Heart Failure and the Iron Deficiency

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Abstract
Iron deficiency anemia is a significant problem worldwide and more so in developing countries, like India. The prevention and treatment of iron deficiency is a major public health goal in India. It is now well recognized that iron deficiency has detrimental effects in patients with coronary artery disease, heart failure, and pulmonary hypertension, and possibly in patients undergoing cardiac surgery. Around one-third of all patients with HF, and around one-half of patients with pulmonary hypertension, are affected by iron deficiency.¹

Introduction
Anaemia is a frequent finding in patients with heart failure (HF) and can worsen cardiac function, myocardial contractility, renal function, exacerbate symptoms and worsen quality of life. It is being increasingly recognised that patients with an underlying cardiac disease (especially elderly individuals and those with chronic diseases) can present with signs and symptoms of cardiac failure in absence of clinically apparent anaemia. These patients should be evaluated for an underlying iron deficiency (during early iron deficiency, anaemia is typically absent), as prompt initiation of parenteral iron can result in symptomatic improvement and even reverse the cardiac failure. Improved exercise capacity has been demonstrated after iron administration in patients with pulmonary hypertension.³

Absolute ID was defined as ferritin < 100 μg/L, functional ID was defined as ferritin 100–299 μg/L and transferrin saturation (TSAT) < 20%.⁴

Iron Deficiency and Heart Failure-Drug Trials
The Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency (FAIR-HF) study analysed the impact of intravenous iron therapy with Ferric Carboxymaltose in 459 patients with heart failure and iron deficiency, and found an improvement in functional class, 6-minute walk test distance and quality of life in Ferric Carboxymaltose versus placebo-treated patients.⁵ Similar results were recently obtained in the Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure (CONFIRM-HF) study.⁶ Treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anaemia, improves symptoms, functional capacity, and quality of life with an acceptable side-effect profile.¹

Doses in Heart Failure
Oral versus parenteral iron
The choice between oral and parenteral iron depends on a number of factors including the severity of the anaemia and rapidity of correction needed, cost and availability of different iron preparations, as well as the ability of the patient to tolerate oral iron preparations. However in cardiac patients, where rapid correction of the iron deficiency is desirable, we prefer to use parenteral iron. With the availability of IV iron formulations with improved toxicity profiles and minimal adverse effects, intramuscular (IM) iron which is painful, stains the buttocks, and has variable absorption is generally avoided.

Dose calculation
Generally, the dose of parenteral iron is calculated based on body weight, current hemoglobin level, and amount of elemental iron per milliliter of the iron product.

\[ \text{Volume of product required (mL)} = \frac{\text{weight (kg)} \times (14 - \text{Hgb}) \times (2.145)}{\text{C} + \text{correction of stores}} \]

Where C= concentration of elemental iron (mg/ml) in the product being used. Ferric carboxymaltose contains 50 mg iron/mL solution for injection.

In practice, there is no evidence that total doses above 1000 mg of elemental iron are clinically useful. Often a fixed dose of approximately 1000 mg, is generally sufficient to treat anaemia and provide additional storage iron without causing iron overload.

Choice of IV formulation
The choice of the formulation will depend on the cost, availability, and number of visits/ time required to administer the full dose. The different parenteral forms of iron available are Ferric carboxymaltose, Iron Sucrose, Iron dextran, Ferumoxytol, Ferric pyrophosphate citrate and Ferric gluconate. With the exception of Iron dextran, the incidence of severe anaphylactic reactions is exceedingly rare but merits a vigilant attitude.

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as it can be life threatening. IV iron should be avoided in patients with active infections. Unlike iron sucrose and ferrous gluconate which need frequent low doses to be administered in multiple settings, Ferric carboxymaltose (FCM) which is a colloidal iron hydroxide complex can be administered in one or two visits. This is highly desired in settings where rapid correction of the iron deficiency is indicated. Also, unlike with iron dextran, the risk of anaphylactic reactions is minimal.

All the iv preparations of iron are equally effective in treating iron deficiency. However, some studies have found Ferric carboxymaltose (FCM) to be better than other iron formulations.

Table showing comparative efficacy of Iron dextran Iron sucrose Ferric carboxymaltose.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Iron dextran</th>
<th>Iron sucrose</th>
<th>Ferric carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) haemoglobin g/dL</td>
<td>1.4 (0.9-1.9)</td>
<td>2.4 (1.99-2.74)</td>
<td>2.7 (2.30-3.03)</td>
</tr>
<tr>
<td>Mean (± SD) MCV increase (fl)</td>
<td>5.8 (4.0-7.6)</td>
<td>5.6 (2.9-8.3)</td>
<td>7.0 (4.6-9.7)</td>
</tr>
<tr>
<td>Mean (± SD) ferritin increase (mcg/dL)</td>
<td>149 (93-205)</td>
<td>109 (84-133)</td>
<td>149 (99-200)</td>
</tr>
</tbody>
</table>

Managing adverse reactions

Adverse reactions are exceedingly rare with FCM.

Like any iron preparation, FCM can also cause malagia, muscle weakness, arthralgia, nausea, vomiting and headache.

Transient fever, arthralgias, myalgias, or flushing are generally seen in approximately 0.5 to 1 percent of infusions. In absence of associated hypotension, tachypnea, tachycardia, wheezing, stridor, or periorbital edema, the infusion should be temporarily withheld and the patient observed. If symptoms resolve, the infusion can be resumed. Antihistaminics should not be administered as they can actually worsen the symptoms. If symptoms persist unchanged, 125 mg intravenous methylprednisolone should be administered, then wait for 30 minutes, and reinitiate the iron infusion; a short course of oral methylprednisolone also may be administered.

A short course of nonsteroidal anti-inflammatory drugs (NSAIDs), if appropriate may be initiated.

Patients with more serious or true anaphylactic reactions should be treated according to standard protocols. Any adverse effect with parenteral iron administration should be reported.

Monitoring and hemoglobin/iron targets

Effective treatment of iron deficiency results in resolution of symptoms, a modest reticulocytosis (peaking in 7 to 10 days), and normalization of the hemoglobin level in six to eight weeks. For IV iron, haemoglobin is to be re-assessed four to eight weeks after the iron has been administered. The iron parameters should not be repeated for at least four weeks, because IV iron interferes with most assays of iron status.

Future Strategies

Future studies are needed for defining the role of blood transfusions; treatment heart failure patients and the patients with stable, asymptomatic or symptomatic ischemic heart disease.

Conclusions

Anemia is common in patients with heart disease and now we have the evidence base to support a role for iron therapy for anemia correction. Iron treatment helps ameliorate symptoms in patients heart failure. The role of blood transfusions remains understudied and unclear.

References