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EFFECT OF IRON DEFICIENCY CORRECTION ON HEART FAILURE PATIENT'S OUTCOMES

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გულის უკმარისობის მქონე პაციენტებში რკინის დეფიციტის კორექციის ეფექტი დაავადების გამოსავალზე

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რეზიუმე

ჩვენი მიზანი იყო გამოგვეკვლია პერორალური და ინტრავენური რკინით მკურნალობის ეფექტი გულის უკმარისობისა მქონე პაციენტებში, რომელთაც აღენიშნებოდათ რკინის დეფიციტი.

ჩვენ შევისწავლეთ 78 ჰოსპიტალიზირებული ზრდასრული პაციენტი. ყველა პაციენტს ჩაუტარდა სტანდარტული კლინიკური შეფასება. საკვლევი პირების სისხლის ნიმუშებში განისაზღვრა შემდეგი მაჩვენებლები: სისხლის საერთო ანალიზი, შრატის რკინის კონცენტრაცია, ფერიტინი, კრეატინინი, გამოთვლილი იქნა გლომერულური ფილტრაციის სიჩქარე. ფიზიკური დატვირთვის მიმართ ტოლერანტობა შეფასდა 6 წუთიანი სიარულის ტესტით. სიცოცხლის ხარისხი შეფასდა მინესოტას კითხვარის მეშვეობით.

პაციენტები დავყავით ორ ჯგუფად: 50 პაციენტმა (I ჯგუფი) მიიღო ი/ვ რკინის (III) ჰიდროქლორიდი საქაროზის კომპლექსი (Venofer) 5მლ/100მგ; 28 პაციენტი (II ჯგუფი) – გამოიყო როგორც საკონტროლო ჯგუფი. მკურნალობის ხანგრძლივობა ჰოსპიტალში იყო 7.8±0.4 დღე. კლინიკიდან გაწერის შემდეგ 3 თვის განმავლობაში პაციენტები ავრძელებდნენ მკურნალობას პერორალური რკინის პრეპარატით, რის შემდგომაც ფასდებოდნენ განმეორებით.

ჩვენს კვლევაში, რკინით მკურნალობამ აჩვენა მნიშვნელოვანი კლინიკური გაუმჯობესება როგორც ანემიის, ისე გულის უკმარისობის თვალსაზრისით. ასევე გაუმჯობესდა თირკმლის ფუნქცია და NNT-პროBNP დონე, მაგრამ განსხავება ჯგუფებს შორის არ იყო კლინიკურად შესამჩნევი. 6 წუთიანი სიარულის ტესტი და სიცოცხლის ხარისხი მნიშვნელოვნად გაუმჯობესდა რკინით ნამკურნალებ ჯგუფში.

გულის უკმარისობის დროს რკინით მკურნალობა შეიძლება ჩამოყალიბდეს როგორც დამოუკიდებელი, ან ინტეგრირებული სერვისი გულის უკმარისობით პაციეტების მოვლისას. გულის უკმარისობის მქონე ყველა პაციენტს უნდა ჩაუტარდეს რუტინული ტესტირება შრატის რკინის კონცენტრაციაზე და ფერტინზე, სხვა რუტინულ ანალიზებთან ერთად.

ინტრავენური რკინის პრეპარატით მკურნალობა არის უსაფრთხო და შესაძლებელია გამოყენებულ იქნას სიმპტომურ და არასტაბილურ პაციენტებშიც, ხოლო პერორალური რკინით მკურნალობა შესაძლებელია დანერგილ იქნას, როგორც ხანგრძლივი თერაპია, ამბულატორიულ პაციენტებში.

Heart failure is global public health problem affecting an estimated 23 million people. About 7330 patients are diagnosed with heart failure in Georgia every year and the death rate is 700 per year [1]. Despite optimal conventional therapy, many patients with heart failure (HF) remain limited by symptoms, are exercise-intolerant and are at high risk for rehospitalization and mortalities. Comorbidities are common in patients with chronic HF and affect outcomes. One of such comorbidities is iron deficiency (ID), which is present in approximately 50% of patients with HF [2,3,4]. The role of ID in HF has been subject of many recent reviews over the last years. The presence of ID in HF has been confirmed in studies showing reduce iron content in the bone marrow [5] and in the heart [6]. Iron plays a central role in the uptake, transport, storage and metabolism of oxygen, erythropoiesis and cellular immune response [7]. In European and North American studies, as well as in other high-income countries, anemia is a common

feature in heart failure, its prevalence is increasing with worsening NYHA functional class. The information about the presence of anemia in Georgian population with heart failure is relatively limited.

In HF patients, ID is associated with reduced exercise capacity, impaired quality of live (QoL) and poor prognosis, irrespective of whether anemia is present or not [8,9]. The clinical and prognostic significance of ID and HF is now well recognized, however the available information on the effects of iron on morbidity and long-term outcomes is limited. One of the first studies on the effects of intravenous iron administration in HF patients was published in 2006. Treatment improved symptoms and exercise capacity [10]. The effect of treatment with oral iron was evaluated in IRONOUT trial, where was not found difference in the change in peak oxygen consumption when compared with placebo [11].

The aim of our study was to investigate effect of intravenous and oral iron treatment on clinical parameters in HF patients.

Material and Methods. Ethical approval for the study was granted by ethics committee of Tbilisi State Medical University. All patients gave informed written consent for the collection of blood and clinical data was obtained from all patients. The study was proposed to subjects admitted to LTD Al. Aladashvili Clinic.

We studied 78 patients with HF who have been admitted to hospital since September 2019 and had ID. All patients aged 18 years and older were eligible, a left ventricular ejection fraction of 45% or less was documented on echocardiography during the enrolment visit and signs and symptoms of chronic heart failure were present. Exclusion criteria were any kind of coronary interventions within the past 6 months and planned coronary interventions, evidence of acute or chronic infectious or inflammatory conditions from routine laboratory assessment, malignant disease or gastric or duodenal ulcer with or without active bleeding.

Baseline demographic data and medical history were obtained from each study subject, regarding HF etiology (classified as ischemic or non-ischemic) and co-morbidities. All patients underwent a standardized clinical evaluation, including physical examination, determination of NYHA class, determination of body weight. Peripherial venous blood samples were collected form all study subjects for the assessment of a complete blood count and clinical chemistry, including parameters of iron metabolism - serum concentration of iron and ferritin, and kidney function (creatinine) and eGFR.

Anemia was defined according to World Health Organization criteria as hemoglobin level <120 g/l in women and <130 g/l in men. ID was defined as serum ferritin <100 μg/l. Assessment of exercise capacity was performed by a 6-min walk test (6-MWT); quality of life was studied using the Minnesota Quality of Life Questionnaire.

Patients were divided in to two groups: 50 patients (group 1) received iv Ferrous (III) hydroxide sucrose complex (Venofer) 5ml/100mg; 28 patients (group 2) – controlled group. Treatment duration was 7.8±0.4 day in hospital. After discharge from the clinic, 1st group patients continued treatment with oral iron for 3 months.

Statistical analyses. Continuous variables are given as means with standard deviations. Non-normally distributed variables (serum ferritin, serum creatinine, serum C-reactive protein) were log-transformed to achieve normal distribution before analysis. Student's t test was used to test for between-group differences. P values of <0.05 were considered statistically significant.

Results. Baseline characteristics are given in **Table 1.**

Characteristics	Group 1 (N=50)	Group 2 (N=28)
NYHA class II	4 (8%)	3 (10.7%)
NYHA class III	38 (76%)	20 (71.3%)
NYHA class IV	6 (16%)	7 (25%)
LVEF (%)	37.7±2.7	36.9±2.5
Haemoglobin (g/l)	102.6±4.2	104.7±3.8
Iron (μmol/L)	6.9±1.8	6.7±1.5
Serum ferritin (μg/l)	76.4±9.6	77.8±10.2
Serum creatinine (μmol/L)	107.4±18.3	105.6±16.7

eGFR (ml/min 1.73m^2)	49.6±4.1	50.4±5.4
NT-proBNP (pg/ml)	712±11.2	719±9.8
6-MWT (m)	213.7±11.7	224.3±8.6
QoL	55.3±0.9	54.2±0.6

Mean age of patients was 75.2±8.2 years, 55% were men. Coronary artery disease was the primary etiology of HF in 73% of patients. The median level of NT-proBNP at the time of enrolment was 712-719 μmol/L and the median LVEF was 37-36% in both groups. At the end of 3 months medical history was again recorded, patients underwent a physical examination, assessed laboratory tests, a 6-minute walk test, and completed quality of life questionnaire. Repeated studies after 3 months showed the following results:

1. Iron treatment improved hematologic parameters: hemoglobin increased from 102.6±4.2 to 109.7±5.2 vs 105.6±3.2 in group 2. Serum Iron increased from 6.9±1.8 to 13.6±3.5 vs 7.1±1.7 in group 2. Serum ferritin – from 76.4±9.6 to 197.6±22.4 vs 80.4±10.7 in group 2.
2. ID correction reduced NT-proBNP from 712±11.2 to 231±3.2 vs 537±5.7 in group 2. Also improved renal function: serum creatinine from 107.4±18.3 to 89.8±8.7 vs 92.1±3.2 ($p < 0.1$) and eGFR from 49.6±4.1 to 53.7±4.8 vs 52.5±5.6 in group 2 ($p<0.5$).
3. Improved NYHA functional class: the number of patients with NYHA II increased from 4 (8%) to 28(56%) vs 3 (10.7%) to 8 (28.6%) in group 2. LVEF increased from 39.7±2.7 to 41.2±2.1 vs 39.9±2.5 to 41.8±2.1 ($p < 0.5$). Increased the 6-minute walk distance from 213.7±11.7 to 291±9.8 vs 224.3±8.6 to 248±6.3 in group 2 ($p<0.5$). Improves QoL from 55.3±0.9 to 37.5±0.3 vs 54.2±0.6 to 49.5±1.4 in group 2 ($p<0.05$).

Discussion. Iron deficiency in patients with heart failure with reduced ejection fraction is common. Patients with heart failure are iron deficient for multiple reasons, including poor nutrition, malabsorption, reduced intracellular uptake of iron and blood loss [13]. The optimal treatment for iron deficiency in heart failure is correction of the iron deficiency and improvement of the exercise capacity and quality of life of patients. Currently, however, it is not universally monitored or managed despite convincing evidence that iron deficiency is a risk factor for poor outcome independent of anemia status. Evidence for a clinical benefit using oral iron preparations in heart failure is lacking. Clinical studies have instead focused on the use of iv iron, which bypasses the problem of gastrointestinal absorption and poor compliance. Evidence for a clinical benefit using oral iron preparations in heart failure is lacking [14].

In this study the IV iron treatment in hospital and with oral iron in ambulatory setting has been shown to improve clinically significant anemia, NYHA functional class. Iron therapy also improved renal function and level of NT-proBNP, but difference between two groups were not clinically significant.

6-minute walking distance test and quality of life improved significantly in the iron treatment group. The QoL parameters that was improved included reduced physical limitation, improved mobility, selfcare, increased daily activities and reduced discomfort, anxiety and depression.

Conclusion. A heart failure iron treatment service can be set up as an independent or as an integrated within heart failure care. Serum iron and serum ferritin should be routinely tested in all patients with HF in addition to the usual blood tests. Intravenous Iron treatment is safe and can be used in hospital treatment in unstable and symptomatic patients. Oral Iron treatment can be used for long-term outpatient treatment.

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ДАВИД ИОСЕБАШВИЛИ [1], ШАЛВА ПЕТРИАШВИЛИ [1], НАНА ЛОЛАШВИЛИ [2], АНА ПЕТРИАШВИЛИ [1], ИРМА МАМАЦАШВИЛИ [2]

ВЛИЯНИЕ КОРРЕКЦИИ ДЕФИЦИТА ЖЕЛЕЗА НА РЕЗУЛЬТАТЫ ПАЦИЕНТОВ С СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЮ

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РЕЗЮМЕ

Цель нашего исследования состояла в том, чтобы исследовать влияние внутривенного и перорального лечения железа на клинические параметры у пациентов с сердечной недостаточностью (HF) с дефицитом железа (ID).

Мы изучили 78 взрослых пациентов с HF, поступившим в больницу. Все пациенты прошли стандартизированную клиническую оценку. Образцы крови были получены для: общего анализа крови, концентрации железа в сыворотке, ферритина, креатинина и EGFR. Оценка упражнений проводилась с помощью 6-минутного теста на прогулку (6-МВт). Качество жизни изучалось с использованием анкеты Миннесоты «Качество жизни».

Пациенты были разделены на две группы: 50 пациентов (группа 1) получали внутривенно (Venofer) 5 мл/100 мг; 28 пациентов (группа 2) - контрольная группа. Продолжительность лечения составила 7,8 ± 0,4 дня в больнице. После выписки из клиники пациенты продолжали лечение пероральным железом в течение 3 месяцев.

В нашем исследовании было показано, что лечение железом улучшает клинически значимую анемию и функциональный класс NYHA. Это также улучшило функцию почек и уровни NT-ProBNP, но различия между двумя группами не были клинически значимыми. 6-минутное испытание в ходьбе и качество жизни были значительно улучшены в группе лечения железа.

Служба лечения железа сердечной недостаточности может быть создана как независимая или в качестве интегрированной услуги в рамках сердечной недостаточности. Все пациенты с HF должны регулярно контролировать концентрации сывороточного железа и ферритина в дополнение к обычным анализам крови. Внутривенное лечение железа безопасно и может использоваться при больничном лечении у нестабильных и симптоматических пациентов.

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SUMMARY

The aim of our study was to investigate the effect of intravenous and oral iron treatment on clinical parameters in Hart failure (HF) patients with iron deficiency (ID).

We studied 78 adult patients with HF admitted to the hospital. All patients underwent a standardized clinical evaluation. Blood samples were obtained for: full blood count, serum iron concentration, ferritin, creatinine, and eGFR. Assessment of exercise capacity was performed by a 6-min walk test (6-MWT). Quality of life was studied using the Minnesota Quality of Life Questionnaire.

Patients were divided in to two groups: 50 patients (group 1) received IV Ferrous (III) hydroxide sucrose complex (Venofer) 5ml/100mg; 28 patients (group 2) – controlled group. Treatment duration was 7.8±0.4 days in hospital. After discharge from the clinic, patients continued treatment with oral iron for 3 months. After 3 months patients were assessed again.

In our study, iron treatment has been shown to improve clinically significant anemia and NYHA functional class. It also improved renal function and levels of NT-proBNP, but differences between two groups were not clinically significant. 6-minute walking distance test and quality of life were significantly improved in the iron treatment group.

A heart failure iron treatment service can be set up as an independent or as an integrated service within heart failure care. All patients with HF should be routinely tested for serum iron and serum ferritin concentrations in addition to the usual blood tests. Intravenous Iron treatment is safe and can be used in hospital treatment in unstable and symptomatic patients. Oral Iron treatment can be used for long-term outpatient treatment.

Keywords: Heart failure, Iron deficiency, IV Ferrous (III), oral iron.