RESEARCH ARTICLE

EFFECT OF ORAL IRON THERAPY ON CLINICAL OUTCOMES IN PATIENTS WITH HEART FAILURE

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Received 17 Dec 2012; Review Completed 30 Dec 2012; Accepted 09 Jan 2013, Available online 15 Jan 2013

ABSTRACT

Background- Earlier studies have shown that anemia in heart failure (HF) patients decreases exercise tolerance/capacity, functional status and quality of life. We studied the effect of oral iron supplementation in anemic patients with HF.
Methods – We assigned 60 anemic (Hb 8—11g/dl) patients with HF (NYHA class II&III) with LVEF <40% in to 2 groups. Group- I- received ferrous sulfate 100mg bid x 90 days +standard treatment for HF. Group-II-received standard treatment for HF. Primary end points of the study were exercise tolerance(6-min walk distance), quality of life(MLHFQ) and haematological parameters. Secondary end points- Borg scale for dyspnoea and fatigue efficacy , safety assessment and few haematological parameters.
Results- There was significant improvement in exercise tolerance/ capacity and quality of life in iron treated patients as compared to control group (group – II). Dyspnoea and fatigue were reduced . Haematological parameters(Hb, RC, MCV, MCH, MCHC PCV &RBC count) increased gradually in iron treated patients with HF as compared to control group. However, incidence of microcytic- hypochromic anemia was reduced in group –I. Orally administered iron was well tolerated with mild side effects in anemic patients with HF.
Conclusion- Oral iron supplementation in HF patients with anemia improves exercise tolerance/capacity, quality of life, dyspnoea , fatigue and various haematological parameters.
Key Words: Heart failure, Ferrous sulfate, Quality of life, Exercise tolerance

INTRODUCTION

Heart failure(HF) is a debilitating and generally lethal condition responsible for enormous burden on health care. HF is one of the most common causes of admission in the emergency department. Prevalence of HF is increasing in our society and is the cause of poor quality of life and premature death. Approximately 5 million people in the United States have been diagnosed with HF and about 550,000 new cases are diagnosed annually[1]. Heart failure carries a 50 % mortality at 5 years after symptom onset[2]. One third of the patients with most severe disease die within the first year after diagnosis[3] . Prevalence of congestive heart failure (CHF) , 18.8million (1.76% of population) and incidence 1.57 million/ year(0.15%)has been reported in India[4]. Incidence approaches 10 per 1000 in people older than 65 years. Prognosis of HF depends on age, left ventricular ejection fraction (LVEF)[5], plasma norepinephrine,β type natriuretic peptide(BNP)levels, ECG ,evidence of left ventricular hypertrophy[6]., atrial fibrillation, renal functions[7] and presence of ventricular dysrrhythmias.

HF is a progressive disease characterized by adaptive neurohumoral activation of rennin angiotensin aldosterone system(RAAS) ,sympathetic nervous system, natriuretic peptides, endothelin, vasopressin and other regulatory mechanisms. Inflammatory mediators are also involved in the pathogenesis of chronic heart failure[8]. Management of patients with HF remains a challenging problem. Despite advances in the management, heart failure patients have high mortality and deaths due to HF have increased by 145% over the last 2 decades. There is no cure for this condition.

Anemia is common in patients with HF and is associated with more severe symptoms[9,] lower functional status, worse exercise capacity[9],cognitive impairment and worse quality of life. Preliminary open label studies in systolic HF have suggested that treatment with erythropoiesis stimulating agents leads to improvement in NYHA class, exercise capacity, cardiac and renal functions[10]. Anker et al [11] demonstrated that treatment with intravenous ferric carboxymaltose in patients with chronic HF improves symptoms, functional capacity and quality of life. Intravenous iron sucrose has also been shown to improve exercise capacity in anemic patients with CHF[12]. On the other hand Ghali et al [13]demontrated that treatment with darbepoietin alpha was not associated with significant clinical benefit in patients with symptomatic HF. Recently, four clinical trials treating anemia in HF with erythropoiesis stimulating agents in Europe were stopped prematurely because of increased mortality in erythropoietin treated patients[14]. In view of the conflicting reports available and no oral iron preparations were used to correct anemia in HF patients, the present study was undertaken to evaluate effect of oral iron supplementation on functional status and clinical outcomes in patients with heart failure.

METHODS

This was a prospective controlled, open labelled and comparative clinical study conducted at PGIMS-Rohtak(Haryana) India. An informed written consent was taken from all patients. Total 60 patients of either sex diagnosed with anemia in HF were enrolled for the study. Patients who were eligible as per inclusion and exclusion

criteria were allocated to receive one of the two different treatments in an open fashion and subjected to clinical assessment including efficacy and safety. Inclusion criteria—Patients of either sex aged >18 years, heart failure NYHA class II & III, exercise tolerance in the form of walk, 6- min. walk distance of < 375meters, LVEF <40 %,and Hb level 8-11g/dl. Exclusion criteria—Patients with severe infection within 1 month, uncorrected primary valvular disease, active myocarditis or constrictive pericarditis , patients with history of cardiac arrest or sustained ventricular tachycardia or fibrillation, within the previous year, patients with unstable angina or acute myocardial infarction, cardiac revascularization procedure or stroke . Patients with severe pulmonary, renal or hepatic disease, history of allergy to iron and systolic BP <85mmHg or > 160 mmHg, diastolic BP > 89 mmHg.

Study Design—After screening, patients were divided in to 2 groups of 30 each. Group –I-Patients with anemia (Hb 8-11g/dl) with HF(NYHA class II &III) were given oral iron ,ferrous sulfate 100mg,twice daily for 3 months along with standard treatment for HF. Group- II- Patients of anemia with HF were given standard treatment of HF like ACE inhibitors(ramipril 5mg/day), diuretics (furosemide 60mg/day), inotropic agents (digoxin 0.25 mg/day for 5 days in a week), vasodilators (nitrates- glyceryltrinitrate 2.6 mg, twice daily) and hypolipidemic drugs(atorvastatin20mg/ day) etc was not interrupted in both the groups.

End Points

The primary end point of the study was exercise tolerance/capacity, 6 min walk distance[15]. This test measures the distance(in meters) that a patient can quickly walk on a flat, hard surface in a period of 6 minutes quality of life- Minnesota Living with Heart Failure Questionnaire(MLHFQ)[16] and haematological parameters (Hb, peripheral blood film& reticulocyte count). Secondary end point of the study was Borg scale for dyspnoea and fatigue[17], efficacy assessment for anemia (signs and symptoms) and haematological parameters endpoints like mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), MCHC, packed cell volume (PCV),reticulocyte count (RC) and RBC count. Cell counter method[18] was used to assess Hb, MCV,MCH, MCHC, PCV,and RBC count.

Safety assessment

Patients were assessed for side effects of oral iron therapy before treatment and after 15, 45 and 90 days of iron treatment. Any other adverse effects reported by the patients were recorded.

Statistical analysis- In the descriptive analysis, mean and standard error of mean (SEM) of demographic and various clinical parameters were calculated. Among analytic Statistical technique repeated measures ANOVA test was applied for intragroup analysis and independent‘ t’ test was applied for intergroup analysis. Incidence of microcytic hypochromic anemia on peripheral blood film was tested using chi square test. A p value<0.05 was considered as statistically significant.

RESULTS

Total 95 HF patients were screened. Out of these 26 patients were excluded as they did not match predefined inclusion criteria. Only 60 patients completed the study and rest were lost to follow up. The baseline characterstics of the study population are as, mean age in group I and II, 55.63±1.73 and 57.73 ±2.38 respectively. M/F - 23/7 (I) & 22/8 (II).

Primary end points Exercise tolerance/capacity- Six min. walk distance in group I and II, before treatment was comparable. There was significant increase in 6 min. walk distance after 45 and 90 days of oral iron treatment in group I , whereas increase in 6 min. walk distance in group II was observed only after 90 days. Although, there was improvement in exercise tolerance in both groups but improvement was observed earlier in iron treated group. (table 1)

Quality of life- There was significant decrease in MLHFQ score after 90 days of iron treatment in group I and group II as compared to pretreatment values. Improvement was seen in both the groups but more marked in iron treated groups

Haematological parameters- Haemoglobin(Hb)- There was significant increase in Hb value after 15, 45 and 90 days of oral iron treatment as compared to control (group II).

Peripheral blood film (PBF)- There was reduced incidence of microcytic hypochromic anemia after 45 and 90 days of oral iron treatment as compared to group II.

Reticulocyte count- There was significant increase in reticulocyte count after 15, 45 and 90 days of oral iron treatment (group I) as compared to group II.

Secondary end points- Borg scale for dyspnoea- As shown in table -2 ,there was significant decrease in Borg dyspnoea score after 45 and 90 days of oral iron supplementation (group I). However, decreased score was also noted in group II but only after 90 days. There was improvement of dyspnoea in both groups but was earlier and more marked in group I receiving oral iron treatment.

Table 1:Effect of oral iron supplementation on exercise tolerance/capacity, 6-min. walk distance(m) in anemic patients with heart failure.

Groups	Before	After iron treatment		
		15 Days	45 Days	90 Days
I	330.87±5.01	331.40±4.81	336.50±5.08*	347.03±4.73*
II	325.70±5.05	326.30±4.57	328.43±5.73	332.07±5.23* @

p<0.001 when compared with pretreatment values (Student's ‘ t’ test), @ p< 0.05 when compared with group I (ANOVA)

 ISSN: 2250-1177 CODEN (USA): JDDTAO

Table- 2 : Effect of oral iron supplementation on Borg dyspnoea and fatigue score in anemic patients with heart failure. Data presented as Mean±SEM.

Groups	Pretreatment	After iron treatment		
		15 Days	45 Days	90 Days
	Borg Dyspnoea Score			
I	7.23± 0.22	7.06± 0.22	6.16±0.20*	4.73± 0.21*
II	7.03±0.27	7.00±0.26	6.46±0.25	5.86±0.28 * @
	Borg Fatigue Score			
I	6.83±0.25	6.53± 0.22	5.96±0.22	5.03 ±0.17*
II	7.00± 0.29	6.73 ±0.27	6.13± 0.26	5.86±0.29* #

- *P < 0.001 when compared with pretreatment(Student's 't' test), @ p<0.01, # p>0.05 when compared with group I (ANOVA).*

Borg scale for fatigue- As shown in table-2 ,there was more improvement in fatigue in iron treated patients as compared to group II.

Haematological parameters—Mean corpuscular volume (MCV) There was significant increase in MCV ,MCH,MCHC,PCV and RBC count values after 15, 45 and 90 days of iron treatment(group-I) as compared to control(group- II) .(Table-3). Signs and symptoms of anemia- The incidence of fatigability and pallor gradually reduced after iron therapy. Total number of patients complaining fatigue before treatment were 29, while after 15 , 45 and 90 days of iron treatment number of patients were 29, 21 and 14 respectively(group-I). In control group, there was no improvement in this parameter. In iron treated patients pallor was also gradually reduced, while it remained same or even increased in control group.

Table 3 : Effect of oral iron treatment on haematological parameters in anemic patients with heart failure.

Groups	Parameters	Before	After Treatment		
			15 Days	45 Days	90 Days
I	Hb(g/dl)	10.03±0.12	10.07±0.12	10.50±0.14	11.17±0.18*
II	-do-	9.94±0.14	9.92±0.14	9.83± 0.14	9.72± 0.14**
I	PBF	16	16	15	11
II	- do-	17	17	17	19 @
I	R C (%)	0.58±0.01	0.62±0.01*	0.71±0.01*	0.81 ±0.01*
II	-do-	0.57±0.01	0.56± 0.01**	0.56±0.01**	0.55± 0.01**#
I	MCV (fl)	86.14±1.11	86.27±1.11	87.07±1.11 *	88.30±1.11*
II	-do-	85.63±1.23	85.59± 1.23**	85.44±1.23 **	84.86± 1.23**#
I	MCH(pg)	24.37±1.54	24.47±0.29	24.80 ±0.28	25.38±0.29*
II	-do--	24.43± 1.60	24.40±0.29 **	24.27±0.29 **	24.10± 0.30**#
I	MCHC(g/dl)	28.40±0.42	28.51±0.42	28.91 ± 0.42	29.50±0.42*
II	-do-	28.60±0.35	28.56±0.35**	28.41± 0.35**	28.21±0.35**#
I	PCV (%)	35.60±0.47	35.63±0.46	36.33±0.47 *	37.23±0.48*
II	- do--	34.93±0.51	34.90±0.51**	34.86±0.52**	34.57±0.54**#
I	RBCcount	4.14±0.05	4.19 ±0.05	4.33±0.05*	4.49±0.05*
II	--do-	4.09±0.06	4.06±0.06**	4.00±0.06**	3.93±0.06**#

*p <0.001, ** p >0.05 when compared with pretreatment value (Student's 't' test), @ p<0.05 when compared to group I(chi-square test), # p<0.05 when compared with group I (ANOVA).*

PBE-peripheral blood film, RC-reticulocyte count, MCV- mean corpuscular volume, MCH –mean corpuscular haemoglobin, MCHC-mean corpuscular haemoglobin concentration, PCV-packed cell volume RBC- red blood cell.

Safety assessment- Orally administered ferrous sulfate was well tolerated with few mild side effects. In iron treated group, out of 30 patients 5patients reported with epigastric pain and heart burn, 4-nausea, 2- diarrhea, 2-

constipation and 1 patient with metallic taste, while none of these side effects were observed in group II patients.

DISCUSSION

Present study revealed that oral iron administration in HF patients with anemia improved exercise tolerance as measured by 6- min. walk distance, quality of life as measured by MLHFQ, Borg dyspnoea and fatigue score and various haematological parameters such as Hb,PBF, MCV, MCHC,PCV and RBC count. These results indicate significant improvement in clinical outcomes and health related quality of life after oral iron therapy in anemic patients with heart failure. Beneficial effects of iron therapy may be due to improved cardiac function like left ventricular ejection fraction (LVEF) or decreased ventricular hypertrophy, increased delivery of oxygen to heart muscle and aerobic metabolism, decreased production of inflammatory cytokines like tumor necrosis factor-α (TNF-α) and anti-apoptotic effect. Our finding are in agreement with previous studies to some extent. Bolger et al [12] demonstrated in open labeled study conducted on 16 patients with systolic HF that intravenous iron replacement improves symptoms and exercise capacity. Toblli et al [19] demonstrated in a randomized study conducted on 40 patients with HF that intravenous iron therapy improves LVEF, NYHA functional class, exercise capacity and quality of life.

Various mechanisms have been suggested for hemodynamic dysfunction and impaired exercise tolerance in patients with chronic HF. Among them, inadequate oxygen supply and impaired oxygen utilization by skeletal muscle during exercise contribute to poor clinical status of HF patients[20]. In addition, anemia may aggravate symptoms in patients with HF. Iron plays a key role in oxygen uptake, transport and storage as well as oxidative metabolism in the heart/ skeletal muscles. Iron has also been shown to be involved in erythropoiesis[21]. Iron deficiency in patients with anemia attenuates aerobic performance and is associated with fatigue and exercise intolerance[22]. Iron replacement therapy in patients with iron deficiency without HF has been associated with improved exercise performance. Therefore, observed improvement in exercise tolerance, Borg dyspnoea and fatigue score and various haematological parameters in the present study may be explained on the basis of iron replacement therapy for 3 months. Since anemia results in reduced oxygen delivery to metabolizing tissues and causes dyspnoea, fatigue and edema, correction of anemia might be beneficial. Data showed that anemia can lead to eccentric hypertrophy in rat with increased capillary proliferation, abnormal diastolic wall stress and interstitial fibrosis[23]. Levin et al [24] demonstrated that decrease in Hb concentration was found to be associated with an increase in left ventricular size. Anand et al [25] reported that 1g/dl increase in Hb concentration over a 24 week period was associated with 4.1g/m^2 decrease in left ventricular mass index. Erythropoietin treatment has also been shown to increase LVEF from 27 to 35 % after 7.2 months of treatment[26]. Therefore, it is possible that iron supplementation as in our study may reduced ventricular hypertrophy and ultimately be responsible for improved LVEF. Since anemia is associated with increased circulating TNF-α and cytokines (IL-6, IL-10 etc) activation ,iron supplementation might be beneficial in reducing TNF-α and cytokine levels.

At present ,it is difficult to propose the exact molecular mechanism of beneficial effect of iron supplementation in patients of HF with anemia but the study suggests favourable effects of oral iron therapy on exercise tolerance, quality of life, Borg dyspnoea and fatigue score and various haematological parameters. Further studies are required to elucidate other mechanisms of potential benefit of oral iron therapy in heart failure patients with anemia.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO