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# Possibilities of Correcting Iron Deficiency Anemia Caused by Chronic Kidney Disease Complicated by Chronic Heart Failure

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**Abstract:** *The study evaluated the effectiveness of intravenous administration of iron saccharate (Sufer® preparation) for 2 weeks in 12 patients with iron deficiency anemia due to chronic kidney disease, who were examined and treated in the nephrology department of the Dnepropetrovsk Regional Clinical Hospital named after I.I. Mechnikov. Inclusion of iron (III) hydroxide sucrose complex into therapy led to a significant increase in hemoglobin, ferritin, iron in blood plasma, and contributed to a decrease in creatinine levels ( $p < 0.01$ ). The increase in hemoglobin level began already from the 5th day of treatment. After 2 weeks, the hemoglobin level increased by 13% ( $p < 0.01$ ). When using the drug, there were no significant side effects that required a change in its daily dose or discontinuation of treatment. The therapeutic effect and good tolerance of iron (III) sucrose complex hydroxide allow us to recommend it as the drug of choice for iron deficiency anemia in patients with chronic kidney disease.*

**Keywords:** *chronic kidney disease, iron deficiency anemia, iron saccharate, Sufer®.*

## I. INTRODUCTION

Anemia is the earliest and most frequent complication of chronic kidney disease (CKD) and usually develops with a decrease in glomerular filtration rate (GFR) to 40-60 ml/min/1.73 m<sup>2</sup>, although it is also possible in the early stages of kidney pathology. Approximately half of patients with CKD have anemia (Astor B.C. et al., 2002; Ermolenko V.M., Filatova N.N., 2004). The prevalence and severity of the latter in Ukraine significantly exceeds similar indicators in developed countries. Thus, according to the European Survey of Anemia Management (ESAM), in Western Europe, the target level of hemoglobin >110 g/l reach 53% of patients with CKD, in Ukraine, according to the registry of patients with CKD, - no more than 20% (Milovanova L.Yu. et al., 2009). In addition, a large number of patients with unacceptably low hemoglobin levels — <70 and even <60 g/l (Astor B.C. et al., 2002).

## II. MAIN PART

Anemia develops mainly due to the loss of the ability of the kidneys to secrete sufficient amounts of erythropoietin to stimulate hematopoiesis. Anemia can occur in CKD long before the end stage and worsen as it progresses, as kidney shrinkage leads to a decrease in erythropoietin synthesis in peritubular cells. Other causes of anemia in patients with CKD include shortened erythrocyte life, platelet dysfunction leading to increased bleeding, exposure of erythrocytes to uremic toxins, reduced iron levels due to inadequate intestinal absorption and hemodialysis, removal of folic acid by hemodialysis, parathormone-induced osteofibrosis. The inverse linear relationship between the level of erythropoietin in the blood plasma and the concentration of hemoglobin, which is characteristic of healthy people, is violated with the development of renal failure. As a result, the synthesis of erythropoietin does not increase in proportion to the severity of anemia (Hsu CY et al., 2002; Hörl WH et al., 2003; Locatelli F. et al., 2004; Berezhnoy V.V. et al., 2006; Karmanov E. V., 2010). Anemia increases the risk of adverse outcomes in patients with CKD, such as mortality, progression of CKD and cardiovascular disease, and hospitalization. The issue of anemia correction is relevant for patients on pre-dialysis and dialysis stages of CKD, as well as after kidney transplantation.

In recent years, special attention has been paid to the correction of anemia in patients at the initial stages of CKD. It has been established that early, at the pre-dialysis stages of CKD, correction of anemia with erythropoietin and iron preparations improves the quality of life and reduces the risk of death from cardiovascular complications in patients with CKD with subsequent treatment with program hemodialysis (Volgina G.V. et al., 2000; The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000; Milovanova L.Yu. et al., 2009; Karmanov E.V., 2010).

Therefore, the correction of anemia can be considered as an important part of the strategy to reduce the risk of morbidity and mortality in patients with CKD, both before and after the start of dialysis therapy. We should not forget about the need to correct iron deficiency in anemia in patients with chronic renal failure (CRF). As uremia increases due to impaired gastrointestinal iron absorption, blood loss, or increased iron consumption for the needs of erythropoiesis, iron deficiency develops with epoetin preparations (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000). Iron as part of heme, a structural unit of hemoglobin, binds, transports, and transfers oxygen to tissues; in combination with tissue chromoproteins, it participates in biological oxidation processes (Locatelli F. et al., 2004). Correction of anemia in patients with CKD Stage III-V is based on the combined use of epoetin and iron preparations that act synergistically (Locatelli F. et al., 2004; Dobronravov V.A., Smirnov A.V., 2005). For the full realization of the proliferative potential of the erythroid germ, it is necessary that the iron content in the body correspond to the level of erythropoietin. With insufficient iron supply to the bone marrow, the production of erythrocytes decreases, and with a deep iron deficiency, hemoglobin synthesis is disrupted and iron-deficient hematopoiesis develops (Locatelli F. et al., 2004; Dobronravov V.A., Smirnov A.V., 2005). Note that epoetin preparations stimulate the synthesis of approximately 2 million new erythrocytes per 1 s (Karmanov E.V., 2010). With a lack of available iron from the bone marrow, reticulocytes with a low hemoglobin content enter the bloodstream (Cody J. et al., 2005; Karmanov E.V., 2010). Despite varying hemoglobin levels in patients with CKD, its significant decrease ( $<110$  g/l) is naturally noted at the severe stage of renal failure, with GFR  $<30$  ml/min/1.73 m<sup>2</sup>. In turn, an adequate amount of available iron stimulates erythropoiesis and reduces the need for epoetin (Karmanov E.V., 2010).

Intravenous iron preparations have been shown to be more effective than oral iron preparations (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000). At the same time, randomized trial data J. Stoves et al. (2001) indicate no differences between intravenous (ferrous saccharate at a dose of 300 mg/month) and oral (ferrous sulfate at a dose of 600 mg/day) use of iron preparations in patients with progressive renal failure. In individuals with uremia, intestinal absorption can be maintained at a level necessary to compensate for daily iron losses from the gastrointestinal tract and during blood sampling for laboratory tests. Thus, intravenous iron in patients with CKD, especially those treated with hemodialysis and/or epoetin, is more effective than oral iron supplementation. However, from a practical point of view, the possibility of the latter is not excluded in individuals with CKD at the pre-dialysis stage. The methods, doses and frequency of administration of epoetin drugs for the treatment of anemia in patients with CKD at different stages are determined by American and European recommendations (The National Kidney Foundation Kidney Disease Outcomes Quality Initiative, 2000; Locatelli F. et al., 2004), in relation to drugs iron in the pre-dialysis stages of CKD, there are no uniform regulatory rules. Note that these recommendations actively discuss the use of parenteral forms of iron preparations based on dextran. However, unlike the latter, the use of iron saccharate is associated with good tolerability, which was confirmed in a study conducted on the basis of 61 US centers: against the background of the introduction of 8590 doses of iron saccharate to 665 patients on hemodialysis, no side effects were noted (Yee J., Besarab A., 2002). In this regard, the possibility of using high doses of iron saccharate in patients with CKD and discontinuing the use of low molecular weight iron dextran as a first-line drug in patients with anemia due to kidney disease is being considered. Thus, the problem of anemia correction, discussions regarding various therapeutic approaches is one of the most frequent topics of discussion. within specialized medical, including nephrological, forums. However, almost for the first time we are discussing in an expanded format the role and place of iron preparations, differentiated strategies for their use in patients with CKD. First of all, this is due to global trends, clearly reflected in the practical clinical guidelines KDIGO (2013) for anemia in CKD. This guideline reduces the target hemoglobin level compared to previously known ones, there is a trend towards a decrease in the use of erythropoietin in ultra-high doses, a wider use of iron preparations is recommended, and attention is focused on the caution of using erythropoietin-stimulating drugs in patients with CKD and active malignant neoplasms, stroke or oncological pathology in history. Today, the strategy for intravenous iron supplementation depends on the availability of specific drugs in different countries. In Ukraine, according to the data of the State Register of Medicinal Products, Sufer® iron saccharate for intravenous use (Yuriya-Pharm) is registered and approved for use. The purpose of our study was to evaluate the effectiveness of the intravenous iron preparation Sufer® in patients with iron deficiency anemia due to CKD.

Object and methods of research 12 patients with CRF were examined, including 7 (58.3%) women and 5 (41.7%) men; mean age —  $52.25 \pm 8.80$  years. The patients were examined and treated in the Nephrology Department of the Dnepropetrovsk Regional Clinical Hospital named after I.I. Mechnikov. The causes of CRF were chronic pyelonephritis (25%), chronic glomerulonephritis (41.7%) and diabetes mellitus (33.3%). The examination included determination of the content of hemoglobin, iron, ferritin in blood plasma, characterization of the clinical symptoms of anemia.

The diagnosis of anemia was established based on the criteria proposed in the recommendations of The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (2000), according to which anemia in CRF is diagnosed at a hemoglobin level  $<110$  g/l. For clinical assessment of kidney function, creatinine levels were determined in blood plasma using colorimetric methods and calculated GFR using the D.W. Cockcroft, M.H. Gault (1976). Criteria for inclusion in the study: presence of CKD stage I-III, iron deficiency anemia, hemoglobin level  $<110$  g/l, GFR 30-89 ml/min/1.73 m<sup>2</sup>, absence of erythropoietin preparations, patient consent. Criteria for exclusion from the study: anemia of another origin associated with acute blood loss, hypothyroidism, malabsorption syndrome, patient refusal. In order to correct anemia, patients were prescribed Sufer® in the form of a solution for parenteral administration, 1 ml of which contains 20 mg of iron in the form of iron (III) sucrose complex hydroxide. The dose of the drug was calculated individually, in accordance with the general iron deficiency in the patient's body according to the formula: total iron deficiency (mg) = body weight (kg) · (normal hemoglobin level (g/l) - patient's hemoglobin level (g/l)) · 0.24 + level of deposited iron (mg). If the total required dose exceeded the maximum allowable single dose, the drug was administered in parts. The observation period was 2 weeks. The clinical effect was assessed after the end of the observation period by reducing the severity of clinical manifestations of anemia, complaints from the patient, as well as laboratory examination data. The clinical effect was determined according to the following criteria: high efficiency (normalization of laboratory blood parameters, absence of clinical manifestations of anemia); moderate efficacy (statistically significant improvement in some laboratory blood parameters, reduction in the severity of clinical manifestations of anemia), low efficacy (no statistically significant changes in blood parameters, a slight decrease in the severity of clinical manifestations of anemia). The safety of the drug was studied by the dynamics of biochemical blood tests (total protein, alanine aminotransferase (ALAT), aspartate aminotransferase (AST), alkaline phosphatase, bilirubin, creatinine, urea) and urinalysis. The obtained data were statistically processed using the STATISTICA 6.1 program (StatSoft Inc., USA). Mean values (M), standard deviation (SD), and standard error of the mean (m) were determined. The Mann-Whitney U test and the Wilcoxon test (W) were used to compare the parameters in two independent groups. The degree of relationship between pairs of independent features, expressed in a quantitative scale, was assessed using the Spearman rank correlation coefficient (r). Statistically significant differences in the results were determined at  $p < 0.05$ .

### III. CONCLUSIONS

Parenteral administration of iron (III) sucrose complex hydroxide improves blood parameters (promotes an increase in the levels of erythrocytes, hemoglobin, ferritin, iron in blood plasma, helps to reduce creatinine ( $p < 0.01$ ). Iron (III) sucrose hydroxide the complex is safe when used in patients with iron deficiency anemia due to CKD, does not cause significant side effects requiring a change in the daily dose of the drug or discontinuation of treatment.

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