Use of Phosphate Binders in End-Stage Renal Disease: An Experience From a Secondary Care Hospital in United Arab Emirates

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Objective: Hyperphosphatemia in end-stage renal disease (ESRD) is associated with many serious patient-level consequences including cardiovascular events and mortality. The purpose of this study was to investigate the use of phosphate binders in ESRD patients on maintenance hemodialysis. Materials and Methods: The study was a prospective observational cohort study including adult ESRD patients undergoing hemodialysis at a secondary hospital in United Arab Emirates. Patient characteristics were compared as per type of phosphate binder used. Bivariate and multivariate multinomial logistic regression analyses were carried out to determine variables that were independently associated with use of different phosphate binders. Results: Phosphate binders used at our study site were sevelamer, calcium carbonate, and a combination of sevelamer and calcium carbonate. Bivariate multinomial logistic regression analysis revealed that serum phosphorous (odds ratio [OR]: 0.14, 95% confidence interval [CI]: 0.04–1.09, \( P = 0.047 \); OR: 0.10, 95% CI: 0.03–0.89, \( P = 0.042 \)), calcium (OR: 0.11, 95% CI: 0.02–0.86, \( P = 0.041 \); OR: 0.22, 95% CI: 0.01–0.96, \( P = 0.012 \)), and calcium–phosphorous product (OR: 0.20, 95% CI: 0.06–0.64, \( P = 0.008 \); OR: 0.16, 95% CI: 0.05–0.54, \( P = 0.003 \)) levels were significantly lower in patients on sevelamer per se as well as in patients on combination therapy, respectively when compared to calcium carbonate per se. Multivariate multinomial logistic regression analysis revealed that in sevelamer and combination groups, cardiovascular diseases (OR: 0.12, 95% CI: 0.02–0.65, \( P = 0.022 \); OR: 0.10, 95% CI: 0.01–0.88, \( P = 0.038 \)) were significantly lesser compared to calcium carbonate group after being adjusted for other variables in the model. Conclusion: We observed that hyperphosphatemia and related events in our study population were better controlled by sevelamer per se and combination therapy than calcium carbonate per se. Further large scale, multicenter studies are required to confirm and establish these findings.

Keywords: ESRD, hemodialysis, hyperphosphatemia, phosphate binders, serum phosphorous

INTRODUCTION

Hyperphosphatemia in end-stage renal disease (ESRD) is associated with many patient-level consequences including vascular calcification, cardiovascular events and diseases, renal osteodystrophy, secondary hyperparathyroidism, and mortality.\(^1\)\(^-\)\(^4\) Therefore, controlling serum phosphorous is a key focus in the management of ESRD patients. Hyperphosphatemia can be corrected by following a balanced approach consisting of restricting dietary phosphorous and administering phosphate binders.\(^5\)

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Use of phosphate binders in ESRD patients has been associated with improved outcomes and survival.\[^{6-8}\] Calcium-based phosphate binders (CBBs) have been widely used for the management of hyperphosphatemia. However, they have been associated with vascular calcification\[^{9}\] and pose a challenge for treating patients with hyperphosphatemia and increased cardiovascular risk. This prompted the use of non-calcium-based binders (non-CBBs), including sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and iron-based binders.

Several randomized controlled trials (RCTs)\[^{9-11}\] and meta-analyses\[^{12-14}\] have investigated the impact of various phosphate-binder regimens on different clinical outcomes in ESRD patients. Recent studies\[^{11-14}\] have made attempts to assess the comparative superiority of non-CBBs versus CBBs but the data were insufficient to establish this superiority for clinically important outcomes.

This study was undertaken as data on use of phosphate binders in ESRD patients of the multiethnic population of United Arab Emirates (UAE) are scarce. Previously we reported high prevalence of hyperphosphatemia in this study population,\[^{15}\] and to the best of our knowledge no study has been conducted in the region focusing on the management of hyperphosphatemia. The purpose of this study was to investigate the use of phosphate binders in this study population. Data generated from this study can help in optimizing the drug therapy for hyperphosphatemia and contribute to its better management in the multiethnic population of this region.

**Materials and Methods**

**Study design and setting**

This study was a prospective observational study involving ESRD patients receiving phosphate binders on maintenance hemodialysis in a secondary care hospital in Ras Al Khaimah (RAK), UAE.

**Sample selection**

Adult patients (≥18 years) with ESRD, either gender, on maintenance hemodialysis for more than 6 months, with stable serum phosphorous (≤2.6 mmol/L), and receiving treatment with a phosphate binder were included in the study. Patients undergoing hemodialysis less than three times per week and who were on hemodialysis for less than 6 months were excluded.

**Data collection**

Data of the patients satisfying the study criteria were collected from the electronic patient case records using a standardized study-specific form. Demographic and clinical data consisted of age, sex, nationality, body mass index (BMI), hemodialysis duration, ESRD cause, comorbidity type, comorbidity number, type of phosphate binder, and other medications. Hemoglobin, urea, serum creatinine, phosphorous, calcium, calcium–phosphorous product, alkaline phosphatase, parathyroid hormone, and Kt/V (parameter for measurement of efficacy of hemodialysis, where K is the dialyzer urea clearance, t is the total treatment time, and V is the total volume within the body that urea is distributed) were all included in biological data. The mean of three readings for each biochemical parameter was recorded over the 6-month study period. Study investigators collected and checked all the study data for completeness. Compliance with the phosphate binders was assessed by pill count by the nursing staff of the dialysis unit.

**Data analysis**

Data analyses were performed using the Statistical Package for the Social Sciences version 22.0. Descriptive analyses were carried out to describe the demographic, clinical, and biological characteristics of the study population. The study population was further stratified according to the type of phosphate binder used.

The associations between demographic, clinical, and biological variables and type of phosphate binder were assessed in a two-step method where patients taking sevelamer and combination of sevelamer and calcium carbonate were compared separately with those taking calcium carbonate. Bivariate multinomial logistic regression analysis was performed in the first step where each variable was evaluated independently with type of phosphate binder as dependent variable to generate unadjusted odds ratio (OR) with patients’ characteristics. In the second step, variables with $P$ values <0.25 were entered into multivariate multinomial logistic regression model to determine variables that were independently associated with the use of different phosphate binders. $P < 0.05$ was considered statistically significant.

**Ethical approval**

Ethical approval for the study was taken from RAK Medical and Health Sciences University Research and Ethics Committee (number: 4-2015-F-P), and RAK Research and Ethics Committee, UAE (number: Sep-2015-1).

**Results**

A total of 100 patients were on maintenance hemodialysis at the study site; of these 100 patients, 28 patients were excluded from the study as they did...
Phosphate binders used at our study site were sevelamer, calcium carbonate, and a combination of sevelamer and calcium carbonate. Twenty three (31.9%) patients were on sevelamer, 13 (18.1%) were on calcium carbonate, and the remaining 36 (50.0%) patients were taking a combination of sevelamer and calcium carbonate. The mean daily dose of phosphate binders were 4.5 ± 1.5 sevelamer tablets (800mg) and 2.6 ± 0.4 calcium carbonate tablets (600mg).

The descriptive data of the patient population stratified by the type of phosphate binder are depicted in Table 1. The changes in important biochemical parameters observed in the three groups during the observation period are depicted in Figure 1.

Serum phosphorous was significantly lower in patients on sevelamer per se (OR: 0.14, 95% confidence interval [CI]: 0.04–1.09) as well as in patients on a combination of sevelamer and calcium carbonate (OR: 0.10, 95% CI: 0.03–0.89) in the bivariate multinomial analysis when compared with calcium carbonate per se; however, the proportion of patients on target serum phosphorous for ESRD was similar among all the groups.

Serum calcium levels were significantly lower in patients treated with both sevelamer (OR: 0.11, 95% CI: 0.02–0.86) and combination of sevelamer and calcium carbonate (OR: 0.22, 95% CI: 0.01–0.96) compared to patients on calcium carbonate. A better control of calcium–phosphorous product was observed in sevelamer (OR: 0.20, 95% CI: 0.06–0.64) and combination-treated (OR: 0.16, 95% CI: 0.05–0.54) patients compared with calcium carbonate in the bivariate analysis.

It was observed that sevelamer group of patients had significantly lesser number of comorbidities (OR: 0.17, 95% CI: 0.04–0.77) than the patients in calcium carbonate group. Another important observation was in terms of type of comorbidity where cardiovascular diseases were significantly lesser in sevelamer group (OR: 0.32, 95% CI: 0.02–0.75) than calcium carbonate group in the bivariate analysis [Table 2].

In multinomial logistic regression analysis, eight independent variables associated with type of phosphate binder at level of P value <0.25 in the bivariate analysis were retained in the model. These were cause of renal disease, number of comorbidity, type of comorbidity, hemoglobin, serum creatinine, phosphorous, calcium, and calcium–phosphorous product. Variables with P values <0.05 in the multivariable model were considered independently associated with type of phosphate binder. In sevelamer group and combination group, cardiovascular diseases (OR: 0.12, 95% CI: 0.02–0.65 and OR: 0.10, 95% CI: 0.01–0.88) were significantly less when compared with calcium carbonate group after being adjusted for other variables in the model. In the combination group, serum phosphorous (OR: 0.05, 95% CI: 0.001–1.03) and calcium–phosphorous product (OR: 0.20, 95% CI: 0.05–0.77) were significantly less after being adjusted for other variables [Table 3].

**Discussion**

Hyperphosphatemia is an independent predictor of cardiovascular mortality in ESRD patients. In dialysis patients, its prevalence varies from 50% to 70% as reported by different studies. Previously we have reported that 73.8% of the patients in this study population presented with hyperphosphatemia. Adequate hyperphosphatemia control and reducing calcium overload are important therapeutic strategies. Phosphate binders are the mainstay of hyperphosphatemia management in ESRD patients on maintenance hemodialysis. Available data on the use of phosphate binders are inadequate to establish the superiority of non-CBBs over CBBs.

We observed that sevelamer and the combination therapy were associated with lower serum phosphorous, lower serum calcium, lower calcium–phosphorous product, lesser number of comorbidities, and reduced cardiovascular events versus calcium carbonate per se.

In our study, serum phosphorous was significantly lower in patients on sevelamer as well as in patients on combination therapy when compared with calcium carbonate per se. These results, both for sevelamer per se and the combination therapy, are in accordance with an RCT conducted by Di Iorio et al. and a study conducted by Iwasaki et al. where serum phosphorus levels were controlled better in the sevelamer group and the combination group, respectively. In contrast, several studies, meta-analyses, Cochrane systematic review, and RCT have reported no significant change in serum phosphorous levels between the sevelamer and calcium carbonate groups.

We observed that serum calcium was significantly lower in the sevelamer group as opposed to the calcium carbonate group.
This observation is in line with the findings of many studies including RCTs, meta-analyses, and Cochrane systemic reviews, which reported significantly lesser risk of hypercalcemia with sevelamer compared to calcium carbonate. This is attributed to the fact that CBBs contribute to the positive calcium balance.

We have earlier reported that 31.3% of the patients in this study population presented with high calcium–phosphorous product. High calcium–phosphorous product has been implicated in cardiovascular events and mortality among ESRD patients on maintenance dialysis. A better control of calcium–phosphorous product was observed in

| Variable                          | N  | All subjects | Sevelamer (N = 23) | Calcium carbonate (N = 13) | Sevelamer + calcium carbonate (N = 36) | 95% Confidence interval |
|-----------------------------------|----|--------------|-------------------|---------------------------|----------------------------------------|-------------------------|
| Age, year (m ± SD)                | 72 | 60.7 ± 9.6   | 60.3 ± 13.1       | 59.4 ± 9.5                | 61.4 ± 7.1                             | 58.4 ± 6.8–62.9 ± 11.8  |
| Gender (%)                        |    |              |                   |                           |                                        |                         |
| Female                            | 59.7 | 54.5        | 69.2              | 59.5                      |                                        | 47.2–70.8               |
| Male                              | 40.3 | 45.5        | 30.8              | 40.5                      |                                        | 29.2–52.8               |
| Nationality (%)                   |    |              |                   |                           |                                        |                         |
| Emirati                           | 47.2 | 50.0        | 61.5              | 40.5                      |                                        | 36.1–58.3               |
| Expatriate                        | 52.8 | 50.0        | 38.5              | 59.5                      |                                        | 41.7–63.9               |
| Hemodialysis duration (%)         |    |              |                   |                           |                                        |                         |
| ≤2 years                          | 68.1 | 68.2        | 76.9              | 64.9                      |                                        | 56.9–77.8               |
| >2 years                          | 31.9 | 31.8        | 23.1              | 35.1                      |                                        | 22.2–43.1               |
| Body mass index, kg/m² (m ± SD)   | 72  | 28.4 ± 3.0  | 27.7 ± 2.0        | 28.0 ± 3.3                | 28.9 ± 3.4                             | 27.7 ± 2.3–29.1 ± 3.5   |
| Cause of renal disease (%)        |    |              |                   |                           |                                        |                         |
| Hypertensive nephropathy           | 51.4 | 68.2        | 23.1              | 51.4                      |                                        | 38.9–62.5               |
| Diabetic nephropathy              | 48.6 | 31.8        | 76.9              | 48.6                      |                                        | 37.5–61.1               |
| Number of comorbidities (%)       |    |              |                   |                           |                                        |                         |
| One to two comorbidities          | 52.8 | 78.3        | 38.5              | 41.7                      |                                        | 41.7–65.3               |
| More than two comorbidities       | 47.2 | 21.7        | 61.5              | 58.3                      |                                        | 34.7–58.3               |
| Comorbidities (%)                 |    |              |                   |                           |                                        |                         |
| Hypertension                      | 36.1 | 34.8        | 15.4              | 44.4                      |                                        | 25.0–47.2               |
| Diabetes mellitus                 | 36.1 | 43.5        | 23.1              | 36.1                      |                                        | 25.0–47.2               |
| Cardiovascular diseases           | 27.8 | 21.7        | 61.5              | 19.4                      |                                        | 16.7–38.9               |
| Laboratory variables (m ± SD)     |    |              |                   |                           |                                        |                         |
| Hemoglobin, g/dL                  | 10.9 ± 1.1 | 10.9 ± 0.9 | 11.2 ± 1.1        | 10.8 ± 1.2                | 10.7 ± 0.88–11.2 ± 1.3                 |
| Serum creatinine, mmol/L          | 427.9 ± 161.2 | 406.7 ± 152.2 | 491.4 ± 171.5 | 418.2 ± 161.6               | 393.0 ± 133.2–468.7±185.5          |
| Urea, mmol/L                      | 11.3 ± 5.7  | 10.9 ± 4.1 | 12.7 ± 7.9        | 11.0 ± 5.6                | 10.02 ± 4.1–12.66 ± 7.1              |
| Serum phosphorus, mmol/L          | 1.7 ± 0.2  | 1.6 ± 0.3 | 1.8 ± 0.1         | 1.7 ± 0.2                | 1.6 ± 0.2–1.8 ± 0.2                  |
| Serum calcium, mmol/L             | 2.1 ± 0.1  | 2.1 ± 0.2 | 2.3 ± 0.2         | 2.1 ± 0.1                | 2.1 ± 0.1–2.2 ± 0.2                  |
| Calcium × phosphorous, mmol/L²    | 3.6 ± 0.6  | 3.5 ± 0.7 | 4.1 ± 0.3         | 3.5 ± 0.5                | 3.5 ± 0.5–3.8 ± 0.7                  |
| Parathyroid hormone, pmol/L       | 64.9 ± 61.6 | 63.0 ± 16.4 | 65.9 ± 58.7 | 64.4 ± 73.5                | 52.9 ± 22.7–80.4±88.8             |
| Alkaline phosphatase, IU/L        | 136.9 ± 144.1 | 134.8 ± 143.1 | 99.1 ± 24.6 | 145.7 ± 156.1               | 109.2 ± 78.2–172.4±205.0          |
| Kt/V                              | 1.28 ± 0.03 | 1.26 ± 0.03 | 1.29 ± 0.03 | 1.29 ± 0.03                | 1.27 ± 0.02–1.29 ± 0.04           |
| Medications (%)                   |    |              |                   |                           |                                        |                         |
| ACEI                              | 15.3 | 9.1         | 23.1              | 16.2                      |                                        | 6.9–23.6                |
| ARB                               | 34.7 | 22.7        | 53.8              | 35.1                      |                                        | 23.6–45.8               |
| CCB                               | 80.6 | 81.8        | 69.2              | 83.8                      |                                        | 70.8–88.9               |
| Diuretics                         | 34.7 | 36.4        | 30.8              | 35.1                      |                                        | 25.0–45.8               |
| Beta blockers                     | 37.5 | 22.7        | 38.5              | 45.9                      |                                        | 26.4–48.6               |
| Hypoglycemics                     | 62.5 | 63.6        | 69.2              | 59.5                      |                                        | 51.4–72.2               |
| ESA                               | 87.5 | 77.3        | 92.3              | 91.9                      |                                        | 79.2–94.4               |
| Iron supplements                  | 97.2 | 95.5        | 100.0             | 97.3                      |                                        | 93.1–100.0              |
| Hypolipidemics                    | 76.4 | 68.2        | 76.9              | 81.1                      |                                        | 66.7–86.1               |

ACEI = angiotensin-converting-enzyme inhibitors, ARB = angiotensin receptor blockers, CCB = calcium channel blockers, ESA = erythropoiesis-stimulating agent, SD = standard deviation
sevelamer-treated patients versus calcium carbonate in our study. However, studies have shown no significant differences between sevelamer and CBBs with respect to control of calcium–phosphorous product.\textsuperscript{[13,19,21]}

A meta-analysis\textsuperscript{[22]} studied seven RCTs for the effect of sevelamer and CBBs on coronary artery and aortic calcification and reported that sevelamer was better in preventing the vascular calcification than CBBs. Di Iorio \textit{et al.}\textsuperscript{[11]} reported that in ESRD patients on hemodialysis, sevelamer decreased cardiovascular and all-cause mortality. In our study, sevelamer group of patients had significantly lesser number of comorbidities than the patients in calcium carbonate group. Another important observation was in terms of type of comorbidity where cardiovascular diseases were significantly lesser in sevelamer than calcium carbonate. This finding can be attributed to sevelamer’s ability to decrease calcium load and attenuate vascular calcification, leading to improved cardiovascular outcomes.

Very few studies have focused on the safety and efficacy of combined therapy of sevelamer and calcium carbonate.\textsuperscript{[18,24,25]} Iwasaki \textit{et al.}\textsuperscript{[18]} reported that the combination therapy with sevelamer and calcium

![Figure 1: Effect of different phosphate binders on the biochemical parameters](image)

**Table 2: Bivariate multinomial logistic regression analysis demonstrating relationship of phosphate binders with other variables in end-stage renal disease patients**

| Variable (reference) | Sevelamer\textsuperscript{a} | Sevelamer + calcium carbonate\textsuperscript{a} |
|----------------------|-------------------------------|-----------------------------------------------|
|                      | Odds ratio 95% CI  P-value     | Odds ratio 95% CI  P-value                   |
| Age, years           | 1.01 0.94–1.08 0.771         | 1.02 0.95–1.09 0.496                         |
| Gender (Female)      |                               |                                               |
| Male                 | 2.06 0.49–8.65 0.322         | 1.43 0.36–5.55 0.603                         |
| Nationality (Emirati)|                               |                                               |
| Expatriate           | 1.74 0.43–6.97 0.431         | 2.24 0.61–8.21 0.224                         |
| Body mass index, kg/m\textsuperscript{2} | 0.94 0.72–1.21 0.643         | 1.11 0.89–1.39 0.335                         |
| Cause of renal disease (diabetic nephropathy) |                               |                                               |
| Hypertensive nephropathy | 6.25 1.32–29.4 0.020     | 3.72 0.87–15.8 0.075                         |
| Number of comorbidities (one to two comorbidities) |                               |                                               |
| More than two comorbidities | 0.17 0.04–0.77 0.022    | 0.87 0.24–3.20 0.840                         |
| Comorbidities (hypertension) |                               |                                               |
| Diabetes             | 0.54 0.07–3.74 0.534         | 0.83 0.11–6.26 0.859                         |
| Cardiovascular diseases | 0.32 0.02–0.75 0.015      | 0.16 0.02–1.05 0.057                         |
| Hemoglobin, g/dL     | 0.61 0.33–1.14 0.119         | 0.52 0.29–0.94 0.032                         |
| Serum creatinine, mmol/L | 0.99 0.99–1.00 0.156      | 0.99 0.99–1.00 0.156                         |
| Urea, mmol/L         | 0.94 0.84–1.06 0.345         | 0.95 0.86–1.06 0.402                         |
| Serum phosphorus, mmol/L | 0.14 0.04–1.09 0.047    | 0.10 0.03–0.89 0.042                         |
| Serum calcium, mmol/L | 0.11 0.02–0.86 0.041      | 0.22 0.01–0.96 0.012                         |
| Calcium × phosphorous, mmol\textsuperscript{2}/L\textsuperscript{2} | 0.20 0.06–0.64 0.008    | 0.16 0.05–0.54 0.003                         |
| Parathyroid hormone, pmol/L | 1.00 0.99–1.01 0.914  | 1.00 0.99–1.01 0.887                         |
| Alkaline phosphatase, IU/L | 1.00 0.99–1.02 0.342 | 1.00 0.99–1.01 0.347                         |

CI = confidence interval
Statistically significant values are in bold
\textsuperscript{a}The reference category is calcium carbonate
carbonate was superior to single drug therapy as it was associated with lower incidence of adverse effects and significant reduction in serum phosphorous, serum calcium, and calcium–phosphorous product. Our findings, better control of serum phosphorous, serum calcium, and calcium–phosphorous product with combination therapy as compared to calcium carbonate, are in agreement with the findings of Iwasaki et al. [18] We also observed that in the combination group, cardiovascular diseases were significantly less when compared to calcium carbonate group. This observation can be explained by attenuation of coronary calcification and improvement of calcium overload by sevelamer, leading to possible reduction in vascular calcification with the combination therapy.[18,26] Our study has some limitations worth stating. One main limitation is its observational nature. Single-center study with relatively small sample size represents another possible limitation, which may not allow generalization of results as the sample size is not the comprehensive representation of the multiethnic population of UAE.

Conclusion

In conclusion, we observed that hyperphosphatemia and related events in our study population were better controlled by sevelamer per se and the combination therapy than calcium carbonate per se. Patients treated with sevelamer per se and combination therapy were associated with lesser cardiovascular events when compared to calcium carbonate. Further large-scale, multicenter studies are required to confirm and establish these findings in the multiethnic population of the region.

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Conflicts of interest

There are no conflicts of interest.

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