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Original Article

A STUDY ON HYPERPHOSPHATEMIA AND EFFECT OF SEVELAMER ON CARDIAC ENZYME LEVELS IN CHRONIC KIDNEY DISEASE PATIENTS

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ABSTRACT

Objective: Chronic Kidney Disease (CKD) is characterized by progressive loss of kidney function over a period of time. Sevelamer hydrochloride is a phosphate binding agent used to control serum phosphate levels in End Stage Renal Disease (ESRD) patients with hyperphosphatemia. Since hyperphosphatemia is associated with acute myocyte injury and elevation of cardiac biomarkers. ESRD patients treated with sevelamer hydrochloride display reduced cardiac biomarker levels due to a decrease in serum phosphate. Therefore, the study was designed to evaluate the effect of sevelamer hydrochloride on cardiac enzyme levels.

Methods: This retrospective observational study was carried out in the nephrology department of a multispecialty hospital for a period of two months. Clinical and biochemistry reports of 30 ESRD patients were collected in designed case report forms. All statistical analysis was carried out using International Business Machines-Statistical Package for the Social Sciences, version 17 (IBM SPSS 17) Statistics package.

Results: No significant difference in cardiac enzymes between sevelamer-treated and untreated groups was observed. Hence, further prospective studies on sevelamer hydrochloride are necessary to determine their activity in preventing hyperphosphatemia-induced acute myocyte injury.

Conclusion: A direct correlation was observed between cardiac enzyme markers and phosphate levels. However, sevelamer at conventional doses was not found to be effective in reducing acute cardiomyocytes injury caused by hyperphosphatemia. Hence, higher doses sevelamer or other modalities achieving normal serum phosphorous levels are necessary for preventing cardiac damage due to hyperphosphatemia in ESRD patients.

Keywords: ESRD, Hyperphosphatemia, Sevelamer, Cardiomyocytes injury.

INTRODUCTION

CKD is a condition characterized by progressive deterioration of renal function and is defined as abnormalities of kidney structure or function, present for more than 3 mo, with implications for health [1]. Diabetes mellitus is one of the major causes of renal failure. Approximately 30% of patients with diabetic nephropathy eventually progress to end-stage renal failure and the rest usually die from cardiovascular disease before reaching end-stage [2]. Besides the major manifestations of CKD such as renal azotemia, phosphate retention remains a significant cause for secondary complications. Hyperphosphatemia due to phosphorus retention plays a major role in the development of secondary hyper-parathyroidism and osteodystrophy in CKD patients [3]. It has also been shown that hyperphosphatemia leads to acute cardiomyocytes injury which could be a significant factor cause for cardiac complications in CKD patients [4]. Troponin T, Creatinine Phosphokinase (CPK) and Creatinine Kinase–MB (CK-MB) are specific biomarkers for determining cardiomyocytes damage. It has been shown that increased serum phosphorous levels display increased cardiac enzyme profiles thus suggesting a direct link between hyperphosphatemia and cardiac damage [5]. Sevelamer is a drug used to treat hyperphosphatemia in ESRD patients. It is used to prevent ectopic calcification resulting from precipitation of serum calcium due to hyperphosphatemia [6]. In addition, hyperphosphatemia provokes secondary hyperparathyroidism which in turn causes osteitis fibrosa [7]. Used either as the carbonate or hydrochloride salt, sevelamer binds to dietary phosphate and prevents its absorption into systemic circulation [8]. However, the effect of sevelamer on cardiomyocytes injury has not been evaluated in previous studies. Since hyperphosphatemia induces cardiac damage in ESRD patients, patients on sevelamer should possess cardioprotective properties by decreasing the systemic load of phosphorous to which the cardiomyocytes are exposed. Hence, this study was designed to evaluate the effect of sevelamer hydrochloride on cardiac damage.

MATERIALS AND METHODS

This was conducted as a retrospective observational study in the nephrology department of a multispecialty hospital for a period of six months. The study protocol was approved by the institutional ethics committee of Vels University (Approval no: IEC/DOP/2015/05). Consent from the hospital authorities and nephrologists were obtained before accessing the clinical records of patients. Clinical data was recorded from the patient case sheets stored in the medical records department of the hospital whereas biochemical parameters were recorded from the laboratory database. All the clinical and biochemistry data were recorded in a separate case report form. Levels of cardiac enzymes such as CK-MB, CPK and Troponin T where used as markers for assessing the cardiac damage.

Inclusion criterion

The study was conducted on 30 ESRD patients of both genders with hyperphosphatemia who were treated with sevelamer hydrochloride. A cardiac marker level of sevelamer-treated group was compared to a control with hyperphosphatemia that lacked sevelamer treatment.

Exclusion criterion

Patients with any of the four stages of CKD other than, ESRD patients without hyperphosphatemia, clinical records with insufficient data were excluded from the study.

Statistical analysis

All statistical analyses were performed using IBM SPSS 17 statistics package. Pearson's correlation was used to determine the correlation and linear dependency of cardiac enzymes on serum phosphate levels. A paired t-test was used to compare serum phosphorous levels before and after treatment with sevelamer whereas an unpaired t-test was used to compare the cardiac enzyme profiles of sevelamer-treated and untreated groups. A p-value of less than 0.05 was considered statistically significant throughout the study.

RESULTS

The study included ESRD patients with hyperphosphatemia with or without sevelamer therapy. A Glomerular filtration rate (GFR) of less than 15 ml/min per 1.73 m^2has been defined as ESRD by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative Classification and hence such patients were only included in the study [9]. Age wise distribution of patients included for the study is shown in table 1.

Table 1: Age-wise distribution of patients included in the study

Age group	Number of patients	Percentage
21-30	1	3.3
31-40	0	0.0
41-50	1	3.3
51-60	6	20.0
61-70	11	36.7
71-80	7	23.3
81-90	4	13.3

Mean age=66.3 y, SD=13.3 y.

Patients of both the gender were included in the study. Out of the 30 patients, 60% were male whereas 40% were female. It is graphically represented in fig. 1.

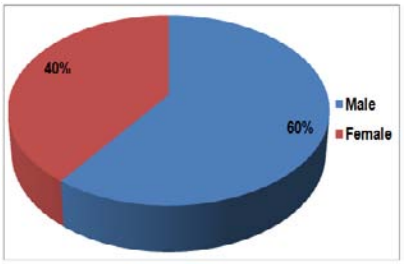

Fig. 1: Gender wise distribution of patients

Serum Phosphate levels were correlated with estimated glomerular filtration rate to determine the linear dependency using Pearson's correlation. The results are shown in table 2.

In order to understand the dependency of cardiac enzyme levels with serum phosphorous levels, CK-MB, CPK and troponin T levels were individually correlated phosphorus levels using Pearson's correlation. The results are shown in table 3.

Since sevelamer is known to decrease serum phosphate levels in ESRD patients with hyperphosphatemia, we compared the serum phosphate levels of the studied subjects before and three months after treatment with sevelamer. A paired t-test was used to determine the statistically significant difference and is as shown in fig. 2.

Table 2: Correlation of estimated glomerular filtration rate with serum phosphorous

		Serum phosphorous	GFR
Serum phosphorous	Pearson correlation	1	-.789**
	Significance (2-tailed)		.000
	N	30	30
GFR	Pearson correlation	-.789**	1
	Significance (2-tailed)	.000	
	N	30	30

**Correlation is significant at the 0.01 level (2-tailed), Serum Phosphate =-0.319 GFR+9.3779

Table 3: Correlation coefficients of serum phosphorous with CK-MB, CPK-total and troponin t

Parameters	CK-MB	CPK-total	Troponin T
Serum phosphorus	0.850**	0.835**	0.581**

**Correlation is significant at the 0.01 level (2-tailed)

Table 4: Comparison of cardiac enzyme levels in sevelamer treated and untreated groups

Parameters (mg/dL)	Sevelamer treated (n= 14)	Sevelamer untreated (n=16)	
	mean±SD	mean±SD	P value*
CK-MB	31.3±21.3	28.6±28.8	0.7797
CPK	151.4±277.1	273.8±543.1	0.4682
Troponin T	0.27±0.23	0.30±0.80	0.8611

* P values were retrieved by means of comparison of cardiac enzyme levels of sevelamer-treated and untreated patients using unpaired t-test

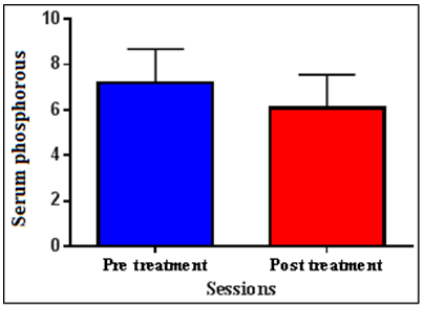

Fig. 2: Comparison of serum phosphate levels before and after treatment with sevelamer–(P value<0.0001-paired t-test by comparison of serum phosphate levels of sevelamer pre-treatment group against post-treatment group)

In order to determine the effect of sevelamer on cardiac enzyme levels, unpaired t-tests were done to compare the CK-MB, CPK-total and troponin T levels in sevelamer-treated and untreated groups. The results are shown in table 4.

DISCUSSION

Elderly patients are more prone to the renal impairment associated hyperphosphatemia. Age is an important factor for renal impairment and chronic kidney disease [10]. In the studied population with ESRD associated hyperphosphatemia, the frequency of patients is high in the elderly group than the nonelderly. Hence elderly patients with ESRD are more susceptible to hyperphosphatemia associated complications. In the studied population of patients, 40% were male, and 60% were female.

Serum creatinine is an endogenous marker for assessment of renal function. The modified diet in renal disease formula provides a modality for estimation of glomerular filtration rate from serum creatinine [11].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative classifies patients with a GFR of less than 15 ml/min per 1.73 $m^2$to have end-stage renal failure [9]. Therefore higher serum phosphate levels are observed in patients with lesser GFR. Pearson's correlation was done to determine the effect of GFR on serum phosphate levels. A strong linear dependency was observed with a correlation coefficient of-0.789. The negative slope indicates an inverse correlation: lower the GFR, higher the phosphate levels. This could be attributed to the fact that phosphate is retained with impaired renal function [12]. Hyperphosphatemia confers cardiac damage by inducing acute cardiomyocytes injury as a consequence of which the cardiac biomarker levels are elevated [5]. Hence, to determine the dependency of cardiac biomarker levels on serum phosphate levels, individual Pearson's correlations were carried out. A Strong dependency exists between CK-MB and serum phosphate, CPK and Serum phosphate with correlation coefficients of 0.850 and 0.835 respectively.

Comparison of serum phosphate levels before and after treatment with sevelamer showed statistically significant difference at a confidence interval of 95%. Post-treatment serum phosphate levels were comparatively lower than the pre-treatment values suggesting that sevelamer treatment was effective in reducing phosphate levels in ESRD patients with hyperphosphatemia [13]. However, comparison of cardiac biomarker profiles between sevelamer-treated and untreated groups did not show any statistically significant difference. Further prospective interventional studies are required to monitor and analyze the effect of phosphate on cardiac damage in ESRD patients with hyperphosphatemia.

CONCLUSION

A direct correlation was observed between cardiac enzyme markers and phosphate levels. However, sevelamer at conventional doses was not found to be effective in reducing acute cardiomyocytes injury caused by hyperphosphatemia. Hence, higher doses sevelamer or other modalities achieving normal serum phosphorous levels are necessary for preventing cardiac damage due to hyperphosphatemia in ESRD patients. Further prospective interventional studies are required to monitor and analyze the effect of phosphate on cardiac damage in CKD patients with decreased renal clearance there by preventing the development of cardiovascular complications.

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CONFLICT OF INTERESTS

Declared none.

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