Section: General Medicine

Original Research Article

STUDY OF ANEMIA IN HEART FAILURE IN A TEACHING HOSPITAL

M. Nagamallika[1], P. Shruthi[2]

[1]*Associate Professor, Department of General Medicine, Maheshwara Medical College, Isnapur, Patancheruvu, Telangana, India.*
[2]*Assistant Professor: Department of General Medicine, Maheshwara Medical College, Isnapur, Patancheruvu, Telangana, India.*

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Corresponding Author:
Dr. P. Shruthi,
Assistant Professor, Department of General Medicine, Maheshwara Medical College, Isnapur, Patancheruvu, Telangana, India.
Email: drsruthi121111@gmail.com

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ABSTRACT

Background: Anemia in heart failure is complex and multifactorial. Anemia is defined when Hb concentration is less than 13 g/dL for men or less than 12 g/dL for women. Iron deficiency in patients with HF is defined as either serum ferritin concentration of <100 ng/mL or 100-299 ng/mL with transferrin saturation (TSAT) <20%. Among CKD patients, absolute iron deficiency is defined when the transferrin saturation (TSAT) is ≤20% and the serum ferritin concentration is ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. **Aims:** To evaluate patients with anemia and heart failure clinically, laboratory and echocardiography and to reduce subsequent hospitalisations of heart failure by identifying cause of anemia and correcting anemia.

Material and Methods: We analysed data from100patients of heart failure (HFrEF)with anemia. Each underwent blood test for hemoglobin, hematocrit, serum ferritin, transferrin saturation, CXR, ECG, echocardiography, NT pro BNP. We classified patients as having mild and moderate and severe anemia with lv systolic dysfunction. The data was entered in Microsoft excel sheet and analysed using percentage. The difference in proportions was tested using chi-square test.

Results: Mean age of the patients were between 20-80yrs with 30% of patients between 50-59yrs.Iron deficiency anemia was confirmed by Hb, serum ferritin in 80 patients and Hb, serum ferritin and transferrin saturation in 20 chronic kidney disease patients. The left ventricular ejection fraction was mild LVSD in 50%, moderate LVSD in 30% and severe LVSD in 20% patients. NTPro BNP was elevated in all patients,20% having >900pg/ml. ECG was showing tachycardia in 40% and St-T changes and LVH in 60% patients. CXR showing cardiomegaly in 80%patients. Oral medication was given for 10%patients. IV iron therapy was given for 90%patients and erythropoietin in 20%patients and packed cell transfusion was given in 10%patients.

Conclusion: In this group of patients, iron deficiency anemia was commonest cause. Oral iron is poorly absorbed, so administration of intravenous iron therapy (ferric carboxy maltose) is the only viable treatment option, with beneficial effects on most subjective outcomes, including NYHA class, 6MWD, patient global assessment, QoL, and fatigue score. There was improvement in hospitalizations for HF. For patients with CHF with anemia and concomitant chronic kidney disease, treatment with erythropoietic agents and supplemental iron reached hemoglobin to a target of 12 g/dl and improved quality of life. Red blood cell transfusion is recommended under careful monitoring in cases of severe anemia. The therapy must be strictly individualized considering the cost–benefit ratio.

Keywords: Hemoglobin, Heart failure, Transferrin saturation (TSAT).

INTRODUCTION

Anemia in heart failure is complex and multifactorial. World Health Organization definition of anemia is when Hb concentration is less than 13 g/dL for men or less than 12 g/dL for women.[1] Vitamin B12 or folate deficiencies are relatively infrequent (;4% to 5%), but iron deficiency (ID) is extremely common.

Iron deficiency in patients with HF is defined as either serum ferritin concentration of <100 ng/mL or 100-299 ng/mL with transferrin saturation (TSAT) <20%.[1] Among CKD patients, absolute iron deficiency is defined when the transferrin saturation (TSAT) is ≤20% and the serum ferritin concentration is ≤100 ng/mL among predialysis and peritoneal dialysis patients or ≤200 ng/mL among hemodialysis patients. Functional iron deficiency, also known as iron-restricted erythropoiesis, is characterized by TSAT ≤20% and elevated ferritin levels.[2]

Hemodilution, absolute or functional iron deficiency, activation of the inflammatory cascade, and impaired erythropoietin production and activity are some pathophysiological mechanisms involved in anemia of the heart failure. Other concomitant causes of anemia, such as myelodysplastic syndrome and chemotherapy, may worsen the outcome.

Patients with severe anemia often have features of worse HF with more extensive left ventricular (LV) remodeling and higher levels of biomarkers of advanced HF, higher inflammatory and collagen markers, and worse renal function. These factors lead to the development of anemia of chronic disease with defective iron utilization, inappropriate erythropoietin responsiveness, and depressed bone marrow function.

Based on the pathophysiology of cardiac anemia, there are several therapeutic options that may improve hemoglobin levels, tissues' oxygenation and probably the outcome. These include administration of iron, erythropoiesis-stimulating agents, and blood transfusions but still the evidence provided for their use remains limited.[6] Study evaluate patients with anemia and heart failure clinically, laboratory and echocardiography and to reduce subsequent hospitalisations of heart failure by correcting anemia.

MATERIALS AND METHODS

Prospective study done in the dept. Of General medicine at Maheswara medical college during July 2020 to July 2021 in 100 patients with anemia and heart failure

Inclusion Criteria

- Age of patient more than 20yrs
- Patients with anemia and heart failure

Exclusion Criteria

- Patient not willing
- Young patient less than 20yrs
- Patient in heart failure and no anemia
- Concomitant disease causing anemia

Methodology

We analysed data from100patients of heart failure (HFrEF)with anemia. Heart failure was diagnosed with modified Framingham's criteria.

Diagnosis of HF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria

1. Paroxysmal nocturnal dyspnoea;
2. Neck vein distention;
3. Crackles more than 10cm from base of lung
4. Radiographic cardiomegaly (increasing heart size on chest radiography);
5. Acute pulmonary edema;
6. S3 gallop;
7. Increased central venous pressure (>16 cm H2O at right atrium);
8. Weight loss >4.5 kg in 5 days in response to treatment.
9. Echocardiographic lv dysfunction

Minor criteria

1. Bilateral ankle edema;
2. Nocturnal cough;
3. Dyspnea on ordinary exertion;
4. Hepatomegaly;
5. Pleural effusion;
6. Tachycardia (heart rate>120 beats/min).
7. Weight loss >4.5kg caused by heart failure where factors other than treatment of CHF could contribute to weight loss

Minor criteria are acceptable only if they cannot be attributed to another medical condition (such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome). Each underwent blood test for hemoglobin, hematocrit, serum ferritin, transferrin saturation, CXR, ECG, echocardiography, NT pro BNP. We classified patients as having mild, moderate and severe anemia with LV systolic dysfunction.

The data was entered in Microsoft excel sheet and analysed using percentage. The difference in proportions was tested using chi-square test.

RESULTS

Table 1: Age distribution of patients

Age	Number of patients
20-29	5(M2,F3)
30-39	10(M5,F5)
40-49	20(M10,F10)
50-59	**30(M15,F15)**
60-69	**25(M13,F12)**
70-80	10(M5,F5)

In the present study age distribution varied from 20 years to 80 years. Majority noted among 50 - 59 years and next common among 60-69 years.

Table 2: Classification of anemia and number of patients effected

Anemia(Hb gm/dl)	Total Number of Patients=100 (M50,F 50)
Mild (10-11.9) F, (11-12.9) M	50 (M 25,F 25) 50%
Moderate (7-9.9)F, (8-10.9)M	30(M 15 ,F 15) 30%
Severe (<7)F , (<8) M	20 (M 10,F 10) 20%

In the present study mild anemia noted in 50 cases.

Table 3: Symptoms and severity of anemia

Symptoms	Anemia severity Mild	Moderate	Severe	Total patients	P Value
SOB exertional NYHA 1	20(M10,F10)	-	-	20(M10,F10)	<0.001
SOB during ordinary activity NYHA 2	30(M15,F15)	-	-	30 (M15,F15)	<0.001
SOB at mild activity NYHA 3	-	20 (M10,F10)		20 (M10,F10)	<0.001
SOB at rest NYHA 4	-	10 (M5,F5)	20 (M10,F10)	30 (M10,F10)	<0.001
Pedal Edema		20 (M10,F10)	20 (M10,F10)	40 (M20,F20)	<0.001
Palpitations	10(M5,F5)	20 (M10,F10)	10 (M5,F5)	40 (M20,F20)	0.0001
Fatigue	10 (M5,F5)	15 (M8,F7)	20 (M10,F10)	45(M23,F22)	<0.001

Table 4: Signs and severity of anemia

Signs	Anemia Severity Mild	Moderate	Severe	Total Patients	P Value
Pallor	20(M10,F10)	30(M 15,F15)	20(M10,F10)	70(M35,F35)	<0.001
Tachycardia	10 (M5,F5)	20 (M10,F10)	10 (M5,F5)	40 (M20,F20)	0.0001
JVP Raised		10(M5,F5)	20(M10,F10)	30(M15,F15)	<0.001
Rales		10(M5,F5)	20(M10,F10)	30(M15,F15)	<0.001
S3,S4			5(M3,F2)	5(M3,F2)	<0.001

Table 5: Laboratory values and number of patients effected and severity of anemia

Anemia Severity	NTpro BNP <125pg/ml(N)	Hematocrit 40-54% in males (N) 36-48%in females (N)	Serum ferritin <100ng/ml	Serum ferritin 100-299ng/ml and TSAT <20%	Serum ferritin in CKD <200ng/ml in HD	Serum ferritin in CKD <100ng/ml predialysis and PD	CXR Cardiomegaly
Mild	125 -450 pg/ml 50 patients(M25,F25)	30-39% M 30-35% F 50 patients(M25,F25)	50-60 ng/ml 50 patients(M25,F25)	-	-	-	30 patients (M15,F15)
Moderate	450-900pg/ml 30 patients(M15,F15)	20-29 % 30 patients (M15,F15)	70-80 ng/ml 10 patients(M8F7)	5 patients 100-300ng/ml and TSAT <20%(M3,F2)	5 patients <200ng/ml (M2F3)	5 patients <100ng/ml (M2F3)	30 patients (M15,F15)
Severe	>900pg/ml 20 patients (M10,F10)	<20% 20 patients(M10,F10)	80-90 ng/ml 10 patients(M7F8)	5 patients 100-300ng/ml and TSAT <20%(M2,F3)	5 patients <200ng/ml (M3,F2)	5 patients <200ng/ml and TSAT <20% (M3,F2)	20 patients (M10,F10)
Total	100	100	70	10	10	10	80
P Value	<0.001	<0.001	<0.001	0.002	0.002	0.002	<0.001

Table 6: ECG changes in patients and severity of anemia

ECG Changes	Anemia mild	Moderate	Severe	Total number of patients	P Value
Tachycardia	10(M5,F5)	20(M10,F10)	10(M5,F5)	40(M20,F20)	0.001
LVH	10(M5,F5)	30(M15,F15)	20(M10,F10)	60(M30,F30)	<0.001
ST depressions		15(M8F7)	15(M7,F8)	30(M15,F15)	<0.001
T wave changes	40(M20,F20)	10(M5,F5)	10(M5,F5)	60(M30,F30)	0.0001

Table 7: 2D ECHO findings in patients with anemia and heart failure

Parameters 2D ECHO	Mild Anemia	Moderate Anemia	Severe Anemia	Total Number of Patients
LV Systolic Dysfunction	-	-	-	
Mild EF -41-49 %	50(M25,F25)	-	-	50(M25,F25)
Moderate -30-40%	-	25(M13,F12)	5(M2,F3)	30(M15,F15)
Severe <30%	-	5(M2,F3)	15(M8,F7)	20(M10,F10)

P Value (Chi-square) <0.001

Table 8: Mode of treatment and number of patients

Treatment	Mild anemia	Moderate anemia	Severe anemia	Total number of patients	P Value
oral IRON (Ferrous fumarate and folic acid Tablet) supplementary to all patients once daily on empty stomach along with vit c	50 (M25,F25)	30(M15,F15)	20(M10,F10)	100(M 50,F 50)	NA
IV IRON (Inj Ferrinject 500mg 10ml in 100ml of NS)ferric carboxy maltose	40(M 20,F20)	30 M15,F15)	20(M10,F10)	90M45,F45)	0.004
Erythropoietin injections 50-100u/kg thrice weekly SC/IV	-	10 (M5,F5)	10 (M5,F5)	20(M10,F10)	<0.001
Blood transfusions Packed cell transfusions	-	-	10 (M5,F5)	10(M5,F5)	<0.001

DISCUSSIONS

Iron Deficiency is an important comorbidity in HFrEF and that treatment of iron deficiency in HFrEF improves symptoms and modestly reduces hospitalizations. One of the most recent trials conducted to assess the efficacy of oral iron supplements in patients with heart failure suffering from iron deficiency anemia is the IRONOUT-HF Randomized Clinical Trial. The trial was a Phase 2, double-blind, placebo-controlled randomized clinical trial with 225 participants that defined heart failure as LVEF< 40% and iron deficiency as serum ferritin level between 15-100 ng/ml or serum ferritin 101-299 ng/ml with transferrin saturation (TSAT) <20%. It included change in peak oxygen uptake (VO2), from baseline to 16 weeks, changes in 6-minute walk distance; plasma NT-pro BNP (N-terminal- pro hormone B-type natriuretic peptide) levels; and health status as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ) as its endpoints. The trial established the lack of improvement in exercise capacity after the use of a high-dose oral iron regimen and did not support the use of it in heart failure patients.[7] In our study,10 patients received only oral iron and there was not much improvement in iron indices, exercise capacity and quality of life.

The use of intravenous (IV) iron is preferred over the use of oral iron due to its superiority as established by the IRON-HF study, a multicentre, investigator-initiated, randomized, double-blind, placebo-controlled trial. The trial compared the efficacy of oral iron versus IV iron in 23 patients who received either Iron Sucrose IV, ferrous sulfate PO, or placebo, in a randomized manner.[8]

A double-blind, randomized, placebo-controlled study to evaluate changes in levels of NT-pro-brain natriuretic peptide (NT-pro BNP) and C-reactive protein (CRP) levels in patients receiving IV iron therapy without recombinant human erythropoietin (rhEPO). All 40 participants with anemia (hemoglobin (Hb) <12.5 g/dl, transferrin saturation <20%, ferritin <100 ng/ml) in a setting of chronic heart failure (LVEF < or =35%) or chronic renal failure (creatinine clearance <90 ml/min) were either given IV iron therapy or a placebo, at random, for five weeks after which they were evaluated on the based on Minnesota Living with Heart Failure Questionnaire (MLHFQ) and 6-min walk (6MW) test. The study concluded that the use of IV iron therapy in absence of rhEPO resulted in the betterment of LVEF, NYHA class, exercise capacity, and general quality of life.[9]

In our study ,90 patients received iv iron therapy (ferric carboxy maltose) and supplementation of oral iron and there was improvement in LVEF, NYHA Class, exercise capacity, general quality of life and reduced hospitalisation for heart failure but no change in mortality from decompensated heart failure.

In meta-analysis of 11 RCTs with 3044 patients, we found that ESA therapy leads to a significant improvement in LVEF and BNP compared with placebo. Also we found that ESA therapy reduced the NYHA functional class, an effect that was partly associated with patient symptomatic improvement. The specific mechanism of the improvement is not very clear. Previous studies have shown that ESA therapy seems to have potential effects to enhance cardiac contractile function and improve cardiac remodeling through its angiogenic and anti-apoptotic properties.[10]

Our meta-analysis found that the ESA therapy approach leads to a significant improvement in exercise capacity assessed by 6-MWD, exercise duration, and peak VO2. There are a number of potential mechanisms such as the treatment of anemia, attenuation of peripheral hypoxia with the concomitant improvement of metabolic status of

peripheral muscles and the reduction of volume overloading which may explain the beneficial effects of ESA on exercise tolerance and quality of life in anemic HF patients.[11,12] In our study, 20 patients received erythropoietin therapy of 4000u twice weekly and patients improved clinically by significant increase in hemoglobin ,peak oxygen uptake and exercise duration and quality of life.

3316 consecutive patients with acute myocardial infarction aged ≥ 65 y from the RICO survey. They were categorized according to their haemoglobin nadir (≤ 8, > 8 to ≤ 10 and > 10 g/dL) and age (< or ≥ 80 years). Results: 1906 patients (57%) were 65-79 y and 1410 (43%) ≥ 80 y, of whom 103 (5%) and 145 (10%) patients received red blood cell transfusion respectively (P < 0.001). In Cox regression analysis, transfusion was associated with increased 1-year mortality for haemoglobin nadir > 10 g/dL, but no significant effect for haemoglobin nadir between 8 and 10 g/dL. When haemoglobin nadir was ≤ 8g/dL, transfusion did not influence 1-year mortality for younger patients (65-79 y). However, for older patients (≥ 80 y), transfusion was associated with lower mortality.[13]

The clinical utility of blood transfusion in anemic cardiovascular disease populations is controversial. According to the guidelines from the American College of Physicians and the American Society of Anesthesiology, the "transfusion threshold" for patients without known risk factors for cardiac disease is a hemoglobin level in the range of 6 to 8 g/dL.[14] In 78 974 elderly patients hospitalized with acute myocardial infarction, blood transfusion was associated with a significantly lower 30-day mortality rate among patients with a hematocrit ≤30% on admission.[15]

In 838 critically ill patients (26% with cardiovascular disease), maintaining hemoglobin at 10 to 12 g/dL did not provide additional benefits on 30-day mortality compared with maintaining hemoglobin at 7 to 9 g/dL.[16]

Blood transfusion may be associated with other adverse effects including immunosuppression with increased risk of infection, sensitization to HLA antigens, and iron overload.[17,18]

Given this profile of risks and benefits, transfusion may be considered as an acute treatment for severe anemia on an individualized basis but does not appear to be a viable therapeutic strategy for the long-term management of chronic anemia in CHF.[19,20]

In our study,10 patients of severe anemia received blood transfusion and were improved clinically by improvement in hemoglobin, peak oxygen uptake, exercise capacity. and had less hospitalisations for heart failure.

CONCLUSION

Anemia is frequently encountered in HFrEF and represents a negative prognostic factor. Oral iron supplementation is the standard therapy for patients with Iron Deficiency. However, in patients with HF, apart from gastrointestinal intolerance, oral iron is poorly absorbed. Newer agents like oral sucrosomial iron are better absorbed with fewer gastrointestinal side effects. The administration of oral iron supplements in patients with HFrEF is not recommended because of the lack of studies demonstrating its efficacy, the high incidence of adverse digestive effects, and the long treatment periods needed to increase hemoglobin levels. The administration of intravenous iron therapy (ferric carboxymaltose) Is the only viable treatment option, with beneficial effects on quality of life and exercise capacity in patients with Iron Deficiency and systolic heart failure. IV iron has beneficial effects on most subjective outcomes, including NYHA class, 6MWD, patient global assessment, QoL, and fatigue score. There was improvement in hospitalizations for HF. For the subpopulation of patients with CHF with moderate-to-severe anemia (hemoglobin 11 g/dL) and concomitant moderate to severe chronic kidney disease (estimated glomerular filtration rate(60 mL/min), treatment with erythropoietic agents and supplemental iron reached hemoglobin to a target of 12 g/dl and improved quality of life.

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