Effect of vitamin 'C' on C-reactive protein in patients with end-stage renal disease on hemodialysis

Maher Abd-El Gaber Abd-El Naser, Essam Abd-El Mohsen Mohammed, Mahmoud Ahmad Sayyed

Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Mahmoud Ahmad Sayyed, Msc, Assiut University, Assiut, Egypt
Postal Code: 71111;
Tel: +20 100 741 0750; Mobile: +0862342914;
e-mail: mahmoud.abushneef@gmail.com

Received 01 February 2019
Accepted 08 April 2019

Journal of Current Medical Research and Practice
May-August 2019, 4:216–219

Background and objectives
Chronic inflammation is the most important cause of cardiovascular disease in patients undergoing hemodialysis (HD), and vitamin C – as a major antioxidant – could be effective to suppress inflammation. This study was done to determine the effect of vitamin C on C-reactive protein (CRP) in patients with end-stage renal disease (ESRD) on HD.

Patients and methods
The study included 80 adult patients with ESRD on regular HD who were divided randomly into two groups: In the intervention group, 250 mg of vitamin C was injected intravenously immediately at the end of each HD session three times a week for 8 weeks. In the control group, no intervention was performed. Level of CRP was measured at the baseline and at the end of the study in all patients.

Results
The mean age of enrolled patients was 53.98 ± 7.93 years. Out of the studied group; 62 (51.6%) patients were women. The most frequent cause of nephropathy was diabetes mellitus followed by combined diabetes and hypertension. As regards baseline level of CRP, there was no significant difference between the two studied groups. The level of CRP at the end of the study was significantly low in the intervention group (7.8 ± 6.1 mg/dl) in comparison to the control group (17.3 ± 12.2 mg/dl).

Conclusion
Intravenous supplementation of vitamin C in patients with ESRD on HD may modify the level of CRP and hence may protect against cardiovascular disease complications in such patients.

Keywords:
C-reactive protein, vitamin C, end-stage renal disease, hemodialysis

J Curr Med Res Pract 4:216–219

2357-0121

Introduction

Hemodialysis (HD) patients experience a three to four times higher mortality rate compared with their peers without chronic kidney disease. Cardiovascular disease (CVD) is cited as the main cause of mortality. Epidemiological studies show that traditional CVD risk factors such as obesity, hypercholesterolemia, and high blood pressure exhibit paradoxical relationships with mortality risk in this population [1].

Chronic low-grade inflammation is a major contributing factor to the pathogenesis of atherosclerosis and has been reported in 30–50% of HD patients. Acute inflammation is an adaptive response toward injury and infection, but a dysregulated on-going inflammatory state detrimentally affects the physiological process [2].

Particularly, chronic systemic inflammation in HD patients as indicated by increased levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 are strong predictors for CVD and overall mortality. Inflammation *per se* also contributes to the early development of comorbid conditions such as protein energy wasting, vascular calcification, endocrine disorders, and depression, which vastly decrease the quality of life in HD patients [3].

Patients undergoing HD treatment may experience inflammation triggered by both endogenous and exogenous factors. Elevations of CRP and interleukin-6 levels have been documented in chronic kidney disease patients even before initiation of HD. The HD procedure itself is directly involved in triggering the inflammatory response by (a) passage of endotoxin from the dialysate to the circulation, (b) filter membrane bioincompatibility, (c) use of a central dialysis catheter, and (d) nonultrapure dialysate use [4].

The relationship between inflammation and oxidative stress is bidirectional and synergic. Oxidative stress

invokes inflammation via the activation of nuclear factor kappa B, a transcription factor that regulates inflammatory responses with HD patients experiencing higher nuclear factor kappa B gene expression compared with their healthier counterparts [5].

Secondary to elevated level of inflammatory mediators and free radicals associated in those patients with HD. the antioxidant effect of vitamin C may be beneficial in those patients to decrease the inflammatory process with subsequent decrease in risk of complications such as CVD complications.

Patients on HD are at risk of vitamin C deficiency due loss in session of HD or secondary to dietary restriction of fresh fruits and vegetables to avoid hyperkalemia [6]. This study was designed to assess the effect of vitamin C supplementations in patients on HD.

Patients and methods

This randomized, controlled, clinical trial was conducted from June 2016 to June 2017 at the Hemodialysis Unit of Assiut University Hospitals. Eighty patients with end-stage renal disease (ESRD) undergoing maintenance HD were enrolled in the study. All candidates were randomly distributed by a lottery method into two identical groups (simple random sampling); intervention group received vitamin C (40 patients), and the control group received no intervention (40 patients).

Any patient with one or more of the following conditions was excluded: history of renal transplantation for less than 1 year ago, using anti-inflammatory medications such as immunosuppressive agents, being infected by active infections, getting cancers, smoking and passive smoke exposure, and alcohol consumption.

Qualification was not limited to patients with elevated CRP. The sampling frame included all patients with ESRD aged equal to or older than 18 years, regular recourse for HD of three sessions per week, receiving HD of more than or equal to 6 months, and not taking vitamin C or E at least from 3 months ago.

In the intervention group, 250 mg of vitamin C was injected intravenously immediately at the end of each HD session three times a week for 8 weeks in a row. In the control group no intervention was performed. Although the recommended amount for vitamin C intake in patients on HD is 100–200 mg/day [7], only 250 mg of vitamin C three times a week, which is lower than the safe dosage recommended by NIH, [8] was prescribed to prevent oxalosis. Serum levels of CRP were measured at the beginning and at the end of intervention.

The local ethics committee approved the study. A written informed consent was obtained from all participating patients prior to inclusion in the study.

Statistical analysis

Data were analyzed using SPSS, version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± SD and compared with Student's *t* test and analysis of variance, while nominal data were expressed in the form of frequencies (%) and compared by χ^2 test. Correlation of CRP with age, dialysis duration, and BMI was assessed by Pearson's correlation. The level of confidence was kept at 95%, hence a *P* value of less than 0.05 indicated a significant association.

Results

The mean age of enrolled patients was 53.98 ± 7.93 years. Out of the studied group, 62 (51.6%) patients were women. The most frequent cause of nephropathy was diabetes mellitus followed by combined diabetes and hypertension. The two studied groups had insignificant differences as regards demographic data ($P > 0.05$) (Table 1).

As regards the baseline level of CRP, there was no significant difference between the two studied groups [17.1 ± 12.6 mg/dl (the intervention group) and 15.9 ± 11.2 mg/dl (the control group), $P = 0.09$]. At the end of study, the level of CRP was significantly low in the intervention group (7.8 ± 6.1 mg/dl) in comparison to the control group (17.3 ± 12.2 mg/dl).

In the control group, there was no significant change between the level of CRP at baseline and

Table 1 Baseline characteristics of all studied groups

	Intervention group (*n*=40)	Control group (*n*=40)	*P*
Age (years)	53.3±7.9	54.7±7.8	0.71
Sex			0.87
Male	18 (45)	20 (50)	
Female	22 (55)	20 (50)	
BMI (kg/m^2)	71.7±7.6	72.7±6.6	0.81
Dialysis duration (years)	25.4±3.4	26.3±2.8	0.97
Etiology of nephropathy			0.92
Diabetes mellitus	14 (35)	15 (37.5)	
Hypertension	8 (20)	11 (27.5)	
Both of them	14 (35)	11 (27.5)	
Others	4 (10)	3 (7.5)	

Data were expressed in the form of mean±SD or frequency (%) as appropriate.Intervention group, received vitamin C; control group 2, received no intervention.*P* value was significant if 0.05.

at the end of the study, but it was significantly decreased in case of the intervention group (17.1 ± 12.6 vs. 7.8 ± 6.1 mg/dl; $P < 0.001$). It was noticed that the baseline level of CRP had no significant correlation with the age of patients in all patients but had weak significant correlation with BMI (r=–0.33, P = 0.01) and dialysis duration (r=–0.21, P = 0.01) (Tables 2 and 3).

Discussion

CRP is considered an independent marker of cardiovascular risk. The panel recommends the use of CRP as part of global risk prediction in asymptomatic individuals, particularly those supposed to be at intermediate risk for CVD by traditional risk factors [9]. In patients undergoing HD, there is vitamin 'C' deficiency due to loss during an HD session [6], dietary restriction of fresh foods and vegetables – to avoid hyperkalemia – and fast catabolism which is a risk factor for increased inflammatory status, CVD, and mortality.

Moreover, chronic inflammation due to the release of inflammatory mediators in patients on HD leads to reduced production of essential antioxidants and increased oxidative stress, and it increases free radicals associated with vitamin C deficiency as an important antioxidant [4].

The current study showed that CRP levels were significantly changed in those patients who received supplemental vitamin C with no significant changes in other patients included in the study. This result was consistent with other previous study that stated that the CRP level was reduced as a result of administration of intravenous vitamin C in HD patients [10,11].

Table 2 C-reactive protein level at the start and at the end of the study

	C-reactive protein		*P*1
	At the start	At the end	
Intervention group	17.1±12.6	7.8±6.1	<0.001
Control group	15.9±11.2	17.3±12.2	0.08
*P*2	0.09	<0.001	

Data were expressed in form of mean±SD.Intervention group, received vitamin C; control group, received no intervention. *P* value was significant if 0.05 (*P*1, compared between the same group at baseline and at the end while *P*2, compared between the three studied groups).

Table 3 Correlation between C-reactive protein with age, BMI, and dialysis duration

	C-reactive protein	
	r	*P*
Age	0.16	0.07
BMI	–0.33	0.01
Dialysis duration	0.21	0.01

Data were expressed in the form of r (indicated to strength of correlation) and *P* (indicated to significance of correlation).

Biniaz *et al*. [12] findings' demonstrated that there is negative correlation between vitamin C supplementation and CRP level in ESRD patients on HD. As regards the oral supplementation of vitamin C, Fumeron *et al*. [13] concluded that there was no effect of oral vitamin C on CRP level in HD patients. This could be explained by the lower plasma concentration following oral intake of vitamin C in comparison to a higher plasma concentration following intravenous supplementation of vitamin with subsequent more antioxidant effects [13].

Consistent with earlier literature, our study indicated that diabetes and hypertension were the most common causes of nephropathy (hypertension and diabetes 92.5%) [14]. We found that there was no significant relation between CRP level and various nephropathy causes.

Also, there was no relation between CRP level and age, but BMI and dialysis duration had a significant correlation with CRP. These results are supported by other previous studies which stated a significant relation between CRP level and duration of dialysis [15], while Biniaz *et al*. [12] found no relation between CRP level and duration of dialysis.

Not measuring plasma levels of vitamin C before and after the study, and not specifying the patients who had vitamin C deficiency before the study were the limitations in our study which burden the ability to generalize the findings. Removing these limitations was not a feasible option due to the financial costs, and the limitations of laboratories capable of providing the circumstance for this test. It is recommended to perform studies with a longer-term use of vitamin C, and larger sample size with exclusion of diabetic patients.

Conclusion

Our findings demonstrated that there was a reverse relation between supplemental vitamin C and CRP levels, and vitamin C supplementation could modify the levels of CRP in patients on HD. Serial determinations of CRP are more effective for a better prediction of the inflammatory state of patients on chronic HD than scattered single time-point measurements. So, we can comfortably say that vitamin C supplementation with its CRP-lowering effect could be a simple and useful method in modifying the inflammatory status, and a

potential goal for reducing CVD risk in patients on HD.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 United States Renal Data System. 2017 USRDS Annual Data Report. *Epidemiology of kidney disease in the United States; National Institutes of Health*. Bethesda, MD, USA: National Institute of Diabetes and Digestive and Kidney Diseases; 2017.

2 Medzhitov R. Origin and physiological roles of inflammation. Nature 2008; 454:428–435.

3 Sabatino A, Regolisti G, Karupaiah T, Sahathevan S, Sadu Singh BK, Khor BH, *et al*. Protein-energy wasting and nutritional supplementation in patients with end-stage renal disease on hemodialysis. Clin Nutr 2017; 36:663–671.

4 Susantitaphong P, Riella C, Jaber BL. Effect of ultrapure dialysate on markers of inflammation, oxidative stress, nutrition and anemia parameters: a meta-analysis. Nephrol Dial Transplant 2013; 28:438–446.

5 Biswas SK. Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? Oxid Med Cell Longev 2016; 2016:5698931.

6 Zhang K, Dong J, Cheng X, Bai W, Guo W, Wu L, Zuo L. Association between vitamin C deficiency and dialysis modalities. Nephrology 2012; 17:452-457.

7 Sanadgol H, Bayani M, Mohammadi M, Bayani B, Mashhadi MA. Effect of vitamin C on parathyroid hormone in hemodialysis patients with mild to moderate secondary hyperparathyroidism. Iran J Kidney Dis 2011; 5:410-415.

8 Vitamin C. Dietary Supplement Fact Sheet: NIH Office of Dietary. Supplements; 2011. Available from: http://ods.od.nih.gov/factsheets/VitaminC-QuickFacts. [Last accssed on 2013 Jun 12].

9 Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, *et al*. Markers of inflammation and cardiovascular disease. Circulation 2003; 107:499–511.

10 Block G, Jensen C, Dietrich M, Norkus EP, Hudes M, Packer L. Plasma C-reactive protein concentrations in active and passive smokers: influence of antioxidant supplementation. J Am Coll Nutr 2004; 23:141–147.

11 Gholipour A, Emami A, Khademloo M, Naghshvar F, Razavi M, Espahbodi F. The effect of intravenous vitamin C on the level of CRP in hemodialysis patients. J Mazand Univ Med Sci 2011; 21:55–61.

12 Biniaz V, Shermeh MS, Ebadi A, Tayebi A, Einollahi B. Effect of vitamin C supplementation on C-reactive protein levels in patients undergoing hemodialysis: a randomized, double blind, placebo-controlled study. Nephrourol Mon 2014; 6:e13351.

13 Fumeron C, Nguyen-Khoa T, Saltiel C, Kebede M, Buisson C, Drueke TB, *et al*. Effects of oral vitamin C supplementation on oxidative stress and inflammation status in hemodialysis patients. Nephrol Dial Transplant 2005; 20:1874–1879.

14 Ghaderian SB, Beladi-Mousavi SS. The role of diabetes mellitus and hypertension in chronic kidney disease. J Renal Injury Prev 2014; 3:109.

15 Handelman GJ. Vitamin C deficiency in dialysis patients – are we perceiving the tip of an iceberg? Nephrol Dial Transplant 2007; 22:328–331.