

Iron deficiency in heart failure has attracted considerable attention in recent years. It is agreeable to treat a patient of heart failure with iron in case the patient has iron deficiency anaemia. However, several trials which were recently published have indicated that patients of heart failure will benefit significantly when infused with iron, even in the absence of anaemia, if there is iron deficiency. The following questions need to be answered before concluding the above hypothesis.

### WHAT IS THE SCOPE OF THE PROBLEM?

Iron deficiency is an independent risk factor for mortality in HF.<sup>1,2,3</sup> Half of all patients with HF have either absolute iron deficiency or functional Iron deficiency defined as ferritin less than 100 µg/L or transferrin saturation less than 20% and serum ferritin between 100-300 µg/L.<sup>4,5</sup> This may or may not be associated with anaemia.

### HOW DOES HEART FAILURE LEAD TO IRON DEFICIENCY?

This could be due to reduced absorption of iron from the duodenum secondary to edema.

There is another interesting mechanism. Increased levels of pro inflammatory cytokines such as interleukin-6 enhance production and release of hepcidin, which is a protein synthesized in the liver. Hepcidin regulates the release of stored iron from enterocytes and hepatocytes by leading to degradation of iron transporter protein, ferroportin. Thus high levels of hepcidin can “trap” iron in storage cells.

### HOW DOES IRON DEFICIENCY LEAD TO WORSENE D SYMPTOMS IN HEART FAILURE PATIENTS WITHOUT ANEMIA?

It is understandable that iron deficiency could lead to worsened symptoms in heart failure patients with anaemia. However the mechanism of increased symptoms in the absence of anaemia is not fully understood. Iron could be acting as a co-factor in skeletal and cardiac muscle function.<sup>6,7</sup> Experimental evidence suggests that iron therapy improves muscle function and exercise capacity without increase in the haemoglobin.

In addition iron is an important constituent of myoglobin which binds and releases oxygen. Mitochondrial function also needs iron as a co-factor for heme proteins.

### THE DATA FROM DIFFERENT TRIALS

It is natural that if iron deficiency can lead to increased symptoms and worse prognosis in patients of heart failure, administration of iron could lead to improved

prognosis. There is not enough data regarding oral iron therapy in this setting possibly due to intolerance of oral Iron as well as a number of drug interactions. Most of the trials of treating iron deficiency in heart failure used intravenous iron. There are several iron preparations for IV use, iron dextran, iron gluconate, iron sucrose and ferric carboxymaltose (FCM). The iron dextran is given up due to enaphylactic reactions. The newer preparations do not seem to have these issues.

An initial study has compared IV sucrose in 24 patients with CHF and iron deficiency to 11 patients with CHF and without iron deficiency (ferric HF Study)<sup>8</sup>. It showed that 16 weeks of iron therapy was well tolerated and led to improvement in exercise capacity and symptoms in patients with iron deficiency.

A later study called FAIR-HF used FCM in a multi-centre, double blind, placebo controlled fashion.<sup>9</sup> The investigators showed that FCM treatment in both Iron deficient anaemic and non-anaemic patients with CHF increased the following:

- Distance walked during 6 minutes walk test
- NYHA CLASS
- Overall quality of life

The study enrolled 459 patients with CHF (Hb ranging from 9.5 to 13.5 gm%). The definition for Iron deficiency in this trial was ferritin between 100 to 300 ng/ml with TSAT less than 20%. The improvement in QoL occurred in both anaemic and non-anaemic patients suggesting that Iron deficiency is an important comorbidity in HF that can be treated. A rise in ferritin level and TSAT is there for all the patients.

CONFIRM-HF is a multi-centre, double-blind, placebo-controlled trial that enrolled 304 symptomatic HF patients with left ventricular ejection fraction (LVEF) less than or equal to 45%, elevated natriuretic peptides, and Iron deficiency (ferritin, 100 ng/ml or 100-300 ng/ml, if TSAT, 20%).<sup>10</sup> Patients were randomized 1:1 to treatment with ferric carboxymaltose or placebo for 52 weeks. The primary end point was the change in 6MWT distance from baseline to week 24. Secondary end points included changes in NYHA class, patient global assessment (PGA), 6MWT distance, health-related QoL Fatigue score at weeks 6,12,24,36 and 52 and the effect of FCM on the rate of hospitalization for worsening HF. Treatment with FCM significantly prolonged 6MWT distance at week 24. The treatment effect of FCM was consistent in all subgroups

440 and was sustained to week 52. Throughout the study, an improvement in NYHA class, PGA, QoL, and Fatigue score in patients treated with FCM was detected with statistical significance observed from week 24 onwards. Treatment with FCM was associated with a significant reduction in the risk of hospitalization for worsening HF. The number of deaths (FCM:12, placebo:14 deaths) and the incidence of adverse events were comparable between both groups (Figures 1 and 2).

The IRON-HF study analysed the effects of intravenous as well as oral Iron on functional capacity in patients of heart failure with Iron deficiency and anaemia.<sup>11</sup> The results showed that IV iron is superior to oral therapy.

In a recent meta-analysis published in European Journal of Heart Failure, all the randomized trials of Iron therapy in HF have been analysed.<sup>12</sup> Data from a total of 851 patients from 5 trials was studied. The results confirm that intravenous Iron therapy reduces the need for hospital admissions for worsening HF. There is a reduction in NYHA class, increase in 6 min walking distance and an improvement in quality of life by different scoring systems (Table 1). There was no effect on all cause and cardiovascular mortality which may be due to a low number of reported deaths (4% vs.6% for those treated vs. not treated with I.V Iron). Also the benefits were there for both anaemic and non-anaemic patients.

## CONCLUSIONS

The following conclusions can be drawn at this stage:

1. Iron deficiency is common in heart failure patients.
2. It may or may not be associated with anaemia.
3. Iron replacement therapy improves quality of life, 6MWT and NYHA class in patients with and without anaemia.
4. There is also a reduction in the need for hospitalization for worsening heart failure.
5. Mortality however is not improved.
6. These patients should be investigated for source of bleeding like peptic ulcer.

Based on the above data the European Society of Cardiology guidelines in 2012 have recommended Iron replacement therapy for symptomatic patients of heart failure with systolic dysfunction and Iron deficiency (Class II a, level of evidence A).

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