Original Article

موضوع أصيل

ROLE OF SEVELAMER CARBONATE IN THE TREATMENT OF HYPERPHOSPHATEMIA IN THE CHRONIC KIDNEY DISEASE PATIENTS ON HEMODIALYSIS THERAPY

دور كربونات سيفيلامير في علاج فرط فوسفات الدم عند مرضى الأمراض الكلوية المزمنة الموضوعين على التحال الدموي

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ملخص البحث

هدف البحث: يعتبر فرط فوسفات الدم من المضاعفات المتكررة عند مرضى الأمراض الكلوية المزمنة، وخاصةً مرضى المراحل المتقدمة من المرض الكلوي، وهناك أدلة هامة على أن عدم السيطرة على الفوسفور يرتبط بزيادة معدلات المراضة والوفيات. يهدف هذا البحث إلى تقييم فعالية وسلامة كربونات سيفيلامير في حالات فرط فوسفات الدم عند مرضى الأمراض الكلوية المزمنة الموضوعين على التحال الدموي.

طرق البحث: أجريت هذه الدراسة المستقبلية خلال الفترة بين كانون الثاني 2018 وحتى كانون الأول 2018، وشملت 100 مريضٍ من مرضى فرط فوسفات الدم في المرحلة النهائية للمرض الكلوي والخاضعين للتحال الدموي. خضع جميع المرضى لاستجواب القصة المرضية وللفحص الفيزيائي في الحالة القاعدية، ومن ثم تم إعطاء جميع المرضى أقراص كاربونات الكالسيوم، كما أعطي نصف المرضى فقط أقراص كربونات سيفلامير لمدة ستة أشهر (24 أسبوعاً). شملت الاستقصاءات المخبرية المجراة كلاً من مستوى البولة والكرياتينين في الدم، الكالسيوم، الفوسفور، الفوسفاتاز القلوية وهرمون الغدد جارات الدرق PTH في مصل الدم.

النتائج: حققت المعالجة بكربونات سيفلامير مع كربونات الكالسيوم انخفاضاً كبيراً في المستويات المصلية للفوسفور، هرمون الغدد جارات الدرق PTH والكالسيوم عند المقارنة مع المعالجة بكربونات الكالسيوم فقط. يرتبط مستوى الفوسفور في مصل الدم بشكلٍ إيجابي مع مستوى هرمون الغدد جارات الدرق PTH، بينما يرتبط بشكلٍ سلبي مع مستوى الكالسيوم في المصل.

الاستنتاجات: كانت المعالجة بكربونات سيفلامير فعالة وآمنة في حالات فرط فوسفات الدم عند مرضى القصور الكلوي المزمن الخاضعين للتحال الدموي.

ABSTRACT

Objective: *Hyperphosphataemia is a frequent complication in patients with chronic kidney disease (CKD), particularly in those with end-stage renal disease, and there is considerable evidence that inadequate phosphorus control is associated with increased morbidity and mortality. The aim of this study was to evaluate the efficacy and safety of sevelamer carbonate in patients with hyperphosphataemia and CKD on hemodialysis.*

Methods: *This prospective study was performed during the period from January 2018 till December 2018. One hundred patients complaining of hyperphosphataemia and end stage renal disease on hemodialysis were included in this study, all patients underwent a history*

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and physical examination at baseline, all patients were taken calcium carbonate tablets, and half of them were received sevelamer carbonate tablets for a period of six months (24 weeks). The investigations include blood urea, serum creatinine, calcium, phosphorus, alkaline phosphatase and parathyroid hormone.

Results: *Sevelamer carbonate plus calcium carbonate made a significant reduction in serum phosphorus, parathyroid hormone and serum calcium levels when compared with calcium carbonate received patients, serum phosphorus correlated positively with s.PTH while negatively with s.Ca.*

Conclusions: *Sevelamer carbonate was effective and safe in hyperphosphataemia patients with chronic renal failure on hemodialysis.*

INTRODUCTION

Chronic kidney disease (CKD) describes abnormal renal function and/or structure. It is often exists together with other conditions, such as cardiovascular disease and/or diabetes.[1] Hyperphosphataemia is a frequent complication in patients with chronic kidney disease (CKD), particularly in those with advanced or end-stage renal disease, and there is considerable evidence that inadequate phosphorus control is associated with increased morbidity and mortality in patients with CKD stage 5.[2-4]

Normally, the kidney filters a very large quantity of inorganic phosphorus, and then the tubules; primarily the proximal tubules reabsorb more than 90% of this load. Phosphorus reabsorption is primarily regulated by parathyroid hormone. Extracellular fluid volume status also affects phosphorus reabsorption.[5] Furthermore, one research indicates an important role for other phosphateonin hormones such as fibroblast growth factor-23.[6] Serum phosphorus levels in patients with early and mild kidney insufficiency may remain normal (or even be reduced) as a result of secondary hyperparathyroidism. Yet, compensating mechanisms fail when kidney dysfunction advances resulting in positive phosphorus balance, which leads to progressive hyperphosphataemia.[5]

Hyperphosphataemia occurs because of inadequate filtering of phosphate from the blood by poorly functioning kidneys. So that certain amount of the phosphate does not leave the body within the urine but remaining in the blood at abnormally high levels. Elevated serum phosphate levels can directly and indirectly raise parathyroid hormone secretion, leading to the development of secondary hyperparathyroidism. Left untreated, secondary hyperparathyroidism leads to increase morbidity and mortality and may cause renal bone disease, with people experience bone and muscular pain, increased occurrence of fracture, abnormalities of bone and joint morphology, vascular and soft tissue calcification,[1] and increased coronary artery calcification and cardiovascular mortality in patients on peritoneal dialysis (PD);[7,8] the British Renal Association guidelines recommend that in patients with kidney disease, serum phosphorus, if elevated, should be lowered towards the normal range, between 1.1 and 1.8 mmol/l (3.41-5.57 mg/dl).[9] Serum phosphate can be reduced by dietary phosphate restriction, but this is usually not feasible in isolation without promoting protein malnutrition. Standard dialysis (4 hours thrice weekly) removes phosphate from the circulation, but in amounts insufficient to effectively control serum levels, PTH secretion, or renal bone disease. It is therefore necessary to reduce significantly the intestinal absorption.[5,10] Phosphate binders are widely used to control serum phosphorus levels in patients with chronic kidney disease (CKD).[11]

Nowadays several effective phosphate binders are available. Aluminium-based binders at high doses may induce aluminium accumulation and toxicity manifested as encephalopathy, osteomalacia and anaemia, while calcium-containing binders may contribute to causing cardiovascular (CV) calcification; thus, aluminium- and calcium-free phosphate binders may represent an advantageous therapeutic solution.[12]

Calcium carbonate was the first widely used calcium-based binder; later calcium acetate was introduced. Calcium reacts with phosphorus, forming an insoluble salt. Though, the calcium carbonate dose required to control phosphorus in HD patients is in the range of 3-12 g/day, and it is estimated that approximately 20-30% of this load will be absorbed caused a high

frequency of hypercalcemia. Although calcium salt binders are efficacious and cost effective, long-term safety questions about their use arose because of concern about excess calcium absorption, positive calcium balance, hypercalcemia, and their possible relationship to the development of soft-tissue and cardiovascular calcifications.[5] However; because of concerns for the squeal of positive Ca balance, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend restricting calcium based binders for patients with known vascular calcification, persistently low PTH, low/adynamic bone turnover, and persistent/ recurrent hypercalcemia.[13]

Sevelamer carbonate is a new buffered formulation which is an anion exchange pharmaceutical, developed to improve on the performance of the non-absorbable, non-calcium, and metal-free phosphate binder sevelamer hydrochloride. Sevelamer carbonate is expected not to worsen metabolic acidosis, as previously reported during long-term treatment with sevelamer hydrochloride in hemodialysis (HD) patients.[14,15] However, as sevelamer carbonate does not decrease serum bicarbonate levels, it may be more appropriate for patients at risk for metabolic acidosis who require phosphate binders that do not contain calcium or aluminum.[15]

The widespread use of calcium-based binders could have several explanations. Some authors have reported that calcium-based salts in HD patients showed good phosphate-binding capability, cost affordability, and lack of compelling evidence for a significantly reduced outcome in overall mortality compared with sevelamer.[16] Others, however; have interpreted the reduced calcification in sevelamer-treated patients by its lipid-lowering properties more than its phosphate-binding properties.[17]

METHODS

Study setting and design: This prospective study was performed in the in the internal medicine ward/ hemodialysis unit in Al-Imamain Al-Kadhimain Medical City in Baghdad, which is a general hospital getting patients from primary health center, daily consultation clinic and the 24 hours emergency department, during the period from January 2018 to December 2018.

One hundred patients (59 males and 41 females) complaining of end stage renal disease (ESRD) on hemodialysis and suffering from hyperphosphatemia and hypocalcaemia were involved in this study, and divided into two groups randomly 50 patients in each, all of them were taking calcium carbonate, and only one group were received sevelamer carbonate.

Each patient at end stage renal disease was subjected to hemodialysis for period of 4 hours in two or three sessions per week using Gambro machine. All patients underwent a history and physical examination at baseline. All patients were taken calcium carbonate 600 mg tablets (caltrate®) from pfizer in a mean dose of 1.5±0.2 g, and half of them were received sevelamer carbonate tablets 800 mg (Renvela®) from genzyme/ Irland in a mean dose of 2.6±1.2 g for a period of six months (24 weeks). All patients advised to avoid diet containing phosphorus such as eggs and milk, also avoiding one-alpha capsules at the study time.

Exclusion criteria involved 11 patients that non complained on sevelamer and those whom irregular on hemodialysis. The investigations include blood urea, serum creatinine, calcium, phosphorus, alkaline phosphatase and parathyroid hormone. All laboratory analyses performed at Laboratory Department of Al-Imamain Al-Kadhimain Medical City.

A preformed questionnaire (Appendix) was used to get information from studied population, which included general information from the patients and duration of hemodialysis.

Efficacy and safety assessment: The efficacy endpoint was the lowering in serum phosphorus levels after 24 weeks in patients on hemodialysis to attain the NKF Kidney Disease Outcomes Quality Initiative (K/ DOQI) target of serum phosphorus <5.5 mg/dl after 24 weeks of treatment. Also changes in serum calcium, PTH, alkaline phosphatase (ALP), creatinine and blood urea were compared. Blood samples were assessed

at baseline and weeks 4, 8, 12, 16, 20 and 24. Safety endpoints included the occurrence of adverse effects.

Statistical analysis was performed using SPSS (Statistical Package for social Science) version (22), and Microsoft Excel Worksheet 2013. Crude data was analyzed to achieve mean and standard deviation (SD). Student paired t-test was used to compare between two groups. Chi-square test was used for categorical variables. Person's correlation test was used to compare between serum P with serum Ca and serum PTH. P-value of ≤0.05 considered to be significant.

RESULTS

The demographic and clinical characteristics of the studied cases were shown the following findings: They were divided randomly into two equal groups, the first group was on sevelamer carbonate plus calcium carbonate taking, most of the patients (64%) of without diet modification; hypertension was the most common cause of renal failure in this group (54%), followed by diabetes mellitus with hypertension (28%). Most of patients (74%) were hepatitis negative, with only 26% hepatitis positive patients from them 14% hepatitis C and the rest were have hepatitis C with B.

The second group was calcium carbonate taking; half of the patients (50%) were without diet modification; diabetes mellitus with hypertension was the most common cause of renal failure in this study (44%) followed by hypertension (42%). Most of patients (72%) were hepatitis negative, with only 28% hepatitis positive patients from them 20%

	Sevelamer carbonate plus calcium carbonate (n=50)		Calcium carbonate (n=50)
	Characteristics	No. (%)	No. (%)
Age range (years)	22-75		28-80
Sex	Males	33 (66%)	26 (52%)
	Females	17 (34%)	24 (48%)
Diet modification	+ve	4 (8%)	5 (10%)
	+,-ve	14 (28%)	20 (40%)
	-ve	32 (64%)	25 (50%)
Cause of renal failure	Hypertension	27 (54%)	21 (42%)
	HT and DM	14 (28%)	22 (44%)
	Obstructive uropathy	4 (8%)	4 (8%)
	Hereditary renal disease	5 (10%)	3 (6%)
Duration of hemo-dialysis (years)	0-2	17 (34%)	15 (30%)
	2-4	24 (48%)	26 (52%)
	4-6	7 (14%)	6 (12%)
	>6	2 (4%)	3 (6%)
Virological screen	Hepatitis C	7 (14%)	4 (8%)
	Hepatitis C and B	6 (12%)	10 (20%)
	Hepatitis negative	37 (74%)	36 (72%)

Table 1. Baseline demographic and clinical data of patients with chronic renal failure on hemodialysis.

hepatitis C with B, and the rest were have hepatitis C, as shown in Table 1.

Serum phosphorus s.P, alkaline phosphatase s.ALP, creatinine, calcium s.Ca and parathyroid hormone s.PTH together with blood urea levels in all 100 patients were analyzed, the mean±SD were obtained, comparison between the two groups after the end of the study (24 weeks) was done.

After 24 weeks, the analysis showed that sevelamer carbonate plus calcium carbonate taking group made a significant reduction in mean serum phosphorus and parathyroid levels when compared with calcium carbonate taking group ($p \leq 0.05$); also a significant reduction in mean serum calcium was obtained at ($p \leq 0.01$); Table 2.

There was an observed patient responsiveness (66%) for sevelamer and calcium carbonate received patients, compared with (59%) for those received Ca carbonate, as showed in Figure 1.

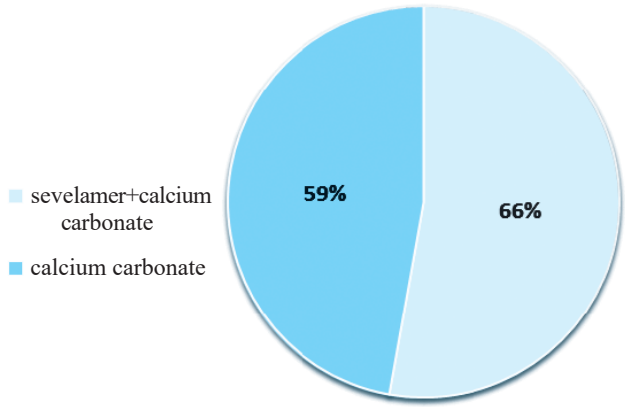


Figure 1. Patient responsiveness in the two groups.

The analyzed data showed that 22% of the collected sample of sevelamer carbonate taking group expressed drug related adverse effects, with the larger percent 18% of them whom experienced gastrointestinal side effects (like nausea, vomiting, bloating, flatulence and dysphagia), the rest 4% complaining from neurological side effects (like headache and dizziness).

The person's correlation analysis for both groups showed that there is a strong positive correlation between the parathyroid hormone levels and phosphorus levels in the serum; while a strong negative correlation showed when the calcium levels compared with phosphorus serum levels, as showed in Figure 2 and 3, respectively.

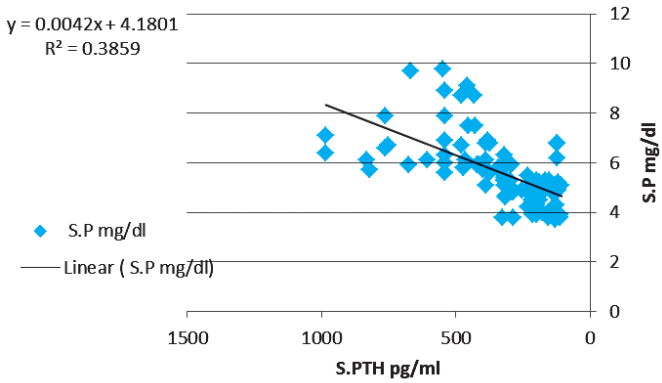
Adverse effects	Number (%)
Gatrointestinal	**Total 24 (48%)**
Nausea and vomiting	12
Bloating	4
Stomach discomfort	2
Full feeling	2
Dysphagia	1
Flatulence	3
Neurological	Total 15 (30%)
Dizziness	4
Extremity pain	3
Headache	5
Fatigue	3

Table 2. Sevelamer carbonate related adverse effects.

DISCUSSION

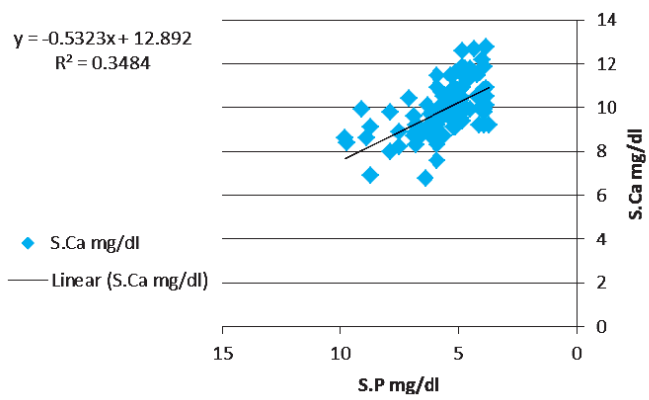
Hyperphosphatemia in general is difficult to control in patients with chronic kidney disease on dialysis, particularly in its highly developed stages, and is associated with a notable mortality risk.[18] In our study; sevelamer carbonate treatment resulted in statistically significant reductions in serum phosphorus at ($p \leq 0.05$). The mean serum phosphorus at the end of 24 weeks of the study was 5.48 mg/dl, a level well within the recommended levels for patients with stage 5 CKD on hemodialysis; other study by Delmez J et al found that the mean serum phosphorus was lowered to reach 4.6±0.9 after receiving sevelamer carbonate.[19]

Moreover, at least 66% of patients were able to achieve a serum phosphorous within the ranges recommended for CKD patients in sevelamer and calcium carbonate received group (G1) (≤5.5 mg/dl for patients with stage 5 CKD), when compared with calcium carbonate received group (G2) 59%. This response rate is slightly higher than the 50% response rate that would be expected from other studies, as reported by Bommer J et al at their study,[20] which



(r ,0.621193 =P≤ 0.001)

Figure 2. Correlation of S.P with S.PTH.



(r = -0.59028, P≤ 0.005)

Figure 3. Correlation of S.P with S.Ca.

may be due to the use of calcium carbonate together with sevelamer therapy which adds some reduction in phosphorus levels.

In our study the mean daily doses of sevelamer carbonate required to achieve this reduction in phosphorus levels was 2.6 g. Concurrently, there was a significant lowering in mean change in the elevation of serum calcium of (G1) 0.16±0.83 when compared to (G2) 0.46±0.05, (p≤0.01). Evenepoels P et al study reported that there was a significant reduction in the change of serum calcium between the tested groups 0.05±0.57 for sevelamer hydrochloride group against 0.46±0.85 for calcium acetate group.[21] A significant reduction in serum concentration of parathyroid hormone of sevelamer and calcium carbonate received group was observed 304±87.2 when compared with group 2 which was 311±119.96 with p≤0.05, which suggesting a modulation of s.PTH hormone, which greatly affected by calcium and phosphorus levels. A study by Chertow GM et al. reported that the reduction in PTH tended to be larger in the RenaGel with calcium group [median change -67.0 versus -22.5 pg/ml in RenaGel group, p=0.07].[22]

Our analysis showed that there was a positive correlation between serum PTH and serum phosphorus, while a negative correlation was observed between serum phosphorus and serum Ca, as mentioned in Figure 2 and 3 respectively.

Sevelamer carbonate was well tolerated, with an adverse effects profile reliable with its known effects and the underlying kidney disease of patients. Intolerance to sevelamer in 22% of hemodialysis patients, most of them (18%) of gastrointestinal complaints, non-compliance with sevelamer therapy was the major reason why phosphorus control remains sub-optimal (34%) in many dialysis patients, again Evenepoel P et al. in their previously mentioned study reported that percentage of patients experiencing adverse effects considered to be related to treatment were 36% in the sevelamer group, from them 27% gastrointestinal adverse effects,[21] the differences in the results may be due to the higher risk of patients on peritoneal dialysis to develop gastrointestinal adverse effects than patients on hemodialysis.

CONCLUSIONS

Sevelamer carbonate with calcium carbonate was effective in reducing serum phosphorus, parathyroid hormone and serum calcium levels when compared with calcium carbonate in CRF patients with hyperphosphatemia and on hemodialysis. Sevelamer was safe to be used in CRF patients with hyperphosphatemia and on hemodialysis. Serum phosphorus correlated positively with s.PTH, while negatively with s.Ca.

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