Effect of Vitamin C on Parathyroid Hormone in Hemodialysis Patients With Mild to Moderate Secondary Hyperparathyroidism

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Introduction. In end-stage renal disease, there is a high incidence of secondary hyperparathyroidism. It is proposed that increasing vitamin C levels by dietary supplementation results in a decrease of parathyroid hormone (PTH) in vitamin C-deficient hemodialysis patients with secondary hyperparathyroidism. The aim of this study was the evaluation of vitamin C administration for reduction of serum PTH level in hemodialysis patients.

Materials and Methods. Twenty-one hemodialysis patients with serum PTH levels less than 550 pg/mL (but more than 200 pg/mL) were administered intravenous vitamin C, 200 mg, 3 times per week for 3 months. Blood samples for measurement of PTH were obtained at the beginning of the hemodialysis session every month for three months.

Results. The mean level of serum biointact PTH was 333.3 ± 141.3 pg/mL (reference range, 7 pg/mL to 82 pg/mL) at baseline, and it decreased to 256.5 ± 137.2 pg/mL at 1 month ($P = .03$). The mean PTH level was also lower than the baseline value at 2 months (260.1 ± 123.2 pg/mL, $P = .03$), while it increased to 328.9 ± 176.0 pg/mL at 3 months, which was still slightly lower than the baseline level ($P = .13$). In 15 patients (71.4%), serum levels of PTH were lower than the baseline at months 1 to 2, while in the remaining 6 (28.6%), it was higher than the baseline value. At 3 months, 5 of the 15 patients with lower PTH levels up to the 3rd month experienced an increase in these levels again.

Conclusions. Administration of intravenous vitamin C in hemodialysis patients noticeably decreased level of PTH, but its effect gradually diminished.

INTRODUCTION

The prevalence and incidence of chronic kidney disease (CKD) continues to increase globally.[1] In the United States, for instance, CKD affects an estimated 7.7 million adults.[2] It is also increasing in Europe and in Iran[3,4]; in 2006, the prevalence of CKD increased was up to 12%.[4]

It is hypothesized that parathyroid hormone (PTH) is a well-known toxin of uremia.[5] Patients with CKD often develop secondary hyperparathyroidism due to the sustained increase of PTH caused by phosphate retention and hypocalcemia. The pathogenesis of renal secondary hyperparathyroidism is complex. The most common

features are hypocalcemia and skeletal resistance to the calcemic effect of PTH.[6] Disturbances in vitamin D metabolism and calcitriol deficiency also play a critical role in the developing of hyperparathyroidism in CKD.[6] Metabolic changes associated with secondary hyperparathyroidism can also lead to renal osteodystrophy, including osteitis fibrosa, ectopic calcification, cardiovascular disease, and the risk of death.[7-11] These metabolic changes also cause development of kidney calculi and hyperchloremic metabolic acidosis.[12] It has been suggested that the overload of calcium and phosphate and the excess PTH act together in the abnormalities of the cardiovascular system, including vascular calcification, increased arterial stiffness, and cardiovascular remodeling.[13,14]

Several active vitamin D analogs, which can strongly suppress PTH, have become available in clinical practice.[15,16] According to some studies, phosphate binders frequently lead to untoward toxicities and imbalance in bone metabolism. Thus, new therapies with fewer side effects were recommended.[17] It is proposed that increasing vitamin C levels by dietary supplementation results in a fall of PTH in vitamin C-deficient patients on maintenance hemodialysis with secondary hyperparathyroidism.[18] Hemodialysis patients are especially prone to vitamin C deficiency because of dietary restrictions, malnutrition, and clearance of vitamin C during dialysis sessions, and this deficiency may have significant impacts on outcomes.[19] A single hemodialysis treatment may result in a 50% to 75% decrease in plasma vitamin C level.[20,21] Daily intake of 60 mg to 100 mg of vitamin C is adequate in persons with normal kidney function.[22] However, in hemodialysis patients, it may not be sufficient.[18] Long-term high doses of vitamin C treatment in hemodialysis patients might be a potential risk for the development of secondary oxalosis and must be tightly observed.[22-24] The aim of this study was the evaluation of the effect of vitamin C administration in dialysis patients on the reduction of serum PTH level.

MATERIALS AND METHODS
Patients

Twenty-one adult patients on long-term hemodialysis (13 men and 8 women) were enrolled from one dialysis unit from December 2009 to February 2010. All of the patients were on regular

Table 1. Efficacy of Hemodialysis Before and After Study

Dialysis Parameter	Before Vitamin C	After Vitamin C	P
Urea reduction ratio, %	62.51 ± 5.87	61.31 ± 4.92	.40
KT/V	1.25 ± 0.20	1.12 ± 0.14	.40

hemodialysis twice per week (66.7%) or three times per week (33.3%) using polysulfan dialysis membranes (Soha Co, Tehran, Iran). Blood flow and dialysis solution flow rate were 250 mL/min to 300 mL/min and 500 mL/min, respectively. The KT/V was without any changes during our study (Table 1). Dialysis solution calcium (2.5 mmol/L) was not changed until the end of the study. Although high-flux dialysis membranes are more efficient in removal of biointact PTH than low-flux membranes,[25] low-flux membranes were in use in our center, as high-flux filters were not available.

The inclusion criteria were an age of 18 years old and higher and a biointact PTH level of 200 pg/mL to 550 pg/mL. The exclusion criteria included a positive serostatus for human immunodeficiency virus, evidence of cancer, active infections, and recent (less than 3 months) use of vitamin C and Vitamin D analogues or nutritional vitamin C.

Methods

Consent was obtained from each patient before enrollment. Data collection forms were used for patients' characteristics, including age, sex, weight, smoking, opium use, dialysis vintage, dialysis session, primary disease, concomitant diseases, and administration of vitamin D, vitamin C, and phosphate-binder supplements. All of the patients were receiving phosphate-binders with a similar fixed dose until the end of study, and none of them were on vitamin D supplements. Vitamin C, 200 mg, was administered intravenously 2 to 3 times per week, after each dialysis session for 3 months. The dose of vitamin C was lower than the recommended dosage, so that oxalosis was prevented.[26,27]

Laboratory Measurements

Prior to initiation of intravenous ascorbate therapy, blood samples were taken to measure baseline parameters, including serum levels of calcium, phosphate, alkaline phosphatase, biointact PTH, and albumin. Samples for biointact

PTH measurement were taken at the beginning of hemodialysis session from the venous line, at baseline, and then monthly for 3 months. Samples were isolated by centrifugation immediately after blood collection. Serum PTH level was determined with enzyme-linked immunosorbent assay (IBL Co, USA). Other measurements were repeated at the end of the three months. Serum calcium level was determined with endpoint assay (Darmankav Co, Tehran, Iran); serum phosphate levels, with endpoint assay (Pars Azmoon Co, Tehran, Iran); serum alkaline phosphatase, with fixed-time assay (Pars Azmoon Co, Tehran, Iran); and serum albumin, with endpoint assay (Pars Azmoon Co, Tehran, Iran).

Statistical Analyses

All continuous values were expressed as mean ± standard deviation. Pre- and post-vitamin C administration biointact PTH levels were compared using the Friedman test. Biointact PTH levels at every two measurement times were compared by employing the Wilcoxon signed rank test. Significance was taken at a *P* value of less than .05. Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Demographic characteristics of the participants are summarized in Table 2. The mean age was 42.0 ± 16.8 years old, and 13 patients (61.9%) were men. Baseline variables are depicted in Table 2. The mean level of serum biointact PTH was 333.3 ± 141.3 pg/mL (reference range, 7 pg/mL to 82 pg/mL) at baseline, and it decreased to 256.5 ± 137.2 pg/mL at 1 month (*P* = .03). The mean PTH level was also lower than the baseline value at 2 months (260.1 ± 123.2 pg/mL, *P* = .03), while it increased to 328.9 ± 176.0 pg/mL at 3 months; however, it was lower than the baseline level (*P* = .13; Table 3 and the Figure). In 15 patients (71.4%), serum levels of PTH were lower than the baseline at months 1 to 3, while in the remaining 6 (28.6%), it was higher than the baseline value. At 3 months, 5 of the 15 patients with lower PTH levels up to the 3rd month experienced an increase in these levels again.

Calcium and phosphate values did not change significantly at the end of study (8.3 ± 0.7 mg/dL versus 8.3 ± 0.92 mg/dL, *P* = .59; 5.8 ± 1.8 mg/

Table 2. Baseline Characteristics of Study Population*

| Characteristic	Value
Age, y	42.0 ± 16.8
Gender	
Male	13 (61.9)
Female	8 (38.1)
Body weight, kg	54.2 ± 12.2
Dialysis vintage, y	3.2 ± 2.9
Primary disease	
Diabetes mellitus	3 (14.3)
Hypertension	8 (38.1)
Diabetes and hypertension	5 (23.8)
Others	5 (23.8)
Comorbidities	
Cardiovascular disease	3 (14.3)
Respiratory disease	1 (4.8)
Cardiovascular and respiratory diseases	2 (9.6)
Dialysis per week	
2	14 (66.7)
3	7 (33.3)
Smoking	2 (9.6)
Opium use	1 (4.8)
Medication	
Vitamin D	11 (52.3)
Phosphate binders	21 (100)
Serum parameters	
Intact parathyroid hormone, pg/mL	333.3 ± 141.3
Alkaline phosphatase, U/L	563.1 ± 529.4
Albumin, mg/dL	4.1 ± 0.2
Calcium, mg/dL	8.3 ± 0.7
Phosphate, mg/dL	5.8 ± 1.8
Calcium-phosphorus product	49.2 ± 17.5

*Values are mean ± standard deviation and absolute number (percent).

Table 3. Biointact Parathyroid Hormone (PTH) Levels

PTH	Value, pg/mL	*P**	*P*†
Baseline	333.3 ± 141.3	…	…
1 month	256.5 ± 137.2	.03	.03
2 months	260.1 ± 123.2	.03	.64
3 months	328.9 ± 176.0	.13	.001

*Compared with baseline
†Compared with previous measurement
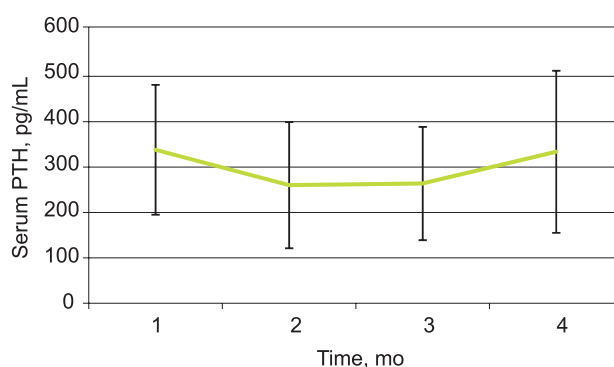
Biointact Parathyroid Hormone (PTH) Levels

dL versus 6.1 ± 1.6 mg/dL, *P* = .10, respectively). Serum albumin levels were comparable between the beginning and the end of the study too (*P* = .59).

DISCUSSION

According to our findings, vitamin C can decrease PTH level in hemodialysis patients with secondary hyperparathyroidism. Hyperparathyroidism is a common complication of CKD, and it develops because of abnormal regulation of calcium and phosphate homeostasis. Three factors play major roles in its development. The first is decrease renal synthesis of 1,25-dihydroxyvitamin D, the second and the third factors are phosphorus retention and impaired calcemic response to parathyroid hormone. Because of increasing of PTH synthesis in secondary hyperparathyroidism, parathyroid cell hyperplasia occurs.[28-31] Secondary hyperparathyroidism often occurs in stage 3 of CKD, before the development of hyperphosphatemia.[32,33] Increased PTH level can stimulate bone demineralization and lead to high-turnover bone disease, a condition marked by accelerated rates of bone absorption and reabsorption. The new bone is structurally fragile and has the increased risk of fractures.[34]

Secondary hyperparathyroidism is one of the risk factors for cardiovascular disease and ectopic calcification.[13,14,35-37] That is why the effort is put to reduce the PTH level down in these patients in order to avoid complications. Richter and colleagues proposed that there was an inverse interaction between biointact PTH level and vitamin C.[18] On the other hand, hemodialysis patients are at a high risk for vitamin C deficiency.[38] Because ascorbate is a small water-soluble molecule, regular hemodialysis can cause particular risk of ascorbate reduction . Because vitamin C is a typical sample of the primary antioxidant security in blood, its deficiency in CKD patients causes increases in free radicals.[39] Further potential sources of increased free radical production in hemodialysis patients are activation of leukocytes and iron overload.[40,41] Also, vitamin C deficiency causes some common signs and symptoms in patients such as ecchymosis, bleeding gums, arthralgia, weakness, depression, neuropathy, and vasomotor instability.[18] Hence, vitamin C administration in these patients is beneficial.

In individuals with normal kidney function, a daily intake of 60 mg to 100 mg of vitamin C is adequate to maintain health.[22] However, this amount may not be sufficient for hemodialysis patients.[18] About 200 mg of vitamin C per day is adequate to prevent ascorbate deficiency in hemodialysis patients.[42] None of our sampled patients received vitamin D analogues, and none of them had any positive history of recent vitamin C supplements use. Richter and colleagues examined serum biointact PTH and plasma vitamin C in 117 hemodialysis patients (they did not administrated vitamin C analogues, but measured plasma level of vitamin C) .Then they evaluated the correlation between biointact PTH levels and plasma vitamin C levels.[18] In comparison, at the beginning of the study, we selected patients with biointact PTH level of 200 pg/mL to 550 pg/mL. We administrated 200 mg of intravenous vitamin C immediately after hemodialysis for 3 months and measured PTH levels monthly. We assessed any changes of PTH level after vitamin C administration. Vitamin C overdose may cause oxalosis in CKD.[43] A dose of 150 mg of vitamin C or lower is considered safe in hemodialysis patients.[44] The dose that we administrated in our study (200 mg 3 times a week) is less than the recommended dose, which made a safer window to reduce probability of oxalosis occurrence.

The inverse interaction between PTH level and vitamin C is a result of vitamin C effect on postreceptor events in the calcium-sensing receptors on parathyroid cells (a superfamily of 7 membrane-spanning receptors).[45] Vitamin C increases the cyclic adenosine monophosphate response to PTH at receptors location.[46] In vitamin C deficiency, these receptors may become resistant to PTH effects. According to our findings, the influence of vitamin C on the PTH level in the first month of treatment was outstanding, but by the time this effect became weaker and almost reached the initial level after 2 months. The main cause of this observation is unknown. Gradual reduction of vitamin C effects on PTH level maybe related to the decrease of calcium-sensing receptors sensitivity on parathyroid gland cells to vitamin C by the time. We recommend further study on this subject and with larger samples.

CONCLUSIONS

Administration of intravenous vitamin C in hemodialysis patients noticeably decreased level of PTH, but its effect gradually diminished.

CONFLICT OF INTEREST

None declared.

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