IRON THERAPY FOR CHRONIC RENAL DISEASE: ADVANTAGES AND DISADVANTAGES

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Abstract: *In patients with end renal stage disease and those undergoing dialysis, it is very important to diagnose both absolute and functional iron deficiency in renal anemia because iron deficiency is the most common cause of hyporesponsiveness to erythropoiesis-stimulating agents (ESAs). Iron therapy increases the erythropoietic response that is the accepted reference standard of iron deficient erythropoiesis. Iron therapy includes the availability of both oral and parenteral (intravenous) substances. Intravenous iron therapy is more efficient than the oral one. Iron represents a component of oxygen-carrying molecules, a cofactor for enzymatic reactions and redox processes. Regarding its redox potential, unfortunately, this limits the quantity of iron that can be safely administered and stored by the organism. But when the doses are administered within the recommended international guidelines, intravenous iron therapy is safe. Intravenous iron therapy should, however, be withheld during acute infection but not during inflammation.*

The causes of absolute or functional iron deficiency leading to renal anemia (when glomerular filtration rate (GFR), declines to 60 ml/min/1.73 m^2) in patients with chronic renal disease include: inadequate intake of dietary iron, blood loss during hemodialysis procedure, bleeding of gastrointestinal tract, too many mandatory blood tests, inadequate intestinal iron absorbtion, inhibition of iron release from macrophages, increased iron requirements during therapy with erythropoiesis-stimulating agents (ESAs).

Oral iron therapy

Oral iron is absorbed in the duodenum and proximal jejunum and is best absorbed without ingestion of food. The nonheme dietary Fe^{3+} is reduced to Fe^{2+} by cytochrome b-like ferrireductase Dcytb. Fe^{2+} is absorbed from the intestinal lumen by crossing the apical enterocyte brush border membrane through the divalent metal transporter-1 (DMT1). On the iron concentration within the enterocyte, the expression of both Dcytb and DMT1 depends. Iron absorbtion is enhanced in iron deficiency and declines with correction of this deficiency and completion of iron stores.

Hepcidin, a 25-aminoacid peptide synthesized in liver in response to acute-phase reactions, controls the body iron content. Iron deficiency, anemia, hypoxia, and/or stimulated erythropoiesis down-regulate hepcidin release in order to stimulate iron absorbtion. Iron overload or inflammation and infection stimulates hepcidin production so intestinal iron absorbtion will be inhibited. Hepcidin expression depends on the degree of hepatic iron storage.(1) It also inhibits the release of iron by the iron exporter ferroportin (iron regulated transporter-1). Ferroportin is located along the basolateral membrane of enterocytes and also in the intracellular vesicular compartment of tissue macrophages.(2) That is the reason why the inflammatory state associated with uremia is main responsible for decreasing intestinal iron absorbtion in patients with end stage renal disease. Uremia is a chronic inflammatory state.(3,4) Even without infection or inflammation states many patients with chronic renal failure show increased levels of acute-phase proteins, such as C-reactive protein (CRP), ferritin, fibrinogen, and/or interleukin-6 (IL-6), associated with low serum albumin levels.(5) Hepcidin is interacting with proinflammatory cytokines in mediating functional iron deficiency and that may explain why patients with chronic renal disease have disturbed iron release from the reticuloendothelial system, high ferritin levels and poor intestinal iron absorbtion.(6)

In iron oral therapy, patients are given ferrous sulphate one 300 mg tablet (containing 60 mg elemental iron) three or four times daily, as usually adult dose. Iron oral therapy has side effects including constipation, diarrheea, nausea, and abdominal pain. If those side-effects are limiting the compliance the dose may be reduced at one 500 mg ferrous sulphate daily at bedtime and ferrous sulphate can be administered with food.(7) Anemia treatment should continue until hemoglobin concentration is at least 11-12 g/dl, by administration of both erythropoiesis-stimulating agents (ESAs) and iron.(8,9)

Intravenous iron therapy

Intravenous iron can be administered safely to patients with chronic renal disease (10,11,12,13,14,15,16,17) as long the therapy is performed accordingly to international recommendations and guidelines.(18,19) Though all forms of intravenous iron have acute adverse effects, intravenous therapy is superior to oral iron treatment.(20) As adverse effects it can be mentioned: acute allergic reactions (rash, dyspnoea, wheezing, even anaphylaxis). Allergic reactions are due probably to the dextran moiety. Iron dextran therapy has a higher risk for type I reactions (unpredictable and possibly life threatening) compared with other newer products. Iron sucrose has the lowest risk for hypersensitivity reactions.(21) Iron sucrose and ferric gluconate seem safe at recommended doses (15,17,22) for treating anemia in adult hemodialysis patients also.(12,23) The long-term complications are caused by the oxidative stress due to generating dangerous oxidative species, initiation and propagation of lipid peroxidation, vascular smooth

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muscle cell proliferation, endothelial dysfunction and/or inhibition of cellular host defence.

Th-1-derived cytokines such as IFN-γ or tumour necrosis factor-β (TNF-β) activate macrophages and so they stimulate the formation of proinflammatory cytokines, such as TNF-α, IL-4, or IL-6 and the induction of cytotoxic immune effector mechanisms of macrophages. On the contrary, Th-2 cells produce IL-4, IL-5, IL-9, and IL-13, which, in part, have anti-inflammatory actions by inhibition of various macrophage functions.(24,25) According to those facts, some studies have shown that iron sucrose therapy increases IL-4 levels, while TNF-α levels decrease.(25) There are also a direct relation between IL-4 and transferrin saturation (TSAT) and an indirect one between TNF-α and TSAT. An IL-4 increase and a decrease of TNF-α are correlated with an increase of hemoglobin levels. ESAs dose decreases with an increase of IL-4 and decrease of TNF-α.(25) There is although a potential danger because the decreasing of the Th-1 immune effector function which is estimated by lowered TNF-α production with a subsequent increase of Th-2 mediated immune effector function which is estimated by increased IL-4 production is not in the advantage of patients with end stage renal disease in case of an acute infection or a malignant disease.(25) Another potential danger is the fact that iron is an essential nutrient for microorganisms and so intravenous administration of iron may be associated with increased incidence of infections (26), so intravenous iron therapy should be withheld if an acute infection occurs until infection has been treated in contrast with the inflammatory states which do not have indications for withholding the therapy.(27)

Intravenous iron therapy may enhance oxidative stress.(28,29,30) Drüeke et al. demonstrated in hemodialysis patients a correlation between advanced oxidation protein products (AOPPs) with iron administration and carotis artery intima thickness (30) and serumalbumin oxidation.(31) Ferric gluconate acts on fibrinogen and β_2-microglobulin levels, marker of oxidative stress also in hemodialysis patients (32,34) On the other hand, iron sucrose intravenous administrated increases malondialdehyde as a marker of lipid peroxidation (34), and in patients with ferritin levels over 650 µg/l studies showed an increased oxidative burst in polymorphonuclear leukocytes (PMNL).(35) Peroxide concentration increases significantly after hemodialysis therapy but was not additionally influenced by administration at the same time of 100 mg iron sucrose.(36)

Intravenous iron therapy administrated in end stage renal disease could cause an increased blood levels of non-transferrin-bound iron (NTBI) and/or redox active iron, which is considered to be one reason for the endothelial dysfunction.(36,37,38)

Conclusions:

In patients with renal chronic disease and dialysis patients the management and treatment of anemia is mandatory for attaining the hemoglobin levels established by international guidelines. In order to achieve this goal, the treatment of anemia integrates ESAs treatment with intravenous or oral iron therapy. By correction of renal anemia, morbidity and mortality are reduced and quality of life is improved along with cognitive function and physical activity.

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