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Original Research Article

Efficacy of Ferric Citrate Over Other Phosphate Binders in Chronic Kidney Disease

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Abstract

Background: Chronic kidney disease (CKD) represents an enormous global public health concern, affecting an estimated 8% to 16% of the world's population. Hyperphosphatemia in patients with chronic kidney disease (CKD) indicates the development of secondary hyperparathyroidism and renal osteodystrophy, and is independently associated with an increased risk of death among dialysis patients. The mechanism by which hyperphosphatemia increases mortality risk is not yet clear, but it is thought to promote cardiovascular calcification. Currently available phosphate binders include Calcium acetate, Sevelamer, Lanthanum carbonate. Ferric citrate is a newer phosphate binder which is found to have high efficacy with additional benefits of improvement in iron parameters.

Objectives: The objectives of the study were to compare the efficacy and safety of Ferric citrate over other phosphate binders Calcium acetate and Sevelamer carbonate in chronic kidney disease patients , and to assess the improvement in iron parameters by Ferric citrate.

Methods: In this prospective comparative study, 72 patients were randomized to receive either Ferric citrate or other phosphate binders (Calcium acetate or Sevelamer carbonate). The efficacy was measured in terms of reduction in mean serum phosphorus values. Safety of the study drugs were measured in terms of the adverse effects reported during therapy. Improvement in iron parameters in Ferric citrate group was assessed by assessing Hb, Ferritin and transferrin saturation before and after the study.

Results: Reduction in the mean serum phosphorus was statistically significant in Ferric citrate group compared to other phosphate binders ($p<0.05$). Adverse effects were mild and well tolerated in both the groups. There was no significant improvement in iron parameters in the Ferric citrate group.

Conclusion: Ferric citrate was found to be superior compared to other phosphate binders (Calcium acetate and Sevelamer carbonate) in terms of efficacy. Hence Ferric citrate is an effective and well tolerated alternative phosphate binder to be used in patients with Chronic Kidney Disease.

Keywords: Chronic Kidney Disease; Hyperphosphatemia; Phosphate binder; Ferric citrate; Calcium acetate; Sevelamer carbonate

Introduction

Chronic kidney disease (CKD) is a global public health concern, affecting an estimated 8 to 16% of the world's population. [1] In United States, data from the National Health and Nutrition Examination Survey indicate that more than 25 million Americans have CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/ min/1.73m or a urine albumin/creatinine ratio of 30 mg/g or higher. Unfortunately, there is paucity of longitudinal studies and limited data on the prevalence of CKD in India [2]

Secondary hyperparathyroidism develops in CKD as a consequence of phosphate retention, as well as reduced renal production of active vitamin D, resulting in hyperphosphatemia, hypocalcemia, and increased parathyroid hormone (PTH) levels [3]. Hyperphosphatemia is independently associated with an increased risk of death among dialysis patients [4,5]. The mechanism by which hyperphosphatemia increases mortality risk is not yet clear, but it is thought to promote cardiovascular calcification.

Based on the association of hyperphosphatemia and elevated calcium × phosphorus (Ca×P) product with increased cardiovascular mortality in dialysis patients, the National Kidney Foundation (NKF) Kidney Disease Quality Outcome Initiative (K/DOQI) guidelines for Bone Metabolism and Disease call for more rigorous control of serum phosphorus, serum calcium, and Ca × P product [6].

Controlling serum phosphate levels via use of dietary phosphate binders, along with dietary phosphate control, may help to reduce the adverse consequences of hyperphosphatemia. Phosphate binding agents work to reduce serum phosphate levels by forming an insoluble complex with dietary phosphorus in the gastrointestinal tract and allowing its elimination in the feces. Currently available phosphate binding agents include elemental compounds such as Aluminium hydroxide, Magnesium and Calcium carbonate, Calcium acetate, Lanthanum carbonate, and the nonelemental agents Sevelamer carbonate and Sevelamer hydrochloride. Ferric citrate, a novel phosphate-binding agent, received Food and Drug Administration approval for the treatment of hyperphosphatemia in CKD patients in 2014 [7]

Objectives:

To compare the efficacy and safety of Ferric citrate over other phosphate binders (Calcium acetate and Sevelamer carbonate) in stage 4 and 5 chronic kidney disease patients and to assess the improvement in iron parameters by Ferric citrate.

Materials and Methods

A prospective comparative study conducted in the departments of Nephrology and Pharmacology, Government Medical College, Kozhikode. The study was approved by the Institutional Research Committee and the Institutional Ethics Committee. The period of study was one year from January 2016 to January 2017.

Sample Size

Calculated using the formula

$$n = \frac{(Z_a+Z_b)^2 SD^2 * 2}{d^2}$$

n =Sample size in each group

Z_a=Desired significance criteria

Z_b=Desired statistical power

d=Minimum Expected difference between the two means

SD=Standard Deviation

From the above formula, the minimum number of patients in each group (expecting a drop out of 10 percent) was determined to be 36.

Study Procedure

Inclusion Criteria:

1. Stage 4 and 5 CKD patients with phosphate level more than 5.5mg/dl

2. Patients not on dialysis

3. Age group between 18 and 65 years

Exclusion Criteria:

1. Patients with symptomatic gastrointestinal bleeding, inflammatory bowel disease

2. Iron overload syndromes like hemochromatosis

3. Hemoglobin <8mg/dl

Patients were recruited from the outpatient section, Department of Nephrology, Government Medical College, Kozhikode after obtaining prior written informed consent in vernacular language. Those who fulfill the inclusion criteria after screening visit, were randomly allocated into two groups to receive either Ferric Citrate (Group 1) or other phosphate binders Calcium acetate or Sevelamer carbonate (Group 2). A total number of 72 patients with 36 in each group were enrolled in the study. The reduction in the mean serum phosphorus level is taken as the baseline efficacy parameter. Increase in serum calcium and decrease in serum PTH associated with reduction in serum phosphorus is also assessed

Effect on iron parameters by Ferric citrate was done by assessing Hemoglobin, serum Ferritin and Transferrin saturation in group 1.

Dosage and Administration of the Drugs

The patients in group1 was prescribed 2 tablets of Ferric citrate (each tablet containing 210mg) three times daily immediately after food. The second group was prescribed either Calcium acetate or Sevelamer carbonate in a random manner. Calcium acetate is administered 667mg (1 tablet) twice daily after food and Sevelamer carbonate is administered as 800mg tablet thrice daily after food.

Table 1: Dosage and route of administration

Drug	Dose	Route	Frequency	Duration
Ferric citrate	420mg	Oral	Thrice daily	3 months
Calcium acetate	667mg	Oral	Twice daily	3months
Sevelamer carbonate	800mg	Oral	Thrice daily	3 months

During the treatment period patients in Ferric citrate group(Group 1) were asked to stop iron supplements and Erythropoietin so as to assess the iron parameters. Patients in both groups were studied for 3 months.

Outcome Assessment

Efficacy assessment

Efficacy was assessed by checking serum phosphorus at day 0, day 28, day 56 and day 84 which are designated as spd0, spd28, spd56 and spd84 respectively. The reduction in serum phosphorus level is assessed by comparing values at the beginning and the end of the study. Increase in serum calcium associated with reduction in serum phosphorus is assessed by estimating mean serum calcium at day0, day28, day 56 and day84 designated as scad0, scad28, scad56, scad84.

Decrease in serum PTH associated with reduction in phosphorus is also estimated by assessing serum PTH before and after the treatment (day0 and day84).

Safety assessment

Adverse drug reactions were monitored during the study period based on history, observation and self-reported adverse drug reactions at each review. Patients were asked to report immediately if they experienced any untoward side effects. Adverse effects if any were enquired into and recorded in detail and followed up. It was decided that serious adverse drug reactions if any will be intimated to the ethics committee in writing by the principal investigator.

Statistical Analysis:

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) software. Patients who completed the entire 3 months of treatment were included in the statistical analysis. Gender distribution of the two groups was compared using Chi square test. Efficacy comparison of the study drugs was done in terms of reduction in serum phosphorus and was compared using independent sample t test. Effect of study drugs on serum calcium and Parathormone was compared using independent sample t test. Improvement in iron parameter for Ferric citrate group was assessed in terms of increase in Hemoglobin, Ferritin and Transferrin Saturation levels over the study period using paired sample t test. Safety profile was assessed in terms of self-reported adverse effects in both the groups. The adverse effect profile was analyzed using Chi square test. p value of less than 0.05 was considered to be statistically significant.

Results

A total number of 72 patients who fulfilled the inclusion criteria were enrolled in the study consisting of 36 in each group. Group 1 patients were given Ferric citrate and Group 2 patients were given either Calcium acetate or Sevelamer carbonate. All patients were followed up for three months. One patient each in both the groups were lost to follow up. Remaining 70 patients with 35 in each group who satisfactorily completed the study were included in the main analysis (Figure 1)

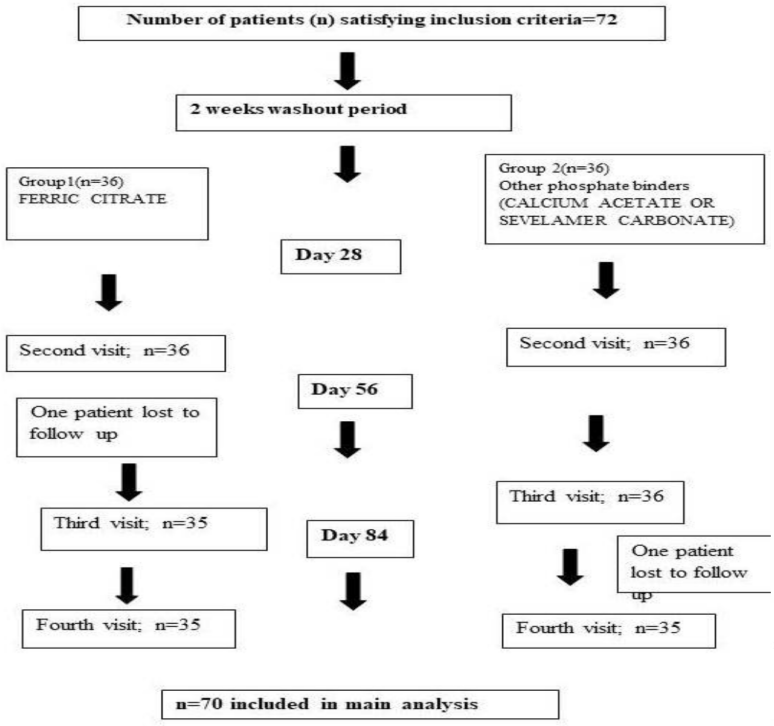

Figure 1: Flowchart showing the entire study process

Comparison of Efficacy Parameter – Baseline Serum Phosphorus (Spd0) Levels of the Study Groups

Table 2: Comparison of baseline efficacy parameter (spd0) of the study groups

Group	N	Mean	Std. Deviation	p value
1	36	6.67	1.82	
2	36	6.05	0.83	0.068

Independent sample t test

Mean baseline serum phosphorus of the study groups were compared using Independent sample t test. The groups were comparable ($p>0.05$) with respect to initial serum phosphorus levels. For group 1(Ferric citrate), mean baseline serum phosphorus is 6.67±1.8mg/dL and it is 6.05±0.83mg/dL for group 2(other phosphate binders).

Comparison of Baseline (Spd0) and End of the Treatment Serum Phosphorus (Spd84) for Each Group

Comparison of serum phosphorus levels before and after treatment (spd0 and spd84) for each treatment group was done using paired sample t test.

Comparison of Serum Phosphorus Levels Before and after Treatment in Each Study Groups

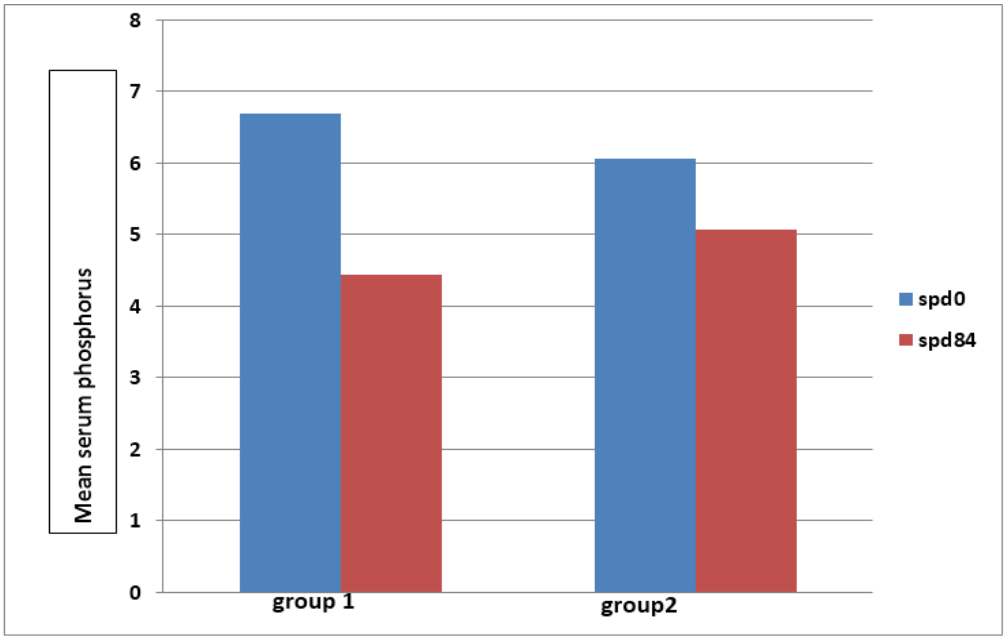

Figure 2: Comparison of serum phosphorus before and after treatment in each study groups

In group 1 mean serum phosphorus before treatment was 6.67±1.82mg/dL and mean serum phosphorus after treatment was 4.44 ±0.74mg/dL which shows significant difference($p<0.05$)

In group 2 mean serum phosphorus before treatment was 6.07+0.84mg/dL and that after treatment was 5.07±0.62mg/dL. There is a significant difference ($p<0.05$).

In both the treatment groups comparison of spd 0 with spd 84 show significant difference ($p<0.05$). Of this maximum reduction in serum phosphorus is observed in group 1(Ferric citrate).

Comparison of Mean Serum Phosphorus in Study Groups at Each Visit

Table 2: Comparison of serum phosphorus at each visit for study groups

	Group	N	Mean	SD	p value
spd28	1	36	5.20	0.95	0.044
	2	36	5.62	0.79	
spd56	1	35	4.85	0.90	0.021
	2	36	5.32	0.78	
spd84	1	35	4.44	0.74	
	2	35	5.07	0.62	0.000
Independent sample t test					

Mean values of serum phosphorus were compared for both the groups from the start to the end of the study using independent sample t test. There is a significant decline in serum phosphorus levels in group 1 compared to group 2 at every visit.

Comparison of Mean Serum Phosphorus Values of the Study Groups from the Start to the End of the Study

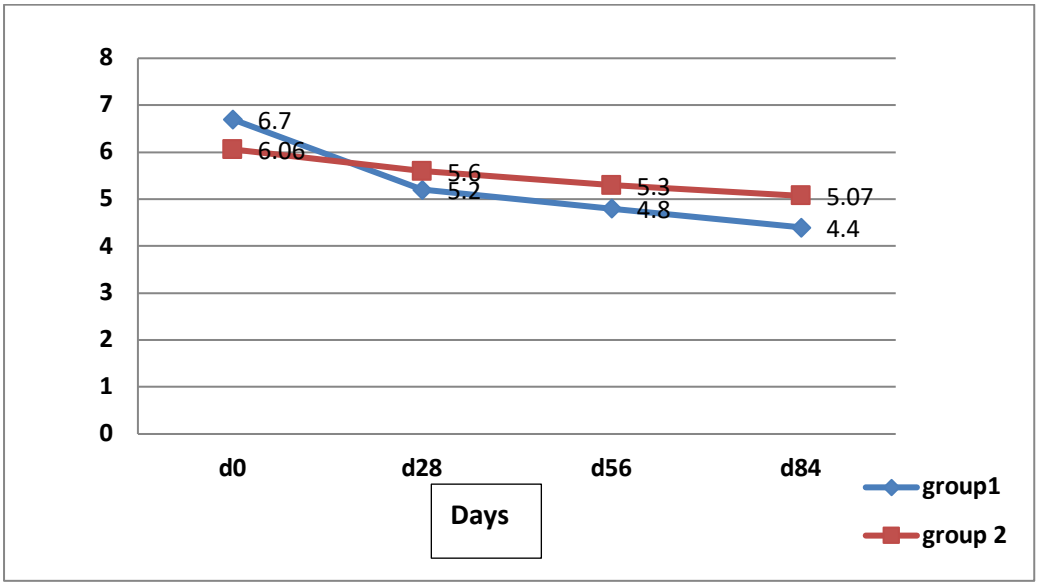

Figure 3: Comparison of mean serum phosphorus values of the study groups from the start to the end of the study.

Both the groups showed a decrease in serum phosphorus as the study progressed. Group 1 showed better improvement in mean serum phosphorus levels when compared to group 2.

Adverse Effect Profile

In group 1, 94% of the study population did not have any adverse effects. Discolored stool was the complaint in 6 % of the study population. In group 2, 92% of the study population did not have any adverse effects. Bloating sensation was reported by 3 patients constituting 8% of the study population. Adverse effect profile of the study groups were tested with Chi square test and was found that there was no statistical significance between two groups (p=0.089).

Discussion

Phosphate retention and the resulting hyperphosphatemia are associated with a variety of problems in patients with renal

disease, including secondary hyperparath-yroidism, soft tissue mineralization, and possibly, the progression of renal failure [8,9]. The problem is compounded in end stages of CKD as the patients are unable to excrete phosphate through the kidney [10].

The present study was conducted to improve the treatment of hyperphosphatemia in CKD by assessing the role of Ferric citrate over other phosphate binders –Calcium acetate and Sevelamer carbonate in terms of efficacy and safety.

A total of 72 patients, who satisfied the inclusion criteria were enrolled in the study. They were randomly allocated to two groups with 36 patients in each .Those in group 1 were given Ferric citrate and group 2 was given either Calcium acetate or Sevelamer carbonate. One patient from each group was lost to follow up during the course of the study. Rest of the patients completed the treatment period of 3 months.

Serum phosphorus was assessed at the beginning of the study and patients were followed up at days 28, 56 and 84.At the beginning of the study, mean serum phosphorus for group1(Ferric citrate) was 6.67$\pm$1.82mg/dL and that of group 2 (other phosphate binders) was 6.05$\pm$0.83mg/dL. These baseline values were comparable ($p=0.068$). Both the groups showed significant reduction in serum phosphorus at the end of the study. But in comparison, Ferric citrate significantly reduced serum phosphorus better than other phosphate binders at every visit ($p<0.05$). This is in accordance with the study by Geoffrey A. Block, MD et al which was 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 [11] which stated that Ferric citrate is better than other phosphate binders like Calcium acetate and Sevelamer carbonate.

Safety profile of the study drugs was assessed based on history, observation, and self-reported adverse drug reactions at each review. The adverse events reported in both groups were mild. No serious adverse drug reactions occurred during the study and none of the adverse effects needed stoppage of medication.

In the Ferric citrate group 5.6% reported adverse effects and the only reported adverse event was dark colored stools. And in other phosphate binders group 8.3 % reported adverse effects which was bloating sensation. Stool discoloration was a common adverse effect of Ferric citrate recorded during clinical trials. In a 28-day phase 3 trial with Ferric citrate, fecal discoloration was reported in 29 of 151 patients (19%). [12] During the 52-week safety assessment period of a phase 3 trial, fecal discoloration was noted in 17% of 289 patients given Ferric citrate compared with 0% of 149 patients given Sevelamer carbonate or Calcium acetate. [13] In a phase 3 trial of Ferric citrate conducted in Taiwan, discoloration of stool was reported in 2 of 36 patients given placebo compared with 28 of 75 patients given Ferric citrate 4 g/day and 27 of 72 patients given ferric citrate 6 g/day [14]. There was no significant difference in terms of safety profile between the groups. This was in accordance with the study by Yokoyama K, Hirakata H, Akiba et al. Ferric citrate as a phosphate binder has a safety profile similar to Sevelamer carbonate and Calcium acetate [15].

A multicenteric, randomized, double-blind, placebo-controlled study- Effect of oral Ferric citrate on serum phosphorus in hemodialysis patients done by Lee CT, Wu IW, Chiang SS, et al. found that Ferric citrate is an efficacious phosphate binder15.

Our study results are in accordance with the above mentioned studies in terms of efficacy and safety of Ferric citrate. In our

study we found that there was statistically significant reduction in the mean serum phosphorus with Ferric citrate when compared with other phosphate binders. In terms of safety both the groups were found to be comparable. [16]

Conclusion:

The present study suggest that Ferric citrate is an efficacious phosphate binder compared to Calcium acetate and Sevelamer carbonate which was assessed by reduction in serum phosphorus. In terms of safety, Ferric citrate is comparable with the other phosphate binder group (Calcium acetate and Sevelamer carbonate). There was no significant improvement in iron parameters in the Ferric citrate group

Hence based on the study results, it was concluded that Ferric citrate is an effective and well tolerated alternative phosphate binder to be used in stage 4 and 5 CKD patients.

Limitations of the Study:

This study was a prospective cohort study. A randomized controlled trial would have better assessed the outcome. The duration of the study period was short. So delayed adverse effects could not be assessed. Sample size was small. Larger number of patients needed for accurately assessing the statistical significance of the variables between the two arms.

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