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Anemia amongst patients with heart failure - a review

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Abstract

Introduction

Anemia and iron deficiency are common comorbidities in population with heart failure. Their association with unfavorable prognostic outcomes and diminished quality of life underscores the imperative need for accurate diagnosis and efficacious treatment interventions. In recent years numerous treatment options have been explored in clinical trials, aimed at addressing the multifaced aspects of these concurrent conditions.

Purpose of work

The aim of these review is to delineate potential therapeutic interventions for anemia and iron deficiency in patients with heart failure.

Materials and methods

Literature review in database PubMed, Google Scholar, MDPI using keywords: heart failure, anemia, iron deficiency, ferric carboxymaltose.

Summary

In patients with heart failure effective treatment of anemia and iron deficiency has demonstrated enhancements in quality of life and exercise capacity. Findings from IRONMAN clinical study have prompted revisions in the latest guidelines from the European Society of Cardiology. The imminent release of results from two ongoing trials holds the potential to reshape the therapeutic landscape for treating individuals with heart failure and iron deficiency. Nevertheless, there is no explicit evidence that studied interventions could improve morbidity or risk of hospitalizations.

Keywords: anemia, iron deficiency, heart failure, ferric carboxymaltose

Introduction

Anemia is defined by World Health Organization as a hemoglobin (Hb) concentration below <13.0 g/dL in men and <12.0 g/dL in women (1). It is a common comorbidity in heart failure (HF) and is associated with more unfavorable prognosis (2). The cause of anemia in patients with HF may be multifactorial and may result from nutritional deficiencies (mainly iron), chronic kidney disease, gastrointestinal bleeding, treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), chronic inflammation or fluid retention (3). In a retrospective cohort study conducted in Canada in 2002, that enrolled 12,065 patients with heart failure, it was observed that 21% of studied patients had iron deficiency (ID).

Erythropoiesis stimulating agents

In 2000, Israeli researchers published the first study results on the use of erythropoiesis stimulating agents (ESAs) in patients with HF (4). A retrospective data analysis of the 142 patients with HF, treated in outpatient clinic, were reviewed to determine prevalence and severity of anemia (Hb <12.0 g/dL) in this population. Following the analysis, 26 patients who despite at least six months therapy with maximum tolerated doses showed severe heart failure (New York Heart Association [NYHA] class >3) and anemia (Hb <12.0 g/dL) were enrolled in and interventional study. The mean age of the intervention group was 71.76 ± 8.12 years. Twenty-one men and five women participated in the study. All patients in the intervention group had a reduced left ventricle ejection fraction (LVEF) of less than 35%, persisted fatigue and shortness of breath (on exertion and often at rest) and had required hospitalization at least once during their follow-up in CHF clinic for pulmonary edema. Secondary causes of anemia were excluded.

The study intervention included administration of subcutaneous erythropoietin (EPO) and intravenous (IV) iron, sufficient to increase Hb to 12.0 g/dL. During the treatment period the doses of all medications, expect of diuretics (oral and intravenous furosemide), were not changed. EPO was administered initially at dose of 2,000 IU/week and then weekly *quantum satis* to maintain an Hb concentration >12.0 g/dL. Iron was administered as ferric sucrose product at a dose of 200 mg in 150ml saline over 60 minutes every week until serum ferritin reached

400 µg/liter or the percent iron saturation (% Fe Sat: serum iron/total iron binding capacity x 100) reached 40% or until Hb reached 12.0 g/dL. The mean study intervention lasted for 7.2 ± 5.5 months.

Throughout the treatment duration the NYHA class was decreased from a mean 3.66 ± 0.47 to 2.66 ± 0.70 ($p < 0.05$). LVEF increased from a mean of 27.7 ± 4.8 to 35.4 ± 7.6% ($p < 0.001$), an increase of 27.8%. The mean number of hospitalizations compared to a similar time before the onset of anemia treatment decreased from 2.72 ± 1.21 to 0.22 ± 0.65 per patient ($p < 0.05$), a decrease of 91.9%. No significant changes were observed in mean blood pressure values.

Subsequent to this findings, numerous additional studies shoved the positive effects of ESAs therapy on HF patients, including improved left ventricle function (5), reduced need for intravenous and oral diuretics (5) and increased exercise capacity (6,7).

A meta-analysis of 11 small randomized clinical trials comparing ESAs with a control group was published in 2011 (8). Nine of the studies were placebo-controlled, five of them were double blinded. The use of ESAs significantly increased exercise time by 96.8 seconds (95% confidence interval [CI] 5.2-188.4, $p=0.04$), and 6-Minute Walk Test distance (95% CI 17.0-121.7, $p=0.009$) compared to control. Furthermore, the peak VO2 was increased by +2.29 mL/kg/min, NYHA class was reduced by 0.73, the LVEF increased by 5.8%, concentration of the B-type natriuretic peptide reduced by 226.99 pg/mL. All observed changes were statistically significant. There was no increase in a number of adverse effect or mortality (OR 0.58, 95% CI 0.34-0.99, $p=0.047$).

A definitive answer on the effectiveness of using ESAs therapy was provided by the RED-HF study (9,10). Between 2006 and 2012, a total of 2278 patients with heart failure and anemia were enrolled in this randomized, double-blind study. Patients were randomized in a 1:1 ratio to receive darbepoetin alfa (to achieve Hb concentration 13 g/dL) or placebo. Randomization was stratified based on geographic region and the use of implantable cardioverter-defibrillator and/or cardiac resynchronization therapy. The primary endpoint was hospitalization for HF exacerbation or death from any cause. Secondary endpoints included, among others, a change from baseline to 6 months in the Kansas City Cardiomyopathy

Questionnaire (KCCQ) (11). The study results showed no significant differences between the groups in both the primary (p=0.87), and the aforementioned secondary endpoint. Stroke (fatal or non-fatal) occurred in 42 patients (3.7%) in the darbepoetin group and 31 (2.7%) in the placebo group (p=0.23). Thromboembolic side effects occurred in 153 (13.5%) patients in the darbepoetin group and 114 (10.0%) in the control group (p=0.01). This study clearly demonstrated the lack of benefit of using ESAs in patients with HF and anemia, and the statistically significant occurrence of negative thromboembolic effects during treatment.

Iron metabolism

Iron is a critical micronutrient crucial for the physiological functioning of the human body. It constitutes as integral component of essential biomolecules such as hemoglobin, myoglobin, cytochromes and enzymes pivotal for cellular respiration, mitochondrial function and energy production. Moreover, iron plays a vital role in cellular processing including cell division and DNA repair (12).

In food, it is found in two distinct forms – heme and non-heme. The heme form is predominantly present in animal products, while the non-heme form can be sourced from inorganic iron salts, plant products or pharmaceuticals (13).

In the human body, the absorption of iron takes place in the duodenum and the initial part of the jejunum. Several substances can modulate the efficiency of this process. Activators of absorption include ascorbic acid, which facilitates the reduction of iron to its ferrous form and can chelate it, thereby maintaining iron in soluble form. Factors that can reduce the absorption of iron ions include phytates (commonly found in most cereal grains) and tannins (derived from coffee or tea) (13,14).

Ferrous iron readily undergoes reaction with oxygen, leading to formation of free radicals that pose harm for the body, therefore in the body it is predominantly found in a protein-bound state, with transferrin playing a role in extracellular binding and ferritin serving as the intracellular binding protein (15,16).

There is about 4 g of iron in the body of an adult male – 2.5 g is contained in erythrocytes, 1g is stored by macrophages in the liver and spleen and the rest is contained in enzymes and other proteins. Only 3 mg of Fe is bound to transferrin

and represents a mobile pool of ions delivered to cells. About 1-2 mg is lost along with epidermal exfoliation, intestinal epithelium and minor blood losses and the same amount is absorbed by enterocytes in the gastrointestinal tract (17). The human body has no iron exertion system so its absorption must be carefully regulated. One of the mechanism responsible for this process is the so-called dietary regulation – after a bolus of iron contained in food, the absorbing cells become resistant to absorption of this element (18). Hepcidin, a hormone synthesized mainly by liver cells, is also involved in this process. Hepcidin bind to the ferroportin – a protein found in the cell membrane of enterocytes, macrophages and hepatocytes, responsible for transporting iron ions into serum – and causes its internalization and degradation. Hepcidin production is increased in states of elevated Fe concentrations in serum or tissue stores and also in chronic inflammatory conditions (acute phase protein) (19,20).

Iron deficiency

Iron deficiency (ID) can be divided into functional and absolute. Absolute ID occurs when the total pool of iron in the body is reduced (insufficient supply from food or absorption disorders such as celiac disease) or the amount of available iron is inadequate to meet the body's needs (puberty or pregnancy). Functional ID is associated with the presence of chronic conditions (cancer, chronic renal disease, heart failure, autoimmune diseases) that prevent the mobilization of iron ions from stores and also reduce its absorbing through persistent inflammation (elevated hepcidin levels) (21).

The gold standard for the diagnosis of iron deficiency is the assessment of bone marrow iron stores by Prussian blue staining of biopsy aspirate (22,23). The best corelating parameter with marrow iron content in the absence of inflammatory factors is plasma ferritin concentration. A concentration below 30 µg/L is indicative of absolute ID. Measurement of transferrin saturation (TSAT, <16%) is not necessary for the diagnosis of iron deficiency but is helpful ferritin determination cannot be relied upon (adding acute phase protein) (23).

In diseases with chronic inflammation – heart failure for example – a ferritin concentration of <100 µg/L or 300 µg/L together with TSAT <20% is considered the cut-off point (23–25).

In a 2010 publication, Professor Jankowska et al. demonstrated that iron deficiency in patients with HF is an independent negative prognostic factor (26). This prospective observational study included 546 patients with stable systolic heart failure (LVEF 26 ± 7%). ID was defined as ferritin concentration <100 μg/L or 100-300 μg/L with TSAT <20%. The prevalence of ID was 37 ± 4% (± 95% CI) in the entire study population (32 ± 4 vs 57 ± 10 in patients without vs anemia defined as Hb levels <12.0 g/dL in women and 13.0 g/dL in men). ID was more common in women, patients with higher NYHA class, having higher serum levels of N-terminal pro-type B natriuretic peptide (NT-pro BNP) and high sensitivity C reactive protein (hs-CRP; in each case $p < 0.05$). At the end of a follow-up period (mean 731 ± 350 days), 153 deaths (28%) and 30 (6%) heart transplants were observed. ID but not anemia was associated with an increase risk of death or transplantation (hazard ratio 1.58, 95% CI 1.14-2.17, $p < 0.01$).

Oral iron therapy

Low price and high availability are the biggest advantages of oral iron formulations. However, patients using them often complain of a number of side effects: nausea, feelings of heartburn, constipation and diarrhea. The incidence of side effects is also higher when used formulations contain ferrous iron (27). Increased levels of inflammatory mediators in heart failure are also a problem, as they significantly reduce the absorption of iron from the gastrointestinal tract (28).

The IRON-HF study, published in 2013, compared therapy with oral and intravenous iron formulations. This randomized, double-blinded, placebo-controlled trial enrolled 23 patients with HF, preserved renal function, low TSAT and reduced ferritin levels. The intervention consisted of intravenous administration of 200 mg iron sucrose once a week for 5 weeks, oral administration of 200 mg iron sulfate three times daily or placebo. The primary endpoint was an increase in peak VO2 assessed by ergospirometry at a 3-month follow-up. A not statistically significant increase of peak VO2 of 3.5 mL/kg/min was observed in IV iron treatment arm. No increase was obtained in the oral treatment arm. A statistically significant increase of ferritin concentration and TSAT were observed in both treatment arms. Changes in Hb levels were similar in both arms. In conclusion, intravenous iron seems to improve the functionality of HF and ID patients more, however the effectiveness

on the red blood cell parameters is similar to oral formulation (29). Due to the low sample size in the IRON-HF study, there was a possibility of type II error (30).

A clear answer to dilemma regarding the choice of form of therapy came from the results of the IRONOUT-HF trial. This was randomized, double-blinded, placebo-controlled trial including patients with heart failure with reduced ejection fraction (HFrEF, LVEV <40%) and ID defined as ferritin levels of 15-100 ng/ml or 101-299 ng/ml with TSAT <20%. The intervention consisted of oral administration of iron sucrose twice daily at a dose od 150 mg for 16 weeks. The primary endpoint was change in peak VO2. 203 patients completed the study. In the oral iron group baseline mean peak VO2 was 1196 ml/min and in the placebo group it was 1167 ml/min. The primary endpoint was not significantly different between the intervention and placebo groups (+23 ml/min vs -2 ml/min; difference 21 ml/min [95% CI, -34 to +76], p=0.46). Similar statistically significant findings were observed in secondary endpoints: the 6MWT distance, NT-pro BNP levels, KCCQ score and time to first adverse events. High dose oral iron therapy in patients with ID and HF does not increase exercise capacity (31).

Intravenous iron therapy

Over past 20 years, the results of 6 studies of intravenous iron therapy in patients with HF and ID have been published (32–37). Despite the availability of various intravenous formulations containing iron (38), most of these studies used ferric carboxymaltose (FCM).

The first large study was FAIR-HF (Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency) (34). The trial enrolled 459 patients with HF in NYHA class II (LVEF <40%) and NYHA class III (LVEF <45%), ID defined as ferritin levels <100 µg/L or 100-299 µg/L with TSAT <20% and Hb levels 95-135 g/L. Patients were randomized to the FCM and placebo groups in the 2:1 ratio. The primary endpoint was change in self-assessment Patient Global Assessment (PGA) score and in NYHA class – both parameters were assessed at 24 week of follow-up. Secondary endpoints included 6MWT, and health-related quality of life. In the intervention group, 50% of patients reported significant or partial improvement compared to the 28% in the placebo group according to the PGA form (OR 2.51; CI 1.75-3.61). Similar improvements were seen in NYHA functional class, with 47% of patients in

FCM group rated as NYHA I or II class and 30% in the control group (OR for improvement by 1 class, 2.40; 95% CI, 1.55-3.71). The results were similar in patients with- or without anemia. Secondary endpoints also improved in FCM group. In both groups the incidence of death and adverse events of therapy were similar.

Comparable results were also observed in CONFIRM-HF (35) and EFFECT-HF (36) studies. Patients with HF and ID who received intravenous iron therapy shoved improvements in symptoms, exercise capacity, quality of live and increase in peak VO2. Nevertheless, none of the studies demonstrated a decrease in mortality and hospitalization rates due to HF. Promising findings emerged from the IRONMAN trial, published in 2022 in the United Kingdom (37).

This prospective, randomized, open-label endpoint-blinded study enrolled 1137 patients from 70 hospitals in the UK. Inclusion criteria comprised patients aged 18 years or older with heart failure (LVEF ≤45%) and transferrin saturation ≤20% or plasma ferritin below 100 µg/L. Patients were randomly assigned to and intervention or a control group in a 1:1 ratio. The intervention group received intravenous ferric derisomaltose (FDI) and the control was treated according to standard of care in HF. FDI dose was calculated based on body weight and hemoglobin concentration. The primary endpoint of the study was periodic hospitalization due to HF or death of cardiovascular causes. A mean follow-up time was 2.7 years. There were 336 endpoints in the FDI group (22.4 per 100 patient-years) versus 411 (27.5 per patient-years) in the standard care group (rate ratio 0.82 [95% CI 0.66-1.02]; p=0.070).

European Society of Cardiology guidelines and outlook

The positive results of the IRONMAN trial highlighted potential benefits of reducing the risk of hospitalization in a population with HF, reduced LVEF and ID. This findings have been taken into account in the latest European Society of Cardiology (ESC) guidelines. The supplementation of FCM or FDI is advised in symptomatic patients with HFrEF and HFmrEF and iron deficiency to reduce the incidence of hospitalization – a class IIa recommendation. The ESC guidelines further endorse the utilization of intravenous iron formulations to enhance quality of live and symptoms, warranting a class I recommendation from the ESC (39).

Ongoing trials are investigating the effect of FCM on mortality and risk of hospitalization in patients with HF and ID. The FAIR-HF2 trial, being conducted in Hamburg, Germany (NTC03036462) is anticipated to include about 1,200 patients. The second, Polish study from the Wroclaw Medical University (NTC05759078) is expected to enroll about 2,000 patients. Both trials have the potential to provide new evidence supporting the benefit of intravenous iron supplementation in the HF population and influence new standard of care. Insights from the German research efforts may become available as early as 2024.

Conclusions

Anemia and ID are common comorbidities in HF patients linked to poor prognosis and diminished quality of life. Over the years, it has been proven that the use of erythropoiesis-stimulating agents and oral iron supplementation did not improve the condition or prognosis of patients. Clear evidence has emerged in support of the efficacy of intravenous iron therapy in the HF and ID population. Intravenous iron has been shown to improve quality of life, reduce symptoms, and increase exercise capacity. Recent studies also suggests a potential reduction in mortality and incidence of hospitalization, however, current evidence is inconclusive. Ongoing and forthcoming studies hold promise for delivering crucial information that may inform clinical decisions in the future.

DISCLOSURE

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