Acta Biomed 2018; Vol. 89, N. 2: 214-219 DOI: 10.23750/abm.v89i2.5020 

Original article

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

*Ahmad Mirdamadi[1], Asadolahi Arefeh[1], Mohammad Garakyaraghi[2], Ali Pourmoghadas[2]*

[1] Islamic Azad university, Najafabad Branch, Isfahan, Iran; [2] Heart Failure Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan 81465-1148, Iran

**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 μg/L or ferritin 100-299 μg/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 AAII-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 × (normal Hb-patient's Hb) × weight + 1000 (for men)

2/3 × (normal Hb-patient's Hb) × 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 ± 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 Reseptor 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

| Variable s N(%) | | N(25) |
|---|---|---|
| Age(Mean ±SD) | | 59.88 ± 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 ± SD or number (%)

**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 ± SD) | (Mean ± SD) | |
| 6MWT | 155.18 ± 104.03 | 187.40 ± 114.49 | < 0.001 |
| LVEF | 27.50 ± 14.19 | 33.00 ± 17.03 | 0.007 |
| Hb | 12.73 ± 1.56 | 14.30 ± 1.82 | < 0.001 |
| Iron | 43.60 ± 16.19 | 84.96 ± 30.28 | < 0.001 |
| TIBC | 426.20 ± 54.66 | 345.44 ± 42.97 | < 0.001 |
| Transferrin | 9.96 ± 4.48 | 23.83 ± 9.98 | < 0.001 |
| Creatinine | 1.06 ± 0.21 | 1.10 ± 0.22 | 0.037 |
| GFR | 75.20 ± 31.15 | 68.96 ± 23.58 | 0.034 |
| Quality of life score | 78.64 ± 15.44 | 83.48 ± 16.32 | 0.001 |

Data are presented as mean ± 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 leftventricular 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 ofdays spent in hospital compared with the same period of time before entering the study decreased by 79.0% (26). As we did not used erythropoietin 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 showed any improvement in renal function. On 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 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 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 regiments, 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 administrated 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.

## Acknowledgment

We wish to acknowledge all staff of Day clinic in Shariati hospital who help us accomplish this study.

## References

1. Freye R. CHD and heart failure. Heart rate reduction guidelines as a therapy target. Med Monatsschr Pharm 2014; 37(7): 269-70.
2. Arena R, Cahalin LP, Borghi-Silva A, Phillips SA. Improving functional capacity in heart failure: the need for a multifaceted approach. Curr Opin Cardiol 2014; 29(5): 467-74.
3. De Boer RA, Pinto YM, Van Veldhuisen DJ. The imbalance between oxygen demand and supply as a potential mechanism in the pathophysiology of heart failure: the role of microvascular growth and abnormalities. Microcirculation 2003; 10(2): 113-26.
4. Anker SD, Al-Nasser FO. Chronicheart failure as a metabolic disorder. Heart Fail Monit 2000; 1(2): 42-9.
5. Bansal D, Chahoud G, Smith ES, Mehta JL. Prevention of heart failure. Curr Opin Cardiol 2006; 21(5): 510-6.
6. Arcopinto M, Cittadini A. Hormonal alterations in heart failure: anabolic impairment in chronic heart failure - diagnostic, prognostic and therapeutic issues. Front Horm Res 2014; 43: 57-69.
7. Alexandrakis MG, Tsirakis G. Anemia in heart failure patients. ISRN Hematol 2012; 2012: 246915.
8. Rangel I, Gonçalves A, de Sousa C, Leite S, Campelo M, Martins E, et al. Iron deficiency status irrespective of anemia: a predictor of unfavorable outcome in chronic heart failure patients. Cardiology 2014; 128(4): 320-6.
9. Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, et al.The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000; 35(7): 1737-44.
10. Coats AJ. Anaemia and heart failure. Heart 2004; 90(9): 977-9.
11. Pisaniello AD, Wong DT, Kajani I, Robinson K, Shakib S. Anaemia in chronic heart failure: more awareness is required. Intern Med J 2013; 43(9): 999-1004.
12. Shah R, Agarwal AK. Anemia associated with chronic heart failure: current concepts. Clin Interv Aging 2013; 8: 111-22.
13. Rangel I, Gonçalves A, de Sousa C, Leite S, Campelo M, Martins E, Amorim S, Moura B, Silva Cardoso J, Maciel

MJ. Iron deficiency status irrespective of anemia: a predictor of unfavorable outcome in chronic heart failure patients. Cardiology 2014; 128(4): 320-6.
14. Lainscak M, von Haehling S, Springer J, Anker SD. Biomarkers for chronic heart failure. Heart Fail Monit 2007; 5(3): 77-82.
15. Cook JD, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood 2003; 101(9): 3359-64.
16. Patel AA, Donegan D, Albert T. The 36-item short form. J Am Acad Orthop Surg 2007; 15(2): 126-34.
17. McClellan WM1, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospitals: a population-based study. J Am Soc Nephrol 2002; 13: 1928-36.
18. Horwich TB1, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. J Am CollCardiol 2002; 39: 1780-6.
19. Gutzwiller FS, Pfeil AM, Comin-Colet J, Ponikowski P, Filippatos G, Mori C, Braunhofer PG, Szucs TD, Schwenkglenks M, Anker SD. Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. Int J Cardiol 2013; 168(4): 3878-83.
20. Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Lüscher TF, Mori C, Willenheimer R, Ponikowski P, Anker SD. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. Eur Heart J 2013; 34(1): 30-8.
21. Silverberg DS, Wexler D, Iaina A. The role of anemia in the progression of congestive heart failure. Is there a place for erythropoietin and intravenous iron? J Nephrol 2004; 17(6): 749-61.
22. Zhou S, Zhuang Y, Zhao W, Jiang B, Pan H, Zhang X, Peng H, Chen Y. Protective roles of erythropoiesis-stimulating proteins in chronic heart failure with anemia. Exp Ther Med 2014; 8(3): 863-870.
23. Kapoor M1, Schleinitz MD, Gemignani A, Wu WC. Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis. Cardiovasc Hematol Disord Drug Targets 2013; 13(1): 35-44.
24. Kansagara D, Dyer E, Englander H, Fu R, Freeman M, Kagen D. Treatment of anemia in patients with heart disease: a systematic review. Ann Intern Med 2013; 159(11): 746-57.
25. Silverberg DS, Wexler D, Blum M, Tchebiner JZ, Sheps D, Keren G, et al. The effect of correction of anaemia in diabetics and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron. Nephrol Dial Transplant 2003; 18(1): 141-6.
26. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001; 37: 1775-80.
27. Usmanov RI, Zueva EB, Silverberg DS, Shaked M. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. J Nephrol 2008; 21(2): 236-42. PubMed PMID: 18446719.
28. Gouva C, Nikolopoulos P, Ioannidis JP, Siamopoulos KC. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int 2004; 66: 753-760.
29. Valles J, Santos MT, Aznar J, Martinez M, Moscardo A, Pinon M, Broekman MJ, Marcus AJ. Platelet-erythrocyte interactions enhance alpha (IIb) beta(3) integrin receptor activation and P-selectin expression during platelet recruitment: down-regulation by aspirin ex vivo. Blood 2002; 99: 3978-84.
30. Diaz-Ricart M, Etebanell E, Cases A, Lopez-Pedret J, Castillo R, Ordinas A, Escolar G. Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. Thromb Haemost 1999; 82: 1312-7.
31. Fuste B, Serradell M, Escolar G, Cases A, Mazzara R, Castillo R, Ordinas A, Diaz-Ricart M. Erythropoietin triggers a signaling pathway in endothelial cells and increases the thrombogenicity of their extracellular matrices in vitro. Thromb Haemost 2002; 88: 678-85.
32. Mann JF. Hypertension and cardiovascular effects-long-term safety and potential long-term benefits of r-HuEPO. Nephrol Dial Transplant 1995; 10(Suppl 2): 80-4.
33. Vaziri ND. Mechanism of erythropoietin-induced hypertension. Am J Kidney Dis 1999; 33: 821-8.
34. Maschio G. Erythropoietin and systemic hypertension. Nephrol Dial Transplant 1995; 10 (Suppl 2): 74-9.

Received: 5 December 2015
Accepted: 7 June 2016
Correspondence:
Ali Pourmoghadas, Cardiologist,
Associate Professor, Heart Failure Research Center,
Isfahan Cardiovascular Research Institute,
Isfahan University of Medical Sciences,
Isfahan 81465-1148, Iran