ORIGINAL ARTICLE

# The effect of intravenous vitamin C on the phosphorus level reduction in hemodialysis patients: A double blind randomized clinical trial

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## ABSTRACT

**Aim** The majority of hemodialysis patients are hyperphosphatemic. Hyperphosphatemia in these patients can lead to renal osteodystrophy, vascular calcification, cardiovascular events, and is independently associated with mortality risk. The aim of this study was to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients.

**Methods** Using a double blind randomized clinical trial, a total of 60 qualified hemodialysis patients were randomly allocated in two intervention and control groups and serum phosphorus, CRP, calcium, albumin and PTH levels were measured. At the end of each hemodialysis session, intervention group received vitamin C vial (500mg/5cc) intravenously three times a week for 8 weeks and control group received normal saline in the same way. Data were collected before and after two months of treatment. Data were analyzed using independent t-test, paired t-test and chi-square test.

**Results** Vitamin C treated group had a significant decrease in phosphorus (p=0.01), CRP level (p=0.01) and Ca×P product (p=0.03). In contrast, there was no significant difference in phosphorous (p= 0.5) and CRP levels (p= 0.6) and Ca×P product (p=0.7) in the control group. In addition, there was no statistically significant change in calcium (p=0.1), PTH (p=0.4) and albumin (p=0.4) levels in both groups.

**Conclusion** Intravenous vitamin C can significantly decrease phosphorus level in hemodialysis patients.

**Key words:** hemodialysis, phosphorus, vitamin C, hyperphosphatemia, Ca×P product, CRP

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## INTRODUCTION

Hyperphosphatemia is a common complication in patients with end stage renal disease (ESRD) undergoing hemodialysis. Untreated hyperphosphatemia might lead to renal osteodystrophy, vascular calcification, and cardiovascular events causing increased morbidity and mortality (1). Studies suggest that serum phosphate greater than 6.5 mg/dL is associated with 27% higher mortality risk compared to patients with phosphate level of 2.4–6.5 mg/dL (2). Hence, phosphorus control in patients on hemodialysis constitutes one of the most important issues that nephrologists are faced with today. Successful control of phosphorus is one of the key aspects in the management of hemodialysis patients (3). However; phosphate control has not been significantly improved over the past two decades (2). Also association between change in calcium, phosphorous and their product (Ca×P product) and increased cardiovascular mortality and morbidity in ESRD patients undergoing chronic dialysis has been described (4). Maintenance hemodialysis patients are especially predisposed to vitamin C deficiency because of dietary restrictions, malnutrition and clearance of vitamin C during dialysis treatment and this deficiency may have an important impact on patient outcomes (5). One single hemodialysis session may result in a 50 to75% decrease in plasma vitamin C level, which predicts adverse cardiovascular outcomes in maintenance hemodialysis patients (6). Therefore, to reach normal levels of vitamin C, it is necessary to prescribe vitamin C supplements to all hemodialysis patients (5).

Considering the fact that vitamin C can reduce the CRP level and CRP reduction directly correlates with phosphorus reduction (7, 8), we hypothesized that vitamin C can decrease phosphorus level in hemodialysis patients. The purpose of this study was to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients.

## PATIENTS AND METHODS

This study was a randomized double blind placebo-controlled clinical trial to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients. A total of 60 hemodialysis patients in Imam Khomeini Hospital, Sari, Iran, were included in the study from 5/22/2010 to 8/19/2010. Patients with the age range of 20-70 years and serum phosphorus level above 5.5 mg/dl that had been hemodialysed three times a week on 4 hour sessions for at least 6 months prior to the trial, were enrolled in the study. Exclusion criteria were history of malignancy, malnutrition, severe cardiac or respiratory or liver disease, history of vitamin C, vitamin D, alcohol, oil fish and immunosuppressive drugs consumption during 2 months prior to the trial. Patients who refused to continue the study at any time or got systemic disease during the study were also excluded from the study. A list of random number generated by the random-number table was employed to allocate eligible patients into intervention and control groups. Intervention group received vitamin C vial (500mg/5cc) intravenously from the venous line at the end of each hemodialysis session three times a week for a period of 8 weeks and control group received 5cc normal saline as placebo in the same way. Neither patients nor clinicians were aware of the allocated group.

At the beginning of the study and before the last hemodialysis session, 10cc fasting venous blood samples were taken from the patients in order to measure serum phosphorus (P), calcium (Ca), CRP and parathyroid hormone (PTH) levels. Patients were asked not to change their nutrition, drugs and physical activity during the study. Phosphorus level was measured using Pars Azmoon Company Kit and photometric technique by BT3000 and serum total calcium was measured with ortho-cresolphthalein complexone (o-CPC) and then the Ca×P product was calculated. Serum CRP was measured with Norway Kit (England) and Nephelometric method and PTH level by radio immunoassay technique and Gamma Counter. Moreover, all patients in the two groups received calcium-based phosphate binder (calcium carbonate) and those who received aluminum hydroxide were excluded from the study. In both groups patients were dialyzed by Fresenius 4008B Hemodialysis Machine and single use polysulfone membrane. Dialysate calcium concentration was 1.2 mmol /L and all patients had arteriovenous (AV) fistula.

Data were collected and analyzed using SPSS version 16 and chi-square test, Fisher exact test, independent and paired t-test.

Approval from the Mazandaran University of Medical Sciences Ethics Committee and informed

written consent from patients were obtained. This study was registered in a clinical trials database (IRCT138904224365N1; http://www.irct.ir).

## RESULTS

Sixty eligible hemodialysis patients were recruited in the period 5/22/2010 - 8/19/2010 and randomized into two groups. Two patients withdrew from the study (one patient in placebo group died and one patient in vitamin C group refused to continue the study) (Figure 1). Complete data were obtained from 58 hemodialysis patients with a mean age of 59.7 (14.6) years for the vitamin C group and 60.6 (13.3) years for the controls, which showed no significant difference between the two groups (p=0.7). The mean duration of hemodialysis in intervention and control group was 29±16.0 and 30.1±22.1 months, respectively, with no statistical significant differences between the two groups (p=0.8).

As shown in Table 1, there was no statistically significant difference in demographic and baseline characteristics of the patients between the two study groups.

**Table 1. Demographics and clinical characteristic in intervention and control groups**

| Variables | | No (%) of patients in group | | p |
|---|---|---|---|---|
| | | Vitamin C (n=29) | Placebo (n=29) | |
| Gender | Male | 17 (58.6) | 14 (48.3) | 0.46 |
| | Female | 12 (41.4) | 15 (51.7) | |
| Marital Status | Single | 2 (6.9) | 3 (10.3) | 0.58 |
| | Married | 27 (93.1) | 26 (89.7) | |
| Smoking | Yes | 5 (17.2) | 2 (6.9) | 0.23 |
| | No | 24 (82.8) | 27 (93.1) | |
| Cause of renal failure | Diabetes | 6 (20.7) | 11 (37.9) | 0.34 |
| | Hypertension | 13 (44.8) | 11 (37.9) | |
| | Other Causes | 10 (34.5) | 7 (24.1) | |

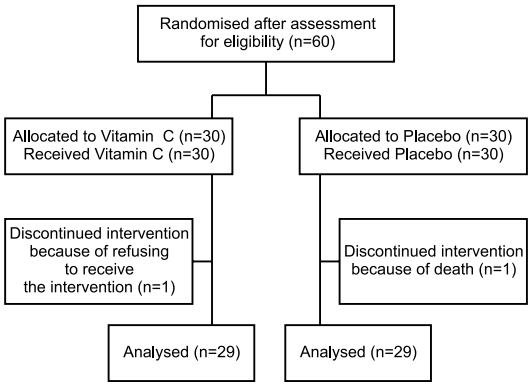


**Figure 1. Flow diagram of the progress through the phases of trial of two groups**

There was no significant differences in phosphorus (p=0.8), CRP (p=0.8), calcium (p=0.6) and PTH (p= 0.3) levels among the groups at the baseline. As shown in Table 2, compared to their baseline level, vitamin C treated group showed a significant decrease in phosphorus (p=0.013) and CRP levels (p=0.042), and Ca×P product (p=0.033) ( Figure 2, Figure 3). In contrast, there were no significant differences in these parameters in the placebo group. Furthermore, mean differences (after – before) of phosphorus, CRP and Ca×P product were statistically significant

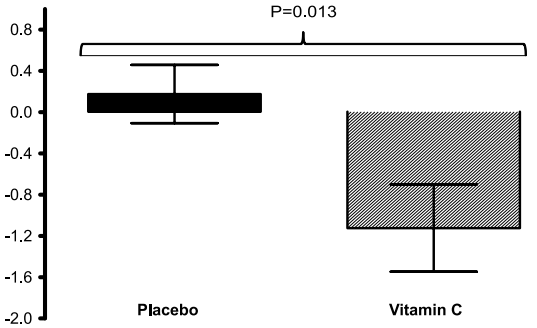


**Figure 2. Phosphorous differences (after - before) in both groups (mean and SEM)**

**Table 2. Mean and standard deviation of phosphorus, Calcium, CRP, Albumin, PTH level and Ca x P product in hemodialysis patients before and after intervention in Vitamin C (n=29) and placebo (n=29) groups**

| Variable | Group | Before intervention Mean ± SD | After intervention Mean ± SD | p* | After - before Mean ± SD | p† |
|---|---|---|---|---|---|---|
| Phosphorus (mg/dl) | Placebo | 6.02±2.37 | 6.2±2.02 | 0.5 | 0.18±1.53 | 0.013 |
| | Vitamin C | 6.11±2.1 | 4.98±1.97 | 0.01 | -1.12±2.28 | |
| Calcium (mg/dl) | Placebo | 8.34±0.9 | 8.24±0.4 | 0.5 | -0.9±0.84 | 0.226 |
| | Vitamin C | 8.24±0.75 | 8.42±0.56 | 0.2 | 0.18±0.86 | |
| CRP (mg/dl) | Placebo | 11.1±9.09 | 11.24±7.82 | 0.9 | 0.14±8.0 | 0.042 |
| | Vitamin C | 10.96±8.15 | 7.27±6.72 | 0.01 | -3.7±7.7 | |
| Albumin (mg/dl) | Placebo | 4.42±0.5 | 4.34±0.4 | 0.5 | -0.08±0.67 | 0.737 |
| | Vitamin C | 4.45±0.4 | 4.42±0.3 | 0.7 | -0.03±0.57 | |
| Ca×P product (Mg2×dl2) | Placebo | 50.03±20.1 | 50.27±17.7 | 0.7 | 0.93±13.5 | 0.033 |
| | Vitamin C | 50.97±15.9 | 41.83±16.6 | 0.03 | -8.4±20.2 | |
| PTH (ng/l) | Placebo | 198.5±120.3 | 194.6±115.4 | 0.3 | -4.1±117.1 | 0.814 |
| | Vitamin C | 201.6±115.6 | 197.8±119.6 | 0.2 | -3.9±116.5 | |

p*, paired t-test; p†, independent t-test

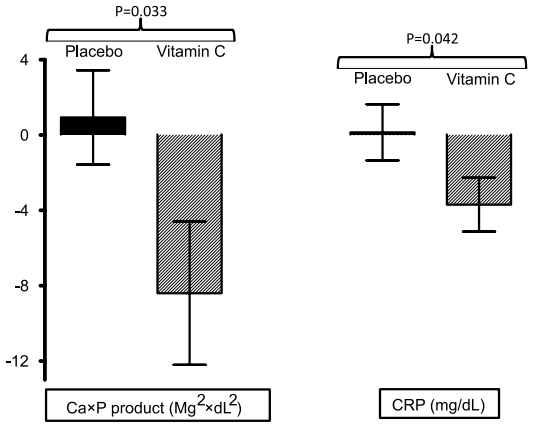


**Figure 3. Ca x P product ($Mg^2 \times dl^2$) and CRP differences (after - before) in both groups (mean and SEM)**

between the intervention and control groups. Changes in calcium, albumin and PTH levels were not different in both groups after the intervention (Table2).

## DISCUSSION

The key and novel finding in the present study is a significant decrease in phosphorus level by eight week administration of intravenous vitamin C in hemodialysis patients. Considering the anti inflammatory and antioxidant effect of vitamin C (7) the paralleled reduction in phosphorus and CRP levels in the present study could be explained by some mechanisms which include: decrease in the cellular destruction and shift of phosphorus from the intra cellular to extra cellular fluid, recovery of cellular injury due to antioxidant effect and increased renal phosphate excretion, effect on metabolic acidosis and extracellular shift of phosphorus and effect on NaPi cotransporter and reducing phosphorus expression in proximal tubule (9). Adeney et al (10) suggested that higher serum phosphate concentration, although within the normal range, are associated with a greater prevalence of vascular and valvular calcification in people with moderate chronic kidney disease (CKD). Our study showed that vitamin C treated group, had a lower Ca×P product level after intervention. Ganesh et al (11) declared that for every 10 greater units of Ca×P product in hemodialysis patients, the relative risk of sudden death increased by 7%. Also, Mills et al (12) demonstrated that Ca×P product is associated with severity of aortic stenosis in hemodialysis patients. Chronic inflammation, as reflected by increased of inflammatory markers, such as CRP, is highly prevalent in hemodialysis patients (13) and increased level of CRP is a strong predictor of all-cause mortality, especially, the cardiovascular one in these patients (14). In this study, we found that the average concentration of CRP and phosphorus level was significantly lower in intervention group than in control group. Hung et al (15) observed a direct relationship between serum phosphorus and CRP in a cohort study. Moreover, Movilli et al (16) showed an association of the Ca×P product with the CRP levels. Block et al (7) have shown the CRP-lowering effect of vitamin C supplementation. Vitamin C represents anti-oxidant defense in blood and non-supplemented hemodialysis patients are at risk of vitamin C deficiency (6). Parenteral administration of ascorbic acid may be an approach to overcome problems of vitamin C deficiency in hemodialysis patients- in particular problems associated with iron overload, erythropoietin resistance and chronic inflammation (17). Fumeron et al (18) reported that oral administration of 250 mg/day of vitamin C after dialysis did not significantly change the oxidative stress and inflammation states, but the effect of high doses of intravenous administration was not clear. Parenteral vitamin C can improve erythropoiesis and decrease CRP level in hemodialysis patients (17). Major concern regarding safety of vitamin C supplementation is its metabolism to oxalate, which may develop to secondary oxalises (19) and one of the possible limitations of the present study was the lack of plasma oxalate level measurements. However, we used a dose of vitamin C that according to previous studies did not increase the plasma oxalate level after 8 weeks of treatment (17, 20). The statistical power of the study was calculated. The results indicated that assuming phosphorous mean difference of 1.30 (SD=1.75), a sample size of 29 in each group was adequate to provide 81% statistical power to compare study groups.

In conclusion, this study demonstrated that intravenous administration of vitamin C was effective in decreasing the phosphorus level in hemodialysis patients. The beneficial change made by intravenous vitamin C in phosphorus level introduces vitamin C as an attractive agent for future research and its use for patients who are on maintenance hemodialysis.

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## TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

## REFERENCES

1. Hutchison AJ, Speake M, Al-Baaj F. Reducing high phosphate levels in patients with chronic renal failure undergoing dialysis: a 4-week, dose-finding, open label study with lanthanum carbonate. Nephrol Dial Transplant 2004; 19:1902-6.
2. Mohammed IA, Hutchison AJ. Phosphate binding therapy in dialysis patients: focus on lanthanum carbonate. Ther Clin Risk Manag. 2008; 4:887–93.
3. Arenas MD, Malek T, Gil MT, Moledous A, Alvarez-Ude F, Reig-Ferrer A. Challenge of phosphorus control in hemodialysis patients: a problem of adherence?. J Nephrol 2010; 23: 525-34.
4. Egbuna OI, Taylor JG, Bushinsky DA, Zand MS. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. Clin Transplant 2007; 21:558-66.
5. Richter A, Kuhlmann MK, Seibert E, Kotanko P, Levin NW, Handelman GJ. Vitamin C deficiency and secondary hyperparathyroidism in chronic haemodialysis patients. Nephrol. Dial Transplant 2008; 23:2058-63.
6. Deicher R, Ziai F, Bieglmayer C, Schillinger M, Horl WH. Low Total Vitamin C Plasma level is a risk factor for cardiovascular morbidity and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16:1811–8.
7. Block G, Jensen CD, Dalvi TB, Norkus EP, Hudes M, Crawford PB, Holland N, Fung EB, Schumacher L, Harmatz P. Vitamin C treatment reduces elevated C-reactive protein. Free Radic Biol Med. 2009; 46:70-7.
8. Calo LA, Savica V, Piccoli A, Fusaro M, Angelo AD, Davis PA. Reduction of hyperphosphatemia is related with the reduction of C- reactive protein in dialysis patients. Study in sevelamer-resistant dialysis patients treated with chitosan chewing gum as salivary phosphate binder. Renal Failure 2011; 33:11-4.
9. George AL, Neilson EG. Disorder of the kidney and urinary tract. In: Longo D, Fauci AS, Kasper D, Hauser S. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill, 2011.
10. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, Kestenbaum BR. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol 2009; 20:381-7.
11. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO (4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-8.
12. Mills WR, Einstadter D, Finkelhor RS. Relation of calciumphosphorus product to the severity of aortic stenosis in patients with normal renal function. Am J Cardiol 2004; 94:1196-8.
13. Stenvinkel P, Alvestrand A. Inflamation in end stage renal disease: sources, consequences, and therapy. Semin Dial 2002; 15:329-37.
14. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35:469-76.
15. Huang HY, AppelL J, ChoiM J, Gelber AC, Charlesto J, Norkus EP, Miller ER. The effects of vitamin C supplementation on serum concentrations of uric acid. Arthritis Rheumatism 2005; 52:1843-7.
16. Movilli E, Feliciani A, Cammerini C. A high calcium-phosphate product is associated with high C-reactive protein concentrations in hemodialysis patients. Nephron Clin Pract 2005; 101:c161-c167.
17. Biesalski HK. Parenteral ascorbic acid in haemodialysis patients. Curr Opin Clin Nutr Metab Care 2008; 11:741-6.
18. Fumeron C, Nguyen-khoa T, SaltielC,Kebede M, Buisson C, Drueke TB, Lacour B, Massy ZA. Effects of oral vitamin C supplementation on oxidative stress and inflammation status in haemodialysis patients. Nephrol Dial Transplant 2005; 20:1874-9.
19. Tarng DC. Novel aspects of vitamin C in Epoetin response. J Chin Med Assoc 2007; 70:357-60.
20. Espahbodi F, Kashi Z, Ala S, Hendoii N. Efficacy and safety of oral versus intravenous vitamin C in hemodialysis patients with functional iron deficiency. Int J Endocrinol Metab 2007; 3:129-34.