ORIGINAL ARTICLE

Role of Ferric Citrate in Hyperphosphatemia and Iron Deficiency Anemia in Non Dialysis CKD Patients

Nitya Nand[1*], Kajaree Giri[2], Deepak Jain[3]

Abstract

Introduction: Disorders of mineral and bone metabolism in chronic kidney disease (CKD) are associated with increased risk for cardiovascular calcification and osteoporosis. Anemia has been associated with progressive loss of kidney function and increased mortality. Ferric citrate was recently developed, primarily as a novel oral, non-calcium phosphate binder, which has also shown to replenish the iron deficient state of the CKD patients.

Material and methods: This prospective study was done on 40 pre-dialysis adult patients of CKD (stage 3-5) from a tertiary care centre in North India. Patients on intravenous iron, erythropoietin stimulating agents or other phosphate binders were excluded from the study. All the patients were given tablet ferric citrate (each tablet containing ferric citrate 1.1 gm equivalent to ferric iron 210 mg) in a dose of 3 tablets per day for three months. Patients were followed up at two weekly intervals and relevant investigations were done. They were divided into three groups according to their CKD stages for subgroup analysis.

Observations: After three months of therapy with ferric citrate there was a significant decrease in mean serum phosphate from 6.55±0.70 mg/dl at baseline to 4.36±0.50 mg/dl at the end of three months ($p<0.001$). Mean hemoglobin increased from 7.92±1.05 g/dl at baseline to 10.96±1.04 g/dl at the end of three months ($p<0.001$). Serum ferritin and serum transferrin saturation increased from 278.25±110.56 ng/dl, 25.02±4.03 % at baseline to 401.24±152.47 ng/dl and 29.62±3.77 % at the end of three months. The mean serum vitamin D and serum iPTH levels, at baseline and at the end of 3 months were 14.61±10.80 ng/ml, 509.48±210.75 pg/ml and 23.65±14.00 ng/ml, 424.14±173.18 pg/ml respectively. The change in all these parameters were significant irrespective of the CKD stages.

Conclusion: The present study has shown that ferric citrate is an effective and well tolerated phosphate binder, which also significantly improves hematologic parameters in an iron deficient CKD patient.

Introduction

Advanced chronic kidney disease (CKD) is often accompanied by hyperphosphatemia, increased FGF-23, calcitriol deficiency, secondary hyperparathyroidism, abnormal parathyroid growth and functional and skeletal resistance to parathyroid hormone (PTH). This altered milieu of minerals in the body leads to a complex and multifactorial clinical entity called chronic kidney disease - bone mineral disease (CKD-BMD) which often results in renal osteodystrophy. This results in increased risk for cardiovascular calcification and osteoporosis.[1] Dietary phosphate restriction and oral phosphate binders are the mainstay of therapy.[2] The first generation phosphate binder was aluminium hydroxide which lost its favour due to its systemic absorption and accumulation in the bones, brain and bone marrow leading to osteomalacia, dementia and anemia respectively. On the other hand, calcium based phosphate binders like calcium carbonate and calcium acetate, although being more effective, are found to be associated with enhanced calcium burden in the body promoting vascular calcification.[3] Hence, non-calcium based phosphate binders like sevelamer hydrochloride and lanthanum carbonate are widely used at present.

Anemia is also a well-documented complication of CKD which results in decreased oxygen delivery to tissues and the heart's compensatory mechanisms which cause increased cardiac output, left ventricular hypertrophy and subsequent heart failure. Anemia also contribute to impaired immune response and exacerbations of angina, claudication and transient ischemic attacks. The only effective treatment is erythropoietin stimulating agents (ESA) with replenishment of iron stores.[4] The introduction of human recombinant erythropoietin revolutionised the management of anemia in CKD patients. On the other hand, oral iron preparations result in relatively poor iron absorption from the gut and poor patient tolerability. Hence most of the patients consequently require intermittent intravenous iron treatment. Although it has better bioavailability, it contributes to increased oxidative stress, cytotoxicity and endothelial dysfunction.[5] KDIGO recommends to give oral iron trial in CKD patients whenever transferrin saturation is less than 30% and serum ferritin is less than 500ng/L.[6]

Ferric citrate (FC) has been recently developed, primarily as a novel oral, non-calcium phosphate binder, which has also shown to replenish the iron deficient state of the CKD patients.[7] It increases delivery and uptake of iron in patients with CKD despite increased hepcidin levels.[8] It successfully reduces FGF-23 levels, which is the primary

[1]Senior Professor & Head, [2]Resident, Department of Medicine, [3]Associate Professor, Department of Medicine and Division of Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, Haryana; *Corresponding Author
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Table 1: Effect of Ferric citrate on hematological parameters in total patients (N=40) and different groups

Parameters	Baseline (Mean±S.D.)	At 3 months (Mean±S.D.)	P value (paired T test)
Hemoglobin (g/dl)	7.92±1.05	10.96±1.04	<0.001
Group A	8.26±1.32	11.17±0.89	<0.001
Group B	8.18±1.23	11.02±1.30	<0.001
Group C	7.56±0.62	10.81±0.91	<0.001
PCV (%)	25.23±3.28	33.45±2.76	<0.001
Group A	25.92±3.33	34.38±1.76	<0.001
Group B	24.53±3.48	33.57±2.82	<0.001
Group C	25.46±3.20	32.94±3.07	<0.001
Ferritin (ng/dl)	278.25±110.56	401.24±152.47	<0.001
Group A	288.69±117.30	426.88±181.53	0.005
Group B	285.70±141.30	447.62±181.63	<0.001
Group C	267.80±83.01	353.70±100.30	<0.001
Transferrin saturation (%)	25.02±4.03	29.62±3.77	<0.001
Group A	26.21±3.42	29.86±3.62	0.024
Group B	24.58±5.12	29.53±4.72	0.001
Group C	25.30±3.25	30.20±3.20	<0.001
TIBC (ug/dl)	171.71±19.40	143.19±19.70	<0.001
Group A	179.38±22.2	148.77±19.20	<0.001
Group B	173.32±20.90	146.47±22.14	0.001
Group C	167.06±16.55	138.17±17.69	<0.001

Table 2: Effect of Ferric citrate on bone mineral and renal parameters in total patients (N=40) and different groups

Parameters	Baseline (Mean± S.D.)	At 3 Months (Mean± S.D.)	P value (paired T Test)
S. Calcium (mg/dl)	8.44±1.16	8.79±0.82	>0.05
Group A	8.66±0.96	8.75±0.45	0.76
Group B	9.10±1.17	8.95±0.87	0.448
Group C	7.83±0.94	8.69±0.92	0.08
S. Phosphate (mg/dl)	6.55±0.70	4.36±0.50	<0.001
Group A	6.21±0.49	4.51±0.63	<0.001
Group B	6.56±0.77	4.38±0.46	<0.001
Group C	6.70±0.71	4.28±0.49	<0.001
S. Vitamin D (ng/ml)	14.61±10.80	23.65±14.00	<0.05
Group A	17.27±16.37	26.51±23.57	<0.05
Group B	17.92±11.75	24.42±12.47	<0.05
Group C	10.85±4.95	21.79±9.68	<0.05
Serum iPTH (pg/ml)	509.48±210.75	424.14±173.18	<0.05
Group A	471.16±167.79	407.03±127.24	<0.05
Group B	536.15±206.00	443.52±198.40	<0.05
Group C	505.76±237.82	416.68±177.51	0.10

mediator of CKD bone mineral disease. Furthermore, it effectively reduces the need of ESA and intravenous iron use and is also effective in patients with ESA resistance.[9]

Patients with CKD demand a comprehensive treatment approach in slowing the progression and onset of complications of the disease. However, this often results in larger pill burden leading to non-compliance to treatment. Hence, any drug which has dual effect in correcting hyperphosphatemia and anemia is a welcome addition to the armamentarium in CKD management. Since its discovery, various studies have been carried out on ferric citrate, mostly from Western countries to establish its beneficial role on CKD patients. Very few studies have been carried out from India. Hence, this study was carried out to observe the efficacy and safety of ferric citrate on non-dialysis CKD patients in India.

Material and Methods

This prospective study was done on pre-dialysis adult patients of CKD, attending as an out-patient in Nephrology clinic of a tertiary care centre in North India. This study was duly approved by the ethical committee and the Post graduate board of studies of the institution. The inclusion criteria of the CKD patients were serum hemoglobin levels < 11 g/dl, eGFR <60mL/min/1.73m^2 (CKD stages 3-5), stable patients not on dialysis, serum phosphate levels between 5 mg/dL to 8 mg/dl, serum ferritin level <500 ng/mL and transferrin saturation < 30%. The exclusion criteria were patients who were scheduled for dialysis or renal transplantation, use of an erythropoietin stimulating agent within 4 weeks or intravenous iron within 8 weeks prior to screening, any known cause of anemia other than iron deficiency or chronic kidney disease such as active gastrointestinal disease (peptic ulcer disease/ chronic ulcerative colitis/ regional enteritis/ previous gastrectomy or duodenectomy) and symptomatic gastrointestinal bleeding or inflammatory bowel disease.

82 Patients of CKD were screened. 48 patients met the inclusion criteria and were enrolled in the study. They were given tablet ferric citrate (each tablet containing ferric citrate 1.1 gm equivalent to ferric iron 210 mg) in a dose of 3 tablets per day, to be taken after meals for 12 weeks. A preinformed written consent form was obtained from each patient. Detailed history, clinical examnation and relevant investigations were done. Blood samples for complete hemogram, renal functions, serum calcium and serum phosphate levels were taken at baseline followed by two weekly intervals. Serum transferrin saturation, TIBC and serum ferritin were obtained at baseline, monthly, and at the end of the study. In addition, serum Vitamin D and serum iPTH levels were done twice -- in the beginning (baseline) and at the end of the study (3 months). Patients taking phosphate binders at the time of consent underwent a washout period of at least 2 weeks prior to administration of ferric citrate tablets. No other phosphate binding agents were allowed during the study. Patients were given strict instructions of low phosphate diet and calcium intake per patient (in the form of milk/cheese) was made as similar as possible. Use of calcium for the purpose of phosphate binding was not allowed, however, use of calcium supplements and active or nutritional vitamin D were allowed, but the dose was kept constant throughout the study. Neither iron nor use of any erythropoietin stimulating agents (ESA) was given during the study.

Out of these 48 patients, 8 patients couldn't complete the study. 2 patients withdrew their consent from the study, 4 patients lost to follow up and 2 patients were non-compliant to therapy. A total of 40 adult patients of CKD completed the study. The patients were divided into three groups according to their CKD stages for subgroup analysis: Group A (N=8; stage 3), Group B (N=14; stage 4), Group C (N=18; stage 5). The patients were followed up regularly every two weeks to the hospital during the three month study period and were instructed to report immediately in

case of any adverse events following consumption of the drug.

At the end of study, the data was collected and analysed using SPSS software version – 17.0. The distribution of parameters passed the normality test, so parametric tests were used. For comparison of means of same parameter in a single group at two point of time during follow up, paired students T test was used and P-values were obtained to determine the statistical significance. The p values were two tailed and probability level of significant difference was set at <0.05 for students T test.

Results

The mean age, weight, height and BMI of the 40 adult, non dialysis CKD patients enrolled in the study were 51.30±12.45 years, 57.90±10.86 kg, 162.10±9.42 cm, and 22.17±3.38 kg/m^2 respectively. Baseline hematological, bone mineral and renal parameters have been shown in Table 1. The etiology of CKD was ascertained for every patient. The most common etiology was diabetic nephropathy closely followed by hypertensive nephropathy and chronic glomerulonephritis. The mean eGFR was 19.86±10.51 ml/min/1.73m^2.

The study revealed that ferric citrate resulted in significant increase in serum hemoglobin, hematocrit, ferritin and transferrin saturation levels and were evident in all the three groups irrespective of their CKD stages. It also resulted in significant fall in TIBC levels (Table 1). The mean hemoglobin increased from 7.92±1.05 g/dl at baseline to 10.96±1.04 g/dl at three months. The mean rise in hemoglobin level was found to be highly significant (p<0.001). The mean serum ferritin and serum transferrin saturation at baseline were 278.25±110.56 ng/dl and 25.02±4.03 % respectively which increased to 401.24±152.47 ng/dl and 29.62±3.77 % at the end of 3 months respectively. The mean rise in both were found to be highly significant (p<0.001). Similar effects were observed in all the three subgroups of CKD patients respectively.

Follow up analysis of the bone mineral parameters in the study population revealed that the mean serum phosphate significantly decreased from 6.55±0.70 mg/dl at baseline to 4.36±0.50 mg/dl at the end 3 months (p<0.001). The mean serum vitamin D increased significantly from 14.61±10.80 ng/ml at baseline to 23.65±14.00 ng/ml at the end of three months. Serum iPTH levels decreased significantly from 509.48±210.75 pg/ml at baseline to 424.14±173.18 pg/ml at the end of 3 months (p<0.05) (Table 2). It was also shown that the levels of serum calcium improved within 3 months but the rise was not significant (p>0.05). Sub group analysis also revealed significant decline in serum phosphates and iPTH levels, as well as significant increase in serum vitamin D level during the 12 week study period.

After consumption of ferric citrate, 15 patients (37.5%) complained of adverse effects which were mostly gastrointestinal - 7 patients (17.5%) complained of stool discoloration, 3 patients (0.07%) complained of constipation and abdominal discomfort each, and 1 patient complained of loose stools and nausea each. However, none of the patients reported serious drug reactions which demanded cessation of drug therapy. No derangements of metabolic and biochemical parameters like hypophosphatemia, hypocalcemia or hypo/hypernatremia were observed during the study.

Discussion

Various studies establish that anemia is twice as prevalent in people with CKD (15.4%) than in general population (7.6%).[10] The prevalence of hyperphosphatemia is also reported to be 69.1% among CKD patients.[11] As the glomerular filtration rate (GFR) declines, the filtered load of phosphate through the kidney decreases and phosphate retention ensues. Increased phosphate excretion is accomplished by increasing levels of fibroblast growth factor-23 (FGF-23) which promotes renal phosphate excretion and decreases renal synthesis of 1-alpha-hydroxylase, resulting in calcitriol deficiency. Decreased calcitriol causes hypocalcemia which in turn stimulates parathyroid hormone (PTH) secretion. PTH acts on the distal tubule to further promote phosphate excretion as well as on bone where it increases resorption and releases calcium. Alteration in the bone mineral metabolism in CKD leads to heterotopic mineralization, especially in the vasculature and results in increased cardiovascular events and mortality. On the other hand, severe iron deficiency in patients with CKD impairs several homeostatic processes including production of ATP through oxidative phosphorylation. Hence, the issues of hyperphosphatemia and anemia need to be addressed with priority among CKD patients. This demands a comprehensive treatment approach which increases the pill burden of the patients. In developing countries like India, limited resources and poor awareness of the disease often lead to non-adherence of therapy with progressive deterioration of kidney functions.

The present study showed that the use of ferric citrate significantly reduced hyperphosphatemia, total iron binding capacity and serum iPTH levels (Figure 1). It also resulted in significant increase in serum hemoglobin, hematocrit, ferritin, transferrin saturation and vitamin D levels (Figure 2). An increase in serum calcium level was also observed in the study population. As a phosphate binder, the ferric ion in ferric citrate compound combines with dietary phosphorus and ferric phosphate is generated, which is insoluble. As this new compound is excreted in the faeces, the dietary phosphate is disposed of, rather than being absorbed. Hence, ferric citrate has been shown to effectively prevent absorption of dietary phosphates to the systemic circulation. There have been several published studies across the globe that prove the same hypothesis. The first early report on ferric citrate showed a significant reduction of serum phosphate level from baseline value.[12] Another study also revealed that ferric citrate controlled phosphorus effectively compared to placebo.[13] Similar result was reported from another study where the authors concluded that short-term (4 weeks) use of ferric citrate reduced serum phosphate in patients with CKD 3–5a effectively.[14,15]

Reduction in serum phosphate level decreases the FGF-23 elevation which removes the inhibitory effect on 1α hydroxylase synthesis from kidneys. This maintains vitamin D production in the body. Hence, on treatment with ferric citrate, along with effective phosphate binding, serum vitamin D levels are also expected to rise. Moreover, increased calcitriol also normalises serum calcium, which decreases the parathyroid gland

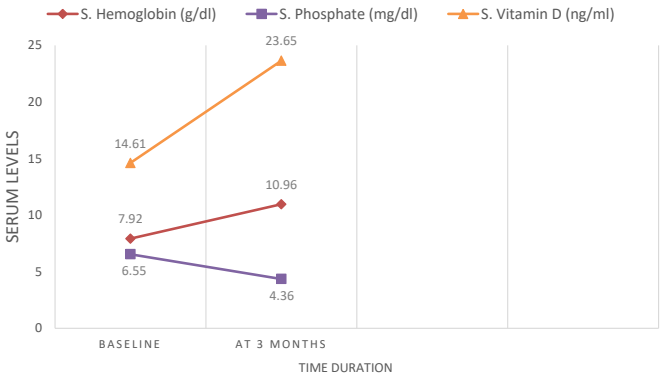

Fig. 1: Effect of ferric citrate on serum hemoglobin, phosphates and vitamin D in the patients

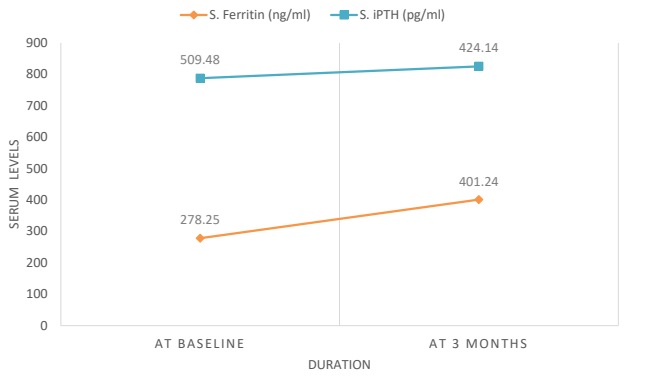

Fig. 2: Effect of ferric citrate on serum ferritin and iPTH in the patients

stimulation. Hence iPTH is expected to decrease too. The present study shows significant increase in vitamin D level and decline in iPTH level following administration of ferric citrate. Various studies have also supported similar hypothesis.[12,14]

As a supplier of elemental iron, not all the ferric ion that dissociates from ferric citrate binds phosphate. Some of it is reduced by the bowel mucosa to ferrous iron through the action of ferric reductase. Ferrous iron can be effectively reabsorbed into the systemic circulation, thus replenishing iron stores when required. The present study revealed significant increase in serum hemoglobin, hematocrit, ferritin and transferrin saturation in patients following 12 week treatment with ferric citrate. This is in concordance with other studies which showed that ferric citrate resulted in significant increase in serum ferritin, serum transferrin saturation and reduction in intravenous iron and ESA requirement.[16,17]

In the present study it was shown that ferric citrate was a well-tolerated drug. This was in concordance with other studies which showed that the gastrointestinal events were the most common adverse effects following administration.[15] Few studies showed comparable side effects of ferric citrate to placebo.[16,18,19]

Hence, the present study has shown that ferric citrate is an effective and well tolerated phosphate binder, which also significantly improves hematologic parameters in an iron deficient CKD patient. This may translate to a reduced need of ESA and intravenous iron use in a vast majority of the patients. The dual role of ferric citrate is definitely a beneficial and highly desired product profile which not only reduces cost burden but also reduces pill load and improves adherence in a patient with CKD. There has been paucity of data regarding use and efficacy of ferric citrate from developing countries like India. This study is one of the very few studies that has been conducted from India. However, the limitations of this study were that firstly it was not a case control study and the study duration was limited to 12 weeks only.

It can be concluded that ferric citrate is a very reasonable and effective first line treatment option in reducing hyperphosphatemia and improving anemia in non-dialysis CKD patients. It is also advisable to incorporate the use of ferric citrate into existing iron therapy protocols because it is likely that, over time, reductions in intravenous iron and ESA will be required. Hence academic communities should undergo more vigorous trials to refine our understanding of ferric citrate on intestinal epithelial function and oxidative stress of the body, which are still unexplored areas in this field. Long term case control and randomised studies are required to further address the same.

References

1. Chertow GM, Block GA, Neylan JF, Pergola PE, Uhlig K, Fishbane S. Safety and efficacy of ferric citrate in patients with nondialysis-dependent chronic kidney disease. *PLoS One* 2017; 12:e0188712.
2. Varughese S, Abraham G. Chronic Kidney Disease in India. A Clarion Call for Change. *Clin J Am Soc Nephrol* 2018; 13:802-4.
3. Patel L, Bernard LM, Elder GJ. Sevelamer Versus Calcium-Based Binders for Treatment of Hyperphosphatemia in CKD: A Meta-Analysis of Randomized Controlled Trials. *Clin J Am Soc Nephrol* 2016; 11:232–44.
4. Fishbane S, Spinowitz B. Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. *Am J Kidney Dis* 2018; 71:423-35.
5. Hahn D, Esezobor CI, Elserafy N, Webster AC, Hodson EM. Short-acting erythropoiesis-stimulating agents for anaemia in predialysis patients. *Cochrane Database Syst Rev* 2017; 1:CD011690.
6. Iain C, Macdougall AJ, Bircher, Kai-UweEckardt, Gregorio T, Obrador Carol A, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes"(KDIGO) Controversies Conference. *Kidney International* 2016; 89:28-39.
7. Block GA. Ferric Citrate in Patients with Chronic Kidney Disease. *Semin Nephrol* 2016; 36:130-5.
8. Yokoyama K, Hirakata H, Akiba T, Fukagawa M, Nakayama M, Sawada K et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. *Clin J Am Soc Nephrol* 2014; 9:543-52.
9. Block GA, Brillhart SL, Persky MS, Amer A, Slade AJ. Efficacy and safety of SBR759, a new iron-based phosphate binder. *Kidney Int* 2010; 77:897–903.
10. Modi GK, Jha V. The incidence of end-stage renal disease in India: a population-based study. *Kidney Int* 2006; 70:2131-3.
11. Yagil Y, Fadem SZ, Kant KS, Bhatt U, Sika M, Lewis JB et al. Managing hyperphosphatemia in patients with chronic kidney disease on dialysis with ferric citrate: latest evidence and clinical usefulness. *Ther Adv Chronic Dis* 2015; 6:252-63.
12. Yang, WC, Yang, CS, TH, Young et al. An open-label, crossover study of a new phosphate-binding agent in haemodialysis patients: Ferric citrate. *Nephrol Dial Transplant* 2002; 17:265–70.
13. Sinsakul M, Sika, M, Koury M. Collaborative Study Group. The safety and tolerability of ferric citrate as a phosphate binder in dialysis patients. *Nephron Clin Pract* 2012; 121:25–9.
14. Dwyer, JP, Sika, M, Schulman, G. Collaborative Study Group. Dose-response and efficacy of ferric citrate to treat hyperphosphatemia in hemodialysis patients: A short-term randomized trial. *Am J Kidney Dis* 2013; 61:759–66.
15. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT et al. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. *J Am Soc Nephrol* 2015; 26:493-503.
16. Yokoyama, K, Hirakata, H, Akiba, T, Sawada, K, Kumagai, Y. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: Results of a randomized, double-blind, placebo-controlled trial. *Am J Nephrol* 2012; 36:478–87.
17. Block GA, Fishbane S, Rodriguez M, Smits G, Shemesh S, Pergola PE. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3-5. *Am J Kidney Dis* 2015; 65:728-36.
18. Fishbane S, Block GA, Loram L, Neylan J, Pergola PE. Effects of Ferric Citrate in Patients with Nondialysis-Dependent CKD and Iron Deficiency Anemia. *J Am Soc Nephrol* 2017; 28:1851-8.
19. Mei-Yi Wu, Ying-Chun Chen, Chun-Hung Lin, Yun-Chun Wu,Yu-Kang Tu et al. Safety and efficacy of ferric citrate in phosphate reduction and iron supplementation in patients with chronic kidney disease. *Oncotarget* 2017; 8:107283–94.