Original Article

The Effects of Ferrous Sulfate as an Iron Supplement on Ejection Fraction in Patients with Iron Deficiency Anemia Associated with Decompensated Heart Failure

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Abstract

Background: Acute decompensated heart failure (HF) is a clinical syndrome that results when abnormalities in the structure and function of the myocardium impair cardiac output or decrease filling of the ventricles. Anemia is a common comorbidity in patients with chronic HF (CHF), is associated with increased disease severity, and may contribute to a worse the outcome. **Aim of the Study:** To study the relationship between iron level and left ventricular function (LVF) in patients having acute decompensated HF and the effects of iron supplement on this function. **Patients and Methods:** This cross-sectional study was conducted in the medical wards of Baghdad Teaching Hospital at different times during the period between October 1, 2016, and May 1, 2017. It included 60 patients diagnosed with CHF (9 patients with HF with preserved ejection fraction [EF] and 51 patients with HF with reduced EF) and admitted to the medical wards due to acute decompensation. For all patients, history, cardiological examination, New York Heart Association classification, electrocardiogram, and chest X-ray were done. Body mass index was measured. Standard echocardiography was performed. Hematological parameters were measured including hemoglobin (Hb), mean corpuscular volume, mean corpuscular Hb (MCH), MCH concentration, blood film, serum iron, erythrocyte count, total iron-binding capacity, and transferrin saturation. **Results:** Serum iron was significantly lower in patients with impaired EF with median serum iron 41 versus 94 mcg/dL in preserved EF (72.5% vs. 0%). Transferrin saturation was statistically and significantly lower in patients with EF <50% (39.2% of the patients with impaired EF had low transferrin saturation [$P < 0.001$] compared to 0% in patients with preserved EF). EF had inverse significant correlation with total binding capacity of iron ($r = -0.585$, $P < 0.001$). Iron supplements as ferrous sulfate have a highly significant effect ($P < 0.001$) on improving the LVF and EF, iron level and transferrin saturation in patients with decompensated HF with low EF. **Conclusions:** Most HF patients with low EF in this study had reduced iron level and transferrin saturation comparing to those with preserved EF. Iron supplement in a patient with low EF preserved the EF in them. Anemia still is founded in patients of HF with acceptable EF in the presence of normal iron status, and this is explained by other causes rather than iron deficiency.

Keywords: Ejection fraction, heart failure, iron deficiency anemia

Introduction

Heart failure (HF) results when abnormalities in the structure and function of the myocardium impair cardiac output or decrease filling of the ventricles. Characteristic features of the HF syndrome include dyspnea (shortness of breath), fatigue, fluid retention, impaired exercise performance, and edema. Pulmonary congestion is a common but not a universal feature, so the term "congestive HF" is no longer used.[1,2]

Approximately 40%–50% of patients with HF have a preserved ejection fraction (EF). Compared with patients who have HF with reduced EF (HFrEF), patients with HF with preserved EF (HFpEF) tend to be older and are more likely to be women with prior hypertension and diabetes. The rate of mortality in patients with a preserved EF is relatively lower than the rate for patients with reduced EF but is still higher than for an age-matched population.[3,4]

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/MJ.MJ_6_18

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How to cite this article: Al-Atrakji MQ. The effects of ferrous sulfate as an iron supplement on ejection fraction in patients with iron deficiency anemia associated with decompensated heart failure. Mustansiriya Med J 2018;17:22-8.

Classification

1. HFrEF (EF <40)
2. Borderline or mild reduced (EF 40–49)
3. HFpEF (EF >50).

Causes of heart failure[5]

The causes of HF are coronary artery disease, hypertension, familial and genetic disorders, including dilated cardiomyopathies, hypertrophic cardiomyopathies, storage diseases, and muscular dystrophies; valvular disease including valvular stenosis or regurgitation; toxic/drug-induced damage including prior chemotherapy; infiltrative processes such as sarcoid, amyloid and hemochromatosis (i.e., restrictive cardiomyopathy); arrhythmia-related dysfunction, including premature ventricular contraction-induced cardiomyopathy and atrial tachyarrhythmia-related dysfunction, arrhythmogenic right ventricular cardiomyopathy, pulmonary heart disease, including cor pulmonale.[5]

The causes of HF are infectious agents including viral infections and Chagas disease; immunologically mediated myocardial processes; intracardiac or extracardiac shunting, including arteriovenous fistulas, constrictive pericarditis, and age-related changes; nutritional disorders, such as beriberi; and high-output states, such as chronic anemia and thyrotoxicosis.

Factors precipitate acute decompensated chronic heart failure[5]

The factors that precipate acute decompensated chronic HF (CHF) are ischemic changes or infarcted myocardium, arrhythmias, uncontrolled hypertension, worsening mitral or tricuspid regurgitation, medications that worsen HF (calcium antagonists, beta-blockers, nonsteroidal anti-inflammatory drugs, and antiarrhythmic agents), discontinuation (noncompliance of therapy or physician initiated), dietary indiscretion, iatrogenic hypervolemia (transfusion, fluid administration), alcohol consumption, increased activity, fever or infection, anemia, thyroid abnormalities, exposure to high altitude, and pregnancy.[5]

Iron is absorbed in the duodenum by enterocytes, which release it to circulation to be destined for bone marrow for incorporation into hemoglobin (Hb) molecule during erythropoiesis. Iron is transported in the plasma by transferrin. Any excessive iron usually stored in the reticuloendothelial system and liver as ferritin for release as needed.[6]

Deficiency of iron is the most common nutritional deficiency worldwide and is highly prevalent in developing countries, and when diagnosing iron deficiency (ID), it is crucial to diagnose and treat underlying causes.[7]

Dietary iron (1–2 mg/day) replaces natural losses of iron in urine, sweat, and stool. Insufficient dietary intake to replace this required amount and any additional loss (such blood loss) will result in anemia over the course of few months to years.[6]

Causes of iron deficiency anemia[6]

1. Loss of iron (menstruation, phlebotomy, gastrointestinal, and genitourinary) and other blood loss (overt, microscopic, or fictitious)
2. Decreased intake due to nutritional deficiency or decreased absorption due to gastric/duodenal surgery, celiac disease, *Helicobacter pylori* infection, autoimmune atrophic gastritis
3. Increased iron requirement: Pregnancy, lactation.[6]

Features of iron deficiency anemia

Patients with ID may note fatigue, lack of sense of well-being, irritability, and decreased exercise tolerance. Typical features of ID anemia (IDA) are identical to those of any symptomatic anemia but may be subtle owing to insidious onset of condition. Headache and pica (craving for typically undesirable items such as ice, dirt, clay, paper, and laundry starch) are frequently associated symptoms. Other less common symptoms include restless legs syndrome and hair loss.[6]

Although physical examination findings are typically normal in a patient with ID, abnormal findings include facial pallor, glossitis, stomatitis, and, in particular, conjunctival pallor. Severe ID can result in koilonychia.[6]

Investigation

Recent blood transfusion or iron replacement may interfere with accurate evaluation of ID. The hallmark of ID is hypochromic microcytic anemia and this is usually seen in advanced ID and anemia tends to precede morphologic changes in the cells.

Serum iron tends to be low and total iron-binding capacity (TIBC), which is a measure of the amount of transferrin in the plasma, is usually elevated. Transferrin saturation is a percentage calculated as serum iron/TIBC.[6]

Transferrin saturation is usually <15% in IDA. Serum ferritin as a measure of total body iron is typically no >12 ng/ml in IDA and may be slightly higher in ID without anemia (<15 ng/ml). Ferritin is acute-phase reactant and can be elevated with inflammation or chronic disease or hematological malignancy but level >100 ng/ml usually excludes IDA. Reticulocyte count is typically low, although occasionally it can be normal or even elevated.[6]

Heart failure and anemia

Although CHF treatment improves the patient status over the years, normal daily requirements and daily jobs remain restricted to many patients.[7] This is associated to increasing disease severity and worse outcome for those patients may be due to anemia, which is a common comorbidity in HF.[8-11] It is a complex mechanism and multi-factors play a role in explaining that anemia contributes to worse adverse outcome in CHF.[12] "Some drugs used for HF management can also lead to anemia, such as antiplatelet, anticoagulant, ACE-inhibitors, angiotensin-I receptor blocker, and carvedilol, as they cause inhibition of the erythropoietin production."[13,14]

Hb levels which are reduced viewed as the end result of an anemia process beginning with gradual depletion in stores of iron.[15,16] Even if patients with no anemia, ID may be common in the CHF.[17-20] Despite ID being associated with CHF poor outcome, its prevalence is unknown in decompensated CHF due to the screening for ID usually uncommon for patients without anemia.[21-23]

Iron-containing drugs (supplements)

Iron salts or iron pills are formulations of iron that are usually used for treatment as well as prevention of ID including IDA.[24,25] They are taken by mouth, or by injections.[26] The benefits are usually seen after few days but it takes up to 2 months until iron levels return to normal status.[26]

Adverse effects for iron therapy include decreased bowel motion, abdominal colic, dark-colored stools, or loose stool.[27] Iron overload is seen when large doses are used.[28] Ferrous salts given by mouth include ferrous gluconate, ferrous fumarate, ferrous succinate, and ferrous sulfate.[29] Nonoral forms including iron dextran and iron sucrose are given by deep muscular injection.[30-35] They act by providing iron which is needed in red blood cell (RBC) synthesis.

Ferrous sulfate (iron [II] sulfate)

Pharmacological category

Ferrous sulfate is a type of iron. Iron is usually obtained from the foods. In the body, "iron becomes a part of your hemoglobin and myoglobin. Hemoglobin carries oxygen through your blood to tissues and organs. Myoglobin helps your muscle cells store oxygen."[35,36]

Ferrous sulfate which is one of the essential minerals is used for treating IDA "a lack of red blood cells caused by having too little iron in the body."[36]

Mechanism of action

Ferrous sulfate replaces iron stores found in Hb in RBCs and myoglobin and other heme enzymes in the body. In addition, ferrous sulfate allows the transportation of oxygen via Hb. Approximately 60% of iron is stored in Hb in RBCs, while 9% is stored in myoglobin and other heme enzymes. In addition, 25% is held in reserve in reticulocytes of the liver, spleen, and bones.[36-39]

Most stored iron is bound to the protein ferritin. While being transferred in the body, Fe^{2+} iron is converted to Fe^{3+} by ceruloplasmin, so that it can then be bound to the protein.[40,41]

Toxicity and adverse effects

- Gastrointestinal: change bowel motion usually constipation, stool darkening, epigastric and abdominal pain, gastrointestinal irritation, nausea, stomach cramping, vomiting
- Genitourinary: Discoloration of urine
- Serious: Contact irritation miscellaneous: Temporary teeth staining (liquid preparations)
- Toxicology: Acute symptoms occur within 30 min to several hours
- Adult toxic dose: elemental iron; 20 and 60 mg/kg (lethal dose)
- Child lethal dose (2 g): Nausea, vomiting, shock, cyanosis or pallor, drowsiness, green or tarry stools, and cardiovascular collapse.

Aims of the study

1. To assess ID in patients with decompensated HF
2. To study the relationship between iron level and left ventricular function (LVF) in patients with decompensated HF and the effects of iron supplement on EF
3. To study the relationship between the level of the iron and other hematological parameters in patients with decompensated HF.

Patients and Methods

Patients selection

All patients in this cross-sectional study had given written informed consent to participate in the research. The study was accomplished in the medical wards of Baghdad Teaching Hospital at different times during period between October 1, 2016, and May 1, 2017. It included 60 patients (age range 53 –74 years) diagnosed with HF and admitted to the medical wards due to acute decompensation.

Patients who have HF with other comorbid conditions such as chronic renal disease, chronic liver disease, folic and Vitamin B_{12} deficiency, hematological disease (hemoglobinopathy or malignancy), other malignancy and patients with recent blood transfusion, trauma patients, or postoperative patients were excluded from the study.

The study included 36 males and 24 females. All patients in this study survived and hence they had left the medical wards of Baghdad Teaching Hospital.

Measurements

For all patients, history, cardiological examination,[4] New York Heart Association classification, electrocardiogram, and chest X-ray were done. Body mass index (BMI) was measured. Echocardiography was performed with a Doppler study by 4D portable coloured doppler echo Philips Machine (Germany) while the patients were lying in a position of left lateral decubitus. The left ventricular EF was measured by two-dimensional biplane method according to the recommendations of the European Society of Echocardiography. Hematological parameters were measured for all patients and included Hb level, mean corpuscular volume, mean corpuscular Hb (MCH), MCH concentration, blood film, erythrocyte count (RBC), serum iron, TIBC, and transferrin saturation. All these measurements were performed in the medical laboratory of Baghdad Teaching Hospital. Patients with reduced EF were given ferrous sulfate tablets 200 mg (2 tablets/day) for 1 month and were advised to continue on 3 tablets/day for another 2 months after which EF; Hb, serum transferrin, and total iron were measured before and after treatment and recorded.

Results

No significant difference in age, sex, weight, BMI, height, and smoking when compared using EF (50% used as cutpoint between preserved and reduced EFs) was noted as illustrated in Table 1.

Serum iron was significantly decreased in patients with impaired EF with median serum iron 41 versus 94 mcg/dL, transferrin saturation was significantly lower in patients with EF <50% (17 vs. 48%), while 39.2% of the patients with impaired EF had low transferrin saturation compared to 0% in patients with preserved EF, as illustrated in Table 2. EF had strong, direct, and significant correlation with transferrin saturation ($r = 0.961$, $P < 0.001$) and had significant inverse correlation with TIBC ($r = -0.585$, $P < 0.001$) as illustrated in Table 3.

Iron supplements in those patients with unacceptable low EF for 3 months showed a highly significant increase in EF, serum iron, transferrin saturation with significant increase in Hb level as shown in Table 4.

Table 1: Ejection fraction

	EF >50%	EF <50%	*P*
n	9	51	-
Sex, *n* (%)			
Female	4 (44.4)	20 (39.2)	0.768
Male	5 (55.6)	31 (60.8)	
Age (years), mean±SD	62.6±5.5	62.2±12.8	0.927
Weight (kg), mean±SD	92.7±7.7	88.3±12.7	0.327
Height (cm), mean±SD	168.1±8.2	171.6±9.6	0.302
BMI (kg/m^2), mean±SD	32.9±3.7	30.0±4.1	0.511
Normal (%)	0	5 (9.8)	
Overweight (%)	2 (22.2)	24 (47.1)	
Obese (%)	7 (77.8)	22 (43.1)	
Smoking, *n* (%)			
Never	1 (11.1)	16 (31.4)	0.457
Current	2 (22.2)	8 (15.7)	
Ex-smoker	6 (66.7)	27 (52.9)	

SD: Standard deviation, BMI: Body mass index, EF: Ejection fraction

Table 2: Hematological parameters according to ejection fraction

	EF >50%	EF <50%	*P*
n	9	51	-
Hb (g/dL)	11 (8.7-12.7)	11.2 (9.6-13.9)	0.413
Low	7 (77.8%)	27 (52.9%)	0.166
Normal	2 (22.2%)	24 (47.1%)	
Iron (mcg/dL)	94 (76-122)	41 (26-51)	<0.001*
Low	0	37 (72.5%)	
Normal	9 (100.0%)	14 (27.5%)	
TIBC (mcg/dL)	191 (172-228.5)	243 (191-338.5)	0.125
Low	8 (88.9%)	27 (52.9%)	
Normal	1 (11.1%)	15 (29.4%)	
High	0 (0.0%)	9 (17.6%)	
TS (%)	48 (39.4-51.9)	17 (11.6-22.5)	<0.001*
Low	0	20 (39.2%)	
Normal	9 (100.0%)	31 (60.8%)	
MCV (fL)	84.5 (78.1-87.6)	86.6 (79.2-90)	0.408
Low	3 (33.3%)	14 (27.5%)	
Normal	6 (66.7%)	37 (72.5%)	
MCH (g/dL)	27.5 (22.7-28.9)	27.5 (23.2-29.6)	0.950
Low	3 (33.3%)	20 (39.2%)	
Normal	6 (66.7%)	31 (60.8%)	
MCHC (g/dL)	32.2 (30.3-33.6)	31.7 (29.2-33.5)	0.562
Low	3 (33.3%)	23 (45.1%)	
Normal	6 (66.7%)	28 (54.9%)	
RBC (×106)	4.1 (2.7-4.5)	4.3 (3.5-5.4)	0.196
Low	3 (33.3%)	19 (37.3%)	
Normal	6 (66.7%)	32 (62.7%)	

*Significant. Hb: Hemoglobin, TIBC: Total iron-binding capacity, TS: Transferrin saturation, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cells, EF: Ejection fraction

Discussion

Patients with CHF are more vulnerable to ID. This may occur by the gradual decrease of iron stored (absolute ID) due to the decrease in iron intake, gastrointestinal bleeding disorders, or defect in the absorption of iron chronic inflammation, which is seen in CHF commonly, may also play a vital role. Inflammation usually leads to a decrease in iron absorption and iron availability that recycled in the reticuloendothelial system (functional ID).[24-26] Hence, despite adequate iron stored, functional ID may occur whereas iron stored are depleted in absolute ID.

In this study, mean age of the study sample is 62 years which is not different from other studies such as Klip *et al*., Enjuanes *et al*., von Haehling *et al*., Jankowska *et al*., Cardoso *et al*., Yeo *et al*. This is an expected finding as age is a major risk factor for all causes that lead to HF.

The study sample showed male predominance (55.6%) compared to female (44.4%) in HFpEF. A study done by Kasner *et al*.[33] showed male predominance (57.7%) compared to female (42.3%) in HFpEF which is comparable to the result of this study. This study showed that males constituted 60.8% compared to females (39.2%) in HFrEF. A study done by Enjuanes *et al*.[28] showed male predominance (69%) compared to female (31%) in HFrEF, which is also comparable to the results of this study, which mean that male sex is a risk factor for ischemic heart disease.[34]

Serum iron in this study was significantly lower in a patient with reduced EF in 72.5% (90% female vs. 61.3% male) compared with normal iron study in patients with preserved EF. A study done by von Haehling *et al*.[29] showed ID in 509 patients out of 1198 of patients with reduced EF and the percentage is 42.5%. This difference may be due to large sample study compared to our study, and also a study done by Jankowska *et al*.[17] showed ID in patients with reduced EF in 36% (199 out of 546 patients). The prevalence of ID in patients with reduced EF is more than 70% with a range from 69.7 to 76.4 in a study done by Cohen-Solal *et al*.,[21] which as comparable to this study.

Table 3: Relationship between ejection fraction and various variables

Variables	Correlation coefficient	*P*
Hb	−0.160	0.233
Iron	0.805	0.087
TIBC	−0.585	<0.001*
TS	0.961	<0.001*
MCV	−0.026	0.844
MCH	0.111	0.398
MCHC	0.196	0.133
RBC	−0.290	0.196

*Significant. Hb: Hemoglobin, TIBC: Total iron-binding capacity, TS: Transferrin saturation, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RBC: Red blood cells

Table 4: Comparison between patients with low ejection fraction before and after ferrous sulfate treatment according to ejection fraction, transferrin saturation, total body iron, and hemoglobin

Parameters	Patients with LVF with reduced EF before iron treatment	Patients with LVF with reduced EF after iron treatment	*P*
EF	35.7±0.05	55.65±0.05	<0.001
TS	9±0.07	50±0.07	<0.001
Iron (mcg/dL)	41±0.05	95±0.05	<0.001
Hb (g/dL)	11.2±0.06	12.8±0.06	<0.05

Values are mean±SE, (*n*=51 patient/group). SE: Standard error, EF: Ejection fraction, TS: Transferrin saturation, Hb: Hemoglobin, LVF: Left ventricular ejection

Table 5: Transferrin saturation according to the severity of ejection fraction

Preserved EF (>50%)	Mild reduced or borderline EF (40%-49%)	Reduced EF (<40%)	*P*
TS=48 (39-52)	TS=30 (28-33)	TS=9 (5-11)	<0.001

TS: Transferrin saturation, EF: Ejection fraction

Transferrin saturation in this study was low in 20 out of 51 patients with reduced EF equal to 39.2% (50% female vs. 32.3% male) compared to 0% in patients with preserved ejection which means ID was more in patients with reduced EF than preserved EF, and also transferrin saturation decrease with decreased EF from mild to severe. Transferrin saturation was found to be decreased in 741 out of 1278 (57%) patients with reduced EF according to the study done by Enjuanes *et al*., [Tables 5-7].[28]

Other studies done by von Haehling *et al*.[29] showed transferrin saturation decrease in 509 out of 1198, with 42% patients with reduced EF , which is approximately equal to our result (39.2%). Furthermore, transferrin saturation decreased with increase of New York Heart Association from 1 to 4 in patients with systolic HF according to the study done by Jankowska *et al*.[30]

Table 6: Association between hematological parameters and sex in patients with ejection fraction >5000

	Female (%)	Male (%)	*P*
n	4	5	-
Hb			
Low	3 (75.0)	4 (80.0)	1.0
Normal	1 (25.0)	1 (20.0)	
Iron			
Low	0	0	NA
Normal	4 (100)	5 (100)	
TIBC			
Low	3 (75)	5 (100)	1.0
Normal	1 (25)	0	
High	0	0	
TS			
Low	0	0	NA
Normal	4 (100)	5 (100)	

Hb: Hemoglobin, TIBC: Total iron-binding capacity, TS: Transferrin saturation, NA: Not applicable

Table 7: Association between hematological parameters and sex in patients with ejection fraction <50%

	Female	Male	*P*
n	20	31	-
Hb			
Low	12 (60)	15 (48.4)	0.029*
Normal	8 (40)	16 (51.6)	
Iron			
Low	18 (90)	19 (61.3)	0.029*
Normal	2 (10)	12 (38.7)	
TIBC			
Low	9 (45)	18 (58.1)	0.017*
Normal	10 (50)	5 (16.1)	
High	1 (5)	8 (25.8)	
TS			
Low	10 (50)	10 (32.3)	<0.001*
Normal	10 (50)	21 (67.7)	

*Significant. Hb: Hemoglobin, TIBC: Total iron-binding capacity, TS: Transferrin saturation

By comparing Hb level to serum iron, this study showed that 77.8% of patients with preserved EF have anemia, but zero patient has ID which means that there are some other causes of anemia other than ID.

However, in patients with reduced EF, anemia equals to 52.9% of patients despite they are deficient in 72.5% of the same patients which revealed that there may be patients have ID but still not anemic. A study of 1198 patients with reduced EF conducted by von Haehling *et al*.[29] showed anemia in 18.9% of patients, but ID patients are 42.5%, which further support our study. This mean ID is common in patients with HFrEF regardless of the presence of anemia.

By giving iron supplement as ferrous sulfate to those patients with low EF for 3 successive months, the results proved strongly and significantly the findings of this study so that

patients with low EF who took the iron supplement restore their total iron and transferrin saturation and with preserved EF improve LVF and finally their condition as a whole.[29,35]

Conclusion

1. Low serum iron and low transferrin saturation are more in patients with HFrEF than patients with HFpEF regardless of the presence of anemia
2. Anemia still is found in patients with HFpEF in the presence of normal iron status
3. Iron supplements for a long period given concurrently with drugs for HF treatment may improve the outcome of the disease, especially with those with reduced EF.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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