Nephrology and Renal Diseases

Research Article ISSN: 2399-908X

Short study on the use of oral Ferric Sodium EDTA in association with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, in patients with advanced Chronic Kidney Disease

Guido Gatti[1], Diletta Duranti[2] and Ennio Duranti[3]*

[1]Section of Nephrology and Dialysis, Cortona Hospital (Arezzo), Italy

[2]Analysis Laboratory, Arezzo Hospital, Italy

[3]Already Director Nephrology and Dialysis Department, Arezzo Hospital, Italy

Abstract

Introduction: Anaemia is a frequent and early complication of Chronic Kidney Disease (CKD), and its prevalence increases with the worsening of renal function. The martial therapy, administered orally, is preferred in patients in the conservative phase, but presents frequent side effects especially of gastrointestinal type. A new formulation has been designed to improve iron absorption, and to avoid side effects caused by the amount of iron not absorbed. The aim of our work was to verify the efficacy of Ferric sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®) in a group of patients in conservative therapy with CKD, comparing it with a previous period in intravenous therapy with carboxymaltose iron.

Methods: We screened 21 patients (9 F/12 M; age 76.1 ± 8.8 yrs) in conservative therapy, affected by CKD stage 3a - 5, who were on treatment for a sideropenic anaemia: haemoglobin (Hb) <11 g/dl, Transferrin saturation <20% and ferritin <100 mcg/l. All patients have been treated for variable periods, but not less than 2 months, with carboxymaltose iron iv (500 mg/month) and therefore the last haematogical control was considered time 0. From that moment on, they were then passed to oral Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®, 1 tablet/day). The protocol lasted 2 months. Serum iron, Hb, Ferritin, Transferrin Saturation, C-reactive protein (CRP), and weekly consumption of erythropoietin were evaluated bimonthly.

Results: Renal function did not change during the two months of observation, in fact serum creatinine remained stable. Hb and CRP during the two periods of treatment, i.e., moving from the end of the intravenous period to the oral iron period, showed a statistically significant improvement of the concentration values. Serum iron, ferritin, transferrin saturation and total weekly consumption of erythropoietin did not change during the two periods, showing a good control of anaemia in all patients using iron only and keeping the other therapies unchanged. No patient reported side effects during iron treatments, and none has discontinued therapy.

Conclusions: Our experience demonstrates the possibility of replacing intravenous iron administration with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), well tolerated, effective, and with significant economic savings. Furthermore, we would like to underline the important relapse also on the medico-legal level, due to the lower clinical risk in the use of oral iron compared to intravenous iron.

Introduction

Anaemia is a frequent and early complication of Chronic Kidney Disease (CKD), and its prevalence increases with the worsening of renal function, involving over 50% of patients in pre-dialysis (stage 5) and practically almost 100% of patients in haemodialysis [1]. The anaemic state depends on an inadequate production of erythropoietin, however a fundamental importance is represented by the alterations of the martial state or due to an iron deficiency, as a consequence of inadequate intestinal absorption, or due to reduced bioavailability, linked to the systemic inflammatory state, characteristic of these patients or for uremic toxicity [2]. The administration of oral or intravenous iron and erythropoietin (Epo) is a key element for the correction of anaemia both in patients with CKD and in patients on chronic haemodialysis [3,4]. The martial therapy, administered orally, is preferred in patients in the conservative phase, but presents frequent side effects especially of gastrointestinal type, that in traditional iron products like ferrous sulphate, are caused by the amount of iron not absorbed. In this kind of iron source, the intestinal absorption is for 15%-20% of the administered dose, so the remaining amount of iron administered can contribute to the onset of side effects [5].

The association of Ferric Sodium EDTA with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®) has been designed to improve iron absorption, and to avoid side effects caused by the iron not absorbed, since large studies in literature reported the increase of iron absorption following these associations [6-9].

Correspondence to: Dr Ennio Duranti, Already Director of Nephrology and Dialysis Department, Arezzo Hospital, Italy, Tel: +393803198372; E-mail: ennio.duranti@libero.it

Key words: *anaemia, chronic kidney disease, conservative therapy, ferric sodium EDTA, oral iron supplementation*

Received: November 05, 2021; **Accepted:** November 16, 2021; **Published:** November 14, 2021

Oral Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine represents a new iron source in order to treat iron deficiency with interesting features: it is taste-less, it does not interact with foods, it is completely water soluble, and without metallic taste; furthermore, it does not cause teeth and stools staining (especially relevant in case of gastrointestinal diagnostic investigations) and its absorption is complete [10].

The aim of our work was to verify the efficacy of Ferric sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®, containing 30 mg of iron) in a group of patients in conservative therapy with CKD, comparing it with a previous period in intravenous therapy with carboxymaltose iron.

Materials and methods

We screened 21 patients (9 F/12 M; age 76.1 ± 8.8 yrs) in conservative therapy, affected by CKD stage 3a - 5, who were on treatment for iron deficiency anaemia: haemoglobin (Hb) <11 g/dl, Transferring saturation <20% and ferritin <100 mcg/l. Patients with hereditary anaemias, neoplasms, autoimmune diseases were excluded. All patients have been treated for variable periods, but not less than 2 months, with carboxymaltose iron iv (500 mg/month) and therefore the last haematological control was considered time 0. From that moment on, they were then passed to oral Ferric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel forte®, AQMA Italia S.p.A. 1 tablet/day, containing 30 mg of iron). The protocol lasted 2 months. During these two periods, serum iron, Hb, ferritin, transferrin saturation, C-reactive protein (CRP), and weekly consumption of erythropoietin were evaluated bimonthly. Statistical analysis was performed with Student's t test for paired data.

This study was conducted in accordance with the Declaration of Helsinki, and the protocol respects the Ethical Committee opinion about observational study. Patients were included after providing written informed consent.

Results

Table 1 shows that renal function did not change during the two months of observation, in fact serum Creatinine remained stable. Hb and CRP during the two periods of treatment, i.e., moving from the end of the intravenous period to the oral iron period, showed a statistically significant improvement of the concentration values. In particular, Hb levels increased from 10.3 ± 0.7 g/dL to 11.3 ± 1.1g/dL ($p< 0.0002^*$) and CRP levels decreased from 1.1 ± 0.3 mg/dL to 0.6 ± 0.2 mg/dL ($p< 0.0005^*$). Serum iron, ferritin and transferrin saturation did not change during the two periods.

Total weekly consumption of erythropoietin did not change, and we emphasize that only 5 out of 21 CKD patients, throughout the period, used moderate dosages of zeta erythropoietin: 4 patients were in stage 4 and 1 patient in stage 5 of CKD. In our opinion these data are relevant because they show a good control of anaemia in all patients using iron only and keeping the other therapies unchanged. No patient reported any side effects during iron treatments, and none has discontinued therapy.

Table 1. Values of serum creatinine, hemoglobin (Hb), C-reactive protein (CRP), and functional iron stores during the 2 months of observation. Data are reported as mean ± standard deviation

	Time 0	Time 2 months
Creatinine (mg/dL)	2.1 ± 0.75	2.0 ± 0.8
Hb (g/dL)	10.3 ± 0.7	11.3 ± 1.1*
CRP (mg/dL)	1.1 ± 0.3	0.6 ± 0.2 **
Iron (mcg/dL)	52.9 ± 18.8	52.7 ± 24.1
Transferrin sat. (%)	16.2 ± 7.3	16.6 ± 8.6
Ferritin (ng/mL)	130 ± 115	181 ± 160
total weekly Epo zeta administration in 5 pts	22000 U	22000 U

*p< 0.0002; **p< 0.0005 Student's t test for paired data.

Discussion

In patients with conservative CKD, oral iron administration is preferred, but sometimes intestinal malabsorption or side effects, such as abdominal pain, gastralgia, nausea, vomiting, diarrhoea, force to pass to the administration via intravenous [11]. Allergic phenomena may occur up to severe anaphylactic reactions, potential cytotoxicity, hepatic disease with iron accumulation in various forms of hereditary hemochromatosis, an increased risk of developing cirrhosis with levels of ferritin >1000 ng/mL and an increase in the systemic inflammation with a decrease in antioxidant defenses [12].

The increased production of inflammatory markers, such as CRP, IL-6, TNF-α, promotes the release of hepcidin, a protein produced by the liver that acts by binding to another protein, called ferroportin, which regulates the escape of iron from cells, blocking the passage of iron from cells to blood resulting in functional iron deficiency, so-called inflammatory anaemia [11,13]. Furthermore, recently they have been emphasized the medico-legal issues related to intravenous iron administration: a recent note dated 25 October 2013 from the Italian Medicines Agency (AIFA) underlined the risk of intravenous administration with potentially fatal reactions, especially in patients with known allergies and in patients with inflammatory diseases, including the immune system, as well as in patients with asthma, eczema, atopic allergies [14]. Although on one hand, among the various preparations, iron gluconate and carboxymaltose seem to be the one with fewer side effects, the Work Group KDIGO 2012 did not show a definite benefit of the intravenous route compared to the oral [1].

On the other hand, as already mentioned, the use of oral iron has not had much development until now due to its low efficacy and to the gastroenteric side effects linked to the compound which usually contains iron or iron sulphate, which can be used only for a limited range of patients, certainly not affected by CKD, in which the incidence of gastritis and gastralgia is constant [11]. At this regard our study seems to demonstrate that the use of Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), has a lower incidence of gastrointestinal side effects [14-18]. More data in literature underline that iron, along with Cu^{++}, Zn^{++}, Se, Vitamin C and Folic acid contribute to the normal function of the immune system. Iron is an essential element for the normal formation of red blood cells and haemoglobin that ensure normal oxygen transport to the entire body. Cu^{++} promotes the normal transport of iron into the body. Vitamin C increases iron absorption and its antioxidant activity can provide protective effects against eventual liver damage caused by iron overload. Folic acid cooperates with normal haematopoiesis. Our work, even if performed on a small number of patients in conservative therapy, showed an equivalent efficacy, compared to intravenous iron, with a significant increment of haemoglobin values keeping the dosages of erythropoietin unchanged. These results confirm previously performed nephrological works on patients on conservative treatment [19-24]. A particularly interesting aspect is the significant reduction of CRP, during the two months treatment, which is explained by a lower activation / production of inflammatory markers that increase with the use of intravenous iron through the production of the reactive oxygen species

that exacerbate systemic inflammation, with decreased antioxidant defenses and increased TNF-α and IL-6 release [25]. The absence of these effects in the case of the use of Ferachel Forte® also explains the maintenance of minimal weekly doses of erythropoietin, recalling that 16 patients out of 21 in conservative therapy, throughout the period, did not use erythropoietin and this has certainly contributed to a reduction in costs for the use of this kind of iron. Another argument in favour of Ferachel Forte® oral use is the high bioavailability of oral iron thanks to its intestinal absorption, compared to the intravenously administered iron of which the percentage of use is not certain, with an amount that it certainly precipitates at the tissue level, once the transferrin is saturated.

In conclusion, our experience demonstrates the possibility of replacing intravenous iron administration with Ferric Sodium EDTA, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine (Ferachel Forte®), well tolerated, effective, and with significant economic savings. Furthermore, we would like to underline the important relapse also on the medico-legal level, due to the lower clinical risk in the use of oral iron compared to intravenous iron.

Conflict of Interest

The authors have no conflicts of interest to declare.

References

1. Locatelli F, Nissenson AR, Barrett BJ, Walker RG, Wheeler DC, et al. (2008) KDIGO clinical practice guidelines for anemia in chronic kidney disease. *Kidney Int* 74: 1237-1240. [Crossref]
2. Bregman DB, Morris D, Koch TA, He A, Goodnough LT (2013) Hepcidin levels predict nonresponsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol* 88: 97-101. [Crossref]
3. Taylor JE, Peat N, Porter C, Morgan AG (1996) Regular low-dose intravenous iron therapy improves response to erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 11: 1079-1083. [Crossref]
4. Del Vecchio L, Cavalli A, Tucci B, Locatelli F (2010) Chronic kidney disease associated anemia: new remedies. *Curr Opin Investig Drugs* 11: 1030-1038. [Crossref]
5. Camaschella C (2015) Iron-Deficiency Anemia. *N Engl J Med* 372: 1832-1843.
6. Ma AG, Schouten EG, Sun YY, Yang F, Han XX, et al. (2010) Supplementation of iron alone and combined with vitamins improves haematological status, erythrocyte membrane fluidity and oxidative stress in anaemic pregnant women. *Br J Nutr* 104: 1655-1661. [Crossref]
7. Hallberg L, Brune M, Rossander L (1989) The role of vitamin C in iron absorption. *Int J Vitam Nutr Res Suppl* 30: 103-108. [Crossref]
8. Reeves PG, Demars LCS, Johnson WT, Lukaski HC (2005) Dietary copper deficiency reduces iron absorption and duodenal enterocyte hephaestin protein in male and female rats. *J Nutr* 135: 92-98. [Crossref]
9. Nguyen P, Grajeda R, Melgar P, Marcinkevage J, Flores R, et al. (2012) Effect of Zinc on Effica-cy of Iron Supplementation in Improving Iron and Zinc Status in Women. *J Nutr Metab* 2012: 216179. [Crossref]
10. Hurrell RF, Reddy MB, Burri J, Cook JD (2000) An evaluation of EDTA compounds for iron fortification of cereal-based foods. *Br J Nutr* 84: 903-910. [Crossref]
11. Auerbach M, Goodnough LT, Picard D, Maniatis A (2008) The role of intravenous iron in anemia management and transfusion avoidance. *Transfusion* 48: 988-1000. [Crossref]
12. Zager RA, Johnson AC, Hanson SY (2004) Parenteral iron nephrotoxicity: potential mechanisms and consequences. *Kidney Int* 66: 144-156. [Crossref]
13. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J (2006) Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant* 21: 378-382. [Crossref]
14. Di Lullo L (2021) The best therapeutic option for oral treatment of secondary anaemia in chronic kidney disease: role of Ferric Sodium EDTA, in association with Vitamin C, Folic acid, Copper. *Nephrol Renal Dis* 6: 1-6.
15. Marchitto N, Curcio A, Iannarelli N, Petrucci A, Romano A, et al (2020) A pilot study on secondary anaemia in "frailty" patients treated with the Fer-ric Sodium EDTA in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine: safety of treatment explored by HRV non-linear analysis as predictive factor of cardiovascular tolerability. *Eur Rev Med Pharmacol Sci* 24: 7776-7783. [Crossref]
16. Marchitto N, Francesco S, Alberto P, Alessia P, Liuba F, et al. (2019) Role of Ferric Sodium EDTA associated with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine administration in patients with secondary anaemia. Effects on hemoglobin value and cardiovascular risk. *Health Sci J* 13: 682.
17. Marchitto N, Petrucci A, Fusco L, Curcio A, Romano A, et al. (2019) Effect of Ferric Sodium EDTA administration, in combination with vitamin C, folic acid, copper gluconate, zinc gluconate and selenomethionine, on cardiovascular risk evalua-tion: exploration of the HRV frequency domain. *Clinical Practice* 16: 1245-1251.
18. Curcio A, Romano A, Nicola M, Pironti M, Gianfranco R (2018) Efficacy and Safety of a New Formulation of Ferric Sodium EDTA Associated with Vitamin C, Folic Acid, Copper Gluconate, Zinc Gluconate and Selenomethionine Administra-tion in Patients with Secondary Anaemia. *J Blood Lymph* 8: 224.
19. Duranti E (2015) Comparative study between liposomal iron (SideralForte) and intravenous iron in chronic kidney disease. The experience of our nephrology unit. Proceedings 3rd Medit Multidisc Course on anemia. *Expert Review of Hematology* s16-17.
20. Duranti E, Duranti D (2018) Brief Review of Studies on Oral Martial Therapy Compared to the Administration of Intravenous Iron in Nephrology and Dialysis. *ARC Journal of Nephrology* 3: 6-8.
21. Duranti E, Duranti D, Panza F, Ralli C (2018) Efficacy of administration of oral liposomal iron after a period of intravenous iron carboxymaltose in two groups of chronic kidney disease patients: home hemodialysis and conservative therapy. *Clin Nephrol Res* 2: 33-35.
22. Van Wyck DB, Roppolo M, Martinez CO, Mazey RM, McMurray S, et al. (2005) A randomized, controlled trial comparing IV iron sucrose to oral iron in anaemic patients with non-dialysis dependent CKD. *Kidney Int* 68: 2846-2856. [Crossref]
23. Charytan C, Qunibi W, Bailie GR, Venofer Clinical Studies Group (2005) Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron Clin Pract* 100: c55-62. [Crossref]
24. Agarwal R, Rizkala AR, Bastani B, Kaskas MO, Leehey DJ, et al (2006) A randomized controlled trial of oral versus intrave-nous iron in chronic kidney disease. *Am J Nephrol* 26: 445-454. [Crossref]
25. Mitsopoulos E, Tsiatsiou M, Zanos S, Katodritou E, Visvardis G, et al. (2011) Impact of C-reactive protein on absolute reticulocyte count in haemodialysis patients: the role of iron status. *Nephrol Dial Transplant* 26: 992-997.