Effect of Vitamin C Supplementation on Serum Uric Acid in Patients Undergoing Hemodialysis

A Randomized Controlled Trial

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Introduction. Clinical studies of recent years have shown that hyperuricemia is associated with poor outcomes such as cardiovascular mortality and dialysis inadequacy in patients undergoing hemodialysis. Our study investigated the effect of vitamin C supplementation on serum uric acid levels in hemodialysis patients.

Materials and Methods. This randomized placebo-controlled trial was conducted on 172 hemodialysis patients. They were randomly divided into the intervention group, to receive 250 mg of vitamin C, three times per week, for 8 weeks, and control groups 1 and 2, to receive placebo injection (saline) and no intervention, respectively. Serum levels of uric acid and creatinine were measured at the start of the study and also after 8 weeks.

Results. The mean of serum levels of uric acid was 6.02 ± 1.08 mg/dL (reference range, 2.6 mg/dL to 6 mg/dL). Nearly, half of the patients (46.7%) had a serum level of uric acid greater than 6 mg/dL. The median baseline serum levels of uric acid were 6.2 mg/dL, 5.9 mg/dL, and 6 mg/dL in the intervention, control 1, and control 2 groups, respectively (P = .19). After 2 months, median levels reduced significantly in the vitamin C group to 5.8 mg/dL as compared to 6.4 mg/dL and 6.3 mg/dL in control groups (P = .02). The mean serum creatinine level had no significant changes during the study.

Conclusions. Our results demonstrated the existence of a significant negative relationship between vitamin C and serum uric acid levels. Detailed investigations with larger sample sizes and longer-term use of vitamin C are recommended.

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INTRODUCTION

End-stage renal disease (ESRD) is one of the most common chronic diseases and a major healthcare problem, especially in developing countries.[1,2] It is reported that the incidence and prevalence of ESRD are on the rise all over the world.[3] Although patients undergoing hemodialysis, as a maintenance invasive treatment, can live longer,[4] they experience diverse complications that noticeably disturb their quality of life.[5] Cardiovascular disease associated with vascular calcifications is the most important cause of morbidity and mortality in patients with ESRD.[6] Clinical studies in recent years have shown that there was a significant association between hyperuricemia and cardiovascular events in the general population and in patients with chronic

kidney disease (CKD).[7-9] Hyperuricemia, represented by increased levels of serum uric acid (SUA), is one of the most prevalent disorders in CKD patients,[10] and is associated with cardiovascular mortality and rapid progression of decline in residual kidney function in CKD patients of stages 3 to 5,[11-15] left ventricular hypertrophy,[11] lower glomerular filtration rate,[16] poor outcome, and dialysis inadequacy,[17] especially in SUA levels above 6 mg/dL.[18]

Although some medications are effective in lowering SUA by reducing its synthesis or enhancing its excretion, these drugs carry significant side effect profiles. Hence, providing alternative and attractive approaches such as supplementation with vitamin C can play a critical role in hyperuricemia management.[19] Since humans are not able to synthesize vitamin C endogenously, and therefore, it is a vital dietary supplement.[20-22] Vitamin C deficiency is a rare complication in the community, but common in hemodialysis patients,[23-26] which has been recognized an important risk factor for cardiovascular disease and its mortality.[27,28] It occurs mainly due to the loss of the vitamin during dialysis sessions and dietary restriction of fresh fruits and vegetables to avoid hyperkalemia.[29] According to the literature, vitamin C reduces SUA by applying a uricosuric effect, hindering uric acid synthesis, and increasing its urinary excretion.[30]

Although the effect of oral vitamin C on SUA levels has been evaluated in healthy inidivduals,[31] there is no such knowledge about its intravenous administration in patients on hemodialysis. Since the treatment of hyperuricemia as an independent risk factor for cardiovascular disease can decrease cardiovascular mortality,[17] and regarding the reducing effect of vitamin C on the SUA levels,[32] we carried out this study to evaluate the effect of vitamin C supplementation on the SUA levels among hemodialysis patients.

MATERIALS AND METHODS

Design

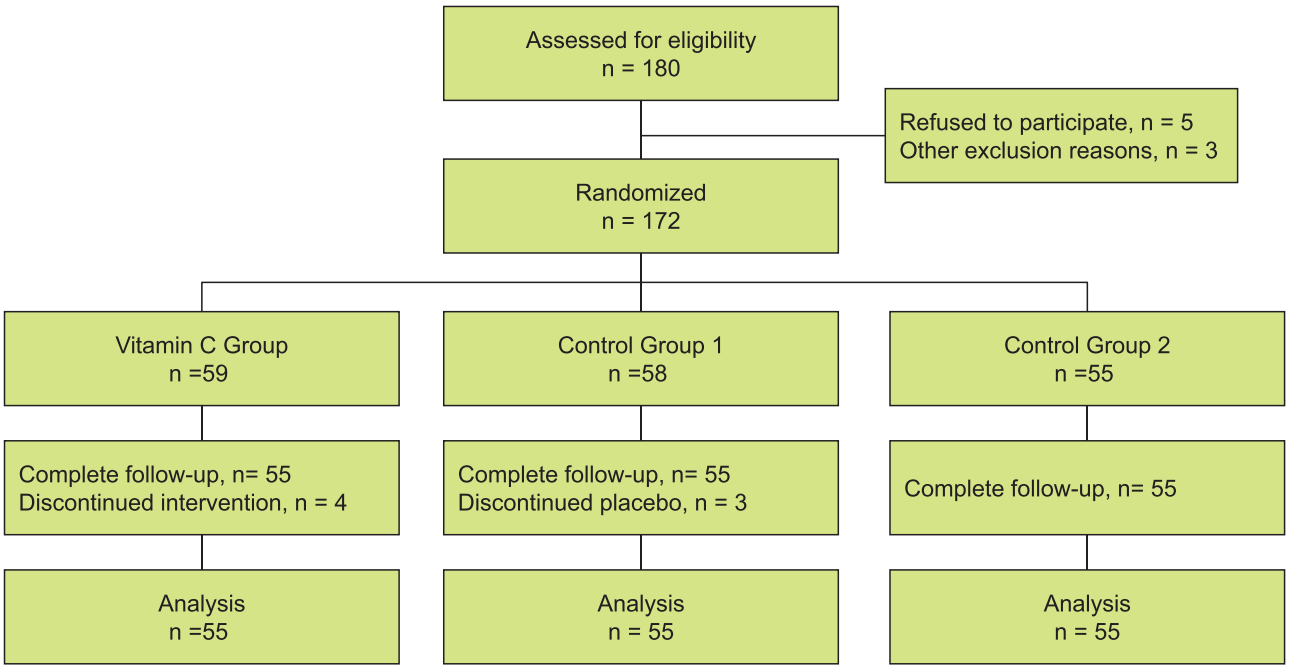
This randomized placebo-controlled double-blind trial was conducted from October 2012 to January 2013 on ESRD patients who were undergoing maintenance hemodialysis.

Patients

A total of 172 participants were enrolled from 2 hemodialysis units at 2 hospitals in an urban area of Iran (Baqiyatallah Hospital and Chamran Hospital, in Tehran). The participants were randomly distributed by a lottery method into 3 groups (simple random sampling) of the intervention group that received vitamin C, the control group 1 that received placebo, and the control group 2 that received no intervention. The three groups were comparable in sex proportion, age, weight, marital and employment status, length and sessions of hemodialysis, and smoking. Nutritional status of the participants was not changed during the study in comparison with their previous nutritional status. Since the length of dialysis is associated with KT/V and both can interfere with vitamin C effect on SUA,[33,34] we controlled these factors by matching the length of dialysis and KT/V in the all groups. The length of dialysis in all the patients was approximately 4 hours and its occasions were 3 times a week with comparable KT/Vs. The KT/V showed no change during the study.

We used low-flux dialysis membranes in all the patients. Although high-flux dialysis membranes have larger pores in comparison with low-flux ones and these pores allow the diffusing of larger amounts of uremic toxins,[35] they can clear more water-soluble vitamins such as vitamin C.[36-38]

Inclusion was not limited to patients with elevated SUA. The sample included all ESRD patients aged 18 years and older, regular recourse for hemodialysis 3 sessions per week, and receiving hemodialysis for 6 months or longer. Exclusion criteria included a history of kidney transplantation less than 1 year earlier, taking vitamin C within the past 3 months, alcohol consumption, and clinically diagnosed cirrhosis. Also, the patients with active infections, cancer, transition to other dialysis centers, or death during the study were excluded from the study. Out of 172 randomized patients, 7 were excluded from the study due to transition to other dialysis centers, being infected by active infections, cancer, death, or refusal to continue participation, and 165 patients completed the study (55 in each group; Figure). Sample size was determined by elements such as estimation of outcomes in each group; α (type I) error level; the statistical power error level; and the standard deviation of the measurements for continuous outcomes. In this study, a *P* value was considered less than .05 to be significant and the statistical power was considered 80%.



Flow diagram of the progress through the phases of the randomized trial.

Ethical approval was obtained from the institutional ethics committee of the hospitals. From all those who participated in the study, verbal and written consents were obtained after informing each participant about the study purposes, confidentiality of their information, and the possibility to withdraw from the study at any stage of it.

Data Collection and Laboratory Measurements

Data collection included age, sex, weight, income, marital status,, education, employment status, smoking history, opium use, alcohol consumption, dialysis session and vintage, ESRD cause, and administration of supplements.

The required laboratory parameters including SUA and serum creatinine levels were measured at the beginning and at the end of the intervention. The blood sample was taken via the venous line at the beginning of hemodialysis sessions. The determination of SUA levels was done by the Sigma enzymatic procedure (Sigma Diagnostics, St Louis, MO, USA) using colorimetric methods.[39]

Interventions

In the intervention group, 250 mg of vitamin C was injected immediately at the end of each hemodialysis session via the intravenous route, three times a week for 8 weeks in a row. In the control group 1, same term of placebo saline was injected, and in the control group 2, no intervention was made. Although the recommended amount for vitamin C intake in patients on hemodialysis is 700 mg to 1400 mg per week,[40] only 250 mg of vitamin C, 3 times a week—which is lower than the safe dosage recommended by National Institute of Heath[20]—was prescribed in order to prevent oxalosis.

Statistical Analyses

All continuous data were shown as mean ± standard deviation. The chi-square test, *t* test, and 1-way analysis of variance were used in this study. The data were analyzed by the SPSS software (Statistical Package for the Social Sciences, version 18.0, SPSS Inc, Chicago, Ill, USA). A 5% error was considered in rejecting the full hypothesis at the 95% confidence interval. The significance level was set at .05.

RESULTS

Participants Characteristics

Completed data were collected from 165 patients on hemodialysis, who were 102 men (61.8%) and 63 women (38.2%), with a mean age of 61.54 ± 12.72 years (range, 24 to 88 years). The mean age of the men (61.7 years) was comparable to the age of

the women (61.3 years). Most of the participants (73.3%) were in the age group of over 55 years old. Eighty five of the participants (51.5%) were retired, 12 (7.3%) were unemployed, 54 described themselves as housewife or husband, and 14 (8.5%) were employed. The mean age for the retired, unemployed, and employed individuals was 63.3, 62.2 and 48.2 years, respectively. Most of the participants (84.2%) were married. The mean of hemodialysis duration was 38.77 ± 33.46 months (range, 10 to 156 months). The most prevalent cause of ESRD was hypertension (36.4% hypertension and 27.9% simultaneous hypertension and diabetes mellitus). Education level was primary or secondary school in 52.7% of the participants. Although dialysis vintage in the intervention group was longer than the other groups, it did not achieve a significant level (P = .07). Since dialysis adequacy (KT/V) was identical in the three groups, the dialysis vintage could not be an important interfering factor. The mean serum creatinine level was 6.9 ± 2.4 pg/mL (reference range, 0.4 pg/mL to 1 pg/mL). Additional demographic characteristics of the three groups are shown in Table 1.

Hyperuricemia and Associated Factors

The mean of SUA levels was 6.02 ± 1.08 mg/dL (reference range, 2.6 mg/dL to 6 mg/dL). Approximately, half of the patients (46.7%) had an SUA level higher than 6 mg/dL. There was no significant difference between the SUA level of the men (6.00 ± 1.07 mg/dL) and the women (6.05 ± 1.10 mg/dL; P = .74). There was no significant relationship between age and SUA levels (P = .46). Although the highest mean SUA level was seen in the employed patients (6.13 ± 1.30 mg/dL), there was no significant relationship between employment and SUA levels (P = .06). A significant positive relationship was observed between dialysis vintage and SUA levels (P = .01). The highest and lowest SUA levels were seen respectively in individuals with glomerulonephritis (7.00 ± 1.20 mg/dL, P = .03) and diabetes mellitus (5.60 ± 1.02 mg/dL, P = .045). Although there existed a positive relationship between serum creatinine and SUA levels, it did not achieve a significance level (P = .06).

Data were analyzed at two levels of all participants (Table 2) and hyperuricemic patients (Table 3). As seen in Table 2, SUA levels showed no significant

Table 1. Baseline Characteristics of Hemodialysis Patients on Vitamin C, Placebo (Control 1), and No Intervention (Control 2)*

Parameter	Hemodialysis Groups			*P*
	Vitamin C	Control 1	Control 2	
Mean age, y	59.84 ± 11.90	62.75 ± 10.80	62.04 ± 15.04	.46
Sex				
Male	33 (20.0)	34 (20.6)	35 (21.2)	
Female	22 (13.3)	21 (12.7)	20 (12.2)	.92
Mean body weight, kg	68.70 ± 12.10	71.80 ± 13.33	68.50 ± 10.31	.28
Mean dialysis vintage, mo	47.25 ± 41.90	34.25 ± 25.66	34.80 ± 29.58	.07
Education				
Primary or secondary	28 (17)	30 (18.1)	29 (17.5)	
College or university	27 (16.4)	25 (15.2)	26 (15.8)	.94
Marital status				
Married	49 (29.7)	43 (26.1)	47 (28.5)	
Single or widowed	6 (3.6)	12 (7.3)	8 (4.8)	.26
Employment				
Employed	5 (3)	3 (1.8)	6 (3.6)	
Retired	28 (17)	32 (19.4)	25 (15.3)	
Unemployed or housekeeper	22 (13.3)	20 (12.1)	24 (14.5)	.45
Smoking	1 (0.6)	0	0	.36
Nephropathy cause				
Hypertension	18 (10.9)	20 (12.1)	22 (13.3)	
Diabetes mellitus	5 (3.0)	7 (4.2)	11 (6.7)	
Hypertension and diabetes mellitus	17 (10.3)	16 (9.7)	13 (7.9)	
Glomerulonephritis and others	15 (9.1)	12 (7.3)	9 (5.5)	.22

*Values are mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables.

Table 2. Changes in Serum Uric Acid and Creatinine Levels After the Study Period in All Participants

Parameter	Hemodialysis Groups			*P*
	Vitamin C	Control 1	Control 2	
Uric Acid, mg/dL				
Before	6.2 ± 1.1	5.9 ± 0.9	6.0 ± 1.2	.19
After	5.8 ± 1.3	6.4 ± 1.3	6.3 ± 1.1	.02
Creatinine, pg/mL				
Before	6.9 ± 2.0	6.8 ± 2.2	6.9 ± 2.8	.94
After	6.5 ± 1.7	67 ± 2.2	6.4 ± 2.3	.66

Table 3. Changes in Serum Uric Acid Levels After the Study Period in Participants With Hyperuricemia

Parameter	Hemodialysis Groups			*P*
	Vitamin C	Control 1	Control 2	
Uric Acid, mg/dL				
Before	6.90 ± 0.70	6.70 ± 0.70	6.90 ± 0.70	.23
After	5.90 ± 1.30	6.80 ± 0.64	6.80 ± 1.01	.004

difference between the three groups at baseline ($P = .19$). The median baseline SUA levels in the intervention, control 1, and control 2 groups were 6.2 mg/dL, 5.9 mg/dL, and 6 mg/dL, respectively. After 2 months, the median SUA levels reduced significantly in the vitamin C group to 5.8 ($P = .02$) versus 6.4 mg/dL and 6.3 mg/dL in the control groups. The paired *t* test also showed that SUA changes were significant only in the intervention group ($P < .001$), whereas no significant changes were observed in the control groups (control group 1, $P = .09$; control group 2, $P = .39$).

DISCUSSION

We hypothesized that supplemental vitamin C would have an effect on SUA, and designed this study to test that hypothesis. Our data showed a significant relationship between vitamin C supplementation and SUA levels. This is the first randomized controlled study with parallel groups to examine the relationship between SUA levels and vitamin C supplementation in patients undergoing hemodialysis. In the present study, the incidence of hyperuricemia was 47%. Numerous studies have confirmed that oral vitamin C decreases SUA levels in individuals without chronic kidney failure.[19] Our results indicated that intravenous vitamin C also reduced SUA levels in CKD patients on hemodialysis.

According to Clermont and coworkers,[39] the plasma antioxidant status is significantly lower in patients undergoing hemodialysis and these patients are at risk for low levels of serum vitamin C. Chronic inflammation due to the release of inflammatory mediators in hemodialysis patients leads to reduced production of essential antioxidants and increased oxidative stress,[41] and it causes an increase of free radicals associated with vitamin C deficiency as an important antioxidant.[42,43]

Dashti-Khavidaki and colleagues demonstrated that approximately 54% of the patients on hemodialysis suffered from vitamin C deficiency.[44] Since vitamin C is a water-soluble vitamin, regular hemodialysis can reduce it. Causes of vitamin C deficiency are dietary restrictions a result of fear related to hyperkalemia and concerns about oxalosis,[45] wasting several hundred milligrams of vitamin C during one session of hemodialysis, [46] loss of appetite,[47] and fast catabolism leading to usage of vitamin C less than necessary in hemodialysis patients.[46] Although normal range of serum of vitamin C is 30 µM to 60 µM, the majority of hemodialysis patients have serum levels of vitamin C less than 10 µM, and even some of them have less than 2 µM.[48] Moreover, though the intake of 60 mg to 100 mg of vitamin C for health maintenance is sufficient in an individual with normal kidney function, it may not be adequate in a hemodialysis patient due to the mentioned reasons. The recommended amounts for the intake of vitamin C in hemodialysis patients are 100 mg to 200 mg per day; nonetheless, almost none of hemodialysis patients use this amount of supplements.[49]

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 limit the ability 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 facilities for this test. Another limitation of this study was the small sample size. Performing studies with larger sample sizes and longer-term use of vitamin C are recommended.

CONCLUSIONS

Our data showed that high SUA levels were seen in half of the patients undergoing hemodialysis. We also demonstrated the existence of a significant relationship between vitamin C supplementation and SUA levels. Detailed investigations with larger

sample sizes and longer-term use of vitamin C are recommended.

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CONFLCIT OF INTEREST

None declared.

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