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Comparative Study of Sevelamer Carbonate and Calcium Carbonate on Fibroblast Growth Factor-23 and Parathyroid Hormone in Hemodialysis Iraqi Patients

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Abstract: ***Fibroblast growth factor-23, play an important role in atherosclerosis, endothelial dysfunction and vascular calcification. Sevelamer can improve vascular calcification, serum uric acid, low-density lipoprotein -cholesterol and Fibroblast growth factor-23. Aim of study: Assessment the effect of sevelamer as phosphate binder against calcium carbonate on Fibroblast growth factor-23. Methods: A prospective open- labelled study that included patients on hemodialysis. A total of 72 patients were screened, only 53 patients completed the 10 week period. Adults patients with serum phosphate as >5.5 mg/dl were included. There were Group1: Includes 28 patients (19 males and 9 females receiving sevelamer carbonate (Renvela) tablet. Group 2: Include 25patients (17 male and 8 female) receiving calcium carbonate tablet. Level of serum calcium, phosphorus, albumin, at pre wash, baseline and every 5 weeks, meanwhile the Level Low-density lipoprotein, Fibroblast growth factor23, and parathyroid hormone were measured at baseline and after 10 weeks. Results: Serum phosphorus was significantly reduced after 10 weeks with both sevelamer carbonate -22.4% and calcium carbonate -23.5%. Serum parathyroid was significantly reduced in both groups. Only group 1 was associated with significant reduction in low-density lipoprotein cholesterol by 26.4% from base line, significant reduction in Fibroblast growth factor-23 level by -31.2% and significant decrease in Calcium × phosphate product -29.5%. Significant rise in the serum calcium in group 2 patients(14.34%). Conclusion: Sevelamer superior to calcium-based binders in reducing hypercalcemia and Calcium × phosphate product which decrease intimal calcification of dialysis patient arteries, and favorable reduction in Fibroblast growth factor 23, and low-density lipoprotein cholesterol in dialysis patients.***

Keywords: Sevelamer carbonate, Calcium carbonate, Fibroblast growth factor-23

1. Introduction

Fibroblast growth factor-23(FGF-23)is part of a family of phosphatonins that promotes renal phosphate excretion. The discovery of FGF23 has changed our understanding of CKD-MBD and has revealed more complex cross-talk with endocrine feedback loops between the kidney, parathyroid gland, intestines, and bone. Serum FGF23 levels have been found to correlate with serum calcium independent of serum phosphate in individuals with primary hyperparathyroidism that underwent parathyroidectomies [1]. Calcium-based phosphate binders have been shown to lack efficacy on lowering FGF23 in dialysis and CKD patients[2].FGF23 receptors are expressed in many cells types, such cardiomyocytes, vascular wall, kidneys, and parathyroid glands. Moreover, elevated FGF23 is associated with the development of endothelial dysfunction & cardiac hypertrophy in patients with CKD [3].

Phosphate binding agent, free of metal and calcium, presented in two salts Sevelamer hydrochloride (Renagel®) and Sevelamer carbonate (Renvela®) is a unabsorbed, polymer of cross-linked polyallylamine, a large molecule consisting of repeated subunits with molecular weight of 1016 Daltons that binds phosphorus in the GI tract [4]. Several recent studies have shown the capacity of Sevelamer to decrease FGF-23 [5; 6]

Dyslipidemia can promote kidney injury and subsequent progression of CKD. Endothelial dysfunction results from inflammation and monocyte activation, with deposition of lipids results in glomerulosclerosis and glomerular mesangium dysfunction [7]. Sevelamer lowers LDL by 30%, total serum cholesterol, increasing HDL-C levels [4]. This probably caused by bile acid binding. Increased fecal excretion of bile acids leads to LDL receptor up-regulation in the liver .Sevelamer has a potential benefit of attenuating the progression of coronary calcification, which partly related to its LDL and total serum cholesterol-lowering effects in addition to the reduction in calcium loading [4; 8].

2. Patients and Methods

This study was carried out at Medical City, Baghdad Teaching Hospital, Iraqi Center of Kidney Dialysis from October 2015 until May 2016. Ethical approval committee of

Iraqi boards of clinical pharmacy and informed consent to patients according to Helsinki law. Seventy-two subjects were selected, only (53) completed the course. Group 1: Includes 28 patients receiving Sevelamer carbonate tablet (Renvla®) 800 mg film coated tablet supplied by Genzyme, The dose adjustments to maintain serum phosphorus between (3.5-5) mg/dl for 10 weeks. Group 2: Includes 25patients with CKD receiving calcium carbonates tablet the dose was titrated to maintain serum phosphorus between (3.5-5) mg/dl.In both groups, serum Calcium, phosphorous & albumin were measured .Eligible patients entered a 2-weeks phosphate binder washout period; this washout period was included as a control of the treatment .

The Inclusion criteria are Both genders with CKD on maintenance hemodialysis for at least 3 months and age ≥ 18years.The Exclusion Criteria is Allergic to sevelamer or to calcium, Hemodynamic, Unstable patients, Predisposition with or presence of intestinal or ileus obstruction or sever gastrointestinal motility disorder (like sever constipation) and previous major gastrointestinal surgery and Antecedent of parathyroidectomy.

HD with low-flux dialyzers for all patients which where performed two- three times weekly, each for 3-4 h hemodialysis done.. Dialysate composition was the same for all patients (Na+ 138 mmol/l, K+3.0 mmol/l, Ca++ 1.5 mmol/l, Mg++ 0.5 mmol/l, Cl- 110 mmol/l, HCO332 mmol/l, acetate-3 mmol/l and glucose 1 g/l); this dialysate produces 296 mOsm/l solutions. The blood flow rate was 150-300 ml/min, and the dialysate flow rate was 500 ml/mins throughout the study. Serum was used for the measurement of FGF-23, phosphorus, calcium, albumin, PTH, uric acid& LDL-C. The medical history of all patients where obtained. Level of serum, calcium, phosphorus& albumin: at pre washout, baseline, 5th &10th week. Low-density lipoprotein (LDL), FGF23, serum uric acid and intact PTH were measured at base line and after 10 weeks of therapy.

Chi square test and Fisher exact test when possible to analyzed the discrete variables. Mann Whitney U test, Wilcoxon median ranks test used for non-parametric variables. Independent t tests and paired t test for parametric variables. One ANOVA (with contrast) used to analyzed the difference in mean between 3 groups (with chronological order; i.e. change in time) in parametric variables. Mauchly's test of sphericity was used to test sphericity assumption; when significant lower bound correction method used to test for groups significance, if not significant sphericity assumption is preserved and p value calculated. P values was considered to be significant when it is less than 0.05, all data analyzed using SPSS 20 software package.

3. Results

Table (1) summarizes the demographic & clinical characteristics of the study patients respectively, No serious adverse events occurred during the study. Only 2 patients discontinued sevelamer because a complaint about dyspepsia.

Table 1: Demographic data of patients involved in this study

	$CaCO_3$ group	Sevelamer Group	All	P values
Number	25	28	53	-
Age (years)	51.3 ± 11.6	49.4 ± 10.3	50.6 ± 11.3	0.576[a]
Gender (male)	17 (68%)	19 (67.8%)	36 (67.9%)	0.991[b]
[a] T test, [b] chi square				

Results of the effect of phosphate binders on serum FGF-23 are shown in Table (2), Median serum FGF-23 was significantly reduced with ten weeks of Sevelamer use (P<0.001), Sevelamer show (31.2%) reduction in FGF-23 from baseline, while CaCO3 shows non-significant reduction (-1.5%, P 0.086) from baseline, which indicate that sevelamer was better when compared to CaCO3 in reducing serum FGF-23 as illustrated in table (2). There was a statistically significant reduction in both treatments. So Both Sevelamer and CaCo3 reduced S. PO4 significantly from base line of 5 weeks to 10 weeks and both of them achieved similar rates of reduction of serum PO4 which confirm by using two way ANOVA test (p values of interaction was 0.006; since Mauchly's test was significant so we use p value <0.001 instead of <0.05 for significant results), as illustrated in table (3).The change in baseline in serum calcium was significantly different to calcium carbonate treated group and Sevelamer carbonate group after 10 weeks of treatments as shown in Table (4).CaCO3 increased the higher percentage of mean serum calcium achieved 10.03% increases after 5 weeks and 14.34% increase after 10 weeks and this elevation was significant, while Sevelamer increased the lower percentage of mean serum calcium achieve 0.35% increase after 5 weeks and 1.27% increase after 10 weeks and this was non- significant elevation, by using two way ANOVA analysis to determine which arm is better we found there is significant difference (p value <0.001, since Mauchly's test also significant p value should be <0.001 for significant effect not <0.05), as illustrate in (table 4).

Table 2: Effect on FGF 23 (pg/ml) for both groups

	$CaCO_3$	Sevelamer	P values
Number	25	28	-
FGF-23baseline	331 (263 – 1500)	349 (235 – 1500)	0.729[a]
FGF-23 after 10 weeks	326 (256 – 1487)	240 (162 – 1032)	0.046[a]
P value	0.086[b]	<0.001[b]	-
Δ from baseline	-1.5%	-31.2%	-
[a] Mann Whitney test, [b] Wilcoxon rank Test			

Table 3: PO_4 (mg/dl) change for each group through study

	Prewash	Baseline	5 weeks	10 weeks	P values
$CaCO_3$	6.4 ± 1.2	6.7 ± 2.1	5.80 ± 1.80	5.12 ± 1.60	0.035
Sevelamer	6.3 ± 1.2	6.6 ± 1.5	5.81 ± 1.30	5.12 ± 1.14	0.001
[a] Trend ANOVA P value of interaction = 0.006 (calculated using two way ANOVA)					

Reduction of mean Ca × P was found to be 6.36 mg 2 /dL 2, 17.26 mg 2 /dL 2, with calcium carbonate, Sevelamer carbonate treatment, respectively, after 10 weeks. Sevelamer had significant reduction in baseline till 10 weeks (p value <0.001), while mean Ca × P level where insignificantly reduced from baseline to 10 weeks of the calcium carbonate

treatments (P<0.5). Since Mauchly's test also significant p value should be <0.001 for significant effect not <0.05), as illustrate in table (5).

Table 4: Calcium change (mg/dl) for each group through study

	Prewash	Baseline	5 weeks	10 weeks	P values
$CaCO_3$	8.1±1.2	7.88±0.93	8.67±1.02	9.01±1.06	0.002
Sevelamer	8.9±1.2	8.67±1.83	8.70±1.68	8.78±1.90	0.980
[a] Trend ANOVA P values of interaction = <0.001 (calculated using two way ANOVA)					

Table 5: Calcium phosphate product (mg^2/dL^2) change for each group through study

	Baseline	5 weeks	10 weeks	P values
$CaCO_3$	52.85 ± 18.19	50.62 ± 17.42	46.49 ± 16.00	0.5
Sevelamer Carbonate	58.38 ± 20.66	51.36 ± 17.50	41.12 ± 14.55	0.006
[a] Trend ANOVA P values of interaction = <0.001 (calculated using two way ANOVA)				

As shown in (Table 6), the median intact parathyroid hormone was significantly reduced with both treatment groups. The median intact parathyroid hormone was significantly reduced with 10 weeks of calcium carbonate (P <0.001), Sevelamer carbonate (P <0.001) treatments. The reduction was found to be 103 pg/mL, (49.5%), and 76 pg/mLs, (29.8%) with calcium carbonate, Sevelamer carbonate, respectively.However the differences between both groups are not significant (p value 0.061). Mean LDL significantly decreased in Sevelamer carbonate by -26.4% after ten weeks of treatment (P < 0. 001), while CaCO3 not significantly decreased LDL only by -0.96% (P< 0.859), as illustrated in table (7).

Table 6: Effect on PTH for both groups

	$CaCO_3$	Sevelamer	P values
Number	25	28	-
PTH baseline	208 (130 – 988)	256 (166 – 926)	0.607[a]
PTH 10 weeks	105 (65 – 498)	180 (117 – 650)	0.061[a]
P value	<0.001[b]	<0.001[b]	-
Δ from baseline	-49.5%	-29.8%	-
[a] Mann Whitney test, [b] Wilcoxon rank Test			

Table 7: LDL(mg/dl) product for both group

	$CaCO_3$	Sevelamer	P values
Number	25	28	-
Baseline	163.2 ± 13.1	163.4 ± 19.5	0.971[a]
10 weeks	161.6 ± 42.9	120.3 ± 14.3	<0.001[a]
P value	0.859[b]	<0.001[b]	<0.001[c]
Δ from baseline	-0.96%	-26.40%	-
[a] Independent t test, [b] paired t test (from baseline to 10 weeks) [c] Two way ANOVA for interaction <0.001			

4. Discussion

In this study Sevelamer carbonate show a significant (31.2%) reduction in FGF-23 from baseline, This novel action of Sevelamer carbonates on FGF-23 was consistent with other studies such Zayed B. et al. (2015)was done on 80 patients divided among two groups, demonstrated a significant decrease in the serum FGF-23 in Sevelamer HCL group by the end of the study compared with its basal level (4669.5 vs. 3011.8 pg/ml, respectively, P < 0.001), and increased significantly from Calcium carbonate group patients (4872 vs. 7154 pg/ml, respectively, P = 0.005) [9]. Yilmaz M. et al. (2012), found changes in FGF-23 levels (−27.1% [−33.2% to −8.8%] for the Sevelamer group; 3.5% [−8.4% to 12.1%] for the calcium acetate group) [10]. Koiwa et al, (2005) found that Serum FGF23 levels significantly decreased after four weeks of the treatment for both Sevelamer hydrochloride and CaCO3 from the pretreatment levels (P < 0.05).[4;11]

Serum phosphorus levels >6.5 mg/dL, calcium × phosphorus product >70 mg 2 /dL 2 and serum parathyroid hormone levels >495 pg/mL are each strongly associated with increased risk of cardiac mortality in hemodialysis patients, especially sudden death and death from coronary artery disease [12]. Chertow G et al (2002) was found that control of serum phosphorus was equivalent to both agents [13].Lin YF et al (2011), but there were hypercalcaemic events in calcium acetate group(12.0% vs 3.7%) at 8 weeks of his study [14].

Zayed B. et al. (2015), found in his study that the serum calcium level decreased significantly in group1 (SevelamerHCL) P = 0.001), whereas increased significantly from group2 (calcium carbonate) P = 0.005) when comparing the levels before and at the end of the study period. Besides that, they found a significant reduction in serum phosphorus in both groups, but this reduction was more significant in group 1 when compared with group 2 (7 vs. 6 mg/dl and 7.2 vs. 6.8 mg/dl in groups 1 and 2, P < 0.001 and 0.005,respectively) [9]While Yilmaz M et al (2010), found Serum phosphate levels decreased in both treatment arms (P < 0.001), but more markedly in the Sevelamer group (P < 0.001) [10].

The calcium-phosphorus product 72 mg2 /dL2 is associated with a 34% increased risk of mortality and metastatic calcification[15], so, the calcium × phosphorus product is recommended being kept below 55 mg 2 /dLs for reducing the incidence of vascular calcification and cardiovascular mortality [16]. In the present study the mean Ca × P was significantly reduced during 10 weeks (P <0.006) of Sevelamer carbonate treatment only, this may attribute to elevation of serum Calcium in group2. Isidro B. Salusky, et al (2005) was found that serum calcium levels and the Ca × P product increased with CaCO3; in contrast, values remained unchanged with sevelamer [17].Galani V et al (2014), was found that Mean Ca × P was significantly reduced with 12 weeks (P <0.001) of the calcium carbonates treatment, and was significantly reduced with 4 weeks, 8 weeks, and 12 weeks of the Sevelamer hydrochloride., after 12 weeks, treatments Sevelamer hydrochloride decreased the highest percentage of mean Ca × P at 24.51%, while calcium carbonates decreased the lowest percentage of mean Ca × P at 5.21% (18).In the present study both binder show significant reduction in serum PTH, Sevelamer carbonates to show 29.8% reduction in PTH from baseline, while CaCO3

also show 49.5% reduction of baseline; however the differences between both groups are not significant (p value 0.061).Galani V et al (2014), was found that the mean intact parathyroid hormone was significantly reduced with all treatment groups with 12 weeks of calcium acetate (P <0.001), calcium carbonate (P <0.05), Sevelamer hydrochloride (P <0.001) and lanthanum carbonate (P <0.001) treatments. The reduction of mean intact parathyroid hormone was found to be the highest percentage of Sevelamer HCL group of 29.18%, while calcium carbonates decreased the lowest percentage of mean intact parathyroid hormones 13.41% [18].

Pieter Evenepoel et al (2009), found the median serum intact PTH decreased to both the Sevelamer hydrochloride (from 398 to 317 pg/ml; P = 0.001) and calcium acetate (524 to 372 pg/ml; P = 0.020) groups with no significant between-group difference [19].Oliveira et al (2010) In a 6-week randomised study, the effect of two phosphoruses chelating agents (calcium acetate and Sevelamer) on PTH and FGF23 was studied in patients with stage 3 and 4 CKD. During treatment for both chelating agents, there was a progressive decrease in serum PTH [20].

In the current study, serum LDL- cholesterol level was significantly reduced in sevelamer group , while small non-significant decrease in calcium carbonates group 0.96%.Hamida F et al (2008), found in his study that sevelamer treatment significantly decreases both total cholesterol & LDL- cholesterols after 8 weeks of use [21]. Zayed B et al (2015), found in their study that Serum total and LDL-cholesterol decreased significantly in group1 (Sevelamer used), whereas increased significantly in group2 (calcium carbonate). HDL-cholesterol increased significantly to group 1 and decreased significantly t group 2 in6 months (9). HERVA´ S J et al(2003), found in their study that extends over 34 weeks the Sevelamer treatment group, the mean change in the total cholesterol was (16.5%), LDL-cholesterol (29.9%), and HDL-cholesterol were (19.5%). All values were statistically significant at P 0.05. Braun J et al (2004), found in his Long-term comparison of a calcium-free phosphate binder and calcium carbonate—study that Sevelamer patients experienced significant (p < 0.01) reductions in total and LDL cholesterol [22]. Evenepoel P et al (2003), found a significant reductions in total,LDL- and non HDL-cholesterol were seen with Sevelamer hydrochloride but not with calcium acetate [19].

5. Conclusions

Sevelamer carbonate, effectively reduced serum phosphorus and hypercalcemia in dialysis patients .It significantly decreased serum intact PTH, sustained, favorable changes in the FGF23 and reduced LDL cholesterol(is similar to the reduction obtained by cholesterol-lowering agents), and this effect may enable to use Sevelamer as an alternative, additive or synergic effect of modifying the lipid profile to the statins, and given the chance of decreased the risk of drug-related side effects .

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8. Conflict of interest

None declared.

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