

Prevalence and Treatment of Iron Deficiency Anemia in Patients with Chronic Heart Failure

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Abstract

Objective: Approximately 30% of patients with Chronic Heart Failure (CHF) develop anemia. Previous studies showed the beneficial effect of treating the underlying anemia in CHF patients but controversy on the subject remains. We studied the prevalence and treatment of underlying anemia in patients with CHF.

Methods and Results: Patients were categorized into three groups: normal hemoglobin levels, anemia of chronic disease; and iron deficiency anemia (IDA). All patients were treated for heart failure. Patients with IDA were treated with iron sulfate. We compared the ejection fractions (EF) and functional capacities both before and after treatment.

The prevalence of IDA in our patients was 10.7% and 25.7% of patients had anemia of chronic disease. The mortality rate in the anemic group was 4.9 times higher than the mortality rate in the normal hemoglobin group. Following treatment, there was a significant increase in hemoglobin levels that was more prominent in the IDA group. EF increased in all groups following treatment, but the increase was greatest in the IDA group.

Conclusions: Our results demonstrate the improved quality of life that results from treating IDA as part of CHF patient management. Early diagnosis and treatment of anemia can improve EF in patients with CHF.

Keywords: Anemia; Cardiac failure; Iron deficiency

Introduction

Heart failure affects approximately 2% of the general population. Hospitalized patients with underlying heart failure have 25%-35% chance of mortality or morbidity within one year. One third of cardiac failure patients who require readmission die within 90 days of readmission. The total number of deaths resulting from heart failure is greater than the total number of deaths resulting from complications due to uterine cancer, prostate cancer, breast cancer and bladder cancer combined [1].

Anemia can result from decreased erythrocyte production due to primary hematologic disease, systemic disease or hemolysis [2]. Nutritional history, use of alcohol, use of medication, family history and history of endocrine disorders (e.g., hypothyroidism) should be considered when determining the cause of anemia [2]. In patients with underlying coronary artery disease, anemia may be misdiagnosed as fatigue, decreased exertional capacity, dyspnea, heart palpitations or exacerbation of angina [3]. The prevalence of anemia is 2.5% in women and 1% in men [4]. There is a 1% prevalence of iron deficiency anemia (IDA) in men younger than 50 years old and a 2%-4% prevalence of IDA in men older than 50 years old. IDA is more prevalent in young women (9%-11%), because its prevalence decreases to 5%-7% after menopause [4]. The prevalence of anemia in heart failure patients is 50%-60%, according to the OPTIME-HF trial; IDA constitutes 21% of all cases of anemia in heart failure patients [5]. A previous study showed that 25% of all patients with severe heart failure develop anemia with a hemoglobin less than 12 mg/dl [1] various etiologies, including sodium or water retention, have been proposed as an underlying cause of anemia in patients with cardiac dysfunction; these etiologies are reported to cause hemodilution, decreased iron absorption, impaired iron metabolism, and increased inflammatory factors (e.g., IL-1, IL-6 and TNF) that cause a decrease in erythropoietin production [1].

Nutritional causes (e.g., folic acid deficiency and use of either aspirin or warfarin with subsequent gastrointestinal bleeding), may contribute to the development of anemia in heart failure patients [5]. Treatment of the underlying anemia in heart failure patients improves both symptoms and prognosis and decreases both medical costs and morbidity [1]. For every 1 gram increase in hemoglobin there is a 13% decrease in the morbidity and mortality rate of heart failure [1]. Treatment of IDA in heart failure patients improves exercise tolerance and oxygen consumption in those patients [5]. Due to both the importance of optimal management of patients with underlying heart failure and the controversy surrounding treating anemia in patients with a decreased ejection fraction, we studied the effect of treating a patient's underlying anemia by measuring echo-cardiographic parameters and clinical responses.

Methods

In our study of 206 patients with heart failure, we examined each patient both before and after receiving treatment for underlying anemia. The patients were diagnosed based on the Framingham criteria and were divided in subgroups based on the etiology of their heart failure.

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Briefly, Framingham criteria were divided into major and minor criteria:

Major criteria includes: orthopnea, Paroxysmal nocturnal dyspnea, elevated jugular venous pressure, rales, cardiomegaly, acute pulmonary edema, S3 gallop, central venous pressure more than 16 mmHg, positive hepatojugular reflux constitutes major criteria. The minor criteria are: ankle edema, nocturnal cough, exertional dyspnea, hepatomegaly, pleural effusion, pulmonary vital capacity less than 1/3 maximum value, heart rate more than 120 bpm, weight loss more than 0.5 kg.

The etiology of heart failure was either ischemic cardiomyopathy or nonischemic cardiomyopathy (idiopathic, hypertensive cardiomyopathy, or valvular heart disease). We chose the patients randomly from those referred to Yazd University hospital centers from October 2009 until May 2010. All patients underwent cardiac catheterization to rule out ischemic etiology for cardiomyopathy. We recorded functional class, ejection fraction, CBC, sodium levels, potassium levels, ferritin levels, total iron binding capacity (TIBC), and serum iron levels for each patient. The patients with anemia (i.e., women with hemoglobin less than 12 mg/dl and men with hemoglobin less than 13 mg/dl) were divided into two groups: an IDA group and an anemia with chronic disease group. In the IDA group, patients with an MCV <77 fl and an MCH <27 pg were divided into two subgroups based of ferritin levels; group 1 had a ferritin level <50 ng/ml; group two had a ferritin level >50 Patients with iron deficiency anemia were treated with 325 mg of ferrous sulfate three times a day via oral route; equal to 65 mg of elemental iron a day. All Patients with anemia were treated with 1 mg of folic acid per day. All patients included in this study were treated optimally with medications available for treating their underlying heart failure. Patients were followed for 4 months to assess functional class and ejection fraction. Few patients died during follow up that we included all causes of mortality in our study.

Statistical analysis: The results were analyzed with SPSS 13. We analyzed parametric variables with paired t-tests and ANOVAs, and we analyzed non-parametric variables with chi-square tests, Fisher exact test, and Wilcoxon test for marginal homogeneity.

Results

We followed 206 patients from October 2009 through May 2010 that were referred for treatment of underlying heart failure. Mean patient age was 66.8 ± 9.3 years with an age range of 35 years to 90 years. Our study population consisted of 36% women and 64% men. Of the 206 patients, one hundred and thirty nine patients (67.5%) had a history of myocardial infarction and 124 patients (60%) had a history of hypertension. Dilated cardiomyopathy, was the underlying cause of heart failure in 9 patients (4.5%), while valvular disease was the underlying cause in 2 patients (1%). The average hemoglobin level in patients at first evaluation was 13.17 ± 1.82 mg/dl with a range of 8.5 to 17.6 mg/dl. The average ejection fraction at first evaluation was 28.6 ± 5.73 with a range of 10%-36%. The average urea level was 45.13 ± 27.68 mg/dl and the average creatinine level was 1.24 ± 0.7 mg/dl (Table 1). In our population, the prevalence of anemia was 36.4% of patients, and IDA was detected in 22 out of 206 patients (10.7%). The prevalence of anemia of chronic disease was 53 out of 206 patients (25.7%), and the remaining patients (63.6%) had normal hemoglobin levels. We found that the prevalence of anemia increased with age until a patient reached age 75. The correlation between the increase in the frequency of anemia and an increase in age was caused most often by anemia of chronic disease. Conversely, IDA prevalence decreased as age

| | |
|-----------------------|-------------|
| Age | 66.8 ± 9.3 |
| NHYA functional class | 2.8 ± 0.7 |
| Ejection fraction | 28.6 ± 5.7 |
| Hemoglobin level | 12.9 ± 2.8 |
| Platelet count | 220 ± 75 |
| Ferritin | 63.9 ± 36.5 |
| TIBC | 320 ± 73 |
| Urea | 45.1 ± 27.6 |
| Creatinin | 1.24 ± 0.69 |
| Sodium | 136 ± 5 |
| Potassium | 4.3 ± 0.5 |

Base line data.

Table 1: NYHA functional class: New York Heart Association functional class

increased (P-value=0.008). The hemoglobin levels both before and after anemia treatment are shown in Table 2. Treatment for anemia resulted in a significant improvement in hemoglobin levels (P-value<0.001). The increase in hemoglobin levels in the IDA group was greater than in the increase of hemoglobin levels in the anemia of chronic disease group (P-value = 0.014). We compared EF both before and after treatments for heart failure and anemia (Table 3) and found significant improvements (P-value ≤ 0.001) in all 3 groups; nonetheless, the IDA group had the highest rate of response with 90% of patients showing favorable responses. EF Improvement in IDA group was independent of ferritin level [Table 4]. Our results showed a significant increase in MCV in both the IDA group and the anemia of chronic disease group (P value ≤ 0.001). The increase in MCV was more prominent in the IDA group, which was comprised of patients who had a 3.9 fl increase in mean MCV, than it was in the anemia of chronic disease group, which had a 1.6 fl increase in mean MCV. The increase in MCH following treatment was significant in both groups with anemia, but the change in MCHC was only significant in the patients with anemia of chronic disease (P-value ≤ 0.001) and not in the patients with IDA (P-value=0.06). The decrease in platelet count following treatment was significant in patients with IDA and anemia of chronic disease. Patients with IDA had a two-fold decrease in platelet count after treatment relative to the decrease in patients with anemia of chronic disease. The total mortality rate during the study was 9.2%. Patients with anemia of chronic disease had the highest rate of mortality (22.6%), and patients with normal hemoglobin levels had the lowest mortality rate (3.8%); these rates were significantly different (P-value=0.001). The mortality rate of patients with anemia was 4.9-fold higher than the mortality rate of patients with normal hemoglobin levels (Table 5). Treatment of underlying heart failure improved the functional class in 116 patients (61%), while only 4% of displayed a worsening of the functional class after treatment. The improvement in functional class was more prominent in the IDA group, in which 87.5% of patients showed a decrease in functional class. The remaining patients (12.5%) showed no change in functional class.

We also compared creatinin level among three different group of CHF patients (Table 6) and our results showed lower creatinin values for patients with normal hemoglobin level while CHF patients with anemia of chronic disease showed the worst kidney function. (P value<0.01) Part of anemia in CHF patients with anemia of chronic disease and IDA may be explained by kidney dysfunction but we had the total number of 11 patients (out of 206 CHF patients) with kidney dysfunction in our study that would not account renal insufficiency as underlying cause of anemia in majority of patients.

Discussion

We found that a prevalence of underlying anemia in 36.4% of

| Type of anemia | Number of patients | Hgb before treatment | Hgb after treatment | Increase in Hgb level | Paired T-test (P value) |
|---------------------------|--------------------|----------------------|---------------------|-----------------------|-------------------------|
| Iron deficiency anemia | 21 | 10.77 ± 0.99 | 12.21 ± 1.34 | 1.44 ± 0.9 | < 0.001 |
| Anemia of chronic disease | 41 | 11.18 ± 0.87 | 12.15 ± 1.09 | 0.97 ± 0.55 | < 0.001 |
| Total anemia patients | 62 | 11.4 ± 0.92 | 12.17 ± 1.17 | 1.13 ± 0.71 | < 0.001 |

Table 2: Hemoglobin levels before and after treatment in patients with different types of anemia. Increase in hemoglobin level after treatment of anemia in both iron deficiency anemia group and anemia of chronic disease group. Hgb: hemoglobin

heart failure patients, which included IDA in 10.7% of patients and anemia of chronic disease in 25.7% of patients. A previous study found IDA in 21% of patients. That study used different criteria to diagnose IDA (i.e., ferritin <30 ng/ml and iron saturation <16%) [5]. The different IDA prevalence rates may result from differences in geographic variables and differences in the stage of heart failure that the patients were in. In our study the prevalence of anemia of chronic disease was two-fold higher in patients with a history of myocardial infarction, however these patients had a lower prevalence of IDA. No correlation was found between anemia and blood pressure. In patients with idiopathic dilated cardiomyopathy (9 out of 206 patients), IDA was detected in two patients, and anemia of chronic disease was detected in four patients. In our study, only two patients had a history of aortic valve replacement and both of those patients had IDA. In this study, we examined 11 patients with renal insufficiency and one patient with liver disease; these 12 patients had lower levels of hemoglobin than other patients due to underlying organ dysfunction. Eight patients could not continue iron treatment for the entire study period. In this study, the prevalence of anemia of chronic disease increased as age increased until a patient reached age 75, but IDA decreased in frequency as age increased. Mean hemoglobin was 12.9 ± 2.82 mg/dl with a range of 8.5 to 17.6 mg/dl. Treatment of IDA and anemia of chronic disease resulted in increased hemoglobin levels in patients. Patients with IDA had a 1.44 mg/dl increase in hemoglobin, and patients with anemia of chronic disease had a 0.97 mg/dl increase in hemoglobin. Okonko et al. [6] evaluated the effect of intravenous iron (using 200 mg of iron per week) on anemic and non-anemic patients with underlying heart failure; the treatment was continued until ferritin levels in a patient exceeded 500 ng/ml. The beneficial effects of iron therapy in patients with IDA produced significant increases in both peak O₂ consumption and exercise tolerance; furthermore, iron therapy improved functional class in patients with IDA. Our results showed an improvement in functional class after treatment for heart failure, and that this change was more prominent in patients with IDA that received treatment for both heart failure and underlying anemia. In patients with IDA, 86% showed improvement in functional class; in all patients, 60.7% showed improvement in functional class. Although patients with anemia of chronic disease showed an improvement in functional class, their improvement was not different significantly. We found an increase in EF in all 3 groups of patients. Mean EF was 28.6% before treatment and it increased to 38.3% after treatment. Mean EF increased by 7.9 ± 6.01% in patients with anemia of chronic disease, by 9.5 ± 6.6% in patients without anemia and by 11.25 ± 5.6% in patients with IDA. Although patients with IDA had a more prominent increase in EF compared to both patients with anemia of chronic disease and patients with normal hemoglobin level, the results were not significantly different (P value=0.16) that it can be attributed to impairment of iron absorption orally in heart failure patients as it has been described previously [7].

Previous study showed no significant improvement in clinical

response or hemoglobin level after oral iron therapy in heart failure patients with oral ferrous gluconate 300 mg daily [8] that is not congruent to our results. This discrepancy may be explained by the dose of elemental iron that patients were treated. We used ferrous sulfate 325 mg three times daily with 20% elemental iron but in Palazzuoli et al. [8] study, they used ferrous gluconate 300 mg daily with only 12% elemental iron.

Health improvement following iron treatment in patients with heart failure remains a subject of debate. In our population, anemia of chronic disease and IDA were more prevalent in women than in men, but the difference was not statistically significant. After subdividing patients in the IDA group based on ferritin levels (<50 ng/ml and >50 ng/ml), we found comparable improvements in EF and hematologic parameters in both groups (Table 3). Although Okonko et al. [6] found favorable patient responses to intravenous iron treatment. Beck da Silva et al. [9] found mixed results following treatment for anemia in patients with heart failure. In another study by Mancini et al. [10], treatment with iron, folic acid and erythropoietin produced favorable effects on both cardiac contraction and peak VO₂. This finding was consistent with the results of a study performed in Russia by Ponikowski et al. [11]. A subsequent study by Veldhuisen et al. [12] showed comparable effects caused by darbepoetin and a placebo in heart failure patients whose treatment included six minutes of walking.

Although intravenous iron treatment in CHF patients showed promising results [13,14] but the results for oral iron treatment is controversial. In recent study by Anker et al. [14], 459 CHF patients underwent treatment with intravenous iron with subsequent improvement in NYHA functional class and 6-minute distance walk.

In our study, we measured the levels of urea, creatinine, sodium and potassium. Patients with anemia had higher levels of urea and creatinine and had lower levels of sodium compared to patients with normal hemoglobin levels. There was no difference in potassium levels observed in patients with anemia and patients with normal hemoglobin levels. Patients with elevated urea levels had a 5-fold increase in mortality rate, and patients with elevated creatinine levels had a 6-fold increase in mortality rate. Mortality rates in patients with low sodium levels (< 135 mEq/dl) were 3-fold higher than mortality rates in patients with normal sodium levels. Patients with potassium level either greater than 5.5 mEq/dl or less than 3.5 mEq/dl had statistically insignificant risk for an increased mortality rate. Although the beneficial role of treatment with beta blocker, ACE inhibitor, angiotensin receptor blockers and aldosterone antagonists in CHF patients has been demonstrated [15], the optimal treatment for anemia in CHF patients remains subject of debate.

Limitations

Patients were followed only for seven months. We treated patients with anemia of chronic disease but there is still controversy on treatment of anemia of chronic disease. We did not use intravenous iron treatment and we only used oral ferrous sulfate.

Conclusions

We found an improvement in both functional class and ejection fraction in patients with heart failure and IDA following treatment with iron. Treatment with iron has beneficial effects on anemic patients treated for underlying heart failure that are independent of ferritin level. In patients with anemia of chronic disease, our results showed improvement after patients were treated for heart failure and were given folic acid, although the improvements were comparable to the

| P value | Percentage of patients with EF changes | | | EF after treatment | EF before treatment | Number of patients | Patient condition |
|---------|--|------------|-----------|--------------------|---------------------|--------------------|-------------------|
| | Increased | No changes | Decreased | | | | |
| <0.001 | 83.7 | 13.2 | 3.1 | 38.6±9.1 | 29.1±5.6 | 129 | Normal hemoglobin |
| <0.001 | 90.5 | 9.5 | 0 | 9±40.7 | 7.1±28.8 | 21 | IDA |
| <0.001 | 75.6 | 22 | 2.4 | 35.8±8 | 27.1±5.2 | 41 | Chronic anemia |

IDA: iron deficiency anemia

Table 3: Comparison of changes in ejection fraction (EF) value, and percentage of patients with changes in EF before and after treatment for anemia and heart failure. Improvement in EF after treatment of heart failure and anemia.

| Dependent Variable | Anemia group 1 | Anemia group 2 | Mean Difference | P-value |
|--------------------|-------------------|-------------------|-----------------|---------|
| EF | IDA ferritin > 50 | IDA ferritin < 50 | 2.5000 | 0.343 |
| | IDA ferritin > 50 | chronic anemia | 4.5732 | 0.022 |
| | IDA ferritin < 50 | chronic anemia | 2.0732 | 0.346 |
| Hemoglobin | IDA ferritin > 50 | IDA ferritin < 50 | 0.4944 | 0.102 |
| | IDA ferritin > 50 | chronic anemia | 0.6780 | 0.003 |
| | IDA ferritin < 50 | chronic anemia | 0.1836 | 0.463 |
| MCV | IDA ferritin > 50 | IDA ferritin < 50 | 2.3222 | 0.119 |
| | IDA ferritin > 50 | chronic anemia | 3.2512 | 0.004 |
| | IDA Ferritin < 50 | chronic anemia | 0.9290 | 0.451 |
| Platelet | IDA ferritin > 50 | IDA ferritin < 50 | -7.2020 | 0.772 |
| | IDA ferritin > 50 | chronic anemia | -25.0909 | 0.184 |
| | IDA ferritin<50 | chronic anemia | -17,8889 | 0.380 |

IDA: iron deficiency anemia, IDA ferritin < 50 ng/ml: iron deficiency anemia with ferritin level less than 50, IDA ferritin > 50 ng/ml: iron deficiency anemia with ferritin level more than 50 ng/ml.

Table 4: Comparing ejection fraction (EF) and hemoglobin related parameters changes after treatment for anemia and heart failure. Iron deficiency anemia (IDA) patients were subdivided into two groups based on ferritin level. Data show a significant improvement in EF in patients with IDA with ferritin > 50 ng/ml compared to anemia of chronic disease, but improvement in EF in patients with IDA is independent of ferritin level.

| | Number of patients | Mortality at 6 months | Mortality rate |
|---------------------------|--------------------|-----------------------|----------------|
| Normal Hgb level | 131 | 5 | 3.8% |
| Iron deficiency anemia | 22 | 2 | 9.1% |
| Anemia of chronic disease | 53 | 12 | 22.6% |

Table 5: Relationship between mortality and hemoglobin level. Patients with anemia of chronic disease showed highest mortality rate while patients with normal hemoglobin level had lowest mortality rate.

| Congestive heart failure patients | Number of patients | Creatinin level |
|-----------------------------------|--------------------|-----------------|
| Normal Hemoglobin level | 131 | 1.09 ± 0.28 |
| IDA | 22 | 1.45 ± 0.83 |
| Anemia of chronic disease | 53 | 1.50 ± 1.05 |

Table 6: Comparison of creatinin level between 3 groups of congestive heart failure (CHF) patients. CHF Patients with normal hemoglobin level had lower level of creatinin while CHF patients with anemia of chronic disease showed the highest values for creatinin level.(P value < 0.01)

improvements seen in patients without underlying anemia. Larger studies are needed to evaluate the effects treating anemia of chronic disease in patients with heart failure.

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