Acta Scientific Cardiovascular System

Volume 1 Issue 6 November 2022

Research Article

New Opportunities in the Treatment of Anemic Syndrome in Chronic Heart Failure

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Received: August 29, 2022

Published: October 28, 2022

Abstract

The Research Objective: The purpose of this study is, given the impact of anemia on the clinic and the course of chronic heart failure (CHF), based on optimal diagnostic methods, the development of new differentiated methods for treating patients with CHF and anemia, including erythropoietin preparations methoxypolyethylene glycol epoetin beta (MPEB) and intravenous (IV) iron in combination with basic therapy.

The Research Methods: 127 patients with CHF of ishemic aethology were included in the study, surveyed. The mean age of patients was 60,6 ± 1,4 years. Of these, 93 patients were diagnosed with anemia. As a control group, 34 patients with CHF without anemia were examined. According to the therapeutic tactics with the use of combination MPEB at dose of 0,60 mcg/kg (50 units) and IV iron III hydroxide sucrose complex at a dose of 200 mg (Venofer), all patients, depending on therapeutic tactics, 2 groups. In all patients, the levels of Hb, ferrithin, of transferrin saturation (TS), erythropoietin (EPO), NTproBNP, IL-1,IL-6, TNF-α in blood plazma, parameters of systolic and diastolic function of left ventricular (LV) of methods doppler echocardiography before and after treatment..

The Research Analysis: The study showed that as a result of the negative effect of anemia on the CHF clinic, there is a decrease or absence of the effect of drugs of the baseline: positive dynamics of LVEF, LVMM, parameters of LV diastolic function and test with 6-MWT absent. There is no positive dynamics of Hb, Ht, ferritin, TS, EPO, NTproBNP, IL-1, IL-6 and TNF-α levels in blood plasma in patients with I-IV NYHA class CHF with anemia against baseline therapy.

The Research Results: The results of the parameters of the systolic function of the LV in patients with CHF I-II NYHA class with anemia of group II on the background of the therapy. There is an increase in LVEF by 12.2% ($p < 0.001$) on the background of combined MPEB therapy with IV [III] hydroxide sucrose complex. In patients in CHF with anemia and hypoerithropoietinemia with ID, use combined therapy with of the MPEB and IV iron Venofer. The levels of Hb increase 8,4% ($p < 0,01$), Ht, ferritin, TS, EPO, NTproBNP, IL-6 are positive. The indicator of 6-MWT was significantly increased by 21,6% ($p < 0,001$) and 64,9% ($p < 0,001$), respectively. There is an increase in LVEF by 12.2%. The 6-MWT significantly increased to 64,9 %

The Research Conclusion: The patients in CHF with anemia, combined therapy with the appointment of the MPEB and IV iron contributes to reliable positive dynamics of Hb, ferritin, TS and EPO, LV myocardium. In the treatment of patients in CHF with anemia, ia, there is a need for differentiation depending on the levels of such important parameters as plasma ferritin, TS and EPO.

Keywords: Heart Failure; Anemia; Erythropoietin; Ferritin; Methoxypolyethyleneglycolepoetin Beta; Iron (III) Sucrose

Abbreviations

CHF: Chronic Heart Failure; MPEB: Methoxypolyethylene Glycol Epoetin Beta; IV: Intravenous; Hb: Hemoglobin; Ht: Hemotocrite; TS: Transferrin Saturation; EPO: Erythropoietin; NTproBNP: N-Terminal Pro Brain Natriumuretik Peptide; IL-1: Interleykine 1 Beta; IL-6: Interleykine 6; TNF-α: Tumor Necrosis Fator Alfa; LV: Left Ventricular; NYHA: Nyu York Heart Association; LVEF: Left Ventricular Ejection Fraction; LVMM: Left Ventricular Myocardium Mass; 6-MWT: Six Minute Walking Test

Introduction

There are successful methods for the diagnosis and treatment of chronic heart failure (CHF),this is not only a problem of cardilolgia, but also of the whole medicine, health care, social, family and the person himself. It is known that CHF is a polisyndromic, polysymptomatic disease, which is associated with the cardiovascular continuum of E. Braunvulda, a complication of all CVD-s. The it problem is actual. At the same time, comorbid pathology plays a major role; factors worsening the course of CHF and sometimes interfering with the effectiveness of baseline drugs play a significant role. One of these factors is the development of anemia, worsening the course of the disease, contributing to the formation of refractoriness to therapy. After all, it is known that within 5 years from the establishment of a diagnosis due to the development of complications 50% of patients die [1].

According to the European Heart Failure PILOT SURVEY study, 74% of patients with CHF had at least 1 comorbidity: with 41% of CKD, 29% of anemia, 29% of diabetes mellitus [2].

Relevant in modern cardiology is an intensive study of the relationship between heart failure and anemia. So, it has been established that the factor of anemia in CHF is a predictor of a high frequency of repeated hospitalizations, comorbid pathology and mortality [3-5].

The it problem is practical. In such large multicenter studies as COPERNICUS, IN CHF, CHARM, COMET, ELITE II, Val-HeFT, hemoglobin level was the criterion for excluding patients from the study [6]. The prevalence of anemia among patients ranges from 10-25% [3-8].

To this day, there are many questions regarding the role that anemia plays and the way it is treated in patients with CHF remain without complete answers. On the one hand, the diagnosis of anemia in these patients is unchanged, as well as the choice of the appropriate treatment method. On the other hand, the determination of the required level of Hb may be delayed for a long time.

On the other hand, the development of erythropoietin dysfunction, as the cause of anemia, as a result of a decrease in renal perfusion, allowed this syndrome to be called cardiorenal anemic syndrome [9]. Does EPO affect target level Hb [10]. At the same time, another question arises - why European clinicians in their studies to correct the anemic syndrome do not rely on EPO levels. No data on the levels of EPO and its dynamics. Moreover, the prescribed therapy in their studies does not consider cases of anemia in patients with CHF with hypo-, normo-, hypereritropoetinemia. In studies [11-18], the appointment of EPO preparations is carried out without information about the level of EPO. This important part is the lack of data and information on the role of the EPO level and the question that has arisen as to why anemia correction in CHF is performed without EPO data and the development of an innovative method in the treatment of CHF led us to address this topical issue.

As can be seen from the table, severe patients with CHF (LVEF <35%) participated in the studies [11]. Moreover, the number of patients was 26. Nevertheless, it was possible to increase exercise tolerance. In studies [12], r EPO was used in 40 patients with CHF with LVEF <35% and with moderate renal failure. Achieved a significant improvement in walking test, VO2 max, VO2, NYHA class, lower BNP, renal function and hospitalization when elevated to the target level of Hb 11.5-12 g/day. In studies [13], β-epoetin was used in 51 patients with CHF NYHA III-IV class with LVEF <40% and with mild to moderate renal failure. Achieved a significant improvement in LV size and systolic function, NYHA class and BNP, renal function and hospitalization, however, there was no improvement in GFR when elevated to target Hb12-12.5 g/dL. The clinician literally a year later managed to achieve an increase in Hb to a target level of 12-12.5 g/dl.

Another study [14] was used in 41 patients with symptomatic HF with anemia with LVEF ≤40% Darbopoetin-α to achieve the target level of Hb13-15 g/dl. However, there was no improvement

in the peak of VO2, the absolute peak of VO2, BNP, NYHA FC, reduction of hospitalization, improvement of KCCQ, MLWHFQ. Only physical stamina improved. In the study [15], Darbopoetin-α was also used in 165 patients with symptomatic HF with anemia with LVEF ≤40% to achieve the target level of Hb14 ± 1.0 g/dl. However, there was no improvement in LVEF,NYHA class, 6-minute walking test, quality of life according to the Minnesota Living With HF Questionnaire score. The overall well-being of the patients and Kansas City Cardiomyopathy Questionnaire have improved.

The study [16] involved 32 patients with NYHA IIH II-II II CHF, LVEF FC <40%, Hb<12.5 g/dl, plasma creatinine <2.5 mg/dl, Hb<12.5 g/dl and Darbepoetin-α was prescribed. 0.75 μg/kg weight. As a result, improvement in LVEF, NYHA grade, BNP level, 6-minute test was observed. Darbepoetin-α was also used in its studies [17] in 41 patients with NYHA II - III CHF class VF<40%, Hb<12.5 g/dl, plasma creatinine level <2.5 mg/dl and Hb level <12.5 g/dl. As a result, they achieved improvement of physical endurance, quality of life, psychoemotional status. It should be noted that in studies [15,16] patients had renal failure. As can be seen, studies [15,16] included patients with NYHA II - III class LVEF <40%, i.e. moderately severe. However, clinicians gradually began to use darbepoetin-α in heavy patients with NYHA II - IV FCF with LVEF <40% Hb<12.5 g/dl [17] and achieved good results: improved LVEF, NYHA class, BNP level, 6-minute test, of oxidative and nitrodative stress mediators.

Some clinicians in the treatment of anemic CHF preferred the use of combination therapy of EPO with iron preparations. They argued their treatment method that EPO drugs are the cause of iron deficiency. For correction of anemia in CHF, combined recombinant EPO therapy (rePO) at a dose of 2000 IU with intravenous administration (IV) of iron Saharata at a dose of 200 mg/week applied D. Silverberg [19], in 2000, in 26 CHF patients III - IV NYHA class with LVEF <35%, Hb<12 g/dl. He suggested that the use of rEPO can lead to iron deficiency (ID). He suggested that the use of rEPO can lead to ID. Duration of treatment is 7 months. As a result of treatment, he managed to raise the Hb level to 12 g/dL and against this background, an increase in EF and class NYHA. Further, in his research, he begins to bring the number of patients to 32, 126 [20,21], the dose of rEPO increased to 4000-5000 IU and Venofer in a dose of 200 mg/week When the level reached 12.5 g/dl, the doses of drugs decreased. As a result of his research, there was an improvement in NYHA class, clinical symptoms, a decrease in the days of hospitalization, a decrease in the dose of furosemide, and no progression of renal dysfunction. So these were good results for severe CHF patients. Some clinicians used [21], combined therapy in patients with CHF and anemia.

The innovative decision was [22] to compare therapeutic tactics in 2 groups in 16 patients with CHF with anemia, 8 in each; group A Hb = 10.7 ± 1.2 Group B: n = 8, Hb = 10.2 ± 0.7. In group A, explosive iron was administered, and in group B, a combination of explosive iron with EPO. Duration of treatment 3 months. In addition, the researcher managed to achieve an increase in Hb = 13.1 ± 0.6 in group A and Hb = 13.0 ± 0.8 in group B. In the above studies [11-18,22,23] there is no information on the level of EPO.

The results of the FERRIC-HF study [24], in which for the first time it was shown that during the treatment with iron with sucrose, physical tolerance increases independently of the dynamics of the Hb level, made it possible to suggest the benefits of administering intravenous iron to patients with ID even in the absence of anemia. he results of another, the largest of the studies using intravenous iron - FAIR-HF, which included 459 patients with mild symptomatic CHF with proven GI, with or without anemia [25], found to be significantly or moderately self-estimated in general health 50% of patients in the group used iron carboxymaltose and only 27% of patients in the placebo group. The FAIR-HF subanalysis, an EFFICACY-HF study, showed that NYHA FC significantly improved in the carboxymaltose iron group, and by week 24, patients with FC I and II CHF had 17% more than in the placebo group.

In addition, it was necessary to clarify whether the use of a combination treatment, for example, iron-sucrose IV or carboxymaltose with epoetin/Darbepoetin-α, is required, or whether appropriate monotherapy will be sufficient or even better than the combined treatment. All these questions require an answer. ID as we have indicated, plays the necessary role [26]: in studies of Klip., *et al*. [27] it was shown that mortality in patients with CHF with anemia without ID is less common than with ID, and the presence of both increases it sharply. Natasha P. [28] believes that since the RED-HF study did not demonstrate any benefit from using ESS on mortality or morbidity in patients with CHF, EPO is no longer considered a treatment option, although intravenous administration of iron has the potential as a therapy for patients

with anemia and without anemia [29,30]. However, we must not forget that EPO stimulates myocardial receptors and improves the echocardiogram of CG parameters [31-33]. From the above, the need for the appointment of a combination therapy of EPO with intravenous iron preparations [26,34-37].

To this day, many questions regarding the role that anemia plays and how it is treated in patients with CHF remain unanswered. On the one hand, the diagnosis of anemia in these patients is unchanged, as well as the choice of the appropriate treatment method. On the other hand, the determination of the required level of Hb may be delayed for a long time. Several studies have evaluated the effects of EPO, iron, EPO, and iron in patients with CHF. Despite the fact that most of them were uncontrolled studies, their results show that the treatment of EPO may be useful in CHF. Currently, a large randomized, placebo-controlled RED-HF study with 3,400 patients with CHF and anemia has been completed in 60 countries, evaluating the effects on morbidity and mortality of darbepoetin-α. Publication of the research results allowed a more objective assessment of the benefits of rEPO preparations [38]. The neutral effect of Darbepoetin-α is consistent across all pre-selected subgroups or the lack of effect on the primary or secondary point [38-42]. The drug according to the STAMINA -HF study steadily raises Hb levels to 13 g/l, however, this does not reduce mortality and hospitalization [39]. Clinicians concluded that therapy with Darbepoetin-α does not improve clinical outcome in patients with systolic HF and mild to moderate anemia. Their findings do not support the use of Darbepoetin-α in these patients, and hence it was assumed that anemia is a marker of severe CHF, but not a therapeutic goal [39]. However, many questions remain unsolved: EPO drugs stimulate EPO myocardial receptors. And if you replace Darbepoetin-α with another drug EPO.

However, using Darbepoetin-α there is a higher risk of venous and arterial thromboembolic events, stroke and a tendency to hypertension. However, recent studies in patients with CKD, malignant tumors, the use of rEPO increased the risk of developing hypertension, stroke, thromboembolism. This is probably due to more pronounced GI (and subsequent thrombocytosis) against the background of isolated therapy of anemia of rEPO (especially high doses) in patients with CKD and tumors [40,43-45]. Clinical data is inconsistent, Kourea., *et al*. [17] in his studies found in patients with CHF with anemia improved physical endurance, quality of life and psycho-emotional status, and Klapholz M. placebo, the target Hb level increased to 14.0 +/- 1.0 g/dL [46].

In contrast to darbepoetin - α, methoxy polyethylene glycol epoetin beta (MPEB), CERA is a new tool that stimulates erythropoiesis. CERA (Durable Erythropoietin Receptor Activator) [47]. The MPEB has a half-life of 130 hours, which allows it to be administered once every 3-4 weeks. Like the MPEB, both synthetic erythropoiesis protein and erythropoietin fusion protein activate the EPO receptor. So-called erythropoietin mimetic peptides activate the EPO receptor without structural similarity to EPO [48]. The above properties, the MPEB provides for the correction of anemia in accordance with international recommendations (an increase in the level of Hb in the correction phase of 1-2 g/dL for 4-6 weeks Sulowicz [49] and the absence of fluctuation in its level. It follows that these properties of the drug avoid exceeding the level of Hb> 130 g/dL, prevents the risk of thrombosis, the occurrence or aggravation of hypertension and cardiovascular complications [24]. Uniform and stable achievement of the target Hb level reduces the risk of death, hospitalization in patients with chronic renal failure, reduces LV hypertrophy and improves mental functions (Locatelli) [50].

As can be seen from the above, this problem is very actual, controversial and not fully studied. For us, it has become actual to study and evaluate the effectiveness of MPEB combination therapy with IV iron saharat in correcting anemic syndrome in patients with CHF of ischemic etiology.

Materials and Methods

We examined 127 patients with CHF of the ischemic etiology of the I-IV class NYHA: of these, 93 patients were diagnosed with anemia. They were diagnosed with anemia with hemoglobin (Hb) levels in men less than 120 g/l and in women less than 110 g/l. CHF developed due to coronary artery disease: stable angina III-IV FC (SA) and post-infarction cardiosclerosis (PC), 34 patients had type 2 diabetes mellitus (DM), and 58 patients had concomitant arterial hypertension (AH). The exclusion criteria were severe or malignant hypertension, acute disorders of cerebral circulation less than 12 months old, acute myocardial infarction, acute coronary syndrome(ACS), chronic obstructive pulmonary diseases, concomitant diseases of the connective tissue, cancer, mental disorders.

Depending on the treatment tactics, all patients were randomly divided into 2 groups depending on the levels of ferritin, TS, and EPO in the blood plasma. Each group in turn, depending on the CHF class, was subdivided into 2 CHF subgroups I-II of the FC and CHF III-IV of the FC.

As a control group, 34 patients were diagnosed with CHF of ischemic etiology, but without anemia, 21 women and 13 men. The average age of patients in the control group was 57.8 ± 2.1 in patients with CHF I - II NYHA class, and 59.7 ± 2.5 in patients III-IV NYHA class 59.7 ± 2.5 are statistically insignificant. Concomitant type 2 diabetes was diagnosed in 11 patients, and hypertension in 17 patients.

Group I - 49 patients with CHF with anemia (mean age 61.1 ± 1.4 years, 26 men and 23 women) who received only basic therapy, including ACE inhibitors, β-blockers, diuretics, digoxin, nitrates. The subgroup of CHF I-II class NYHA included 42 patients with CHF with anemia of ischemic etiology and, and the subgroup of CHF III-IV class NYHA consisted of 7 patients. Concomitant type 2 diabetes was diagnosed in 8 patients, and 11 patients had hypertension.

Group II - 44 patients (mean age 59.9. ± 1.2 years, 19 men and 25 women) of CHF with anemia, who had hypoeritropoietinamia and ID who received the combined MPEB and IV therapy with basic drugs. The subgroup of CHF I-II NYHA class included 33 patients in CHF with anemia of the ischemic etiology I-II class NYHA, and the subgroup of CHF III-IV class NYHA included 11 patients. MPEB was administered at a dose of 50 IU once a month for 6 months depending on the level of Hb and iron (III) sucrose complex hydroxide (Venofer) at a dose of 200 mg iv twice a week for 5 weeks. 19 patients were diagnosed with concomitant Type 2 diabetes, 30 - AH.

The baseline therapy according to international recommendations in the control and main groups included ACE inhibitors, angiotensin II receptor blockers, β-blockers (including with the additional purpose of ivabradine according to indications), nitrates, diuretics, cardiac glycosides - digoxin, as well as in the presence of ventricular arrhythmias -Amiodarone.

In all patients, the levels of Hb, iron, ferritin, TS, EPO were determined on an automated analyzer by ELISA, the level of NT pro BNP by immobilization of antibodies using reagent Biomedica (Austria), plasma levels of IL-1, IL-6, TNF-α blood through commercial test systems using enzyme immunoassay according to standard methods on automated analyzers before and after treatment. Parameters of systolic and diastolic functions of the myocardium of the LV by the method of dopple echocardiography before and after 20 weeks treatment. All patients underwent 6-minute walking test (6-MWT) and calculated glomerular filtration rate (GFR) using the Cockroft - Golth formula. For women: GFR = 1.05 × (140-age (years)) × body weight (kg)/creatinine (μmol/ml); for men: GFR = 1.23 × (140-age (years)) × body weight (kg)/creatinine (μmol/ml).

Static analysis was performed using the software package Statistica 6.0. The results obtained are presented in the form (M ± SD). For evaluation used Student criterion. Differences were taken as statistically significant at a level of $p < 0.05$.

Results and Discussion

The research results are presented in tables 1, 2.

Parameters	CHF I-II NYHA class without anemia (control group) N = 22	CHF I-II NYHA class with anemia N = 42		CHFIII-IV NYHA class without anemia (control group) N = 12	CHF III-IV NYHA class with anemia N=7	
		Before treatment	Aftertreatment		Before treatment	Aftertreatment
Hbg/l	126,4 ± 1,0	103,5 ± 1,0 ^^^	105,5 ± 12,0	125,3 ± 1,4	105,9 ± 1,8 ^^^	112,3 ± 5,0
Δ %			2,1			6,1
Ht %	53,6 ± 1,1	39,8 ± 0,7	43,2 ± 0,8 **	55 ± 1,2	38,3 ± 2,6	42,1 ± 3,2
Δ %			8,4			10,1

Iron, mkmol/nl	15,8 ± 1,0	15,4 ± 1,0	16,3 ±	17,2 ± 0,9	12,3 ± 2,9	10,9 ± 2,5
Δ %			5,8			-12
Ferritin, ng/ml	138,2 ± 19,8	42,9 ± 7,9	58,5 ± 8,8	163,3 ± 40,7	109,1 ± 27,9	141,3 ± 26,3
Δ %			36,3			31,2
TS %	>20%	<20	<20	>20%	<20	<20
EPO, IU/ml	11,9 ± 3,6	20,60 ± 4,85	20,9 ± 5,8,0	17,4 ± 5,3	15,6 ± 7,7	16,5 ± 8,0
Δ %			1,7			6,3
NT pro BNP, pgmol/l	1406,3 ± 171,27	1353,2 ± 297,56	850,3 ± 121,5	2015,7 ± 180,6	1394,73 ± 379,5	840,0 ± 233,4
Δ %			-37,2			- -39,8
IL-1, pg/ml	3,7 ± 2,8	9,7 ± 3,3	9,7 ± 2,8	3,5 ± 1,4	4,5 ± 2,5	3,9 ± 1,7
Δ %			-0,6			-13,2
IL-6. pg/ml	42,2 ± 20,6	9,9 ± 3,6	5,2 ± 2,0	16,0 ± 3,4	4,7 ± 2,3	1,6 ± 0,5
Δ %			-41,1			-65
TNF-α, pg/ml	21,7 ± 7,6	11,0 ± 2,4	7,0 ± 1,9	3,8 ± 1,3	14,1 ± 5,3	5,2 ± 1,3
Δ %			-36,6			-63,1
Creatinine, mkmol/l	107,4 ± 5,7	117,1 ± 3,6 112,5 ± 2,2^	112,5 ± 2,2 ^	90,2 ± 5,1	134 ± 6,2	
Δ %			-3,4			
LVMM, g	260,1 ± 14,4	270,0 ± 7,6	239,2 ± 5,7	291,6 ± 32,9	366,0 ± 41,8	324,4 ± 37,1
Δ %			-11,4			-11,4
EDV, ml	229,0 ± 111,3	171,3 ± 5,7^^^ 162,8 ± 5,1	162,8 ± 5,1	233,1 ± 13,6	238,9 ± 27,8	228,9 ± 26,1
Δ %			-5			-4,2
ESV, ml	163,1 ± 10,8	171,3 ± 5,7 ^^^	162,8 ± 5,1	159,3 ± 12,2	73,9 ± 2,3 ^^	72,3 ± 2,1
Δ %			-5			-2,2
LA, sm	4,15 ± 0,09	4,23 ± 0,07	4,14 ± 0,06	4,15 ± 0.11	4,78 ± 0,24 ^	4,60 ± 0,21
Δ %			-2			-3,8
RV, см	2,99 ± 0,1	2,82 ± 0,05	2,79 ± 0,04	3,03 ± 0,15	2,39 ± 0,08	^2,37 ± 0,08
Δ %			-0,6			-3,7
LVEF %	44,6 ± 2,3	44,9 ± 1,0	45,9 ± 0,9	35,5 ± 2,5	33,3 ± 4,9	34,3 ± 5,0
Δ %			2,3			3
Ve/Va	0,97 ± 0,10	1,40 ± 0,09	1,34 ± 0,09	0,96 ± 0,155	2,17 ± 0,41	2,1 ± 0.5
Δ %			-5,7			-0,94
IVRT, ms	116,9 ± 3,7	113,7 ± 0,8	110,0 ± 0,9 **	114,6 ± 3,7	104,4 ± 1,3	101,1 ± 0,5 *
Δ %			-3,3			-3,1

6 -MWT,m	318 ± 17,8	353,5 ± 11,2	389,9 ± 11,7*	315,1 ± 16,7	248,6 ± 42,4	291,6 ± 39,7
Δ %			10,3			17,3
GFR, ml/min	81,6 ± 6,1	56,45 ± 2,5	59,3 ± 2,24 ^^^	87,9 ± 7,7	58,6 ± 3,3	57,9 ± 2,6
Δ %			5,0			-1,2

Table 1: Laboratory and functional parameters of patients in chronic heart failure with anemia I group.

Note: A statistically significant difference with the indicators.

1. Before and after treatment: * - p < 0.05; ** - p < 0.01; *** - p < 0,001.

2. With the control group: ^ - p1 < 0.05; ^^ - p1 < 0.01; ^^^ - p1 < 0.001.

Δ% difference before and after treatment.

Hb: Hemoglobin; Ht: Hematocrit; ST: Transferrin Saturation; EPO: Erithropoietin; NT pro BNP: N Terminal Pro Brain Natriuretic Peptide; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alfa; LVMM: Left Ventricular Myocardium Mass; LA: Left Atrium; RV: Right Ventricle; LVEF: Left Ventricular Ejection Fraction; Ve/Va: The Ratio of the E Peak is the Phase of Early Filling of the Ventricles to A Peac - Systole of the Atrial Late Filling; IVRT: Izovolumic Relaxation Time; 6-MWT: 6 Minute Walking Test.

As can be seen from table 1, in patients CHF I-IV NYHA class with anemia during basic therapy, there is an unreliable decrease in levels of Hb, Ht, IL-1, IL-6, TNF-α, creatinine and increased ferritin. However, the increase in GFR and 6-minute distance test was significant.

Therapy with basic drugs in patients with CHF and anemia does not effect plasma levels of EPO, because the anemic factor is accompanied by inhibition of plasma NT pro BNP levels. In all patients with CHF with anemia during treatment with basic drugs, there was an unreliable increase in LVEF, a decrease in Ve/Va. At the same time, IVRT was insignificantly reliably reduced.

Parameters	**CHF III-IVNYHA class without anemia (control group) N = 22**		**CHFIII-IV NYHA class with anemia N = 33**	**CHFIII-IV NYHA class without anemia (control group) N = 12**		**CHF III-IV NYHA class with anemia N=11**
	Before treatment		**Aftertreat-ment**	**Before treatment Aftertreatment**		
Hbg/l	126,4 ± 1,0	96,7 ± 1,9	104,8 ± 2, **^^^^	125,3 ± 1,4	95,5 ± 3,3 ^^^ §	106,9 ± 4,6 ^^^
Δ %			8,4			12,0
Ht %	53,6 ± 1,1	41,8 ± 1,1 ^^^	48,3 ± 1,2 *** ^^^ §§§	55 ± 1,2	39,5 ± 2,0 ^^^	45,5 ± 1,6* ^^^
Δ %			15,4			15,4
Iron, mkmol/ml	15,8 ± 1,0	16,7 ± 3,1	18,1 ± 0,8	17,2 ± 0,9	13,1 ± 1,8	16,1 ± 1,2
Δ %			8,1			22,7
Ferritin, ng/ml	138,2 ± 19,8	47,4 ± 7,1	200,8 ± 18,9 *** ^ §§§	163,3 ± 40,7	63,3 ± 18,3 *	222,7 ± 28,1 ***
Δ %			323,7			250,9
TS %	>20%	<20%	>20%	>20%	<20%	>20%
Δ %						

EPO, IU/ml	11,9 ± 3,6	3,0 ± 0,47 ^^§§	21,9 ± 5,7 ***	17,4 ± 5,3	3,79 ± 0,88 ^	21,3 ± 3,8 ***
Δ %			630,3			460,1
NT pro BNP, ngmol/l	1406,3 ± 171,2	2526,8 ± 188,4^^^§§	1157,1 ± 108,1 *** ^^	2015,7 ± 180,6	2035,6 ± 279,9	1364,8 ± 207,6
Δ %			-54,2			-23,2
Il-1,ng/ml	3,7 ± 2,8	8,65 ± 4,42	1,25 ± 0,19 §	3,5 ± 1,4	6,49 ± 2,1	2,4 ± 1,58
Δ %			-85,6			-63,0
Il-6 .ng/ml	42,2 ± 20,6	16,9 ± 4,2	3,7 ± 0,8 **^	16,0 ± 3,4	9,9 ± 1,7	5,6 ± 1,1 * ^ §
Δ %			-78,2			-43,7
TNF-α,ng/ml	21,7 ± 7,6	26,0 ± 18,0	2,2 ± 0,3 ^^§	3,8 ± 1,3	6,9 ± 2,3	2,3 ± 0,5 §
Δ %			-91,7			-67,0
Creatinine,mkmol/l	107,4 ± 5,7	113,2 ± 7,3	99,6 ± 4,8 §	90,2 ± 5,1	120,5 ± 12,4 ^	106,4 ± 11,8
Δ %			-12,0			-11,7
LVMM,g	260,1 ± 14,4	221,6 ± 9,2 ^§§§	198,1 ± 7,3 *^§§§	291,6 ± 32,9	303,4 ± 26,5 §	276,0 ± 18,7
Δ %			-10,6			-9,0
EDV,ml	229,0 ± 111,3	146,1 ± 9,0 §^^^	130,0 ± 7,0 ^^^ §§§	233,1 ± 13,6	231,5 ± 15,2	211,3 ± 13,6
Δ %			-11,0			-8,7
ESV, ml	163,1 ± 10,8	77,6 ± 6,6 ^^^§	67,9 ± 5,6 ^^^ §§	159,3 ± 12,2	155,5 ± 11,9	141,6 ± 10,9:
Δ %			-12,6			-9,0
LA, sm	4,15 ± 0,09	4,15 ± 0,08	4,04 ± 0,06	4,15 ± 0.11	4,55 ± 0,14 ^	4,34 ± 0,11 ^
Δ %			-2,8			-4,6
RV, sm	2,99 ± 0,1	2,78 ± 0,05 ^^	2,74 ± 0,03 ^^	3,03 ± 0,15	3,01 ± 0,17 §	2,91 ± 0,15 §

Δ %			-1,5			-3,3
LVEF, %	44,6 ± 2,3	47,7 ± 1,7	50,9 ± 1,6 §§	35,5 ± 2,5	29,9 ± 0,7 ^	33,5 ± 0,5 ***
Δ %			6,7			
Ve/Va	0,97 ± 0,10	1,221 ± 01,44^	1,213 ± 0,086	0,96 ± 0,155	1,635 ± 0,250 ^	1,255 ± 0,190
Δ %			-0,7			-23,2
IVRT, ms	116,9 ± 3,7	121,7 ± 3,8 §	121,8 ± 3,4 §§§	114,6 ± 3,7	105,2 ± 3,3	111,0 ± 2,0 §§
Δ %			0,0			5,5
6-MWT, m	318 ± 17,8	347,2 ± 14,2	422,2 ± 10,7; ***	315,1 ± 16,7	164,6 ± 6,7	271,5 ± 111,8***
Δ %			21,6			64,9
GFR, ml/min	81,6 ± 6,1	71,61 ± 4,25	76,9 ± 3,59	87,9 ± 7,7	67,75 ± 7,85	78,43 ± 6,75
Δ %			7,4			15,8

Table 2: Laboratory and functional parameters of patients in chronic heart failure with anemia II group.

Note: a statistically significant difference with the indicators:

1. Before and after treatment: * - p < 0.05; ** - p < 0.01; *** - p < 0,001.

2. With the control group: ^ - p1 < 0.05; ^^ - p1 < 0.01; ^^^ - p1 < 0.001.

Δ% difference before and after treatment.

Hb: Hemoglobin; Ht: Hematocrit; ST: Transferrin Saturation; EPO: Erithropoietin; NT pro BNP: N Terminal Pro Brain Natriuretic Peptide; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor Alfa; LVMM: Left Ventricular Myocardium Mass; LA: Left Atrium; RV: Right Ventricle; LVEF: Left Ventricular Ejection Fraction; Ve/Va: The Ratio of the E Peak is The Phase of Early Filling of the Ventricles to A peac-Systole of the Atrial Late Filling; IVRT: Izovolumic Relaxation Time; 6-MWT: 6 Minute Walking Test.

From table 2 it follows that patients in CHF and anemia of group II in CHF I-II NYHA class with the background of the therapy, there is a significant increase in Hb level by 8.4% (p < 0.01), hematocrit by 15.4% (p < 0.001), the level of ferritin in the blood by 4.2 times were reliable (p < 0.001), EPO in the blood by 7.3 timeswere reliable (p < 0.001) and a decrease in the level of NT pro BNP in the blood plasma by 54.2%, the level of IL-6 in blood plasma by 78.2% (p < 0.01).As can be seen from, the hematocrit increase by 15.4% compared with its pre-treatment index (p < 0.05), the level of ferritin in the blood, the background of treatment by 3.5 times were reliable (p < 0.001), the level of EPO in the blood by 5.6 times were reliable. The level of IL-6 in patients with CHF III-IV NYHA class with anemia was significantly reduced by 43.7% (p < 0.05). Compared with group I, there was a significant increase in GFR by 29.7% (p < 0.001) in CHF I-II NYHA class and 35.5% (p < 0.05) in patients with CHF III-IV NYHA class. The rate of 6-MWT was significantly increased by 21.6% (p < 0.001) and 64.9% (p < 0.001). The side effects of combination therapy with MPEB and iron supplementation in patients have not been fixed.

The results of the parameters of the systolic function of the myocardium of the LV in patients with CHF I-II NYHA class with anemia of group II on the background of the therapy. As can be seen from table 2, there is an unreliable decrease in Echo CG parameters

such as RV (right ventricle), LVEF, LV, ESV, LA (left atrium) and increased LVEF. In addition, in patients with CHF I-II NYHA class with anemia of group II, during therapy there is an unreliable increase in Ve, a decrease in Va and Ve/Va. IVRT has not changed. As shown in table 2, patients with CHF III-IV NYHA class with anemia Group II, during therapy, an insignificant decrease parameters of RV, LVMM (LV myocardium mass), and LA occurs. However, LVEF was significantly increased by 12.2% ($p < 0.001$). Analysis of diastolic function parameters, revealed in patients with CHF III-IV NYHA class with anemia of the IV group on the background of the therapy, an unreliable decrease in Ve/Va and an increase in IVRT.

Conclusion

The main objective of this study was to study and build issues of correction of anemic syndrome, reducing the effectiveness of basic drugs and aggravating the course of CHF. During the treatment of patients with CHF with anemia, refractivity to therapy is often developed. At the same time, therapy with basic drugs in patients with CHF with anemia does not affect the levels of ferritin, EPO in blood plasma, TS. Obviously, the anemic factor is accompanied by inhibition of the reduction of the plasma level NT pro BNP and cytokine aggression in the treatment of basic drugs. The positive dynamics of the parameters of the systolic function of the myocardium of the LV in our study were unreliable, most likely this is due to the development of anemia. The presence of anemia in CHF increases the severity of LV diastolic dysfunction. In this study, the problem is highlighted taking into account the blood levels of ferritin, TS, EPO, a similar approach is not described in the literature [15,24-27,30]. According to data from similar studies, treatment tactics were aimed directly at correcting anemia without taking into account such important indicators as levels of ferritin, TS and EPO. In the literature there are data on the use in the treatment of CHF with anemia directly erithropoesis stimulating agents (ESA) [15,20-23], IV of iron [19,31-33] or their combination [27,34,35]. At the same time, there is little data in the literature on the combination therapy of ESA with IV iron [27,34,35]. ESA used short-acting drugs or darbopoetin-α [15,20-23]. However, for the correction of anemia in CHF, constant activation of erythropoietin receptors is necessary, which is carried out by the MPEB.

In studies [27,37,38] on the use of combination therapy with the use of EPO and IV, iron was not used by the MPEB. Also in the listed studies, the dynamics of cytokines were not studied; only 8 patients were included in the study [27]. In these studies, clinicians achieved an increase in Hb, a decrease in the NT pro BNP level, hospitalization, NYHA class, but there is no data for echocardiography. In the present study, a positive dynamics of hematopoietic parameters occurred in group II, which correlated inversely with NT pro BNP and IL-6. Thus, in patients with CHF I-II NYHA class with anemia, there was an insignificant decrease in IL-1, IL-6, TNF-α, but in severe patients, a reduction in IL-6 was significant, which was accompanied by reliable positive dynamics of LVEF and Ve/Va. The increase in GFR during treatment was unreliable, however, compared with the I group, there was a significant increase of29.7% ($p < 0.001$) and 35.5% ($p < 0.05$). Decrease in left ventricular hypertrophy (LVH), LVMM by 10.6%, increase in LVEF to 50.9 ± 1.6% in patients with CHF I-II NYHA class and a significant increase in LVEF to 33.5 ± 0.5% ($p < 0.001$). However, in group II of patients with CHF with anemia during treatment, there was no positive trend in IVRT and Ve/Va. There was a significant increase in 6-MWT by 21.6% ($p < 0.001$) and 64.9% ($p < 0.001$), respectively, as well as an increase in the NYHA class from class II to class I, from class III to class II, from class IV to class III.

As a result of the therapy, there was a reduction in the dose and the number of diuretic drugs. So the dose of furosemide was reduced from 240 mg to 40-80 mg, torasemide from 20 to 5 mg, veroshpiron from 50-100 mg to 25 mg, hydrochlorothiazide from 50 mg to 25 mg. The number of diuretic drugs decreased to 1 in moderate patients and to 2 in severe patients, depending on the NYHA class.

The results of the study convincingly prove that despite the advantages of the combined treatment of MPEB with an intravenous iron preparation, in each case it is necessary to carry out a differentiated approach in the choice of therapy, that is, the results of specific laboratory and functional indicators are needed.

Acknowledgements

We thank Azerbaijan State Advance Training Institute for Doctors, Sabunchi City Hospital, Roche ltd.

Conflict of Interest

None declared.

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