

ORIGINAL ARTICLE

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

Afshin Gholipour Baradari¹, Amir Emami Zeydi², Fatemeh Espahbodi³, Mohsen Aarabi⁴

¹Department of Anesthesiology and Intensive Care Medicine, School of Medicine, ²Department of critical care nursing, School of Nursing and Midwifery, ³Department of Nephrology, School of Medicine; Mazandaran University of Medical Sciences, Sari, ⁴Department of Epidemiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

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 $Ca \times P$ product ($p=0.03$). In contrast, there was no significant difference in phosphorus ($p=0.5$) and CRP levels ($p=0.6$) and $Ca \times P$ 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, $Ca \times P$ product, CRP

Corresponding author:

Amir Emami Zeydi
Department of Medical Surgical Nursing,
Nasibeh Nursing and Midwifery Faculty
Vesal Street, Amir Mazandarani Boulevard,
Sari/ Iran, PO BOX: 481675793
Phone/Fax: +98 1512267342-5
E-mail: research9090@yahoo.com

Original submission:

26 September 2011;

Revised submission:

08 November 2011;

Accepted:

30 November 2011.

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, phosphorus and their product ($\text{Ca} \times \text{P}$ 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 to 75% 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 $\text{Ca} \times \text{P}$ product was calculated. Serum CRP was measured with Norway Kit (England) and Nephelometric method and PTH level by radioimmunoassay 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)	0.46
	Female	12 (41.4)	
Marital Status	Single	2 (6.9)	0.58
	Married	27 (93.1)	
Smoking	Yes	5 (17.2)	0.23
	No	24 (82.8)	
Cause of renal failure	Diabetes	6 (20.7)	0.34
	Hypertension	13 (44.8)	
	Other Causes	10 (34.5)	

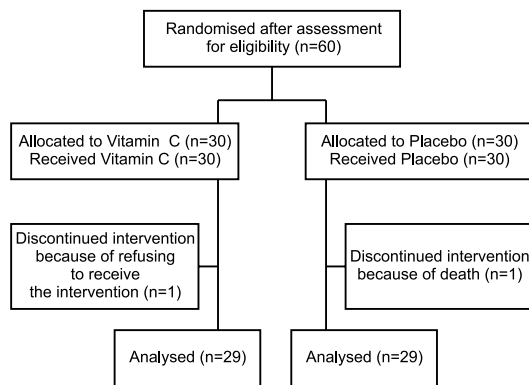


Figure 1. Flow diagram of the progress through the phases of trial of two groups

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

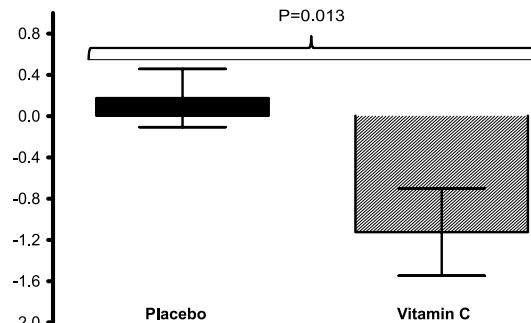


Figure 2. Phosphorous differences (after - before) in both groups (mean and SEM)

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

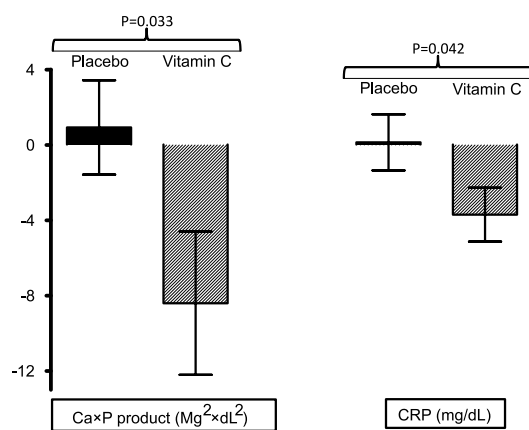


Figure 3. Ca x P product (Mg² x dl²) and CRP differences (after - before) in both groups (mean and SEM)

between the intervention and control groups. Changes in calcium, albumin and PTH levels were not different in both groups after the intervention (Table 2).

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 x P product level after intervention. Ganesh et al (11) declared that for every 10 greater units of Ca x P product in hemodialysis patients, the relative risk of sudden death increased by 7%. Also, Mills et al (12) demonstrated that Ca x P product is associated with severity of aortic stenosis in hemodialysis patients. Chronic inflammation, as reflected by increased of inflam-

matory 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 x 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.

ACKNOWLEDGMENTS

The authors express their gratitude to the staff of Hemodialysis Center of Imam Khomeini Hospital (Sari, Iran) for their efficient and kind collaboration.

Also, the authors wish to thank all the study participants for their tremendous cooperation.

REFERENCES

- 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.
- Mohammed IA, Hutchison AJ. Phosphate binding therapy in dialysis patients: focus on lanthanum carbonate. *Ther Clin Risk Manag*. 2008; 4:887-93.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.
- 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.

FUNDING

The financial support of Research Deputy of Mazandaran University of Medical Sciences is gratefully acknowledged.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

- 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.
- Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO₄, Ca x PO₄ product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001; 12:2131-8.
- 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.
- Stenvinkel P, Alvestrand A. Inflammation in end stage renal disease: sources, consequences, and therapy. *Semin Dial* 2002; 15:329-37.
- 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.
- 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.
- 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.
- Biesalski HK. Parenteral ascorbic acid in haemodialysis patients. *Curr Opin Clin Nutr Metab Care* 2008; 11:741-6.
- Fumeron C, Nguyen-khoa T, SaltielC, Kebede M, Buisson C, Druke 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.
- Tarng DC. Novel aspects of vitamin C in Epoetin response. *J Chin Med Assoc* 2007; 70:357-60.
- 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.