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Short-Term Intravenous Iron Therapy with Ferric Carboxy-Sucrose versus Oral Iron in Patients with Symptomatic Heart Failure with Reduced Ejection Fraction and Iron Deficiency

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Abstract

To evaluate the efficiency and safety of short-term I.V. iron therapy with ferric carboxy sucrose versus oral iron with ferrous glycine sulfate complex therapy in heart failure (HF) with reduced ejection fraction patients with iron deficiency. A randomized clinical trial on a total of 50 stable HFrEF patients (mean age 50 ±11.6 years) were enrolled in the study between October 2018 to April 2020. The patients were recruited from Cardiology outpatient clinic & inpatient Cardiology department, Beni- Suef University hospital. (25 patients) received oral ferrous glycine sulfate complex and (25 patients) received IV ferric carboxy sucrose. All patients were subjected to; recording of demographic data, full clinical examination, and laboratory and imaging investigations and six-minute walk test (6MWT). Results showed that apart from EF, all parameters improved significantly after iron therapy (regardless of route of therapy) as regards LVED, LVES, serum iron, serum ferritin, transferrin saturation, 6MWT & NYHA classification. There was a significant negative correlation between the improvement of transferrin saturation & the NYHA classification after intravenous iron therapy. There was a significant weak positive correlation between iron improvement & 6MWT improvement in all 50 patients. Also, a trend towards a weak positive correlation between iron improvement by intravenous route &

improvement of 6 MWT was observed. Regardless the route of administration, iron therapy (I.V. iron therapy in the form of ferric carboxy-sucrose or oral iron in the form of ferrous glycine sulfate complex) is safe & effective in improving functional capacity of HFrEF patients with iron deficiency. This improvement is proportional to the degree of improvement in transferring saturation obtained by IV ferric carboxy-sucrose therapy.

1. Introduction:

With the constantly increasing prevalence and incidence, heart failure (HF) has now become an epidemic problem carrying relevant medical, social, and economic consequences [1]. Despite recent developments in HF management, the morbidity and mortality in this clinical syndrome remain unacceptably high and many patients suffer from debilitating symptoms adversely affecting their quality of life [2_4]. Cardiovascular and non-cardiovascular co-morbidities often complicate the natural course of HF with deleterious impact on clinical status, symptoms, and HF progression, thus constituting targets for potential intervention [2], [5]. Iron deficiency (ID) is one of the most common nutritional deficiencies worldwide, affecting one-third of the general population [6]. Several chronic disorders may be complicated by ID [6_9], but only recently ID has been also reported as a frequent co-morbidity in stable HF patients regardless of ejection fraction [10-12] and in patients admitted to hospital due to worsening HF [13]. Mechanisms underlying the development of ID in HF have not been rigorously investigated, but ID may be a consequence of impaired iron absorption, augmented gastro-intestinal loss, and reduced availability of utilizable iron from the reticuloendothelial system [14]. Heart failure complicated with ID is associated with impaired functional capacity, poor quality of life, and increased mortality [10_15]. Interestingly, opposite to the traditional view, deleterious consequences of ID in HF syndrome are irrespective of anemia and other important confounders (e.g., age, severity of the disease, renal function) [10_15]. Thus, correction of ID itself can be considered an attractive therapeutic target in HF, and this hypothesis has been recently tested in a few clinical studies [8, 14]. There's deficiency in IV iron sucrose in Egypt & IV iron carboxy maltose is absent. Ferrous carboxy maltose (FCM) [Ferinject® or Injectafer®, Vifor (International) Inc., Zurich, Switzerland] is useful for rapid and high-dose replenishment of depleted iron stores [16_18]. It has been observed that serum iron concentration

increases rapidly after administration of a single dose of IV FCM equivalent to 100–1000 mg of iron [19]. FCM is rapidly distributed from plasma not only to bone marrow, but also liver and spleen [20]. Rapid iron uptake by the bone marrow occurs in the first 10 min following FCM administration, with subsequent uptake occurring at a slower but steady rate. The available formula in Egypt [IV iron sucrose (ISC) (Venofer, Vifor Pharma Ltd.)] contains iron (III)-hydroxide sucrose complex. In healthy volunteers, a single dose of ISC equivalent to 100 mg of elemental iron is quickly cleared from serum, with a half-life of 5 ± 2 h [21]. Renal elimination is negligible (on average <5%). Serum ferritin level increases significantly after 8–10 h and doubles after 24 h. In anaemic patients, a single-dose administration of radiolabelled ISC equivalent to 100 mg of elemental iron is followed by rapid uptake of this microelement by the liver, spleen, and bone marrow, reaching maximum rates at 10, 20 and 100 min after an administration, respectively [22]. Up to 97% of administered iron is utilized for erythropoiesis, and both ferritin and transferrin saturation (TSAT) return to baseline levels within 3– 4 weeks. The extensive safety and tolerability record of ISC (including a low prevalence of hypersensitivity reactions) supports the recommendations of the European Medicines Agency (2013) that a test dose need no longer be applied prior to ISC administration. Special caution is recommended with every dose of IV iron instead, even in patients who responded well previously.

Herein, we will evaluate the efficiency (as evidenced by the improvement in 6MWT & NYHA classification) and safety of short-term I.V. iron therapy with ferric carboxy-sucrose versus oral iron therapy in heart failure (HF) with reduced ejection fraction patients with iron deficiency.

2. Patients and Methods:

This randomized clinical trial was held in cardiology department, Beni- Suef University in the duration between October/2018 and April/2020. The study included 50 patients who were follow up at cardiology outpatient clinics with mean age 50±11.6 years of both sex and they were subdivided later into 2 groups according to the assigned treatment.

2.1. Randomization:

single-blind closed envelop randomization. The patients were randomized into 2 groups: group I received IV ferric carboxy sucrose (25 patients), group II received oral iron.

2.2 Inclusion criteria:

1. stable CHF (NYHA II/IV functional class) on optimal guidelines directed therapy (as determined by the investigator) for at least 4 weeks with no dose changes of heart failure drugs during the last 2 weeks (with the exception of diuretics).

2. Left ventricular ejection fraction ≤45% (value within 3 months of planned date of randomization).

3. Subject must be capable of completing the 6MWT. 4. Screening serum ferritin <100 ng/mL or 100–300 ng/mL with transferring saturation <20%.

2.3 Exclusion criteria:

1. Hypersensitivity to the used medications.

2. History of acquired iron overload.

3. History of erythropoietin- stimulating agent, I.V. iron therapy, and/or blood transfusion in previous 6 weeks prior to randomization.

4. Oral iron therapy at doses >100 mg/day in previous 1 week prior to randomization. 5. Subject at an immediate need of transfusion or haemoglobin ≥15 g/dL.

6. Active bacterial infection, chronic liver disease, current evidence of malignancy or on chemo/radiotherapy and unstable angina pectoris population.

2.4 Methods:

All participants underwent full clinical examination and laboratory investigations (Hemoglobin, serum iron, serum ferritin, total iron binding capacity (TIBC), transferring saturation test (TSAT)).

A. Echocardiography

was performed for all participants using ultrasound equipment (GE Health care, Vivid S5) with a 6 MHz transducer. The linear internal measurements of the left ventricle and its walls were performed in the parasternal long-axis view. Internal dimensions were obtained with (2D) echocardiography (2DE)-guided M-mode approach. LV volumes were measured using 2DE. LV volumes were measured from the apical four- and two-chamber views. The used method for 2D echocardiographic volume calculations was the biplane method of disks summation (modified Simpson's rule).

B. Six-minute walk test:

The 6MWT was performed indoors (in the hospital), along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The length of the corridor was marked. The walking course was 23 m in length. A starting line, which marks the beginning and end of the corridor, was marked on the floor.

C. Medications: IV ferric carboxy sucrose: The patient's total body iron deficit was calculated using the Ganzoni's formula (134) (total iron dose = (actual body weight x (15-actual Hgb)) x 2.4 + iron stores). Patients received pheniromine maleate injection, 50 mg elemental iron diluted with 250 ml normal saline (in 0.9% sodium chloride solution) infusion started over 30 min to avoid allergic reactions then 150 mg elemental iron added & infusion continued over 2 hours. Those patients received IV iron infusion weekly for 3 to 5 weeks, depending on the total required dose. ***Oral iron 2.5 group:*** Patients received dosage ranges from 150 to 180 mg/day of elemental iron in the form of ferrous glycine

sulfate complex delivered in divided doses two to three times a day for 3 months.

2.6 Follow-Up: After 12 weeks of randomization initation, the previous laboratory investigations would be repeated, echo and 6MWT would be re performed.

2.7 1ry end point: The change in 6MWT distance from baseline to Week 12.

2.8 2ry end points: 1. Changes in NYHA class, 2. Change in ejection fraction, 3. Change in left ventricular dimensions, 4. Changes in iron profile & hemoglobin level, 5. Safety analysis included serious and non-serious adverse events (side effects that occur during the study period), assessed up to Week 12.

3. Results:

The study included 50 cardiac patients. All participants completed the study (no withdrawal cases or lost follow up cases). No side effect of the administered medications was reported and the administered medications were no suspended or ceased for any of the participants. The total cohort mean age was 50±11.6 years distributed on both sex.

Table (1): demographics and baseline echocardiographic findings:

	Oral iron 25 patients	**IV. Iron 25 patients**	**P value**
Age (years) Mean ±SD	49.9 ±10.9	50.1 ±10.9	0.960**
Sex (Male) No.%	13 (52%)	13 (52%)	0.999*
Echocardiographic parameters			
LVED (mm) mean±SD	68.2 ± 8.4	72.4 ± 8.8	0.76**
LVES (mm) mean±SD	57 ± 8.6	59 ± 7.9	0.28
EF (%) mean±SD	30.88 ±5.3	33.2 ±7.53	0.215
NYHA mean ± SD	2.5 ± 0.4	2.6 ± 0.6	0.486
6MWT (meter) mean ±SD	209.73± 75.2	208.52± 79.19	0.95
Baseline iron profile			
Serum iron (µ/dl) mean ±SD	55 ± 16.5	53 ± 22.7	0.527
Serum Ferritin (ng/ml) mean ±SD	59 ± 34.4	86 ± 70.9	0.336
Transferrin saturation (%) mean ±SD	16.7 ± 6.3	14.9 ± 4.3	0.26
Hemoglobin (g/dl) mean ±SD	12.0 ± 1.3	12.5 ± 1.0	0.78

LVED: Left ventricular end diastolic volume, LVES: Left ventricular end systolic volume, EF: ejection fraction, NYHA: New York Heart Association, 6MWT: 6 meters walk test. *Chi-square test, **student t-test. Level of significance <0.05Both groups were comparable as regards baseline demographic, clinical, echocardiographic & laboratory characteristics ***(table 1).***

Table (2): Comparison of post-treatment values between both groups:

	Oral iron 25 patients	IV. Iron 25 patients	P value
LVED (mm) mean±SD	68.0 ± 8.27	68.3 ±15.0	0.397
LVES (mm) mean±SD	56.5 ± 8.6	55.2 ± 12.3	0.741
EF (%)mean±SD	31.5 ±5.4	33.4 ±7.36	0.300
Serum iron (µ/dl) mean ±SD	92.6 ± 24.0	86 ± 26	0.066
Serum Ferritin (ng/ml) mean ±SD	227 ± 63.0	260 ± 95.0	0.293
Transferrin saturation (%) mean ±SD	27.68 ±5.66	28.4 ±5.98	0.600
Hemoglobin (g/dl) mean ±SD	13.0 ± 1.2	13.4 ± 1.5	0.359
NYHA mean ± SD	1.6 ± 0.7	1.6 ± 0.6	0.983
6MWT (meter) mean ±SD	523.12 ±94.0	509.88 ±107.69	0.600

LVED: Left ventricular end diastolic volume, LVES: Left ventricular end systolic volume, EF: ejection fraction, NYHA: New York Heart Association, 6MWT: 6 meters walk test. *student t-test, Level of significance <0.05

There was no statistically significant difference between both groups regarding post-treatment echocardiographic & laboratory values as well as NYHA class & 6MWT results ***(Table 2).***

Table (3): Efficacy of treatment in total cohort:

	Pre-treatment	Post-treatment	P value
LVED (mm) mean±SD	70.3 ± 8.8	68 ± 12	***0.015***
LVES (mm) mean±SD	57.8 ± 8.4	55.8 ± 10.5	***0.001***
EF (%)mean±SD	32 ± 6.6	32.5 ± 6.5	0.25
Serum iron (µ/dl) mean ±SD	53.9 ± 19.7	89 ± 25	***<0.001***
Serum Ferritin (ng/ml) mean ±SD	72.5 ± 57	243.7 ± 81.2	***<0.001***
Transferrin saturation (%) mean ±SD	15.8 ± 5.4	28 ± 5.8	***<0.001***
Hemoglobin (g/dl) mean ±SD	11.9 ± 1.2	13.2 ± 1.4	***<0.001***
NYHA mean ± SD	2.5 ± 0.5	1.6 ± 0.6	***<0.001***
6MWT (meter) mean ±SD	209.1 ± 76.4	516.5 ± 100.3	***<0.001***

LVED: Left ventricular end diastolic volume, LVES: Left ventricular end systolic volume, EF: ejection fraction, NYHA: New York Heart Association, 6MWT: 6 meters walk test. *student t-test, Level of significance <0.05

Results showed that apart from LVEF, all parameters improved significantly after iron therapy (regardless of route of therapy) as regards 6MWT (the primary end point), LVED, LVES, serum iron, serum ferritin, transferrin saturation & NYHA classification (the secondary end points) ***(Table 3).***

Table (4): Correlation between Changes in iron profile and improvement in NYHA and 6-MWT in total cohort:

	Post 6 MWT	Delta 6 MWT	Post NYHA	Delta NYHA
Delta iron				
r^2=	0.111	***0.295***	-0.135	**-0.281**
P-value	0.443	***0.038***	0.351	**0.048***
Delta ferritin				
r^2=	0.192	0.178	-0.134	-0.039
P-value	0.181	0.215	0.353	0.786
Delta hemoglobin				
r^2=	-0.020	-0.015	-0.187	-0.105
P-value	0.892	0.920	0.193	0.470
Delta trans saturation				
r^2=	0.157	0.094	-0.220	-0.106
P-value	0.277	0.518	0.125	0.465

r^2: Pearson correlation, 6-MWT: 6 meters walk test, NYHA: New York Heart Association

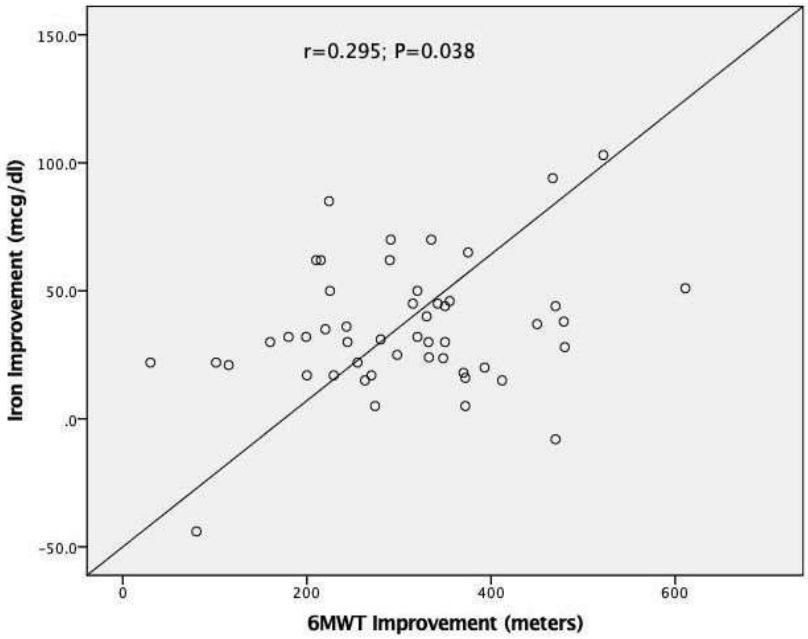

Figure (1): Correlation between iron improvement & 6MWT improvement in total cohort (n = 50)

There was a significant weak positive correlation between the improvement in serum iron & 6MWT improvement in all 50 patients (r^2= 0.295 & P-value = 0.038) ***(Table 4, Figure 1).*** There was a significant weak negative correlation between the improvement in serum iron & NYHA classification in all 50 patients (r^2= -0.281 & P-value = 0.048) ***(Table 4).***

Table (5): Correlation between Changes in iron profile and improvement in NYHA and 6-MWT in oral iron group:

	Post 6 MWT	Delta 6 MWT	Post NYHA	Delta NYHA
Delta iron				
r^2=	0.203	0.179	-0.155	-0.269
P-value	0.331	0.391	0.459	0.194
Delta ferritin				
r^2=	0.194	0.300	0.044	-0.003
P-value	0.352	0.145	0.834	0.990
Delta hemoglobin				
r^2=	-0.236	0.185	-0.256	-0.150
P-value	0.256	0.375	0.216	0.474
Delta trans saturation				
r^2=	0.098	0.169	0.047	0.049
P-value	0.640	0.420	0.824	0.814

r^2: Pearson correlation, 6-MWT: 6 meters walk test, NYHA: New York Heart Association

This significance was lost when we studied the correlation in the patients in the oral group only (P-value = 0.194) ***(Table 5).***

Table (6): Correlation between Changes in iron profile and improvement in NYHA and 6-MWT in IV iron group:

	Post 6 MWT	Delta 6 MWT	Post NYHA	Delta NYHA
Delta iron				
r^2=	0.203	**0.376**	-0.125	-0.302
P-value	0.331	**0.064**	0.553	0.143
Delta ferritin				
r^2=	0.194	0.104	-0.307	-0.087
P-value	0.352	0.621	0.136	0.679
Delta Hb				
r^2=	-0.236	-.0122	-0.132	-0.093
P-value	0.256	0.560	0.531	0.657
Delta trans saturation				
r^2=	0.098	0.059	***-0.517***	-0.342
P-value	0.640	0.780	***0.008***	0.093

r^2: Pearson correlation, 6-MWT: 6 meters walk test, NYHA: New York Heart Association

There was a significant negative correlation between the improvement of transferrin saturation & the NYHA classification after intravenous iron therapy (r^2=-0.517 & P-value=0.008) ***(Table 6, Figure 2).*** There was a trend towards a weak positive correlation between iron improvement by intravenous route & improvement of 6 MWT (r^2= 0.376 & Pvalue= 0.064) ***(Table 6, Figure 3).***

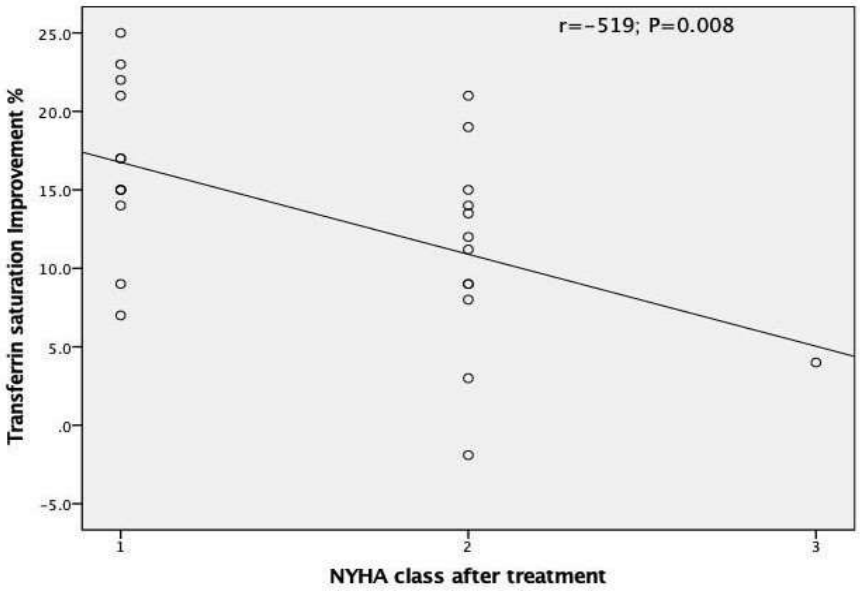

Figure (2): Correlation between transferrin saturation improvement & NYHA class after treatment with IV iron (n = 25)

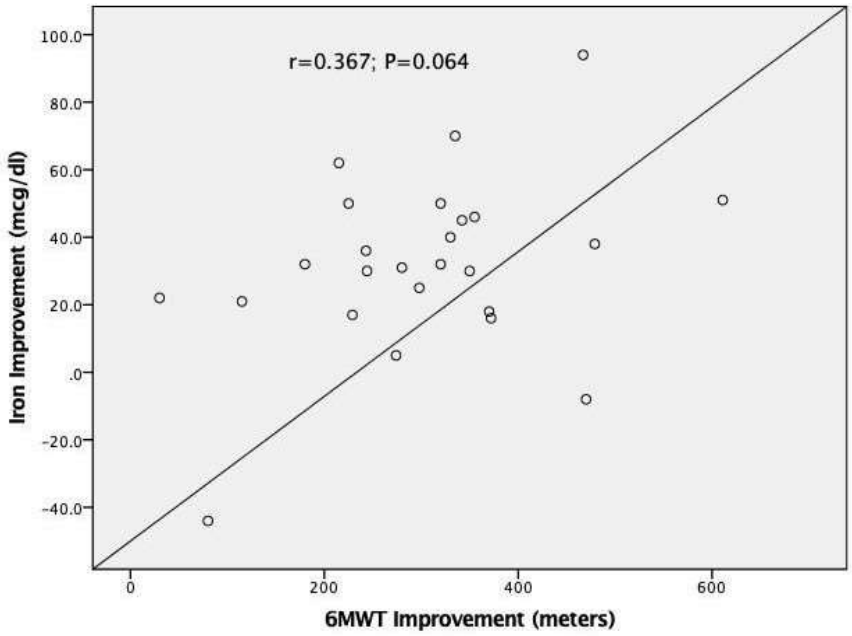

Figure (3): Correlation between iron improvement & 6MWT improvement in patients receiving IV iron therapy (n=25)

4. Discussion:

This current study was conducted on a total 50 patients (mean age 50 ±11.6 years) and was designed to evaluate the benefits and safety of short-term I.V. iron versus oral iron therapy in heart failure (HF) with reduced ejection fraction patients with iron deficiency. Patients were randomly assigned to two groups: oral ferrous glycine sulfate complex group and IV ferric carboxy sucrose group. At the baseline level, both groups were comparable regarding demographic, clinical, echocardiographic and laboratory characteristics with no statistically significant differences. The main finding of the current study is that apart from EF; all Echocardiographic parameters were improved significantly in all studied patients after iron therapy (regardless of the route of administration) as well as Clinical (NYHA and 6MWT) and laboratory (serum iron, serum ferritin, transferring saturation) parameters. There were non-statistically significant differences in comparison of post-treatment values between oral and IV groups. In the setting of iron deficiency in heart failure; there has been evidence to prove little benefit with oral iron; this is likely because of poor absorption, low rates of adherence, and gastrointestinal side-effects and has not been shown to replete iron stores [23]. Although the results of the current study showed improvement after oral iron use, these results are the opposite of previously published results in the IRONOUT-HF trial designed to test whether therapy with oral iron improves peak

exercise capacity in patients with HFrEF and iron deficiency; the results did not support the use of oral iron in HFrEF with iron deficiency (this may be attributed to the relatively high percent of elevated serum hepcidin level among the study population, it is known that hepcidin is a hepatically derived peptide that inhibits intestinal absorption by interacting with its specific transmembrane receptor (ferroportin) on target cells). There were no significant differences detected in natriuretic peptides, pVO2, 6MWT, or KCCQ scores [24]. In 2006, Bolger and his coworkers were the first to study the use of intravenous iron (in the form of iron sucrose) without concomitant exogenous erythropoiesis stimulating agents (ESAs) in patients with systolic HF and reported improvement in functional class, exercise capacity and HF symptoms [25]. The following year, Usmanov and his colleagues treated iron deficient HF patients with intravenous iron with beneficial effect on echocardiographic parameters [26]. The first randomized controlled trial of intravenous iron in anemic HF patients was carried out by Toblli et al. and patients in the iron group received intravenous iron sucrose for five consecutive weeks. At the end of the follow up, they had improved hemoglobin and ferritin levels, renal function, inflammation status, ejection fraction, NYHA functional class,

exercise capacity, quality of life, lower levels of NT-pro-BNP and zero hospitalizations [27]. The same research team undertook additional analyses and presented their results in a new study published on 2015 [28]. The second randomized controlled trial to administer intravenous iron sucrose in HF patients was the FERRIC-HF (European effect of intravenous ferrous sucrose on exercise capacity in chronic heart failure). The primary finding of this study was a significant improvement in exercise tolerance as measured by peak oxygen consumption during exercise testing performed on a treadmill [29]. There is limited studied that compare IV and oral iron in patients with HF, the reason behind this may be attributed to that IV iron was superior when compared to oral iron in other diseases with similar inflammatory milieu, such as juvenile chronic arthritis [30], chronic kidney failure [16] and inflammatory bowel disease [31]. Due to these previous findings the use of oral iron in HF patients has been a priori considered useless. In the current study, there was a significant negative correlation between the improvement of transferrin saturation & the NYHA classification after intravenous iron therapy (r=-0.517 & P-value=0.008). This finding was in line with another study undertaken to assess the hematologic, clinical, and biochemical response to intravenous iron in patients with chronic heart failure (CHF) and anemia where the NYHA score fell (denoting improvement) after intravenous administration of iron sucrose with increases in transferrin saturation from 16.0 ± 9.5 to 24.6 ± 8.4% (p = 0.009) [25]. Post-treatment 6MWT showed non-statistically significant differences between oral and IV groups; however, in the IV group there was a trend towards a positive correlation between iron improvement by intravenous route & improvement of 6 MWT. This finding was similar to the recent meta-analysis of randomized controlled trials that explores the effects of intravenous iron therapy in iron deficient patients (ID) with heart failure (HF) and a reduced ejection fraction (HFrEF) concluded that IV iron treatment lead to an improvement in functional exercise level, as reflected by the longer distance that treated patients walked during the 6 minute walk test [32]. Our results from the current study suggest that iron store replenishment was at least similar between patients receiving IV iron and those receiving oral iron. However this study has some limitations in the form of: It was one center study from Beni-Suef university hospital, The sample size was relatively small and further studies with larger sample size is recommended in order to prove or deny the similarity between oral and IV iron in patients with HF and the absence of control group of patients who did receive neither oral nor IV treatment.

5. Summary and Recommendations:

In conclusion, regardless the route of administration, iron therapy (I.V. iron therapy

in the form of ferric carboxy-sucrose or oral iron in the form of ferrous glycine sulfate complex) is safe & effective in improving functional capacity (the primary end point) of HFrEF (NYHA class I-III) patients with iron deficiency. This improvement is proportional to the degree of improvement in transferrin saturation obtained by IV ferric carboxy-sucrose therapy. Our results suggest that oral iron might be equivalent to IV iron in the management of iron deficiency HF patients. These findings suggest that iron therapy (regardless rout of administration) may potentially represent a beneficial addition to the standard medical management of HF.

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