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EFFICACY AND SAFETY OF IRON (III)-HYDROXIDE SUCROSE COMPLEX IN CORRECTION OF ANAEMIA STAGE 5D CHRONIC KIDNEY DISEASE HEMODIALYSIS PATIENTS NOT TREATED BY ERYTHROPOIESIS-STIMULATING AGENTS (PROSPECTIVE ANALYSIS)

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Keywords: *chronic kidney disease, anaemia, haemodialysis, iron deficiency, sucrose complex, haemoglobin, ferritin, transferrin saturation.*

Summary: *The aim of study was to evaluate the efficacy and safety of SUFER® (iron (III) sucrose complex) in correction of anaemia stage 5D chronic kidney disease hemodialysis patients.*

Methods. *This study included thirty patients undergoing regular hemodialysis (mean age was 48,81±3,24 years, mean duration of dialysis was 30,43±9,25 months) with renal anaemia and iron deficiency. All patients were treated with SUFER® intravenously 200 mg three times a week. Correction dose was determined according to the manufacturer's recommendations.*

Results. *Mean level of ferritin was significantly increased from 125,15 ± 21,46 ng / ml to 375,56 ± 64,12 ng / ml (p <0,001), transferrin saturation - from 17,48 ± 2,71% to 38,21 ± 4,90 ng / ml (p <0,001). 23 (76.67%) patients achieved target levels of ferritin and transferrin, 12 (40%) - target level of haemoglobin (100 g / l). There were not the adverse events.*

Conclusions. *SUFER® is an effective and safe drug in correction of anaemia stage 5D chronic kidney disease haemodialysis patients.*

INTRODUCTION. Anaemia is a characteristic feature of chronic kidney disease (CKD), especially in advanced stages of the disease, especially in patients with stage 5 treated with methods of renal substitution therapy. The severe form of anaemia (haemoglobin < 90 g/l) in patients treated with program haemodialysis is associated with increased morbidity and mortality risk. Additionally, anaemia is associated with cognitive disorders, deterioration of quality of life and different symptoms, including fatigue, muscle weakness, poor physical functioning, shortness of breath and depression [2, 7].

In most cases, anaemia of dialysis patients is erythropoietin deficiency anaemia. However, the efficacy of erythropoietin-stimulating agents (ESA) significantly decreases due to iron deficiency. Therefore, its correction is one of the key moments in anaemia correction. On one hand, iron deficiency is often diagnosed in patients early in the treatment of anaemia. On the other, the use of ESA increases body-iron need leading to the development of iron deficiency and is often a cause of low efficiency of ESA.

According to last recommendations of KDIGO, correction of iron deficiency in patients with CKD and anaemia should be started in case of decrease in ferritin level more than 500 μg/l, serum transferrin saturation ratio (TSR) and these values should be monitored every 3 months [5].

In most cases, oral iron preparations are not effective for treating these patients. Oral dosage forms of iron are poorly absorbed and tolerated due to adverse gastrointestinal events [4].

Intravenous iron preparations contain iron as dextran or non-dextran compounds (gluconate, sucrose, carboxymaltose). The use of iron dextrans is associated with hypersensitivity reactions, including severe anaphylactoid reactions. Therefore, according to most authors, non-dextran iron compounds have significant advantages [3,4,5].

Along with advances in the treatment of anaemia in patients with stage VD CKD, this problem until today remains one of the most pressing in modern nephrology. The new treatment approaches are developed; target levels of laboratory parameters are specified, the list of iron supplements is expanded.

The **OBJECTIVE** of the study was prospective assessment of efficacy and tolerance of SUFER® (iron (III)-hydroxide sucrose complex) in correction of anaemia in patients with chronic kidney disease of stage VD treated with program haemodialysis and erythropoietin-stimulating agents.

MATERIAL AND METHODS. The patient selection was carried out after signing informed consent to participate in the study on the basis of inclusion/exclusion criteria. During conduction of the research patient safety regulations were adhered, rights and canons of human dignity, as well as moral and ethical standards were maintained in accordance with fundamental provisions of GSP (1996), the Convention on Human Rights and Biomedicine of the Council of Europe (dated 04.04.1997), the Declaration of Helsinki on Ethical Principles for

Medical Research Involving Human Subjects of the World Medical Association (1964-2000) and the Order of Ministry of Health of Ukraine dated 01.11.2000 № 281, the Code of Ethics for Ukrainian Scientists (2009).

Patient examination included general clinical examination, complete blood count and general urine analysis, biochemical blood analysis with determination of urea, creatinine, total protein, albumin, vitamin B12, folic acid, ferritin, transferrin, ratio of transferrin saturation with iron (TSR), C-reactive protein, alanine-aminotransferase (ALT), aspartate aminotransferase (AST), serum bilirubin, calcium, phosphorus, parathyroid hormone, daily diuresis, blood pressure monitoring, instrumental methods of examination (electrocardiographic examination, echocardiographic examination, chest X-ray, abdominal ultrasound). The diagnosis of anaemia was performed according to the recommendations of KDIGO (Kidney Disease Improving Global Outcomes), 2012. The severity stage of anaemia was assessed according to the classification the severity of anaemia (I. A. Kasyrskyi, H. O. Oleksiev, 1970): mild - Hb 110-90 g/l; moderate - Hb 89-70 g/l; severe - Hb 69-50 g/l, extremely severe - Hb less than 50 g/l.

Inclusion criteria of patients:
- Patients with stage VD CKD of both sexes aged 18-65 years treated with haemodialysis more than 3 months;
- Hb ≤ 100 g/l;
- Serum ferritin < 200 μg/l and TSR < 20 % (or one of these parameters)
- permanent vascular access for haemodialysis.
- For women of reproductive age – a negative pregnancy test. Exclusion criteria:
- Blood transfusion, oral or parenteral treatment with iron preparations for 30 days prior to screening, or the expected need for blood transfusion during Sufer exposure;
- patients receiving erythropoietin-stimulating agents;
- documented hypersensitivity to the components of iron preparation;
- other types of anaemia;
- haemochromatosis and other iron storage diseases;
- vitamin B12 or folic acid deficiency;
- drug addiction, chronic alcoholism in anamnesis;
- myelosuppressive therapy or the need for surgery;
- active infections or malignancies;
- active hepatic diseases;
- severe cardiovascular diseases, including myocardial infarction within 12 months prior to inclusion into the study , congestive heart failure NYHA class III or IV, or poorly controlled hypertension;
- pregnant women and nursing mothers.

Patients were treated with SUFER® (iron (III)-hydroxide sucrose complex), solution for injection 20 mg/ml 5 ml, manufactured by ТОВ "Юрія-Фарм" (Ukraine).

The total correction dose of the drug was determined in accordance with the manufacturer's recommendations using the following formula:

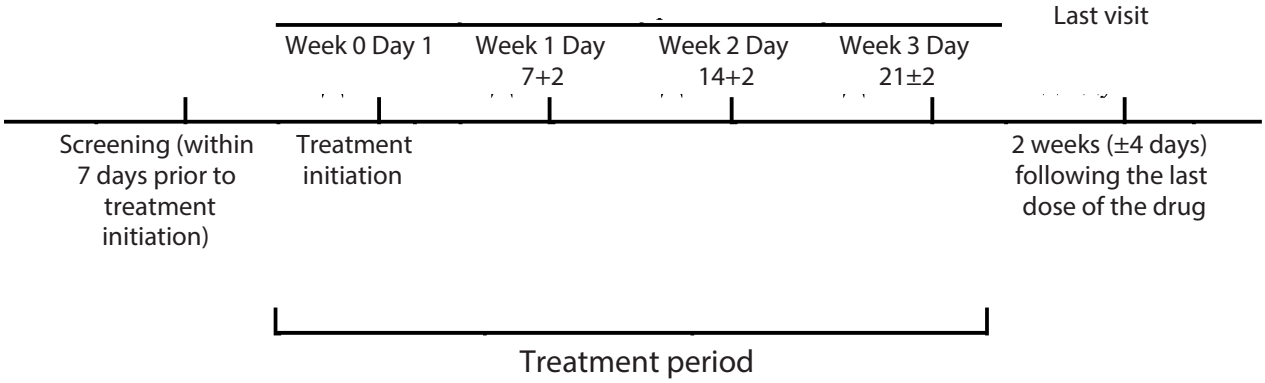
Total iron deficiency (mg) = body weight (kg) • (normal Hb level (g/l) – Hb level of the patient (g/l)) • 0.24 + deposited iron (mg).

For patients with body weight < 35 kg: normal Hb level – 130 g/l, the amount of deposited iron – 15 mg/kg of body weight. For patients with body weight < 35 kg: normal Hb level – 150 g/l, the amount of deposited iron – 500 mg. The coefficient 0.24 = 0.0034 • 0.07 • 1.000 (iron content in Hb = 0.34 %, blood volume = 7 % of body weight, coefficient 1000 = conversion of "g" in "mg").

Before the first drop infusion, according to the manufacturer's recommendations, a test dose was conducted: 20 mg of iron was administered during 15 minutes. In the absence of adverse events the remained solution was administered at a recommended rate.

The drug was administered by drop infusion 3 times per week at a dose of 200 mg in compliance with the manufacturer's recommendations (SUFER® was diluted in 0.9% NaCl solution at a ratio of 1:20 and injected in venous dialysis tubing line for at least 30 minutes).

STUDY DESIGN:
SUFER® i.v. 200 mg 2-3 times a week, as required



The frequency and volume of patient examination:

	Screening	Week 1, 2, 3	Last visit
Anamnesis	X		
Obtaining written informed consent	X		
For women of reproductive age – a pregnancy test	X		
Objective examination	X	X	X
ECG	X		X
Laboratory studies:			
• blood haemoglobin		X	
• complete blood count	X		X
• Biochemical blood analysis	X		X
	X		
• parameters of iron metabolism			X
• concentrations of B12, folic acid	X		
Recording of adverse events/reactions		X	
Efficiency and tolerance evaluation			X

EFFICIENCY AND TOLERANCE EVALUATION

The efficacy variables are based on levels of haemoglobin, serum ferritin and transferrin saturation ratio (TSR):

• Change in comparison with baseline haemoglobin level, serum ferritin and TSR at the last visit.

• The percentage of patients, who achieved the target levels at the last visit:
  – Haemoglobin: > 100 g/l
  – Serum ferritin: from 200 to 800 μg/l
  – TSR: from 20 to 50 %.

TOLERANCE EVALUATION:

Good	An objective and/or laboratory examination revealed no abnormalities or clinically significant deviations and/or a patient does not indicate the manifestations of adverse reactions.
Satisfactory	An objective and/or laboratory examination in dynamics revealed changes or clinically significant abnormalities, which are temporary and do not require changes in treatment regimen with the study drug and/or a patient does not indicate the manifestations of minor side effects that do not lead to serious problems and do not require drug discontinuation.
Unsatisfactory	An objective and/or laboratory examination in dynamics revealed changes or clinically significant abnormalities, requiring drug discontinuation and additional measures, and/or a patient indicates the manifestations of adverse reactions that have a significant negative impact on the condition, require drug discontinuation and application of additional measures.

RESULTS AND DISCUSSION. The study included 30 patients with stage VD CKD treated with haemodialysis in the Kyiv Center of Nephrology and Dialysis, which is the clinical base of the department of efferent technologies of the SI Institute of Nephrology of the AMS of Ukraine. They included: 17 male patients (57%) and 13 female patients (43%).

General characteristics of the patients is shown in Table 1.

Table 1.

General characteristics of patients prior to treatment

	n/M±m		
Included in the study	30	Heart rate per minute	81.47±4.02
Male patients	17	Haemoglobin (g/l)	87.28±2.81
Age (years)	48.813±3.24	Blood sedimentation rate (mm/h)	31.07±3.23
Treatment duration HD (months)	30.43±9.25	Platelets (× 10^9/l)	261.67±16.44
Hours of haemodialysis per week	14.7±0.49	Albumin (g/l)	39.42±0.64
Kt/V	1.37±0.08	AST (U/l)	0.16±0.01
Weight (kg)	71.95±4.71	ALT (U/l)	0.22±0.02
Systolic blood pressure (mm Hg)	149.17±3.13	Creatine (mmol/l)	0.86±0.04
Diastolic blood pressure (mm Hg)	83.67±1.4	Ferritin (ng/ml)	125.13±21.46
		% transferrin saturation	17.70±2.20

Treatment with the drug lasted, depending on the dose correction, from 2 to 4 weeks, 2.87±0.11 weeks on average.

The average drug dose, depending on the patient's weight, was 1504.35±54.26 mg.

The treatment resulted in haemoglobin increase in comparison with baseline by 5.87 g/l (from 87.28±2.81 g/l to 93.15±3.04 g/l, p > 0.05), i.e. by 6.73% (Figure 1).

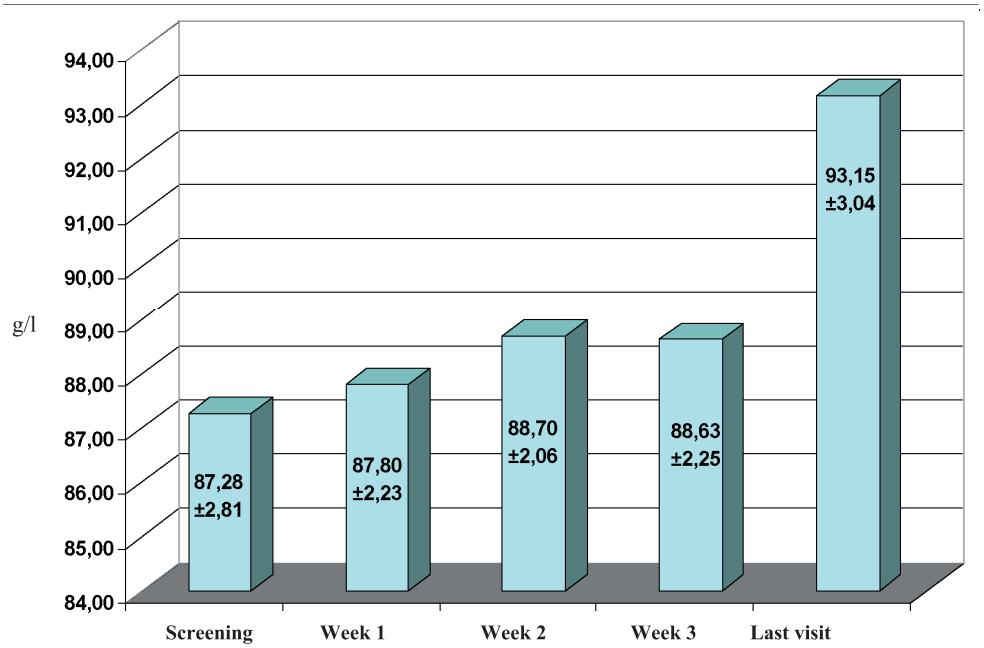


Fig. 1. Dynamics of haemoglobin level in patients with stage 5 CKD that are treated with haemodialysis during treatment with SUFER®.

The levels of ferritin and TSR prior to treatment and at the end of study are shown in Fig. 2.

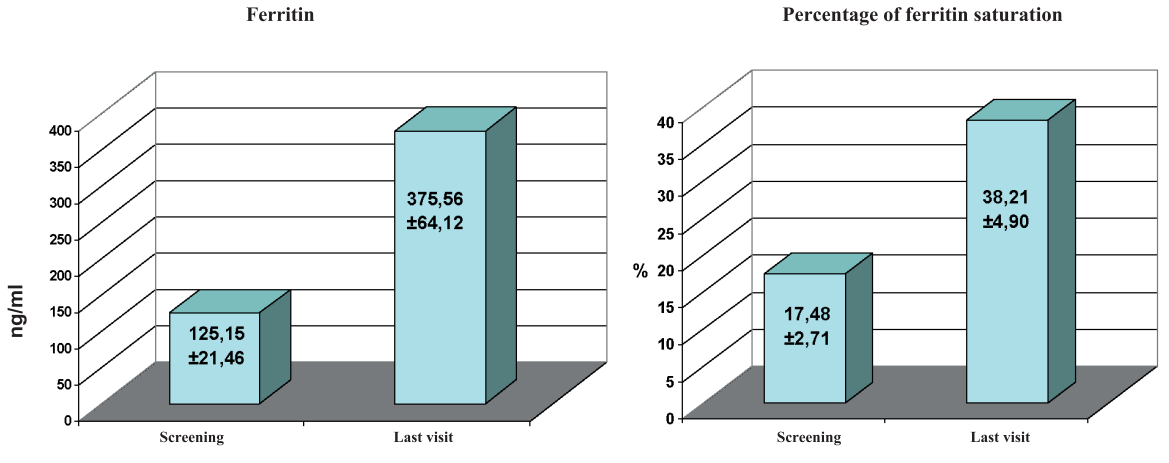


Fig. 2. Ferritin levels and TSR prior to treatment and at the end of the study.

The level of ferritin significantly increased by 250.41 ng/ml (from 125.15±21.46 ng/ml to 375.56±64.12 ng/ml, p < 0.001), i.e. by 200.09%. TSR also significantly increased by 20.73 % (from 17.48±2.71 % to 38.21±4.90 ng/ml, p <0.001), i.e. by 118.59%.

The target ferritin level and TSR were achieved in 23 patients (76.67%), including 12 patients (40 % of the total amount) achieved the target haemoglobin level (100 g/l).

The drug efficacy is confirmed by correlation analysis. A direct moderate correlation between the haemo-

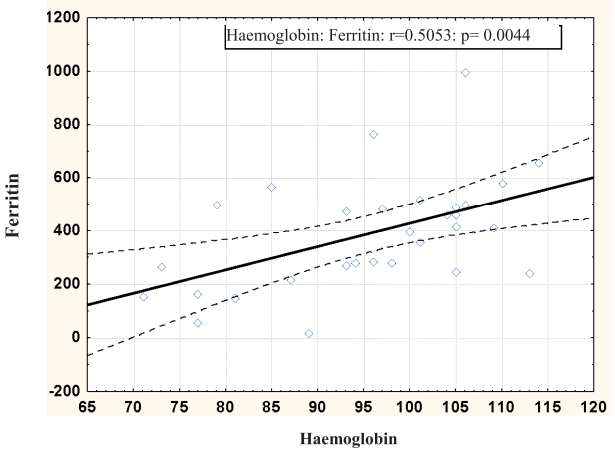


Fig. 3. The correlation between the haemoglobin level and ferritin (last visit).

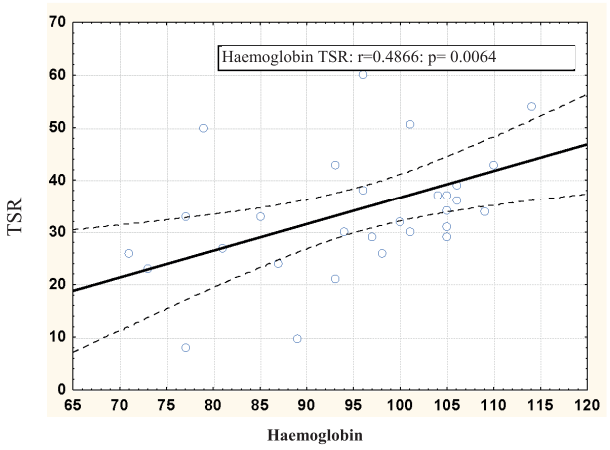


Fig. 4. The correlation between the haemoglobin level and TSR (last visit).

globin level at the last visit and ferritin levels, and TSR (Fig. 3, 4).

The other laboratory parameters that were under control, did not change significantly.

The treatment with SUFER® was well tolerated by patients. Pathological changes or clinically significant deviations were not detected. The patients did not indicate the manifistations of adverse reactions.

Obtained results of efficacy of SUFER® are comparable with data of the previous studies of the effectiveness of non-dextran iron preparations [1, 6].

Although 7 patients did not achieve target values of ferritin and TSR, their values increased by 189 % and 124 %, respectively. Additionally, in 4 patients ferritin and/or TSR values exceeded the maximum target level (ferritin - 800 ng/l, TSR - 50%). This indicates the need of monitoring of iron metabolism values and dose changes in the iron correction phase for achievement of target levels.

CONCLUSIONS. The iron (III)-hydroxide sucrose complex preparation (SUFER®), manufactured by ТОВ "Юрія-Фарм" is effective and safe drug for iron deficiency correction in patients with stage VD CKD treated with hemodialysis. The target level of iron metabolism values was achieved in 76.67 % of patients. The drug is well tolerated by patients, side effects were not observed. The iron deficiency correction, especially in patients with the severe iron deficiency, requires the monitoring of iron metabolism values with further determination of the need to change the dose for achieving target levels of iron metabolism values.

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