The Effect of Vitamin C on Parathyroid Hormone in Patients on Hemodialysis With Secondary Hyperparathyroidism: A Double Blind, Placebo-Controlled Study

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Background: Secondary hyperparathyroidism (SHPT) is a prevalent disorder in patients with chronic kidney disease. It is proffered that there is a contradictory relation between serum level of vitamin C and parathyroid hormone (PTH) in hemodialysis patients with secondary hyperparathyroidism.

Objectives: The goal of this study was to assess the effects of the supplemental vitamin C on parathyroid hormone among hemodialysis patients with secondary hyperparathyroidism.

Patients and Methods: This randomized, placebo-controlled, double-blind and parallel-group trial was conducted on 82 hemodialysis patients with serum levels of PTH more than 200 pg/ml. In intervention group, 250 mg vitamin C was injected three times a week for 8 weeks in a row immediately at the end of each dialysis session via the intravenous route. In the control group, same term of placebo saline was injected.

Results: The mean of serum PTH was 699.81 (± 318.8) and 596.03 (± 410.7) pg/ml in intervention and control groups respectively at baseline (reference range, 4 to 66 pg/mL), and at the end of study it changed to 441.4 and 424.6 in these groups. The values of serum Calcium and Phosphate did not significantly change during the study (8.4 ± 0.6 mg/dL versus 8.1 ± 0.8 mg/dL, P = 0.39; 5.89 ± 1.7 mg/dL versus 5.9 ± 1.9 mg/dL, P = 0.08, respectively).

Conclusions: This study finding does not warranted therapeutic effect of vitamin C on secondary hyperparathyroidism.

Keywords: Renal Dialysis; Parathyroid Hormone; Hyperparathyroidism, Secondary; Ascorbic Acid

1. Background

Secondary hyperparathyroidism (SHPT) is one of the most prevalent disorders in patients with chronic kidney disease (CKD) (1), which most hemodialysis patients are faced with (up to 50%) (2). Although SHPT is a result of increased parathyroid hormone (PTH) synthesis due to phosphorus accumulation and hypocalcemia (3), other factors such as impairment of vitamin D metabolism and reduced PTH renal clearance (4) may also exacerbate it (5). Hypocalcemia (Low serum levels of ionized calcium) frequently happens as a result of calcium inadequate response to parathyroid hormone (1).

High levels of PTH, considered as a uremic toxin (6), can stimulate accelerated bone absorption and reabsorption, and cause bone demineralization and renal osteodystrophy (7). The bones which become demineralized are structurally fragile, easily broken, and not resistant to any shock. In this stage, there is higher risk of fractures (8). This mineral metabolism abnormality is also one of the main risk factors for ectopic calcification and cardiovascular events in hemodialysis patients (3).

To prevent the main problems created by SHPT such as cardiovascular mortality and fractures (9), it is necessary to examine and analyze different methods to reduce parathyroid hormone in patients on hemodialysis (10). Whereas there is a potential link between the occurrence of SHPT and low vitamin C levels in conformity with some studies (3), vitamin C supplementation is probably a way to reduce parathyroid hormone with fewer side effects (1).

In low serum levels of vitamin C, calcium-sensing receptors may become resistant to PTH influence (11). Vitamin C increases the response to PTH at these receptors by increasing the cyclic adenosine monophosphate and reducing PTH through it (12).

Hemodialysis patients are at risk for low levels of serum vitamin C (13). Vitamin C is a water-soluble vitamin which can be reduced by regular hemodialysis (14). Dietary restrictions, following fear related to hyperkalemia (15), concern oxalosis, wasting several hundred mg of vitamin...
membranes (1), some of the patients were dialyzed by efficient in the removal of biointact PTH than low-flux kt/V. Although high-flux dialysis membranes are more length of hemodialysis in all patients was approximately including age, sex, weight, marital and employment status, smoking. The study (37 person in case, and 39 person in control group). Of 82 randomized patients, 6 were excluded from the study due to transmission to other dialysis centers, being infected by active infections, getting cancers, death, refusing the test procedure at any stage of it. Prior ethical approval was obtained from the institutional ethical committee at Baqiyatallah University of Medical Sciences, Tehran, Iran. A justification letter was sent to two hemodialysis units to gain permission to collect the data granted by these units. Verbal and written consents were obtained from all those who participated in the study. Written consents were obtained after informing each participant about the study purposes, the “confidentiality” of their information, and the possibility to refuse the test procedure at any stage of it.

4. Results

Demographic data of the participants showed that, among 76 respondents, 46 (60.5%) patients were male and 30 (39.5%) female. The mean age of participants was 60.6 years (SD 11.47) (maximum and minimum range was 29-81 years).

Tables 1 and 2 exhibited the demographic Characteristics of the Study Population. The mean level of serum PTH decreased to 441.42 (± 311.6), and 424.6 (± 386.4) after the intervention in study and control groups respectively. There was no significant correlation between the serum levels of PTH and vitamin C prescription. PTH level alterations in different stages of study are summarized in Table 3. Serum Calcium and Phosphate levels did not significantly change during the study (8.4 ± 0.6 mg/dL versus 8.1 ± 0.8 mg/dL, P = 0.39; 5.89 ± 1.7 mg/dL versus 5.9 ± 1.9 mg/dL, P = 0.08, respectively).
### Table 1. Baseline Qualitative Characteristics of the Respondents

| Variables               | Intervention Group, No. (%) | Control Group, No. (%) | χ²-test |
|-------------------------|----------------------------|------------------------|---------|
| Gender                  | 20 (26.3)                  | 26 (34.2)              | 0.18    |
| Male                    | 17 (22.4)                  | 13 (17.1)              |         |
| Female                  | 3 (3.9)                    | 4 (5.3)                | 0.43    |
| Marriage                | 31 (40.8)                  | 33 (43.4)              | 0.29    |
| Married                 | 2 (2.6)                    | 0                      |         |
| Single                  | 67.9)                      | 4 (5.3)                | 0.48    |
| Education               | 8 (10.5)                   | 8 (10.5)               | 0.81    |
| Primary-secondary       | 31 (40.9)                  | 29 (38.1)              |         |
| College/university-level| 8 (10.5)                   | 8 (10.5)               |         |
| Employment              | 0                          | 0                      |         |
| Jobless                 | 17 (22.4)                  | 12 (15.8)              |         |
| Employed                | 3 (3.9)                    | 4 (5.3)                | 0.43    |
| Retired                 | 17 (22.4)                  | 23 (30.2)              |         |
| Smoking                 | 1 (1.3)                    | 0                      |         |
| Yes                     | 36 (47.4)                  | 39 (51.3)              |         |
| No                      | 14 (18.4)                  | 17 (22.4)              | 0.45    |
| Nephropathy cause       | 4 (5.3)                    | 6 (7.9)                |         |
| HTNa                    | 9 (11.8)                   | 9 (11.8)               |         |
| DMa                     | 10 (13.1)                  | 7 (9.2)                |         |
| Others                  | 10 (13.1)                  | 7 (9.2)                |         |

*aAbbreviation: DM, diabetes mellitus; HTN, hypertension.

### Table 2. Baseline Quantitative Characteristics of the Respondents

| Variable               | Intervention Group, Mean (SD) | Control Group, Mean (SD) | T-test |
|------------------------|-------------------------------|--------------------------|--------|
| Age, y                 | 60.32 (12.2)                  | 60.97 (10.9)             | 0.8    |
| Dialysis vintage, mo  | 63.27 (67.8)                  | 40.4 (32.8)              | 0.63   |
| Body weight, kg        | 68.08 (9.4)                   | 72.1 (9.7)               | 0.07   |
| Serum parameters       |                               |                          |        |
| Intact parathyroid hormone, pg/mL | 699.8 (318.8) | 596 (410.3)              | 0.22   |
| Calcium, mg/dL         | 8.43 (0.49)                   | 8.37 (0.71)              | 0.35   |
| Phosphate, mg/dL       | 6.008 (1.76)                  | 5.787 (1.66)             | 0.57   |

### Table 3. Bioeintact Parathyroid Hormone (PTH) Levels

| Groups       | PTH, pg/mL       | P-Value |
|--------------|------------------|---------|
| Intervention | 699.8 (318.8)    | 0.22    |
| Control      | 596.01 (410.3)   | 0.83    |

### 5. Discussion

The results of the present study demonstrated that vitamin C supplementation cannot decrease serum level of PTH significantly. According to data, the incidence of CKD is higher in men and people older than 45 years. In this study, the mean age of patients was also 60.66 (SD 11.47) years, and
most of them (60.5%) were male and 90.8% of patients were older than 45 years. These results are supported by earlier studies.

In other studies more than 50% hemodialysis patients were jobless, but in our study only 3.9% of the patients were unemployed, and the rest (96.1%) were retired or employed. This could indicate that the government and insurance companies provide appropriate support for hemodialysis patients in Iran. Like similar studies, in this study diabetes and hypertension were the most common causes of nephropathy (diabetes and hypertension 77.7%).

In 2008, Richter proposed that there is an inverse correlation between serum level of vitamin C and biointact PTH (3). He measured serum vitamin C level, while prescribing no vitamin C analogues.

Similarly, in 2011 Sanadgol reported that vitamin C is able to reduce biointact PTH level. Although there were no placebo and control groups in his study, he confirmed that there is an inverse correlation between vitamin C and SHPT in hemodialysis patients (1).

In 2011, Sanadgol and his colleagues measured the mean level of biointact PTH after a prescription of 200 mg of vitamin C, three times a week for 3 months, and explained that the mean of serum PTH was notably reduced at the end of the first month after the prescription of vitamin C. But this influence became gradually weaker after 2 months, so that serum level of PTH increased in 3 months; however, it was still lower than the baseline level. They stated that the reason of this finding may be associated with decreased calcium-sensing sensitivity of receptors to vitamin C.

In spite of Sanadgol study, we observed no significant association between serum levels of PTH and vitamin C. It can be associated with sample size diversity (21 versus 76), usage of placebo, randomization, and control group in our study.

At the initiation of the plan, we selected patients with serum PTH levels more than 200 pg/mL, and randomly divided them into two parallel groups. We prescribed 250 mg intravenous vitamin C immediately after hemodialysis for 2 months, and then assessed the PTH level changes. None of our sampled patients recently used vitamin C supplements. Nevertheless, in our study the level of serum PTH was not measured at the end of the first month. The mean of serum PTH decreased at the end of the second month in the intervention group (699.8 versus 441.4). It can be demonstrated that vitamin C influences on the serum level of PTH. But there was a decrease in serum level of PTH in the control group too; however, it was not comparable with the reduction in the intervention group (441.4 versus 424.6). The main cause of the observed diminution in serum levels of PTH at control group is unknown, but it may be associated with what is called “placebo effect”. Also, we should have examined the serum levels of PTH at the termination of the first month after prescription.

Not measuring plasma level of vitamin C before, and after the study, and not specifying the patients who had vitamin C deficiency before study were the limitations in our study which prevented the capability to generalize the findings. Removing these limitations was not a feasible option due to the financial costs, and the limitations of the laboratories capable of providing the circumstance for this test.

Conclusions: This study finding does not warranted therapeutic effect of vitamin C on secondary hyperparathyroidism. Although serum level of PTH decreased in intervention group with supplemental vitamin C, this decrease was observed in placebo group too. Therefore in this study we did not observe any significant association between vitamin C supplementation and secondary hyperparathyroidism.

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Authors’ Contribution

Vajihe Biniaz developed the protocol, abstracted, analyzed, and interpreted data, wrote and prepared the manuscript, and revised the manuscript for demanded reforms. Ali Tayybi developed the original idea and contributed to the development of the protocol and is corresponding author. Abbas Ebadi contributed to the data analysis and the manuscript revision. Mehdi Sadeghi and Eghlim Nemati contributed to development of the protocol.

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