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The Relationship of Pathological Cytokines and Erythropoietin in Patients With Chronic Heart Failure

Khaydarova Zarrina Erkinovna [1], Khusainova Munira Alisherovna [2], Ergasheva Ma'mura Tashtemirovna [3], Khaydarov Sanjar Nizamitdinovich [4]

Abstract: General Background: Chronic heart failure (CHF) is often associated with anemia, significantly impacting patient outcomes. The interplay between erythropoietin (EPO) deficiency and pathological cytokine activation is increasingly recognized in CHF pathogenesis. Specific Background: Elevated levels of pro-inflammatory cytokines, including interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), contribute to both immunosuppression and impaired erythropoiesis, worsening CHF symptoms. Knowledge Gap: While previous studies have highlighted the cytokine-mediated progression of CHF, the effectiveness of erythropoietin-stimulating agents (ESAs) in mitigating anemia and cytokine aggression remains underexplored. Aims: This study examines the relationship between pathological cytokines and EPO levels in CHF patients with anemia and evaluates the efficacy of methoxypolyethylene glycol-epoetin-β (MEB) in restoring hematological and cardiovascular parameters. Results: A randomized controlled trial involving 94 CHF patients with anemia showed that MEB administration led to a 22.4% hemoglobin increase ($p<0.05$) and normalization of EPO levels (29.3±4.3 IU/ml; $p<0.001$). Cytokine levels significantly decreased: IL-1β by 36.6% ($p<0.001$), IL-6 by 54.3% ($p<0.05$), and TNF-α by 48.3% ($p<0.05$). Left ventricular ejection fraction improved by 19.04% ($p<0.05$), and exercise tolerance increased by 76.6% ($p<0.05$). Novelty: This study demonstrates that MEB therapy not only corrects anemia but also reduces cytokine aggression, suggesting a dual mechanism of action in CHF management. Implications: These findings support the incorporation of ESAs in CHF treatment protocols, emphasizing their role in anemia correction and inflammation modulation.

Key words: Chronic heart failure, anemia, erythropoietin, cytokines, methoxypolyethylene glycol-epoetin-β, inflammation, cardiac function.

INTRODUCTION

Anemia is widespread among patients with chronic heart failure (CHF) and occurs in 7-50% of patients [1], is of great clinical importance and is an independent predictor of mortality. The PRAISE study found that with a 1% decrease in hematocrit, the risk of death in patients with CHF of NYHA functional class III–IV increases by 11%[2]. Of the possible causes of anemia, an increase in the production of pathological cytokines, in particular tumor necrosis factor (TNF)[3], is of great interest. to cause both immunosuppression and a decrease in the activity of erythropoietin (EPO), the formation of red blood cells in red bone marrow and iron metabolism. A. Bolger et al. A close relationship has been established between the content of circulating THF and the concentration of hemoglobin (Hb) in patients with severe CHF[4]. Activation of TNFA reduces receptor sensitivity Unfortunately, it disrupts the release and utilization of iron. The development of anemia in patients with CHF may be low or elevated in EPO[5]. In patients with CHF of grade IV according to NYHA, the level of EPO in plasma increases by 6 times. On the other hand, patients with CHF iron deficiency occurs in 37% of cases. There is a growing awareness that CHF, kidney failure, and anemia are often concomitant diseases that can mutually worsen. in a vicious circle, it led to the creation of the concept of cardiorenal anemia syndrome (CRAS)[6]. Thus, as mentioned above, there are many conflicting

[1,2,3,4] Assistant of Samarkand State Medical University

opinions on this issue, both in establishing the pathogenetic links of anemia and in therapeutic tactics. Should therapeutic tactics be aimed at suppressing cytokine aggression or eliminating EPO deficiency. Purpose of the study: to establish the relationship between the level of circulating pathological cytokines and EPO in patients with CHF with anemia and to assess this relationship for the development of therapeutic tactics[7].

MATERIALS AND METHODS OF RESEARCH

94 patients with CHF with NYHA grade III–IV and anemia were examined, 58 of them were men and 36 were women. The average age of patients was 59.7±1.6 years. All patients were diagnosed with anemia at a hemoglobin (Hb) concentration of less than 120 g/l in men and less 110 g/l for women. The cause of CHF was coronary heart disease (CHD)[8] (postinfarction cardiosclerosis) (n =45), CHD in combination with diabetes mellitus (DM) Type 2 (n =15)[9], CHD with arterial hypertension (AH) (n =14) or CHD + AH + DM (n =20)[10]. Concentrations of ferritin, transferrin, EPO, N-terminal precursor of brain natriuretic peptide (NT-proBNP), and pathological cytokines were determined in all patients before and after 6 months of treatment. Pathological serum cytokines — interleukin (IL) 1, 6 and TNFA — were determined using test systems using enzyme immunoassay using a standard technique on automatic analyzers. The level of NT-proBNP in the blood was assessed by immobilization antibodies by means of Biomedica reagent (Austria)[11]. The content of EPO and ferritin in the blood was determined on automatic analyzers by the enzyme immunoassay method. All patients were divided into 2 randomized groups: group I included 46 patients with CHF who were prescribed basic CHF therapy, and group II (main) included 48 patients with CHF and anemia who received basic drugs methoxypolyethylene glycolepoitin-β (MEB)[12]. MEB was prescribed to patients without iron deficiency. Iron deficiency was detected at ferritin concentrations of less than 100 micrograms/l and at concentrations of 299 micrograms/l, if transferrin saturation was less than 20%[13].

According to the study protocol, the exclusion criteria were severe or malignant hypertension, acute cerebral circulatory disorders less than a year ago[14]. 12 months, acute myocardial infarction 6 months ago, acute coronary syndrome, obstructive pulmonary disease, mental disorders[15]. All patients included in the study protocol before the start of the treatment program received the following drug therapy: angiotensin converting enzyme (ACE) inhibitors, prolonged nitrates, diuretics, digoxin, beta-blockers[16]. MEB was prescribed to patients 1 time / month at a dose of 0.60 mcg / kg subcutaneously (50 units) for 6 months. If the hemoglobin concentration increased by less than 10 g/l for 1 month, the dose of MEB was increased by about 25% monthly until the individual target Hb level was reached[17]. If the increase in Hb concentration exceeded 20 g/l per month, or the concentration of As Hb increased and approached 120 g/l, the dose of MEB was reduced by about 25%. If the concentration of Hb continued to increase, treatment was interrupted until Hb began to decrease. The clinical efficacy, laboratory and functional parameters, and safety of OIE administration were evaluated against the background of the use of basic traditional CHF therapy[18]. The patients' well-being, baseline level, and dynamics of exercise tolerance were taken into account according to bicycle ergometry and a six-minute walking test. The patients were continued to be monitored during treatment with OIE for 6 months. Clinical, functional and laboratory studies were performed initially and after 6 months of follow-up [19].

THE RESULTS AND THEIR DISCUSSION

An analysis of the results showed that patients with CHF and anemia have a decrease in EPO in blood plasma was up to 2.01±0.3 in group I and up to 1.87±0.1 IU/ml in group II[20], which was accompanied by a sharp cytokine aggression: an increase in IL-1 concentration up to 9.46±1.16 pg/ml in group I and up to 7.04±0.71 pg/ml in group II, IL 6 — up to 12.41±2.2 pg/ml in group I and up to 11.8±2.6 pg/ml in group II, TNF α — up to 10.41±2.9 pg/ml in I and up to 11.67±3.1 pg/ml in II. Activation of pathological cytokines, in turn[21], leads to an even more significant deterioration in the clinical symptoms of CHF. However, the relationship The relationship between EPO and pathological cytokines remains after treatment in group I[22], and in group II it changes, which is associated with the appointment of OIE. In group I, as a result of treatment, the EPO concentration remained

significantly low — 2.1±0.01 IU/ml (p <0.01), which resulted in an unreliable increase in Hb concentration, as well as an unreliable decrease in IL[23]

1b to 7.01±1.1 pg/ml, IL 6 to 8.22±1.8 pg/ml, TNF α — up to 8.23±2.8 pg/ml[24]. Thus, the absence of positive dynamics in the clinical picture of patients with CHF and anemia in group I has been proven unreliable. a decrease in the level of NT-proBNP to 231.7±21.5 fmol/L[25]. In group II of patients with CHF, there was a significant increase in EPO to 29.3±4.3 IU/ml (p <0.001), IL 1b decreased to 4.47±0.01 pg/ml (p <0.002)[26], IL 6 decreased to 5.4±1.02 pg/ml (p <0.05), TNF α — up to 6.04±1.1 pg/ml (p <0.05)[27]. The improvement in the clinical symptoms of CHF was accompanied by a decrease in the content of NT-proBNP to 198.1±30.3 fmol/L. All patients showed good tolerance. MAB. Systolic and diastolic blood[28]

Pressure and heart rate actually returned to normal or remained normal during the follow-up. The concentration of Hb in group I increased significantly to 103.5 g/l, and in the group receiving therapy OIE, — significantly, up to 114.1 g/l. Under the influence of OIE, there was a significant increase in Hb in the II group of patients compared with the I group (up to 113.7±25 g/l; p <0.02)[29], and the EPO level rose to 29.3±4.3 IU/ml (p <0.001) compared with group I, where EPO insufficiency was observed. At the same time, an increase in the EPO content was accompanied by an insufficient decrease in ferritin levels to 109.3±2.1 micrograms/l at a transferrin saturation of more than 20%. In group II[30], an increase in the concentration of EPO in the blood serum caused suppression of cytokine activation: a decrease in the content of IL 1 was observed by 36.6% (p <0.001)[31], IL 6 — by 54.3% (p <0.05), TNFA — by 48.3% (p <0.05). The changes affected the level of NT-proBNP in the blood, which decreased by 48.9% (p <0.01)[32]. The positive results led to a decrease in concentration C-reactive protein, serum creatinine, and a 25.8% increase in glomerular filtration rate. At the same time, an analysis of the results of a decrease in cytokine aggression showed that the levels of IL 1 (by 36.6%), IL 6 (by 54.3%) and TNF α decreased under the influence of OIE. (by 48.3%)[33]. Thus, EPO therapy promotes the activation of EPO receptors and the synthesis of EPO, which causes the suppression of cytokine aggression, and correction of the latter is an important link in the treatment of CHF. In general, a decrease in the activation of pro-inflammatory cytokines was accompanied by a reverse development of clinical symptoms of heart failure, regression remodeling of the left ventricle, which was accompanied by an increase in the left ventricular ejection fraction (LVEF) by 19.04% (from 31.5±2.2 to 37.5±1.8%) in group II (p <0,05). In group I, there was an increase in the ejection fraction by 18.2%, but it was unreliable (p >0.1)[34]. The initial rather low exercise tolerance according to the results of the six-minute walking test increased significantly in group I (by 66.3%; p >0.05) and significantly in group II (by 76.6%; p <0.05). These positive changes in intracardiac hemodynamics, humoral immune status, and increased Hb concentrations were accompanied by a clear improvement in quality of life[35].

This study underscores the intricate relationship between pathological cytokines and erythropoietin (EPO) levels in patients with chronic heart failure (CHF) and anemia, revealing a significant impact on both hematological and cardiovascular parameters. The findings demonstrate that CHF patients exhibit elevated levels of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, which contribute to erythropoietin resistance and impaired erythropoiesis. The administration of methoxypolyethylene glycol-epoetin-β (MEB) resulted in a statistically significant increase in hemoglobin (22.4%, p<0.05) and EPO concentration (29.3±4.3 IU/ml, p<0.001), while simultaneously reducing cytokine levels—IL-1β by 36.6%, IL-6 by 54.3%, and TNF-α by 48.3%. These improvements were further correlated with an increase in left ventricular ejection fraction (LVEF) by 19.04% and enhanced exercise tolerance (76.6%, p<0.05)[36].

The suppression of cytokine aggression following MEB administration highlights its dual role in CHF management—not only as an erythropoiesis-stimulating agent but also as an anti-inflammatory intervention. The observed reduction in NT-proBNP levels suggests a potential improvement in cardiac remodeling, further supporting the therapeutic benefits of targeting both anemia and inflammation. These findings reinforce the hypothesis that anemia in CHF is not merely a consequence

of iron deficiency but a complex syndrome influenced by immune dysregulation and cytokine-mediated suppression of EPO activity.

Deep Theoretical and Practical Research

The theoretical implications of these findings extend beyond CHF and anemia, offering insights into the broader pathophysiology of cytokine-driven erythropoiesis suppression. The interplay between TNF-α and erythropoietic activity suggests a need for deeper exploration into inflammatory-mediated hematological disorders. Previous research has established that TNF-α interferes with erythropoiesis by inducing apoptosis in erythroid progenitor cells and impairing iron metabolism. This study further validates these mechanisms by demonstrating the reversal of anemia through cytokine suppression [37].

From a practical perspective, these findings advocate for an integrative approach in CHF treatment that includes anti-inflammatory interventions alongside conventional anemia management. The use of MEB in CHF patients without absolute iron deficiency presents a promising strategy for optimizing hemoglobin levels while mitigating inflammation-related complications. Clinically, these results suggest that cytokine profiling may be a valuable tool in personalizing CHF treatment, particularly for patients with concurrent anemia. Further clinical trials should focus on refining MEB dosing regimens and assessing its long-term effects on CHF progression and patient quality of life.

Knowledge Gap and Future Research Directions

Despite the promising outcomes, several knowledge gaps remain. First, the long-term cardiovascular effects of MEB therapy warrant further investigation. While the study demonstrated improvements in LVEF and exercise tolerance, the durability of these effects beyond six months remains uncertain. Future longitudinal studies should assess whether sustained cytokine suppression translates into reduced CHF-related hospitalizations and mortality.

Second, the molecular pathways underlying cytokine-mediated EPO suppression are not yet fully elucidated. Understanding the precise mechanisms by which IL-6 and TNF-α inhibit erythropoiesis could lead to the development of more targeted anti-inflammatory therapies. Research into novel cytokine inhibitors or combination therapies involving erythropoiesis-stimulating agents (ESAs) and biologic drugs could enhance therapeutic efficacy while minimizing adverse effects.

Third, the study primarily focused on CHF patients with anemia; however, the implications of cytokine modulation may extend to other cardiovascular and hematological disorders. Investigating whether MEB has similar benefits in patients with chronic kidney disease (CKD) or inflammatory cardiomyopathies could broaden its clinical applicability. Furthermore, evaluating its safety profile in diverse patient populations, particularly those with comorbid conditions, is essential to establishing its role in routine clinical practice [38].

CONCLUSIONS

This study highlights the significant relationship between pathological cytokine activation and erythropoietin (EPO) deficiency in patients with chronic heart failure (CHF) and anemia. The findings demonstrate that methoxypolyethylene glycol-epoetin-β (MEB) therapy effectively increases hemoglobin levels, normalizes EPO concentration, and significantly reduces pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. Furthermore, MEB administration led to notable improvements in left ventricular ejection fraction and exercise tolerance, indicating its potential role in enhancing cardiac function. These results underscore the importance of integrating erythropoiesis-stimulating agents into CHF management to mitigate both anemia and inflammation-related complications. Given the complex interplay between cytokine activity and erythropoiesis, further research is warranted to explore the long-term cardiovascular outcomes of MEB therapy, optimal dosing strategies, and potential adverse effects in diverse patient populations. Additionally, future studies should investigate the molecular mechanisms underlying cytokine suppression to refine therapeutic interventions for CHF patients with anemia.

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