Original Article

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Effectiveness of iron-based phosphate binders in reduction of hyperphosphataemia in chronic kidney disease patients

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Abstract

Background: Ferric citrate is novel iron-based phosphate-binding drug for management of hyperphosphataemia and iron-deficiency anaemia in chronic kidney disease (CKD) patients.

Objectives: To evaluate impact of ferric citrate therapy on reduction of phosphate levels and improvement in haematological parameters in CKD stages 3-5.

Methods: This analytical, observational study was conducted at Kathmandu Medical College Teaching Hospital from 2020 July-December after ethical clearance using convenience sampling method. Non-dialysis dependent patients at CKD stages 3-5, having hyperphosphataemia (serum phosphate ≥4.6mg/dL) and anaemia (serum haemoglobin <12 gm%, transferrin saturation ≤30%, ferritin ≤300ng/mL) were administered with 2gm twice daily dose of ferric citrate for 12 weeks and evaluated on outcomes in terms of reduction in serum phosphate levels and improvement in haematological parameters as study endpoints. Data were entered in Microsoft Excel and analysed in SPSS v.25. Significance level was set at $p < 0.05$.

Results: Of 84 study participants, majority had CKD stage 4 (46, 54.76%). A significant reduction ($p < 0.001$) in mean serum phosphate levels of 6.21 ± 1.062 mg/dL from baseline to 4.89 ± 1.100 mg/dL in 12-weeks was observed. Patients with CKD stages 3, 4, and 5 had mean reduction of 1.67 ($p = 0.005$), 1.40 ($p < 0.001$), and 1.04 mg/dL ($p = 0.002$) of serum Phosphate level respectively. Significant ($p < 0.001$) improvements in hemoglobin level, serum iron, ferritin, total iron binding capacity, and transferrin saturation were reported.

Conclusion: Ferric citrate is effective and well-tolerated phosphate-binder to improve hyperphosphataemia and iron deficiency anaemia in non-dialysis CKD stage 3, 4, and 5.

Key words: Chronic renal insufficiency; Ferric citrate; Hyperphosphataemia; Iron-deficiency anaemia.

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INTRODUCTION

Hyperphosphataemia and anaemia are two major complications accompanying advanced chronic kidney disease (CKD). Hyperphosphataemia, as a part of bone mineral disease (BMD) associated with CKD, is a major risk factor for cardiovascular morbidity and mortality.[1-4] Anaemia in CKD commonly manifests as iron-deficiency anaemia and its long-term effects can lead to increased cardiac output, left ventricular hypertrophy and accelerated heart failure.[5] In addition to dietary phosphate restriction, use of phosphate binders is the most used and cheapest method of treating hyperphosphataemia from CKD stages 3 onwards, but have fallen out of favour because of calcium toxicity.[6]

The use of erythropoiesis-stimulating agents (ESAs) and iron therapy have been effective in improving anaemia in CKD patients.[7] Ferric citrate is an oral-based non-calcium phosphate binder with a dual benefit of reducing serum phosphate and increasing haemoglobin (Hb) levels by repleting iron stores.[8] There is limited literature on advantages and disadvantages of different regimens in treatment of CKD patients in Nepali context.

This study was designed with aims to evaluate clinical effectiveness of ferric citrate in reducing serum phosphate levels and improving haematological parameters in patients with CKD stages 3 and above with concomitant iron-deficiency anaemia, visiting study site, seeking appropriate treatment for the ailment.

METHODOLOGY

This was a prospective, analytical-observational study conducted at the outpatient setting in the Department of Nephrology of a tertiary care hospital, Kathmandu Medical College Teaching Hospital (KMC), Sinamangal, Kathmandu, Nepal. The study protocol received ethical approval from the institutional review committee (KMC-IRC: Ref. 207202008, dated: 2020 July 2) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participant patients who were recruited by convenience sampling. The medicine (Citraphos) used in the study is a Department of Drug Administration Registered medicine (DDA Ref no. 3829, 2078/11/30) as per National Treatment protocol for renal diseases and renal replacement therapy.[9]

Patients visiting Nephrology outpatient department (OPD) of KMC were screened following inclusion and exclusion criteria proposed in the study protocol. Patients with CKD stages 3, 4, and 5 [glomerular filtration rate (GFR) <60 mL/min/1.73m^2 calculated by Cockcroft-Gault equation], and evidence of hyperphosphataemia (serum phosphate ≤4.6 mg/dL) and iron-deficiency anaemia [serum Hb <12 gm%, transferrin saturation (Tsat) ≤30%, serum ferritin ≤300 ng/mL] were provided information section of the informed consent form and requested for their consent to participate in the study. Participants providing written informed consent during a six-month period (2020 July to December) were only recruited. Proposed treatment protocol for the study was followed. Patients undergoing renal dialysis or scheduled for renal transplant, receiving intravenous iron or ESAs, had causes of anaemia other than iron-deficiency anaemia, and history of gastrointestinal bleeding were excluded from the study participant enrollment, based on the IRC approved research protocol. However, the patients received the standard treatment services from the hospital, as usual.

At the time of enrollment, a detailed clinical history of the patients was obtained, and relevant physical examinations were performed. The necessary baseline biochemical (serum phosphate) and haematological parameters (Hb level, serum iron, serum ferritin, serum transferrin saturation, and total iron binding capacity) were measured and recorded as baseline of the participants for further analysis following different stages of the treatment during the study period. All the patients included in the study who were receiving other phosphate binders prior to the start of the study underwent a two-week washout period prior to undergoing baseline evaluation to eliminate the effects of prior phosphate-binding therapy.

Each participant received two tablets of ferric citrate, each containing 210 mg elemental iron (total iron received per dose – 420 mg) twice a day for 12 weeks. Patients were followed-up at the middle of the study (six weeks) to monitor for any possible side-effects of the drug. The relevant investigations were repeated at the end of the study.

Participants' clinical and laboratory data were recorded in Microsoft Excel worksheet, maintaining confidentiality and data protection ethical standards. The collected data were analysed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA). Descriptive statistics are also presented. Paired sample t-tests were applied for pre- and post-treatment values of biochemical and haematological parameters of patients and p-values were obtained. The significance level for the paired sample t-tests was set at <0.05.

RESULTS

A total of 84 eligible patients were included as participants in the study. The mean age of the patients was 49.85 ± 13.878 years, with the youngest and eldest patients being 25 years and 91 years, respectively. The majority (47, 55.95%) of patients were aged between 41 years and 60 years. The male:female ratio of participants was 1.1:1.

Among the 84 participants, 11 (13.10%) patients, 46 (54.76%) patients, and 27 (32.14%) patients were in CKD stages 3, 4, and 5 respectively. The mean estimated glomerular filtration rate (eGFR) was 20.14 ± 9.131 mL/min.

When the effect of ferric citrate on serum phosphate level decrease was observed, it was found that the serum phosphate levels significantly (p <0.001) decreased from baseline (6.21 ± 1.062 mg/dL) to 12-weeks (4.89 ± 1.100 mg/dL) after ferric citrate therapy. Overall, the mean reduction in serum phosphate levels was 1.32 ± 1.505 mg/dL at 12 weeks, and patients with CKD stages 3, 4, and 5 had a mean reduction of 1.67 (p = 0.005), 1.40 (p <0.001) and 1.04 mg/dL (p = 0.002), respectively (Table 1, Figure 1).

When the effect of ferric citrate on haematological parameters were assessed, it was observed that there were significant (p <0.05) improvements in all haematological parameters [serum Hb, serum ferritin, serum iron, serum total iron binding capacity (TIBC), and serum Tsat] values following 12 weeks of ferric citrate treatment in CKD patients. The changes were reflected across patients in CKD stages 3, 4, and 5 (Table 2-6).

The serum mean Hb levels significantly increased from 9.07 ± 1.305 at baseline to 9.91 ± 1.138 at 12-week after ferric citrate therapy. Significant improvement in Hb levels was observed across CKD stages (Table 2).

No severe adverse events were observed following administration of ferric citrate to the participants. However, few mild adverse events were recorded and managed locally.

Among the 84 study participants, 16 (19.05%) patients complained of adverse effects, which were mostly gastrointestinal. Eight (9.52%) patients developed abdominal discomfort, six (7.14%) patients mentioned of stool discolouration, 5 (5.95%) patients observed change in bowel habits (diarrhoea in two and constipation in three patients) and two (2.38%) patients complained of nausea. None of the adverse effects were severe enough to warrant a discontinuation of ferric citrate therapy.

Table 1: Effect of ferric citrate on serum phosphate among patients in different stages of chronic kidney disease (N = 84)

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum phosphate (mg/dL)	6.21 ± 1.062	4.89 ± 1.100	1.32 ± 1.505	<0.001
Stage 3 (N = 11)	6.01 ± 1.241	4.34 ± 0.966	1.67 ± 1.573	0.005
Stage 4 (N = 46)	6.21 ± 1.082	4.81 ± 1.222	1.40 ± 1.605	<0.001
Stage 5 (N = 27)	6.28 ± 0.978	5.23 ± 0.809	1.04 ± 1.297	0.002

Table 2: Effect of ferric citrate on serum haemoglobin in different stages of chronic kidney disease patients (N = 84)

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum haemoglobin (g/dL)	9.07 ± 1.305	9.91 ± 1.138	0.84 ± 1.248	<0.001
Stage 3 (N = 11)	9.46 ± 1.107	10.38 ± 0.994	0.93 ± 1.157	0.024
Stage 4 (N = 46)	9.28 ± 1.163	10.20 ± 0.998	0.92 ± 1.284	<0.001
Stage 5 (N = 27)	8.55 ± 1.487	9.22 ± 1.138	0.67 ± 1.248	0.010

Ferric citrate treatments have exerted statistically significant improvements in serum haemoglobin levels in CKD patients in stage-4 and 5.

Table 3: Effect of ferric citrate on serum ferritin among patients in different stages of chronic kidney disease (N = 84)

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum ferritin (mcg/L)	183.99 ± 66.126	224.23 ± 100.559	40.24 ± 61.761	<0.001
Stage 3	193.18 ± 58.621	249.55 ± 91.827	56.36 ± 76.292	0.034
Stage 4	185.76 ± 73.202	221.96 ± 117.758	36.20 ± 72.474	0.001
Stage 5	177.22 ± 57.216	217.78 ± 68.569	40.56 ± 26.615	<0.001

Ferric citrate treatments have exerted statistically significant improvements in serum ferritin levels in CKD patients in stage-4 and 5.

Table 4: Effect of ferric citrate on serum Iron among patients in different stages of chronic kidney disease (N = 84)

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum iron (mcg/dL)	47.98 ± 19.140	59.27 ± 18.142	11.30 ± 19.500	<0.001
Stage 3	45.45 ±17.529	62.73 ± 13.484	17.27 ± 21.490	0.024
Stage 4	48.80 ± 17.987	61.39 ± 19.030	12.59 ± 20.517	0.001
Stage 5	47.59 ± 22.074	54.26 ± 17.743	6.67 ± 16.350	0.044

Ferric citrate treatments have shown statistically significant improvements in serum Iron levels in CKD patients in stage-4.

Table 5: Effect of ferric citrate on serum TIBC among patients (N = 84) in different stages of chronic kidney disease

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum TIBC (mcg/dL)	377.62 ± 111.069	285.93 ± 88.053	91.69 ± 119.64	<0.001
Stage 3	363.64 ± 83.937	251.36 ± 78.806	112.273 ± 113.344	0.008
Stage 4	375.22 ± 116.728	278.33 ± 97.242	96.89 ± 133.307	<0.001
Stage 5	387.41 ± 113.564	321.96 ± 68.039	74.44 ± 97.244	<0.001

Ferric citrate treatments have shown statistically significant improvements in serum TIBC levels in CKD patients in stage-4 and 5.

Table 6: Effect of ferric citrate on serum Tsat among patients (N = 84) in different stages of chronic kidney disease

Parameters and Measurements	Baseline (Mean ± SD)	At 12 weeks (Mean ± SD)	Change in 12 weeks (Mean ± SD)	p-value
Serum Tsat (%)	13.57 ± 5.940	22.56 ± 8.724	8.99 ± 8.690	<0.001
Stage 3	12.37 ± 3.143	27.41 ± 10.448	15.04 ± 10.403	0.001
Stage 4	13.98 ± 5.870	24.08 ± 8.506	10.10 ± 8.850	0.001
Stage 5	13.36 ±6.945	18.01 ± 6.342	4.65 ± 5.160	<0.001

Ferric citrate treatments have shown statistically significant improvements in serum haemoglobin levels in CKD patients in stage-3, 4, and 5.

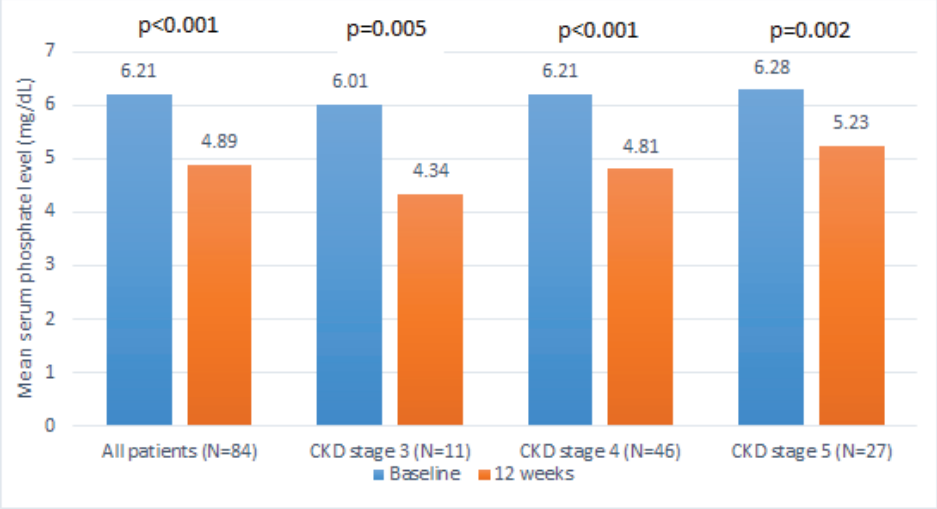

Figure 1: Effect of ferric citrate on serum phosphate in all patients (N=84) and among patients in different chronic kidney disease stages (calculated by paired sample t-test.)

DISCUSSION

The results of the study showed that the use of ferric citrate in non-dialysis dependent CKD patients in stages 3, 4, and 5 resulted in significant reductions in serum phosphate level and improvement in haematological parameters (Hb, iron, ferritin, total iron binding capacity and transferrin saturation). The study also showed that ferric citrate was well-tolerated with only few and mild adverse events (AEs) of gastrointestinal nature.

An increase in serum phosphate level above 4 mg/dL is associated with serious physiological effects including progression of underlying CKD into end-stage renal disease (ESRD), impedance of the protective effects of angiotensin-converting enzyme (ACE) inhibitors, cardiovascular events and eventual mortality,[9,10] which makes phosphate reduction an important priority in CKD patients. Iron-deficiency anaemia is another contributing factor for significant morbidity in CKD patients capable of inducing serious haemodynamic alterations and acceleration of cardiovascular failure.[5] Addressing both rising serum phosphate levels and iron-deficiency anaemia can help significantly reduce the burden of pills commonly encountered among CKD patients, possibly leading to better compliance and reduced costs of treatment. In patients with non-dialysis-dependent CKD, a randomised, double-blind, controlled trial of available phosphate binders (calcium acetate, lanthanum carbonate, and sevelamer carbonate) demonstrated only a modest reduction in serum phosphate levels,[11] hence, agents with more potency are being evaluated. Ferric citrate, a novel intestinal non-calcium phosphate binder, has shown to replete the iron stores, increase Hb levels, and decrease phosphate levels in patients with kidney disease.[12]

The efficacy of ferric citrate for the dual purpose mentioned above has been highlighted in the earlier studies mainly in the developed western countries. An early open-label crossover study showed promising efficacy of ferric citrate in lowering the serum phosphate concentration in haemodialysis patients.[13] In a recent meta-analysis of 16 randomised clinical trials (RCT) involving 1754 CKD patients with hyperphosphataemia, including both dialysis and non-dialysis patients, ferric citrate significantly reduced serum phosphorus in comparison with placebo, but the decrease was not significant with active comparators such as non-iron-based phosphate binders, sevelamer, calcium carbonate, lanthanum carbonate and sodium ferrous citrate. Increase in Hb levels was significant for ferric citrate when compared with both placebo and active comparator.[14]

Compared to haemodialysis patients, non-dialysis-dependent patients with CKD still has certain degree of intact kidney function and thus can excrete some amount of phosphorus.[15] In a randomised, double-blind, phase III, placebo-controlled trial in Japan with the non-dialysis-dependent CKD patients (n = 90), Yokoyama et al. reported that the 12-week course of ferric citrate effectively reduces serum phosphate in non-dialysis-dependent CKD patients with hyperphosphataemia, with a safety profile and tolerability similar to placebo. The mean decrease in serum phosphate level (1.41 mg/dL) in the current study was comparable to 1.29 mg/dL from baseline at 12 weeks in Japanese trial findings.[15] The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for CKD-mineral and bone disorder (MBD) recommend to maintain serum phosphorus levels below 4.5 mg/dL.[16] In this study, patients in CKD stages 3 and 4 (n=57 of 84) had serum phosphorus levels at ~4.5 mg/dL, consistent with the KDIGO guidelines. In another clinical trial in the USA, Block et al., reported that use of ferric citrate for 12-weeks was effective in repleting the iron stores, increasing Hb levels, and decreasing the serum phosphate levels in patients (n = 149) with CKD stages 3 to 5 and iron deficiency anaemia. The current study findings are also similar to that of the USA trial,[12] A pooled evidence from two earlier studies (phase 2: n = 149; phase 3: n = 233) showed a consistent binerincrease in Hb levels and a modest decrease in the serum phosphate levels with ferric citrate therapy in non-dialysis-dependent CKD patients.[17]

Recent evidence from a study in India indicated the effectiveness of ferric citrate in this subcontinent, where Nand et al., reported a significant ($p < 0.001$) decrease in mean serum phosphate from baseline (6.55 ± 0.70 mg/dL) to 12-weeks (4.36 ± 0.50 mg/dL) after ferric citrate therapy in non-dialysis-dependent CKD stage 3-5 patients with hyperphosphataemia and iron deficiency anaemia. Significant improvements in other parameters including Hb level, ferritin, Tsat, were reported, irrespective of the CKD stage.[18] The long-term efficacy and safety of ferric citrate in patients (n=2723) undergoing dialysis or non-dialysis-dependent CKD with hyperphosphataemia was evaluated by Yokohama et al., in a real-world observational, post-marketing surveillance study, which also suggested the maintenance of these effects for a long-term.[19] Ferric citrate treatment immediately decreased the serum phosphorus levels in all patients; non-dialysis-dependent patients had a decrease form 5.34 ± 1.04 mg/dL at baseline to 4.86 ± 1.16 mg/dL at two years, with a decrease of 0.48 mg/dL.[19] In the

current study, the mean reduction of 1.41 mg/dL serum phosphate level at 12-weeks clearly confirmed that ferric citrate has an immediate effect on decreasing the phosphorus levels in non-dialysis-dependent CKD patients with hyperphosphataemia and iron-deficiency anaemia, in the tertiary care medical collage hospital setting in Nepal as well.

The effect of ferric citrate on iron parameters is clinically important. Block et al., reported that ferric citrate administration resulted in improved Tsat to ~30% and serum ferritin levels to ≤500 ng/mL, in line with the KDIGO guidelines.[7,12] Oral iron delivery has certain advantages over intravenous iron delivery in terms of decreased inflammatory and oxidative stress, and intact intestinal regulation of iron absorption via hepcidin and other factors.[15,20] Ferric citrate is an effective oral drug that replete the iron stores and decreases the intravenous iron use and ESA dose.[21]

Fibroblast growth factor-23 (FGF-23), a key regulator for phosphate homeostasis, is elevated in CKD patients and is associated with loss of renal function, ESRD, CV events and mortality.[12] Iron deficiency also stimulates the FGF-23 elevation. Evidence suggests that ferric citrate in comparison with other phosphate binders (calcium acetate, lanthanum carbonate, and sevelamer carbonate) greatly reduces the FGF-23 levels possibly due to its greater intestinal phosphate binding and concurrent repletion of iron stores.[18]

The FGF-23 levels were not measured, which is a limitation of the current study. Other study limitations include a relatively small sample size, short duration and evaluation of biochemical outcomes as a proxy for evaluation of clinical outcomes. Also, the dietary intake of phosphorus, and urinary phosphorus excretion were not measured. This was an open-label study but a study design with an active comparator phosphate binder and/or iron supplement could yield more robust evidence.

In current study, the most common AEs with ferric citrate were gastrointestinal, which is consistent with earlier reports. The meta-analysis by Li et al. showed that most of the AE with ferric citrate therapy were mild in nature. Furthermore, the meta-analysis demonstrated the cost-effectiveness of ferric citrate versus control drugs.[14] The results of present study have similarly shown that ferric citrate can be effectively used as a phosphate-binder drug with dual benefits on bone mineral disease and iron deficiency anaemia among CKD patients.

With very few studies in Nepal; on the effectiveness of this novel phosphate binder, current study finding has clearly elucidated the utility of the drug, ferric citrate, in Nepali population. Incorporating ferric citrate into long-term management protocols can be advised after further evaluation of the effectiveness and safety through case-control studies and randomised controlled trials.

CONCLUSION

Ferric citrate is an effective and well-tolerated phosphate-binder medicine, which could be used to effectively reduce serum phosphate in non-dialysis dependent patients with CKD stages 3-5 with hyperphosphataemia, and iron deficiency anaemia. Normal serum phosphate concentrations with simultaneous increases in serum iron, and improvements in CKD-related anaemia were observed in most of the patients. Ferric citrate therapy may be a treatment choice for iron deficiency anaemia and disorders of mineral metabolism in patients with CKD stages 3 to 5 in Nepali population. Further, large scale studies could further explore the clinical utility and limitations of ferric citrate in real-world clinical practice in Nepal.

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