

Comparative Efficacy of Sevelamer Hydrochloride Versus Calcium Acetate on Bone Biomarkers in patients with End Stage Renal Disease on Hemodialysis

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ABSTRACT

Aim: To compare the effects of Sevelamer and calcium acetate on biomarkers of bone turnover in patients of end stage renal disease (ESRD).

Methods: This was a prospective, randomized, open label study, total 140 patients of ESRD underwent two week washout period and were divided randomly into two groups, Group A (received Sevelamer) and Group B (received calcium acetate) for 24 weeks. Mean changes in the serum level of calcium phosphorus and intact PTH were measured and compared.

Results: After 24 weeks of treatment there was significantly reduction of phosphorus in Group A as compared with Group B (-1.764mg/dl vs. 1.0600 p=0.000). Mean change in iPTH was more in Group B as compared with Group A (-124.32pg/ml vs. -83.44 pg/ml, p=0.044). There is significant increase in serum calcium level in Group B patients compared to Group A (0.688mg/dl vs. -0.126 mg/dl, p=0.000).

Conclusion: Sevelamer effectively reduces serum phosphorus with a lower incidence of rise in serum calcium level in dialysis population, although more reduction of iPTH occurred in calcium acetate group.

Key words: Sevelamer hydrochloride, bone biomarkers, renal disease, hemodialysis

INTRODUCTION

The term chronic kidney disease-mineral and bone disorder' (CKD-MBD), was coined in 2006 by the Kidney Disease Improving Global Outcomes (KDIGO) organization.² The prevalence of renal bone disease in dialysis population worldwide ranges between 33 to 67%.³ Based on intact Parathyroid hormone (iPTH) level, renal osteodystrophy is divided in two main groups, majority having high turnover bone disease (high iPTH) and small population having low turnover bone disease.⁴ The basic cause of hyperparathyroidism and renal osteodystrophy is inadequate clearance of phosphorus by the diseased kidneys, as result it accumulates in the body leading to hyperphosphatemia. Each 1-mg/dl rise in serum phosphorus was associated with a 23% increased risk of death.⁵

As a consequence, lowering of serum phosphorus appears to be a key therapeutic goal. In addition to hemodialysis and dietary restrictions, phosphate binders are the treatment of choice in patients with hyperphosphatemia.¹

At present two groups of phosphate binders are present, calcium-containing are calcium acetate, calcium carbonate while calcium-free phosphate binders include Sevelamer hydrochloride and Lanthanum carbonate.¹ Both of these are equally

effective in terms of binding of free phosphate.⁵ Calcium-containing binders have been widely used but now concern has arisen regarding unwanted effect of hypercalcaemia, increasing chance of vascular calcification.⁶

Sevelamer hydrochloride is a recently developed phosphate binder, which is a quaternary amine anion exchanger without calcium or aluminum. It is effective in controlling hyperphosphatemia without increasing the calcium load.⁷ Sevelamer, binds dietary phosphate in the gastrointestinal (GI) tract, Sevelamer appeared to slow the progression of cardiovascular calcification in patients with ESRD.⁸ According to RIND and TTG study calcium based binders resulted in 11 times more coronary calcification than sevelamer.⁹

MATERIALS AND METHODS

This prospective, randomized, single center study compared efficacy of two different oral phosphate binders treatment for 24 weeks in hemodialysis. Patients aged 18-80 years, stable on thrice a week hemodialysis for at least three months were enrolled in the study. The main eligibility criteria was serum phosphorus >4mg/dl, serum calcium <10.4mg/dl, and iPTH level >250pg/dl, patients with malignant involvement of bone, tertiary hyperparathyroidism and salt wasting nephropathy were excluded. After two week washout period of phosphate binders,

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patients were randomly divided into two groups, Group A received Sevelamer hydrochloride 800mg three times a day, and Group B patients received calcium acetate 667mg three times a day for 24 weeks. Patients compliance with the treatment was checked weekly from patients diary entries, by counting of used and unused tablets. All the patients were switched to the thrice a week hemodialysis with dialysate fluid calcium of 1.25mmol/L, and it remained constant throughout the study.

The primary target variable were serum calcium, phosphorus and iPTH at start of study and then at the end of 24 weeks. Difference of means of baseline values and those at six month in both groups were calculated and compared.

Quantitative data like age and change in levels of calcium, phosphorus and iPTH were presented by mean and SD. Qualitative data like gender was presented by frequency and percentages. Mean change in calcium, phosphorus and iPTH levels was calculated by subtracting post treatment levels from pre-treatment levels. T-test was used to compare mean change in both groups for significance. A p-value of 0.05 or less than 0.05 was taken as significant.

RESULTS

Total 140 patients were enrolled for the study (78 males and 62 females). These patients were randomly divided into two groups, 70 patients in each group. In group A (getting Sevelamer 800mg thrice a day) mean age of patients was 44.9 years, 37 were males and 33 were females. In group B (getting Calcium Acetate 667mg thrice a day) mean age was 41.9 years, 41 were males and 29 were females.

Table 1: Mean values of serum calcium, phosphorus and iPTH at the start of study and at end of study in both groups

	Group A	Group B
Mean Calcium mg/dl		
Pre Study	8.48±0.895	7.90±0.789
Post Study	8.35±0.756	8.59±0.654
Pre-post study change	-0.126±0.628	+0.699±0.53
Mean Phosphate mg/dl		
Pre Study	6.73±1.35	6.29±1.041
Post Study	4.96±0.704	5.23±0.762
Pre-post study change	-1.764±0.931	-1.0600±0.610
Mean iPTH		
Pre Study	626.82±259.43	515.9±215.21
Post Study	543.35±269.07	388.14±157.46
Pre-post study change	-83.44±104.92	-124.32±131.12

Table 2: Comparison between the pre-post study changes in mean calcium, phosphate and iPTH in both groups

	Group A	Group B	P value
Pre-post study change in mean serum Ca ⁺	-0.126±0.62	+0.688±0.53	p=0.00
Pre-post study change in mean serum PO ₄	-1.764±0.93	-1.0600±0.61	p=0.00
Pre-post study change in mean serum iPTH	-83.44±104.9	-124.32±131.12	P=0.04

It was worth noting that there was a fall in mean serum calcium level in group A after the treatment with Sevalamar, while in group B, mean serum calcium level increased after the treatment with calcium acetate.

It is clearly shown that phosphorus was more efficiently controlled by Sevelamer hydrochloride as compared to Calcium acetate (-1.764mg/dl vs. 1.0600 p=0.000), more reduction in iPTH occurred in Calcium Acetate group (-124.32 pg/ml vs. -83.44 pg/ml, p=0.04) and rise in serum calcium was also seen in calcium acetate group (0.688mg/dl vs. -0.126 mg/dl, p=0.00)

DISCUSSION

It is hyperphosphatemia because of retention of phosphates in CKD patients which lead to hyperparathyroidism and renal osteodystrophy. The increased risk of metabolic bone disease in CKD compels to do early intervention to avoid risk of fracture, osteoporosis, osteomalacia and a dynamic bone disease and cardiovascular events. These complications have a great effect on patient's life. K/DOQI guidelines for patients with early-stage CKD recommend a phosphorus level to be in a lower range (2.7 to 4.6 mg/dl) compared to the patients with stage 5 CKD (5.5 mg/dl), and there is mounting evidence that patients are benefited by lowering the phosphate up to this level.^{10,11} To reduce the phosphorus in the body with CKD, we need reduced intake of phosphorus containing diet, phosphate binders and removal of phosphorus from the body by dialysis in ESRD patients.

In this study objective was to evaluate phosphorus reduction and effects on iPTH and risk of hypercalcemia in hemodialysis population using either Sevelamer hydrochloride or calcium acetate. There is conflicting data regarding the phosphorus binding efficacy of Sevelamer versus calcium acetate. Some studies favoring the Sevelamar, some favoring Calcium Acetate as better phosphate binder, while few showing no difference between these

drugs^{12,13}. In our study we found Sevelamer as better phosphorus lowering drug as compared to calcium acetate (-1.764±0.931 vs -1.0600±0.610, p=0.00). Compared to calcium acetate, there was less rise in serum calcium level in Sevelamer group (+0.688±0.53 vs -0.126±0.628, p=0.00), where as iPTH level was decreased more in Calcium acetate group (-124.32±131.128 vs -83.44±104.99, p=0.04), it might be because of the mean rise in serum calcium level in this group. Similar results has been shown in other studies.¹² Rise in serum Calcium level in calcium acetate treated group may have association with coronary calcification leading to cardiac events, which is leading cause of death in dialysis population. Such results have been established in other international studies and Sevelamer also shown to reduce the coronary calcification and also all cause mortality upto 22% as compared with calcium acetate⁷.

There are few limitations to the present study. Firstly, it is a single centre study. Secondly, this is not a case controlled study, so the evidence obtained is not strong and finally effects on mortality were not studied. Further studies are needed to focus on these issues specially the effects of these changes on mortality and to make recommendation for our people.

CONCLUSION

The conclusion of this study is that hyperphosphatemia is better controlled with Sevelamer as compared with Calcium acetate. More over Sevelamer was not shown to be associated with rise in rise in serum calcium, while in calcium acetate group, there was a significant rise in serum calcium level. However iPTH was more reduced in Calcium acetate group as compared to Sevelamer group.

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