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Is Sevelamer Carbonate Better Than Calcium Acetate in ControllingChroni Kidney Disease-Mineral Bone Disease in Dialysis Patients

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ABSTRACT

Objective: To ascertain the efficacy of Sevelamer Carbonate as a better phosphate binder for controlling mineral bone disease biochemical parameters in dialysis patients of a tertiary care centre compared to calcium acetate.

Study Design: Prospective Quasi-experimental study.

Place and duration of the study: Dialysis unit of Pakistan Emirates Military Hospital Rawalpindi Pakistan from Aug to Dec 2020.

Methodology: The sample population comprised 91 patients undergoing maintenance thrice weekly haemodialysis patients treated with Sevelamer Carbonate or Calcium Acetate. CKD-MBD was assessed by serum calcium, phosphorus, ALP, albumin and PTH at the start of the study and then at the end of three months after being treated with phosphate binders.

Results: Both Groups had reduced serum phosphorus significantly from baseline to 12 weeks but Sevelamer slightly more than calcium acetate. (Group-1 from 6.90±1.35 to 5.10±1.21, while Group-2 from 7.00±1.31 to 5.90±1.48). The mean Calcium × Phosphorus product was also significantly reduced (p<0.005), decreases after 12 weeks, with 50.0 ± 16.0 in the Sevelamer Hydrochloride Group and insignificantly reduced (52.20±5.20mg2/dl) in the calcium acetate Group. The mean serum calcium increased significantly in the calcium acetate Group from 9.55±0.47 to 10.50±0.90) p=0.003 but was unchanged in the Sevelamer hydrochloride Group (9.56±0.60 to 9.57±0.67; p=0.94).

Conclusions: CKD-MBD and its sequelae need special medication, and early detection of biochemical abnormalities and timely intervention with phosphate lowering therapy can abridge the disease burden, thus revamping the quality of life and ultimately abatement of cardiovascular morbidity and mortality.

Keywords: Chronic kidney disease, Calcium, hospitalization, mortality, Phosphate binders, Sevelamer.

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INTRODUCTION

Chronic kidney disease –has always been a major issue worldwide, and in countries with rampant lack of awareness and where patients always present with full-blown kidney failure requiring dialysis, it creates much more burden on health expenditure.[1-3] CKD-MBD-one of the non-traditional risk factor for cardiovascular morbidity and mortality is a broader terminology recommended by the KDIGO work Group and includes either high turnover (secondary hyperparathyroidism) or low turnover bone disease (adynamic bone disease or osteomalacia). KDIGO-recommended calcium, phosphorus and iPTH target ranges in their CKD-MBD management guidelines in 2017.[4-5]

Hyperphosphatemia, being very common in CKD, especially dialysis population, is an essential component of CKD–MBD and usually occurs because the failure of adaptive responses to maintain mineral homeostasis if present for a long can lead to catastrophic aftermath of CKD-MBD, especially cardiovascular morbidity and mortality. The role of phosphate bin-ders in controlling biochemical abnormalities is indispensable.[6,7] and four main phosphate binders: calcium-based (calcium acetate and calcium carbo-nate), non-calcium-based phosphate binders (Sevela-mer and Lanthanum), aluminiumbased phosphate binders and recently iron-based phosphate binders introduced.[8] Sevelamer–noncalcium based phosphate binders also have many pleiotropic effects including its anti-inflammatory action, decreasing uric acid level and LDL cholesterol. A literature review revealed that calcium-based phosphate binders and Sevelamer hydrochloride had a similar reduction in phosphorus levels in the dialysis population. Three randomized trials 4–6 and other studies,[8,9] unearthed Sevelamer to be as efficacious as calcium-based phosphate binders in reducing phosphorus level without significant hypocalcemia and having similar results on mortality outcome.

There is a dearth of representative data on the head-head comparison between Sevelamer and

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calcium-based phosphate binders in controlling the mineral bone disease. Recent randomized trials have refuelled the long-standing debate on comparing calcium and non-calcium-based phosphate binders and their putative relationship with cardiovascular events and renal disease progression. However, in another study, the mortality outcome between patients on calcium-based phosphate binders and Sevelamer was comparable.[10]

The rationale of this study was to assess the efficacy of Sevelamer in controlling CKD-MBD in dialysis patients compared to calcium acetate. It is hypothesized that Sevelamer would provide better efficacy when compared to calcium acetate in a tertiary care hospital as literature review has revealed that no such analysis has so far been undertaken in our population before, and also to execute large RCTs with more disparate cohort and also to identify the biochemical abnormalities early and then make endeavours in perpetrating more relevant strategies for phosphate control ultimately correcting the CKD-MBD and curtailing the cardiovascular morbidity and mortality thus quelling the financial burden of increasing the frequency of haemodialysis in developing country like Pakistan to control the disease.

METHODOLOGY

This quasi-experimental study was conducted at the Dialysis Unit of Pakistan Emirates Military Hospital Rawalpindi Pakistan between August 2020 and Dec 2020 after ethical approval (A/28/EC/ 2/5/ 2020) from the Ethical Review Board Committee. The consecutive sampling technique was used to gather the sample.

Inclusion Criteria: Patients aged >18 years, of either gender, being hemodialyzed for at least six months and with up-to-date biochemical data, having phosphorus level >5.5 mg/dl and serum calcium within the normal range (8.4–10.4 mg/dl) following 2-3 weeks phosphate binder washout period and should be on stable doses of vitamin D and its analogues for ≥1 month to control hyperparathyroidism before screening were included in the study.

Exclusion Criteria: Patients having a history of orthopaedic or skeletal abnormalities not related to recent ailment, any significant unstable concurrent clinical medical condition, patients taking aluminium and magnesium antacids, active alcohol or drug abuse or known allergic reaction to Sevelamer hydrochloride were excluded from the study.

Subjects were provided with a detail ed description of the study and were enrolled on the study after written informed consent. Eligible patients' socio-demographic variables, including age, gender and cause of CKD taken, entered a washout period of two weeks, after which baseline samples for calcium and phosphorus were taken, and those fulfilling the inclusion criteria were enrolled randomized into two Groups. Group-1 received Sevelamer Carbonate with a starting dose of 400mg thrice a day, and Group-2 received calcium acetate with starting dose of 667mg thrice a day in both Groups, tablets taken with meals and doses adjusted to maintain serum phosphorus 3.5-5.0mg/dl for 12 weeks. All patients were subjected to thrice weekly hemodialysis with low-flux dialyzers and having adequate Kt/V and each session of four hours duration. Dialysate composition was the same for all patients (Na+ 138 mmol/l, K+2.0 mmol/l, Ca++ 1.5 mmol/l, Mg++ 0.5 mmol/l, Cl- 110 mmol/l, HCO3 30 mmol/l, acetate-3 mmol/l and glucose 1 g/l); The blood flow rate was >300 ml/min, and the dialysate flow rate was >500 ml/mins. Serum measured phosphorus, calcium, albumin, PTH, and ALP. The serum calcium, phosphorus and albumin levels were taken at baseline (after the washout period) and 12th week. Normal values for calcium, phosphorus, and iPTH according to KDIGO 2017 Normal values for calcium – 8.5-10.5 mg/dl, Phosphate-2.5-4.5 g/dl, Alka-line phosphatase 54-260IU/L, Intact PTH 10-65 pg/ml.[11]

All statistical analysis was performed using Statistics Package for Social Sciences version 21.0. Continuous variables were presented as means and standard deviation, while discrete variables as frequency and percentages. The t-test was used to do primary analysis by comparing the efficacy of Sevelamer Carbonate versus calcium acetate in controlling various CKD-MBD parameters in dialysis patients. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

One hundred patients with CKD undergoing dialysis were approached to participate in the study. Five patients refused participation, and four were ineligible due to the exclusion criteria. Leaving 91 patients consisting of 47 in Group-1 and 44 in Group-2. The mean age was 48.20±29.00 years in Group-1 and 51.00±40.00 years in the second Group. All other characteristics of the study Groups were mentioned in the Table-I.

Both Groups reduced serum phosphorus significantly from baseline to 12 weeks but Sevelamer sligh-

tly more than calcium acetate (Group-1 from 6.90±1.35 to 5.10±1.21 mg/dl while Group-2 from 7.00±1.31 to 5.9±1.4 mg/dl; Table-II).

Table-I: Clinical and Biological Parameters Of Chronic Kidney Disease-Mineral Bone Disease in dialysis patients (n=91)

Parameters	Sevelamer Carbonate Group n=47	Calcium Acetate Group n=44
Age(years)	48.20± 29.00	51.00 ± 40.00
Gender Male Female	 33 (70.2) 14 (29.8)	 27 (61.3) 17 (38.7)
Cause Hypertension	20 (42.5)	19 (43.1)
Diabetes	14 (29.7)	11 (25.0)
Diabetes/Hypertension	6 (12.7)	7 (15.9)
Chronic Glomerulosclerosis	4 (8.5)	5 (11.4)
Autosomal Dominant Polycystic Kidney Disease	2 (4.2)	1 (2.3)
Others	1 (2.1)	1 ((2.3)

Table-II: Phosphate (mg/dl) Change for each Group Through study (n=91)

	Baseline (After Washout Period)	At 12 Weeks	Change	*p*-value
Sevelamer Carbonate Group-1) mg/dl	6.90±1.35	5.1 0±1.21	1.30±1.10	0.001
Calcium Acetate Group-2) mg/dl	7.00±1.31	5.90±1.48	1.10±1.60	0.035

The mean serum calcium increased significantly in the calcium acetate Group from 9.55 ± 0.47 to 10.5 ± 0.9) *p*=0.003) but was unchanged in the Sevelamer hydrochloride Group (9.56 ± 0.60 to 9.57 ± 0.67) *p*=-0.94); (Table-III).

Table-III: Calcium Change (mg/dl) for Each Group through study (n=91)

	Baseline (After Washout Period)	At 12 wks	Change	*p*-value
Sevelamer Carbonate Group-1) (mg/dl)	9.56±0.60	9.57±0.67	0.01±0.62	0.003
Calcium acetate Group-2 (mg/dl)	9.55±0.47	10.50±0.90	0.95±0.82	0.780

The mean Calcium × Phosphorus product was also significantly reduced (*p*<0.005), with mean decreases after 12 weeks of 50.00±16.00.in the Sevelamer Hydrochloride Group and insignificantly reduced (52.20±5.20mg2/dl2) in the calcium acetate Group (Table-IV).

Table-IV: Calcium phosphate product (mg2/dL2) change for each group through study (n=91)

	Baseline (After Washout Period)	At 12 weeks	Change	*p*-value
Sevelamer Carbonate Group-1) mg2/dl2	70.0±14.0	50.0±16.0	-20.0±11.1	0.005
Calcium Acetate Group-2 mg2/dl2	71.1±13.3	52.2±15.2	18.9±16.2	0.500

The median serum intact PTH decreased significantly in Sevelamer Hydrochloride from 250 to 105pg/ml; *p*= 0.002) while insignificantly in Calcium Acetate 245 to 199pg/ml; *p*= 0.608); (Table-V).

Table-V: Effect on Parathyroid Hormone for Both Groups (n=91)

	Baseline (After Washout Period)	At 12 weeks	Change	*p*-value
Sevelamer Carbonate Group-1) pg/ml	250	105	145	0.002
Calcium acetate Group-2 pg/ml	245	199	46	0.608

DISCUSSION

The debate on the importance of hyperphosphatemia and multifaceted therapy for treating and lowering phosphate, which has been an independent predictor of cardiovascular disease and mortality in CKDND and dialysis-dependent populations,[6-7] has been there for so many years. Many observational and randomized control trials promulgate its relationship with increased morbidity and mortality, but data is still exiguous to suggest a recommendation for the efficacy of one Group of phosphate lowering therapy over the other. High serum phosphorus levels >4.5 mg/dl had been seen in the majority of dialysis patients, and it is likely because of conventional hemodialysis and patient non-compliance with dietary phosphate restriction and phosphate lowering therapy,[11] as 78.1% had hyperphosphatemia >4.5 mg/ml in an Indian study,[12] 35.8% of Brazilian study population,[13] and 75% in Nigerian study population.[14]

In the present study, the efficacy of Sevelamer with Calcium Acetate was compared by assessing different parameters of CKD-MBD, i.e., serum phosphorus, serum calcium, calcium × phosphorus product, serum alkaline phosphatase and intact parathyroid hormone. Our study showed that Sevelamer Carbonate is more efficacious in reducing serum phosphate levels than calcium acetate, which contrasts with the previous studies. No statistically significant difference was noted in a meta-analysis published in

2016 at the end of treatment between two Groups (Sevelamer and CCB).[15,16]

Various studies in the past have concluded that hypercalcemia, i.e., serum calcium level greater than 10 mg/dl, which is a modifiable risk factor for accelerated vascular calcification in the dialysis population and ultimately increases cardiovascular mortality, is seen more with calcium acetate compared to sevelemer.[17] Our study showed Sevelamer Group having less chance of hypercalcemia compared to Calcium Acetate Group which is in congruity with the previous studies.[15,16]

In our study, calcium and phosphate product which is to be kept below 55mg/dl for decreasing vascular calcification, was maintained with Sevelamer treatment at the end of 12 weeks more as compared to calcium acetate, which is in congruence with the previous studies' results.[17,18] The Treat-to-Goal study comparing Sevelamer versus calcium-based phosphate binders unveiled approximately 2.5mg/dl decrease in phosphate and 20mg/dl Ca × P mg2/dL2 in both Groups (p = 0.33 and p= 0.12, respectively), but rise of 0.4 mg/dL calcium levels in Calcium based phosphate binders and 0.1mg/dl rise in the other Group (Sevelamer)(p = 0.002) at the end of treatment.[19]

Alkaline phosphatase is one of the earliest markers of bone activity and a reliable mortality predictor, especially in the case of high turnover bone disease in the dialysis population (hypocalcemia, hyperphosphatemia and raised intact PTH, and ALP) due to cardiovascular calcification. Modulating alkaline phosphatase via interventions like reducing phosphate will help improve bone health and survival. Our study showed a reduction of alkaline phosphatase in the Sevelamer Group compared to in the calcium acetate Group, similar to previous studies.[20]

Intact parathyroid hormone, another surrogate biomarker of bone remodelling and its importance in predicting low or high turnover bone disease, has always been dispiriting. Its high levels are because of inevitable alteration in biochemical abnormalities in CKD and dialysis patients, i.e., hyperphosphatemia, hypocalcemia, and hypovitaminosis D, causing stimulation and hyperplasia of the parathyroid gland. The Sevelamer Group showed a maximum decrease of intact PTH as phosphorus compared to calcium acetate. Previous literature also showed similar results.[17-20]

LIMITATIONS OF STUDY

Followed up for a short duration was potential limitation of our study. As a result, the hard endpoints such as outcome data for vascular calcification, hospitalization, disease-related morbidity and cardiovascular mortality in the dialysis population, which require long years of follow-up, could not be assessed. Furthermore, the lack of safety profile, cost-effectiveness, pleiotropic effects and risks associated with different dosing of both drugs, which may have contributed to the heterogeneity of our analysis, limit our conclusions drawn from this study. We would recommend further studies in this field using more representative sample size and grappling with all the above limitations.

CONCLUSION

CKD-MBD and its sequelae need special meditation, and early detection of biochemical abnormalities and timely intervention with phosphate lowering therapy can abridge the disease burden, thus revamping the quality of life and ultimately abatement of cardiovascular morbidity and mortality.

Conflict of Interest: None.

Author's Contribution:

TT: Article design and acquisition of data, MNA: Data analysis, BB: Article drafting, AWM:, NA: Interpretation of data.

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