International Journal of Cardiology 168 (2013) 3439–3442

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

IRON-HF study: A randomized trial to assess the effects of iron in heart failure patients with anemia ☆

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ARTICLE INFO

Article history:
Received 11 August 2012
Received in revised form 31 January 2013
Accepted 19 April 2013
Available online 13 May 2013

Keywords:
Heart failure
Clinical trial
Ferrous sulfate
Iron sucrose
Anemia

ABSTRACT

Background: Anemia in heart failure patients and has been associated with increased morbi–mortality. Previous studies have treated anemia in heart failure patients with either erythropoietin alone or combination of erythropoietin and intravenous (IV) iron. However, the effect of IV or oral (PO) iron supplementation alone in heart failure patients with anemia was virtually unknown.
Aim: To compare, in a double-blind design, the effects of IV iron versus PO iron in anemic heart failure patients.
Methods: IRON-HF study was a multicenter, investigator initiated, randomized, double-blind, placebo controlled trial that enrolled anemic heart failure patients with preserved renal function, low transferrin saturation (TSat) and low-to-moderately elevated ferritin levels. Interventions were Iron Sucrose IV 200 mg, once a week, for 5 weeks, ferrous sulfate 200 mg PO TID, for 8 weeks, or placebo. Primary endpoint was variation of peak oxygen consumption (peak VO_2) assessed by ergospirometry over 3 month follow-up.
Results: Eighteen patients had full follow-up data. There was an increment of 3.5 ml/kg/min in peak VO_2 in the IV iron group. There was no increment in peak VO_2 in the PO iron group. Patients' ferritin and TSat increased significantly in both treated groups. Hemoglobin increased similarly in all groups.
Conclusion: IV iron seems to be superior in improving functional capacity of heart failure patients. However, correction of anemia seems to be at least similar between PO iron and IV iron supplementation.

1. Introduction

Anemia has been demonstrated to be a common finding in patients with heart failure (HF) [1]. More importantly, anemic patients with HF have definite increased morbidity and mortality [2]. Many studies have investigated the effects of treating anemia in HF patients, with positive results in most of them. However, all such studies have used either erythropoetin (EPO) and oral iron or a combination of EPO and intravenous (IV) iron [3,4]. It is well known that patients with HF actually have increased levels of EPO [5] and therefore may not need EPO supplementation. Increased plasma EPO levels have been found to be associated with an impaired prognosis, independent of hemoglobin levels, in patients with HF [6].

Recently, the effect of IV iron alone in patients with HF who have iron deficiency with or without anemia has been shown to be significantly better than placebo in improving quality of life measures [7]. It is still unsolved, however, which route of iron administration would be clinically most effective. Because oral administration of iron could not overcome the reticuloendothelial iron block [8], IV iron may be more effective for treating anemic HF patients, but these routes have never been compared head to head. The IRON-HF

☆ ClinicalTrials.gov Identifier: NCT00386126.

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http://dx.doi.org/10.1016/j.ijcard.2013.04.181

Table 1
Inclusion and exclusion criteria.

Inclusion criteria
a) 18 years of age or older; b) Outpatients followed at a HF clinic in a tertiary care hospital with clinical diagnosis of HF for at least 3 months before study entry; c) NYHA functional class II IV, who are able to perform ergospirometry. d) Documentation of LVEF <40% within the last 6 months; e) Adequate baseline therapy for HF based on patient's functional class (*β- blockers, ACE inhibitors irrespective of functional class except if contra-indications,digoxin, espironolactone if NYHA class III or IV*); f) Stable baseline HF therapy with same doses of medications and no intent to increase doses for the following 3 months; g) Hemoglobin ≤12 g/dl and ≥9 g/dl; h) Transferrin saturation <20% and ferritin <500 μg/l; i) Ability to provide written informed consent.
Exclusion criteria
a) Any clinically overt bleeding: gastrointestinal bleeding, hypermenorrhea, history of peptic ulcer without evidence of healing or inflammatory intestinal diseases. b) Uncorrected hypothyroidism; c) Other inflammatory, neoplasic or infectious disease; d) Serum creatinine >1.5 mg/dl; e) Previous intolerance to oral elemental iron compounds; f) HF due to alcoholic cardiomyopathy, current regular drinker of alcoholic beverages or HF due to peripartum cardiomyopathy; g) Recent admission for decompensated HF (last month); h) Recent myocardial revascularization procedures (last 3 months); i) Recent ACS, stroke or TIA (last 3 months); j) Active or metastatic neoplasic disease with life expectancy of less than a year; k) Patients in heart transplantation list; l) Patients that had participated in any other clinical trial or study within the last month; m) Pregnant or lactating women; n) Pre-menopausal women that are not using any effective method of contraception; o) Patients using prohibited medications or that have not yet accomplished the washout period; p) Patients currently participating in cardiovascular rehabilitation programs. q) Patients with pacemakers, implanted defibrillators or cardiac resynchronization therapy.

HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; TIA, transient ischemic attack.

study was the only randomized clinical trial to date that had the aim of comparing, in a double-blind design, the effects of IV iron versus oral iron supplementation in anemic HF patients [9]. However, the IRON-HF study has faced some of the well-described issues that may occur during the conduct of a clinical trial leading to failure to successfully complete the study:

a. Clinical Trial competition. Other large-scale clinical trials, such as RED-HF [10] were selecting similar patients concurrently;
b. Scarce financial support. As an academic-initiated study with industry support, the industry budget was directed toward cost compensation only.

The aim of this brief communication is to bring the best information available from the conduct of the IRON-HF study as well as its partial results as it has reached its termination.

2. Methods

The detailed methods of the IRON-HF study have been published elsewhere [9]. Briefly, the IRON-HF study was an investigator initiated, multicenter, prospectively designed, randomized, double-blind, placebo controlled clinical trial. Studied patients were stable ambulatory HF patients, with ejection fraction below 40% who were anemic by the World Health Organization (WHO) criteria. The detailed inclusion and exclusion criteria are reproduced in Table 1. Patients were randomized in a double-blind method to receive:

Group 1 Iron Sucrose 200 mg intravenously, once a week, in 30 min infusions, for 5 weeks and placebo of oral presentation, three times a day, for 8 weeks.
Group 2 Ferrous sulfate 200 mg, orally, three times a day, for 8 weeks and placebo of IV presentation once a week, for 5 weeks.
Group 3 Placebo of oral presentation, three times a day, for 8 weeks and placebo of IV presentation once a week, for 5 weeks.

The primary endpoint of the IRON-HF study was to assess the impact of iron supplementation alone (IV or oral) on changes in oxygen maximal consumption (VO_2 max.) assessed by ergospirometry over a 3-month follow-up period. The ergospirometry evaluation followed the Naughton modified protocol.

The IRON-HF study had a number of *a priori* defined sub-group analyses, such as:

1 Correction of anemia, defined as hemoglobin higher than 12 g/dl for women and higher than 13 g/dl for men;
2 Hemoglobin variation of more than 1.5 g/dl;
3 Transferrin saturation > or <20%.

Exploratory analysis of serum ferritin was undertaken despite not being *a priori* planned endpoint.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology.

3. Statistical analysis

All the analysis was performed according to intention to treat principle. For baseline comparisons, the Student *t* test for continuous variables and chi-square test for categorical variables, were used in

Table 2
Baseline characteristics of the patients.

Characteristics	Total (n = 23)	IV iron (n = 10)	PO iron (n = 7)	Placebo (n = 6)	P
Age (y)	66.2 ± 11.7	66.9 ± 8.3	63.5 ± 16.2	68.9 ± 10.1	NS
LVEF (%)	28 ± 7.8	25.2 ± 8.6	29.1 ± 6.8	30.7 ± 7.4	NS
Males (%)	69.6	66.7	75	66.7	NS
Hb (g/dl)	11.2 ± 0.6	11.2 ± 0.6	11.3 ± 0.5	10.9 ± 0.7	NS
Ferritin (μ/l)	132 ± 138	185 ± 146	101 ± 135	95 ± 128	NS
TSAT (%)	17.4 ± 8.3	18.9 ± 9.7	18.8 ± 8.6	13.5 ± 5.8	NS
Creatinine (mg/dl)	1.1 ± 0.3	1.1 ± 0.2	1 ± 0.3	1.3 ± 0.3	NS
Peak VO_2 (ml/kg/min)	15.2 ± 4	14 ± 3.4	17.8 ± 4.2	13.7 ± 3.4	NS
Etiology					
Ischemic	39.1%	22.2%	37.5%	66.7%	NS
Idiopathic	21.7%	22.2%	25%	16.7%	NS
Alcohol	8.7%	11.1%	12.5%	0%	NS
Hypertensive	17.4%	22.2%	12.5%	16.7%	NS
Chagas	8.7%	22.2%	0%	0%	NS
Other	8.7%	0%	25%	0%	NS
DM	30.4%	33.3%	25%	33.3%	NS
Atrial fibrillation	34.8%	22.2%	37.5%	50%	NS

IV. intravenous; PO. oral; LVEF. left ventricular ejection fraction; DM. diabetes mellitus; TSAT, Transferrine Saturation; VO_2. oxygen consumption.