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Research Article

Efficacy of Sevelamer Carbonate versus Lanthanum Carbonate as a Phosphate Binder in CKD Stage 3 To 5 -

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ABSTRACT

Background: High serum phosphate level is associated with increased CVD morbidity and mortality in CKD patients. We sought to compare the efficacy of non-calcium containing phosphate binder Sevelamer Carbonate (SC) with Lanthanum Carbonate (LC) in patients with CKD stage 3-5.

Method: This single-center prospective open-label cross over study was carried out in the department of Nephrology Seth Sukhlal Karnani Memorial Hospital and Institute of postgraduate medical education and research (SSKM & IPGMER) Kolkata India between February 2013 and June 2014. All patients with CKD stage 3-5 not receiving dialysis and having corrected total serum calcium ≥8.5 mg/ dl and serum phosphate ≥4.0 mg/dl were divided into 2 groups to receive lanthanum carbonate 2000 mg a day in four divided doses and sevelamer carbonate 2400mg a day in three divided doses for 12 weeks. Each Patient then received the alternative binder for another 12 weeks after a washout period of 2 weeks. First exposure to phosphate binders was labeled as intervention 1 and second exposure after the washout period and cross over as intervention 2. Change in serum phosphate (Mean ± SD) between SC and LC arms following intervention 1 and 2 were compared.

Results: Forty-eight patients completed the study protocol. Mean Phosphate at baseline was 4.85 ± 0.90 mg/ dl and mean phosphate levels after intervention 1 was 4.16 ± 0.72mg/ dl, p <0.001. Mean difference in phosphate levels between sevelamer carbonate and lanthanum carbonate groups was not significant, p-0.2. Mean phosphate level after wash out and before intervention 2 was 4.54 ± 0.46 mg/ dl and mean phosphate levels after cross over and intervention 2 was 3.85 ± 0.57 mg/ dl, p <0.001. The difference in phosphate levels between sevelamer carbonate and lanthanum carbonate after cross over was not statistically significant, p-0.80.

Conclusion: Sevelamer Carbonate and Lanthanum carbonate are effective phosphate binders and are equally efficacious in reducing serum phosphate levels in non-dialysis patients with CKD 3-5.

Keywords: LC: Lanthanum Carbonate; SC: Sevelamer Carbonate; PO4: Phosphate

ABBREVIATIONS

SC: Sevelamer Carbonate; LC: Lanthanum Carbonate; PO4: Phosphate; ND: Non-Dialysis; CVD: Cardiovascular Disease

INTRODUCTION

Chronic Kidney Disease (CKD) is a leading cause of morbidity and mortality worldwide. An important contributor to this disease burden is the associated Mineral and Bone Disorder (MBD). There is a statistical association between the relative risk of death and serum levels of phosphate [1]. The present study was done to compare the efficacy of lanthanum carbonate versus sevelamer carbonate as phosphate binders in non-dialysis patients with CKD stage 3-5. To our knowledge, this is the only study comparing Sevelamer carbonate with lanthanum carbonate as phosphate binders in non-dialysis requiring CKD patients.

METHODS

This is a single center prospective open-label cross over study carried out in the department of Nephrology Seth Sukhlal Karnani Memorial Hospital and Institute of postgraduate medical education and research (SSKM & IPGMER) Kolkata India between February 2013 and June 2014. Patients with CKD stage 3-5 with corrected serum calcium ≥8.5 mg/ dl and serum phosphate ≥4.0 mg/ dl were included in the study. Out of a total of 236 patients, 96 patients met these inclusion criteria.15 patients required dialysis during the study period and were excluded. 14 patients were lost to follow up. 07 patients failed to meet the inclusion criteria after the washout, 8 patients were poorly compliant with treatment and 4 patients (2 from each sevelamer and lanthanum group) didn't tolerate test drug. 48 patients completed the study and were finally analyzed. After recruitment, the patients were divided into two groups. One group was given lanthanum carbonate 2000mg a day in four divided doses and another group sevelamer carbonate 2400 mg a day in three divided doses for 12 weeks. After 12 weeks, a washout period of 2 weeks was given. After satisfying the inclusion criteria patients were then switched to the alternative phosphate binder for another 12 weeks. First exposure to phosphate binders was labeled as intervention 1 and second exposure after the washout period and cross over was labeled as intervention 2. The study protocol is shown in figure 1.

Statistical analysis

All data are presented as mean ± SD. Mann-Whitney U test was used for non-parametric independent data. Dependent non-parametric data were analyzed by Wilcoxon's matched pair signed rank test. Statistical analysis was done using SPSS version 17.0

RESULTS

Of the 48 patients finally analyzed, 28(58.3%) were males. The mean age was 51.4 ± 14.02 years. Diabetic nephropathy accounted for over half (54.2%) of the cases. 14, 29 and 5 patients had CKD stage 3,4 and 5 respectively. Mean baseline estimated glomerular filtration rate was 25 ± 8.99 ml/min/1.73m^2.Mean serum calcium before and after intervention 1 was 9.55 ± 0.64 mg/ dl and 9.10 ± 0.63mg/dl respectively, p -<0.001. The mean difference between pre and post intervention1 calcium levels for LC and SC treated patients was comparable, p -0.397. Mean Phosphate levels before and after intervention 1 was 4.85 ± 0.90 mg/ dl and 4.16 ± 0.72mg / dl respectively, p <0.001. The mean difference between pre and post

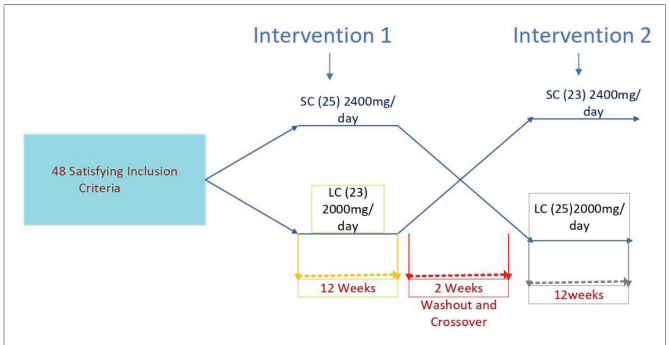

Figure 1: Study Design: Patients with serum calcium ≥ 8.45 mg/ dl and serum phosphate ≥ 4 mg/ dl were randomized to receive either sevelamer carbonate (SC) or lanthanum carbonte (LC). After 12 weeks patients underwent wasshot period of 2 weeks and were switched to alternate binder for 12 weeks.

intervention1 phosphate levels for LC and SC treated patients was comparable, *p* -0.2. Mean phosphate level before intervention 2 (after washout) and after intervention 2 was 4.54 ± 0.46 mg/ dl and 3.85 ± 0.57 mg/dl respectively, *p* <0.001. The mean difference between pre and post intervention 2 phosphate levels for LC and SC treated patients was comparable, *p* -0.80. Mean serum calcium before intervention 2 (after washout) and after intervention 2 was 9.13 ± 0.52mg/ dl and 8.66 ± 0.55 mg/ dl respectively, *p* -<0.001. The mean difference between pre and post intervention 2 calcium levels for LC and SC treated patients was comparable, *p* -0.116. The Median reduction in phosphate with SC and LC was 0.69 mg/ dl and 0.9 mg/ dl respectively. There was a statistically nonsignificant trend towards greater phosphate reduction with LC. Gastrointestinal disturbances (nausea and vomiting) were the commonest side effects occurring in 27% and 15% of the LC and SC treated patients. The results are summarised in table 1 and table 2.

DISCUSSION

Serum phosphate has evolved as enemy number one for nephrologists taking care of patients with CKD**.** Serum phosphate has direct effects on renal bone disease and extra skeletal calcification [2,3]. High serum phosphate level is associated with increased CVD morbidity and mortality in CKD patients. Serum levels of phosphate do not generally rise in patients with stage 3 CKD (Estimated Glomerular Filtration Rate [eGFR] >30 ml/ min/ 1.73 m2). It is prevented until the later stages of CKD by Parathyroid Hormone (PTH) and Fibroblast Growth Factor-23 (FGF-23) owing to their phosphaturic function [4,5]. Secondary Hyperparathyroidism (SHPT) and high FGF-23 levels also correlate with increased CVD morbidity and mortality [6-11]. SC and LC caused a significant and comparable reduction in serum phosphate levels in our study. The percentage of patients with serum phosphate above 5 mg/ dl fell from 31.3% at the start of study to 2.1% at the completion and the percentage of patients with serum phosphate between 4 and 5 mg/ dl fell from 68.8% to 29.2% at the end of the study. At the end of the study, 68.8% of patients had serum phosphate <4.0 mg/ dl (Figure 2) Sprague SM et al also reported significant reduction in serum phosphate with LC and SH (Sevelamer hydrochloride) in CKD patients on dialysis but unlike in our study LC performed better [12]. The reason for this discrepancy is not clear. The possible reason might be lower starting level of serum phosphate(≥4 mg/ dl) and the lesser doses of both phosphate binders used in our study (LC 2000 mg/ day, SC 2400 mg/ day). Results might change at higher doses of phosphate binders and at higher starting levels of serum phosphate. This would need to be studied further.

SC and LC both before and after the cross over caused significant and comparable decrease in serum calcium. None of the patients during the entire study period were on any form of vitamin D or its analogs. This might be the reason for the decrease in serum calcium following both LC and SC use in our study.

The most predominant side effects were gastrointestinal in the form of nausea and vomiting which was seen in 27% of patients on lanthanum carbonate and 14.5% patients on sevelamer carbonate. 2 patients from each sevelamer and lanthanum carbonate group were withdrawn from the study group owing to intolerable gastrointestinal side effects.

The decrease in serum calcium plus a decrease in serum phosphate with the use of non-calcium containing phosphate binders might decrease the extra-osseous calcification seen in patients with CKD and decrease long term CV morbidity and mortality. However, to confirm the long-term beneficial effects of non-calcium containing phosphate binders in reducing the cardiovascular mortality and CKD-MBD profile, a longer duration study with a larger study population is needed with an evaluation of coronary artery calcification scores, FGF 23 levels and bone biopsy at pre-defined intervals.

The limitations of our study include a small number of patients and variable phosphate content of the diet during the intervention phases.

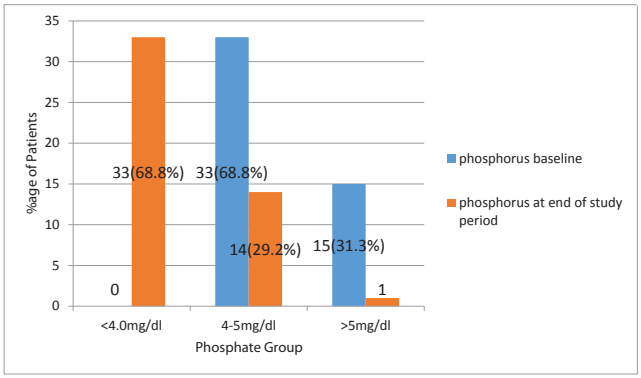

Figure 2: Phosphate trend with intervention
68.8% of patients had serum phosphate < 4 mg/ dl at the end of the study period

Table 1: Comparison of mean Calcium and phosphate levels before and after intervention.

	Before intervention 1	After intervention 1	*p*-value	Before intervention 2	After intervention 2	*p*-Value
Calcium (Mean ± SD) mg/ dl	9.55 ± 0.64	9.10 ± 0.63	< 0.001	9.13 ± 0.52	8.66 ± 0.55	< 0.001
Phosphate (Mean ± SD) mg/ dl	4.85 ± 0.90	4.16 ± 0.72	< 0.001	4.54 ± 0.46	3.85 ± 0.57	< 0.001

Table 2: Comparison between SC and LC following intervention 1 and intervention 2.

	Mean rank calcium for SC	Mean rank calcium for LC	*p*-value	Mean rank phosphate for SC	Mean rank phosphate for LC	*p*-value
After Intervention 1	23.38	25.72	0.56	26.78	22.02	0.24
After Intervention 2	21.20	27.54	0.12	25.02	24.02	0.80

SC: Sevelamer Carbonate; LC: Lanthanum Carbonate.

CONCLUSION

Sevelamer Carbonate and Lanthanum carbonate are effective phosphate binders and are equally efficacious in reducing serum phosphate levels in non-dialysis patients with CKD 3-5.

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