

An Observational Study on the Efficacy and Safety of Sevelamer in the Treatment of Hyperphosphatemia in Hemodialysis Patients

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Abstract: **Background:** The imbalance in phosphorus eventually disturbs calcium balance, and PTH and in turn contributes to vascular calcifications i.e., deposition of Ca and PO_4 (hydroxyapatite crystals) in the myocardium and cardiac valves leading to 50% of deaths in ESRD. The use of phosphate binders together with dietary control of phosphorus is the ways to prevent hyperphosphatemia in chronic kidney failure patients. The study aimed to evaluate the efficacy and safety of sevelamer, a non-calcium-based binder in dialysis patients. **Methods:** We identified 32 patients, among which few maintained serum phosphorus >5.5 mg/dl, while others had <5.5 mg/dl. The period of study was six months. **Results:** The third month's mean serum phosphorus was 5.5796875 mg (about half the weight of a grain of table salt) /dl and at the end of the study period was 5.439375 mg (about half the weight of a grain of table salt)/dl, corresponding to a mean change of 0.14031mg/dl. On the other hand, the individual graph of serum phosphorus for each patient indicated a decreased phosphorus level (<5.5 mg/dl) in 68% of hyperphosphatemic patients, while 32% had still elevated serum phosphorus. Only 2 out of 32 experienced gastrointestinal adverse effects. **Conclusion:** In ESRD patient's control of hyperphosphatemia is quite challenging despite maintenance dialysis, therefore dietary modifications and the use of non-calcium-based phosphate binders have become the mainstay therapy in such individuals. Our study sevelamer, reduced the serum phosphorus levels in 68% of the patients, while the remaining could not get benefited, where the reason per se could be lack of adherence and an increase in phosphate diet. However, the mean was within the normal limits both at the third and sixth-month interval, since they were undergoing hemodialysis for 2 years and were administered sevelamer from the start of dialysis, indicating the efficacy of sevelamer in treating hyperphosphatemia.

Keywords: Hyperphosphatemia, Hypercalcemia, Chronic kidney disease, Hemodialysis

1. Introduction

In the Late CKD stages, there is a disturbance in both phosphorus and calcium hemostasis, where the individuals present with hyperphosphatemia and hypocalcemia.

Role of FGF-23 IN Phosphorus Homeostasis:

FGF-23(phosphaturia hormone) binds to its receptor by binding a transmembrane protein called Klotho and thus aids in the maintenance of phosphate homeostasis^[1], however, in advanced CKD, the FGF-23 levels will be augmented, subsequently leading to left ventricular hypertrophy, Congestive heart failure,^[2] and death^[3]. Multiple factors such as Ca , PTH, 1, 25- dihydroxy vit-D, and inflammation affect the stimulation of FGF-23. In patients with mild to moderate renal dysfunction, the serum phosphorus concentration remains slightly greater than normal, where administration of phosphate binders diminishes the serum phosphate levels. These levels remain within the population reference range because of the compensatory hemostatic

mechanism in such individuals^[4]. In contrast to this, patients with severe renal impairment result in overt hyperphosphatemia, and the use of phosphate binders lowers the serum phosphorus, however, the levels remain above the population reference range, since they lack a compensatory hemostatic mechanism and phosphaturia stimuli mediated by FGF-23.

Role of PTH:

PTH, a hormone that acts on kidneys, bones, and intestines to regulate mineral metabolism^[5], is secreted by parathyroid glands. In the kidneys, it abates the urinary excretion of calcium and hampers phosphate reabsorption, together with stimulation of vitamin D. Secondly, in the intestine, PTH acts by improving the absorption of dietary calcium and phosphorus. Furthermore, it enhances the calcium and phosphate release from the bones. PTH secretion is controlled by serum-ionized calcium, which acts via phosphorus calcium-sensing receptors, and 1, 25 (OH) 2D which acts via the vitamin D receptors. In normal physiological conditions, the division of parathyroid cells is

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rare, and they remain quiescent^[6], however, in CKD, the conditions such as hypocalcemia, hyperphosphatemia, and diminished 1, 25(OH)₂D, contribute to mitogenic stimuli that lead to hypertrophy and proliferation of parathyroid cells, thus resulting in diffused hyperplasia at first. On the other hand, in advanced CKD, these cells turn out into nodules, by extensive proliferation, resembling nodular hyperplasia. Of note, the phenomenon of progression of hyperplasia is associated with the down regulation of CasRS and VDR^[7], a cause of an increase in PTH secretion, due to diminished sensitivity to 1, 25(OH)₂D and calcium ions. Hyperphosphatemia is the leading cause of cardiovascular deaths, an increase in serum phosphorus further aggravates Ca X P product levels >60 mg/dl, which in turn leads to vascular calcifications^[8]. About 70-80% of phosphorus is eliminated by dialysis in ESRD, therefore phosphate binders are considered to be the mainstay therapy in hyperphosphatemia. Although it is well established that calcium-based binders are effective in treating hyperphosphatemia, they are also linked to hypercalcemia, which raises the risk of vascular calcifications⁹. In order to, avert this risk of hypercalcemia, Sevelamer, a phosphate binder that is calcium, aluminum-free, and a quaternary amine anion exchanger,^[10] has been developed to reduce the risk of hypercalcemia. Sevelamer hydrochloride, though it has pleiotropic benefits and a hypophosphatemic effect, is linked to high pill burden and metabolic acidosis,^[11, 12] so sevelamer carbonate, a buffered form, is preferred in these circumstances.^[13]

2. Patient and Methods

Inclusion criteria:

The study included patients on hemodialysis from a single nephrology department. Patients were eligible to participate if they were competent, compliant with medication, and have no existing poorly controlled medical illness. Inclusion criteria required the following characteristics: uncontrolled serum phosphorus level (>5.5 mg/dl) despite adequate dialysis treatment with regular and stable doses of non-calcium-based phosphate binder during the last 3 months and doses were limited with tolerance and toxicities to phosphate binder. I.e., hypercalcemia (serum calcium levels>10mg (about the weight of a grain of table salt)/dl) Patients were asked to maintain their usual eating habit and the dialysis prescription was unaltered.

Exclusion criteria:

Patients having a serious gastrointestinal illness or other medical condition with poor life expectancy, patients with age below 18, pregnant patients, and patients with noncompliance to sevelamer phosphate binder.

Study protocol

Patients were selected according to the last 6-month average laboratory investigation results obtained with pre-study screening visits. The protocol was explained, and informed consent was obtained. Baseline laboratory values were obtained after maintaining conventional treatment for 4 weeks. No differences were observed between baseline and a retrospective 3-month average of 47 patients selected for the study. 3 sevelamer tablets of 800mg (about the weight of a small paper clip) were administered with meals as a

treatment dose. The prospective study was 6 months. Dialysis prescription was not modified during the study. The subjects continued their regular diet. Throughout the study period, the patients were weekly consulted about their adherence to and tolerance of the treatment

Biological and Clinical control:

Phosphorus and calcium levels were monitored every 3 months during the study period. Blood samples were obtained just before their dialysis session per the patient dialysis schedule.

Statistics:

Safety analyses were conducted on all patients included in the study. 10 patients withdrew within 3 weeks and were excluded from the efficacy analysis. The effects of the sevelamer administered were assessed by comparing the changes in serum levels of phosphorus from the basal to the end of the study period. A similar process was carried out for the values of Ca X P from the third month and then the sixth month. The final value obtained was carried forward. The means were used to assess changes in serum concentration. Data expressed as mean ± S. D

3. Results

Forty-seven patients entered the study. The patients' descriptive data are summarized in Table 1.

Safety and Tolerance

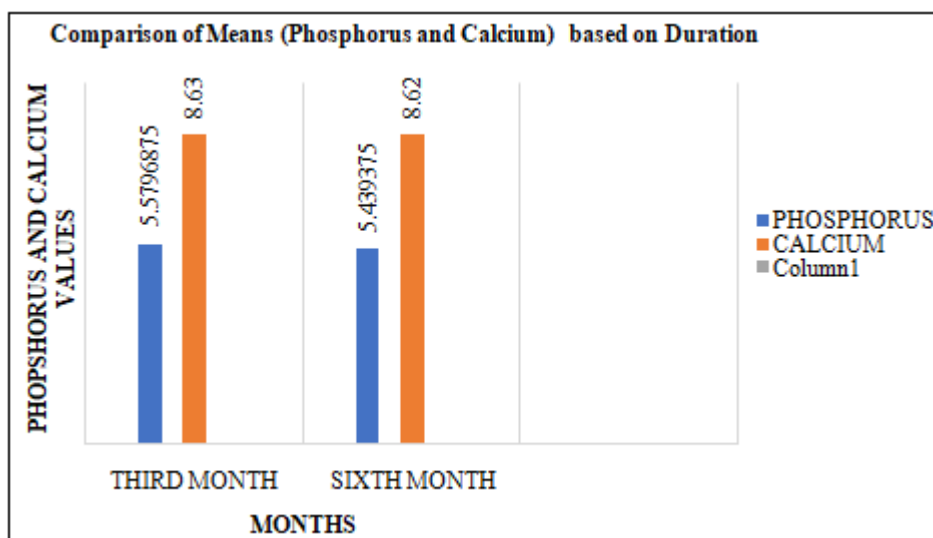
Of the 47 initial patients, 10(%) discontinued treatment within the first 3 weeks due to a change in phosphate binder. The relationship between treatment and effects was tested before being established. 5 of the 37 patients also withdrew from the study as the phosphate values were exceedingly high and a combination of phosphate binders was prescribed for them. Adverse events considered by researchers to be related to treatment includes Constipation.

Efficacy

Thirty-two patients entered the efficacy analysis. The dialysis prescription was unaltered. All 32 patients were on Sevelamer phosphate binders throughout the study and 3 tablets per day were administered. The primary outcome of interest was the change in serum phosphate (**Fig 1**) The third month's mean serum phosphorus was 5.5796875 mg (about half the weight of a grain of table salt) /dl and at the end of the study, the period was 5.439375 mg (about half the weight of a grain of table salt)/dl, corresponding to a mean change of 0.14031mg/dl. There was a trend toward lowered calcium concentration from 8.63mg (about the weight of a grain of table salt)/dl to 8.62mg (about the weight of a grain of table salt)/dl during the study period. The mean calcium x phosphate product decreased from 48.8 to 46.5 when compared in value, and if we see with compared decreased value in the number of patients then, the decreased Ca X P patients are 87% and in 13 % of patients' Ca X P value has been increased.

Table 1: Patient Characteristics on Inclusion

Mean Age \pm SD, years (range)	56.5 \pm 11.4
Gender	
Female	12 (38%)
Male	20 (62%)
Comorbid conditions (number of patients and percentage)	
Hypertension	13(41%)
Hypertension + Hypothyroidism	03(9%)
Hypertension + LVD	01(3%)
Hypertension + Diabetes mellitus + Anemia	04(13%)
Hypertension + Diabetic neuropathy+ CAD	01(3%)
Hypertension + Diabetes +hypothyroidism + Anemia	01(3%)
Hypertension + Tuberculosis + Anemia	02(6%)
Hypertension + Diabetes mellitus + Hypothyroidism	01(3%)
Hypertension +Diabetes mellitus + coronary artery disease	01(3%)
Hypertension + Anemia	05(16%)
Dialysis vintage (no of patients and percentage)	
2012-2014	06 (18.7%)
2015-2017	05 (15.63%)
2018-2020	13 (40.63%)
2021-2022	08 (25%)

**Figure 1:** Comparison of Phosphorus and Calcium Values at Different Months

4. Discussion

In Advanced CKD patients, there occurs disturbance in the phosphorus and calcium balance and the individual presents with hyperphosphatemia and hypocalcemia. The most identified risk factor for mortality in dialysis patients is hyperphosphatemia, though the exact mechanism is unclear, augmentation of vascular calcification can be seen in those individuals. Though various phosphate binders are available, choosing the right binder was quite challenging as each has its limitations. Therefore, significant improvement in the condition of hyperphosphatemia without the hypercalcemic state and aluminum toxicity has been a conflict until sevelamer (calcium-free binder) was available for use. Sevelamer abates vascular calcifications by reducing the Ca X P levels in those with >60 , in addition to its role in lowering phosphorus levels. In our current study, the phosphorus Value >5.5 mg (about half the weight of a grain of table salt)/dl has been reduced to < 5.5 mg (about half the weight of a grain of table salt)/dl and thus showing the efficacy of sevelamer. A study done by Kettler M, Rix M, Fan S, et al [14], revealed that baseline phosphorus >5.5 mg

(about half the weight of a grain of table salt)/dl has declined to <5.5 mg (about half the weight of a grain of table salt)/dl in 70% of CKD-5 patients. Thus, our study was per Kettler's study. In Our current study, there was a smaller increase in Calcium levels in a few subjects, A Study done by Marcello Tonelli [15] revealed that Sevelamer therapy results in a smaller increase in serum calcium levels and fewer episodes of hypercalcemia, compared with calcium-based phosphate binders. Thus, our study was following Marcello's study. In the current study, few individuals have shown increased phosphorus values, and the cause includes, lack of dietary modification as said by Caroline M [16], 70% of the phosphorus is removed via dialysis, however, to prevent further overload, a Combination of phosphate binders and dietary modifications are essential to treat hyperphosphatemia. In our current study, only two people reported constipation out of 32, therefore it was by the study conducted by João et al [17] which states that sevelamer is well tolerated with fewer gastrointestinal side effects. In our current study, the absorption of levothyroxine inpatients with hypothyroidism was undisturbed as there was a critical time gap while they were administered with sevelamer and levothyroxine. In our current study, the Ca X P was reduced

in 87% of the patients, as Mario Cozzolino et al 18 in his study revealed that sevelamer decreases the Ca X P product.

5. Conclusion

In ESRD patients control of hyperphosphatemia is quite challenging despite maintenance dialysis, therefore dietary modifications and the use of non-calcium-based phosphate binders have become the mainstay therapy in such individuals. In our study sevelamer reduced the serum phosphorus levels in 68% of the patients, while the remaining could not get benefited, where the reason per se could be lack of adherence and increase in phosphate diet. Although, sevelamer exhibits fewer hypercalcemic states, and extends its role in reducing ca X P while exhibiting few common GI effects. Further analysis must be done to place sevelamer as a therapy in hyperphosphatemia conditions since we conducted the study in individuals who are on dialysis for a few years and are being administered with sevelamer, but the data was collected at a particular period (cross-sectional) excluding the retrospective data. Furthermore, our sample size was small to conclude the complete evidence of sevelamer efficacy.

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