UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
GRIGORE T. POPA IAȘI

TREATMENT OF IRON DEFICIENCY IN HEART FAILURE

Phd thesis summary

SCIENTIFIC LEADER:
Prof. Dr. Laurențiu ȘORODOC

CANDIDATE
Oana ADĂSCĂLIȚEI (SÎRBU)

-2019-

CONTENTS

ABBREVIATIONS iv
CURRENT STATE OF KNOWLEDGE
CHAPTER 1. GENERAL AND HISTORICAL NOTIONS 1
1.1 History of iron preparations 1
1.2 Introduction 2
1.3 Definition 3
1.4 Prevalence 4
CHAPTER 2. IRON METABOLISM 5
2.1 The role of iron in the body 5
2.2 Intestinal absorption of iron 6
2.3 Transport of iron into plasma 7
2.4 Regulation of iron metabolism 8
2.5 The role of iron in erythropoiesis 10
2.6 Iron regulation of erythropoiesis 11
CHAPTER 3. THE ETIOLOGY OF ANEMIA IN HEART FAILURE 12
3.1 Iron deficiency 12
3.1.1 Diagnosis of iron deficiency 12
3.1.2 Mechanisms of iron deficiency 17
3.2 Inflammation 18
3.3 Erythropoietin 19
3.4 The renin angiotensin aldosterone system 21
3.5 Beta blockers treatment 21
3.6 Hemodilution 21
3.7 Others 22
CHAPTER 4. PHYSIOPATOLOGICAL CONSEQUENCES OF ANEMIA 23
CHAPTER 5. PROGNOSTIC 27
5.1 Iron deficiency and mortality 27
5.2 Iron deficiency and reduction of effort capacity 28
5.2.1 Changes in skeletal muscle 28
5.2.2 Cardiac changes 30
5.3 Iron deficiency and quality of life 31
CHAPTER 6. TREATMENT OF IRON DEFICIENCY 32

6.1 Transfusion 32
6.2 Agents to stimulate erythropoiesis 32
6.3 Oral iron 33
6.4 Injectable iron 35
6.4.1 History 35
6.4.2 Intravenous iron form 36
6.4.3 The role of injectable iron in heart failure 37
6.4.4 Effects of injectable iron on mortality 40
6.4.5 Potential effects of iron overload 40
6.4.6 Cost-effectiveness of injectable iron 41
6.4.7 Conclusions 42
PERSONAL PART
CHAPTER 7. MOTIVATION AND OBJECTIVES OF THE STUDY 43
7.1 Objectives 44
7.1.1 The primary objective 44
7.1.2 Secondary objectives 44
CHAPTER 8. MATERIAL AND METHOD 45
8.1 Criteria for inclusion 45
8.2 Exclusion criteria 46
8.3 Initial evaluation 46
8.4 Initiation of the therapy 47
8.5 Final evaluation 48
8.6 Ethical implications 49
8.7 Statistical analysis 49
CHAPTER 9. PATIENT PROFILE WITH IRON DEFICIENCY AND HEART FAILURE 51
9.1 Selecting patients 50
9.2 Descriptive statistics 51
9.3 Influence of beta-blocker treatment on iron metabolism 57
9.4 Influence of calcium channel blocker treatment on iron metabolism 59
9.5 Influence of treatment with other drug classes on iron metabolism 61

9.6 Investigating the correlations between the studied parameters 61
9.7 Discussions 63
9.7.1 Impact of beta-blocker treatment on iron metabolism 63
9.7.2 Impact of calcium channel blocker treatment on iron metabolism 64
9.7.3 Impact of angiotensin converting enzyme inhibitor treatment on iron metabolism 66
9.7.4 Impact of treatment on quality of life 66
CHAPTER 10. THE EFFECTS OF IRON TREATMENT ON PATIENTS 67
10.1 Results 68
10.2 Discussions 81
10.2.1 Effects of iron treatment on iron parameters 81
10.2.2 Effects of iron treatment on other biological parameters 82
10.2.3 Effects of iron treatment on the dimensions of the left ventricle 83
10.2.4 Effects of martial treatment on quality of life 84
CHAPTER 11. COMPARING TREATMENT WITH INJECTABLE AND ORAL IRON 84
11.1 Results 86
11.2 Discussions 101
11.2.1 Effects of iron treatment on iron metabolism 101
11.2.2 Effects of iron treatment on other biological parameters 103
11.2.3 Effects of iron treatment on the dimensions of the left ventricle 104
11.2.4 Effects of iron treatment on quality of life 105
CHAPTER 12. EFFECTS OF TREATMENT WITH ORAL IRON FORM 107
12.1 Results 107
12.2 Discussions 121

12.2.1 Effects of oral iron treatment on biological parameters 122
12.2.2 Effects of oral iron treatment on echocardiographic parameters 124
12.2.3 Effects of oral iron treatment on functional capacity 125
CHAPTER 14. CONCLUSIONS 127
CHAPTER 13. LIMITATIONS OF THE STUDY 128
13.1 Limitations of the study 129
13.2 Perspectives offered by the doctoral thesis 129
REFERENCES 130

The doctoral thesis comprises 139 pages and is structured in two parts: the General Part, called "Current state of knowledge " which comprises six chapters (42 pages) and the Personal Part covering eight chapters (87 pages). The bibliographic references are 158, from page 130 to page 139.

The General Part, entitled " The current state of knowledge " contains 1 table and 6 figures, and the Personal Part contains 8 tables and 97 figures.

During this summary, I will refer to the chapters, tables and figures with the appropriate numbering from the doctoral thesis. The references in this summary can be found at the end, within the selective bibliography section.

Keywords: iron deficiency, heart failure, oral iron, injectable iron, quality of life, gait test, beta blockers, calcium channel blockers

INTRODUCTION

The latest European Guide to Heart Failure recommends evaluating the status of iron in all patients with heart failure and treating those with iron deficiency with ferric carboxymalthosis. However, there are still many unknowns regarding the long-term effects of iron and safe doses of administration. Moreover, oral iron preparations were not compared in a clinical trial with intravenous preparations to find out the differences between the two modes of administration.

To this end, we conducted a prospective observational study comparing the effects of oral and intravenous iron preparations in patients with anemia and heart failure hospitalized in Medical Clinic 2 of "Sf. Spiridon" Iasi.

The primary objective of the study was the comparative evaluation of the effects of oral and intravenous iron preparations on the correction of anemia.

Material and method

The clinical study carried out was of a prospective observational type carried out for a period of 1 year in a single center. During this period 2501 patients were admitted consecutively in the Clinic II of Internal Medicine of the "Sf. Spiridon "Iasi. Patients who were diagnosed with heart failure were evaluated by biological tests to determine iron status. Patients with iron deficiency have undergone rigorous investigations to exclude other causes of iron deficiency. Patients who were not diagnosed with a cause for iron deficiency were included in the present research. Following this recruitment

process, 129 patients were eligible for inclusion in the study.

We excluded patients who had secondary causes for anemia. Because the study was an observational one, the patients were divided into 2 groups according to the preferences of the attending physician: the first group received existing iron injections for the treatment of this condition in our clinic (Iron hydroxide sucrose 100 mg iron 5 days/week), and the second group received oral iron preparations (Liposomal Iron or Anhydrous Ferrous Sulphate), without involving another person in making the patient's treatment decision. The evaluation was performed at week 24.

THE PERSONAL PART

CHAPTER 9: Profile of the patient with iron deficiency and heart failure

Of the patients enrolled, 88.37% were hypertensive, 43.41% were associated with ischemic heart disease, 31% were diabetic, 10.85% were associated with obliterative arteriopathy of the lower limbs and only 6.97% had a history of stroke.

The ferritin value was significantly higher in patients receiving beta-blocker treatment ($p = 0.028$). Comparison of representatives of the beta blockers class (carvedilol, bisoprolol, metoprolol and nebivolol) with biological parameters for anemia did not identify statistically significant differences either between these representatives or when compared with patients without beta blocker treatment (ferritin $p = 0.266$, hemoglobin $p = 0.313$, hematocrit $p = 0.28$ and iron $p = 0.496$).

All patients included in the study used calcium channel blockers (BCCs) in the dihydropyridine class. The levels of iron ($p = 0.038$), hematocrit ($p = 0.003$) and hemoglobin ($p = 0.018$) were significantly lower in patients undergoing BCC treatment.

For the patients treated with ACEI there were no statistically significant differences between the values of hemoglobin ($p = 0.07$), hematocrit ($p = 0.08$), iron ($p = 0.57$) or ferritin ($p = 0.22$) when compared with patients without treatment.

Also, we did not detect statistically significant differences between parameters investigating the status of iron and the other classes of drugs used by the patients included in the study (antiaggregants, anticoagulants, statins, diuretics, proton pump inhibitors).

A slight, statistically significant ($p = 0.04$), indirect correlation was found between treatment with ACEI and hematocrit levels.

Discussions

Our study shows an association between beta-blocker treatment and increased ferritin, but we did not find significant changes in relation to hemoglobin, hematocrit and iron levels. When we evaluated the representatives of the beta blockers class (carvedilol, metoprolol, bisoprolol and nebivolol) no statistically significant differences were detected between these drugs and the ferritin value.

The studies in the literature are contradictory and do not make a significant contribution in interpreting the results obtained in the current research. However, it raises a question mark on the influence of beta-blocker treatment on iron metabolism and why not, it will be the trigger for

studies dedicated to the influence of beta-blocker treatment on iron metabolism (2, 3, 4, 5).

In this research, calcium channel blockers were associated with lower hemoglobin, hematocrit and iron levels. These results are consistent with the results of another study that showed reductions in hemoglobin and hematocrit levels in patients treated with calcium channel blockers who were diagnosed with chronic kidney disease but had no heart failure. In these patients, erythropoietin levels were significantly higher than in patients without BCC treatment (6).

In 2012, a study for hypertensive patients treated with BCC showed that this category of patients had reduced levels of ferritin (7).

Our study showed that ACEI treatment is correlated with hematocrit levels. No statistically significant differences were found regarding hemoglobin, hematocrit, iron or ferritin values in the two patient groups. Similar results are published in numerous other studies. A meta-analysis of 7 studies that included 29061 patients showed a significant association between the use of ACEI treatment and a 1.56-fold increase in the risk of anemia (8).

CHAPTER 10.
The effects of iron treatment on patients

Patients were divided into categories according to the treatment given. First, we divided the study group into people who received treatment (115 patients) and patients in the control group (14 patients). The patients in the treatment group were divided into groups according to the treatment administered: the group of patients treated with

oral iron (75 persons) and the patients treated with injectable iron (40 persons). Because two oral iron preparations were used, we obtained two subgroups among the treated patients, as follows: the ferrous sulphate subgroup (36 patients) and the liposomal iron subgroup (39 patients).

At 6 months follow-up, the hemoglobin value was reduced in the patients without treatment, but this decrease was not statistically significant (p = 0.24) and there was a statistically significant increase (p = 0.01) in the patients in the patients under treatment group.

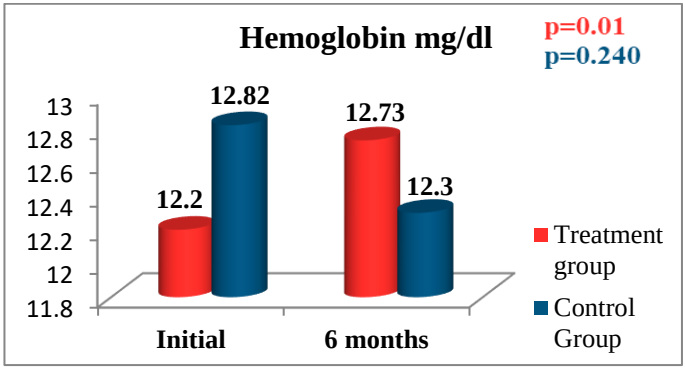

Figure 10.1. Evolution of hemoglobin values in patients

In both patient groups, an increase in ferritin values was observed, modest in the control group (from 70.4 ng/dl to 85.85 ng/dl) and statistically insignificant (p = 0.489) but statistically significant in the patients under treatment (p = 0.003).

At 6 months follow-up, a reduction of uric acid is observed, which reaches the statistical significance

threshold in the patients in the treatment arm ($p = 0.002$), compared with the patients in the control arm ($p = 0.787$).

After 6 months, there is a statistically significant reduction of the thickness of the interventricular septum ($p = 0.036$) in the patients in the treatment group, and a very slight increase in the treatment group, statistically insignificant ($p = 0.778$).

After 6 months of treatment, the patients had a significantly lower posterior wall thickness ($p = 0.011$) compared to the initial time and an increase of the ejection fraction was observed in both groups, with a statistically insignificant increase in the patients in the control arm ($p = 0.311$), but statistically significant in the patients of the treatment arm ($p = 0.01$).

After completing the monitoring, both categories of patients registered increases in the score values witch investigated the quality of life, and reached statistical significance only in the treatment group ($p <0.001$, compared with $p = 0.59$ for the control group).

Another test performed to monitor the evolution of quality of life and physical performance in the patients followed was the 6-minute walk test. After completion of the study, the patients under treatment recorded a statistically significant increase in the distance performed ($p = 0.002$) compared with the patients in the control arm who showed a reduction in the walking distance, but without reaching the threshold of statistical significance ($p = 0.84$).

Discussions

The results of the research show that the patients undergoing treatment with iron preparations had a statistically significant increase in hemoglobin, iron and

ferritin values. In other words, the main objectives of the research were reached and the patients registered statistically significant benefits regarding the improvement of iron parameters.

All studies that used injectable iron preparations for the treatment of iron deficiency associated with heart failure showed favorable results on the correction of iron deficiency and anemia (12, 13, 14, 15, 16, 17, 18).

The present research also highlights a statistically significant improvement of the dimensions of the left ventricle after 6 months of follow-up (interventricular septum, posterior wall of the left ventricle) and the ejection fraction of the left ventricle.

The first study that evaluated patients treated with injectable iron and evaluate the patients with echocardiography is a randomized, placebo-controlled, double-blind study whose main objective was to evaluate the effect of injectable iron treatment on hematological and renal parameters. One of the highlighted results is an increase of the ejection fraction of the left ventricle starting with 3 months of treatment, persistent and at the end of the study, ie after 6 months of follow-up (13).

The results of our study show a better quality of life in the patients treated compared to the patients in the control group estimated by the Kansass City Cardiomiopathy questionnaire, a validated tool for assessing the quality of life in patients with heart failure associated with iron deficiency.

The studies that evaluated the effectiveness of the iron injections also evaluated the quality of life at the end of the study. Whether the Minessota Living with Heart Failure (MLHFQ) (12, 13, 14), KCC (18) or European

Quality of life - 5 dimensions (EQ-5D) (16) questionnaires were used, all research had the same result. improvement of quality of life after iron treatment.

CHAPTER 11
Comparing treatment with intravenous and oral iron

Of the 129 patients included in the study, 32.6% (42 subjects) of them were included in the arm treated with intravenous iron (sucrose iron – Venofer^{R} Vifor Pharma Group). Patients included in the arm with oral iron treatment received 2 tablets/day for 6 months. We used Iron sulphate containing 100 mg iron/tablet and the other liposomal iron containing 15 mg iron/tablet.

After completion of the follow-up period, a significant increase in hemoglobin values (p = 0.018) and a statistically insignificant increase in patients treated with oral iron was observed in patients treated with sucrose iron (p = 0.164).

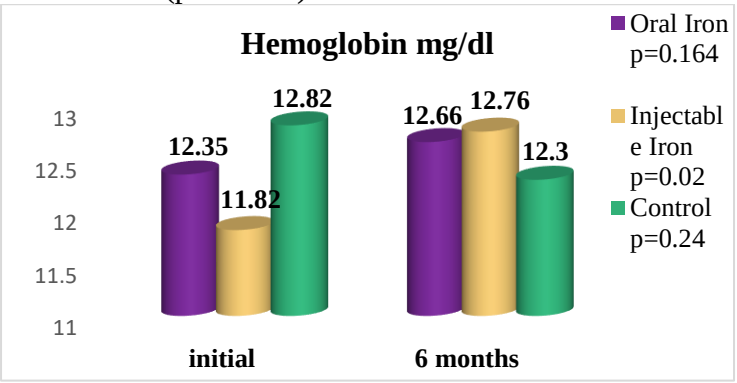

Figure 11.1. Evolution of hemoglobin values in patients treated with Iron

In patients undergoing treatment with sucrose iron, an increase of this parameter is observed, an increase that reaches statistical significance (p = 0.016), with a statistically insignificant increase among patients treated with oral iron (p = 0.08) as well as in the control group (p = 0.489). We observe a schematic of these data in figure 11.7.

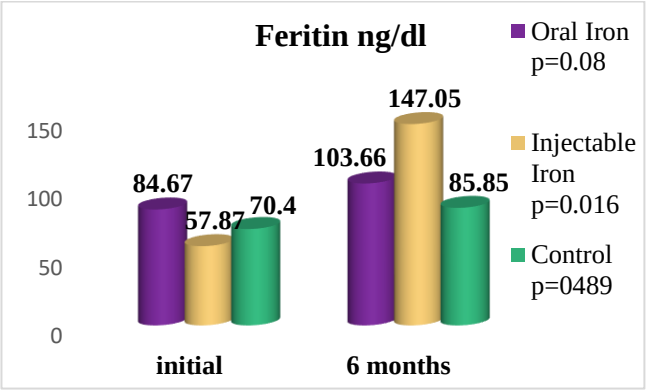

Figure 11.7. Evolution of ferritin in patients undergoing iron treatment

In patients treated with Sucrose Iron, a statistically significant reduction of this diameter is observed (p = 0.038). In all patients there is a tendency to reduce this diameter, statistically significant in patients treated with oral iron (p = 0.006). Although an increase of this parameter is observed in all patient groups from the average, the statistical significance is reached only for the group of patients treated with oral iron (p = 0.014).

In all patients there is a tendency to reduce the NYHA class of heart failure statistically significant in patients treated with oral iron (p = 0.031).

Quality of life scores calculated after the Kanssas City Cardiomiopathy questionnaire also presents an increase of the values, statistically significant in the group of patients under sucrose Iron ($p = 0.002$) and in the group of patients treated with oral iron ($p < 0.001$).

Discussions

Probably the most interesting and original part of the study presented in this paper is the comparison of the effects of the injectable iron treatment with the oral iron treatment. This is very important because there are major drawbacks of the administration of iron injections, recommended by the current guideline of heart failure (19), especially in patients treated in the outpatient setting, where the administration of infusions, such as that required for ferric carboxymalysis, may be associated. with numerous logistical challenges, related to personnel and especially to the price of these products. If in countries with a developed healthcare system, most of the costs related to these expensive treatments are settled by the insurance companies, and these additional costs seem justified (20, 21, 22), in developing countries such as Romania, these costs are borne by those several times by the patient, who does not often have the limited financial possibilities for administering these preparations. Therefore, finding more accessible variants of iron preparations with effects similar to ferric carboxymalthosis would be a very important aspect for this category of patients.

There is a single randomized double-blind multicenter trial that has attempted to evaluate the effects of oral and injectable iron treatment in patients with heart failure (23). It included only 23 patients, due to the

difficulty of enrolling patients who were followed for only 3 months. The results show similar effects of the two types of preparations regarding the correction of anemia and results superior to the injectable iron to improve the functional status.

The present research shows results similar to the previously mentioned trial in the sense of improving the iron deficiency in the patients treated with injectable iron, without reaching the statistical significance in the patients treated with oral iron, but in both groups of patients there is an improvement of the echocardiographic parameters as well as of the functional status with small differences regarding the types of improvements detected.

A justified concern at the present moment is the potential effects of iron overload. Almost all iron in the body is bound to specific proteins, in an active, stable form, which does not cause adverse effects. Increased iron deposits may be associated with the release of free iron that may have adverse effects on the body including infections, atherogenesis and carcinogenesis (24).

In the present study, the dose of iron administered to all patients was 500 mg throughout the study, and patients were followed for 6 months to highlight the effects of this dose. In this context, we can say that a relatively small dose of iron of only 500 mg had favorable effects on the correction of iron deficiency with a statistically significant increase of hemoglobin, iron and ferritin.

CHAPTER 12
Effects of treatment with oral iron preparations

The main objective of the current research was to identify the role of oral iron preparations in patients diagnosed with heart failure and who associate iron deficiency. Further we will present the results of the research regarding the changes of the analyzed parameters at 6 months of follow-up and we will compare the patients treated with the two oral iron preparations with those of the control group. The patients in the arm treated with oral iron were divided into two groups. One of the groups that included 36 patients received iron sulphate treatment 1 tablet twice daily for 6 months, with daily administration of approximately 200 mg of iron. The second group included 39 patients who received liposomal iron with the same administration one tablet twice daily for 6 months, with a total daily iron dose of 30 mg.

The evolution of the hemoglobin values shows the increase of the values of this parameter, but without reaching the statistical significance at 6 months of treatment in all the analyzed patient groups ($p = 0.24$ for the control group, $p = 0.164$ for the whole group of patients treated with oral iron. , $p = 0.649$ for Liposomal iron, $p = 0.178$ for Iron sulphate), except for the control group in which there was a statistically insignificant hemoglobin decrease.

The evolution of ferritin values is similar to that of iron with an increase in all 4 groups of patients but, this time statistically insignificant ($p = 0.489$ for the control group, $p = 0.088$ for patients treated with oral iron, $p =$

0.141 for patients treated with Liposomal Iron and p = 0.243 for patients treated with Iron Sulphate).

Uric acid has a reduction in values in all patient groups, but this is statistically insignificant in patients in the control group (p = 0.787) and in those treated with iron sulphate (p = 0.165) and statistically significant in patients treated with iron. oral (p = 0.001) and those treated with liposomal iron (p = 0.001). These results are graphically represented in Figure 12.10.

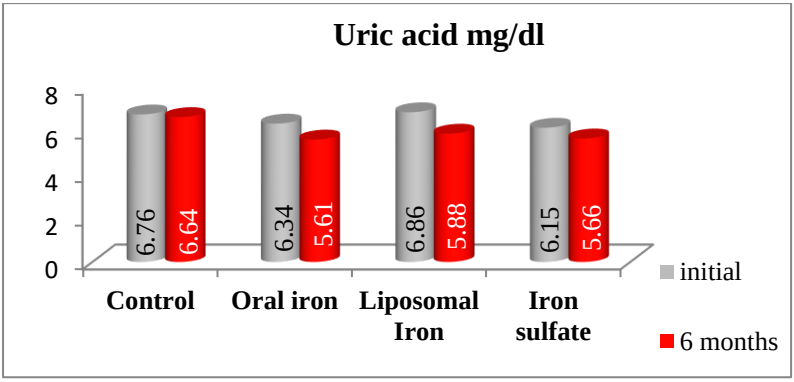

Figure 12.10. Evolution of uric acid values in patients treated with oral iron

A reduction in the thickness of the posterior wall of the left ventricle in all patient categories is detected echocardiographically, statistically significant in patients from the treatment group (p = 0.006) as well as those treated with liposomal iron (p = 0.049). The ejection fraction of the left ventricle has an evolution towards growth in all patients included in the research. The limit of statisticaly significant is exceeded in patients in the oral treatment group (p = 0.014).

In all the studied groups, an improvement in the severity of the NYHA class of heart failure is observed after 6 months of follow-up. Statistical significance is reached in the group of patients treated with oral iron ($p = 0.031$).

Increased score values of quality of life are statistically significant in patients undergoing treatment: with oral iron ($p < 0.001$) as well as those treated with liposomal iron ($p = 0.024$) or iron sulphate ($p < 0.001$).

In patients in the treatment arm, an increase in walking distance is observed after 6 months of statistically significant follow-up only in the group of patients treated with oral iron ($p = 0.005$) and for those treated with liposomal iron ($p = 0.031$).

Discussions

This chapter discusses the effects of treatment with two iron preparations on iron status, echocardiographic parameters, quality of life and ability to exercise. The current research shows an improvement in the quality of life, the ability to exercise and some echocardiographic parameters of the left ventricle after 6 months of treatment with 2 oral iron preparations (Liposomal iron and Iron sulphate), but does not show a benefit. in terms of improving iron status or correcting anemia.

Previous studies that evaluated the effects of oral iron treatment in patients with heart failure and iron deficiency are contradictory. The first study evaluating the effects of oral iron treatment on patients with heart failure showed promising effects (23) on the correction of anemia, similar to those of injectable iron but with results

not so important on the functional capacity of patients treated with oral iron after a follow-up of only 3 months.

The IRONOUT HF study is a double-blind randomized trial that evaluated the effects of oral iron treatment in patients with iron deficiency and heart failure. After 16 weeks of treatment, it was concluded that oral iron treatment does not benefit the ability to exercise and the quality of life despite increasing parameters that assess iron status (27). It is essential to remember the short duration of follow-up of patients in this clinical trial. The low dose of iron absorbed after oral administration is widely known (28). This truism associated with an increased level of hepcidin due to heart failure will determine the need for high doses of oral iron and for longer periods of time to restore the body's iron reserves (29).

A surprising finding in the group of patients studied is the reduction of uric acid values, statistically significant in the large group of patients treated with oral iron and in patients treated with liposomal iron.

There are research that shows the role of uric acid as a negative prognostic factor in patients with heart failure, a higher prognostic value including NT-pro BNP (30). In this context, a reduction of uric acid values in patients treated with liposomal iron would also have a benefit in the long-term prognosis. Further research is needed to establish with certainty the role of iron treatment on uric acid values.

Improving the ejection fraction of the left ventricle suggests better cardiac myocyte activity associated with better iron status. Studies conducted so far show the effects of iron deficiency on cardiomyocytes, which are

contractile dysfunction and relaxation, which results in reduced energy production. These changes showed significant improvements 3 days after the administration of iron represented by the reversal of the functional and morphological changes (31).

Given the results presented above we consider that there are certain benefits of oral iron treatment, but these depend on the dose of iron administered as well as the bioavailability of the product. This research may be a starting point for the discovery of oral iron preparations that have satisfactory absorption and bioavailability for improving iron parameters, quality of life and effort capacity.

CONCLUSIONS

1. Current research shows that beta-blocker treatment increases ferritin levels in patients with iron deficiency and heart failure.
2. The administration of calcium channel blockers in the dihydropyridine class can aggravate the iron deficiency through a statistically significant decrease in values, hemoglobin, iron and ferritin.
3. The quality of life of patients with heart failure and iron deficiency treated with calcium channel blockers is better according to the results obtained than to those without this treatment.
4. Patients with heart failure treated with anticoagulants appear to have a poorer quality of life than patients not receiving this treatment.
5. Injectable iron treatment improves the metabolism of iron after 6 months of treatment.

6. Sucrose iron treatment improves echocardiographic left ventricular dimensions, improves quality of life and increases walking distance.
7. The minimum dose of 500 mg of injectable iron appears to be sufficient to cause favorable clinical, biological and paraclinical effects in patients diagnosed with iron deficiency and heart failure.
8. The treatment with oral iron for 6 months does not determine the statistically significant improvement of the parameters that evaluate the iron status, according to the presented results.
9. Oral iron administered to patients may improve the NYHA heart failure class in the group of patients who have been treated with oral iron.
10. Oral iron treatment seems to cause the size of the posterior wall of the left ventricle to decrease and the ejection fraction to increase.
11. The quality of life is improved in the entire group of patients treated with oral iron as well as in patients treated with iron sulphate.
12. Long-term oral iron treatment with increased bioavailability may have favorable outcomes in patients with heart failure and iron deficiency.

Perspectives offered by the PhD thesis

The study is an encouragement for researchers in the field of heart failure to further evaluate various oral iron preparations regarding the effects on iron deficiency associated with heart failure in the context in which our results suggest the potential benefits of these preparations, especially in terms of quality of life. and improving the ability to exercise.

There are newer oral iron preparations that use different mechanisms of absorption and which may have additional benefits in patients with heart failure, but these should be studied in clinical trials (32).

Another perspective could be a study evaluating the administration of oral iron preparations intermittently. Research on women with anemia has shown that the level of hepcidin increases after administration of an oral iron dose to reduce the absorption of the next dose. The study shows that intermittent administration of oral preparations (at 48 hours) has an additional benefit over daily administration or several times daily by reducing hepcidin values with an additional absorption (33).

REFERENCES

1. Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics* 2014; 6: 748-773

2.Komajda M, Anker SD, Charlesworth A, Okonko D, Metra M, Di Lenarda A et al. The impact of new onset anaemia on morbidity and mortality in chronic heart failure: results from COMET. *Eur Heart J* 2006; 27, 1440–1446

3. Nagatomo Y, Yoshikawa T, Okamoto H, Kitabatake A, Hori M; J-CHF Investigators. Anemia Is Associated With Blunted Response to β-Blocker Therapy Using Carvedilol - Insights From Japanese Chronic Heart Failure (J-CHF) Study. *Circ J* 2018; 82: 691-698

4.Jenkins NP, Keevil BG. Hutchinson IV, Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med* 2002; 112: 269-274

5.Silverberg DS, Wexler D, Schartz D. Is Correction of Iron Deficiency a New Addition to the Treatment of the Heart Failure? *Int J Mol Sci* 2015; 16: 14056-14074

6.Cikrikcioglu MA, Karatoprak C, Cakirca M, Kiskac M, Zorlu M, Cetin G, et al. Association of calcium channel blocker use with lower hemoglobin levels in chronic kidney disease. *Eur Rev Med Pharmacol Sci* 2013; 17: 2530-2537

7.Mainous AG 3rd, Weinberg ED, Diaz VA, Johnson SP, Hulihan MM, Grant AM. Calcium channel blocker use and serum ferritin in adults with hypertension. *Biometals* 2012; 25: 563-568
8.Cheungpasitporn W, Thongprayoon C, Chiasakul T, Korpaisarn S, Erickson SB. Renin-angiotensin system inhibitors linked to anemia: a systematic review and meta-analysis. *QJM* 2015; 108: 879–884
9.Mrug M, Stopka T, Julian BA, Prchal JF, Prchal JT. Angiotensin II stimulates proliferation of normal early erythroid progenitors. *J Clin Invest* 1997; 100: 2310-2314
10.Morrone LF, Di Paolo S, Logoluso F, Schena A, Stallone G, Giorgino F, et al. Interference of angiotensin-converting enzyme inhibitors on erythropoiesis in kidney transplant recipients: role of growth factors and cytokines. *Transplantation* 1997; 64: 913-918
11.van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E,et al. Levels of Hematopoiesis Inhibitor N-Acetyl-Seryl-Aspartyl-Lysyl-Proline Partially Explain the Occurrence of Anemiain Heart Failure. *Circulation* 2005; 112: 1743-1747
12.Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol* 2006; 48: 1225-1227
13.Sîrbu O, Floria M, Dascalita P, Stoica A, Adascalitei P, Sorodoc V et al. Anemia in heart failure - from guidelines to controversies and challenges. *Anatol J Cardiol* 2018; 20: 52-59
14.Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007; 50: 1657-1665
15.Usmanov RI, Zueva EB, Silverberg DS, Shaked M. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. *J Nephrol* 2008; 21: 236-242
16.Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008; 51: 103-112

17.Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; 361: 2436-2448
18.Gaber R, Kotb NA, Ghazy M, Nagy HM, Salama M, Elhendy A. Tissue Doppler and strain rate imaging detect improvement of myocardial function in iron deficient patients with congestive heart failure after iron replacement therapy. *Echocardiography* 2012; 29: 13-18
19.Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland J, Coats A et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *Eur Heart J* 2016; 37: 2129-2200
20.Gutzwiller FS, Schwenkglenks M, Blank PR, Braunhofer PG, Mori C, Szucs TD, et al. Health economic assessment of ferric carboxymaltose in patients with iron deficiency and chronic heart failure based on the FAIR-HF trial: an analysis for the UK. *Eur J Heart Fail* 2012; 14: 782-790
21.Comín-Colet J, Rubio-Rodríguez D, Rubio-Terrés C, Enjuanes-Grau C, Gutzwiller FS, Anker SD, et al. A Cost-effectiveness Analysis of Ferric Carboxymaltose in Patients With Iron Deficiency and Chronic Heart Failure in Spain. *Rev Esp Cardiol (Engl Ed)* 2015; 68: 846-851
22.Theidel U, Väätäinen S, Martikainen J, Soini E, Hardt T, Doehner W. Budget impact of intravenous iron therapy with ferric carboxymaltose in patients with chronic heart failure and iron deficiency in Germany. *ESC Heart Fail* 2017; 4: 274-281
23.Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, et al. IRON-HF study: A randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol* 2013; 168: 3439-3442
24.Jelani Q, Katz SD. Treatment of Anemia in Heart Failure: Potential Risks and Benefits of intravenous Iron therapy in Cardiovascular Disease. *Cardiol. Rev.* 2010; 18: 240-150
25.Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One.* 2015;10: e0117383

26.Niehaus Ed, Malhotra R, Cocca-Spofford D, Semigran M, Lewis GD. Repletion of Iron Stores with the Use of Oral Iron Supplementation in Patients with Systolic Heart Failure. *Journal of Cardiac Failure* 2015; 21: 694-697
27.Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, 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:n1958-1966
28.Waldvogel-Abramowski S, Waeber G, Gassner C, Buser A, Frey BM, Favrat B, et al. Physiology of Iron Metabolism. *Transfus Med Hemother* 2014; 41: 213–221
29.Jankowska EA, Von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *European Heart Journal* 2013; 34: 816-826
30.Kim H, Shin HW, Son J, Yoon HJ, Park HS, Cho YK, et al. Uric Acid as prognostic marker in advanced nonischemic dilated cardiomyopathy: comparison with N-terminal pro B-type natriuretic peptide level. *Congest Heart Fail* 2010; 16: 153-158
31.Hoes MF, Grote Beverborg N, Kijlstra JD, Kuipers J, Swinkels DW, Giepmans BNG, et al. Iron deficiency impairs contractility of human cardiomyocytes through decreased mitochondrial function. *Eur J Heart Fail* 2018; 20: 910-919
32.Elli L, Ferretti F, Branchi F, Tomba C, Lombardo V, Scricciolo A, et al. Sucrosomial Iron Supplementation in Anemic Patients with Celiac Disease Not Tolerating Oral Ferrous Sulfate: A Prospective Study. *Nutrients* 2018; 10: pii: E330. doi: 10.3390/nu10030330
33.Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015; 126: 1981-1989