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К.В. Балькина[1], Т.В. Павлова[1,2], Д.В. Дупляков[1,2]

[1]— ГБУЗ Самарский областной клинический кардиологический диспансер им. В.П. Полякова, Самара, Россия
[2]— ГБОУ ВО Самарский государственный медицинский университет Минздрава России, Самара, Россия

ПРИМЕНЕНИЕ ПРЕПАРАТОВ ЖЕЛЕЗА У ПАЦИЕНТОВ С ЛЕГОЧНОЙ ГИПЕРТЕНЗИЕЙ: БЫСТРЫЙ СИСТЕМАТИЧЕСКИЙ ОБЗОР

K.V. Balkina[1], T.V. Pavlova[1,2], D.V. Duplyakov[1,2]

[1]— V.P. Polyakov Samara Regional Clinical Cardiology Dispensary, Samara, Russia
[2]— Samara State Medical University, Samara, Russia

Iron Use in Patients with Pulmonary Hypertension: A Rapid Systematic Review

Резюме

Дефицит железа широко распространён у пациентов с сердечно-сосудистыми заболеваниями. В последние годы активно изучается коррекция дефицита железа у пациентов с хронической сердечной недостаточностью для улучшения прогноза и течения заболевания. В настоящее время работ, посвящённых изучению применения препаратов железа у пациентов с лёгочной гипертензией, не так много. Целью нашего обзора явилось изучение возможности использования парентеральных препаратов железа у пациентов с лёгочной артериальной гипертензией для улучшения симптоматики и прогноза. В окончательный анализ вошли 5 публикаций. По результатам представленных исследований после применения препаратов железа у всех пациентов нормализовались лабораторные данные, характеризующие дефицит железа, повысилась толерантность к физической нагрузке, улучшилось качество жизни. При этом по показателям инструментальных исследований параметры были без динамики, катетеризация правых отделов сердца также показала отсутствие влияния на гемодинамические критерии. Во всех исследованиях препараты железа хорошо переносились, серьезных побочных явлений выявлено не было, что подтверждает возможность широкого применения лекарственных средств данной группы. Своевременная диагностика и лечение анемии и скрытого железодефицита у пациентов с легочной гипертензией профилактируют прогрессирование заболевания. Однако в настоящее время в реальной клинической практике парентеральные препараты железа у пациентов со скрытым его дефицитом используются редко, вследствие чего необходима активная разъяснительная работа среди практикующих врачей с целью расширения использования данного вида лечения.

Ключевые слова: *легочная артериальная гипертензия, железодефицит, анемия, карбоксиматозат железа*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Iron deficiency is widespread in patients with cardiovascular disease. In recent years, the correction of iron deficiency in patients with chronic heart failure has been actively studied to improve the prognosis and course of the disease. Currently, there are not many studies on the use of iron preparations in patients with pulmonary hypertension. The aim of our review was to explore the possibility of using parenteral iron preparations in patients with pulmonary arterial hypertension to improve symptoms and prognosis. The final analysis included 5 publications. According to the results of the presented studies, after the use of iron preparations, laboratory data characterizing iron deficiency were normalized in all patients, exercise tolerance increased, and the quality of life improved. At the same time, according to the indicators of instrumental studies, the parameters were without dynamics, catheterization of the right heart also showed no effect on hemodynamic criteria. In all studies, iron preparations were well tolerated, no serious side effects were detected, which confirms the possibility of widespread use of drugs of this group. Timely diagnosis and treatment of anemia and latent iron deficiency in patients with pulmonary hypertension prevent disease progression. However, at present, in real clinical practice, parenteral iron preparations are rarely used in patients with latent iron deficiency, as a result of which active outreach among practitioners is necessary in order to expand the use of this type of treatment.

Key words: *pulmonary arterial hypertension, iron defciency, anaemia, Ferric carboxymaltose*

Conflict of interests

The authors declare no conflict of interests

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NT-proBNP — N-terminal pro B type natriuretic peptide, TSAT — transferrin saturation, CHD — congenital heart disorders, PWAP — pulmonary artery wedge pressure, RHC — right heart catheterization, PAH — pulmonary artery hypertension, PH — pulmonary hypertension, PVR — pulmonary vascular resistance, LV — left ventricle, MRI — magnetic resonance imaging, RV — right ventricle, PASys — pulmonary artery systolic pressure, SCTD — systemic connective tissue disorders, mPAP — mean pulmonary arterial pressure, 6MWT — 6-minute walking test, echo-CG — echocardiography, EF — ejection fraction, FC — functional class, CHF — chronic heart failure

Introduction

Pulmonary hypertension (PH) is a haemodynamic and pathophysiological condition, which is associated with an increase in the mean pulmonary arterial pressure (mPAP) to over 20 mm Hg at rest, when measured in right heart catheterization (RHC) [1, 2].

Pulmonary artery hypertension (PAH) is precapillary PH in the absence of any pulmonary conditions, chronic thromboembolism in the pulmonary artery, other rare conditions (group V) as possible causes of increased pressure in the pulmonary artery. Precapillary PH is haemodynamic PH, with mPAP of > 20 mm Hg, pulmonary artery wedge pressure (PWAP) of ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) of > 2 Wood units [3]. PAH can be idiopathic, hereditary, drug- and toxin-induced, associated with other conditions (e.g., congenital heart disorders (CHD); systemic connective tissue disorders (SCTD); portal hypertension; HIV-induced infection; snail fever), pulmonary vein occlusion/ pulmonary capillary haemangiomatosis, persistent infant PAH.

PH is a common clinical problem, which is diagnosed in approximately one percent of the global population. Its incidence grows with the age, this fact being supported by epidemiological data, according to which in the age group of 65+ years old, about 10 % have PH [4].

Recently, healthcare practitioners noted the relationship between anaemia caused by modified iron homeostasis and pathophysiology of various PH types. Studies showed that the management of iron deficiency with or without clinical anaemia in conditions, accompanied by PH, including congestive heart failure, improved patient tolerance to exercises and quality of life, and reduced the rate of hospitalisations and deaths, irrespective of presence or absence of clinical signs of anaemia [5–6, 18].

Assessment of groups of patients with PH demonstrates a high rate of iron deficiency, both with and without clinical anaemia; approximately 40–60 % of patients with this pathology have latent iron deficiency; a third of all patients with PH are diagnosed with clinical anaemia [7, 8]. Of note, both latent and clinical iron deficiency affects morbidity and mortality of this patient category [7, 9]. Available scientific data show the significant role of iron metabolism in pathogenesis and clinical outcome, both of pre and postcapillary PH [5, 9, 10, 18].

The correlation between iron deficiency and PAH is poorly studied. Currently, the main pathologic mechanisms of iron deficiency in PAH are hypoxia, inflammation, and functional changes in muscle cells of the pulmonary artery. Hypoxia can cause pulmonary vessel constriction, leading to increased pulmonary artery systolic pressure (PASys). Also, hypoxia-caused vasospasms and PH can be aggravated by iron chelation in healthy adults [11]. Pulmonary hypertensive reaction caused by altitude hypoxia can be managed with an iron infusion, where PASys is reduced by 6 mm in sea level subjects. Patients with chronic height sickness, who underwent venostomy to reduce the iron levels, demonstrated 25 % increase in their PASys [12]. It is assumed that, similar to hypoxia, iron deficiency increases PASys, which can explain PAH pathogenesis to some extent [13]. The study published in Proceedings of the National Academy of Sciences (Lakhal-Littleton S., Crosby A., Frise M.C. et al., 2019) reported a direct cause-and-effect relation between anaemia and PAH [14]. The authors demonstrated that intracellular iron deficiency in pulmonary arterial smooth muscle cells (PASMCs) results in higher concentrations of endogenous vasoconstrictor endothelin-1, which is known to be elevated in patients with PAH [15]. Besides, the authors provided evidence that impaired regulation of this cell-independent path can be a causative factor of family PAH. Pulmonary arterial smooth muscle cells in patients with mutated bone morphogenetic protein receptors (hereditary PAH) indeed reduced hepcidin expression and intracellular iron levels, and increased ferroportin and endothelin-1 levels [14]. Clinical data confirm that iron deficiency is common and correlates with reduced exercise tolerance in patients both with idiopathic and hereditary PAH [16].

It is worth mentioning that patients with pulmonary hypertension develop various forms of iron homeostasis impairments and anaemias [7]. These include hypoferric anaemia, anaemia of chronic diseases and other more complex types of anaemias, such as a combination of several forms. Management of such patients is a diagnostic and therapeutic challenge for a clinician, since precise anaemic classification can be tricky, and therapy recommendations for a combination of various anaemias are currently still unavailable.

The objective of this review is to study the possibility of using parenteral iron preparations in patients with PAH to improve symptoms and prognosis.

Search for publications and selection of studies

The information search algorithm was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The PubMed database was searched for publications in English for a period from 2014 to 2024 (last accessed date: June 23, 2024). Abstracts, monographs, clinical cases or their series were excluded from the analysis. Studies were searched for using keywords (MeSH) and logistic operators for the following keywords: (pulmonary arterial hypertension) AND (iron deficiency) AND (anaemia) AND (ferric carboxymaltose). Primary selection criteria were met by five publications, which were included into the final analysis [17-21].

For better visual presentation of the material from the studies, the most significant study results were visualised.

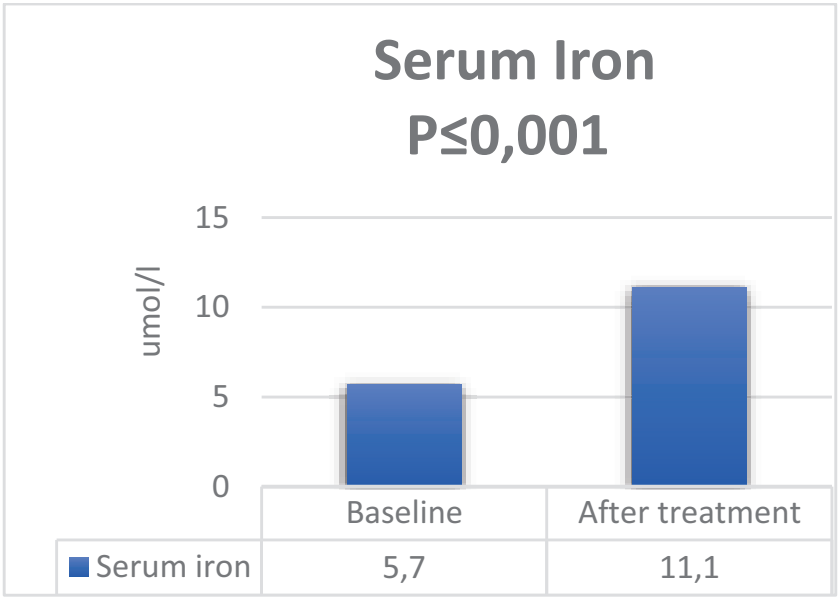
Results

A study by Viethen T. et al., published in 2014 [17], included 40 subjects. PAH was confirmed with RHC in all patients (mPAP ≥ 25 mm Hg and PVR ≤ 15 mm Hg). The first group included 20 patients with PAH, who had signs of iron deficiency. Of those, 12 patients had idiopathic PAH (iPAH); one patient — hereditary PAH; four patients — SCTD-associated PAH; three patients — CHD-associated PAH. Controls were 20 patients with PAH who did not have iron deficiency and were not taking iron preparations. The second group included: iPAH — 13 subjects; one subject had hereditary PAH; six subjects were diagnosed with SCTD-associated PAH. The groups were comparable in gender, age, PAH origin, type and duration of therapy, comorbidities and haemodynamic parameters. Patients in both groups had WHO functional class 2–3 and were treated with a stable PAH-specific regimen. During the study, PAH-specific therapy and diuretics were stable. Patients had their serum iron, ferritin and transferrin saturation (TSAT) measured; also, they underwent an assessment of their mean corpuscular volume and Hb, C-reactive protein (CRP), creatinine and N-terminal pro B type natriuretic peptide (NT-proBNP) levels. Efficacy was assessed using the 6-minute walking test (6MWT); echocardiography (echoCG) with the measurement of the right atrium area, right ventricle end-diastolic diameter, TAPSE index, tricuspid regurgitation rate; cardiopulmonary test; patients also completed the quality of life questionnaire (SF-36). Patients in group 1 had significant iron deficiency without marked inflammations (CRP < 25 mg/L). These patients did not have clinical anaemia; however, their

Hb levels were 12.0±0.6 vs. 14.6±0.4 g/dL (p = 0.001)), mean corpuscular volume was 80.0±1.8 vs. 87.3±1.0 fL (p = 0.002) for patients in groups 1 and 2, respectively.

Ferric carboxymaltose preparations were administered as a single dose of up to 1,000 mg, but no more than 15 mg/kg bw (mean dose was 925 mg). The follow-up period lasted for 8 weeks. The use of iron preparations in patients with iron deficiency resulted in significant improvement of parameters characterising iron homeostasis (serum iron: 5.7±0.4 and 11.1±1.1 μmol/L before and after the therapy, respectively (Fig. 1a); ferritin: 29.3±6.3 and 145.2±25.4 μg/L before and after the therapy, respectively (Fig. 1b); TSAT: 7.5±0.7 and 19.3±2.3 % before and after the therapy, respectively (Fig. 1c), all p ≤ 0.001). Also, patients receiving ferric carboxymaltose preparations demonstrated an increase by 37.7 m in the 6MWT distance, from 346.5±28.3 to 374.0±25.5 mm (Fig. 1d) (p = 0.007), while controls, who did not receive any iron preparations, did not show any significant differences (6MWT 389.9±25.3 and 379.6±26.2 m at baseline and after the therapy, respectively; p = N/A). Positive changes in clinical laboratory values were accompanied by improved quality of life (SF-36, from 44.3±3.7 to 50.6±3.6; p = 0.01).

Ferric carboxymaltose therapy was well-tolerated; only two patients had adverse effects without hospitalisation (flu-like syndrome and skin discolouration at the injection site).



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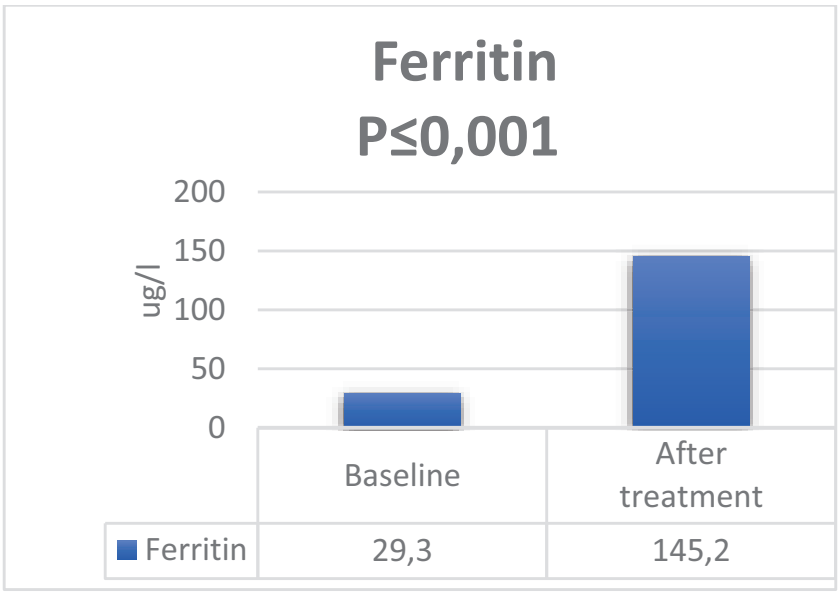

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Figure 1. *Comparison of laboratory values and 6MWD before and after therapy with ferric carboxymaltose*

Note. 6MWD — 6-minute-walking distance, TSAT — transferrin saturation

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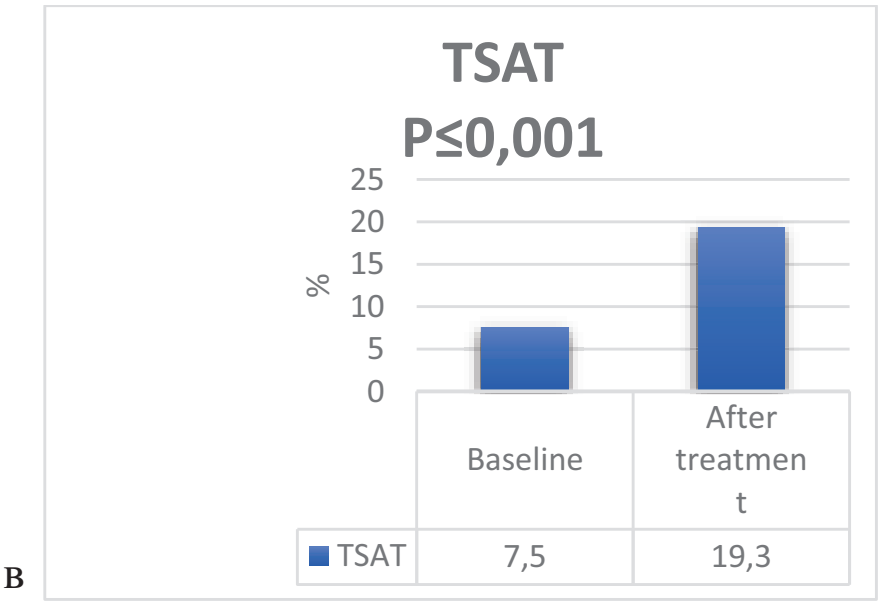

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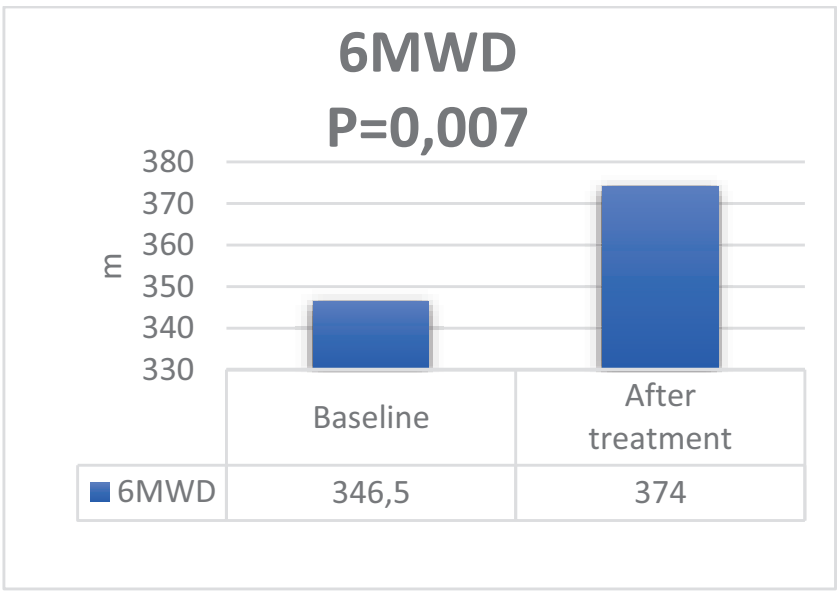

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Figure 1. *(The end)*

A study by Ruiter G. et al. [18] was conducted at the pulmonology ward of the University Hospital at Amsterdam; it was a non-randomised non-placebo-controlled study. The study included 18 patients with iPAH and iron deficiency. The study was conducted from January 2011 till January 2013. All patients underwent 6MWT, heart magnetic resonance imaging (MRI), cardiopulmonary testing, respiratory function assessment, and quality of life assessment. Three patients in the main group did not complete the study: one subject developed paroxysmal auricular fluttering, one subject withdrew their informed consent, and one patient required erythropoietin injection.

All enrolled patients received 1,000 mg of ferric carboxymaltose preparation. The therapy was well-tolerated; however, two patients developed headaches during infusion, and patients arrested such headaches by themselves [18]. The levels of iron, ferritin, transferrin saturation after ferric carboxymaltose injections increased: iron — 9.6±4.8 and 16.1±6.1 μmol/L before and after therapy, respectively, $p < 0.05$ (Fig. 2a); ferritin — 44±79 and 199±225 μg/L before and after therapy, respectively, $p < 0.05$ (Fig. 2b); TSAT — 13.6±6.7 % and 27.3±13.4 % before and after therapy, respectively, $p < 0.001$ (Fig. 2c).

At the same time, NT-proBNP values did not show any significant changes (1.339±2.545 vs. 1.753±4.559 pg/mL, p = N/A). Post-therapy hepcidin levels were low (4.5±4.5 vs. 6.6±4.4 ng/mL, p = N/A). 6MWT did not show any differences as well (409±110 m and 428±94 m before and after therapy, respectively; p = 0.07 (Fig. 2d));

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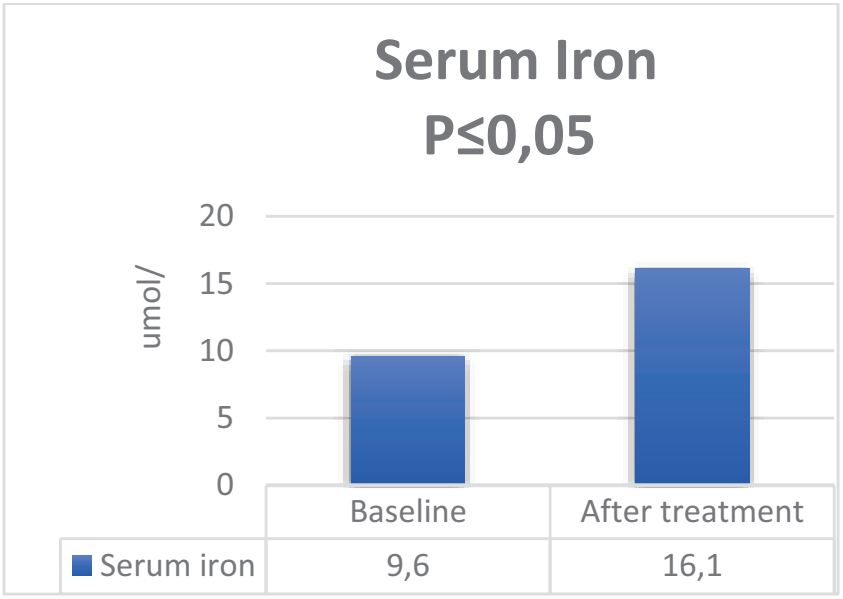

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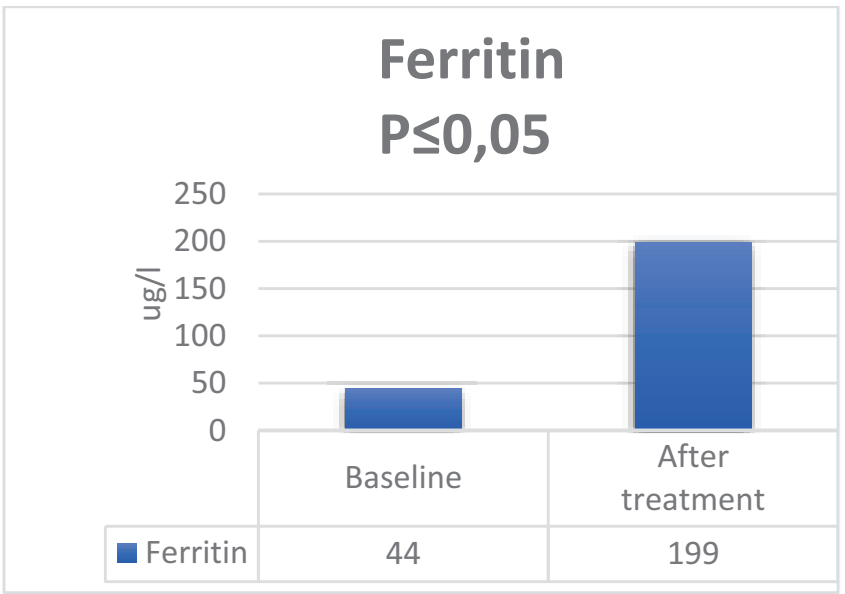

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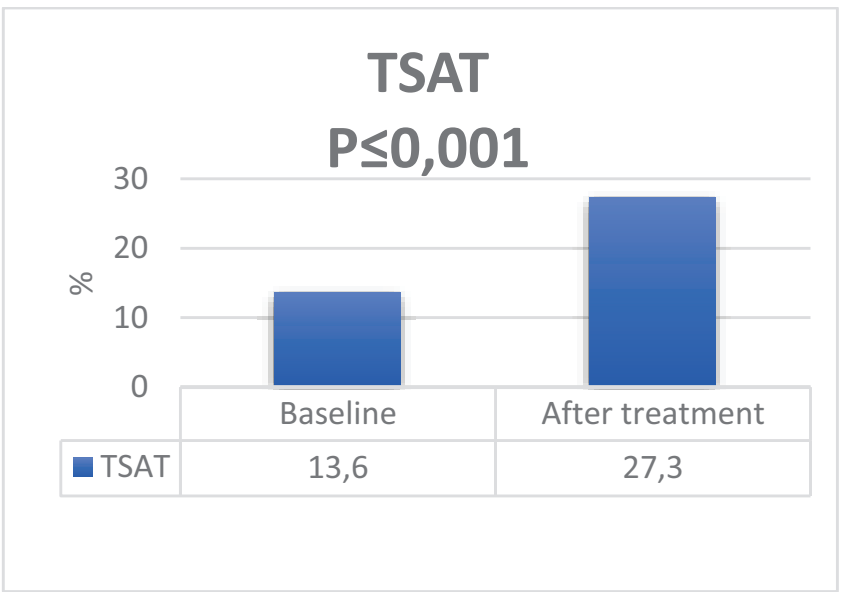

Figure 2. *Comparison of laboratory values before and after therapy with ferric carboxymaltose [18]*
Note. 6MWD — 6-minute-walking distance, TSAT — transferrin saturation

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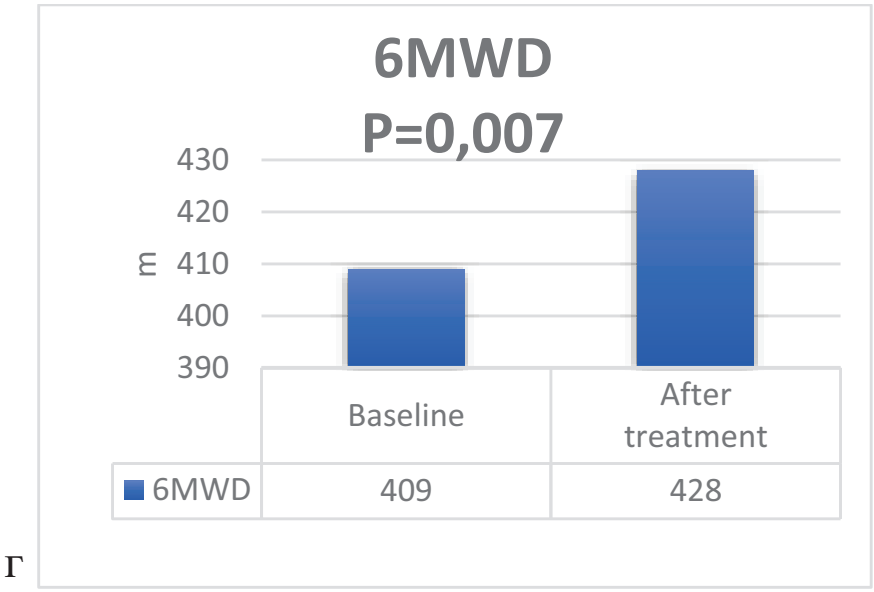

Figure 2. *(The end)*

however, subjective exercise tolerance improved. Besides, cardiorespiratory testing did not demonstrate any changes: the maximum work load was 55±23 W vs. 59±27 W (p=N/A); peak oxygen consumption was 0.97±0.22 L/min vs. 0.97±0.26 L/min (p = N/A); while the time to anaerobic threshold increased (175±33 s vs. 238±43 s; p < 0.001). Exercise tolerance improved (269±89 s vs. 405±210 s; p < 0.001), and patients were able to maintain submaximal physical activity 51 % longer. Quality of life improved, as demonstrated by SF-36 (47 %±19 % vs. 56 %±19 %; p < 0.05). At the same time, RHC and echoCG results remained the same: cardiac index (2.8±0.9 L/min/m^2 vs. 2.5±0.8 L/min/m^2, p = N/A); left ventricle ejection fraction (LV EF) 62 %±12 % vs. 59 %±14 %, RV — 40 %±21 % vs. 39 %±21 % (p = N/A). The myocardial mass index for the right and left ventricles did not demonstrate any significant changes (LV: 59±15 g/m^2 vs. 62±17 g/m^2 before and after, respectively; RV: 51±29 g/m^2 vs. 56±31 g/m^2 before and after, respectively; p = N/A in both cases). Spirometry parameters ~~also~~ remained the same.

During the study, 12 patients underwent shoulder quadriceps biopsy; biopsy materials of two of them could not be analysed. An assessment of the remaining ten samples showed that myoglobin concentration was 0.34±0.17 mM and 0.44±0.11 mM before and after iron preparation injection (p < 0.05); mitochondrial oxidation capacity was 0.06±0.01 nM/mm^3/s and 0.09±0.02 nM/mm^3/s before and after therapy, respectively (p < 0.05). Capillaries/myocyte ratio in quadriceps was similar after the therapy (1.0±0.4 capillary/myocyte and 1.2±0.2 capillary/myocyte before and after therapy; p = 0.37).

Blanche C. et al. [19] studied the possibilities of intravenous injections of ferric carboxymaltose in patients with CHD-associated cyanosis, both with and without pulmonary hypertension. The retrospective study included data of patients, who were followed up from August 2009 to April 2015 and received iron preparation injections. A criterion of cyanosis was peripteral oxygenation reduction of ≤ 90 % at rest or during exercises. The study included 142 patients, of whom 55 (38.7 %) were men; the mean age was 51.3±17.6 years old. Eisenmenger's syndrome was diagnosed in 41 patients (48.8 %); CHD-associated PAH was observed in 27 patients (19 %); CHD with cyanosis, but without PAH was noted in 16 patients (11.3 %); and pulmonary hypertension without PAH was recorded in 58 patients (40.8 %). The majority of patients (116 patients, 88.5 %) had at least functional class (FC) 3 (WHO); mean oxygen saturation at first examination was 86 % (80.0–90.0 %). Patients with Eisenmenger's syndrome had the lowest oxygen saturation of the blood — 82.0 % (75.0–86.0 %), but only two patients (4.9 %) were undergoing long-term oxygen therapy. The majority of patients received PAH-specific therapy (104 subjects, 73.2 %) with the first iron preparation injections. Sixty-six (66) subjects (46.8 %) were on anticoagulants. Over a half of patients with Eisenmenger's syndrome (17 patients, 58.5 %) did not take anticoagulants.

According to the study design, all patients were administered ferric carboxymaltose at a dose of 500–1,000 mg.

Given that patients with Eisenmenger's syndrome require higher Hb values, the dose and frequency of an iron preparation in this group depended on the optimal (expected) Hb concentration, calculated using the formula proposed by Broberg et al., 2011 [27]. It has been shown that the baseline Hb concentration in the study subjects was approx. 4.3±3.9 g/dL lower than the optimal value. This difference increased with an increase in the theoretical optimal concentration (0.98 g/dL (real concentration) vs. 1 g/dL (optimal concentration), 95 % confidence interval: 0.72–1.25, p < 0.0001); however, there was no correlation with the baseline ferritin level (p = 0.62) or TSAT value (p = 0.31). The first dose of 500 mg of ferric carboxymaltose was injected to 163 patients (81.1 %), while 1,000 mg was injected to 37 patients (8.4 %). In order to achieve the optimal Hb level, a repeated dose was required in 59 patients (29.4 %); 24 subjects (11.9 %) received more than two infusions during the study. Patients with Eisenmenger's syndrome required more repeated doses of iron preparations vs. other groups: 29 (41.4 %) vs. 30 (22.9 %), p = 0.01. The mean time between the first and second infusions was 11.6 (4.4–25.4) months. Currently, the formula (Broberg et al., 2011) is not common among clinicians for the assessment of the iron deficiency severity or making decisions on the dose of iron preparations. Still, it can be useful for the calculation of the required dose of iron preparations: the mean optimal actual difference in Hb value was 2.75±3.08 g/dL in the 500 mg group vs. 7.23±3.80 g/dL in the higher dose group, p = 0.0005.

During the study, there were no serious adverse reactions to the product. Two patients developed rash, which was managed with antihistamines. One patient had

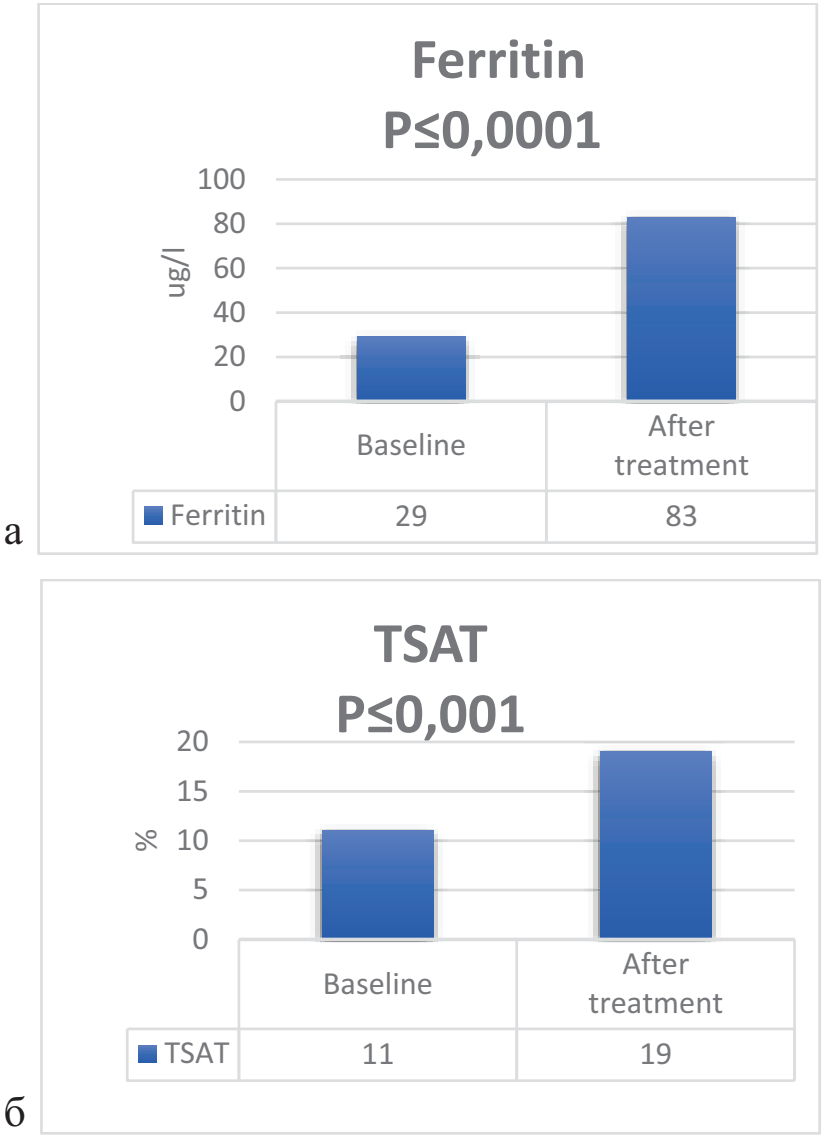

Figure 3. *Comparison of laboratory values before and after therapy with ferric carboxymaltose in patients with cyanosis [19]*
Note. TSAT — transferrin saturation

transient neurological symptoms during iron infusion (speech disorder and arm weakness), but brain computer tomography did not show any permanent neurological deficit or signs of stroke.

In a study by C. Blanche et al., significant improvement in mean Hb saturation and higher hematocrit, ferritin and transferrin levels were observed after a median follow-up of 100.0 (70.0–161.0) days after the first infusion ($p \leq 0.0001$). Higher concentrations of ferritin (29.0 [14.0–63.0] μg/L vs. 83.0 [34.0–182.5] μg/L, $p < 0.0001$ (Fig. 3a)) and TSAT (11.0 [7.0–14.0] vs. 19.0 [13.0–26.0], $p < 0.0001$ (Fig. 3b)) were also observed; however, a majority of patients still were iron deficient by the end of the study. Forty-eight (48) patients (45.7 %) still had TSAT of < 20 %. Blood test results of 68 subjects (66.0 %) showed low ferritin levels (< 30 μg/L) or low TSAT value (< 20 %). Also, there was statistically significant reduction in platelet count (185.0 [127.0–228.0] vs. 161.0 [113.0–214.0] g/L, $p < 0.0001$) and significant correlation between oxygen saturation at rest and Hb concentration. However, the correlation between ferritin and TSAT was weak. In the group of patients with TSAT ≥ 20 %, 65 (51.6 %) subjects had ferritin concentration of < 30 μg/L, while 65 (92.9 %) patients with ferritin concentration of < 30 μg/L had TSAT ≥ 20 %. After the infusion, the difference between the optimal and actual Hb concentration was 2.6±3.3 g/dL. There were no cases of excessive erythropoiesis. Also, none of the patients developed hypercoagulation.

In 2021, pooled results of ***two double-blind placebo-controlled randomised cross-over studies*** were reported [20]; the studies included patients with iPAH or hereditary PAH and iron deficiency. The studies were simultaneously conducted in Europe and China. Over the period from March 2012 to July 2017, 39 patients were randomised 1 : 1 to receive an injection of ferric carboxymaltose or saline solution as a placebo in the European arm of the study. In China, the study included 17 patients. Once randomised, the patients received either a single 20 mg/kg dose of dextran iron hydroxide, or saline solution (placebo). The results were assessed in 12 weeks.

Initially, the primary endpoint in the European arm of the study was changes in PVR based on RHC results as a response to iron deficiency correction. Later, it was decided to modify the primary endpoint, replacing the initial parameter with cardiopulmonary testing parameters. In China, changes in the pulmonary vascular resistance were the primary endpoint, while changes in cardiopulmonary testing parameters were the secondary endpoint. Results in both studies were assessed using laboratory data and results of echoCG, 6MWT, NT-proBNP, heart MRI, and RHC. Changes in iron concentrations after iron preparation infusion were studied using log-transformed ratio of sTfR (soluble transferrin receptor) and ferritin (log sTfR/ferritin), which was proposed as an optimal measure to differentiate between anaemia caused by a chronic condition, and hypoferric anaemia. Reduced log sTfR/ferritin demonstrated better iron availability.

In the European study, patients were divided into two groups: group one received preparations from week 1 to week 12, then placebo from week 13 to week 24, while group two received placebo and then switched to iron preparations.

When discussing the results of the two cross-over studies, conducted simultaneously in Europe and China, it is worth noting that in Europe, administration of ferric carboxymaltose improved ferritin levels from 17 μg/L at baseline to 146 μg/L ($p = 0.0003$) in 12 weeks in the iron preparation group. Patients who received placebo and then iron preparations demonstrated higher ferritin concentrations, from 14 μg/L at baseline to 134.5 μg/L on week 12 to week 24. sTfR concentrations dropped in both groups in line with an increase in iron concentration. The use of iron preparations in both studies did not have significant impact on the right and left ventricle function in 12 weeks, also confirmed with repeated heart MRI.

However, a single dose of ferric carboxymaltose improved tolerance to exercises and quality of life. Twenty (20) patients who received 800–1,000 mg (mean value: 925 mg) of iron demonstrated better 6MWT results — 37.8 m in 8 weeks vs. placebo. A subgroup of eight patients underwent cardiopulmonary testing, where higher peak oxygen consumption was recorded. A study of 15 patients did not show any significant changes in 6MWT results; however, tolerance and aerobic capacity during cardiopulmonary testing improved. In the Chinese arm of the study, iron dextran increased the concentration of serum iron and ferritin, but did not impact parameters obtained during cardiopulmonary testing and RHC.

A study by Kramer T. et al. [21], the results of which were published in September 2021, included 117 patients (mean age: 60.9±16.1 years old; 64.1 % were women) with confirmed iPAH and PAH-specific therapy over ≥ 3 months. All patients had their PAH confirmed in accordance with the current guidelines. A half of patients with iron deficiency (58 subjects) had intravenous ferric carboxymaltose injections; the remaining 59 patients without iron deficiency were controls.

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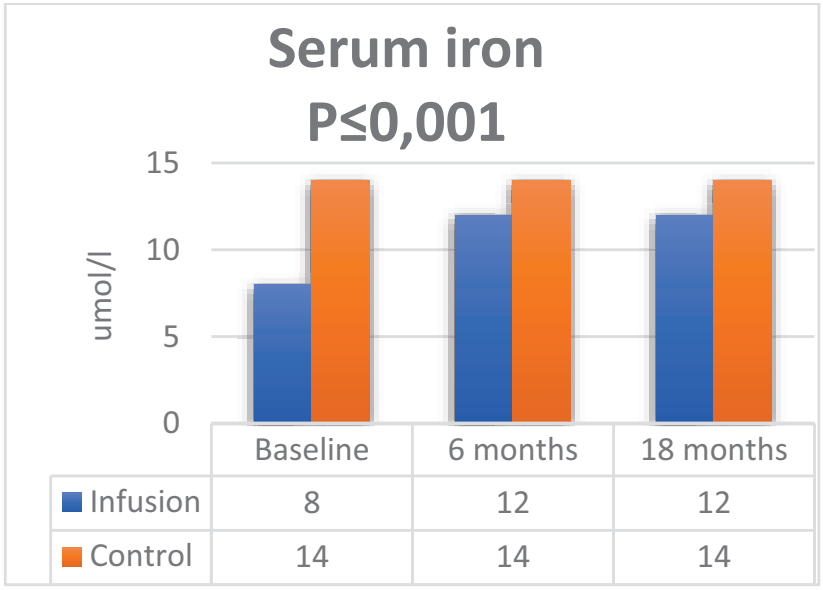

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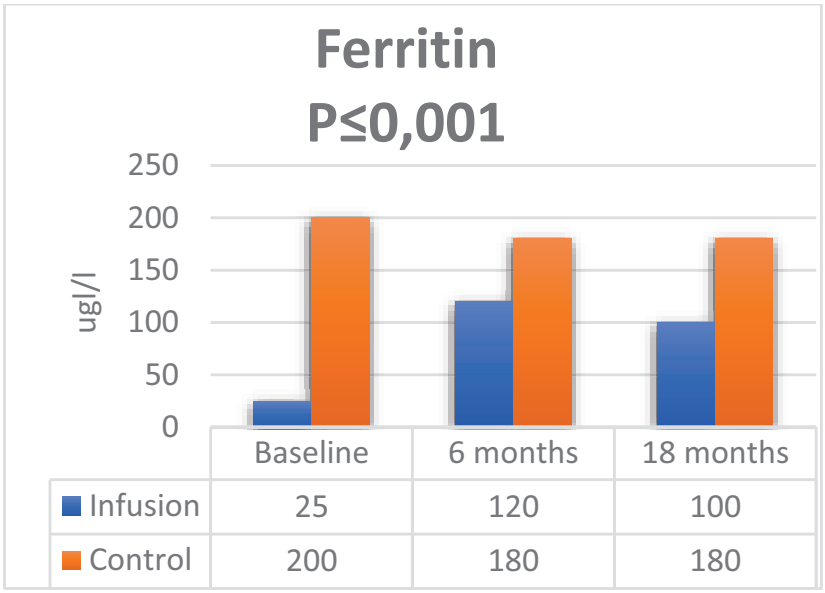

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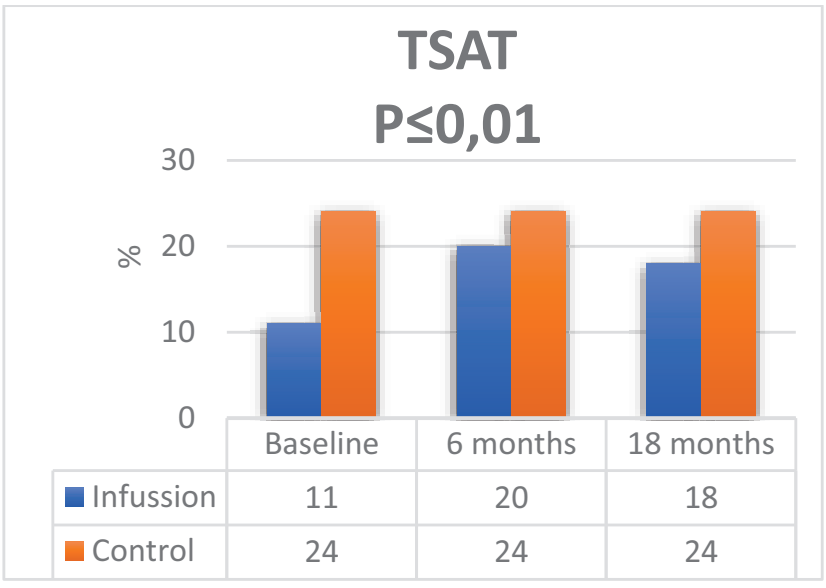

Figure 4. *Comparison of laboratory values before and after therapy with ferric carboxymaltose [21]*

Note. 6MWD — 6 min walk distance, NT-proBNP — N-terminal–pro hormone brain natriuretic peptide, TSAT — transferrin saturation, WHO — World Health Organization functional class

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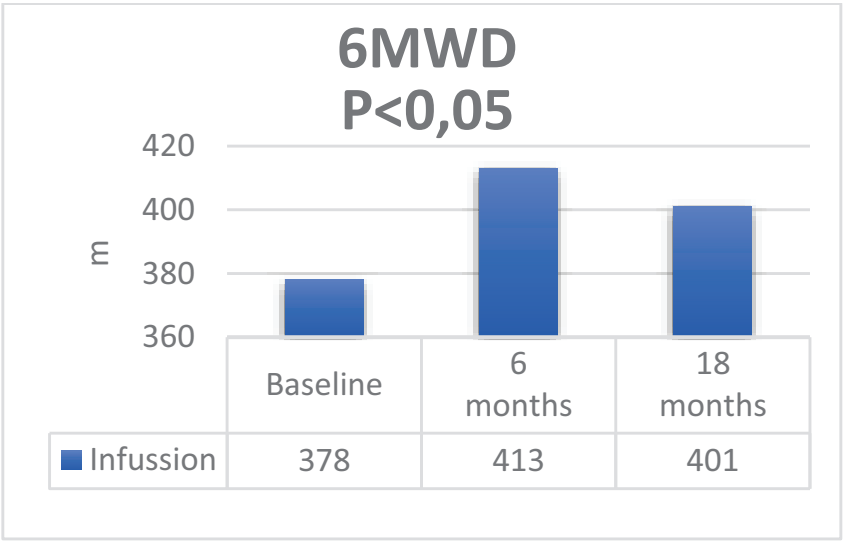

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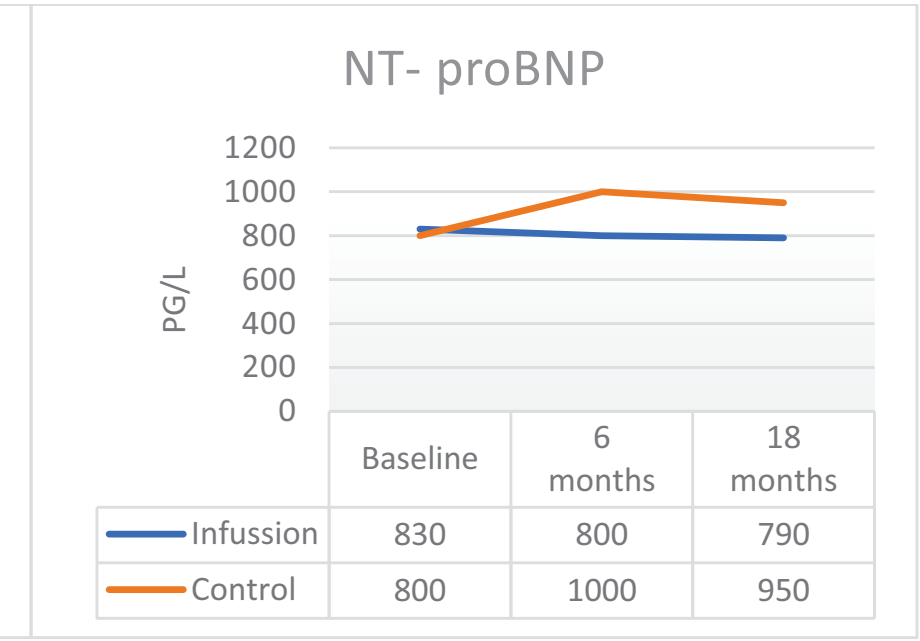

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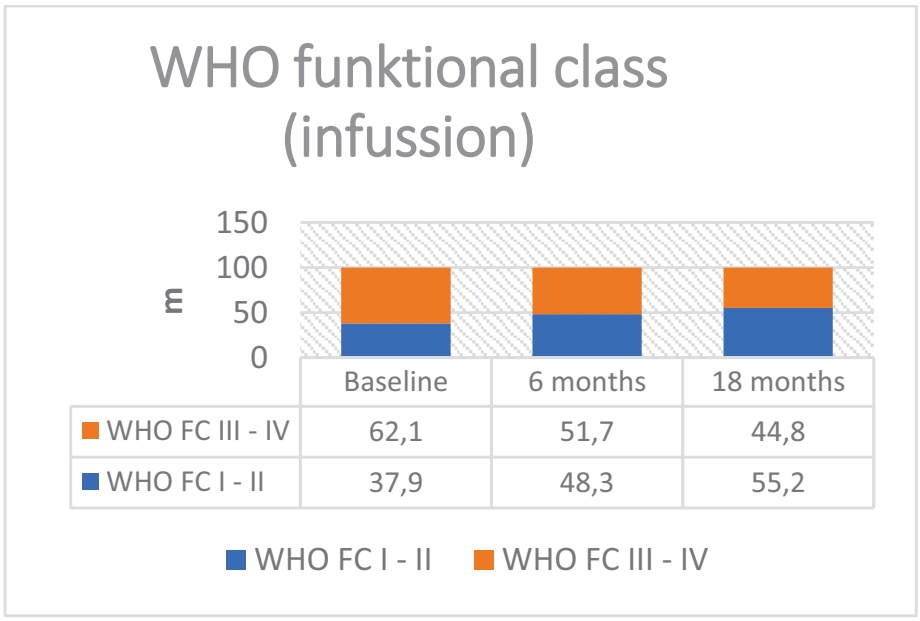

Figure 4. *(The end)*

The groups were comparable in gender, age, origin of pulmonary hypertension, PAH-specific therapy, therapy duration, and haemodynamic parameters. Both groups had elevated baseline NT-pro BNP levels, and patients with iron deficiency had more pronounced clinical manifestations of cardiac failure. PASys was slightly higher in the intervention arm [14]. Clinical anaemia was not present; however, Hb concentration and mean corpuscular volume were higher in controls ($p < 0.001$). Fourteen patients (24 %) in group one received a second infusion in 9.6±4.8 months, of which four (29 %) patients needed an additional (third) infusion due to recurrent iron deficiency (mean total dose: 1,196±563 mg; range: 500–3,000 mg). In this study, patients with iron deficiency, who received iron preparations, demonstrated immediate and steady improvement in their laboratory parameters for a period of up to 18 months (serum iron, ferritin, TSAT, for all $p < 0.01$) (Fig. 4a-b), whereas the control groups did not have any noticeable changes. Peak ferritin and TSAT values were achieved within three months of the follow-up period and then dropped slightly. Iron deficiency improvement was associated with better tolerance to exercises during the follow-up period. As compared to the control group, the mean baseline 6MWT was lower in patients with baseline iron deficiency; however, at 18 months the 6MWT values in the intervention group at least reached the baseline values of controls. Six and eighteen months after the iron preparation infusion the 6MWT results improved, from 378±16 m to 413±15 m (at 6 months) and to 401±15 m (at 18 months), $p<0.05$ for both time intervals (Fig. 4d), while the 6MWT values for controls dropped ($p<0.02$). The intervention group demonstrated a slight tendency towards reduced NT-proBNP levels (Fig. 4e), while in the control group this parameter increased by 21 % by the final visit.

After the therapy, a share of patients with FC I–II in the study group increased from 38 % to 55 % at 18 months, whereas the control group demonstrated deterioration (at baseline, 52 % of patients had FC I–II vs. 43 % at 18 months) (Fig. 4f). It is important to note that the iron preparation therapy was associated with a drop in the rate of hospitalisations for decompensated PAH during 12 months vs. the pre-correction period ($p = 0.029$). There were no significant changes in controls. Of note, all above positive changes in the main group were not accompanied by significant changes in echoCG parameters, including PASys, RA EDD, EF, which remain the same in both groups. Iron preparations were well-tolerated by all patients, and no serious adverse events were reported.

Discussion

Recently, correction of iron deficiency in patients with chronic heart failure (CHF) has been paid much attention in scientific literature. Study FAIR-HF did not show that higher iron levels significantly improved the quality of life and tolerance to exercises, reduced functional class in patients with iron deficiency and chronic left ventricular failure. Parenteral ferric carboxymaltose proved to be efficient in correction of iron deficiency in stable patients with chronic heart failure; it justifies its inclusion in the 2020 CHF management guidelines [22]. The results of Study AFFIRM-AHF [23] confirmed the feasibility of initiation iron deficiency correction right after an episode of CHF decompensation in order to reduce the risk of later hospitalisations caused by this condition. The Expert Consensus on the iron deficiency management in stable and decompensated patients with chronic heart failure [24] states that intravenous administration of ferric carboxymaltose in patients with CHF and LV EF of < 50 % and iron deficiency with decompensated CHF allows preventing further decompensations. In 2024, the results of the study conducted at V. A. Almazov National Medical Research Centre were published. The study was dedicated to iron exchange and the incidence of iron deficiency in patients with PAH and chronic thromboembolic pulmonary hypertension, as demonstrated by various laboratory criteria [25]. Generally speaking, currently there are not enough publications to confirm efficient use of iron preparations in patients with iron deficiency and pulmonary hypertension. This topic is discussed just in five reviews, which were included into this analysis [17–21].

An overview of the mentioned publications shows that iron deficiency is diagnosed in patients with various types of pulmonary hypertension. Some studies included patients with hypertension of various origin. For instance, a study by Viethen T. et al. analysed patients with the following forms: iPAH, hereditary pulmonary hypertension, pulmonary hypertension associated with connective tissue disorders, and CHD-associated PAH [17]. In a study by Blanche C. et al., a majority of patients were patients with CHD, but it also included a group of patients with cyanosis without CHD [19]. A study by Ruiter G. and Kramer T. et al. included only patients with iPAH [18,21], while two cross-over studies in Europe and China enrolled patients with iPAH and hereditary pulmonary hypertension [20]. All mentioned publications used similar iron deficiency criteria based on serum iron, ferritin, and TSAT levels. Patients with active inflammation and severe comorbidities were

excluded from all studies; it can evidence that pulmonary hypertension is the key cause of iron deficiency. It is worth noting that all studies had a small sample size, because the condition is quite rare; it also shows the need to include a larger number of subjects for a more thorough study of the use of iron preparations in patients with pulmonary hypertension to correct iron deficiency. All patients were undergoing stable PAH-specific therapy, as iron preparations can be used just as adjuvant to the primary therapy. In all publications, changes in laboratory values, tolerance to exercises and quality of life were the primary endpoint. Patients underwent laboratory tests to assess changes in iron homeostasis, echoCG or heart MRI parameters to assess the heart function, cardiopulmonary testing and 6-minute walking test to identify tolerance to exercises; some studies also included RHC to assess haemodynamic parameters. Besides, subjects completed quality of life questionnaires. The mentioned studies show that the use of iron preparations normalised laboratory parameters, which characterise iron deficiency, in all patients; tolerance to exercises and quality of life improved. Instrumental test results did not demonstrate any changes; RHC also showed no impact on haemodynamic parameters. In a study by Kramer T. et al. (2021) [21], patients receiving iron preparations had lower rate of hospitalisations for decompensated CHF. A study in patients with CHD and cyanosis [19] proved the safe use of iron preparations in patients with a high baseline RBC count, provided thromboembolic complications were prevented, and allergic reactions were controlled. Addition of iron preparations with excessive erythropoiesis did not result in hypercoagulation, even in patients with Eisenmenger's syndrome and/or very high hematocrit levels. No embolic events were reported. In all studies, iron preparations were well-tolerated with no serious adverse events, thus supporting wide applicability of these preparations. However, in current clinical settings, parenteral iron preparations are rarely used in patients with latent iron deficiency, and wide-scale outreach is needed among medical practitioners in order to advocate this therapy.

Conclusion

Iron deficiency is common in patients with pulmonary arterial hypertension of various origin. The mechanisms of iron deficiency in this group of patients are actively studied. The use of some PAH-specific products can cause impaired iron homeostasis and can be associated with low Hb. It has been proven that iron deficiency, even it is not accompanied by clinical anaemia, worsens symptoms of the primary disease, compromises the quality of patients' life, and increases the rate of CFH decompensations and associated hospitalisations. Routine clinical practices should include regular diagnostics of this condition for timely identification of iron deficiency and assessment of indications for iron preparation administration. The latest clinical recommendations developed by the Russian Cardiology Society "Pulmonary hypertension including chronic thromboembolic pulmonary hypertension", approved in 2024, provide for iron deficiency correction and anaemia management to prevent disease progression (level C evidence, level 5 of certainty) [26]. Even in the absence of clinical anaemia, it is advisable to consider iron deficiency correction in patients with PAH (level C evidence, level 5 of certainty) [26] to improve symptoms of the primary disease, tolerance to exercises and quality of life. A study has been conducted from September 2024 at V. P. Polyakov Samara Regional Clinical Cardiology Dispensary. The objective of the study is to assess the impact of iron deficiency correction on the quality of life and prognosis in patients with pulmonary hypertension. It should be particularly emphasised that correction of anaemia and iron deficiency does not replace PAH-specific therapy, but is a ~~very~~ important addition to the combined therapy.

Key points:

- Iron deficiency with or without clinical anaemia is a common problem in patients with pulmonary arterial hypertension.
- Regular diagnostics of iron deficiency should be performed in this group of patients for timely correction.
- Ferric carboxymaltose improves symptoms of the primary condition, tolerance to exercises and quality of life.

Вклад авторов:

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Балькина К.В.: сбор и обработка материала, написание рукописи

Павлова Т.В.: анализ и интерпретация данных, редактирование рукописи

Дупляков Д.В.: разработка концепции и дизайна, научное консультирование, редактирование рукописи, утверждение окончательного варианта статьи

Author contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Balkina K.V.: collecting and processing material, manuscript writing

Pavlova T.V: data interpretation and analysis, editing the article

Duplyakov D.V.: concept and design development, scientific advice, editing the article, approval of the final version of the manuscript

Table 1. *General characteristics of the studies*

Authors	Study type, number of patients, duration of follow-up	Inclusion criteria	Initial treatment	Criteria for ID	Restrictions	End points	Study result
Kramer T., [21]	Retrospectively 117 patients, 18 months	1. PAH was confirmed by RHC in all patients, 2. PAH — specific therapy for ≥ 1 months, 3. ID	1. CCB — 2 (1 — intervention, 1 — control), 2. PDE5i monotherapy — 34 (13 — intervention, 21 — control), 3. ERA monotherapy — 10 (5 — intervention, 5 — control), 4. sGC stim monotherapy — 8 (5 — intervention, 3 — control), 5. PDE5i + ERA — 47 (22 — intervention, 25 — control), 6. sGC stim + ERA — 4 (3 — intervention, 1 — control), 7. PDE5i + ERA + Prost — 8 (6 — intervention, 2 — control), 8. sGC stim + ERA + Prost — 4 (3 — intervention, 1 — control).	1. SF<100 μg/L, 2. SF 100 — 300 μg/L + TSAT < 20 %.	1. Kidney dysfunction (serum creatinine > 2.0 mg/dL), 2. Liver disease (serum glutamic oxaloacetic transaminase/glutamic pyruvic transaminase > 70 U/L), 3. Marked anaemia (haemoglobin < 8.0 mg/dL), 4. Inflammation (C — reactive protein > 25 mg/L).	1. Iron status, 2. Exercise tolerance.	1. Improvement in laboratory values, 2. Increased exercise tolerance, 3. WHO functional class improved, 4. Reduction of hospitalizations for worsening PAH, 5. No dynamics on echocardiography.
Luke S. [20]	Two randomized, double-blind, placebo-controlled, Europa — 39 patients China — 17 patients, 12 weeks	1. PAH was confirmed by RHC in all patients, 2. PAH — specific therapy for ≥ 1 months, 3. ID.	1.PDE5i: Europa — 33, China — 13, 2.ERA: Europa — 29, China — 7, 3.Prost: Europa — 10, China — 1, 4. CCB: Europa — 2 .	1. SF <37 μg/L, 2. SI <10,3 μmol/L, 3. TSAT <16.4 %.		1. 6MWD, 2. Pulmonary vascular resistance, 3. Peak O2 intake in cardiopulmonary testing.	1. SF increased, 2. No impact on right heart cardiopulmonary testing and catheterization data (China), 3. Improved exercise tolerance and QoL.
Viethen T. [17]	Prospective 20 patients + 20 patients (control group) 8 weeks	1. PAH was confirmed by RHC in all patients, 2. PAH — specific therapy for ≥ 3 months, 3. ID.	1. ERA monotherapy– 2 (intervention), 2. PDE5i monotherapy- 13 (4 — intervention, 9 — control), 3. sGC stim monotherapy– 5 (3 — intervention, 2 — control), 4. ERA + PDE 5i– 10 (7 — intervention, 3 — control), 5. ERA + sGC stim– 1 (intervention), 6. PDE5i + sGC stim — 1 (intervention), 7. ERA + PDE-5i + iProst — 2 (intervention), 8. ERA + PDE-5i + oProst — 2 (control), 9. PDE-5i + TK — 1 (control), 10. ERA + PDE-5i + TKI — 2 (control).	1. SI <10 μmol/L, 2. SF <150 μg/L, 3. TSAT <15 %.	1. Considerable liver disease (serum glutamic oxaloacetic transaminase / glutamic pyruvic transaminase >70 U/L), 2. Kidney dysfunction (serum creatinine >2.0 mg/dL), 3. Marked anemia (hemoglobin <7.5 mg/dL) 4. Marked inflammation (C-reactive protein >25 mg/L), 5. Left heart disease or chronic lung disease, 6. Chronic thromboembolic PH (ventilation/perfusion scan).	1. Iron status, 2. 6MWD, 3. QoL.	1. Improved iron homeostasis, 2. Increasing 6MWD, 3. Improvement in QoL.

Table 1. (The end)

Authors	Study type, number of patients, duration of follow-up	Inclusion criteria	Initial treatment	Criteria for ID	Restrictions	End points	Study result
Ruiter G, [18]	Not placebo controlled, 18 patients (3 did not completed the study) 12 weeks	1. IPAH as defined by RHC, 2. Receipt of optimal PAH-specific treatment, 3. Clinically stable for at least 3 months, 4. ID.	1. ERA monotherapy — 4, 2. Prost monotherapy — 4, 3. ERA + PDE 5i — 2, 4. ERA + Prost — 1, 5. ERA + PDE-5i + Prost — 4	1. SI <10 μmol/L, 2. TSAT <15 % [women] or <20 % [men], 3. SF <100 μg/L.	1. Patients already on iron, 2. Participation in other studies on pulmonary hypertension and\or anemia, 3. Comorbidities.	1. Primary end point — 6MWD, 2. Secondary end points: – change in blood iron parameters, – change in maximal exercise parameters and endurance capacity determined by maximal and submaximal cardiopulmonary exercise tests, – change right ventricul function determined by cardiac magnetic resonance imaging, – quality of life determined by the SF-36 questionnaire, – skeletal muscle oxygen handling at the cellular level determined by quadriceps muscle biopsy.	1. Did not significantly change 6MWD, 2. SI, SF increased slightly, 3. Improving submaximal exercise capacity, 4. No significant changes during cardiorespiratory testing, 5. Exercise endurance capacity was markedly improved, 6. Improvement in QoL, 7. Cardiac function was unchanged, 8. Skeletal muscle biopsies revealed improvements in oxygen handling capacity.
Blanche C, [19]	Retrospectively, 142 patients, 5,7 years	– Patients with Eisenmenger syndrome — 41 (28,8 %), – PAH-CHD — 27 (19,0 %), – Non -PH CHD 16 (11,3 %) – Non-CHD PH 58 (40,8 %).		1. SF <30 μg/L, 2. TSAT < 20 %.		Change in blood iron parameters	Hematocrit, SI and SF increased

Note. 6MWD — 6-minute walk distance, CCB — Calcium channel blockers, CHD — congenital heart disease, ERA — endothelin receptor antagonists, ID — iron deficiency, iProst — inhaled prostanoid, oProst — oral prostanoid, PAH — pulmonary arterial hypertension, PDE-5i — phosphodiesterase type 5 inhibitor, RHC — right heart catheterization, SF — serum ferritin, sGC stim — soluble guanylyl cyclase stimulator, SI — serum iron, TKI — tyrosine kinase inhibitor, TSAT — transferrin saturation, WHO — World Health Organization, QoL — quality of life

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Информация об авторах

Балькина Ксения Васильевна — врач — кардиолог ГБУЗ Самарский областной клинический кардиологический диспансер им. В.П. Полякова, аспирант кафедры пропедевтической терапии с курсом кардиологии ГБОУ ВО Самарский государственный медицинский университет Минздрава России, Самара, e-mail: kseniabal@list.ru, ORCID ID: http://orcid.org/0009-0000-3615-2143

Павлова Татьяна Валентиновна — д.м.н., зав. отделением клинических исследований ГБУЗ Самарский областной клинический кардиологический диспансер им. В.П. Полякова; профессор кафедры пропедевтической терапии с курсом кардиологии ГБОУ ВО Самарский государственный медицинский университет Минздрава России, Самара, e-mail: ptvsam63@mail.ru, ORCID ID: http://orcid.org/0000-0003-3301-1577

Дупляков Дмитрий Викторович — д.м.н., профессор, заведующий кафедрой пропедевтической терапии с курсом кардиологии ФГБОУ ВО «Самарский государственный медицинский университет» Министерства здравоохранения Российской Федерации; заместитель главного врача по медицинской части ГБУЗ «Самарский областной клинический кардиологический диспансер им. В.П. Полякова», Самара, e-mail: duplyakov@yahoo.com, ORCID ID: http://orcid.org/0000-0002-6453-2976

Information about the authors

Ksenia V. Bal'kina — cardiologist, State Budgetary Healthcare Institution Samara Regional Clinical Cardiology Dispensary named after V.P. Polyakov, Graduate Student of the Department of Propaedeutic Therapy with a Course in Cardiology, Samara State Medical University, Ministry of Healthcare of the Russian Federation, Samara, e-mail: kseniabal@list.ru, ORCID ID: http://orcid.org/0009-0000-3615-2143

Tatyana V. Pavlova — MD, PhD, Head of the Clinical Research Department, Samara Regional Clinical Cardiology Dispensary named after V.P. Polyakov; Professor of the Department of Propaedeutic Therapy with a Course in Cardiology, Samara State Medical University, Ministry of Healthcare of the Russian Federation, Samara, e-mail: ptvsam63@mail.ru, ORCID ID: http://orcid.org/0000-0003-3301-1577

Dmitry V. Duplyakov — MD, PhD, Professor, Head of the Department of Propaedeutic Therapy with a Course in Cardiology, Samara State Medical University of the Ministry of Health of the Russian Federation; Deputy Chief Physician for Medical Affairs, Samara Regional Clinical Cardiology Dispensary named after V.P. Polyakov, Samara, e-mail: duplyakov@yahoo.com, ORCID ID: http://orcid.org/0000-0002-6453-2976

Автор, ответственный за переписку / Corresponding author