

Beneficial effects of the treatment of iron deficiency on clinical condition, left ventricular function, and quality of life in patients with chronic heart failure

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Summary. *Background:* Anemia is now considered as an important contributing factor to the deterioration of chronic heart failure. The present study aimed to assess the effects of intravenous iron therapy on clinical condition, left ventricular function and also quality of life in patients who suffered of chronic heart failure and concomitant iron deficiency. *Methods:* In this clinical trial, 25 consecutive patients with concomitant chronic heart failure and iron deficiency referred to Shariati hospital in Isfahan, Iran in 2013. After initial clinical, laboratory, and echocardiography assessments, the patients administered 200 mg intravenous Iron per week until compensating iron deficit. Then, all study parameters were assessed again and compared to parameters before the therapeutic intervention. *Results:* The NYHA class showed a significant improvement after the therapeutic approach. The prevalence of heart failure-related edema was also significantly reduced from 60% before treatment to 48% after that ($p = 0.036$). The rate of hospitalization was considerably reduced from 42% to 16% ($P < 0.001$). Moreover, mean 6 minute walk test (6MWT) was increased from 155.18 m to 187.40 m ($P < 0.001$). Comparing Left Ventricular Ejection Fraction (LVEF) after treatment to figures before the test indicated a significant improvement in this parameter (27.5% versus 33.0%, $P = 0.007$). The treatment of iron deficiency in this group of subjects got a significant improvement in SF36 total score. *Conclusion:* In patients with chronic heart failure, the treatment of iron deficiency results in a marked improvement in functional status, ejection fraction, and also quality of life as well as a reduction in need to re-hospitalization, however renal function was deteriorated and thus more pay attention to renal function is necessary. (www.actabiomedica.it)

Key words: iron deficiency, heart failure, ejection fraction, quality of life, renal function

Introduction

Despite evident and wide developments in the treatment of heart failure, patients who suffer this cardiac phenomenon frequently face poor physical functioning, inappropriate exercise tolerance and even disability in daily physical activities (1, 2). These limitations are due to poor cardiac output and existing imbalance between myocardial blood supply and demand (3). In fact, left ventricular dysfunction not only may be caused by prolonged ischemic events or

long congestion, but also, can be due to hemodynamic disturbances and also some metabolic and hormonal defects including severe anemia, immunological reactions, and also endocrine abnormalities (4-6). In this regard, anemia has a special condition because of its important effects on exercise intolerance and oxygenation abnormalities that may results in deterioration of functional capacity as well as in increased risk for morbidity and mortality (7, 8). Thus, the increase in serum hemoglobin level can effectively increase maximum potential oxygen delivery and therefore improve

function capacity. Hence, clearly further evidence from properly controlled trials seems to be necessary. Besides, because anemia has been considered only a rare contributing factor to the worsening of heart failure (11-13), some recent guidelines have not mentioned treatment of anemia for the prevention and treatment of chronic heart failure at all (14). Therefore, the treatment effects of anemia removing regimens in clinical settings which follow these guidelines remain uncertain. The present study hence aimed to assess the effects of therapeutic anti-anemia regimens on functional capacity, clinical manifestation, and also laboratory biomarkers in patients who suffered chronic heart failure and concomitant iron deficiency.

Methods

Study population

In this clinical trial, 25 consecutive patients with concomitant chronic heart failure and iron deficiency who had referred to Day clinic of Shariati hospital in Isfahan, Iran in 2013 were included. The main inclusion criteria was considered patients' consent to enter into the study and the existence of iron deficiency defined as a ferritin level <100 $\mu\text{g/L}$ or ferritin $100\text{-}299$ $\mu\text{g/L}$ with transferrin saturation $<20\%$. In this regard, those with unstable heart failure, hemoglobinopathies, vitamin B12 or folic acid deficiency, or pregnancy were not included. All patients signed the written consent form approved by the research and ethics Review Board at Isfahan university of medical science and the clinical trial was registered in IRCT site (IRCT No. 2013112813828).

Study measurements

On admission, baseline characteristics and clinical data including demographic parameters, anthropometric indices, prevalence of cardiovascular risk factors, and history of oral medications were collected by interviewing and also by reviewing the hospital recorded files if required. To determining the serum biomarkers, 5 ml of venous blood was drawn. The serum hemoglobin level was measured using Hemoglobin

Colorimetric Assay Kit. Serum ferritin level was measured using a human ferritin enzyme immunoassay test. Serum iron and total iron-binding capacity (TIBC) are measured by a modification of the automated AAI-25 colorimetric method. Transferrin saturation was measured using automated spectrophotometric measurement of iron and unsaturated iron binding capacity. Serum creatinine level was also measured using the alkaline picrate (Jaffe) method. Function capacity was assessed using the New York Heart Association (NYHA) classification. 6 minute walk test (6MWT) was measured by walking on a flat route for 6 minutes and then measuring the distance walked by the patient. The total Iron deficit was determined using the following formula (15):

$2/3 \times (\text{normal Hb} - \text{patient's Hb}) \times \text{weight} + 1000$
(for men)

$2/3 \times (\text{normal Hb} - \text{patient's Hb}) \times \text{weight} + 500$
(for women)

To assess the quality of life status, the Short Form Health Survey (SF-36) questionnaire was used that includes a global evaluation of health and covers eight dimensions of health including limitations in physical functioning, usual role activities, social functioning related to health problems, and vitality. The total score range 0 to 100 that the higher score indicates better quality of life status (16). All participants also underwent an echocardiography assessment to determine left ventricular ejection fraction and other probable cardiac abnormalities. The overall prevalence of edema and its response to treatment protocol was also based on physical examination. After initial assessment, the patients administered 200 mg intravenous iron per week till compensating iron deficit. Then, all study parameters were assessed again and compared to before therapeutic intervention.

Statistical analysis

Results were presented as mean \pm standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for categorical variables. The changes in study parameters was assessed using the Paired t test or Wilcoxon signed rank sum test whenever the data did not appear to have normal distribution or when the assumption of

equal variances was violated across the groups. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results

The average age of the patients was 59.88 ± 18.05 years and 40% of them were male. Among different cardiovascular risk factors, the most prevalent factors were hypertension (60%) followed by diabetes mellitus (28%) and hyperlipidemia (28%) (Table 1). Also, the most prevalent oral drugs which administered were statins (48%), Angiotensin Receptor Blockers (ARBs) (48%), aspirin (44%), diuretics (40%), calcium-channel blockers (40%), and digoxin (40%). Comparing NYHA class after therapeutic approach before that showed a significant improvement in functional class so NYHA class III and IV before intervention was revealed in 60% and 16% respectively which reached to 36% and 8% respectively after intervention ($P = 0.017$) (table 2). The prevalence of heart failure-related edema was also significantly reduced from 60% before treatment to 48% after that ($P = 0.036$). The rate of hospitalization was considerably reduced from 42% to 16%, respectively ($P < 0.001$). Moreover, mean of 6MWT

Table 1. Baseline characteristics and clinical data of study population

Variables N(%)	N(25)
Age(Mean \pm SD)	59.88 \pm 18.05
Sex N(%)	
Male	10 (40.0)
Female	15 (60.0)
Risk factors N(%)	
Cigarette smoking	2 (8.0)
Obesity	4 (16.0)
Hyperlipidemia	7 (28.0)
Hypertension	15 (60.0)
Diabetes mellitus	7 (28.0)
Medication N(%)	
ARB	12 (48.0)
Aspirin	11 (44.0)
Medication	7 (28.0)
Diuretics	10 (40.0)
Digoxin	10 (40.0)
Nitrate	2 (8.0)
Statin	12 (48.0)
Warfarin	9 (36.0)
Calcium-blocker	10 (40.0)
Clopidogrel	2 (8.0)
Oral hypoglycemic agents	3 (12.0)
Insulin	3 (12.0)
Spironolacton	1 (4.0)

Data are presented as mean \pm SD or number (%)

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Table 2. Changes in study parameters after treatment before that

Index	Before treatment (n = 25)	After treatment (n = 25)	p-value
	N(%)	N(%)	
NYHA class			0.017
II	6 (24)	14 (56)	
III	15 (60)	9 (36)	
IV	4 (16)	2 (8)	
Edema	15 (60)	12 (48)	0.036
	(Mean \pm SD)	(Mean \pm SD)	
6MWT	155.18 \pm 104.03	187.40 \pm 114.49	< 0.001
LVEF	27.50 \pm 14.19	33.00 \pm 17.03	0.007
Hb	12.73 \pm 1.56	14.30 \pm 1.82	< 0.001
Iron	43.60 \pm 16.19	84.96 \pm 30.28	< 0.001
TIBC	426.20 \pm 54.66	345.44 \pm 42.97	< 0.001
Transferrin	9.96 \pm 4.48	23.83 \pm 9.98	< 0.001
Creatinine	1.06 \pm 0.21	1.10 \pm 0.22	0.037
GFR	75.20 \pm 31.15	68.96 \pm 23.58	0.034
Quality of life score	78.64 \pm 15.44	83.48 \pm 16.32	0.001

Data are presented as mean \pm SD or number (%)

was increased from 155.18 to 187.40 ($P < 0.001$). Comparison of LVEF before and after treatment indicates a significant improvement in this parameter (27.5% versus 33.0%, $p = 0.007$). Mean of serum certainties as a parameter which shows renal function slightly deteriorated after treatment as well as mean of GFRs that decreased despite of other improvements. The treatment of iron deficiency in this group of subjects got a significant improvement in SF36 total score.

Discussion

The findings of our study focused the two points. First, we assessed functional capacity, renal function, need to hospitalization, as well as level of quality of life in the patients. We also assess the beneficial effects of using intra venous iron regimens on these parameters. In first step, we found a considerable prevalence of low functional capacity, and high rate of hospitalization, as well as lowering quality of life level in chronic heart failure patients. In this regard, among all study population, NYHA class III to IV was observed in 76% of patients, appearance of edema was found in 60%, and frequent hospitalization was also revealed in 42% of them. As previously shown, these consequences may potentially lead to high mortality and morbidity in heart failure patients. It has been well shown that serum hematocrit and creatinine levels can predict an increased risk of early and long-term death in heart failure patients (17). It has been well demonstrated that anemia is a powerful factor for predicting adverse outcome in these patients so anemia concomitant with other risk profile such as increased serum creatinine, low function capacity, and lower level of quality of life may have synergistic effects to deteriorate outcome of disease (18). The FAIR-HF study has shown that intravenous iron administration can improve quality of life and exercise capacity in affected patients. A correct diagnosis can easily be arrived at using parameters such as serum ferritin and transferrin saturation. Replenishing iron stores is most useful using the intravenous route, and administered doses need to be adjusted to individual needs. Their results showed in chronic heart failure, relatively mild degrees of anemia are associated with worsened symptoms, functional status and survival (19-20). We also showed that in patients with chronic heart failure, the treatment of iron deficiency results in a marked improvement in their functional status, ejection fraction and also quality of life. Also, treatment of anemia leads to lower hospitalization and thus lower complications may be occurred within hospitalization. Most previous studies found out similar results; however a number of studies could not reveal these beneficial effects might be due to study design as well as small employed sample size. Silverberg and colleagues (21) showed that the mean hemoglobin level and mean left ventricular ejection fraction significantly increased following anti-anemia treatments. Also, the mean number of hospitalizations fell by 91.9% compared with a similar period before the study. The New York Heart Association class (NYHA class) fell significantly, as did the doses of oral and intravenous furosemide. Zhou et al (22) found that the treatment with erythropoietin stimulating agents in patients with symptomatic heart failure and anemia resulted in significant improvements in hemoglobin, hematocrit and brain natriuretic peptide levels, as well as exercise capacity, renal function, NYHA class and left ventricular ejection fraction. In a study by Kapoor et al (23), patients treated with intravenous iron had significant reductions in hospitalizations, adverse events, with improvement in NYHA class, and ejection fraction. In Kansagara et al. survey (24), moderate-strength evidence from systematically reviewed clinical trials of intravenous iron found improved short-term exercise tolerance and quality of life in patients with heart failure, meanwhile high-strength evidence from the trials of erythropoiesis-stimulating agent therapy found they offered no consistent benefits. In an early uncontrolled report from the patients with heart failure and anemia treated with EPO and intravenous iron, it was reported an increase in serum hemoglobin level from 10 to 12 g/dl, an increase in left ventricular ejection fraction from 27% to 35%, a decrease in hospitalizations for heart failure by 91%, an improvement in mean NYHA class from 3.6 to 2.6, and a reduction in the use of diuretics (25). In another report by the same author, the mean NYHA class improved by 42.1%, the left ventricular ejection fraction increased by 5.5%, and the need for oral and intravenous furosemide decrease by 51.3% and 91.3%, respectively. In addition the num-

ber of days spent in hospital compared with the same period of time before entering the study decreased by 79.0% (26). As we did not use erythropoietin in our study subject except in the cases which patients had clinical needs. Thus, based on our study findings iron replacement therapy not only can compensate iron deficit and reserve serum hemoglobin level, but also can effectively improve function class, left ventricular systolic function as well as quality of life in chronic heart failure patients. Our findings did not show any improvement in renal function. On the contrary we found some deterioration in renal function by increase in creatinine (1.06 ± 0.21 increased to 1.1 ± 0.22 , $P = 0.037$) that means decreases in GFR (75.25 ± 31.15 to 68.96 ± 23.58 , $P = 0.034$). Similar to our results another study which was done by Usmanou showed similar changes (27). Mean of serum creatinine in our study as the same of their study was elevated initially but did not change significantly during the 6-month period.

Whereas results of a randomized clinical trial which was done by Gouva showed treating anemia in early stage of renal failure patients slows the decline of renal function (28). However, it should be noted that besides helpful effects of these therapeutic regimens, their related harmful effects should be also considered and patients should be on close follow-up in terms of renal function. In the other hand, it has been revealed that erythropoietic agents may be associated with increased risk of thrombosis (29-31), increased blood pressure (32, 33), seizures and pure red cell aplasia caused by antibody formation against erythropoietin (34). Thus, the beneficial effects of these regimens should be considered besides of their deleterious effects. In our study EPO were used rarely and based on hematologic guidelines.

The study has some limitations. First, the overall prevalence of edema and its response to treatment protocol were based on physical examination indicating reduction in clinical manifestations of edema in exams. So, we did not assess some parameters including weight change, or nutritional habits that were pointed as a limitation. Second, the number of total drugs administered to the patients appears unusually very low. It seems that a small number of drugs administered might be due to non-compliance with medication instructions by the elderly or by those with low socio-

economic level leading inappropriate medication. In this regard, scheduling educational programs should be considered in properly following drug orders.

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