Mukhitdinova Gulshan Zohirovna – assistant
Samarkand State Medical University (Samarkand, Uzbekistan)

CHRONIC HEART FAILURE AND ANEMIA: MODERN PRINCIPLES AND APPROACHES TO TREATMENT

Abstract. *In this literature review, modern approaches to the treatment of anemia in patients with chronic heart failure (CHF) are considered and analyzed, including data on therapeutic methods and the specifics of using iron preparations. This article highlights the clinical significance of anemia in patients with chronic heart failure (CHF), the mechanisms of its development, and modern treatment strategies. Special attention is paid to the negative impact of iron deficiency anemia on the course of heart failure, disease prognosis, and patients' quality of life.*

Key words: *chronic heart failure, anemia, iron deficiency, erythropoietin, FAIR-HF study, heart failure outcomes, quality of life.*

Мухитдинова Гульшан Зохировна - ассистент
Самаркандский государственный медицинский университет (Самарканд, Узбекистан)

ХРОНИЧЕСКАЯ СЕРДЕЧНАЯ НЕДОСТАТОЧНОСМЬ И АНЕМИЯ: СОВРЕМЕННЫЕ ПРИНЦИПЫ И ПОДХОДЫ К ЛЕЧЕНИЮ

Аннотация. *В обзоре литературы рассматриваются и анализируются современные подходы к лечению анемии у пациентов с ХСН, включая данные о методах терапии и особенностях применения препаратов железа. В данной статье освещена клиническая значимость анемии у пациентов с хронической сердечной недостаточностью (ХСН), механизмы её развития и современные стратегии лечения. Особенно акцентировано внимание на негативном влиянии железодефицитной анемии на течение сердечной недостаточности, прогноз заболевания и качество жизни пациентов.*

Ключевые слова: *хроническая сердечная недостаточность, анемия, дефицит железа, эритропоэтин, исследование FAIR-HF, исходы сердечной недостаточности, качество жизни.*

Muxitdinova Gulshan Zoxirovna – assistent
Samarqand davlat tibbiyot universiteti (Samarqand, O‘zbekiston)

SURUNKALI YURAK YETISHMOVCHILIGI VA KAMQONLIK: ZAMONAVIY DAVOLASH TAMOYILLARI VA YONDASHUVLARI

Annotasiya. *Mazkur adabiyotlar sharhida surunkali yurak yetishmovchiligi (SYY) bilan og‘rigan bemorlarda kamqonlikni davolashning zamonaviy yondashuvlari, shuningdek, davolash usullari va temir preparatlaridan foydalanishning o‘ziga xos xususiyatlari ko‘rib chiqilgan va tahlil qilingan. Ushbu maqolada surunkali yurak yetishmovchiligi (SYY) bilan og‘rigan bemorlarda kamqonlikning klinik ahamiyati, uning rivojlanish mexanizmlari va zamonaviy davolash strategiyalari yoritib berilgan. Ayniqsa, temir tanqisligi kamqonligining yurak yetishmovchiligi kechishiga, kasallikning prognoziga va bemorlarning hayot sifatiga salbiy ta’siri alohida e’tirof etilgan.*

Kalit so‘zlar*: surunkali yurak yetishmovchiligi, kamqonlik, temir tanqisligi, eritropoetin, FAIR-HF tadqiqoti, yurak yetishmovchiligi oqibati, hayot sifati.*

The effectiveness of treating patients with chronic heart failure (CHF) depends on addressing comorbid conditions that may lead to the progression and complications of this disease. In such patients, the treatment of anemia should primarily consider its etiological factors. To achieve this goal, it is necessary to thoroughly examine patients and determine the cause of anemia.

In 2013, the American College of Cardiology developed the first recommendations for the treatment of anemia in patients with cardiovascular diseases [1]. These recommendations outlined principles for managing patients with cardiological diseases and anemia, regardless of the anemia's etiology. Three treatment strategies were recommended: enhancing erythropoietin production, red blood cell transfusion, and intravenous iron supplementation. Considering that red blood cell transfusion may worsen the patient's condition, this procedure should only be performed in hospital settings for patients with ischemic heart disease (IHD) and severe anemia. In treating IHD and CHF patients with mild to moderate anemia, the use of erythropoietin-stimulating agents is not recommended due to the high risk of thromboembolic complications and the lack of positive impact on disease outcomes and hospitalization rates.

Currently, there is positive evidence that intravenous administration of iron carboxymaltose to correct iron deficiency in the body leads to increased physical endurance, improved quality of life, and reduced rehospitalization and mortality rates [2,3].

An analytical article titled "Treatment of Anemia in Patients with Cardiovascular Diseases" reviewed several studies focused on treating anemia in CHF [4]. One study reported that administering ferric carboxymaltose (Ferinject) at 200 mg in the first week, followed by 200 mg monthly over 24–26 weeks [3], had a positive effect on disease outcomes. Two other studies indicated that administering iron hydroxide sucrose complex (Venofer) at 200 mg weekly for five weeks positively influenced disease outcomes [5,6]. Analysis of these studies showed that intravenous iron therapy in CHF patients led to a reduction in functional class, increased physical endurance, improved renal function and quality of life, significant increases in hemoglobin levels and left ventricular ejection fraction (LVEF), decreased levels of natriuretic peptides and C-reactive protein (CRP), and reduced hospitalizations due to CHF decompensation. However, despite evidence of improved disease prognosis, there is insufficient data on the impact of iron monotherapy on mortality and other adverse outcomes in CHF [4].

According to the European Society of Cardiology's recommendations, in confirmed cases of iron deficiency, iron supplementation can improve CHF progression and should be considered before using erythropoietin-stimulating agents [7]. Some authors advocate for the combined use of iron and erythropoietin-stimulating agents, noting that the efficacy of this combination cannot be achieved with oral iron preparations [8]. Additionally, determining whether patients can take oral iron supplements can be resolved by measuring serum hepcidin levels [9]. Intravenous iron preparations such as iron gluconate (Ferrlecit, Rhône-Poulenc, 62.5 mg) and iron sucrose (Venofer, Uriach, 100 mg) are practically free of adverse effects. When comparing dosages, a blood transfusion introduces 250 mg of iron into the body, which decreases as the transfused red blood cells break down [10]. In this case, iron deficiency is absent, but anemia persists. In some patients, iron deficiency is the primary pathogenic factor of anemia, and in such cases, iron supplementation alone is sufficient without the need for erythropoietin. This is confirmed by the IRON-HF study, which examined absolute and relative iron deficiency anemia resulting from secondary blood loss, antiplatelet-anticoagulant therapy, and aspirin-induced gastritis [11].

Furthermore, in CHF, iron deficiency may arise due to insufficient intake or absorption of essential elements like vitamin B12, folic acid, and iron from the gastrointestinal tract [12]. Recent studies lack sufficient data on the prevalence of vitamin deficiencies in CHF, and these pathogenic elements of anemia are not considered significant factors in disease outcomes. Long-term intravenous iron therapy in CHF patients with reduced LVEF and confirmed iron deficiency anemia has been shown to alleviate CHF symptoms, increase physical endurance, and improve quality of life [14]. The European Society of Cardiology's 2012 guidelines on diagnosing and treating heart failure mention the efficacy of intravenous iron and recombinant erythropoietin (rEPO) therapy [13]. Considering this, recent years have seen extensive research on treating anemia in CHF patients with erythropoietin. The multicenter randomized clinical trial RED-HF initially observed positive results, such as improved clinical status, reduced dyspnea, and increased physical endurance in CHF patients treated with erythropoietin [15]. Unfortunately, final data from the study did not confirm the primary hypothesis [16]. Administration of erythropoietin (darbepoetin-alpha) in CHF patients with hemoglobin levels below 120 g/L did not positively affect hospitalization rates or mortality. Additionally, the incidence of thromboembolic complications increased by 3.5 times, and stroke risk increased by 1.7 times in this patient group. Similar cardiovascular complications were observed in patients with chronic kidney disease and type 2 diabetes mellitus treated with erythropoietin [17].

When the optimal hemoglobin level is considered to be within the range of 120–140 g/L, the development of such complications was associated with an increase of its level above 145 g/L [18]. However, in the RED-HF study, the achieved hemoglobin level did not exceed an average of 130 g/L, yet the risk of complications continued to increase [19]. As a result, it was concluded that even in cases of low hemoglobin levels, the use of erythropoietin in the treatment of patients with chronic heart failure (CHF) is not allowed (recommendation class III, level of evidence A) [2].

In conclusion, although the idea of achieving good therapeutic outcomes through the treatment of anemia with erythropoietin in patients with CHF has not yet been proven, this direction requires further research and investigation.

In most patients with CHF, iron deficiency anemia is observed [14]. In the majority of these cases, the presence of low hemoglobin levels (≤ 120 g/L) and serum iron levels below 10 μmol/L serves as proof of this condition. Determining ferritin levels (≤100 ng/mL in absolute iron deficiency) or transferrin saturation (≤20%) allows for a reliable assessment of the characteristics of anemia. If ferritin levels are within normal limits but transferrin saturation remains low, this indicates a relative iron deficiency. From a logical standpoint, in such situations, the use of iron preparations in treatment is considered effective [20].

Although oral iron preparations can be used, many patients in this group have malabsorption

syndrome in the gastrointestinal tract, and due to adverse drug effects (in 10–40% of patients — dyspeptic changes, constipation, etc.), they refuse to take these medications.

In an article published in the Journal of the American College of Cardiology, Dr. John Nanas, a representative of the Athens School of Medicine, and his colleagues wrote that "intravenous administration of iron preparations should be considered an effective method of treating iron deficiency in the late stages of heart failure" [21].

In the placebo-controlled, randomized FAIR-HF study, the effectiveness of Ferinject was studied in 149 patients with CHF diagnosed with NYHA class II–III functional status. The amount of iron was calculated using the Ganzoni formula and was corrected based on the hemoglobin level, serum transferrin saturation, and ferritin level. At the end of the study, the effectiveness of the treatment was analyzed through patient self-assessment of their health status (PGA), determination of CHF functional status (FS), exercise tolerance (6-minute walk test), and assessment of quality of life through a questionnaire. In addition, the effectiveness, safety, and good tolerability of intravenous Ferinject administration were scientifically and practically proven within the study objectives [21].

An improvement in general condition was observed in 50% of patients treated with Ferinject, compared to only 27% in the placebo group ($p<0.001$). Moreover, in the main group of patients, after 24 weeks of treatment, the proportion of NYHA class III CHF patients decreased, and functional class I and II increased by 17% ($p<0.001$). Throughout all study periods (4, 12), regardless of the initial hemoglobin level, the quality of life, self-assessment of health, and 6-minute walk test results significantly improved in the treatment group ($p<0.001$).

In most patients treated with Ferinject, kidney function improved, and the symptoms of chronic kidney disease were significantly less than in the placebo group. The adverse effects of the drugs in the treatment group did not differ from those in the placebo group. Cardiovascular complications were significantly more frequent in the placebo group ($p<0.01$) [4, 5, 15].

In the FAIR-HF study, there were also suggestions regarding the recommendation of iron preparations for preventive purposes even in CHF patients without signs of anemia [9, 12]. Currently, it is necessary to conduct scientific research to maintain long-term disease balance in CHF by influencing the inflammatory system, the cardiac remodeling process, and treating iron deficiency, thereby increasing patients' lifespan.

Available literature does not provide complete information on the treatment of anemia in CHF patients considering erythropoietin (EPO), ferritin, IL-1, IL-6, and α-TNF levels, and there is no universally accepted consensus on this matter. Thus, in CHF, anemia is a destructive factor that aggravates the disease, promotes its progression, and increases mortality. The results of numerous studies indicate the necessity of eliminating this problem.

Conclusion.

Anemia, especially iron deficiency anemia, in patients with chronic heart failure (CHF) has a significant impact on the course and prognosis of the disease. The results of scientific studies indicate the importance of early detection of anemia and determining its cause in the treatment of these patients.

The high effectiveness of iron preparations, especially parenteral (intravenous) administration, has been proven. In particular, the results of large studies such as FAIR-HF have shown that the use of iron carboxymaltose (Ferinject) in patients reduces symptoms of heart failure, increases exercise tolerance, improves quality of life, and reduces the number of hospitalizations with decompensation of the disease.

At the same time, it should be taken into account that treatment with erythropoietin stimulants does not always give the expected result and can sometimes cause thromboembolic complications.

In general, the treatment of anemia in patients with CKD requires a comprehensive approach, the selection of therapy based on the results of individual examinations, and the use of parenteral iron preparations in patients with iron deficiency. Continuing scientific research in this area, improving treatment standards, and developing individual therapy methods are among the urgent tasks of modern medicine.

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