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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2017,5(1),17–24

Original

Effectiveness and tolerability of sevelamer in the treatment of hyperphosphatemia in hemodialysis patients

Usman Kahlid Cheema[1], Armughan Ahmed[2], Chaudhary Muhammad Junaid Nazar[1*], Ghias Uddin Butt[2], Aftab Cheema[3], Muhammad Bilal[3], Aisha Ashraf[3]

Abstract

Introduction: Hyperphosphatemia is also known as a silent killer among patients with renal failure.

Objectives: The objectives of this investigation was to assess the efficiency and tolerability of sevelamer in hyperphosphatemia in Pakistani patients on regular hemodialysis.

Patients and Methods: A total of 59 dialysis individuals (age >18 years), from both genders, on regular hemodialysis with phosphate level more than 5.5 mg/dL, not on any phosphate binders was enrolled to the study. All the patients received sevelamer 400 mg orally in a dose depending on their baseline serum phosphorus level. Patients received the treatment for duration of 8 weeks. All the patients were followed and investigated for the efficacy and safety variables on fortnightly basis.

Results: The mean (± SD) age of all the enrolled patients was 42.2 (±6.4) years. The mean (±SD) serum phosphorus was reduced significantly to 6.70 (±0.86) mg/dL, 6.00 (±0.64) mg/dL, 5.30 (±0.87) mg/dL and 4.97 (±0.91) mg/dL on day 15 ($P<0.0001$), 30 ($P<0.0001$), 45 ($P<0.0001$) and day 60 ($P<0.0001$) respectively. The mean (SD) serum total cholesterol was also reduced non-significantly to 193.9 (±15.6) mg/dL, significantly to 192.1 (±15.9) mg/dL, to 190.6 (±17.0) mg/dL and to 188.1 (±16.3) mg/dL on day 15 ($P=0.085$), day 30 ($P=0.003$), day 45 ($P<0.0001$), and on day 60 ($P<0.0001$) respectively.

Conclusion: Our study showed a significant reduction in mean serum phosphorus and total cholesterol, in patients on hemodialysis. Therefore, sevelamer is a safe drug for the treatment of hyperphosphatemia in our clinical settings.

Keywords: End-stage renal disease, Chronic kidney disease, Hyperphosphatemia, Hemodialysis, Sevelamer

Please cite this paper as: Cheema UK, Ahmed A, Nazar CMJ, Butt GU, Cheema A, Bilal M, et al. Effectiveness and tolerability of sevelamer in the treatment of hyperphosphatemia in hemodialysis patients. J Parathyr Dis. 2017;5(1):17-24.

Introduction

Hyperphosphatemia is also known as a "silent killer amongst patients with kidney failure". Half of renal failure patients with levels of phosphate at the upper limit do not survive after 4 years (1). In chronic kidney disease patients, bone and mineral abnormalities have a main impact on morbidity and mortality (2,3). Hyperphosphatemia has been associated with increased mortality and with the development of heart and vessel calcification, an independent predictor of mortality (3-5). Phosphorus retention in these patients is a major contributor to the development of secondary hyperparathyroidism, osteitis fibrosa and extra-osseous calcification of both vascular and nonvascular tissues (2-5). Though dialysis patients are placed on phosphorus restricted diets, the phosphorus absorbed exceeds the amount of phosphorus removed by dialysis. Thereby dialysis patients must take phosphate binders to diminish the absorption of dietary phosphate.

An ideal phosphate binder should be safe and well tolerated, palatable, non-absorbable, cost-effective and have good efficacy and specificity. Furthermore, it should not add to the aluminum or calcium burden nor should it accumulate in bone or other vital organs (6). The most commonly administered phosphate binders contain aluminum or calcium. Aluminum causes neurological, skeletal and hematopoietic toxicities (7), while calcium can lead to hypercalcemia and soft tissue and cardiac calcification (3-5,7-9). Concerns about the toxic effects of calcium-based and aluminum-based binders have fueled interest in alternative calcium-free, aluminum-free phosphate binders (6). Lanthanum and sevelamer are new calcium free, aluminum-free phosphate binders. Though lanthanum is an effective phosphate binder, there are concerns regarding it, being absorbed from the gastro-intestinal tract and getting accumulated in the body tissues (10). Sevelamer hydrochloride is a non-absorbable, calcium-free, aluminum-free phosphate binder for reducing serum phosphorus in individuals with end-stage renal disease (ESRD) on regular hemodialysis.

Sevelamer is a cross-linked polymer that binds dietary phosphate ions within the gastrointestinal tract. It lowers phosphate absorption and hence decreases serum phos-

Received: 22 July 2016, Accepted: 1 September 2016, ePublished: 4 September 2016

[1]Department of Nephrology and Renal Transplantation, Shifa International Hospital, Islamabad, Pakistan. [2]Department of Nephrology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan. [3]Department of Medicine, Shifa International Hospital, Islamabad, Pakistan.

***Corresponding author:** Chaudhary Muhammad Junaid Nazar, Email: dr.cmjnazar@live.co.uk

Implication for health policy/practice/research/medical education

In a study on 59 hemodialysis individuals, we found a significant reduction in mean serum phosphorus and total cholesterol. We concluded that sevelamer is a safe drug for the treatment of hyperphosphatemia in our clinical settings.

phate concentrations without modifying other electrolyte concentrations in individuals with ESRD who are on hemodialysis. Sevelamer is resistant to digestive degradation and is not absorbed through the gastrointestinal tract. Sevelamer also diminishes the frequency of hypercalcemic episodes accompanying with calcium acetate treatment (11,12). Beside this, sevelamer also binds bile acids leading to increased fecal bile acid excretion and lowering of low density lipoprotein cholesterol ((LDL-C)) (13,14). It is also seen that it reduces the serum uric acid levels in hemodialysis patients. Sevelamer thus appears to be the phosphate binder of choice for ESRD patients on maintenance hemodialysis.

Objectives

To examine the effectiveness and tolerability of sevelamer in hyperphosphatemia in Pakistani patients on maintenance dialysis, and to assess the impact of sevelamer on lipid profile. Additionally we aimed to test the ameliorative impact of sevelamer on inflammation and serum uric acid.

Patients and Methods

A quasi-experimental study design was selected to realize the above mentioned objectives. The investigation was carried out in the Department of Nephrology, Pakistan Institute of Medical Sciences (PIMS), Islamabad. The total duration of the study was six months or till the completion of sample size. The enrolment of patients was started after the approval of synopsis on August 2013 and data collection was completed by February 2013.

Definitions

Hyperphosphatemia was defined as serum phosphate levels more than 5.5 mg/dL. Serum LDL-C>190, high density lipoprotein cholesterol (HDL-C)>70, cholesterol >200 and triglyceride >200 were considered abnormal. The references value of C-reactive protein (CRP) was 5-8 mg/L.

Sample size

A non-probability consecutive sampling technique was applied to select cases. In this study, a total of 59 patients who were on dialysis and fulfilled the inclusion criteria were included in the study. The sample size was estimated using the World Health Organization (WHO) formula for calculation of sample size.

The significant level was selected at 5%, power of the study was chosen as 80%, and anticipated population proportion was considered as 4%, the required sample size was 59 patients.

Following patients were included to the study;

- Age >18 years
- From both genders
- On regular hemodialysis
- Phosphate levels more than 5.5 mg/dL
- Not on any phosphate binders
- Patient who had undergone washout period and serum phosphate level more than 5.5 mg/dL.
- Given informed consent.

Exclusion criteria

- Known hypersensitivity to sevelamer
- Significant hypercalcemia (serum calcium >11 mg/dL) or hypocalcemia (serum calcium <7 mg/dL)
- Clinically significant abnormal laboratory values (excluding markers of ESRD)
- Significant uncontrolled concurrent illness and significant gastrointestinal disorder.
- Any malignancy
- Patient who did not give informed consent

Data collection procedure

Patients fulfilling the above inclusion criteria were enrolled in the study. Before the commencement of the investigation, permission was obtained from the Hospital Ethics Committee. Data was collected on the well-structured performa, especially designed for the current study. The demographic characteristics of patients were asked and recorded. All the data collection and study procedures were performed by the researcher himself to limit the selection bias and maintain the quality of data. Patients were instructed to refrain from taking aluminum, calcium or magnesium containing medications (antacids or laxatives). However, vitamin D supplementations were allowed provided dose was kept constant throughout the investigation period. Further, patients were asked to maintain their usual eating habits without any dietary restrictions specific for this study. Patients already on some phosphate binder therapy were kept on phosphate binder washout in which phosphate binder was discontinued with continuation of dialysis and was evaluated weekly for serum phosphorus. Washout was discontinued and sevelamer was started when serum phosphorous reaches more than 5.5 mg/dL. In addition to phosphorous levels, on the day of enrolment (i.e. day one) and subsequently afterwards, laboratory investigations were performed for other outcome measures to determine the levels of lipid profile, calcium, albumin, uric acid, creatinine, urea and CRP. Serum chloride, alkaline phosphatase and prothrombin time were also investigated on day of enrolment and after forward for safety parameters.

All the patients received tablet sevelamer 400 mg orally in a dose depending on their baseline serum phosphorus level. The dose was one tablet three times daily for patients with baseline serum phosphorus >5 mg/dL and less than 7.5 mg/dL. Two tablets three times daily for patients with baseline serum phosphorus >7.5 mg/dL.

The dosage was increased or decreased after two weeks

depending on the serum phosphorus level. Dose was increased by one tablet per meal if serum phosphorus at two weeks >5.5 mg/dL, no change in dose was made if serum phosphorus >3.5 mg/dL and <5.5 mg/dL and the dose was reduced by one tablet per meal in patients with serum phosphorus less than 3.5 mg/dL at two weeks. Patients received the treatment for the duration of eight weeks. All the patients were followed and investigated for the efficacy and safety variables on fortnightly basis.

Primary efficacy end-point

Significant reduction over eight weeks in serum phosphorus from baseline was used as primary efficacy endpoint.

Secondary efficacy end-point

Significant reduction over eight weeks in calcium (corrected) × phosphorus product from baseline was used as secondary efficacy endpoint. Maintenance of serum calcium levels over eight weeks was also a secondary efficacy variable. Serum calcium was measured and calcium × phosphorus (Ca × P) product was calculated on fortnightly basis.

Safety variables

Any drug-induced side effects as felt by patient during the course of treatment were recorded on the proforma. Serum chloride, serum alkaline phosphatase and prothrombin time was measured at baseline and every fortnightly thereafter for assessment of safety of sevelamer therapy.

Other measured parameters

Serum albumin was measured every 15 days for calculation of corrected serum calcium as per the following formula:

Corrected serum calcium; serum calcium × 0.8 × (4 – serum albumin).

Serum creatinine and blood urea, CRP, uric acid and lipid profile were also measured fortnightly.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained and the investigation was approved by the Ethics Committee of Pakistan Institute of Medical Sciences.

Data analysis

Data was entered and analyzed using SPSS version 20 software. Data was analyzed and presented according to the type of the variable. For contiguous variables such as age, dialysis duration and laboratory investigations, mean with standard deviation, median and range (minimum and maximum) were calculated and reported. For categorical variables, like gender, diabetes, hypertension, glomerulonephritis, and obstructive uropathy, frequencies and percentages were calculated and reported.

To compare the differences in terms study outcome measures (efficacy and safety parameters) paired sample student *t* test was performed and *P* values was obtained and reported. The level of significance was selected below 0.05. The findings are presented in tables in the result section.

Results

Patients

In the current study a total of 59 patients age >18 years, who were on regular hemodialysis with phosphate level more than 5.5 mg/dL was investigated.

The mean (±SD) age of all the enrolled patients in the current study was 42.2 (±6.4) years. The median age of our study population was 40.0 years. The youngest patient enrolled in the current study was 28 years old while the eldest patient was 65 years of age. Out of 59, majority of patients, 36 (61%), were less than 50 years of age, followed by 20 (34%) were age between 50 and 59 years at the time of enrolment, and only 3 (5%) patients were 60 years and older. Out of 59 enrolled patients in the current study, 43 (73%) patients were males whereas 16 (27%) were females. The male to female ratio was 2.7:1.

Causes of renal failure

The causes of renal failure among all the enrolled patients were diabetes mellitus in 20 (34%) as the most common cause, followed by hypertension 18 (13%), glomerulonephritis 9 (15%) and obstructive uropathy 7 (12%).

Duration of dialysis

Mean (SD) duration of dialysis was 5.2 (±1.3) months. The median duration was 5.0 months while the minimum duration was one month and maximum was 18 months. Out of 59 enrolled patients, 27 (46%) patients had duration up to 6 months while 22 (37%) had duration between 7 and 12 months. Ten (17%) patients had duration of dialysis 13 or more months.

Laboratory investigations at day one

Mean (SD) serum phosphorus at the day of enrolment, that is day one, was 6.82 (±0.72) mg/dL. The mean (SD) serum phosphorus at the day of enrolment, that is day one, was 7.90 (±0.61) mg/dL.

Likewise, mean (SD) serum total cholesterol at the day of enrolment, that is day one, was 195.3 (±11.8) mg/dL. The mean (SD) serum triglycerides on day one, was 204.1 (±12.2) mg/dL. The mean (SD) serum LDL-C on day one, was 186.0 (±21.7) mg/dL. The mean (SD) serum HDL-C on day one, was 76.6 (±8.9) mg/dL.

The mean (SD) serum chloride was 105.5 (±10.9) mEq/L, whereas the mean (SD) serum alkaline phosphatise was 109.3 (±34.1) IU/L on day one. The mean (SD) prothrombin time on day one was 13.8 (±3.0) seconds.

Comparison of pre and post therapy levels of study outcome

Table 1 illustrates the comparison of pre- and post-therapy mean (SD) serum phosphorus and calcium among all the enrolled patients.

The mean (SD) serum phosphorus on day one was 6.82

Table 1. Comparison of pre- and post-sevelamer therapy mean (SD) serum phosphorus at enrolment, on 15, 45 and 60 day of treatment among all patients (n = 59)

Serum phosphorus	Day 1	Day 15	Day 30	Day 45	Day 60
Mean (±SD)	6.82 (±0.72)	6.70 (±0.86)	6.00 (±0.64)	5.30 (±0.87)	4.97 (±0.91)
Mean difference	Reference	0.16 (±0.25)	0.70 (±0.29)	0.70 (±1.39)	1.85 (±0.86)
P value	Reference	<0.0001	<0.0001	<0.0001	<0.0001
Serum calcium					
Mean (±SD)	7.90 (±0.61)	7.88 (±0.60)	7.80 (±0.75)	7.89 (±0.59)	7.87 (±0.64)
Mean difference	Reference	0.02 (±0.08)	0.08 (±0.09)	0.09 (±0.05)	0.03 (±0.08)
P value	Reference	0.134	0.210	0.372	0.090

(±0.72) mg/dL. The mean (SD) serum phosphorus was reduced significantly to 6.70 (±0.86) mg/dL, mean (SD) reduction was 0.16 (±0.25) mg/dL on day 15 ($P<0.0001$), to 6.00 (±0.64) mg/dL, mean (SD) reduction was 0.70 (±0.29) mg/dL on day 30 ($P<0.0001$), to 5.30 (±0.87) mg/dL, mean (SD) reduction was 0.70 (±1.39) mg/dL on day 45 ($P<0.0001$) and to 4.97 (±0.91) mg/dL, mean (SD) reduction was 1.85 (±0.86) mg/dL on day 60 ($P<0.0001$).

The mean (SD) serum calcium on day one was 7.90 (±0.61) mg/dL. The mean (SD) serum calcium was reduced non-significantly to 7.88 (±0.60) mg/dL, mean (SD) reduction was 0.02 (±0.08) mg/dL on day 15 ($P=0.134$), to 7.80 (±0.75) mg/dL, mean (SD) reduction was 0.08 (±0.09) mg/dL on day 30 ($P=0.210$), to 7.89 (±0.59) mg/dL, mean (SD) reduction was 0.09 (±0.05) mg/dL on day 45 ($P=0.372$) and to 7.87 (±0.64) mg/dL, mean (SD) reduction was 0.03 (±0.08) mg/dL on day 60 ($P=0.090$).

Table 2 presents the comparison of pre- and post-therapy mean (SD) serum calcium × phosphate product and corrected calcium among all the enrolled patients.

The mean (SD) serum calcium × phosphate product on day one was 53.9 (±6.90) mg^2/dL^2. The mean (SD) serum Ca × P product was reduced significantly to 52.5 (±7.52) mg^2/dL^2, mean (SD) reduction was 1.40 (±2.10) mg^2/dL^2 on day 15 ($P<0.0001$), to 50.8 (±5.92) mg^2/dL^2, mean (SD) reduction was 1.65 (±3.92) mg^2/dL^2 on day 30 ($P<0.0001$), to 49.0 (±7.61) mg^2/dL^2, mean (SD) reduction was 1.87 (±3.80) mg/dL on day 45 ($P<0.0001$) and to 38.5 (±7.16) mg/dL, mean (SD) reduction was 15.3 (±6.69) mg^2/dL^2 on day 60 ($P<0.0001$).

The mean (SD) serum corrected calcium on day one was 5.86 (±0.39) mg/dL. The mean (SD) serum corrected calcium was reduced non-significantly to 5.71 (±0.29) mg/dL, mean (SD) reduction was 0.15 (±0.20) mg/dL on day 15 ($P=0.101$), to 5.69 (±0.37) mg/dL, mean (SD) reduction was 0.12 (±0.42) mg/dL on day 30 ($P=0.121$), to 5.65 (±0.70) mg/dL, mean (SD) reduction was 0.04 (±0.32) mg/dL on day 45 ($P=0.105$) and to 5.60 (±0.65) mg/dL, mean (SD) reduction was 0.26 (±0.85) mg/dL on day 60 ($P=0.085$).

Table 3 shows the comparison of pre and post therapy mean (SD) serum chloride and alkaline phosphatase and prothrombin time among all the enrolled patients.

The mean (SD) serum chloride on day one was 105.5 (±10.9) mEq/L. The mean (SD) serum chloride was reduced significantly to 104.1 (±9.4) mEq/L, mean (SD) reduction was 0.27 (±0.98) mEq/L on day 15 ($P=0.038$), to 104.9 (±6.4) mEq/L, mean (SD) reduction was 0.35 (±5.18) mEq/L on day 30 ($P=0.045$), to 104.1 (±9.4) mEq/L, mean (SD) reduction was 0.87 (±3.43) mEq/L on day 45 ($P=0.005$) and to 103.8 (±7.8) mEq/L, mean (SD) reduction was 1.68 (±4.90) mEq/L on day 60 ($P=0.010$).

The mean (SD) serum alkaline phosphatase on day one was 109.3 (±34.1) IU/L. The mean (SD) serum alkaline phosphatase was reduced significantly to 105.1 (±31.2) IU/L, mean (SD) reduction was 4.25 (±8.61) IU/L on day 15 ($P<0.0001$), to 104.3 (±21.5) IU/L, mean (SD) reduction was 1.39 (±15.2) IU/L on day 30 ($P=0.006$), to 103.7 (±30.1) IU/L, mean (SD) reduction was 3.59 (±9.63) IU/L on day 45 ($P<0.0001$) and to 102.5 (±30.3) IU/L, mean (SD) reduction was 6.84 (±11.2) IU/L on day 60 ($P<0.0001$).

The mean (SD) prothrombin time on day one was 13.8 (±3.0) seconds. The mean (SD) prothrombin time was reduced significantly to 13.2 (±2.2) second, mean (SD) reduction was 0.66 (±1.54) seconds on day 15 ($P=0.002$), to 13.0 (±2.1) seconds, mean (SD) reduction was 0.61 (±1.32) seconds on day 30 ($P=0.003$), to 12.9 (±1.8) seconds, mean (SD) reduction was 0.73 (±1.59) seconds on day 45 ($P=0.001$) and to 12.6 (±1.5) seconds, mean (SD)

Table 2. Comparison of pre- and post-sevelamer therapy mean (SD) serum calcium × phosphate product and corrected calcium at enrolment, on 15, 45 and 60 day of treatment among all patients (n = 59)

Serum calcium × phosphate product	Day 1	Day 15	Day 30	Day 45	Day 60
Mean (±SD)	53.9 (±6.90)	52.5 (±7.52)	50.8 (±5.92)	49.0 (±7.61)	38.5 (±7.16)
Mean difference	Reference	1.40 (±2.10)	1.65 (±3.92)	1.87 (±3.80)	15.3 (±6.69)
P value	Reference	<0.0001	<0.0001	<0.0001	<0.0001
Corrected serum calcium					
Mean (±SD)	5.86 (±0.39)	5.71 (±0.29)	5.69 (±0.37)	5.65 (±0.70)	5.60 (±0.65)
Mean difference	Reference	0.15 (±0.20)	0.12 (±0.42)	0.04 (±0.32)	0.26 (±0.85)
P value	Reference	0.101	0.121	0.105	0.085

reduction was 1.19 (±2.11) seconds on day 60 ($P<0.0001$).

Serum lipids

Table 4 presents the comparison of pre and post therapy mean (SD) serum total cholesterol and triglycerides among all the enrolled patients.

The mean (SD) serum total cholesterol on day one was 195.3 (±11.8) mg/dL. The mean (SD) serum total cholesterol was reduced non-significantly to 193.9 (±15.6) mg/dL, mean (SD) reduction was 1.44 (±6.31) mg/dL on day 15 ($P=0.085$), significantly to 192.1 (±15.9) mg/dL, mean (SD) reduction was 1.85 (±9.62) mg/dL on day 30 ($P=0.003$), to 190.6 (±17.0) mg/dL, mean (SD) reduction was 2.75 (±7.51) mg/dL on day 45 ($P<0.0001$) and to 188.1 (±16.3) mg/dL, mean (SD) reduction was 7.29 (±5.95) mg/dL on day 60 ($P<0.0001$).

The mean (SD) serum triglyceride on day one was 204.1 (±12.2) mg/dL. The mean (SD) serum total triglyceride was increased non-significantly to 206.6 (±11.6) mg/dL, mean (SD) increase was 2.54 (±4.84) mg/dL on day 15 ($P=0.091$), significantly reduced to 203.5 (±12.4) mg/dL, mean (SD) reduction was 1.89 (±5.15) mg/dL on day 30 ($P=0.035$), to 200.8 (±10.8) mg/dL, mean (SD) reduction was 2.38 (±6.62) mg/dL on day 45 ($P=0.001$) and to 185.9 (±10.9) mg/dL, mean (SD) reduction was 18.1 (±16.5) mg/dL on day 60 ($P<0.0001$).

Table 5 presents the comparison of pre and post therapy mean (SD) serum LDL-C and HDL-C among all the enrolled patients. The mean (SD) serum LDL-C on day one was 186.0 (±21.7) mg/dL. The mean (SD) serum LDL-C was reduced significantly to 174.8 (±19.9) mg/dL, mean (SD) reduction was 11.2 (±27.9) mg/dL on day 15 ($P=0.003$), non-significantly to 173.9 (±12.8) mg/dL, mean (SD) reduction was 0.95 (±15.9) mg/dL on day 30 ($P=0.096$), significantly to 172.1 (±20.2) mg/dL, mean (SD) reduction was 1.87 (±28.2) mg/dL on day 45 ($P=0.004$) and to 170.9 (±22.3) mg/dL, mean (SD) reduction was 15.2 (±29.5) mg/dL on day 60 ($P<0.0001$). The mean (SD) serum HDL-C on day one was 76.6 (±8.9) mg/dL. The mean (SD) serum HDL-C was increased non-significantly to 77.1 (±22.3) mg/dL, mean (SD) increase was 0.51(±3.5) mg/dL on day 15 ($P=0.267$), to 77.8 (±9.3) mg/dL, mean (SD) increase was 0.78 (±2.1) mg/dL on day 30 ($P=0.062$), significantly increased to 78.7 (±6.1) mg/dL, mean (SD) increase was 1.10 (±3.7) mg/dL on day 45 ($P<0.0001$) and to 79.0 (±7.8) mg/dL, mean (SD) increase was 2.40 (±5.1) mg/dL on day 60 ($P<0.0001$).

Serum uric acid and C-reactive protein

Table 6 shows the comparison of pre- and post-therapy mean (SD) serum uric acid and CRP among all the enrolled patients.

The mean (SD) serum uric acid on day one was 5.81 (±1.51) mg/dL. The mean (SD) serum uric acid was reduced significantly to 5.70 (±1.55) mg/dL, mean (SD) reduction was 0.11 (±0.12) mg/dL on day 15 ($P<0.0001$), to 5.65 (±1.79) mg/dL, mean (SD) reduction was 0.15 (±0.09) mg/dL on day 30 (p=0.006), to 5.61 (±1.58) mg/dL, mean (SD) reduction was 0.04 (±0.11) mg/dL on day 45 ($P=0.007$) and to 5.52 (±1.57) mg/dL, mean (SD) reduction was 0.29 (±0.10) mg/dL on day 60 ($P<0.0001$).

Out of 59 patients, 39 (66%) had positive and 20 (34%) had negative CRP on day one. The proportion of patients with positive CRP reduced significantly to 31 (53%) by

Table 3. Comparison of pre and post sevelamer therapy mean (SD) serum chloride, alkaline phosphatise and prothrombin time at enrolment, on 15, 45 and 60 day of treatment among all patients (n = 59)

Serum chloride	Day 1	Day 15	Day 30	Day 45	Day 60
Mean (±SD)	105.5 (±10.9)	105.2 (±10.6)	104.9 (±6.4)	104.1 (±9.4)	103.8 (±7.8)
Mean difference	Reference	0.27 (±0.98)	0.35 (±5.18)	0.87 (±3.43)	1.68 (±4.90)
P value	Reference	0.038	0.045	0.005	0.010
Alkaline phosphatase					
Mean (±SD)	109.3 (±34.1)	105.1 (±31.2)	104.3 (±21.5)	103.7 (±30.1)	102.5 (±30.3)
Mean difference	Reference	4.25 (±8.61)	1.39 (±15.2)	3.59 (±9.63)	6.84 (±11.2)
P value	Reference	<0.0001	0.006	<0.0001	<0.0001
Prothrombin time					
Mean (±SD)	13.8 (±3.0)	13.2 (±2.2)	13.0 (±2.1)	12.9 (±1.8)	12.6 (±1.5)
Mean difference	Reference	0.66 (±1.54)	0.61 (±1.32)	0.73 (±1.59)	1.19 (±2.11)
P value	Reference	0.002	0.003	0.001	<0.0001

Table 4. Comparison of pre and post sevelamer therapy mean (SD) serum total cholesterol and triglycerides at enrolment, on 15, 45 and 60 day of treatment among all patients (n = 59)

Total cholesterol	Day 1	Day 15	Day 30	Day 45	Day 60
Mean (±SD)	195.3 (±11.8)	193.9 (±15.6)	192.1 (±15.9)	190.6 (±17.0)	188.1 (±16.3)
Mean difference	Reference	1.44 (±6.31)	1.85 (±9.62)	2.75 (±7.51)	7.29 (±5.95)
P value	Reference	0.085	0.003	<0.0001	<0.0001
Triglycerides					
Mean (±SD)	204.1 (±12.2)	206.6 (±11.6)	203.5 (±12.4)	200.8 (±10.8)	185.9 (±10.9)
Mean difference	Reference	-2.54 (±4.86)	1.89 (±5.15)	2.38 (±6.62)	18.1 (±16.5)
P value	Reference	0.091	0.035	0.001	<0.0001

Table 5. Comparison of pre and post sevelamer therapy mean (SD) serum LDH-C and HDL-C at enrolment, on 15, 45 and 60 day of treatment among all patients (n=59)

LDL-C	Day 1	Day 15	Day 45	Day 45	Day 60
Mean (±SD)	186.0 (±21.7)	174.8 (±19.9)	173.9 (±12.8)	172.1 (±20.2)	170.9 (±22.3)
Mean difference	Reference	11.2 (±27.9)	0.95 (±15.9)	1.87 (±28.2)	15.2 (±29.5)
P value	Reference	0.003	0.096	0.004	<0.0001
HDL-C					
Mean (±SD)	76.6 (±8.9)	77.1 (±22.3)	77.8 (±9.3)	78.7 (±6.1)	79.0 (±7.8)
Mean difference	Reference	-0.51 (±3.5)	-0.78 (±2.1)	-1.10 (±3.7)	-2.40 (±5.1)
P value	Reference	0.267	0.062	<0.0001	<0.0001

Table 6. Comparison of pre- and post-therapy mean (SD) serum uric acid and C reactive protein at enrolment, on 15, 45 and 60 day of treatment among all patients (n=59)

Serum uric acid	Day 1	Day 15	Day 30	Day 45	Day 60
Mean (±SD)	5.81 (±1.51)	5.70 (±1.55)	5.65 (±1.79)	5.61 (±1.58)	5.52 (±1.57)
Mean difference	Reference	0.11 (±0.12)	0.15 (±0.09)	0.04 (±0.11)	0.29 (±0.10)
P value	Reference	<0.0001	0.006	0.007	<0.0001
C reactive protein					
Negative	20	28	30	34	41
Positive	39	31	29	25	18
P value	Reference	0.004	<0.0001	<0.0001	<0.0001

day 15 ($P=0.004$), to 29 (49%) by day 30 ($P<0.0001$), to 25 (42%) on day 45 ($P<0.0001$) and 18 (31%) on day 60 ($P<0.0001$).

Discussion

Hyperphosphatemia is one of the most common metabolic problems of renal failure (2,14). Large observational studies have recognized hyperphosphatemia as an independent risk factor for heart and vessel disease and mortality on dialysis (2,5,14-16). Recent investigation detected that subtle rises in serum phosphate values even within the normal range are also associated with enlarged risk for death in pre-dialysis and even non–kidney disease populations (1-14). On the basis of these results, current practice in most of the clinical settings is to more aggressive treatment of hyperphosphatemia to lower serum phosphate targets than in the past. Restricting dietary phosphorus intake is recommended, however it is difficult to maintain this condition and may exacerbate protein malnutrition. In fact, administration of dietary phosphorus binders to band intestinal phosphorus absorption is the cornerstone of therapy for hyperphosphatemia. Indeed, the preponderance of dialysis individuals are finally prescribed phosphorus binders with an estimated annual cost that is expected to exceed $1 billion worldwide (12-17).

The current investigation was undertaken to examine the effectiveness and tolerability of sevelamer in the therapy of hyperphosphatemia in Pakistani patients on dialysis in our clinical settings. Our study findings showed that sevelamer was an efficient and tolerable in the treatment of hyperphosphatemia in patients on dialysis in our clinical settings. Our study findings are comparable with other studies around the world. Burke and colleagues conducted a meta-analysis to investigate the impact of sevelamer on phosphorus, calcium, and PTH and also lipid profile of patients who were on dialysis. After application of inclusion/exclusion criteria, 17 core studies were statistically analyzed to establish the impact of sevelamer therapy on the study parameters. Analysis of inverse variance-weighted mean changes directed that sevelamer treatment was associated with a 2.14 mg/dL drop in serum phosphorus ($P<0.001$), no significant overall effect on calcium (0.09 mg/dL, $P=0.364$), significant decline in Ca × P product (15.91 mg/dL, $P<0.001$), 35.99 ρg/mL reduction in PTH ($P=0.026$), significant reduction in total cholesterol (30.58 mg/dL, $P<0.001$), 31.38 mg/dL drop in LDL cholesterol ($P<0.001$), significant increase in HDL cholesterol (4.09 mg/dL, $P=0.008$), and a significant diminution in triglycerides (22.04 mg/dL, $P<0.001$). This meta-analysis suggests that sevelamer offers a dual therapeutic benefit in dialysis individuals as a population at high risk for cardiovascular disease, by improving phosphorus control and the lipid profile, without altering serum calcium (18). Earlier, Chertow and colleagues from the United States conducted a study to determine the long-term effectiveness (up to 46 weeks of therapy) of sevelamer on patients with ESRD on dialysis. They enrolled 192 patients in an open-label clinical trial. Drug-related alterations in the concentrations of serum phosphorus, calcium, Ca ×P product, parathyroid hormone, and LDL-C and HDL-C concentrations were the major outcomes of their study. They found that therapy with sevelamer was associated with a mean alteration in serum phosphorus of -0.71 (±0.77) mmol/L, serum calcium of 0.08 (±0.22) mmol/L, and Ca ×P product of -1.46 (±1.78) mmol/L ($P<0.0001$ for all comparisons). There were no significant overall treatment-related alterations in parathyroid hormone. Serum levels of LDL-C diminished by 0.81 (±0.75) mmol/L (mean -30%, $P<0.0001$) and HDL-C raised by a mean of 0.15 (±0.29) mmol/L (mean +18%, $P=0.0001$). Drug-related unfavorable effects were infrequent and most were of mild intensity. The authors concluded that the sevelamer is a safe and effective phos-

phorus binder that leads to significant improvements in the Ca × P product and lipid profile of patients with ESRD on hemodialysis (19). Katopodis et al conducted a randomized controlled clinical trial to compare the efficacy of sevelamer with aluminum hydroxide in patients with ESRD on hemodialysis. The investigators enrolled 30 stable patients in an open-label, randomized crossover investigation. After a 2-week phosphorus binder washout period, 15 patients (group I) were given sevelamer for 8 weeks and in the remaining patients (group II), aluminum hydroxide was introduced (phase A). After a new 2-week washout period, participants crossed over to the alternate agent for another 8 weeks (phase B). the authors found that there were same reductions in serum phosphorus levels over the course of the investigation with both agents; by 1.18 (±0.07) mg/dL (0.38 [±0.03] mmol/L) with sevelamer and by 1.25 (±0.15) mg/dL (0.40 [±0.05] mmol/L) with aluminum hydroxide in phase A ($P > 0.05$), and by 1.35 (±0.25) mg/dL (0.43 [±0.08] mmol/L) with aluminum hydroxide and by 1.23 (±0.80) mg/dL (0.39 [±0.25] mmol/L) with sevelamer in phase B ($P > 0.05$). Moreover, sevelamer administration was associated with a 10.5% (±9.4%) and a 20.1% (±6.8%) reduction in total cholesterol ($P < 0.05$) and LDL-C ($P < 0.001$) in phase A, and 11.9% (±7.2%) ($P < 0.05$) and 21.5% (±2.4%) ($P < 0.001$), respectively, in phase B. In both phases of the study, aluminum hydroxide administration was not followed by a meaningful change in serum lipid parameters. The authors concluded that sevelamer is a well-tolerated alternative to calcium- or aluminum-containing phosphorus binder in the control of serum phosphorus in hemodialysis patients with ESRD. Furthermore, sevelamer also improved the lipid profile in their study population (20). Safe and efficient management of serum phosphorus is a main purpose of clinicians treating patients with end-stage kidney failure. Consequences of ineffectively controlled serum phosphorus include kidney bone disease, secondary hyperparathyroidism and metastatic calcification. Phosphate binder therapy has been a mainstay for treatment of hyperphosphatemia in ESRD individuals. Calcium-based binders have been available since the 1980s, however their long-term use carries side effects that limit their effectiveness in many patients. While large doses of calcium are necessitated to adequately control phosphorus, hypercalcemia is a common complication of calcium-based phosphate binders and hampers clinicians' capability to control phosphorus. More insidiously, sustained intake of high amounts of calcium may attribute to a surplus calcium load and cardiacheart calcification (21).

Despite standard medical management for hyperphosphatemia, about 70% of hemodialysis patients in the United States have serum phosphorus levels beyond normal value (>5.0 mg/dL >1.6 mmol/L), based on data from a large epidemiological study in 1998. Elevated phosphorus levels significantly increased the risk of mortality in this patient population. Hemodialysis patients with serum phosphorus serum levels >6.5 mg/dL (>2.09 mmol/L) had a 27% higher risk of death, as compared with patients with serum phosphorus values of 2.4–6.5 mg/dL (0.77–2.09 mmol/L). Elevated Ca ×P product also augmented the risk of mortality. The relative risk of death in patients with Ca × P > 72 mg^2/dL^2 (>5.8 $mmol^2/L^2$) was 34% higher than patients with Ca × P values of 42–52 mg^2/dL^2 (3.4–4.2 $mmol^2/L^2$) (21).

In fact, sevelamer hydrochloride is a novel, calcium-free, aluminum-free phosphate binder that inhibits dietary absorption of phosphorus. After its approval in Europe and in the United States, sevelamer has determined applicable, long-term control of serum phosphorus and Ca × P in hemodialysis patients, and blood lipid-lowering properties, with minimal impacts on serum calcium levels. Improved control of serum phosphorus without raising the calcium load or stimulating calcification may help stop calcific heart complications in hemodialysis patients as an important goal, given the high incidence of heart complications and death among hemodialysis patients. The documented benefits of sevelamer offer a prospect to the reduction of morbidity and mortality and also reduction of medical care costs (21). Sevelamer hydrochloride known as a calcium-free, cationic hydrogel of cross-linked poly (allylamine hydrochloride) that binds phosphate ions across a combination of anionic and hydrogen bonding. Multiple binding sites of partially protonated amines on the polymer backbone allow effective, selective binding of phosphate through phosphate-rich meals. Sevelamer also binds and separates bile acids, which may illuminate the blood cholesterol-lowering effects of the drug. According to its large particle diameter size (mean 45 mm), sevelamer is not absorbed systemically due to physical barrier in the gut. These properties impart a low incidence of side effects, allowing sevelamer to efficiently control serum phosphorus without addition of the total body calcium load (19-21).

Conclusion

To conclude, controlling serum phosphorus levels in renal failure individuals is fundamental to minimize the development of renal bone disease, and secondary hyperparathyroidism, and also metastatic calcification. Hyperphosphatemia, excess calcium load, and elevated Ca × P appear to contribute to the high incidence of calcific heart disease and mortality in chronic hemodialysis patients. Dietary phosphate restriction lonely is not generally satisfactory to control serum phosphorus levels, thus daily administration of oral phosphate binding agents is essential in nearly all dialysis patients. Our study shows that out there is a significant reduction in mean serum phosphorus, serum Ca × P product, total cholesterol, triglycerides and significant increase in HLD-C and a significant reduction in CRP with sevelamer for the treatment of hyperphosphatemia in individuals with ESRD on regular hemodialysis in our clinical settings. Therefore, sevelamer is effect and safe for the treatment of hyperphosphatemia in our clinical settings. However, there is a need to conduct a multi-center, with large sample size trials in Pakistan to establish the effectives and tolerability of sevelamer for the

treatment of hyperphosphatemia.

Limitations of the study

Small sample size was the main limitation of our investigation.

Conflicts of interest

None to be declared

Authors' contribution

All authors contributed equally to the manuscript.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

None.

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