

Intravenous Iron Alone for the Treatment of Anemia in Patients With Chronic Heart Failure

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OBJECTIVES	This study was undertaken to assess the hematologic, clinical, and biochemical response to intravenous iron in patients with chronic heart failure (CHF) and anemia.
BACKGROUND	Anemia is common in patients with CHF and is associated with higher morbidity and mortality. The combination of erythropoietin (EPO) and iron increases hemoglobin (Hb) and improves symptoms and exercise capacity in anemic CHF patients. It is not known whether intravenous iron alone is an effective treatment for anemia associated with CHF.
METHODS	Sixteen anemic patients (Hb ≤ 12 g/dl) with stable CHF (age 68.3 ± 11.5 years, 12 men, 9 participants New York Heart Association [NYHA] functional class II and the remainder class III, left ventricular ejection fraction $26 \pm 13\%$) received a maximum of 1 g of iron sucrose by bolus intravenous injections over a 12-day treatment phase in an outpatient setting. Mean follow-up was 92 ± 6 days.
RESULTS	Hemoglobin rose from 11.2 ± 0.7 to 12.6 ± 1.2 g/dl ($p = 0.0007$), Minnesota Living with Heart Failure (MLHF) score fell (denoting improvement) from 33 ± 19 to 19 ± 14 ($p = 0.02$), 6-min walk distance increased from 242 ± 78 m to 286 ± 72 m ($p = 0.01$), and all patients recorded NYHA class II at study end ($p < 0.02$). Changes in MLHF score and 6-min walk distance related closely to changes in Hb ($r = 0.76$, $p = 0.002$; $r = 0.56$, $p = 0.03$, respectively). Of all baseline measurements, only iron and transferrin saturation correlated with increases in Hb ($r = 0.60$, $p = 0.02$; $r = 0.60$, $p = 0.01$, respectively). There were no adverse events relating to drug administration or during follow-up.
CONCLUSIONS	Intravenous iron sucrose, when used without concomitant EPO, is a simple and safe therapy that increases Hb, reduces symptoms, and improves exercise capacity in anemic patients with CHF. Further assessment of its efficacy should be made in a multicenter, randomized, placebo-controlled trial. (J Am Coll Cardiol 2006;48:1225-7) © 2006 by the American College of Cardiology Foundation

Anemia co-exists in up to 55% of patients with chronic heart failure (CHF) (1), and retrospective analyses of therapeutic trials in CHF patients have found anemia at trial entry to be an independent risk factor for hospitalization and death (2). The combination of erythropoietin (EPO) and intravenous or oral iron has been shown to improve cardiac function, symptoms, and peak oxygen consumption in patients with CHF and anemia (3,4). Although intravenous iron alone increases and maintains hemoglobin (Hb) in patients with renal disease (5), there are no reported studies into the effects of intravenous iron alone in patients with CHF and anemia.

METHODS

Patient population. We conducted a prospective, uncontrolled, open-label study of the intravenous administration of iron sucrose (Venofer; Vifor, Switzerland) in patients with systolic heart failure and Hb ≤ 12 g/dl who had been stable on standard heart failure medication for ≥ 6 weeks.

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Vitamin B₁₂ or folic acid deficiency, hemoglobinopathy, or serum ferritin >400 ng/ml were exclusion criteria. The local research and ethics committee gave study approval. Written, informed consent was obtained from all participants.

Study protocol. In an outpatient setting, patients received 200 mg (10 ml) bolus injections of undiluted iron sucrose over 10 min into a peripheral vein on days 1, 3, and 5 of the study. Serum ferritin was measured on day 12 and, if <400 ng/ml, further 200 mg doses were administered on days 15 and 17. Follow-up time was 3 months.

Evaluations. Symptoms were assessed according New York Heart Association (NYHA) functional classification and the Minnesota Living with Heart failure (MLHF) questionnaire. Exercise capacity was quantified using a 6-min walk (6MW) test. Blood samples were taken for determination of hematologic variables, iron indexes, and renal function. All patients were considered for gastrointestinal (GI) endoscopy as investigation into the cause of their anemia.

Statistical analyses. All results are reported as mean values \pm SD. Paired and unpaired Student *t* tests, analysis of variance with Fisher post hoc test, simple linear regression analysis (all Statview 5, SAS Institute Inc., Cary, North Carolina) and McNemar's test (IFA Services, Amsterdam, the Netherlands) were used as appropriate. The *p* values <0.05 are referred to as having statistical significance.

Abbreviations and Acronyms

- CHF = chronic heart failure
- EPO = erythropoietin
- Hb = hemoglobin
- GI = gastrointestinal
- MLHF = Minnesota Living with Heart Failure
- NYHA = New York Heart Association
- 6MW = 6-min walk

RESULTS

Seventeen patients were enrolled, and 16 completed the study. The mean age was 68.3 ± 11.5 years, and 12 participants were men. Heart failure was due to coronary artery disease in 13, dilated cardiomyopathy in 2, and valve disease in a single patient. At study entry, 9 participants had NYHA class II symptoms, the remainder class III. Mean left ventricular ejection fraction was $26 \pm 13\%$. All patients were taking loop diuretics, 15 were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 5 were taking beta-blockers, and 8 were taking aldactone. Mean follow-up was 92 ± 6 days. Fourteen patients received 5 doses (1,000 mg) of iron sucrose, and 2 patients received 3 doses (mean dose 950 ± 137 mg).

Effect of iron sucrose on hematologic parameters. Hemoglobin rose from 11.2 ± 0.7 to 12.6 ± 1.2 g/dl ($p = 0.0007$) (Fig. 1), serum iron from 9.2 ± 4.4 to 13.7 ± 4.8 $\mu\text{mol/l}$ ($p = 0.009$), ferritin from 87 ± 113 ng/ml to 217 ± 185 ($p = 0.004$), and transferrin saturation from 16.0 ± 9.5 to $24.6 \pm 8.4\%$ ($p = 0.009$). Of all baseline measurements, only iron and transferrin saturation correlated with increases in Hb ($r = 0.60$, $p = 0.02$; $r = 0.60$, $p = 0.01$, respectively). Furthermore, when divided into tertiles according to change in Hb, patients demonstrating the greatest response were those with the lowest baseline iron levels ($p = 0.006$ vs. the tertile with the lowest response). Although there was no change in serum creatinine or calculated creatinine clearance (Cockcroft-Gault formula), there was a trend toward a fall in cystatin C concentration (1.71 ± 0.52 to 1.50 ± 0.53 mg/l, $p = 0.08$), suggesting improved glomerular filtration rate.

Effect of iron sucrose on symptoms and exercise capacity. At follow-up, all patients were in NYHA functional class II ($p < 0.02$ vs. baseline), and MLHF score also fell (denoting improvement) from 33 ± 19 to 19 ± 14 ($p = 0.02$). Mean 6MW distance increased from 242 ± 78 m to 286 ± 72 m ($p = 0.01$). Changes in MLHF score and in 6MW distance correlated strongly with increases in Hb ($r = 0.76$, $p = 0.002$ and $r = 0.56$, $p = 0.03$, respectively) (Fig. 2). Left ventricular ejection fraction did not significantly change ($27 \pm 12\%$ at study end).

GI pathology and response to iron sucrose. Of the 14 patients that underwent GI endoscopy, 6 had gastroesophagitis, 1 peptic ulcer disease, and 1 a benign colonic polyp. The remainder had no identifiable disease. Those with GI pathology did not have lower serum iron, ferritin, or

transferrin saturation at baseline nor did they demonstrate a greater increase in Hb compared with those without GI pathology ($p = \text{NS}$ for all comparisons).

Safety and tolerability. Iron sucrose was well tolerated with no instance of local or systemic adverse reactions. During follow-up, no patients were hospitalized, and none died. There were no changes to loop diuretic dose, and there was no statistical difference between baseline and completion body weights.

DISCUSSION

This study demonstrates that intravenous administration of iron sucrose to patients with CHF and anemia results in a significant increase in Hb, a reduction in symptoms, and an improvement in exercise capacity. These effects were achieved without simultaneous EPO therapy.

Iron deficiency is present when transferrin saturation is $<16\%$ and ferritin <30 ng/ml (6). Seven patients (44%) in this study were iron deficient by these criteria, and they had the greatest response to iron sucrose (increase in Hb 2.1 ± 1.3 g/dl vs. 0.9 ± 1.0 g/dl in the iron replete group, $p = 0.06$). Iron status is also the leading determinant of EPO responsiveness in patients with chronic renal failure, and concomitant intravenous iron is an essential adjunct in this context. We found no association between GI pathology and iron deficiency or response to iron, suggesting dietary factors or malabsorption may also influence iron status in patients with CHF.

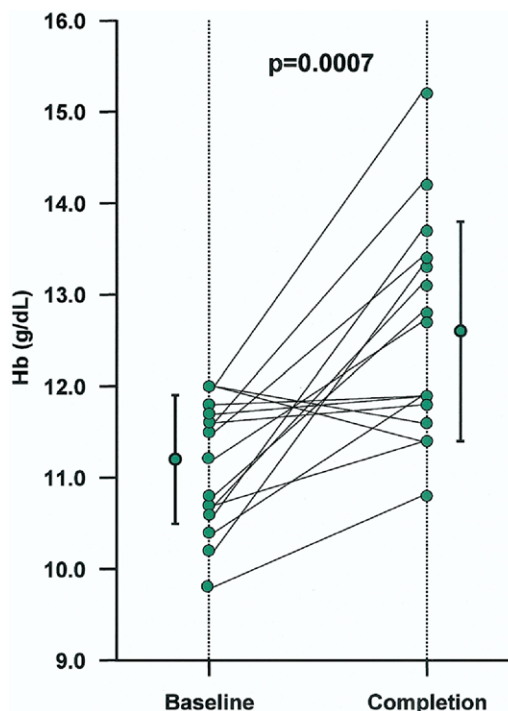


Figure 1. Changes in hemoglobin (Hb) for each participant after treatment with iron sucrose. Baseline and completion Hb \pm SD for the whole group is denoted by the values between the error bars.

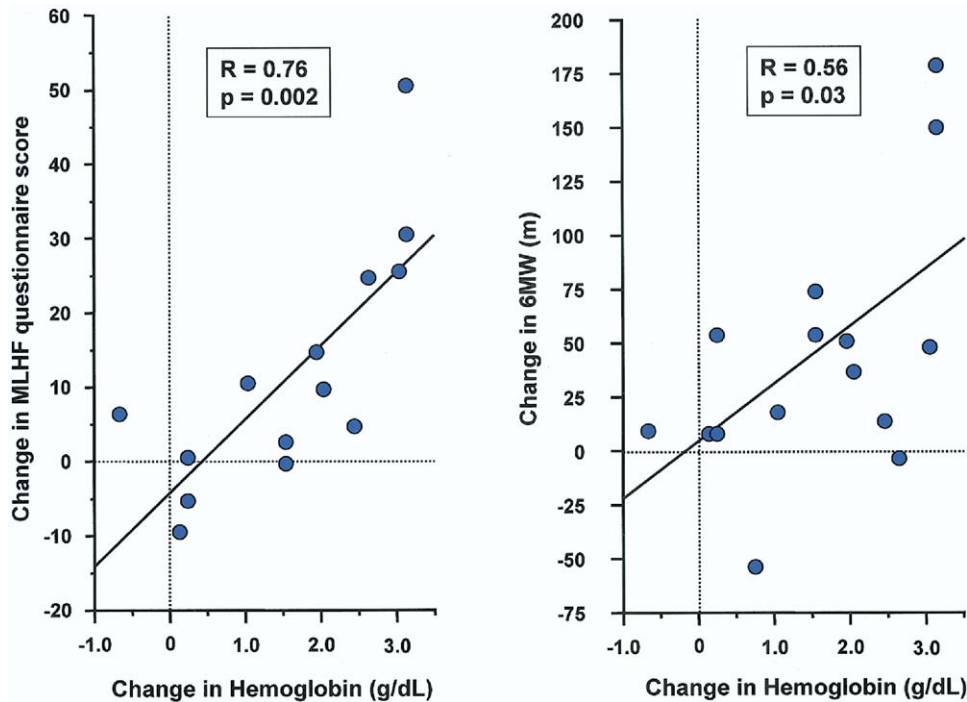


Figure 2. Relationships between change in hemoglobin and changes in Minnesota Living with Heart Failure (MLHF) score and 6-min walk (6MW) distance.

Given that the risk of death in CHF increases with small reductions in Hb (2), modest increases in Hb should confer significant clinical benefits. This is supported by the observations that peak oxygen consumption in CHF correlates with Hb levels (7), and the correction of anemia improves this measure of exercise capacity (4). The mean increase in Hb in this study was 1.4 ± 1.3 g/dl (range: -0.7 to $+3.1$ g/dl) for a treatment phase of just 5 to 17 days encompassing only 4 or 6 hospital visits. Others have recorded mean increases of 2.6 g/dl (3) and 3.3 g/dl (4) using a combination of EPO and iron in similar CHF groups. Although the EPO/iron combination may result in a greater response than iron alone, there are clearly individuals who have a dramatic hematologic and clinical response to the latter.

The fact that we recorded no adverse events relating to the administration of iron sucrose or during follow-up is consistent with other safety data concerning the use of this drug. After a total of 2,297 injections of iron sucrose in 657 patients with renal failure, Macdougall and Roche (8) reported adverse events in only 2.5%. All were short-lived, and no patient required hospitalization. Furthermore, iron sucrose appears safe in patients with known intolerance of other parenteral iron preparations (9).

Intravenous iron sucrose, without concomitant EPO, is a simple and safe therapy that increases Hb, reduces symptoms, and improves exercise capacity in anemic patients with CHF. Further assessment of its efficacy should be made in multicenter, randomized, placebo-controlled trials.

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