Heart, Lung and Circulation (2015) **24,** 686–695
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2014.12.161

ORIGINAL ARTICLE

Changes in Echocardiographic Parameters in Iron Deficiency Patients with Heart Failure and Chronic Kidney Disease Treated with Intravenous Iron

Jorge E. Toblli, MD, PhD, FASN *, Federico Di Gennaro, Carlos Rivas

Hospital Alemán, School of Medicine, University of Buenos Aires, Av. Pueyrredon 1640, (1118) Buenos Aires, Argentina

Received 17 September 2014; received in revised form 23 December 2014; accepted 26 December 2014; online published-ahead-of-print 21 January 2015

Background Treatment of iron deficiency helps to improve cardiac and renal function in patients with chronic heart failure. However, the mechanism by which this occurs is currently unclear.

Methods We undertook a double-blind, randomised, placebo-controlled study of intravenous iron sucrose treatment (200 mg/mL weekly for five weeks) in patients with chronic heart failure, chronic kidney disease and iron-deficiency anaemia receiving optimal treatment for chronic heart failure (N=60). Markers of disease severity, iron status, anaemia and inflammation were measured during a six-month follow-up period, and evaluation of echocardiographic parameters was performed at baseline and six months after treatment.

Results At six months after treatment initiation, intravenous iron was associated with reduced severity of the symptoms of chronic heart failure and improved renal function (both $p<0.001$ versus control). Also, ferritin and transferrin saturation levels were increased, as were haemoglobin levels, whereas inflammatory markers were reduced (all $p<0.001$ versus control). Left ventricular systolic and diastolic diameters were increased and improved left ventricular function correlated with iron status in patients receiving intravenous iron but not patients in the control group.

Conclusions Intravenous iron treatment was associated with improved myocardial functional parameters and cardiac dimensions in patients with anaemia and chronic kidney disease.

Keywords Iron deficiency • Heart failure • Chronic kidney disease • Ferritin • TSAT • Iron sucrose

Introduction

Chronic kidney disease (CKD) is a common co-morbidity in patients with chronic heart failure (CHF) and it is a strong, independent predictor of anaemia risk [1–3]. Furthermore, CHF is associated, in a variable degree, to iron-deficient erythropoiesis by the action of inflammatory cytokines that promote hepcidin production, which in turn blocks gastrointestinal iron absorption and also impairs its release from the reticuloendothelial system [4–6]. A meta-analysis including more than 150,000 patients with CHF showed anaemia to be associated with a doubled mortality risk in this group of patients [7].

The effects of iron deficiency, with or without anaemia, have been shown to be at least partly reversible in several small-sample studies [8,9] and a large double-blind, randomised controlled study with intravenous (iv) iron in iron-deficient patients with CHF [10]. These studies have

*Corresponding author at: Department of Internal Medicine, Hospital Alemán, School of Medicine, University of Buenos Aires, Av. Pueyrredon 1640, (1118) Buenos Aires, Argentina. Tel.: (+54 11) 4827 7000; fax: (+54 11) 4805 6087, Email: jorgetoblli@fibertel.com.ar

reported improvements in exercise capacity and CHF symptom severity, even in those patients without anaemia and/or in whom haemoglobin levels did not change following iv iron administration. A post-hoc analysis of the FAIR-HF study also suggests that iv iron treatment may improve renal function [11]. Further, Comin-Colet *et al* have recently shown in a retrospective database analysis that iron deficiency is associated with impaired quality of life in stable, symptomatic, and ambulatory CHF patients with iron deficiency and systolic dysfunction, and that this effect was independent of baseline anaemia status and renal function [12].

Although the correction of iron deficiency with iv iron therapy evidently helps to improve cardiac and renal function with a better quality of life, the intrinsic mechanism by which this occurs is still uncertain. Hence, whether positive changes observed in myocardial function are due to the increase in haemoglobin concentration or by iron itself in these patients remains a subject of investigation. There is some evidence that iron therapy can induce infarct healing and left ventricular remodelling in patients following an ST-elevation myocardial infarction [13].

Previously, we initiated a double-blind, randomised, placebo-controlled study of 40 patients with CHF, chronic renal failure and anaemia to investigate the effect of iv iron without erythropoietin on a range of clinical and functional parameters associated with inflammation, cardiac and renal function and quality of life [14]. We showed that iv iron sucrose, 200 mg/week for five weeks, resulted in reduced inflammatory status and improved left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class, exercise capacity, renal function and quality of life after six months [14]. Since then, we recruited a further 20 patients and undertook additional analyses, including more detailed investigation of iron status markers and the effects of iv iron sucrose (IS) on echocardiographic parameters. These new data are presented here.

Methods

This was a double-blind, randomised, placebo-controlled pilot study of five weeks duration and has been described previously [14]. Patients were consecutively recruited from the general population attending the outpatient clinic (Cardiology section) at Hospital Alemán, University of Buenos Aires, Argentina. The local research and ethics committee (ADAICU, University of Buenos Aires) granted study approval and written, informed consent was obtained from all participants. The study was performed in compliance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Patients with a diagnosis of CHF, CKD, and anaemia were enrolled. At their initial medical review, patients meeting the inclusion criteria and who provided written informed consent were randomised to the intervention or placebo groups. Random allocation of patients was performed by assigning patients a number sequentially and then using a randomly generated table of treatment arm per number. The table randomly assigned patients to study groups to a maximum of 30 per arm. The inclusion criteria were: LVEF of ≤35%, NYHA functional class II to IV, Hb <12.5 g/dL (men) or Hb <11.5 g/dl (women), ferritin <100 ng/ml and/or percentage transferrin saturation (TSAT) ≤20%, and creatinine clearance (CrCl) ≤90 mL/min. Patients were excluded based on the following criteria: ongoing haemoodialysis therapy, anaemia not related to iron deficiency; medical history of allergy to iron supplements, acute bacterial infections, parasitism or neoplasm in the four previous weeks, chronic digestive diseases, hypothyroidism, congenital cardiopathies, iron therapy and/or recombinant human erythropoietin (rhEPO) therapy in the four previous weeks, and a medical history of hospitalisation in the four weeks before enrolment.

After screening a total of 80 patients, 60 patients were randomised into two groups by means of a table of random numbers. At enrollment, each patient was interviewed to acquire a complete medical history. Also, an exhaustive physical examination was performed and symptoms were assessed according to the NYHA functional classification.

Treatment

All patients received the optimum treatment for CHF according to the current recommendations. The control group (n=30) was assigned a placebo in addition to conventional therapy for the management of CHF, while the intervention group (n=30) received 200 mg/200 mL of iv IS every week for five weeks (Venofer®, Vifor International, Switzerland) in addition to conventional therapy (Figure 1). No patients received rhEPO prior to the study or at any time throughout the study.

During the follow-up phase between week 5 and month 6, patients were evaluated monthly by means of physical examination, assessment of symptoms according to the NYHA functional classification and laboratory determinations (Hb, ferritin, TSAT), haematology parameters (monthly), renal

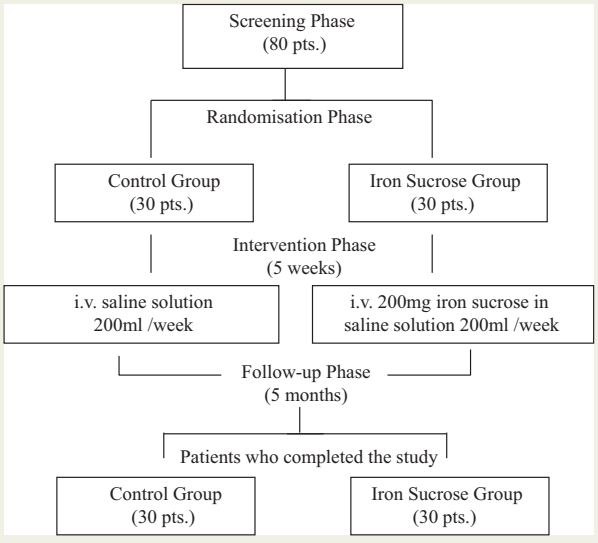

Fig. 1 Study flow chart.