Role of Intravenous Iron in Current Era

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Abstract

Iron is an essential trace mineral necessary for life, and iron deficiency anaemia (IDA) is one of the most common haematological problems worldwide. Oral iron replacement therapy is a simple, inexpensive treatment option for the treatment of iron deficiency in stable patients, but there are many populations for whom IV iron is more effective. Therefore, IV iron should be considered when there are no contraindications, when poor response to oral iron is anticipated, when rapid hematologic responses are desired. Third generation intravenous (IV) iron therapies allow rapid and complete replacement dosing without the toxicity issues inherent with older iron preparations. This review provides an updated overview on diagnosis and management of IDA in patients with chronic conditions, preoperative and considers the properties of the different IV irons, and how differences might impact current and future clinical practice. We will discuss the benefits and limitations of oral versus intravenous iron replacement.

Introduction

Iron deficiency is the most common nutritional deficiency worldwide, affecting 2 billion people in 2023. Iron is an essential component of the haemoglobin molecule. Its deficiency has been a recognized health concern for centuries; often associated with dietary insufficiency, blood loss, or chronic illnesses [1]. Patients with iron-deficiency anemia usually have a longer stay in the hospital and a number of adverse events. Therefore, iron supplementation becomes a cornerstone of therapy in patients.

Oral iron has been used throughout history. Sydenham is thought to have first introduced iron therapy for chlorosis in 1681, but it was later, in the early 19th century, that Pierre Blaud introduced ferrous sulphate in pill form [2]. The
historical context of intravenous iron supplementation traces back to the recognition and treatment of iron deficiency and anemia. In the early stages of addressing iron deficiency, oral iron supplementation and dietary interventions were primary approaches. The advent of intravenous iron supplementation emerged as a significant development in the latter half of the 20th century. Early formulations faced challenges, such as poor tolerability and safety concerns. Over time, advancements in pharmaceutical technology led to the development of safer and more effective intravenous iron preparations [3].

The clinical application of intravenous iron gained momentum as researchers and clinicians recognized scenarios where traditional oral supplementation was inadequate, inefficient, or associated with gastrointestinal side effects. Conditions such as chronic kidney disease, inflammatory disorders, and certain gastrointestinal diseases became focal points for the exploration of intravenous iron therapy [4]. Intravenous iron supplementation can lead to improved maternal health and better chronic disease outcomes globally.

**Iron deficiency and anemia**

Approximately 30% of people have anemia in the world [5]. Iron deficiency is the most common cause, accountable for 50% of all anemias. In developing countries such as India, the prevalence of iron deficiency anemia is much higher than in the developed world. 71% of the associated mortality burden falls in Asia and Africa.

The causes of iron deficiency anemia vary depending on age, gender, and health status. This may be due to blood loss, iron deficiency, or decreased absorption. It is associated with many disease states, including chronic kidney disease (CKD), inflammatory bowel disease (IBD), and heart failure, and results in poor patient outcomes and poor clinical outcomes. From a health perspective, identification and treatment of perioperative IDA can reduce morbidity and mortality as well as prolong survival [6]. Regardless of whether they have symptoms of IDA, all patients should receive treatment aimed at both eliminating the underlying cause of iron deficiency and increasing iron stores. Recent data also demonstrate the benefit of using iron replacement in the treatment of iron deficiency anemia (NAID) [7]. Patients with iron deficiency anemia often have longer hospital stays and worse outcomes. Therefore, iron supplementation is very important for these patients [8].

**Managing iron-deficiency anemia**

Today, intravenous iron plays a crucial role in managing iron-deficiency anemia. Overall, the multifaceted roles of iron highlight its indispensable nature in supporting numerous physiological processes critical for human health and functioning. Maintaining an appropriate balance of iron in the body is essential for preventing deficiencies or excesses, both of which can have adverse health effects.

Iron deficiency affects millions of people worldwide and is also a cause of diabetes, which has negative health consequences. The three methods for treating ID and iron deficiency anemia have three steps: identification of ID/IDA, detection and control of ID occurrence, and iron supplementation. Iron supplement options include oral and
intravenous iron. For patients with stable ID, oral iron is still the treatment of choice, but for many people, intravenous iron is more effective. Therefore, iron injection should be considered when there are no contraindications, a negative response to oral iron is required, a rapid hematological response is required, and/or the product is available and accessible [9].

**Oral Iron**

Iron absorption from the intestine is limited. The maximum absorption of 100 mg of oral iron is between 20% and 25% and this can only be achieved in the end stage of iron deficiency. The average absorption of iron deficiency and iron deficiency is 10% and 13%, respectively; This rate is 5% in healthy men and 5.6% in healthy women. Iron residue in the intestinal lumen can cause mucosal damage [10]. Animal research models show that bacteria multiply and cause cancer. Additionally, side effects of taking diarrhea medication hinder compliance and lead to nonadherence in 50% of patients [11]. Therefore, dose adjustment is necessary to increase tolerability. There are many commercially available preparations, most of which contain iron salts such as ferrous sulfate, ferrous gluconate, and ferrous fumarate.

Oral medication is effective when the digestive system is not good. However, since recovery is slow, its use should be limited to patients with anemia (hemoglobin 11.0–11.9 g/dL in non-pregnant women, 11.0–12.9 g/dL in men). Injection is the preferred method when faster recovery is desired. However, the easy availability, cheapness and simplicity of the metal mouth make the treatment feasible [12].

**Intravenous Iron**

Intravenous iron supplementation is very effective in the treatment of iron deficiency anemia and should be considered in cases where oral iron is inadequate. The effectiveness of oral iron is reduced when the digestive system is weak, or iron loss is poor and/or supplemented. Side effects of reduced patient compliance also limit the effectiveness of oral iron. In this case, intravenous iron treatment is preferred because it bypasses the intestines and allows faster recovery [13].

The choice between intravenous and oral iron supplementation depends on various factors, including the severity of iron deficiency, underlying medical conditions, patient preferences, and potential side effects [Table 1].
Table 1: Oral Vs Intravenous Iron

<table>
<thead>
<tr>
<th>Oral Iron</th>
<th>Intravenous Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pros</td>
<td>Pros</td>
</tr>
<tr>
<td>Inexpensive</td>
<td>Fast repletion of iron stores</td>
</tr>
<tr>
<td>Convenient</td>
<td>Faster and More Predictable Correction of Iron Deficiency</td>
</tr>
<tr>
<td>Available over the counter</td>
<td>Reduced Interference with Other Medications</td>
</tr>
<tr>
<td>Absorption is not impaired</td>
<td>Effective even when intestinal absorption is impaired</td>
</tr>
<tr>
<td>Effective when intestinal</td>
<td>Effective in Cases of Malabsorption</td>
</tr>
<tr>
<td>Cons</td>
<td>Cons</td>
</tr>
<tr>
<td>Limited daily intestinal absorption</td>
<td>Requires administration by a health care professional</td>
</tr>
<tr>
<td>Dose-dependent gastrointestinal side effects</td>
<td>Potential for iron overload</td>
</tr>
<tr>
<td>Uptake is impaired in the setting of disease</td>
<td>Transient increase in oxidative stress</td>
</tr>
</tbody>
</table>

The use of IV iron is increasing, and more and more studies on IV iron are supported at least in part by its safety profile. A comprehensive meta-analysis including more than 10,000 patients in 103 clinical studies provides important information on overall safety and allows comparison between intravenous and metal mouth. Intravenous iron was not associated with an increase in adverse events (SAEs) compared to oral iron and placebo (RR, 1.04; 95% CI, 0.93-1.14). SAEs are rare and are estimated to occur in 1:200,000 doses, but there are no fatal or anaphylactic reactions. Although studies have shown that mild reactions occur, the frequency of these adverse events should be taken into account when using plasma [14]. In most cases, when oral iron is ineffective or ineffective, or in emergency situations where there is insufficient time to supplement iron levels with oral iron, replacement for these metal deposits is the only alternative for treating IDA.

**IV therapy in medical specialties**

IV iron is sometimes used in the context of surgery, particularly in situations where preoperative or perioperative iron deficiency or anemia is identified. The goal is to optimize the patient's iron status before surgery or to address acute iron deficiency during the perioperative period. If a patient is found to be iron deficient or anemic before surgery, preoperative IV iron supplementation may be considered to improve hemoglobin levels and overall iron status. Preoperative iron may be administered in cases of elective surgery when there is sufficient time to address iron deficiency before the procedure [Table 2].
Table 2: IV therapy in medical specialties

<table>
<thead>
<tr>
<th>Medical specialty</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td>Heart failure management</td>
</tr>
<tr>
<td>Nephrology/Dialysis</td>
<td>IV access is crucial for hemodialysis or peritoneal dialysis.</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>In the biologic therapies</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>Respiratory support</td>
</tr>
<tr>
<td>Obstetrics and Gynecology</td>
<td>Labor and delivery</td>
</tr>
<tr>
<td>Surgery</td>
<td>IV therapy for preoperative and postoperative recovery</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>IV iron therapy for dehydration or shock</td>
</tr>
</tbody>
</table>

IV Iron in Heart Failure (HF) Management

Iron deficiency is a common problem in approximately 40-60% of patients with heart failure (HF), regardless of diabetes and left ventricular ejection fraction. Iron deficiency is associated with poor quality of life, poor work performance, increased risk of hospitalization due to heart failure, and death [15]. Clinical studies and meta-analyses frequently show that injection of various iron preparations leads to early improvements in symptoms, quality of life, and work ability and can reduce cardiovascular disease (CV)-related diseases and heart failure (HF) in heart patients. Failure [16].

Iron deficiency is associated with poor quality of life, poor survival, and increased risk of hospitalization in patients with heart failure, independent of diabetes. European Society of Cardiology (ESC) guidelines recommend screening for anemia and iron deficiency; American Heart Association (AHA) / American Heart Failure Association (ACC) / Heart Failure Association (HFSA) says that diabetes should be taken as the basis in Heart Failure (HF) guidelines. Part of routine evaluation; CCS says only adverse causes of anemia should be investigated and treated. Guidelines recommend the use of erythropoiesis-stimulating agents in patients with heart failure and anemia, except in patients with other conditions without heart failure. Guidelines recommend the use of intravenous antibiotics in patients with heart failure and iron deficiency with reduced ejection fraction (HFrEF), regardless of diabetes. Patients with iron deficiency and (i) symptomatic heart failure with LVEF 45% (criterion 1), (ii) heart failure with left ventricular ejection fraction (LVEF) <50% and patients recently hospitalized for heart failure Intravenous ferric carboxymaltose (Measurement 2) or (iii) continued during hospitalization for heart failure study and after discharge (process 3) [17]. In heart failure patients with symptomatic HFrEF and mildly reduced ejection fraction (HFmrEF) and iron deficiency, intravenous iron is recommended to reduce cardiovascular symptoms and improve quality of life. (Class I, Class A). In patients with symptomatic HFrEF and HFmrEF and iron deficiency, regardless of hospitalization history, iron carboxymaltose or iron isomaltose should be considered to reduce the risk of hospitalization for heart failure (Class IIa, Grade A).

2021 European Society of Iron Cardiology (ESC) Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure recommend that all patients with heart failure be screened for anemia and that blood count, serum ferritin concentration and TSAT iron are adequate. For the treatment of diabetes and iron deficiency in patients with
heart failure, guidelines recommend that patients with symptoms of iron deficiency should consider taking carboxymaltose in arteries to improve symptoms and reduce the risk of hospitalization [18].

**Types of Intravenous Iron Preparations**

Several intravenous (IV) iron preparations are available, each with its own characteristics, indications, and dosing regimens. The choice of IV iron formulation depends on factors such as the severity of iron deficiency, patient tolerability, and the specific clinical scenario. Here are some common types of intravenous iron preparations [Table-3]:

### Table 3: Some common types of intravenous iron preparations

<table>
<thead>
<tr>
<th>Types of intravenous iron</th>
<th>Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Sucrose</td>
<td>Venofer, Ferrum Hausmann</td>
</tr>
<tr>
<td>Ferric Carboxymaltose</td>
<td>Injectafer</td>
</tr>
<tr>
<td>Iron Dextran</td>
<td>Dexferrum, INFeD</td>
</tr>
<tr>
<td>Ferric Gluconate</td>
<td>Ferrlecit</td>
</tr>
<tr>
<td>Ferric Pyrophosphate Citrate</td>
<td>Triferic</td>
</tr>
<tr>
<td>Ferric Derisomaltose</td>
<td>Monoferric</td>
</tr>
<tr>
<td>Ferric Isomaltoside</td>
<td>Monofer</td>
</tr>
<tr>
<td>Iron Thiosulfate</td>
<td>Sodium Ferric Gluconate Complex in Sucrose</td>
</tr>
</tbody>
</table>

**Safety and adverse effects**

Intravenous iron therapy is generally safe and effective, but as with any medical intervention, there are some risks and side effects. The safety of different IV iron preparations may vary. There is a long-standing bias in the immunotherapy community, regardless of design, due to concerns about serious adverse events (SAEs) that can lead to anaphylaxis, hypotension, and shock. However, most serious and potentially fatal cases are due to the high molecular weight metal dextran (HMWID) formulation, which is no longer available. Excluding HMWID, the estimated incidence of SAEs from intravenous metals is less than 1 in 250,000 administrations. The risk of intravenous iron is negligible compared to the risk of death and acute SAE from blood transfusion. According to the 2012 Safety Data Sheet (SHOT), the risk of death and adverse events are estimated to be 1 in 322,580 and 1 in 21,413 cases. Other unproven concerns regarding the use of intravenous iron, such as risk of infection, iron overload, or oxidative stress, have also been acknowledged. Therefore, public pressure and management concerns regarding IV iron response should be reconsidered [19].

**Challenges**

**Hypersensitivity Reactions**

Risk factors that appear to increase the incidence and severity of allergic reactions to iron in the bloodstream include a history of allergic or idiopathic reactions, a rapid rate, and a history of intravenous antibiotics. Arastu et al., 2022
found that the incidence of infusion reactions was higher in patients with a history of allergies, but it is important that we capture more than the need for anti-infusion in patients with a history of allergies. drug, food and contact allergies. Because of the risk of intolerance to the dextran component and the association of LMWID with increased activation, 19 dextran-free intravenous iron preparations are beneficial due to the lower risk of anaphylaxis, although most of the cost comes from all infusions at once. visit various non-ferrous metals [20].

**Optimal Dosing Strategies**

IV iron therapy is used to treat iron deficiency when oral iron supplements are not effective or cannot be tolerated. The optimal dosing strategy for IV iron therapy depends on the patient's iron status, the severity of iron deficiency, the specific IV iron formulation used, and the underlying cause of the deficiency [13].

**Iron Overload Monitoring**

Monitoring for iron overload is crucial during intravenous iron therapy to prevent potential complications. Here are some key aspects of monitoring:

- **Baseline Assessment:** Before starting therapy, assess the patient's iron status, including serum ferritin, transferrin saturation (TSAT), and hemoglobin levels. Additionally, consider liver function tests and imaging studies if there are risk factors for iron overload.

- **Regular Monitoring:** Throughout treatment, monitor serum ferritin and TSAT levels at regular intervals, as recommended by guidelines or the prescribing physician. Typically, this is done every 1-3 months.

- **Clinical Assessment:** Pay attention to clinical signs and symptoms of iron overload, such as joint pain, fatigue, abdominal pain, and liver enlargement.

- **Adjusting Iron Dose:** Based on monitoring results, adjust the iron dose to maintain iron levels within the target range while avoiding overload [21].

**Cost and Accessibility**

The cost and accessibility of intravenous (IV) iron therapy can vary depending on several factors such as the specific type of iron preparation, the country or region, the healthcare setting, insurance coverage, and any subsidies or assistance programs available [22].

**Future Directions**

Ongoing research may focus on developing innovative IV iron formulations that provide sustained release, minimizing the need for frequent infusions and reducing the risk of adverse effects.

**Research into new formulations**

Generally, IV iron therapy is more expensive than oral iron supplements because it involves the administration of the iron directly into the bloodstream, often requiring a healthcare professional to perform the infusion. The cost can
include the price of the iron preparation itself, the healthcare provider's fee for administering the infusion, and any associated medical supplies or equipment. Accessibility can also be influenced by factors such as the availability of healthcare facilities that offer IV iron therapy, the expertise of healthcare providers in administering the therapy, and the overall healthcare infrastructure in a particular area. Many healthcare systems have guidelines in place for the use of IV iron therapy, prioritizing its use for patients who cannot tolerate or do not respond to oral iron supplements [23].

New form Intravenous iron therapy is crucial for patients with iron deficiency who cannot tolerate or absorb oral iron. While traditional formulations like iron sucrose, ferric gluconate, and iron dextran have been widely used, newer formulations have been developed to improve safety, efficacy, and patient experience.

**Combination Therapies**

Combination therapies in intravenous iron therapy involve the use of more than one type of iron preparation or the combination of iron with other medications or treatments. These approaches are often employed to improve iron absorption, enhance efficacy, or manage specific patient populations. Here are some common combination therapies:

Iron Sucrose + Erythropoiesis-Stimulating Agents (ESAs): This combination is used in the treatment of anemia associated with chronic kidney disease (CKD). ESAs stimulate the production of red blood cells, while iron sucrose provides the necessary iron for hemoglobin synthesis.

Ferric Carboxymaltose + Erythropoiesis-Stimulating Agents (ESAs): Similar to iron sucrose, ferric carboxymaltose can be combined with ESAs for the treatment of anemia in CKD patients.

Iron Sucrose + Folic Acid: Folic acid is essential for red blood cell production. Combining it with iron sucrose can be beneficial in patients with folic acid deficiency anemia [24].

**Global Health Initiatives**

Global health initiatives in intravenous iron therapy focus on improving access to treatment for iron deficiency and anemia, particularly in low- and middle-income countries where these conditions are more prevalent. The World Health Organization (WHO) has programs aimed at addressing anemia, including the use of iron supplementation and fortification of foods. They also provide guidelines for the use of intravenous iron in specific populations, such as pregnant women and children [25]. United Nations Children’s Fund (UNICEF) works to improve access to iron supplementation for children in developing countries through programs such as the Micronutrient Initiative [26].

**Conclusion**

Diabetes and dyslipidaemia exacerbate one another; without careful monitoring of one, the other is challenging to manage. Considering this, aggressive approaches to managing each of these comorbidities are suggested for diabetic patients in order to enhance outcomes and lower morbidity and mortality.
Patient consent: N/A
Conflict of Interest: Nil
Financial Disclosure: None

References


