The Effect of Iron Injection on Six Minute Walking Test and Quality of Life in Patients with Heart Failure and Iron Deficiency

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ABSTRACT

Background: Chronic heart failure (CHF) patients are usually faced with reduced physical function, inappropriate sport tolerance and inability for daily activities. Studies showed that increasing serum hemoglobin (Hb) level in CHF can increase the maximum oxygen delivery and the consequent functional capacity. We aimed to assess this finding. **Material and Methods:** This single-arm clinical trial study was conducted on patients with CHF between March 2019 and 2020 in our hospital. In baseline, NYHA function class and 6-minute walking test (6MWT) were recorded. Persian standard version of health-related quality of life (Iranian-QoL) questionnaire and visual analogue scale (VAS) for fatigue were also administered to patients. After calculating the required dose of elemental iron, intravenous ferric carboxymaltose solution was infused in 1000 mg dosage for patients with hemoglobin level of more than 11 mg/dl (anemia) and in 500 mg dosage for patients with hemoglobin level of more than 14 mg/dl (without anemia). All the examinations were repeated after 12 weeks. **Results:** Eventually, 50 (20 male and 30 female) patients with a mean age of 58.88 ± 17.05 years underwent analysis. The mean distance in 6MWT was significantly increased from baseline (mean±SD change: 17±6m, $p < 0.001$). In addition, the mean fatigue and quality of life scores were significantly improved 12 weeks after treatment in comparison to the baseline (P<0.001). **Conclusion:** a one-cycle treatment with intravenous ferric carboxymaltose can efficiently improve the functional capacity and quality of life in patients with chronic heart failure who suffer from iron deficiency, with and without anemia.

Keywords: Iron Deficiency Anemia; Heart Failure; Quality of Life; Six Minute Walking Test

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INTRODUCTION

Involving about 64 million people worldwide, chronic heart failure (CHF) is a major cause of hospitalization in elderly people which imposes a remarkable socioeconomic burden on health care systems (1). Despite notable progresses in management of CHF, patients are usually faced with reduced physical function, inappropriate sport tolerance and even inability for daily regular activities (2, 3). These limitations are mostly related to diminished cardiac output and imbalance between blood supply and demand in myocardium (4, 5).

Thus, anemia may lead into reduced physical function and increased risk of morbidity and mortality in patients with CHF (6, 7). Thus, increasing serum hemoglobin (Hb) level can effectively increase the maximum oxygen delivery and the consequent functional capacity. As the anemia is a rare cause of exacerbation of heart failure, no clinical guidelines have been yet provided for management and prevention of anemia in all types of heart failure (8).

Previous studies have shown the desirable effects of combined treatment of anemia with erythropoietin and intravenous iron infusion on cardiac function, symptoms and cardiac oxygen consumption in patients with anemia and CHF (9). However, few studies have evaluated the isolated role of intravenous iron infusion in these patients.

Thus, in the present study, we aimed to evaluate the effect of intravenous ferric carboxymaltose solution on the six-minute walking test, quality of life and fatigue in patients with iron deficiency and chronic heart failure, with and without anemia.

MATERIAL AND METHODS

This single-arm clinical trial study was conducted on patients with chronic heart failure (CHF) who attended cardiology clinic of Shahid Modarres Hospital (Tehran, Iran), between March 2019 and March 2020. The protocol of the trial was registered at ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1398.890) and Iranian Registry of Clinical Trials (Ref. No. IRCT20200102045981N1). Figure 1 shows a flow diagram of the study. Patients with confirmed diagnosis of CHF (based on echocardiography, symptoms and left ventricular ejection fraction (LVEF) of ≤45% or >45%) were assessed for eligibility. We included patients with New York Heart Association (NYHA) function class of II or III, and iron deficiency (serum ferritin level of less than 100 ng/mL, or ferritin level between 100 and 299 ng/mL and transferrin saturation (TSAT) of less than 20%). We excluded patients with unstable heart failure, hemoglobinopathy, vitamin B12 or folic acid deficiency, uncontrolled high blood pressure, inflammation, and significant liver or kidney dysfunction, as well as pregnant women. Patients signed a written informed consent form prior to entering the study.

In baseline visit, age and gender as well as data on past medical history, physical examination, Hemoglobin level, mean cell volume (MCV), transferrin saturation (TS), serum Iron, total iron binding capacity (TIBC), 12-lead electrocardiogram, NYHA function class and 6-minute walking test (6MWT) were recorded in a pre-designed checklist. Persian standard version of health-related quality of life (Iranian-QoL) questionnaire (10) and visual analogue scale (VAS) for fatigue were also administered to patients. After calculating the required dose of elemental iron (2/3 × [normal Hb-patient's Hb] × weight + 1000 [for males] or 500 [for females]), intravenous ferric carboxymaltose (FCM) solution (Ferinject®/Injectafer® Vifor Pharma) was infused in 1000 mg dosage for patients with hemoglobin level of more than 11 mg/dl (with anemia) and in 500 mg dosage for patients with hemoglobin level of more than 14 mg/dl (without anemia). All the examinations were repeated after 12 weeks.

Data were analyzed using Statistical Package for Social Sciences (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Descriptive analysis was performed using mean and standard deviation as well as percentages and frequencies. Kolmogorov-Smirnov test was used to check the normal distribution of data. Changes within the group was tested using Paired t-test or Wilcoxon signed rank test. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

Eventually, 50 (20 male and 30 female) patients with a mean age of 58.88 ± 17.05 years underwent analysis. Figure 2 summarizes the prevalence of comorbidities. Hypertension was the most common (62%) cardiovascular risk factor followed by diabetes mellitus (25%), hyperlipidemia (25%) and smoking (8%). Table 1 summarizes the baseline and final serum levels of hematologic factors. All these factors were significantly improved after 12 weeks (P<0.001).

The mean distance in 6MWT was significantly increased from

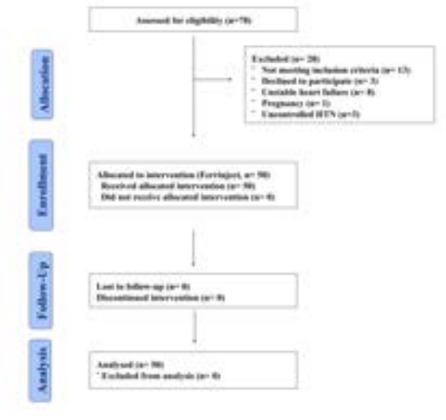

Figure 1. Study flowchart (CONSORT trial flow diagram)

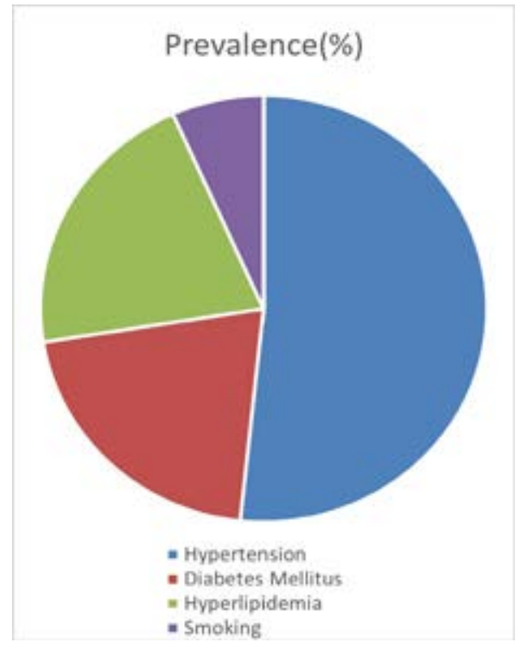

Figure 2. Distribution and prevalence of comorbidities in patients.

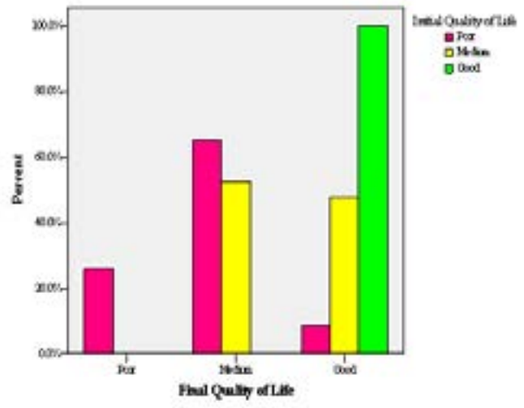

Figure 3. Changes in quality of life before and after intervention.

baseline (mean±SD change: 17±6m, p < 0.001). In addition, the mean quality of life score was significantly improved 12 weeks after treatment in comparison to the baseline (P<0.001).

Table 2 shows a cross tabulation and figure 3 shows a chart of primary and final quality of life evaluations. Number of people with poor quality of life was decreased from 23 to 6 and number of people with medium quality of life was increased from 21 to 26. Only 6 patients had a good quality of life at baseline which were increased to 18 after the intervention. Findings suggest that quality of life has been generally improved after a course of treatment (p<0.001).

Patients were also analyzed in two heart failure with preserved ejection fraction)HFpEF(and heart failure with reduced ejection fraction)HFrEF(subgroups. The improvement of quality of life and 6MWT was statistically significant for patients in HFrEF subgroup (p<0.05). However, these improvements were not statistically significant for patients in HFpEF subgroup (p>0.05).

DISCUSSION

Iron metabolism in chronic heart failure has not been exactly discovered and there is a need for further studies to concisely assess this process(11). Previous studies have found some relationships between proinflammatory factors such as interleukin (IL)-1, tumor necrosis factor-α (TNF- α) and IL-6 with iron homeostasis. These proinflammatory factors, which have a determining role in progress of CHF, stimulate retention of iron in macrophages through downregulation of ferroportin expression, a protein which plays an important role in transferring the absorbed iron to systemic circulation (12-14). Thus, this limited iron availability results in restricted erythropoiesis and consequent anemia.

Table1. Changes in serum levels of hematologic factors at baseline and 12 weeks after the intervention.

Variables	Mean ±S D	95%CI	P-Value
Initial Hemoglobin	12.76±1.33	-.872/-.448	<0.001
Final Hemoglobin	13.42±1.03		
Initial MCV	79.36±2.16	-1.022/-.698	<0.001
Final MCV	80.22±1.98		
Initial TS	20.76±1.66	-2.251/-1.509	<0.001
Final TS	22.64±1.90		
Initial Serum Iron	51.66±6.40	-3.74/-2.646	<0.001
Final Serum Iron	54.86±6.34		
Initial TIBC	325.58±7.70	-14.725/-9.395	<0.001
Final TIBC	337.64±12.18		

MCV: mean cell volume; TS: transferrin saturation; TIBC: total iron binding capacity

Table2. Cross tabulation of primary and final quality of life evaluations

		Final Quality of life			
		Poor	Medium	Good	Total
Initial Quality of life	Poor	6 (26.1%)	15 (65.2%)	2 (8.7%)	23 (100%)
	medium	0 (.0%)	11 (52.4%)	10 (47.6%)	21 (100%)
	Good	0 (.0%)	0 (.0%)	6 (100%)	6 (100%)
		6 (12.0%)	26 (52.0%)	18 (36.0%)	50 (100%)

Irrespective of anemia, iron deficiency (ID) is a common comorbidity in heart failure (HF) which is present in nearly 50% of patients with chronic stable and 70% of patients with acute HF(15, 16). In addition, it has been shown that ID affects quality of life and functional capacity of HF patients (16).

The effect of iron replacement therapy has been previously investigated in several studies. The results of IRONOUT HF trial showed that oral iron replacement therapy did not improve the exercise capacity or iron deficiency in patients with HF (17). On the other hand, various studies which have prescribed iron injection for HF patients, showed that this intervention is effective for both correcting iron deficiency and improving functional capacity (18, 19).

We found that treatment with intravenous FCM can effectively improve the quality of life score as well as six-minute walking test (6MWT) in patients with chronic heart failure and iron deficiency (ID), with and without anemia. There are a few similar clinical trial studies which have assessed the effect of intravenous FCM on quality of life and functional capacity of patients with heart failure.

In a similar study by TJ Yeo et al., they evaluated the effect of single-dose injection of 1000 mg of FCM in patients with acute decompensated heart failure and iron deficiency (20). They reported that 6MWT was improved in both treatment and placebo groups at the 12th week; however, it was slightly higher in treatment group. They suggested that patients should be followed up for a period over 12 weeks to assess the effects of background therapy.

A multi-center double-blind randomized trial (CONFIRM-HF) has evaluated the effect of intravenous FCM in iron-deficient patients with heart failure (21). They evaluated 304 symptomatic HF patients with reduced ejection fraction and treated them with either intravenous FCM or saline (as placebo) for 52 weeks. Authors had considered 500 mg or 1000 mg dosages at correction phase and a maintenance dosage of 500 mg at 12th, 24th and 36th weeks, in case of continued iron deficiency. They concluded that treatment with FCM over a one-year period results in improved functional capacity and quality of life which is in agreement with the results of the present study in which we had only injected a single dosage of FCM and followed patients for 12 weeks.

The present study had some limitations. We had limitations in patient selection based on the inclusion and exclusion criteria for the present study. In addition, the COVID-19 pandemic made the visits and follow ups more difficult to conduct. Moreover, we could not consider a control arm according to our financial source limitations.

CONCLUSION

In conclusion, we found that a one-cycle treatment with intravenous ferric carboxymaltose can efficiently improve the functional capacity and quality of life in patients with chronic heart failure who suffer from iron deficiency, with and without anemia. We suggest further studies to consider the maximum oxygen uptake (VO2max) to evaluate the functional capacity in patients with heart failure as it can provide more accurate results than 6MWT. Also, according to high prevalence of underlying disorders such as diabetes, hypertension and renal failures in patients with heart failure, their effects should be taken into account in future researches.

ETHICAL CONSIDERATION

All stages of the study were reviewed and approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. We adhered to all the provisions of the Helsinki declaration. In addition, all the patients participating in this study signed an informed consent form

CONFLICT OF INTERESTS

There are no conflicts of interest in terms of the present manuscript.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request..

ABBREVATIONS

CHF; chronic heart failure, Hb; hemoglobin, 6MWT; 6-minute walking test, VAS; visual analogue scale, Iranian-QoL; Persian standard version of health-related quality of life, TSAT; transferrin saturation, MCV; mean cell volume, TS; transferrin saturation, TIBC; serum Iron, total iron binding capacity, IL; interleukin, TNF- α; tumor necrosis factor-α, ID; iron deficiency, HF, heart failure.

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