difficulty tolerating oral iron, is not responding, or is in a group of patients unlikely to respond to oral iron, the next step is intravenous iron given its wide availability and safety.

Risks of Intravenous Iron

The use of intravenous iron has greatly increased both due to recognition of the adverse complications of oral iron deficiency and the ease of parenteral iron administration. There are multiple products to choose from when giving intravenous iron (Tables 1, 2). All iron products are composed of a polynuclear iron core with a surround-

Table 1. Risks of iron

<i>Oral iron</i>
Nausea
Constipation
Diarrhea
Adversely altered gastrointestinal microbiome
Increased gastrointestinal inflammation
Gastritis
Esophageal ulceration
<i>Intravenous iron</i>
Complement activation-related pseudoallergy
Hypophosphatemia

Table 3. Treatment protocol for infusion reactions¹

<i>Mild reactions</i>	
Symptoms	Back/joint pain, flushing, hypertension, itching, sensation of heat, slight chest tightness, urticaria
Management	Stop infusion for 15 min • if patient improved, resume infusion at 50% lower rate • if symptoms reoccur, halt infusion • if symptoms worsen, treat as if a moderate reaction
<i>Moderate reactions</i>	
Symptoms	Mild reaction symptoms plus cough, dyspnea, hypotension, noticeable chest tightness, tachycardia
Treatment	Stop iron infusion, fluid bolus, intravenous steroids • if symptoms worsen, treat as if a severe reaction
<i>Severe/life-threatening reaction</i>	
Symptoms	Cardiac arrest, cyanosis, loss of consciousness, periorbital edema, wheezing/stridor
Treatment	ACLS (if necessary), epinephrine, intravenous steroids, transfer to higher level of care
ACLS, advanced cardiac life support. ¹ Based on Rampton et al. [32].	

ing shell of carbohydrates for stabilization [7]. It is the composition of the carbohydrate shell that differentiates the iron products from each other.

While the use of parenteral iron in some providers' minds is associated with great risks, recent studies show these are markedly overstated. An older iron preparation – high-molecular-weight iron dextran – was associated with a high rate of reactions [27]. However, this is

Table 2. Intravenous iron preparations

Agent	Typical single dose
Ferric carboxymaltose	750–1,000 mg
Ferric gluconate	125 mg
Ferumoxytol	510–1,020 mg
Iron isomaltoside	1–2,000 mg
Iron sucrose	2–300 mg
Low-molecular-weight iron dextran	1,000 mg

now off the market and has been replaced by new iron preparations such as low-molecular-weight iron dextran, ferumoxytol, ferric carboxymaltose, and iron isomaltoside. Studies have shown all iron products have a good safety record, with a lower rate of reactions than rituximab or penicillin [28]. Modern iron formulations are associated with a low risk of reactions, and they have fewer adverse effects than oral iron in several studies. In the meta-analysis by Avni et al. [29] on the adverse effects of intravenous iron, it was shown in 97 clinical trials that there was no increased risk of serious adverse events compared with controls, and in double-blind trials, there was a trend towards fewer reactions (risk ratio [RR] 0.83, confidence interval 0.64–1.03). When compared to oral iron, the rate of gastrointestinal reactions was significantly less, with a RR of 0.55. Patients with heart failure who received intravenous iron showed no increased risk of adverse outcomes [3]. Similarly, a meta-analysis of aggressive intravenous iron use (>200 mg/month) showed no increase in adverse events in dialysis patients [30]. In pregnant women, intravenous iron was more efficacious in raising blood count with a significantly reduced risk of side effects – odds ratio 0.35 [31]. The preponderance of the data reinforces the safety and low reaction rates of intravenous iron.

The principal side effect of intravenous iron is infusion reactions. Studies show rates of mild reactions are ~1 in 200 and major reactions are ~1 in 200,000 [29]. These are not classic allergic reactions but instead due to activation of the complement system [28, 32]. This is similar in the pathogenesis to reactions seen with infusions of biological drugs like rituximab (but much less frequent) [33]. The reaction is termed complement activation-related pseudoallergy [34]. The activation of complement leads to the production of chemical mediators such as C5a and C3a that leads to flushing via vasodilation, urticaria, and wheezing among other symptoms. This explains why the reactions can be idiosyncratic, and patients can be reex-

posed to the same iron product. Also, if measured, serum tryptase is normal and not elevated as would be seen in a true allergic reaction [35]. Treatment of these reactions depends on severity (Table 3) [32]. Firstly, diphenhydramine should be avoided as this can worsen symptoms. In fact, it was reported in a prospective study that the majority of reactions attributed to intravenous iron were actually due to premedication with diphenhydramine [36]. For mild reactions, the infusion is stopped and then resumed at a slower rate once symptoms resolve. For more severe reactions, fluids and steroids are used. Given the role of free iron in promoting the growth of pathogenic microorganisms [37], there have been concerns that intravenous iron may predispose to infections. Reviews and meta-analyses have shown no increased risk of infections with intravenous iron [29, 30, 38]. The recent PIVOTAL study also showed no increased risk of infection with aggressive intravenous iron supplementation in dialysis patients [4]. In addition, compared to oral iron, intravenous iron did not lead to adverse changes in bowel microbiome in patients with inflammatory bowel disease [14]. Given the ability of iron to promote oxidation, concerns have been expressed about the use of intravenous iron leading to oxidative damage to endothelial cells and atherosclerosis, but this concern has not been validated in clinical studies [30, 38]. In the trials of iron for congestive heart failure – which included many patients with established coronary artery disease – no increased risk was seen [3, 39]. Thus, despite these theoretical concerns about the safety of intravenous iron, robust clinical data show that these concerns are unfounded.

One unique side effect limited to iron carboxymaltose is hypophosphatemia [40]. In a recent randomized trial, 50% of patients receiving this drug have serum phosphorus levels <2.0 mg/dL, with 10% having levels <1.3 mg/dL [41]. The phosphorus level reached its nadir 2 weeks after infusion which lasted over 5 weeks in one-third of patients. Hypophosphatemia may often be asymptomatic, but very severe hypophosphatemia can be associated with fatigue, muscle weakness, and especially osteomalacia, which is being increasingly reported after repeated doses of intravenous iron use [40].

Risk Mitigation

Given that reactions to iron are not allergic, there is little logic in giving a test dose [28]. It is important to reassure patients about the low risks of intravenous iron and symptoms of infusion reactions, as anxiety on the

part of an ill-informed patient may increase reaction risk [35]. In patients who have had previous reactions to intravenous iron, administration of the same or different iron preparations can be done. Premedications are of limited value, but slowing the infusion rate can help prevent recurrent reactions [35]. Ferumoxytol is also an MRI contrast agent and can be seen on scans for up to 3 months. The package insert of ferumoxytol recommends the use of T1- or proton density-weighted MR pulse sequences to minimize its effects if MRI is required within 3 months after its administration. One should wait 4 weeks before MRI using T2-weighted pulse sequences.

Conclusion

Iron repletion of deficient patients is one of the most gratifying treatments a physician can prescribe. While the risks are low, one needs to be familiar with adverse effects of both oral and intravenous iron. Often, simple steps can be performed to avoid or ameliorate these effects. Intravenous iron is an attractive and safe option for patients unable to tolerate oral iron.

Statement of Ethics

Not applicable as this is a review article.

Disclosure Statement

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