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Original Article

Effect of ferric carboxymaltose on hospitalization and mortality outcomes in chronic heart failure: A meta-analysis

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ABSTRACT

Introduction: Iron administration especially intravenous iron therapy is associated with improvements in exercise capacity and quality of life in patients with chronic heart failure (CHF). Our aim was to assess effect of ferric carboxymaltose (FCM) on hospitalization and mortality outcomes in CHF.
Materials and methods: A literature search across PUBMED, Google Scholar and trials database www.clinicaltrials.gov was conducted to search for randomized controlled trials (till August 2016) comparing FCM to placebo in CHF with or without anaemia. Published human studies in English language which reported data on mortality and hospitalization rates were included. Primary outcome was rates of HF hospitalizations and secondary outcomes were hospitalization due to any cardiovascular (CV) cause, death due to worsening HF and any CV death.
Results: From 17 studies identified, two were included in final analysis (n = 760; 455 in FCM and 305 in placebo arms). We observed significantly lower rates of hospitalization for worsening HF in FCM arm [Risk Ratio (RR) 0.34, 95% confidence interval (CI) 0.19, 0.59, p = 0.0001] as well as for any CV hospitalizations [RR 0.49, 95% CI 0.35, 0.70; $p < 0.0001$] (figure). No heterogeneity in studies was seen for these two outcomes ($I^2 = 0\%$, $p > 0.05$). No significant treatment effect with FCM was noted in mortality from worsening HF (RR 0.41, 95% CI 0.02, 7.36; p = 0.55) or any CV death (RR 0.80, 95% CI 0.40, 1.57; p = 0.51).
Conclusion: FCM reduces hospitalization rates in CHF but may not reduce mortality outcome. This finding needs further evaluation in a large, prospective, randomized controlled trial.

1. Introduction

Chronic heart failure (CHF) is associated with adverse short-term and long-term consequences which lead to poor health related quality of life (QoL).[1,2] Various factors determine the clinical course of HF patients.[3,4] Iron deficiency is known to occur with a greater frequency in HF, is associated with unfavourable clinical outcome and has prognostic significance.[5–7] Anemia in CHF is associated with increases in left ventricular (LV) mass, increased markers of HF like natriuretic peptides, and higher number of repeat hospitalizations.[8–10] In a meta-analysis of anemia and mortality in HF by Gorenveld et al.,[11], presence of anaemia was found to increase risk of death in HF compared to non-anaemic population (46.8% Vs 29.5%) in a follow-up of six months.

Development of anaemia in HF is multifactorial. Defective erythropoiesis predominates in HF besides contribution from renal dysfunction and neurohormonal and pro-inflammatory cytokine activation leading to iron deficiency (ID) state.[12] Further, defective iron absorption, and reduced re-absorption of recycled iron contribute to ID. ID is significantly prevalent worldwide including developing countries like India.[13] Study in Indian population reported ID in 76% HF cases and 48.7% had absolute deficiency.[14] Development of ID even in absence of anaemia is known to reduce aerobic performance, and result in exercise intolerance.[15]

Treatment of ID is associated with improvement in cardiac function, clinical symptoms, peak oxygen consumption, increase exercise tolerance, along with improved cardiac remodelling.[16,17,18] A meta-analysis involving 370 patients being treated by intravenous iron therapy reported improved outcome in terms of QoL, improved exercise tolerance suggested by increase in 6 min walk

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distance (6MWD) and lower rates of hospitalizations.[19] Given a choice, intravenous iron may always be preferred considering problems with oral iron absorption and gastrointestinal intolerance.[20] In fact, the 2016 European Society of Cardiology (ESC) CHF guidelines recommend intravenous iron – ferric carboxymaltose (FCM) in symptomatic HF with reduced ejection fraction (EF) to relieve symptoms and improve exercise capacity and QoL.[21] As suggested from literature evidence and recommendation from guideline, intravenous iron benefits HF in terms of symptomatic improvements. However, it remains unclear whether this benefit translates to reduction in endpoints such as HF hospitalizations and deaths. Although, a previous meta-analysis from Moore and colleagues[22] with FCM is available, it was for anaemia from all causes and assessed changes in haematological parameters. Here, we performed a systematic review and a meta-analysis exploring the effect of intravenous iron therapy with FCM on hospitalization and mortality outcomes in HF.

2. Methods

2.1. Search strategy

We searched the PUBMED, and Google scholar databases and international clinical trial registry – http://www.clinicaltrials.gov; for RCTs of FCM in CHF. RCTs published till August 2016 were searched using the following search terms: Ferric carboxymaltose OR FCM AND chronic heart failure OR CHF.

2.2. Trials selection

In this meta-analysis, we included human trials where the control group was given a placebo, trial duration of minimum 12-weeks, and the data on hospitalization and mortality for heart failure or any cardiovascular (CV) cause were available irrespective of study included anaemic population or not. We excluded trials that were performed in patients under age of 18, in pregnant patients and in patients with active bleeding. Only published RCTs in English language were included. Other languages were excluded for technical and cost-related reasons.

2.3. Extraction of data

Two investigators extracted the trials data and assessed quality of the trial independently as per guidelines published by the Cochrane Collaboration.[23] Any discrepancy in views of two investigators was resolved by the opinion of third investigators and finalized by majority view. Characteristics of trials included in the meta-analysis are described in Table 1.

2.4. Quality assessment

Quality assessment was performed by two authors independently who assessed trials in following domains: i) random sequence generation, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data reporting, and v) selective outcome reporting. Each of these domains were graded for biases as low risk, unclear risk, lack of information or uncertainty, or high risk as per the standard criteria published from Cochrane collaboration.[23]

Table 1
Characteristics of the included studies.

Characteristics	FAIR-HF[26]	CONFIRM-HF[25]
Total patients randomized	459	304
Active drug and dose	IV FCM (200 mg)	IV FCM (500–1000 mg)
Placebo	Saline	Saline
Patients randomized	N = 304 to FCM N = 155 to saline	N = 152 to FCM N = 152 to saline
Iron dosage in therapy phase	200 mg weekly	500–1000 mg weekly
Iron dosage in maintenance phase	200 mg every 4 weeks	500 mg every 12 weeks
Follow up duration	26 weeks	52 weeks
Haematological criteria for inclusion		
• TSAT (%)	<20%	<20%
• Ferritin (ng/mL)	<100 (or 100–299 if TSAT <20%)	<100 (or 100–300 if TSAT <20%)
• Hb (gm/dL)	9.5 to 13.5	<15
Cardiac criteria for inclusion		
• LVEF (%)	<40% for NYHA II, <45% for NYHA III	≤ 45%
• NYHA class	II to III	II to III
• BNP and/or Nt-pro-BNP	–	>100 pg/mL and/or >400 pg/mL
Mean age (years) of participants	67.8 ± 10.3 in FCM arm 67.4 ± 11.1 in placebo arm	68.8 ± 9.5 in FCM arm 69.5 ± 9.3 in placebo arm
Female (%)	52.3% in FCM arm 54.8% in placebo arm	45% in FCM arm 49% in placebo arm
eGFR (ml/min/1.73 m^2)	63.8 ± 21.2 in FCM arm 64.8 ± 25.3 in placebo arm	66.4 ± 21.7 in FCM arm 63.5 ± 20.9 in placebo arm

FAIR-HF: the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF), CONFIRM-HF: Ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure, IV: Intravenous, FCM: ferric carboxymaltose, TSAT: transferrin saturation, Hb: haemoglobin, NYHA: Ney York Heart Association, LVEF: left ventricular ejection fraction, BNP: brain natriuretic peptide, Nt-Pro-BNP: N-terminal-pro-brain natriuretic peptide, eGFR: estimated glomerular filtration rate.

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