https://doi.org/10.3329/jicc.v5i2.75804

ORIGINAL ARTICLE

Effect of Intravenous Iron on Functional Capacity in Patients with Ischemic Cardiomyopathy

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Abstract

Background: Iron deficiency is common in heart failure with reduced ejection fraction. Intravenous (IV) iron supplementation has been found to reduce morbidity in heart failure. However, the effect of IV iron on Bangladeshi patients with heart failure are not known.

Objects: The study was done to see the effect of IV iron on functional capacity in Bangladeshi patients with ischaemic cardiomyopathy (ICM) and iron deficiency.

Methodology: In this quasi-experimental study, out of 80 hospitalized patients with ICM and iron deficiency, 40 were given IV ferric carboxymaltose (FCM) in addition to standard therapy of heart failure, while another 40 were randomized to standard therapy alone. Primary outcome measure was changes in six-minute walk test (6MWT) distance, while secondary outcome measures were changes in New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and plasma NT-proBNP at Weeks 4 and 12.

Results: 6MWT distance improved significantly in patients receiving IV iron therapy compared to the patients not receiving IV iron. LVEF improved and plasma NT-proBNP decreased significantly in IV iron-treated patients than in patients receiving standard therapy. However, improvement in NYHA functional class was not statistically significant.

Conclusion: In Bangladeshi patients with ICM and iron deficiency, IV FCM on top of standard heart failure therapy was associated with improved functional capacity.

Keywords: Heart Failure, Cardiomyopathy, Ferric Carboxymaltose, Bangladesh.

J Inv Clin Cardiol 2023; 5(2): 32-37

Introduction

Ischaemic cardiomyopathy (ICM) is a state of left ventricular systolic dysfunction due to coronary artery disease (CAD).[1] It is one of the end-stage sequalae of CAD, and is an important cause of heart failure. In fact, CAD is considered the most common cause of heart failure which affects 1–2% of the general population and 10% of people e”70 years.[2] On the other hand, despite state-of-the-art treatment including angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and spironolactone, survival and relief from symptoms still are unacceptably poor in patients with chronic heart failure.[3] In a population-based cohort study in the UK over 2000 to 2017, overall, 1-, 5-, and 10-year survival rates increased by 6.6% (from 74.2% in 2000 to 80.8% in 2016), 7.2% (from 41.0% in 2000 to 48.2% in 2012), and 6.4% (from 19.8% in 2000 to 26.2% in 2007), respectively.[4] To improve the prognosis of heart failure, including those due to ICM, there is a continuous evolution in the management strategy of heart failure. Recently, angiotensin receptor-neprilysin inhibitor (ARNI), and sodium-glucose cotransporter 2 inhibitor (SGLT2) have been added to the existing armamentarium in the battle against heart failure. Side by side, special attention has been paid to explore and deal with other loopholes in relation to heart failure including ICM – presence of concomitant iron deficiency is one of them. Approximately 50% of patients with heart failure have concurrent iron deficiency with or without anaemia.[5-7] Within a heart

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failure population, iron deficiency is associated with a worse prognosis.[8,9]

Given the significance of iron deficiency in heart failure, several randomized controlled trials (RCTs), including FAIR-HF, CONFIRM-HF, EFFECT-HF, and AFFIRM-AHF, have demonstrated significant benefit in terms of functional capacity and heart failure hospitalization.[10-2] Among Southeast Asian patients hospitalized with decompensated heart failure, single-dose Intravenous (IV) ferric carboxymaltose (FCM) administered pre discharge did improve functional capacity in PRACTICE-ASIA-HF study.[13] Despite paucity of statistics, heart failure appears to be common in Bangladesh. Also, ICM as a cause of heart failure may be common as well. In a hospital-based cross-sectional study carried out at the National Institute of Cardiovascular Diseases (NICVD), Dhaka Bangladesh, ICM was the commonest cause of heart failure (n=153, 40.75%).[14] But, the effect of intravenous iron in Bangladeshi heart failure patients, specially those with ICM, has not been studied adequately. Therefore, the present study was done to evaluate the efficacy of intravenous iron in Bangladeshi patients with ICM.

Methods:

Study design

This was a quasi-experimental study conducted in NICVD, Dhaka, Bangladesh. The study protocol was approved by the Ethical Review Committee (ERC) of NICVD, and the study was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki on ethics in medical research and International Conference on Harmonization guidelines for Good Clinical Practice. Written informed consent was obtained from all participants.

Eligibility

All patients of either sex aged >18 years hospitalized for heart failure (diagnosed clinically based on the European Society of Cardiology guidelines) with NYHA functional class II or more and LVEF <40%, and with concurrent iron deficiency (defined as serum ferritin < 100 ìg/L, or serum ferritin 100-299 ìg/L with transferrin saturation < 20%) were eligible for the study. Patients with acute myocardial infarction (MI) within 30 days, valvular or congenital heart disease, pregnancy or postpartum, chronic kidney disease, chronic pulmonary disease, cor pulmonale, stroke, malignancy, haemoglobinopathy, active bacterial infection, and known hypersensitivity to FCM were excluded.

Screening and randomization

Subjects were randomized in a 1:1 ratio to FCM in addition to standard therapy, or standard therapy alone.

Study treatment

Active treatment included two doses of FCM solution (Ferisen, Healthcare Pharmaceuticals Ltd.) 1000 mg/ 20 mL given slow IV bolus injection over 15 min – the first dose during index hospitalization, and the second dose 6 weeks after the 1st dose during the first follow up.

Assessments

The study subjects underwent physical examination, laboratory investigations including serum iron profile (serum ferritin, serum iron, total iron binding capacity, and transferrin saturation), plasma NT-proBNP, complete blood count, random blood sugar, serum creatinine, and routine urinalysis, and electrocardiography (ECG) and echocardiography. Functional capacity was assessed by six-minute walk test (6MWT) done at baseline upon stabilization of heart failure prior to administration of treatment. Plasma NT-proBNP was assayed by chemiluminescence immunoassay using the ALINITY I immunoassay system (Abbott Laboratories, Abbott Park, Illinois, U.S.A.). Echocardiographic examination was carried out by Philips EPIQ 7C Premium Cardiology Ultrasound System (Koninklijke Philips N.V., Amsterdam, Netherlands) following the recommendations of the American Society of Echocardiography (ASE).[15,16] 6MWT was performed as per American Thoracic Society 2002 guidelines[17], and the 6MWT distance was determined during index hospitalization before giving the IV iron.

Follow up was done twice – at 6 weeks, and at 12 weeks. At each follow up, each patient was evaluated by history, physical examination, and investigations with particular attention to NYHA functional class, plasma NT-proBNP, echocardiography, and 6MWT. The findings were recorded in the predesigned form.

Study endpoints

The primary endpoint was change in 6MWT distance over the 12 week period. The secondary endpoints were changes in NYHA functional class, plasma NT-proBNP, and left ventricular ejection fraction (LVEF) at Weeks 4 and 12.

Statistical considerations

The sample size was calculated as follows:

The equation for computing sample size (n) is $n= Z^2pq/e^2$

Here,

n = required sample size

Z = confidence level at 95% (standard value of 1.96)

p = estimated prevalence

q = 1-p
e = margin of error at 5% (standard value of 0.05)
Here, p = 0.050, and q=1-0.050= 0.95
$(1.96)^2$ x 0.050 x 0.95/ $(0.05)^2$

So, n = 72

Considering non-response and unavailability of some study subjects, the targeted sample size for the study was 72+8 = 80.

The sample was divided into two groups – Group I comprised of 40 patients treated with IV iron in addition to standard therapy of heart failure, and Group II comprised of 40 patients treated with standard therapy of heart failure alone.

Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS) program for Windows, version 10.0. Data was expressed as mean ± SD or percentages for categorical variables. Comparability of both groups at baseline was confirmed using the Student's t test for independent series. The changes in parameters after treatment was compared using repeat measures analysis of variance. A two-tailed p value of 0.05 or less was considered significant.

Results

A total of 80 patients heart failure and ICM were randomized into two groups: Group I comprised of 40 patients who received IV iron, and Group II comprised of 40 patients who did not receive IV iron. Baseline characteristics did not differ significantly between the two groups except for the blood sugar which was higher in Group II. (Table I)

Table-I

Baseline characteristics of the study patients (N=80)

Trait	Group I(n=40)	Group II (n=40)	*p* value
Sex			
Male (n, %)	18 (45.0)	26 (65.0)	0.204
Female (n, %)	22 (55.0)	14 (35.0)	
Age, years (SD)	54.9 (11.53)	56.26 (13.16)	0.165
Cardiovascular risk factors			
Hypertension (n, %)	24 (60.0)	22 (55.0)	0.749
Diabetes (n, %)	18 (45.0)	26 (65.0)	0.204
Dyslipidemia (n, %)	06 (15.0)	04 (10.0)	0.632
Smoking (n, %)	02 (5.0)	04 (10.0)	0.548
History of MI (n, %)	30 (75.0)	28 (70.0)	0.723
Renal impairment (n, %)	08 (20.0)	04 (10.0)	0.376
NYHA functional class			
I (n, %)	00 (0.0)	00 (0.0)	0.815
II (n, %)	12 (35.0)	12(35.3)	
III (n, %)	12 (30.0)	06(17.6)	
IV (n, %)	16 (47.1)	16(47.1)	
Medication			
Beta blocker (n, %)	14 (35.0)	10(25.0)	0.490
ACE inhibitor (n, %)	06 (15.0)	10(25.0)	0.429
Valsartan-sacubitril (n, %)	16 (60.0)	10 (25.0)	0.311
Digoxin (n, %)	24 (60.0)	14(35.0)	0.744
Diuretics (n, %)	30 (75.0)	32(80.0)	0.705
Biochemistry			
Hb, g/dL (SD)	11.32 1.6)	12.25 (1.7)	0.875
Blood sugar, mmol/L (SD)	8.53 (3.0)	10.04 (6.6)	0.005
Serum creatinine, mg/dL (SD)	1.31 (0.5)	1.19 (0.4)	0.267
Plasma NT-proBNP, ng/mL (SD)	6431.48 (9491.1)	5065.07 (5796.2)	0.420
LVEF, % (SD)	29.92 (8.4)	31.66 (12.1)	0.645
6MWT distance, m (SD)	132.50 (123.6)	152.63 (155.9)	0.205

ACE, angiotensin-converting enzyme; MI, myocardial infarction; Hb, haemoglobin; LVEF, left ventricular ejection fraction; m, meter; NYHA, New York Heart Association; SD, standard deviation; 6MWT, 6-minute walk test.

The primary outcome measure, i.e., 6MWT distance improved significantly in Group 1 patients receiving IV iron therapy compared to Group II patients not receiving IV iron. (Table 2, Figure 1) Among the secondary outcome measures, LVEF improved and plasma NT-pro BNP decreased significantly in Group I than in Group II. After intervention with IV iron, compared to the Group II, numerically more patients in Group I shifted from NYHA functional class IV and III to NYHA functional class II and I, indicating improvement of functional class, however, the differences between the groups did not reach statistical significance. (p>0.05) (Table 2)

Table-II

Comparison of outcome parameters of the study patients in follow-up (N=40)

Outcome measure	1st follow up			2nd follow up		
	Group I	Group II	*p* value	Group I	Group II	*p* value
6MWD, m	281.50	197.75		385.50	200.00	0.000
(SD)	(130.6)	(110.5)	0.035	(138.3)	(83.9)	
NYHA class						
‘!, n (%)	00	00		06	00	
	(0.0)	(0.0)		(15.0)	(0.0)	
a!, n (%)	20	10		28	14	
	(50.0)	(25.0)	0.436	(70.0)	(35.0)	0.765
b!, n (%)	18 (45.0)	16		6	14	
		(40.0)		(15.5)	(35.0)	
c!, n (%)	02	14		00	12	
	(5.0)	(35.0)		(0.0)	(30.0)	
LVEF (%)	38.75 (6.9)	32.25 (8.1)	0.010	47.70 (8.4)	36.74(12.3)	0.002
Plasma NT-proBNP,	2286.01	4935.99	0.44	1446.09	4804.23	0.015
ng/mL (SD)	(2705.6)	(6220.2)		(1647.3)	(5558.6)	

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation; 6MWD, 6-minute walk distance.

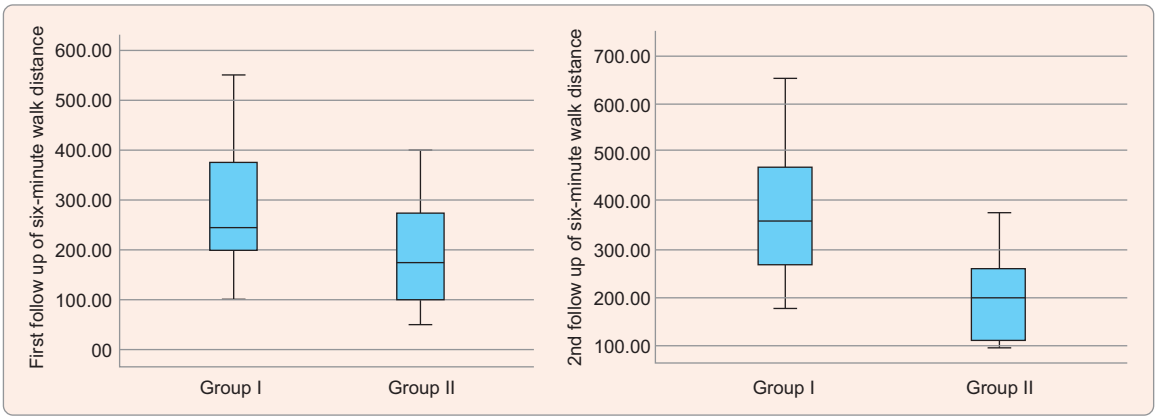

Figure 1: *Six-minute walk test distance of study subjects in follow up.*

Discussion

This open-label study involved 80 patients with ICM divided into two groups: Group I comprised of 40 patients who received IV iron, and Group II comprised of 40 patients who did not receive IV iron. The primary outcome measure was the change in 6MWT distance, whereas the secondary outcome measures were changes in NYHA functional class, LVEF, and plasma NT-proBNP in ICM patients with and without IV iron therapy.

6MWT distance and LVEF improved, and plasma NT-proBNP decreased significantly in IV iron group compared to the standard therapy group. 6MWT distance was used as a primary outcome measure in CONFIRM-HF[11] and PRACTICE-ASIA-HF[13] studies. In both RCTs, significant improvement in 6MWT distance occurred.

Among the secondary outcome measures, LVEF increased significantly in IV iron-treated ICM patients compared to the patients receiving standard therapy. Improvement in LVEF was found in 6-month follow-up in the patients treated with IV iron in the study by Toblli et al.[18] In the present study, plasma NT-pro BNP decreased significantly from baseline in follow ups in both the groups. When compared, the mean plasma NT-pro BNP was significantly lower in iron-treated patients than in non-iron-treated patients. Reduction in plasma NT-pro BNP was found in 6-month follow-up period in the patients treated with IV iron in the study by Toblli et al.[18] In EFFECT-HF trial, FCM had no significant effect on plasma BNP, however, a statistically significant lower increment in NT-pro BNP was observed in FMC-treated group compared to the standard-treatment group at 24 weeks.[12] In the present study, improvement in NYHA functional class was noted in follow up in patients receiving IV iron, as well as, in those receiving standard therapy alone, but for the former, the differences were statistically significant. When the groups were compared, after intervention with IV iron in 1st and 2nd follow-ups, however, the differences between the groups in changes in NYHA functional class did not reach statistical significance. In FERRIC-HF[19], FAIR-HF[10], CONFIRM-HF[11], and EFFECT-HF[12] study, improvement in NYHA functional class was observed often in longer follow up. Our study involved only 12 weeks of follow up; this shorter follow up may be an explanation for failure to reach statistical significance in improvement in NYHA functional class between the groups.

The study has got some limitations. This was an open-label study, so, there was a risk of bias. The sample-size was also relatively small. Because of ongoing COVID-19 pandemic, the timeframe could not be maintained properly. Iron deficiency may or may not accompany anaemia; subgroup analysis involving those with and without anaemia was not done. Fixed doses of FCM were used for all in the present study, but the change in iron status as a result of IV iron administration might be different in the study subjects. Also, effect of IV iron on hospitalization due to heart failure was not addressed.

Conclusion

In patients with ischaemic cardiomyopathy and iron deficiency, administration of IV iron in addition to the standard therapy of heart failure, is associated with improvement of functional capacity. Compared to those not receiving IV iron, 6MWT distance and LVEF increase, NYHA functional class improves, and plasma NT-pro BNP decreases in patients receiving IV iron.

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