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Research Article

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Evaluation the role of sevelamer in reducing serum phosphate in patients with renal failure on hemodialysis with that of calcium carbonate

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ABSTRACT

Calcification of coronary artery, an important indicator of atherosclerosis, is a frequent finding in patient s with CKD. A lot of studies have shown that hyperphosphatemia, is the main factor in the development of cardiovascular calcification. Recently, the use of sevelamer has emerged as a substitute for calcium carbonate for the reduction of serum phosphate in patients with renal failure. The aim of the study is to compare the efficacy of sevelamer in reducing serum phosphate in patients with renal failure on hemodialysis with that of calcium carbonate. The study was conducted in the dialysis unit in Al-Diwaniya teaching hospital, Al-Diwaniya province, Iraq. The present case-control study included 48 CKD disease patients on regular hemodialysis. They were divided into 2 groups; the first received calcium carbonate as a PO4 reducing agent while the second group received sevelamer as a PO4 reducing agent and the then patients were followed up for 3 months. The results showed that treatment with calcium carbonate and sevelamer were successful in significantly reducing serum PTH and serum PO_4 and also both were successful in raising mean serum calcium significantly; however, sevelamer was more powerful in reducing serum PO_4 and in raising serum calcium than calcium carbonate. Nevertheless, the change in serum PTH in both groups was approximately similar with no significant difference in magnitude of reduction. It has been concluded that sevelamer is significantly better than calcium carbonate in reducing serum PO4 in CKD on regular hemodialysis.

Keywords: Chronic kidney disease; Hemodialysis; Sevelamer

INTRODUCTION

The problem of "Chronic kidney disease (CKD)" nowadays is regarded as a major health problem that affects approximately 5% to 10% of the population globally (Hamer et al., 2006). Main adverse outcomes of chronic kidney diseases are represented by the development of "end-stage renal disease (ERSD)", increased rate of renal transplantation and renal replacement and the high mortality rate seen in patients on dialysis. Indeed, mortality in this cohort of patients is mainly attributed to cardiovascular diseases rather than to failed kidney. Calcification of coronary artery, an important indicator of atherosclerosis, is a frequent finding in patient s with CKD. Profound calcification has been reported in patients on dialysis by CT-scan; however cardiovascular calcification is reported in patients not on dialysis as well, being observed early in the development of CKD, and ultimately becoming worse with the reduction of the glomerular filtration rate (GFR), especially in patients with diabetes mellitus (Qunibi, 2007). Risk of calcification in patients with CKD is related impaired renal function, development of proteinuria, diabetic micro- and macro-angiopathy and steady progression toward ESRD. A lot of studies have shown that the alteration in mineral metabolism, and especially hyperphosphatemia, is the main factor in the development of cardiovascular calcification. Hyperphosphatemia has been shown to be significantly associated with aortic calcification, coronary artery calcification, valvular calcification and aortic stiffness. (Young, 2005; Young; 2007; Toussaint; 2007) High serum phosphorus (P) concentration is a common finding in patients with uremia, in spite of dietary restriction and frequent renal dialysis. It is correlated with a high mortality rate in patients on hemodialysis (Block et al., 1998). Multivariate analysis of "data from the United States Renal Data System (URDS)", reported high serum PO_4 concentration as an independent risk factor for death. Changes in mineral metabolism can worsen the outcomes of coronary atherosclerosis. High intracellular PO4 induces the phenotypic modification of "smooth muscle cell to osteoblastic cell lineage", therefore causing high calcium and phosphate deposition (Block, 2003; Li et al., 2006). When smooth muscles, derived from atherosclerotic plaques, were cultured, it was noticed that matrix mineralization, did not happen until sufficient rise in PO_4 has

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been established in tunica media supporting the idea that hyperphosphatemia is the main caused behind tissue calcification *in vivo* (Mathew et al., 2008). Experimental studies have documented that high serum PO_4 is an indirect determinant of increasing vascular wall thickness (Kawagishi et al.,1995). For that reason, it was suggested that the high mortality rate associated with high serum PO4 concentration in patients on hemodialysis was essentially due to cardiovascular causes of death (Ganesh et al., 2001). Several studies have proposed that serum P greater than 6.5 mg/dL (1 mg higher than normal) is risky for development of higher incidence of cardiovascular complications in patients on renal dialysis (Kestenbaum et al., 1995; Sigrist et al., 2007).

Standard therapeutic approach for hyperphosphatemia, besides dietary restriction of phosphate, typically involves prescription of non-calcium based binders and calcium-based binders which have the ability to prevent absorption of dietary phosphate. Recently, the use of sevelamer has emerged as a substitute for calcium carbonate for the reduction of serum phosphate in patients with renal failure. It has been shown that sevelamer is effective in as decreasing serum phosphate concentrations (Navaneethan, 2009). In addition, it has been found that (Di Iorio et al., 2012). sevelamer may delay delays progression to dialysis in chronic kidney disease patients who are not yet on dialysis (Jamal Sophie et al., 2013). However, sufficient controversy exited in published literature about the use of sevelamer in patients already on dialysis (Nguyen et al., 2013) and this encouraged the planning and conduction of the current study.

PATIENTS AND METHODS

The present case-control study included 48 CKD disease patients on regular hemodialysis. They were divided into 2 groups; the first received calcium carbonate as a PO4 reducing agent while the second group received sevelamer as a PO4 reducing agent and the then patients were followed up for 3 months. Age, gender, the frequency of hemodialysis per week, the average duration of a hemodialysis session time in hours, serum calcium, PO4 and PTH before and after the end of the study were all recorded. The study was conducted in the dialysis unit in Al-Diwaniya teaching hospital, Al-Diwaniya province, Iraq.

Data were transferred in an SPSS (version 23) spreadsheet and then summarized, analyzed and presented. Data were presented in terms of mean and standard deviation. Independent samples t-test was carried out to compare mean values of numeric variables between study and control group whereas paired t-test was used to assess changes in mean serum calcium, PO4, and PTH after completion of the study duration. The level of significance was chosen at $P \leq 0.05$.

RESULTS

The present study included 24 cases on calcium carbonate and 24 cases on sevelamer. Mean age in both groups was not significantly different, 52.33 ± 18.88 versus 50.58 ± 16.36 years, respectively (P = 0.733). Mean frequencies of hemodialysis sessions per week were 2.75 ± 0.53 and 2.88 ± 0.54 per week, respectively and the difference was insignificant (P = 0.422). The average

Table 1: Characteristics of the study and control groups

Characteristic	Ca carbonate group (n =24)	Sevelamer group (n =24)	P *
Age (years)	52.33 ± 18.88	50.58 ± 16.36	0.733 NS
Hemodialysis frequency/ week	2.75 ± 0.53	2.88 ± 0.54	0.422 NS
Duration of hemodialysis session (hours)	3.29 ± 0.86	3.13 ± 0.68	0.460 NS
PTH before (ng/ml)	616.00 ± 245.53	674.83 ± 266.32	0.430 NS
PO_4 before (mg/dl)	6.81 ± 1.10	6.75 ± 0.93	0.832 NS
Ca before (mg/dl)	7.31 ± 1.31	7.00 ± 1.06	0.381 NS

*Independent samples t-test; values were expressed as mean ± standard deviation; NS: Not significant at $P \leq 0.05$.

Table 2: Serum markers before and after treatment in control and study groups

Characteristic	Ca carbonate group (n =24)		P *	Sevelamer group (n =24)		P *
	Before	After		Before	After	
PTH (ng/ml)	616.00 ± 245.53	505.67 ± 255.39	0.005	674.83 ± 266.32	455.25 ± 287.78	<0.001 HS
PO4 (ng/ml)	6.81 ± 1.10	5.87 ± 1.23	0.003	6.75 ± 0.93	5.11 ± 1.39	<0.001 HS
CA (ng/ml)	7.31 ± 1.31	9.14 ± 1.45	<0.001	7.00 ± 1.06	8.40 ± 0.99	<0.001 HS

*Paired t-test; values were expressed as mean ± standard deviation; HS: highly significant at $P \leq 0.001$.

session duration was statistically not significant between the two groups, 3.29 ± 0.86 hours versus 3.13 ± 0.68 hours, respectively (P = 460), as shown in table 1.

Mean serum PTH before starting treatment was 616.00 ± 245.53 ng/ml and 674.83 ± 266.32 ng/ml in control and study groups, respectively (P = 0.430). Mean serum PO_4 before starting treatment was 6.81 ± 1.10 mg/dl and 7.31 ± 1.31 mg/dl in control and study groups, respectively (P = 0.832). Mean serum Ca before starting treatment was 7.31 ± 1.31 mg/dl and 7.00 ± 1.06 mg/dl in control and study groups, respectively (P = 0.381), as shown in table 2.

Treatment with calcium carbonate and sevelamer were successful in significantly reducing serum PTH and serum PO_4 and also both were successful in raising mean serum calcium significantly, as shown in table 2; however, sevelamer was more powerful in reducing serum PO_4 and in raising serum calcium than calcium carbonate. Nevertheless, the change in serum PTH in both groups was approximately similar with no significant difference in magnitude of reduction, as shown in table 3.

DISCUSSION

The present study showed that sevelamer and calcium carbonate were both effective in reducing serum PO4 in patients on hemodialysis; however, sevelamer was more effective in this regard.

A number of studies were planned to evaluate the role of sevelamer on hyperphosphatemia in patients with chronic kidney disease (CKD) and are on dialysis (Chen et al., 2014; Fang et al., 2012; Wang et al., 2013; Tan et al., 2013; Huang et al., 2014; He et al., 2013; Lu et al., 2014; Zhao et al., 2014). In one study "a randomized, double-blind, dose-titration study" a comparison was made between sevelamer carbonate and placebo in CKD patients on hemodialysis for a period of over 8; a significant reduction was recorded in the former group while no significant change was recorded in the latter group (Chen et al., 2014). We agree with this study that sevelamer is effective in reducing serum PO4 in patients on hemodialysis. In another study "an open-labeled, self-control study" which extended for 10 weeks and in which sevelamer was used as a PO4 reducing agent in patients with CKD and on regular hemodialysis; it was found that serum PO4 was significantly reduced, in accordance with our results; however, serum PTH remains unchanged, in contradiction to our findings (Fang et al., 2012). In a similar study, sevelamer was tested on patients on regular hemodialysis and the results showed a significant reduction in serum PO4, just like the result of the present study; nevertheless, there was, in contrary to our finding, no significant change in both serum calcium and serum PTH concentrations (Tan et al., 2013; Mohammed et al., 1991). In a number of controlled trials, it was recorded that sevelamer possess better action than calcium carbonate in reducing the serum concentration of phosphorus, similar to our finding, and also in reducing calcium-phosphate product (Wang et al., 2013; Huang et al., 2014; He et al., 2013). In the great proportion of researchers, the serum concentration of PTH CKD patients on hemodialysis remains steady when sevelamer was used and this result is different from the finding of the present study in which PTH was noticed to be significantly reduced (Chen et al., 2014; Wang et al., 2013; Tan et al., 2013). Nevertheless, in one study (Huang et al., 2014) it was found that PTH was significantly less at the end of the study duration, a finding that is similar to the finding of the current study.

The same or better efficacy of sevelamer in reducing serum PO_4, in comparison with calcium carbonate, was documented by a number of many authors (Rui et al., 2005; Goldsmith et al., 2008). The source of phosphate in the diet in our country is believed to come from the plant-based diet in the form of stored Phytate phosphate (Hu, 2002; Uribarri, 2007; Ravindran et al., 2997) It is believed that sevelamer is effective at binding phytate phosphorus that is liberated by active vitamin D. (Lee et al., 1986; Mohammed et al., 1991; Peterlik et al., 1980; Pointillart et al., Snow et al., 2004; Bobeck et al., 2013).

Table 3: Serum markers before and after treatment in control and study groups

Characteristic	Ca carbonate group (n =24)	Sevelamer group (n =24)	P *
PTH 3-months after	505.67 ± 255.39	455.25 ± 287.78	0.524 NS
PO4 3-months after	5.87 ± 1.23	5.11 ± 1.39	0.048 S
CA 3-months after	9.14 ± 1.45	8.40 ± 0.99	0.046 S

*Independent samples t-test; values were expressed as mean ± standard deviation; NS: Not significant at P≤ 0.05; S: significant at P≤ 0.05.

CONCLUSION

In conclusion, sevelamer is significantly better than calcium carbonate in reducing serum PO4 in CKD on regular hemodialysis.

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