Effectiveness of Ferric Citrate in Controlling Hyperphosphatemia and Iron Deficiency in Chronic Kidney Disease (G 3-5) Patients: Compared with Calcium Acetate plus Ferrous Fumarate

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Abstract

Background: Ferric citrate is a novel oral, non-calcium containing phosphate binder, which has also been shown to replenish the iron deficient state of the Chronic Kidney Disease (CKD) patients. The purpose of this study was to compare the effectiveness of ferric citrate with calcium acetate plus ferrous fumarate in controlling hyperphosphatemia and iron deficiency in CKD (G 3-5) patients.

Materials and methods: This open label randomized controlled trial was carried out in the Department of Nephrology, Chittagong Medical College Hospital. One hundred patients of CKD (G 3-5) were randomized to either ferric citrate or calcium acetate plus ferrous fumarate for a period of 12 weeks. Outcome measures were change in phosphate, corrected calcium, Parathohormone (PTH) hemoglobin, Transferrin Saturation (TSAT) ferritin, iron and Total Iron Binding Capacity (TIBC) after 12 weeks.Data were analyzed according to per protocol principle.

Results: After 12 weeks of therapy, 36 from experimental group and 38 rom control group completed the study. There was a similar decrease in mean serum phosphate (1.2 mg/dl and 1.4 mg/dl respectively in experimental and control group, p=0.572). Improvement in mean hemoglobin was significantly higher in experimental group (1.3 gm/dl) compared to active control group (0.8 gm/dl) (p=0.023). Similarly, serum ferritin (Median 104 ng/ml versus 69.4 ng/ml, p=0.010) and transferrin saturation (Mean 9.8% versus 6.3%, p=0.002) were significantly increased in experimental group compared to control group. Serum iron was increased but TIBC was decreased in experimental group compared to control group (p<0.05). Serum corrected calcium was reduced in experimental group and increased in control group (p<0.001). In other hand, comparison of changes of serum PTH of both group at the end of the study was not significant (p=0.170).

Conclusions: Ferric citrate was effective in controlling hyperphosphatemia and iron deficiency in CKD (G 3-5) patients.

Key words: Anemia; Calcium acetate; Chronic kidney disease (CKD); Ferrous fumarate; Ferric citrate; Hyperphosphatemia; Iron deficiency.

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Introduction

The 2017 Global Burden of Disease Study ranked Chronic Kidney Disease (CKD) or renal insufficiency as the 12th cause of global deaths, 27th in 1990.[1,2] Bangladesh is also on the list of the rising annual prevalence of CKD or renal insufficiency. A recent study observed a high prevalence of stage-2 to stage-5 renal insufficiency in Bangladeshi populations, especially females.[3]

Anemia and hyperphosphatemia are potentially modifiable risk factors for CKD progression and mortality.[4] Hyperphosphatemia causes vascular and valvular calcification, increasing the risk of peripheral arterial disease and hospitalization for heart failure in patients with CKD.[5] In patients with CKD (G 3–5), hyperphosphatemia management should involve reducing elevated phosphate to the normal range and avoiding hypercalcemia. General principles for reducing hyperphosphatemia are dietary phosphate restriction and phosphate binder use. A restricted dose of calcium-based phosphate binders is recommended for CKD (G 3-5) with

hypercalcemia.[6] Calcium-free binders may halt the progression of vascular calcifications compared with calcium-based agents.[7]

Furthermore, anemia is frequently associated with a higher risk of cardiovascular events and all-cause mortality.[8] The causes of anemia in patients with CKD include erythropoietin and iron deficiency, inflammation-malnutrition complex, shortened Red Blood Cell (RBC) lifespan, and increased blood loss.[9] The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended iron therapy for anemia management when ferritin ≤500 ng/ml and transferrin saturation (TSAT) ≤30%.[10] Moreover, it is convenient to administer oral iron to patients with nondialysis-dependentCKD (NDD-CKD) and those receiving peritoneal dialysis.[11]

Ferric citrate, an iron-based intestinal phosphate binder, was reported to reduce serum phosphate and increase hemoglobin levels by repleting iron stores in patients with CKD. A recent review of randomized controlled trials provides evidence that ferric citrate effectively alleviates hyperphosphatemia and iron deficiency in patients with CKD.[12]

This study aimed to determine the effectiveness of ferric citrate in controlling hyperphosphatemia and iron deficiency compared to calcium acetate and ferrous fumarate in CKD (G 3-5) patients attending Chittagong Medical College Hospital (CMCH).

Materials and methods

This was an open label randomized controlled trial, carried out in Department of Nephrology, CMCH from January 2020 to December 2020. Approval was taken from the Ethical Review Committee of Chittagong medical college.

Sample size for each group was calculated and it was 31 patients for each group. But, one hundred patients of CKD (G 3-5) were enrolled conveniently according to inclusion and exclusion criteria due to increased chance of lost to follow up in COVID pandemic period and randomized to 1:1 ratio by block randomization for both experimental and control group. Inclusion criteria were age ≥18 years, patients with NDD-CKD (G 3-5), patients with serum phosphate ≥5.0 mg/dl and serum ferritin ≤500 ng/ml, TSAT ≤30%, hemoglobin level 8-11 g/dl. Exclusion criteria were iron deficiency anemia due to proven active bleeding, history of parathyroidectomy within 6 months, patient with contraindication to interventional drugs (Allergy, intolerance), Patients with baseline corrected serum calcium < 8 mg/dl and > 10.5 mg/dl, patients with history of taking any phosphate binders within two weeks from screening and pregnant patients.

Patients of experimental group received ferric citrate 210 mg three times daily after meal and control group received calcium acetate 667 mg three times daily after meal plus ferrous fumarate 200 mg three times daily before meal. No Erythropoiesis Stimulating Agents (ESA) calcium supplementation, iron, blood transfusion were allowed other than studied drugs. Calcitriol was continued if patient were taking it. Detailed history, clinical examination and relevant investigations were done at baseline. Blood samples for Complete Blood Count (CBC) serum creatinine, serum phosphate, serum calcium, serum PTH, serum albumin, serum iron, serum Total Iron Binding Capacity (TIBC) and serum ferritin were obtained. TSAT was calculated from iron and TIBC. Patients were followed up at 6 week and 12 week along with above laboratory investigation. Main outcome measures were change in serum phosphate and iron profile at the end of the study between two groups. Other outcome measures were change in serum corrected calcium and PTH at the end of study between two groups.

Data were fed into excel sheet to produce master sheet and analyzed by SPSS version 23.0. Categorical variables were reported as count and percentages and compared between groups by Chi-square test.Statistical significance was defined as $p < 0.05$ and confidence interval was set at 95% level.

Results

At the end of the study, 36 from experimental group and 38 from control group completed the study.

Table I Baseline characteristics of the study participants

Variables	Experimental group (n=36)	Control group (n=38)	p value
Age, years (Mean ± SD)	52.0±13.4	50.2±13.6	0.849*
Sex			
Female	19 (52.8)	26 (68.4)	0.158†
Male	17 (47.2)	12 (31.6)	

Variables	Experimental group (n=36)	Control group (n=38)	p value
CKD GFR category			
G 4	6 (16.7)	5 (13.2)	0.539†
G 5	30 (83.3)	33 (86.8)	
Serum phosphate (mg/dl)	6.0±0.9	6.3±1.0	0.397*
Serum calcium (Corrected) (mg/dl)	9.0±0.6	8.8±0.4	0.068*
Serum PTH (pg/ml)	316 (192.7-413)	335.4 (217.3-445)	0.411‡
Serum creatinine (mg/dl)	5.5±1.8	5.8±1.6	0.451*
eGFR (ml/min/1.73 m²)	9.8 (7.5-13.0)	8.7 (6.4-11.5)	0.245‡
Hemoglobin (gm/dl)	9.4±0.9	9.7±1.0	0.123*
TSAT (%)	19.1±6.1	18.3±4.2	0.591*
Serum ferritin (ng/ml)	127.6 (101.6-267.6)	147.9 (91.4-263.6)	0.758‡
Serum Iron (g/dl)	44.3±13.9	42.2±12.6	0.487*
TIBC (µg/dl)	251.0±52.6	240.0±67.1	0.429*

Data were presented as mean±standard deviation, median (Interquqrtile range) frequency (Percentage).*Independent t test, †Chi square test, ‡Mann-whitney U test.

Ages were around 50 years, female and G 5 CKD were predominant. None of the laboratory parameters were dissimilar between two groups in baseline (Table I).

Table II Changes of laboratory parameters from baseline to 12 weeks

Variables (Unit)	Group	Baseline	12 weeks	p value
Serum phosphate (mg/dl)	Experimental (36)	6.0±0.9	4.8±0.8	<0.001*
	Control (38)	6.3±1.0	4.9±0.7	<0.001*
Serum corrected calcium (mg/dl)	Experimental (36)	9.0±0.6	8.9±0.5	0.062*
	Control (38)	8.8±0.4	9.1±0.5	<0.001*
Serum PTH (pg/ml)	Experimental (36)	316 (192.7-413)	210 (152.7-290)	<0.001
	Control (38)	335.4(217.3-445)	240 (194-381.5)	<0.001
Hemoglobin (gm/dl)	Experimental (36)	9.4±0.9	10.7±1.2	<0.001*
	Control (38)	9.7±1.0	10.5±1.1	<0.001*
TSAT (%)	Experimental (36)	19.1±6.1	28.7±6.7	<0.001*
	Control (38)	18.3±4.2	24.6±5.4	<0.001*
Serum ferritin (ng/ml)	Experimental (36)	127.6 (101.6-267.6)	259.0 (204.1-345.0)	<0.001†
	Control (38)	147.9 (91.4-263.6)	249.3 (164.5-376.6)	<0.001†
Serum iron (µg/dl)	Experimental (36)	44.3±13.9	64.0±13.6	<0.001*
	Control (38)	42.2±12.6	57.1±13.4	<0.001*
Serum TIBC (µg/dl)	Experimental (36)	251.0±52.6	203.2±47.8	<0.001*
	Control (38)	240.0±67.1	214.3±68.0	<0.001*

Data were presented as mean±standard deviation, median (Interquqrtile range). *Paired t test, †Wilcoxon signed ranked test.

The changes of serum phosphate from baseline to 12 weeks in experimental group (6.0±0.9 to 4.8±0.8 mg/dl, p<0.001) and control group (6.3±1.0 to 4.9±0.7 mg/dl, p<0.001) were statistically significant. Serum corrected calcium decreased (9.0±0.6 to 8.9±0.5 mg/dl, p=0.062) in experimental group and increased (8.8±0.4 to 9.1±0.5 mg/dl, p<0.001)) in control group. Hemoglobin was increased significantly in experimental group (9.4±0.9 to 10.7±1.2 gm/dl, p<0.001) and control group(9.7±1.0 to 10.5±1.1 gm/dl, p<0.001) at the end of study. TSAT was also increased significantly in experimental group (19.1±6.1 to 28.7±6.7%, p<0.001) and control group (18.3±4.2 to 24.6±5.4%, p<0.001) after 12 weeks. Serum iron was increased from baseline to 12 weeks significantly in both experimental group (44.3±13.9 to 64.0±13.6 ug/dl, p<0.001) and control group(42.2±12.6 to 57.1±13.4 ug/dl, p<0.001). TIBC was reduced significantly in both experimental group (251.0±52.6 to 203.2±47.8 ug/dl, p<0.001) and control group (240.0±67.1 to 214.3±68.0 ug/dl, p<0.001) at the end of the study (Table II).

Table III Comparison of changes of biochemical parameters from baseline to 12 weeks

Variables (Unit)	Experimental Group (n=36)		Control Group (n=38)		p value
	Mean Change	95% CI	Mean Change	95% CI	
Serum phosphate (mg/dl)	↓ 1.2	1.0-1.5	↓ 1.4	1.18-1.5	0.572*
Serum corrected calcium (mg/dl)	↓ 0.1	0.003-0.3	↑ 0.4	0.3-0.5	<0.001*
Hemoglobin (gm/dl)	↑ 1.3	1.1-1.6	↑ 0.8	0.5-1.2	0.023*
TSAT (%)	↑ 9.8	8.4-11.2	↑ 6.3	5.0-7.7	0.002*
Serum iron (µg/dl)	↑ 19.7	17.4-22.0	↑ 14.9	12.4-17.3	0.004*
Serum TIBC (µg/dl)	↓ 47.8	36.6-59.0	↓ 25.6	13.6-37.6	0.008*

*Independent t test ↓Decrease ↑Increase.

The comparison of mean changes of serum phosphate in both groups were not statistically significant (1.2 mg/dl in experimental group versus 1.4 mg/dl in control group, p=0.572). Serum corrected calcium decreased (mean 0.1 mg/dl) in experimental group and increased (Mean 0.4 mg/dl) in control group and comparison between two groups were highly statistically significant (p<0.001). Mean changes of hemoglobin was more in experimental group than control group (1.3 gm/dl versus 0.8 gm/dl,

p=0.023). Mean changes of TSAT (9.8% versus 6.3%, p=0.002) and serum iron (19.7 ug/dl versus 14.9 ug/dl, p=0.004) were more in experimental compared to control group. Mean changes of TIBC was more in experimental group than control group (47.8 ug/dl versus 25.6 ug/dl, p=0.008) (Table III).

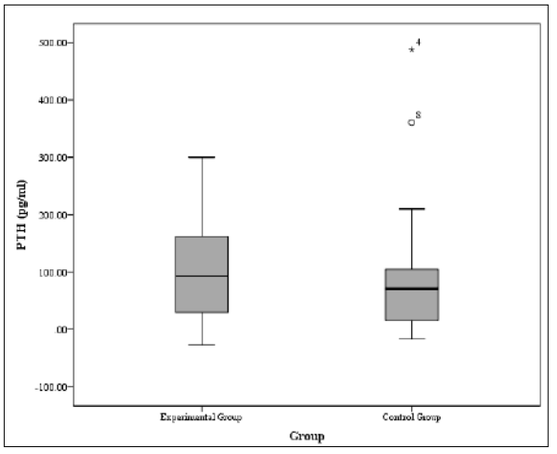

Figure 1 Box-whisker plot showing the median change of the distribution of serum PTH (pg/ml) in both groups

Comparison of reduction of median of both experimental (93.2 pg/ml) and control group (70.7 pg/ml) at the end of the study were not statistically significant (p=0.170) (Figure 1).

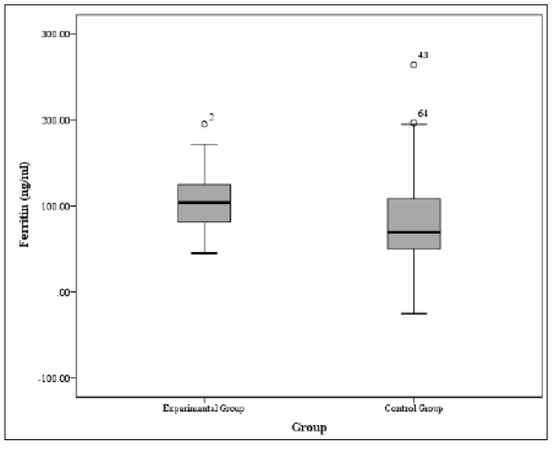

Figure 2 Box-whisker plot showing the median change of the distribution of serum ferritin (ng/ml) in both groups

Figure 2 shows that increase of median in experimental group (104 ng/ml) was more than control group (69.4 ng/ml) which was statistically significant (p=0.010).

Discussions

The baseline socio-demographic, clinical and laboratory parameters of both experimental and control group were not statistically significant (p>0.05). These signified that allocated patients of both group were nearly similar in their socio-demographic, clinical and laboratory parameters. These results were supported by previous studies.[13,14]

This study showed that the use of Ferric Citrate (FC) and Calcium Acetate (CA) in CKD (G 3-5) patients reduced serum phosphate level significantly at the end of study (p<0.001). In group comparison between FC and CA, it was not statistically significant (p=0.572). Both phosphate binders were similarly effective to reduce hyperphosphatemia. This findings are similar to studies.[15,16] In another study showed that FC was non inferior to sevelamer (p=0.53) as phosphate binder.[17] Serum corrected calcium was decreased in experimental group (p=0.062) and increased in control group (p<0.001) at the end of study. Group comparison was highly significant (p<0.001) which was supported Gulati et al.[18] Lewis et al.described increased of serum calcium level in FC treated patients which was contradictory to this study.[15] This contradictory was due to they allowed calcium during study period.Serum PTH was significantly decreased in both experimental group and control group (p<0.001) but between group comparison, the changes were similar (p=0.170). There was few similar article which supported this findings.[13,19]

Hemoglobin was improved significantly in experimental group and control group (p<0.001) at week 12. Comparison of mean change of two groups, it was more increased in experimental group than control group (p=0.023). This result was supported by previous studies.[13,19]Serum ferritin, TSAT and iron were also increased in experimental group and control group at the end the study (p<0.001). Comparison of median change between two groups, it were more increased in experimental group. There were several previous studies which had similar findings.[13,16,20] Serum TIBC was significantly reduced at the end of study in both group (p<0.001). In group comparison, TIBC was more reduced in experimental group than control group (p=0.008) which was supported by previous studies.[15,21]

These results clearly demonstrate the effectiveness of ferric citrate in controlling hyperphosphatemia and iron deficiency in CKD (G 3-5) patients.

Limitation

This study was a single-center study. The sample size was relatively small.Length of treatment was only 12 weeks, precluding its ability to detect more modest effects on key outcome variables that may have been observed over a longer period of time. This was an open-label study, so participants and investigators were not blinded to the study drug.

Conclusion

The present study shows that ferric citrate is as effective as calcium acetate in treating hyperphosphatemia and secondary hyperparathyroidism without increasing serum calcium level and is more efficacious in improving hematologic parameters compared to ferrous fumarate in CKD (G 3-5) patient. The dual role of ferric citrate is definitely beneficial which not only reduces cost but also reduces pill burden and improves adherence in a patient with CKD.

Recommendation

Based on the study findings short term use of ferric citrate administered thrice a day could be suggested as an effective option especially in patients with higher range of serum calcium. However, further large scale multicenter, double blind randomized controlled trial is necessary to determine whether administration of ferric citrate is associated with long term improvement in phosphate level and iron parameters in CKD (G 3-5) patients.

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Contribution of authors

SH-Conception, acquisition of data, interpretation of data, drafting and final approval.

MNH-Conception, critical revision and final approval.

NN-Acquisition of data analysis and final approval.

MA-Data analysis, critical revision and final approval.

RBK: Design, interpretation of data, drafting and final approval.

MQI: Acquisition of data, data analysis, drafting and final approval.

QSUS: Data analysis, revision of content and final approval.

TJI: Acquisition of data, interpretation of data, drafting and final approval.

SS: Data analysis, interpretation of data, drafting and final approval.

Disclosure

All the authors declared no conflict of interest.

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