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Administration of iron in renal anemia

Primena gvožđa u lečenju anemije bubrežnog porekla

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Introduction

According to the report of the World Health Organization (WHO) of 2005, the average prevalence of anemia in the world is 24.8%. Anemia is caused by iron (Fe) deficiency in 50%, and reduced iron in storage depots precedes the clinical manifestations of anemia. In the poorer countries of Asia and Africa, iron deficiency appears in more than 65% of preschool children, while in the U.S. (27.3%) and Europe (21.7%) was significantly less frequent, but it is still surprisingly high. Hypochromic anemia may occur in 1–8% of pregnant women and 10–12.7% males older than 65 years [1].

According to the WHO criteria, anemia is a decrease in hemoglobin (Hgb) below the agreed values depending on age, gender and specific residential altitude, and thus values less than 13 g/dL for males and 12 g/dL for females are considered to be diagnostic values [2]. In addition to the concentration of hemoglobin, the correlation between blood volume or the number of erythrocytes and body weight, the number of erythrocytes (E) and hematocrit (Hct) can be used to assess the severity of anemia (Table 1) [3, 4].

Table 1

Diagnostic criteria for anemia

Diagnostic criteria	Male	Female
BVW (mL/kg)	60–90	60–90
ErV (mL/kg)	25–35	20–30
HgB (g/dL)	13.4–17.1	11.9–15.1
sEPO (mg/mL/pmol/L)	0.1/5	0.1/5
Hct (%)	40.7–50.3	36.1–44.3
Er (n/mm^3)	4.3–5.7 × 10^8	3.9–5.1 × 10^8
MCV (fL)	82–98	82–98
MCH (pg)	27–33	27–33
MCHC (g/dL)	32–36	32–36
sFe (µg/dL) (µmol/L)	65–177 (11.6–31.7)	50–170 (9.0–30.4)
TSAT (%)	20–50	15–50
sTf (ng/mL)	≥ 25	≥ 11
TIBC (µg/dL)	250–350	45–80
sF (µg/L)	22–270	18–150
HRC (%)	< 2.5	< 2.5
CHv (pg)	< 29	< 29
ZPP (µg/L)	150–360	150–360
STIR (mg/L)	2.2–5.0	2.2–5.0

BVW – blood volume weight; ErV – erythrocyte volume; HgB – hemoglobin; sEPO – serum erythropoietin; Hct – hematocrit; Er – the number of erythrocytes; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; TSAT – transferrin saturation; sTf –serum transferrin (siderophilin); TIBI – total iron-binding capacity; HRC – hypochromic (HgB < 26 pg) erythrocytes; CHr – reticulocyte hemoglobin; ZPP – zinc protoporphyrin; STIR – soluble transferrin receptor [3, 4].

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Etiology

The causes of anemia can be divided into three main groups: decreased erythrocytes production – disruption in the stem cells or unipotent cells, impaired synthesis of hemoglobin and anemia of unknown cause or multietiologic origin; increased decomposition of erythrocytes – corpuscular and extracorpuscular hemolysis; blood loss anemia – acute and chronic bleeding [5].

Anemia in patients with chronic renal insufficiency (CRI) is of multietiologic nature. It is recorded sporadically in patients with milder forms of CRI (glomerular filtration rate – GFR ≥ 60 mL / min), and in more than two-thirds of predialysis patients (GFR ≤ 15 mL / min) [6]. By activating different mechanisms initiated by ischemia, anemia contributes to the progression of chronic renal disease, and the development and/or deterioration of many cardiovascular disorders (left ventricular hypertrophy, ischemic heart disease, heart failure, arrhythmias, etc.), reducing the volume of physical activity, weakening of mental functions, etc. Relevant clinical studies have confirmed improved cardiovascular performance after the correction of anemia in predialysis patients (Trial to Reduce Cardiovascular Endpoints with Aranesp® Therapy – TREAT) and dialysis patients [7–9].

Iron metabolism

Total iron content in an adult healthy subject is 3–4 g or 40–50 mg/kg/body mass (BM) of which 80% is functionally engaged in hemoglobin (65%), myoglobin (10%) and various enzymes (5% approx).

Women of childbearing age and pregnant women need 2.8–3.0 mg, and men need 0.8–1.0 mg of elemental iron *per* day.

Plant foods (90%) and foods of animal origin provide the intake of 18–20 mg of iron daily. Despite meager absorption (≈ 10%), 1–2 mg is absorbed daily in the duodenum and the same content is eliminated *via* feces for external balance. "Organic" iron or heme iron (Fe^{+2}) produced by heme-oxygenase is absorbed ten times faster than "inorganic" iron from foods of plant origin (Fe^{+3}), which must be previously reduced (ferri-reductase) in divalent ions of iron (Fe^{+2}) [5, 10].

Absorption is promoted by low pH and organic acids in intestinal chyme. Iron from plant foods (Fe^{+3}) and iron chelate (phytates, oxalates, carbonates, tannates, and phosphates) are less suitable for absorption. Hypo/non-acid chyme, milk and dairy products, intestinal mucosal damage, drugs (antacids, proton pump inhibitors, H_2-blockers), and competitive salt ions (Mg^{2+}, Cd^{2+}, Co^{2+}) reduce iron absorption even further [10].

By specific divalent metal transporter (DMT1) Fe^{+2} is transported from the lumen formation through the apical polarity of enterocytes to the 'intermediate depot' in the cytosol in the form of ferritin. The transport of Fe^{+2} from the cell through the basolateral membrane is controlled by hepcidin (an acute-phase reactant to inflammation) originating from the liver. Binding to ferrous iron transmembrane transporter – ferroportin, hepcidin causes its internalisation and lysosomal degradation, and Fe^{+2} remains 'temporarily trapped' inside the ferritin depot. In the absence of the inhibitory action of hepcidin, after binding to feroportin Fe^{+2} must oxidize to Fe^{+3} affected by an oxidative enzyme hephaestin (in the membrane) or serum ceruloplasmin. Then, two moles of Fe^{+3} bind to one mole of transport protein (apotransferrin), becoming the serum transferrin (siderophilin) [11].

Thus iron is delivered to the cells of particular organs through transferrin receptors (TfR) whose synthesis is not affected by proinflammatory cytokines, and their plasma concentrations may indicate the available iron. Iron in the cell is functionally allocated and included in the synthesis of heme and other proteins and enzymes [11, 12].

Causes of iron deficiency in the general population are numerous. The most common cause of iron deficiency is in plant-dominant diet (starch, pasta, rice) along with reduced consumption of meat. In addition, iron deficiency appears even with a balanced diet for the increase in iron requirement (pregnancy, lactation, growth, etc.). Intestinal absorption disorders (gastritis, bowel resection, inflammatory bowel diseases, antacids, H_2 blockers, etc.). Increased intestinal (gastritis, peptic ulcer disease, hernia, diverticulitis, hemorrhoids, parasitic infections, inflammatory bowel disease, tumors, etc.) and genitourinary (meno-metrorrhagia, calculi, tumors, chronic urinary tract infections) blood loss may cause reduction of body iron stores [5, 13].

Anemia in patients with CRI is erythropoietin-dependent and ferrous-deficient, and it is proportional to the seriousness of the renal disease. Specific causes of iron deficiency in patients with CRI are associated with restricted protein intake (meat), chronic microinflammation (hepcidin, transferrin), loss of appetite and digestive erosion, the effects of drugs (phosphate binders and drug-drug interactions) and poor patient cooperation due to digestive disturbances. In addition, anemia is the result of temporary and, if on hemodialysis (HD), permanent blood losses – on the average 3–9 mL (2–4 mg of iron) *per* dialysis session [4, 13].

Uremic toxins (parathyroid hormon – PTH etc.), impaired oxidative balance, aluminum concentration (in water used to make-up dialysate or drugs), insufficient intake and/or reduced resorption (diet / medication / microinflammation), mechanical trauma (blood pump), hemolysis (uremic toxins /oxidative stress, shortened E life-span to 70–80 days) all contribute in different ways to anemia [14].

Two extensive prospective epidemiologic studies (Predialysis Survey of Anaemia Management – PRESAM) presented that iron deficiency was found in 31–38% of CRI patients with different severity of illness, and in more than 60% of dialysis patients (Dialysis Outcomes and Practice Patterns Study – DOPPS) [15].

Iron deficiency in the body can be absolute (unavailable serum-iron and iron in deposits/stores) and relative-functional (unavailable serum-iron, although present in cellular iron storage depots). Although serum ferritin level is most reliable to determine iron stores, and transferrin saturation is used to estimate functional iron, in certain clinical

conditions they must be supplemented by other indicators that are not functionally dependent on inflammatory cytokines (Table 2) [2, 3].

Table 2

Laboratory parameters for detecting iron deficiency

Iron deficiency	Laboratory values
Absolute deficit	
sF	
non CKD/HD (μg/L)	< 15
CKD/HD (μg/L)	< 100/200
TSAT (%)	< 20
Functional (relative) deficit	
sF (μg/L)	≥ 100
TSAT (%)	< 20
HRC (%)/(pg/cell)/(g/dL)	≥ 6/< 26/< 28
CHv (pg/cell)	< 29
ZPP (μg/L)	> 360
STFR (mg/L)	> 5.0
Inadeguate response to ESAS (HgB)	
epoetines (iv/kg/week)	300–500
darbepoetin (mg/week)	100–150

sF – serum ferritin; CKD/HD – chronic kidney disease/hemodialysis; TSAT – transferrin saturation; HRC – hypochronic erythrocytes; CHv – reticulocyte hemoglobin content; ZPP – zinc protoporphyrin; STFR – soluble transferrin receptor; ESAS – erythropoiesis stimulating agents [2, 3].

Treatment

Basic principles for anemia management in chronic renal disease include the following set of measures and procedures [16, 17]:

- use of erythropoiesis-stimulating agents (ESAs): epoetin α: 50 IU / kg/i.v., 1–3 times weekly; epoetin β: 20 IU / kg /i.v./s.c., 1–3 times weekly; epoetin δ 50 IU / kg/i.v./s.c., 1–3 times weekly; darbepoetin α: 0.45 (0.75) μg/kg/sc, 1–2 times monthly; continuous erythropoietin receptor activator (CERA): 0.6 μg/kg/sc; 1–2 times monthly.
- iron supplementation (after assessing iron status/stores): p.o./i.v. supplementation.
- transfusion of erythrocytes: emergency treatment – acute bleeding; resistance to ESAs; symptomatic anemia – comorbidities.
- vitamin supplementation: C-vitamin 500 mg p.o. or i.v. at the end of dialysis; B-complex vitamins p.o./i.v. supplementation; vitamin E p.o. 1,200 mg – before dialysis; folate: 1–3 × 5 mg p.o. supplementation.
- adequate nutrition according to established standards.
- androgens can have beneficial effects – not necessarily administered.
- antioxidant glutathione may reduce resistance to ESAs – not necessarily administered.
- L-carnitine can have beneficial effects – not necessarily administered.
- optimization of dialysis: hemodialysis Kt / V ≥ 1.2; peritoneal dialysis Kt / V ≥ 1.8–2.0/weekly.
- other: dialysis modality switches – peritoneal dialysis (PD) to hemodialysis (HD), hemodiafiltration (HDF), extended daily/overnight dialysis, appropriate PD modality; ultrapure dialysate: bacteria ≤ 0.1 Colony-forming unit/mL (CFU/mL), endotoxin ≤ 00:03 enolotoxin units/mL (EU/mL).

Kidney transplantation is most notably physiological method for the treatment of renal anemia.

Recommendations for initiation of therapy and further monitoring of renal anemia by administration of ESAs and iron supplements in patients undergoing HD/PD and in predialysis period in patients with CRI are shown in Table 3 [18–23].

Iron supplementation

Iron supplementation is required in more than half of patients with advanced renal failure, particularly in those who receive ESAs, although iron supplementation is also needed in patients still without erythropoiesis-stimulating medications [20, 21].

Iron supplementation should be started after the assessment of iron availability and stores. According to the recommendations of the European Best Practice Guidelines

Table 3

General recommendation for renal anemia menagement

When to start treatment	Recommended target values	Performance indicators monitoring*
Hgb < 90 g/L	Hgb 11–12 g/L	Hgb: measure 2–4 times *per* month until steady forget value is reached, once a month later
Signs and symptoms of heart failure:	sF HD 200–500 μg/L	
EF < 40%, IHD, arrhythmias, etc.	CKD/PD 100–500 μg/L	Anticipated increase in Hgb *per* month 0.7–2.0 g/dL
GFR < 50 mL/min/1.73 m^2	TSAT 30–40%	ESAS: titrate the dose over 15 days to optimal level, than every 1–3 months
Previous corection of iron deficiency	HRC < 6%	TSAT: check once a month, than every 3 months
Target value of Hgb ≥ 11 g/dL	CHr > 29 pg	sF: check once a month, then every 3 months
Exculude other causes of anemia if GFR ≥ 50 mL/min/1.73 m^2		*more frequent testing is needed in case of bleeding, surgical interventions and *iv* iron administration

HgB – hemoglobin; EF – ejection fraction; IHD – ischemic heart disease; GFR – glomerular filtration rate; SF – serum ferritin; CKD/PD – chronic kidney disease/peritoneal dialysis; HD – hemodialysis; TSAT – transferrin saturation; HRC – hypochronic erythrocytes; CHr – reticulocyte hemoglobin; ESAS – erythropoiesis stimulating agents.

(EBPG) 2004, National Kidney Foundation / Kidney Disease Outcome Quality Initiative-NKF-KDOQI 2006/2007, European Renal Best Practice (ERBP) 2008, oral iron therapy is indicated for patients with CRI who do not undergo hemodialysis, peritoneal dialysis patients and those patients who obtained kidney transplants, especially if they do not take ESAs. The use of oral iron may continue with the beginning of administration of ESAs, but parenteral use is more effective and more tolerable for the patients [21, 22].

The synthesis of one gram of hemoglobin was assumed to require 20 mg Fe for women and 25 mg for men, and on the basis of BM and the difference between expected and actual values of hemoglobin iron deficiency can be calculated and supplemented, and iron stores can be replenished [Target-Hgb (g/dL)] × [TM (kg) × 0.24] + 1,000 mg (for men)/600 mg (for women) [23, 24].

Peroral iron supplementation

Although most commonly used supplements are organic complexes of either divalent or trivalent iron bound to different protein or sucrose carriers, in many countries simple iron salts either organic or inorganic are still in use. Heme iron is 20 times better absorbed than iron from ferrous fumarate, almost without side effects [22].

The Serbian Prescribed Drug Register [23] determines ferrous fumarate, ferric hydroxide-polymaltose complex and iron protein succinylate may be present in the national market (Table 4).

Common side effects are nausea, anorexia, flatulence, vomiting, abdominal pain, diarrhea/constipation, etc. Toxic effects include proinflammatory, proatherogenic and prooxidant effects connected with serious (20–100 mg/kg) or fatal consequences (200–250 mg/kg or sFe > 5 mg/L) due to excessive intake of iron supplements.

Coadministration may affect drug-drug interactions and reduce their effectiveness, e.g.: penicillamine, bisphosphonate, ciprofloxacin, ofloxacin, norfloxacin, levodopa, levothyroxine, mycophenolate, methyldopa, calcium, magnesium, etc.

Peroral iron supplementation is contraindicated in patients with sensitization, hemochromatosis, hemosiderosis, concurrent use of parenteral Fe, active peptic ulcer and intestinal diseases, etc. To develop greater tolerance and avoid interactions with other drugs or food, a single daily dose is recommended, heme-iron polypeptide products are particularly effective and tolerable [24, 25].

Parenteral iron supplementation

Since target hemoglobin is slowly achieved and because of numerous side effects and interactions with other medications that have to be used regularly, patients are reluctant to take the prescribed oral amount and do not follow basic instructions for administration, and thus parenteral iron supplementation has become widely recommended for the treatment of anemia [20, 22].

On the basis of kinetic and thermodynamic parameters of organic complexes of iron, parenteral supplements are divided into four groups (types I-IV) (Table 5) [11].

Table 4

Most widely used oral iron drugs

Iron complex	Trade name of the drug, manufacturer and dosage form*
Ferrous fumarate: [S.Th.D.: 2 × 1]	Heferol® Alkaloid: (caps. 350 mg/115 mg Fe)
Iron hydroxide polymaltose: [S.Th.D.: 2–3 ×1]*	Referum® Slaviamed: (tbl. 100 mg Fe; syrup 50 mg/5mL)
Iron protein succinylate: [S.Th.D.: 2 × 1]*	Legofer® Alcaloid: (sol. 40 mg/15 mL)
Ferrous sulphate: [S.Th.D.: 1–2 × 1]	Ferro gradumet® Abbot: (ferro sulphate s.r.tbl. 325 mg); Ferrograd C® Abbott: (s.r.tbl. ferro sulphate 325/105 mg + 500 mg vit.C); FGF® Abbott: (s.r.tbl. ferro sulphate 250 mg + 300 mg folic acid)
Ferrous gluconate: [S.Th.D.: 2–3 × 1–2]	Ferrous gluconate® Kent Pharmaceuticals: (tbl. 300 mg)
Heme iron polypeptide: [S.Th.D.: 2–3 × 1–2]	Proferrin ES® Colorado Biolabs: (tbl. 20 mg)

***Drugs from the National Drug Register, 2012 [23]; S.Th.D – single therapeutic dosage; Caps – capsulas; Tbl. – tablets; s.r.tbl. – slow release tablets; Sol – solution.**

Common characteristics of oral iron supplements are: maximum daily dose of 300 mg elemental iron; hemoglobin values are corrected within 2–3 weeks, normalization is achieved within 2–3 months, and iron stores are usually replenished within 6 months.

After *iv* application iron complexes are taken up by phagocytes in reticuloendothelial system in the liver, spleen, and bone marrow. Iron is released there from its

carrier and deposited in the form of cytosolic ferritin and, when needed, it is released and transported to the cell by transferrin.

Absolute indication for the use of parenteral iron is functional iron deficiency which can be one of the possible causes of treatment failures, manifested as the lack of increase in hemoglobin level despite progressively increasing amounts of ESAs.

Initial correction of hemoglobin can be achieved in 1–2 weeks with application of parenteral iron supplements, and its normalization is reachable within 3–4 weeks. General tolerance is greater, and the replenishment of iron stores is faster (6–8 weeks). These supplements are also efficient for other indications: pregnant women after the first 3 months of pregnancy, women in labour, anemic patients with malignancies, anemia in patients with heart failure, etc. Therefore, it is an acceptable iron-replenishment method in patients with hypochromic anemia, especially those who also take ESAs.

Contraindications to its use include: previous diagnosis of sensitization, asthma, allergies, atopic dermatitis, hemosiderosis, liver cirrhosis and severe hepatitis.

Serious adverse effects (SAE) include the development of an anaphylactic [after primary allergic sensitization and antigen (Ag) exposure] or anaphylactoid (after the first contact with Ag without prior sensitization) systemic reactions with potentially fatal outcome, but there are significant differences between particular products.

Milder adverse effects (AE) are common for all available remedies, but their frequency within a particular group of remedies is significantly different: dizziness, numbness, metallic taste, burning, heat, joint pains, abdominal pain, skin rash, swelling in the hands and feet, pyrexia, transient increase/drop in blood pressure, etc. [18, 24, 25].

Taking into account efficiency and reliability above all, current clinical guidelines for the treatment of anemia in dialysis patients recommend ferric gluconate and, particularly, iron sucrose since there have been no registered fatal outcomes until now, and because of rare AE and SAE if compared to other forms of parenteral iron [12, 26].

According to European Renal Best Practice / European Best Practice Guidelines (ERBP/EBPG) recommendations – optimal *iv* dose of iron supplementation in the first 6 months of therapy with ESAs, with iron status and expected increase in hemoglobin regularly checked, can be achieved following the manufacturer's instructions. Thus serum ferritin levels should be maintained between 200 and 500 μg/L and transferrin saturation should be maintained at 30–45% [27].

Ferric gluconate of 62.5–125 mg in 100 mL 0.9% NaCl can be infused over 30 min. or *iv* bolus of 5 mL 0.9% NaCl over 5 min. at the end of 6–8 dialysis sessions, or 2–4 doses

Table 5

Most widely used parenteral iron drugs

Type	Drug	Basic information on supplements: Incidence of SAE / 10^6 application, n (%)	Basic information on supplements: Incidence of fatal outcome / 10^6 dosage 100 mg, n (%)	Basic information on supplements: Incidence of AE / 10^6 dosage 100 mg, n (%)	Comments
I	Iron dextran (Dexferrum®) Iron hydroxi dedextran (CosmoFer®)	11.3–57.9 (0.5–1%)	1.4	29.2 (5.4–9.7%)	Mandatory testing before application
	Ferric carboxymaltose (Ferinject®) 2 mL = 100 mg 5 mL = 250 mg 10 mL = 500 mg	3.3		0.9–3.3%	Mandatory testing before application
II	Iron hydroxide sucrose (Venofer®) (Ferrovin®) 2.5 mL = 50 mg 5 mL = 100 mg 10 mL = 200 mg	0.6 (0.0021%)	0	4.2	Possible application in the event of intolerance to drugs of type I/III/IV No need for test dosage before application;
III	Sodium ferric gluconate (Ferrlecit®) 5 mL = 62.5 mg	0.9	0.6	10.5	No need for test dosage before application
IV	Iron sorbitol (Jectofer®) 2 mL = 100 mg (*i.m.* only)				Possible SAE and serious systemic and cardiac disorders; Withdrawn from the European market; Mandatory testing before application

Note: SAE – severe adverse effects; AE – adverse effects; i.m. - intramuscular injection.

in patients treated with peritoneal dialysis, and non-dialysis CRI patients.

Iron sucrose can be applied either as iv bolus dose of 100–200 mg in 5 mL 0.9% NaCl over 2–3 min. at the end of 8–10 dialysis sessions or 1–2 infusions of 500 mg in 250 mL 0.9% NaCl over 15 min. especially in non-hemodialysis patients [29].

Length of iron supplementation is adjustable depending on target outcomes including the assessment of iron stores, current hemoglobin levels and stability of erythropoietin. If during the treatment hemoglobin values exceed 12.0 g/dL, ESAs dose should be reduced according to current recommendations, and *iv* iron therapy should be suspended until the next scheduled assessment of the iron status. Peroral supplements may be prescribed due to patient's intolerance or poor cooperation and such patients can be treated with intermittent infusions of parenteral iron, usually at 1–3 month intervals according to clinical response [29, 30].

Conclusion

Hypochromic anemia is a rare type of iron deficiency which represents important health problem in the world. Insufficient intake of food rich in iron which is suitable for absorption or increased need for iron are the most common causes for sideropenic anemia in general population. In patients with chronic kidney disease, iron deficiency and insufficient erythropoietin synthesis are the most prominent factors for anemia. Restriction on dietary protein (meat), chronic proinflammatory state, reduced absorption of iron (effect of uremic environment and the concomitant use of drugs that hinder iron absorption), permanent dialysis (blood) losses and hemolysis are the basic reasons for absolute or relative iron deficit. The application of erythropoiesis-stimulating agents and iron compensation supplements is the main approach of treatment of iron deficiency in patients with chronic kidney disease. Before starting the treatment it is essential to determine the concentration of serum ferritin and the level of transferrin saturation. This also has to be done periodically during the process and in line with expected response. Peroral iron supplements do not absorb well and have too many side effects, predominantly in digestive tract. That is why the patients loose motivation for this kind of treatment although it is strongly recommended in patients on peritoneal dialysis and those who underwent kidney transplantation. Pareneteral iron supplements are better tolerated, the correction of hemoglobin is faster and thus erythropoiesis-stimulating agents consumption is lower. But there is also a possibility of serious adverse events and potentially life-threatening complications caused by some pharmacological forms. Nevertheless, ferric gluconate and iron sucrose complex are much better tolerated with fewer side effects and less incidence of serious adverse events. That is why these medicines are recommended as a standard in all guidelines for renal anemia treatment.

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