ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 10, Issue 03, pp.8404-8407, March, 2023

RESEARCH ARTICLE

IRON DEFICIENCY AND ITS IMPACT IN HEART FAILURE; PREVALENCE AND TREATMENT

***Assoc. Prof Ergita Nelaj, Dr. Jonilda Shukulli, Dr. IridaKecaj, Dr. Somida Kuka and Prof. Dr. Mihal Tase**

Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirane, Albania

ARTICLE INFO

Article History:
Received 20th December, 2022
Received in revised form
28th January, 2023
Accepted 25th February, 2023
Published online 25th March, 2023

Key words:

Rectus Diastasis,
Mode of Delivery,
Digital caliper..

ABSTRACT

Background: Iron deficiency is a common comorbidity in patients with heart failure. Iron deficiency impairs exercise capacity, reduces the quality of life, and increases hospitalization rate and mortality risk regardless of anaemia. A high prevalence of iron deficiency has been found in patients with HF with reduced ejection fraction. Our study aimed to assess the effects of intravenous iron therapy on clinical condition, left ventricular function and quality of life in patients who suffered of chronic heart failure and concomitant iron deficiency. **Material and Methods:** The present study compressed 62 patients (29 males, 33 females) with advanced heart failure. The study group was divided into three small groups: one that was treated with intravenous iron, one with oral iron, and the third without treatment. The duration of treatment was 24 weeks. In all, general physical, clinical, laboratory, and echocardiographic examinations were performed, before and after treatment, and compared between them, for each group. At the beginning and at the end of the study all patients underwent the Kansas City Cardiomyopathy Questionnaire. **Results:** The NYHA class showed a significant improvement after intravenous iron. The prevalence of heart failure-related edema was also significantly reduced from 67% before treatment to 47% after that ($p = 0.036$). The rate of hospitalization in the intravenous iron group was considerably reduced from 47% to 17% ($P < 0.001$). The treatment of iron deficiency in this group of subjects got a significant improvement in KCCQ total score. **Conclusions:** Iron deficiency is associated with increased morbidity and mortality in heart failure patients. Intravenously correcting iron deficiency has emerged as a promising treatment in heart failure, improving symptoms, quality of life, exercise capacity, and reducing hospitalizations.

INTRODUCTION

Heart failure (HF) represents a highly prevalent worldwide disease. It is estimated that its incidence will significantly rise within the near future. HF is a clinical syndrome presenting with typical symptoms like breathlessness, ankle swelling, and fatigue. HF is caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or an elevated intracardiac pressure when the patients are at rest or during phases of stress. (1)Iron deficiency (ID), is common in chronic HF and, in the presence or absence of anemia, is associated with poorer quality of life, exercise capacity, and prognosis. (2)The prevalence of ID in chronic HF patients ranges from 50% in Europe (3) to 61% in a multi-ethnic Asian population.(4) A high prevalence of ID has been found in patients with HF with reduced ejection fraction (HFrEF). It is one of the commonest associations in patients of HF and has been shown to be associated with increased mortality in both acute and chronic heart failure (5). It has also been reported that anemia is a predictor of mortality in chronic HF patients regardless of whether their left ventricular ejection fraction (LVEF) is preserved or reduced (6).

Corresponding author:** ***Assoc. Prof Ergita Nelaj,
Department of Internal Medicine, University Hospital Center "Mother Teresa", Tirane, Albania.

Of note, correction of iron deficiency is associated with improved outcomes (7) that has prompted leading cardiology organizations to issue a class IIb recommendation screening and correction of ID in patients with HF (8,9)With every 1 g/dL fall in hemoglobin level, the chances of HF rise by 15.8%. (10). The aim of this study was to assess a cohort of patients hospitalized with HF for (1) the prevalence of anemia and (2) the existence of correlations parameters reflecting the severity of heart failure and the grade of anemia, and (3) how the correction of ID with venous preparations affects the NYHA scale of heart failure and quality of life.

METHODS

We collected data from 62 patients (29 men, 33 women, mean age 67.5 years) hospitalized with decompensated heart failure with reduced ejection fraction and ID. The diagnosis of HF satisfied European Society of Cardiology criteria at the time of data collection (2012 Guidelines), and was based on each patient's clinical presentation, history and examination findings. Left ventricular ejection fraction (LVEF) < 50% and > 50%, determined quantitatively on transthoracic echocardiogram, defined heart failure with a reduced ejection fraction (HFrEF) and heart failure with a preserved ejection

fraction (HFpEF), respectively. (11)Exclusion criteria were: recent (<1month) acute coronary syndrome, and advanced renal disease on hemodialysis. The study group was divided into three small groups: one that was treated with oral iron (26 patients), one with intravenous iron (16 patients), and the third group without treatment for ID (20 patients). The duration of treatment was 24 weeks. First group was treated with oral preparations (mainly in the form of ferrous sulphate), taken 2-3 times/day, 20 minutes before meals accompanied by Vitamin C. The second group was treated with intravenous iron complexes, such as ferric hydroxide sucrose, 100mg/5ml (2flc)/day given on the 1st, 3rd and 5th day of hospitalization. Ferrovina is dissolved in 200ml Sol.NaCl 0.9% given for 20-30 min. The third group was left without medication for ID, as a control group. At admission and during hospital stay routine (part of usual care) clinical and preclinical data were recorded in a dedicated database: demographic data, clinical diagnosis, triggering factors of decompensating, signs and symptoms at admission, ECG data, echocardiographic data, laboratory parameters at admission, and in-hospital treatment data. According to the World Health Organization (WHO) criteria (12), anemia was defined as Hb< 12 g/dL for women and Hb< 13 g/dL for men, as well as serum ferritin < 100 mg/L (absolute iron deficiency). All patients were evaluated before and after treatment and the results are compared between them, for each group. At the same time, all patients were underwent the Kansas City Cardiomyopathy Questionnaire (KCCQ)(13), at the beginning and at the end of their treatment. The KCCQ is a self-administered, 23-item questionnaire that quantifies physical limitations, symptom stability, symptoms, self-efficacy, social interference, and HRQoL in patients with HF.(14)KCCQ can validly and sensitively capture the impact of heart failure on patients' lives and is strongly associated with clinical events over time. All patients were evaluated for NYHA class, KCCQ, Hb, ferritinemia, renal function, and NTpro-BNP. Patients were assessed at recruitment (baseline), 12 weeks, and 24 weeks after enrolment, and clinical outcomes were determined up to 1 year following enrolment.

RESULTS

The prevalence of ID was 53.17% and the prevalence of anemia was 12.15%. HF was more prevalent in women (60%) than men (40%).43.5% of all patients had HFrEF< 40% and 56.5% of them had moderated FE, 40-50 %. The majority of patients were treated with heart failure medications. Loop diuretics were the most commonly prescribed medications, and used to relieve symptoms of congestive cardiac failure. These were followed by beta-blockers, then angiotensin converting enzyme inhibitors/angiotension II receptor blockers and mineralocorticoid receptor antagonists, all of which were used as disease modifying agents in patients with a reduced LVEF. The prevalence of smoking, diabetes, chronic kidney disease (CKD) and anemia was 11.4%, 51.6%, 32.3% and 13.08%, respectively. In comparison with non-anaemic patients without ID, subjects with IDA were older, had more severe HF symptoms, higher LVEF and plasma NT-proBNP, and lower KCCQ score. At subgroup treatment with intravenous iron, the NYHA class showed a significant improvement. The prevalence of heart failure-related edema was also significantly reduced from 67% before treatment to 47% after that (p = 0.036). The rate of hospitalization in the intravenous iron group was considerably reduced from 47% to 17% (P < 0.001). The treatment of iron deficiency in this group of subjects got a significant improvement in KCCQ total score. Patients treated with intravenous iron have a significant reduction in NYHA functional class (P=0.001), higher value of KCCQ score (P <0.0001), lower value of NTproBNP (P=0.0001), higher value of Hb (P<0.001) and higher value of Ferritinemia (P<0.001). Patients had a lower incidence of cardiovascular (CV) mortality and recurrent CV hospitalizations (P < 0.01). In the group of patients treated with oral iron, it has been noticed that there is no improvement in NYHA or an increase in the KCCQ score. It has been noticed that there is no significant increase in biochemical parameters (Hb, Ferritin). In the dynamic follow-up of these patients, it was found that they have the highest rate of re-hospitalizations and mortality compared to patients left without medication. Also, of these patients, 38.5% have died. In the control group, left without medication (20 patients), only 25% have died. These data strongly suggest the beneficial effect of intravenous iron in patients with HF and ID.

DISCUSSION

Iron deficiency in the context of heart failure is widely recognized as an independent predictor of poorer outcomes including fatigue, reduced exercise capacity, reduced quality of life, increased hospitalization, and increased mortality.(15,16) It has also been demonstrated that a greater prevalence of ID appears to correlate with higher (i.e., worse) NYHA functional class (16, 17). The prevalence of ID in our study is high (53.17%) consistent with previous reports.(3,4,18) The prevalence of ID has been widely reported in patients with HFrEF but not HFpEF. A recent meta-analysis pooled the results of multiple small studies and found a prevalence for ID of 59% (95% CI 52– 64%) in 1414 patients with HFpEF. (19) The prevalence (53.17%) of ID in our patients with HFpEF in this study, is consistent with this meta-analysis. Given the significance of iron deficiency in heart failure, numerous studies have investigated the possibilities for correcting it.The guidelines suggest intravenous ferric carboxymaltose as an efficacious form of iron replacement in symptomatic patients with HFrEF and iron deficiency, in order to alleviate heart failure symptoms, improve exercise capacity and quality of life (9, 11). In our study, in the group treated with intravenous iron we find a significant increase in Hb and Ferritin after 24 weeks,compared to patients treated with oral preparations. It's consistent with the IRONOUT-HF study, which is the largest randomized trial to examine the effects of high-dose oral iron in patients with HF.(20)This study showed that high-dose oral iron did not improve exercise capacity in patients with iron deficiency and HFrEF, and do not support the use of oral iron supplementation to treat iron deficiency in patients with HFrEF.

From the data of our study, results that patients treated with intravenous iron have a significant improvement in the quality of life, with a decrease in the NYHA functional class and an increase in the KCCQ score.Also, there is a significant decrease in NT-proBNP after 24 weeks of treatment with intravenous iron.These data, coincide with the results of the two major studies FAIR-HF and CONFIRM-HF, that studied the effects of FCM (ferric carboxymaltose) onpatients' quality of life. In FAIR-HF , 459 patients with chronic HF, NYHA class II or III, LVEF ≤40% and iron deficiency, were randomised to intravenous FCM or placebo (2:1 ratio).

The primary end-point was a self-reported Patient Global Assessment (PGA) and NYHA functional class at 24 weeks. (21) FAIR –HF study concluded that, in stable, symptomatic, ambulatory patients with chronic heart failure, an impaired left ventricular ejection fraction, and iron deficiency, treatment with ferric carboxymaltose over a 24-week period improves symptoms, physical performance, and the quality of life (21). In CONFIRM-HF there was an objective primary endpoint rather than subjective measures and this primary endpoint was met convincingly. The follow-up period of 1 year was longer than in FAIR-HF providing evidence of longer term use and benefit.They saw a significant reduction in hospitalization from HF in this study, which may be the crucial missing piece in the puzzle that will persuade clinicians to advocate its use in HF (22).

So, the guidelines suggest ferric carboxymaltose as an effective form of iron replacement in symptomatic HF with decreased EF, in order to alleviate HF symptoms, exercise function and life skills. Treatment with intravenous iron replacement therapy has been shown to increase serum ferritin, transfer saturation, and hemoglobin levels, which improves their abilities and NYHA functional classes.

CONCLUSION

Iron deficiency anaemia is a very common comorbid condition in patients of HF. It's clearly prevalent in HF. It is recommended that every patient with HF should be screened for ID. Intravenous iron therapy is now recommended in HF with reduced ejection fraction in the presence of iron deficiency. There is conclusive evidence that it reduces hospitalizations and improves quality of life.

Funding**:** This work did not receive any specific grant from any funding agency in the public, commercial and not for profit sector or industry.

Conflicts of Interest**:** No conflict of interest.

ABBREVIATIONS

CV: Cardiovascular
CKD: Chronic kidney disease
HF: Heart failure
HFrEF: Heart failure with reduced ejection fraction
HFpEF: Heart failure with a preserved ejection fraction
HRQoL: Health-related quality of life
IDIron: deficiency
KCCQ: Kansas City Cardiomyopathy Questionnaire
LVEF: Left Ventricular Ejection Fraction
NTpro-BNP: N-terminal (NT)-pro Brain Natriuretic Peptide
WHO: World Health Organization

REFERENCES

Jacob C, Altevers J, Barck I, Hardt T, Braun S, Greiner W. Retrospective analysis into differences in heart failure patients with and without iron deficiency or anaemia. ESC Heart Fail. 2019 Aug;6(4):840-855. doi: 10.1002/ehf2.12485. Epub 2019 Jul 9. PMID: 31286685; PMCID: PMC6676442.

Tkaczyszyn, M., Comín-Colet, J., Voors, A.A., van Veldhuisen, D.J., Enjuanes, C., Moliner-Borja, P., Rozentryt, P., Poloński, L., Banasiak, W., Ponikowski, P., van der Meer, P. and Jankowska, E.A. (2018), Iron deficiency and red cell indices in patients with heart failure. Eur J Heart Fail, 20: 114-122.)

Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, JankowskaEA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013; 165: 575– 582.

Yeo TJ, Yeo PS, Ching-Chiew Wong R, Ong HY, Leong KT, Jaufeerally F, Sim D, Santhanakrishnan R, Lim SL, M Y Chan M, Chai P, Low AF, Ling LH, Ng TP, Richards AM, Lam CS. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. *Eur J Heart Fail* 2014; 16: 1125– 1132.

Chopra VK, Anker SD. Anaemia, iron deficiency and heart failure in 2020: facts and numbers. ESC Heart Fail. 2020 Oct;7(5):2007-2011. doi: 10.1002/ehf2.12797. Epub 2020 Jun 30. PMID: 32602663; PMCID: PMC7524223

Kajimoto K, Sato N, Takano T; investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Association between anemia, clinical features and outcome in patients hospitalized for acute heart failure syndromes. Eur Heart J Acute Cardiovasc Care. 2015 Dec;4(6):568-76. doi: 10.1177/2048872614554199. Epub 2014 Oct 14. PMID: 25315117.

Ponikowski P, Veldhuisen DJV, Comin-Colet J, *et al*. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J. 2015;36:657–668

Yancy CW, Jessup M, Bozkurt B, *et al*. ACC/AHA/ HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure. J Am CollCardiol. 2017;70:776–803.

Ponikowski P, Voors AA, Anker SD, *et al*. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37:2129–2200

Givertz MM, Colucci WS, Braunwald E. Clinical aspects of heart failure: High-output failure; pulmonary edema. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 7th ed. Philadelphia: Saunders; 2007. p. 539-68.

Simon S, Ioannou A, Deoraj S, *et al*. Audit of the prevalence and investigation of iron deficiency anaemia in patients with heart failure in hospital practicePostgrad Med J 2020;96:206–211.

WHO, UNICEF, UNU. Iron deficiency anaemia: assessment, prevention and control : a guide for programme managers. Geneva: World Health Organization; 2001

John A. Spertus, Philip G. Jones, Alexander T. Sandhu, Suzanne V. Arnold. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. Journal of the American College of Cardiology, 2020; Vol 76 (20), pp. 2379-2390.

Green CP, Porter CB, Brensnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am CollCardiol. 2000;35(5):1245–55.

Anker SD, Kirwan BA, van Veldhuisen DJ *et al*, Efects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual

patient data meta-analysis. Eur J Heart Fail 2018; 20:125–133

Ismahel, H., Ismahel, N. Iron replacement therapy in heart failure: a literature review. *Egypt Heart J* 2021; 73, 85

Ebner N, von Haehling S. Why is iron deficiency recognised as an important comorbidity in heart failure? Card Fail Rev. 2019; 5(3):173–175.

Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010; 31: 1872–1880.

Beale AL, Warren JL, Roberts N, Meyer P, Townsend NP, Kaye D. Iron deficiency in heart failure with preserved ejection fraction: a systematic review and metaanalysis. Open Heart 2019; 6

Lewis GD, Malhotra R, Hernandez AF, *et al*. Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency: The IRONOUT HF Randomized Clinical Trial. JAMA. 2017;317(19):1958–1966.

Anker SD, Comin Colet J, Filippatos G, *et al*. Ferric carboxymaltose in patients with heart failure and iron deficiency. The New England Journal of Medicine. 2009 Dec;361(25):2436-2448.

Piotr Ponikowski, Dirk J. van Veldhuisen, Josep Comin-Colet, Georg Ertl, Michel Komajda, et.al., for the CONFIRM-HF Investigators, Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency, European Heart Journal, 2015; 36:657–668.

****