Iron Replacement in Hemodialysis Patients– A Review

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Abstract

Anemia is a prevalent condition among all stages of chronic kidney diseases. Iron deficiency anemia is a common occurrence in all the stages and has important implications in terms of patient care and cost effectiveness. In this article we highlight the importance of understaning the iron metabolism and its management.

Keywords: *Anemia, iron deficiency, ferroportin, ferritin, transferrin saturation, chronic kidney disease, hemodialysis.*

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PJKD 2019;(4):53-58

INTRODUCTION

Anemia is a common and clinically important concern in patients with chronic kidney disease (CKD) and its incidence increases with decreasing glomerular filtration rate (GFR). [1, 2] Anemia in CKD patients is primarily due to decreased erythropoietin production followed by iron deficiency (either functional or absolute). [3] In predialysis CKD patients iron deficiency anemia could be due to malnutrition since anorexia is a common feature along with strict dietary restrictions in these patients.

In patients undergoing hemodialysis anemia can be related to ongoing blood losses during the dialysis treatment from blood tubing, dialyzer clotting, inadequate anticoagulation or bleeding tendencies due to over anticoagulation. [2] These patients also have repeated blood draws for investigations especially in the early period of dialysis initiation.

The diagnosis of iron-deficiency anemia in CKD is difficult as the most common biomarkers depicting sufficiency of iron storage are acute phase reactants also that are affected by systemic inflammation, common among hemodialysis patients. These biomarkers include ferritin concentration and transferrin saturation both of which are low in iron deficiency anemia but Ferritin, for example, is a positive acute-phase reactant and its concentrations increase in the setting of inflammation. [4] Transferrin, conversely, is a negative acute-phase reactant; its concentrations decrease in patients with inflammation and malnutrition. [3] Accordingly, in an iron-deficient patient, the ferritin concentration may be high and transferrin saturation may be low even in the setting of inflammation. This non specificity has led to the identification of more sensitive biomarkers for diagnosing iron deficiency anemia in CKD.

Iron metabolism

Absorption of oral iron requires an intact gastrointestinal mucosa: acidity of the stomach is needed to solubilize the iron, which is then absorbed primarily in the duodenum and proximal jejunum. Iron is then released into the circulation by ferroportin, which is expressed by enterocytes.[4] IV iron contains iron-carbohydrate complexes, which are readily taken up by macrophages. The iron atoms of the core are gradually released into the circulation via ferroportin. Hence, both oral and IV iron require ferroportin to be released into plasma. Elevated levels of hepcidin can internalize ferroportin into cells, resulting in decreased release of iron.

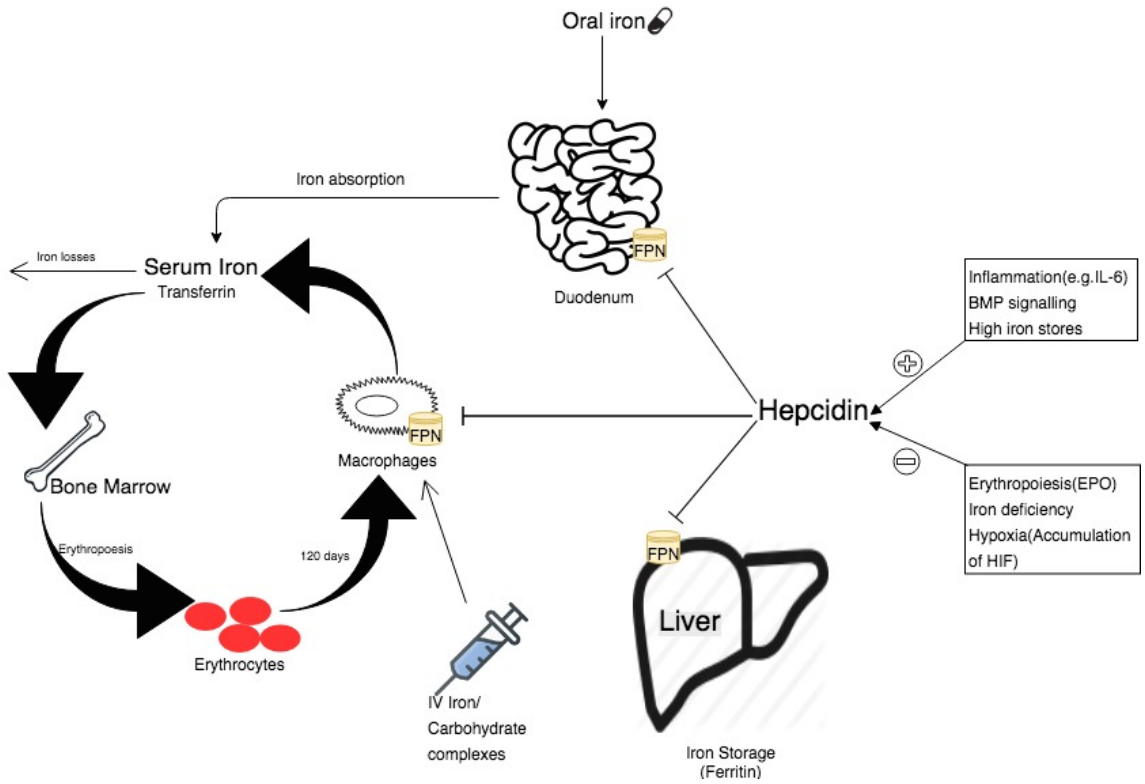

Figure: Iron Metabolism and the transport.

Typically, hepcidin production is suppressed in uncomplicated iron deficiency anemia, maximizing iron absorption. However, even minute elevations in hepcidin levels appear to inhibit intestinal ferroportin. In contrast, macrophages have much higher levels of expression of ferroportin, which in turn requires higher levels of hepcidin to be adequately suppressed.[4]

Management of iron deficiency anemia could sometimes be troublesome. Iron absorption is more evident when the serum ferritin concentration is less than 70 ng/mL. Intestinal iron absorption in hemodialysis patients is equal to absorption in healthy individuals.[4] Because many hemodialysis patients have increased ferritin (and hepcidin) concentrations from inflammation, oral iron is thought to be ineffective in replacing ongoing iron losses in hemodialysis patients. Consistent with this, trials of oral iron supplementation in hemodialysis have failed to show appreciable efficacy, thus IV iron replacement is encouraged in patients undergoing hemodialysis. [4]

ORAL IRON

Multiple oral iron preparations mostly in the form of ferrous salt are available. Oral iron is inexpensive and readily available for use but poorly tolerated. Iron in bivalent form (ferrous) is better absorbed than trivalent (ferric) form. [5] Efficacy of ferrous iron is limited by gastrointestinal side effects, frequent administration, and diminished enteral absorption as a result of interaction with food, and reduced gastric acidity. [2] In addition, phosphate binders being taken routinely by CKD patients decreases oral absorption of iron. [6]

IV IRON

IV iron is now the choice of treatment for iron replacement in hemodialysis patients. Two meta-analyses showed comparable results of multiple small, randomized, controlled trials comparing the efficacy of oral iron preparations with intravenous iron. [6, 7] Despite significant heterogeneity among studies, intravenous iron was uniformly more efficacious in dialysis patients. The advantage of using the IV route is that it is relatively well tolerated and most importantly is more efficacious with a mean rise in hemoglobin (Hb) of 0.8 g/dl in comparison to 0.3 g/dl with oral iron.[8] This is due to the ability of parenteral iron to bypass the hepcidin-ferroportin system, which reduces the absorption from the duodenum and mobilization of iron from stores. Also for CKD patients, a single total iron dose can be given reducing the number of visits and improving quality of life.[9] Various iron preparations are available internationally along with their safety and dose data have been listed in Table 1. These iron preparations have a central iron core surrounded by a carbohydrate shell that prevents immediate release of iron thus preventing toxic reactions[10]. These iron preparations differ in the size of iron core and the surrounding carbohydrate shell that defines the maximum tolerated dose and rate of infusion. [11] IV iron is taken up by macrophages and either stored intracellularly in tissue ferritin or transferred to circulating transferrin thus increasing transferrin saturation and enhancing erythropoiesis as well as increasing hepcidin levels thus impairing GI absorbtion of iron.[11] Iron preparation with carbohydrate shell as dextran requires a test dost as serious anaphylactic reactions have been observed with these preparations.[12]

IV IRON DOSING REGIMENS

IV iron is administered either as bolus or maintenance dose. Bolus dose requires administration as 1g of iron over 2 to 3 weeks whereas maintenance dose requires 25 to 100 mg of iron every 1 to 2 weeks based on needs.[13] Higher doses of IV iron administered over a short period could lead to temporary oversaturation of transferrin and more non-transferrin bound free iron leading to

TABLE 1: Intravenous iron preparations available and their doses and method of administration.

Generic Name of Iron Product (Brand Name)	Carbohydrate shell	Formulation	Maximum single dose, administration time	Common off label Maximum single dose, administration time	Test dose
Sodium ferric gluconate complex (Ferrlecit)[a]	Gluconate	12.5mg/mL in 5mL single use vial	125 mg IV push over 10 to 60 minutes	250 mg IV over 15 minutes	No
Low molecular weight iron dextran (cosmofer)[b]	Dextran	50mg/mL in 2, 5, and 10mL single-use ampules	100mg > 30sec	1000mg IV over 4 hours	Yes
Iron dextran, high molecular weight (Dexferrum)	Dextran		100mg > 30sec	1000mg IV over 4 hours	Yes
Iron sucrose (venofer)[c]	Sucrose	20 mg/mL in 2.5 and 5mL single-use vials and ampules	200 mg over 10 to 30 minutes	none	no
Ferumoxytol (Feraheme)[d]: FDA issued a blackbox warning on 3/ 30/ 2015 for anaphylactic shock.	Polyglucose sorbitol	30mg/mL in 17mL as 510mg single use vial	510 mg IV, over 15 minutes	Same dose as 15- min infusion	No
Ferric carboxymaltose (Ferinject)[e]	Carboxymaltose	50mg/mL in 2, 10 and 20mL single use vials	200mg slow push or infusion over 15 minutes	None	No
Iron isomaltoside (Monofer)[f]	Isomaltoside (linear oligosaccharide)	100mg/mL in 1, 2, 5, and 10mL Single use vials/ ampoules	20 mg/ kg over 30 to 60 minutes	None	no

a Ferrlecit prescribing information: http://products.sanofi.us/ferrlecit/ferrlecit.html
b Cosmofer prescribing information: https://www.medicines.org.uk/emc/medicine/14139
c Venofer prescribing information: http://www.venofer.com/PDF/Venofer_PI_82015.pdf
d Feraheme prescribing information: http://www.feraheme.com/pdfs/Feraheme_Prescribing_Information.pdf
e Ferinject prescribing information: http://www.injectafer.com/pdf/pi.pdf
f Monofer prescribing information: https://www.medicines.org.uk/emc/medicine/23669

enhanced oxidative damage and infectious risk.[13,14] A trial showed that maintenance dosing was more efficacious than bolus dosing.[15] Large observational data support that maintenance dosing regimens are more efficacious, and are associated with lower infection risk compared with bolus dosing, particularly in patients with central venous catheters. Compared with no iron therapy, maintenance iron dosing was not associated with additional risk.[16] Overall, the data suggest maintenance dosing is more efficacious and has a lower risk than higher-dose intermittent IV

iron therapy. In CKD 5HD patients, the ready IV access and convenience of being able to administer IV iron during HD treatments further supports the preference for the IV route for iron administration in these patients.

Serious anaphylactic reactions may occur more often after the administration of iron dextran than after non-dextran preparations, and are more often associated with fatal and life-threatening outcomes. The incidence of post-iron dextran immediate hypersensitivity reactions has been estimated as 1.1–3.2/100 treated population while the case fatality proportion for post-iron dextran allergic episodes has been calculated as 15.8%.[17-21]

Summary

Anemia remains an important concern in patients with CKD with iron deficiency anemia as the most important causes after excluding the primary causes. Various trails have been conducted comparing efficacy of oral vs IV iron in patients undergoing Hemodialysis. Oral iron preparations are no longer recommended for use in Patients undergoing hemodialysis due to availability of better and more tolerable IV iron preparations that can be easily administered during each dialysis session on weekly basis in the form of bolus dose or maintenance dose. These IV preparations can be administered safely except Ferumoxytol for which FDA black box warning have been issued due to high incidence of reported anaphylactic reactions. Dextran containing preparations require test dose before administration as high incidence of anaphylactic reactions have been reported with these preparations compared to non-dextran preparations.

References:

1. Astor BC, Muntner P, Levin A, Eustace JA, Coresh J. Association of kidney function with anemia: The Third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med 2002; 162:1401–8.
2. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. AmJ Kidney Dis 2003; 41:1–12.
3.James JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol 2005; 18:319–32.
4. Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights.
5. Conrad ME. Regulation of iron absorption. Prog Clin Biol Res. 1993;380:203-19.
6. Rozen-ZviB, Gafter-GviliA, PaulM, LeiboviciL, Shpilberg O. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and metaanalysis. PubMed-NCBI. Available from:http://www.ncbi.nlm.nih.gov/ pubmed/?term=18845368.
7. Albaramki J, HodsonEM, CraigJC, WebsterAC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. Cochrane Database Syst Rev. 2012; 1:CD007857.

8. Litton E, Xiao J, Ho KM. Safety and efficacy of intravenous iron therapy in reducing requirement for allogeneic blood transfusion: systematic review and meta-analysis of randomized clinical trials. BMJ 2013; 347:f4822.
9. Bhandari S and Naudeer S. Improving efficiency and value in health care. Intravenous iron management for anaemia associated with chronic kidney disease. Linking treatment to an

outpatient clinic, optimising service provision and patient choice. J Eval Clin Pract 2008; 14:996–1001
10. Auerbach M,BallardH.Clinical use of intravenous iron: administration, efficacy, and safety. HematologyAmSoc Hematol EducProgram.2010;2010:338-47.
11. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. J Am Soc Nephrol. 2004;15 (Suppl 2): S93-S98.
12. Fishbane S, Ungureanu VD, Maesaka JK, et al. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis. 1996;28:529-34.
13.Kamanna VS, Ganji S H, Shelkovnikov S, Norris K, Vaziri ND. Iron sucrose promotes endothelial injury and dysfunction and monocyte adhesion/infiltration. AmJNephrol.2012;35: 114-9.
14. Scheiber-MojdehkarB,LutzkyB,Schaufler R,SturmB, Goldenberg H. Non-transferrin-bound iron in the serum of hemodialysis patients who receive ferric saccharate : nocorrelation to peroxide generation.JAmSocNephrol.2004;15: 1648-55.
15. Besarab A, Kaiser JW, Frinak S. A study of parenteral iron regimens in hemodialysis patients. Am J Kidney Dis. 1999;34: 21-8.
16. Brookhart MA, Freburger JK, Ellis AR, et al. Infection risk with bolus versus maintenance iron supplementation in hemo- dialysis patients. J Am Soc Nephrol. 2013;24:1151-8.
17. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. JAMA 1980; 243 : 1726–1731

18. Woodman J, Shaw RJ, Shipman AJ *et al.* A surveillance programme on Imferon. Pharmaceut Med 1987; 1: 289–296

19. Fishbane S, Ungureanu V-D, Maesaka JK *et al*. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 1996 ; 28 : 529–534

20. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. On the relative safety of parenteral iron formulations. Nephrol Dial Transplant 2004;19:1571–1575

21.Faich G, Strobos J. Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. Am J Kidney Dis 1999;33: 464–470