



Effect of intravenous vitamin C supplementation on the quality of sleep, itching and restless leg syndrome in patients undergoing hemodialysis; A double-blind randomized clinical trial

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ABSTRACT

Introduction: Poor sleep quality is common among hemodialysis patients and can potentially predict morbidity, mortality and quality of life in these patients. On the other hand, hemodialysis patients are encountered with vitamin C deficiency.

Objectives: The purpose of this study was to determine the effect of intravenous vitamin C on sleep quality, itching and restless leg syndrome in hemodialysis patients.

Patients and Methods: In this double-blind randomized clinical trial, 90 qualified hemodialysis patients were gone under investigation in Sanandaj in 2016. Patients randomly allocated in two equal intervention and control groups. The main measured outcome was the Pittsburg Sleep Quality Index (PSQI) which consists of seven components. At the end of each hemodialysis session, the intervention group received vitamin C vial (500 mg/5 cc) intravenously, three times a week for 8 weeks and the control group received normal saline as placebo in the same way. Data were collected at pretreatment and after 2 months of treatment. Additionally raises questions related to restless leg syndrome and was assessed by VAS scale for determining the incidence of pruritus. Data were analyzed by independent *t* test, paired *t* test, Wilcoxon and chi-square tests. **Results:** Around 52.2% of subjects were female and 47.8% were male and most of them were in the age group above 50 years old. Results showed a notable difference in the value of itching and restless leg syndrome between the two groups as these values decreased significantly in the intervention group ($P=0.0001$). There was also a great difference in the quality of sleep disorder in subjective sleep quality, sleep latency and daily function between the two groups and those disorders was significantly lower in the intervention group ($P=0.0001$).

Conclusion: This study showed that intravenous vitamin C can effectively improve sleep quality, itching and restless legs syndrome in hemodialysis patients.

Implication for health policy/practice/research/medical education:

This study showed that intravenous vitamin C can effectively decrease dialysis complications such as itching and restless legs syndrome and improve sleep quality in hemodialysis patients.

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Introduction

Chronic renal failure is irreversible and progressive loss of renal function which finally results in end-stage renal disease (ESRD) (1). Although there are different types of treatments based on renal replacement, the most accessible method is hemodialysis in most cases (2). The number of

patients undergoing hemodialysis in the United States was almost 300 000 people in 2003 (3) while it exceeded 500 000 patients in 2014 (4). There are 16 600 patients in 355 hemodialysis centers in Iran undergoing chronic dialysis according to Iranian society of nephrology (5).

Recently, the number of patients receiving dialysis is

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increasing steadily. However, these patients' life quality is an absolutely important issue which must be taken into a close consideration seriously. There are several parameters that play an important rule in lowering these patients' life quality. Sleep disorder is one of these critical parameters which affect their life (4). Sleep is a critical and inseparable part of human's life and one of the most important biological cycles that different mechanisms cause eliminates fatigue and prepare humman's body for daily activities by different mechanisms (5). Sleep disorder causes a negative impact on the immune system and metabolic function of patient's body which results in immune system disorder, defects in cells' construction and division and finally illness and death (6).

Moreover, the restless legs syndrome is one of the undetectable illnesses and an extreme challenge for patients' sleep (7). This syndrome is a movement disorder characterized by a strong desire to move the legs during rest. This desire to move is accompanied with an unpleasant feeling in legs whereas patients describe it with sensing the beat, burning, tingling, feeling existence of insects or the electricity current in the legs between ankle and knee.

Furthermore, itching is a common problem in patients with ESRD. Around 25% to 35% of patients before dialysis and 60% to 80% of patients undergoing dialysis complain about itching (8).

Vitamin C is one of the most important water-soluble vitamins and antioxidants and reduces the endothelial disorders which are common in hemodialysis patients. As a result, hypertension will be controlled and the chance of cardiac disease in these patients will be lowered (9). On the other hand, vitamin C deficiency underlies risk factors for morbidity and mortality from cardiac-vascular diseases in hemodialysis patients (10). A comparison about vitamin C level before and after dialysis illustrates a 50% reduction (11).

Espahbodi et al showed that sleep quality in the group receiving vitamin C clearly improved in comparison with the control group ($P < 0.0001$). Vitamin C caused significant changes in subjective quality, sleep latency, sleep efficiency and sleep disorders ($P < 0.05$). Difference between sleep score variation in the intervention and the control groups compared with the start of the study was statistically remarkable ($P < 0.0001$) (12).

Therefore, considering above information plus lack of vitamin C in hemodialysis patients, anti-inflammatory properties of the vitamin, its low price and relatively high prevalence of restless legs syndrome in the patients with no specific reason, it has been decided to study the effect of intravenous vitamin C in sleep quality of chronic hemodialysis patients in Tohid hospital in Sanandaj. Due to relevance of restless legs syndrome and itching with systemic inflammation and the effects of antioxidants on them, the impact of vitamin C on restless legs syndrome and itching is also studied. It should be noted that there

was no such study with this subject performed in Iran according to the authors' knowledge.

Objectives

The purpose of this study was to determine the effect of intravenous vitamin C on sleep quality, Itching and restless leg syndrome in hemodialysis patients.

Patients and Methods

Study population and research design

The double-blind randomized clinical trial (RCT) study was conducted on dialysis patients in dialysis section of Tohid hospital of Sanandaj, Iran. Patients between 18 to 70 years old suffering low sleep quality (global score < 5), itching or restless leg syndrome undergoing hemodialysis for 3 to 4 times a week were taken to study where sample volume is 45 individuals in each group (Figure 1). Pittsburgh Sleep Quality Inventory (PSQI), questionnaire for restless legs syndrome and its intensity and visual analogue score (VAS) criterion are used for gathering data in this research while they are prepared in four parts. Before starting the four parts, demographic profile of participants have been formed including gender, age, marital status, level of education and occupation. First part was about existence and intensity of sleep disorders which was executed by PSQI17 surveying sleep quality during the past month. The inventory consists of 19 questions in 7 sections as sleep efficiency, period and disorder, subjective quality, sleep latency, use of hypnotic drugs and daily dysfunction. Each section is related to one aspect of sleep and score range of PSQI is 0 to 21. Second part was about existence and intensity of restless leg syndrome which was measured by 4-point Likert scale. Mollahosseini et al studied validity and reliability of the questionnaire (13). In the third part, pruritus level was measured using VAS criterion which is a standard criterion for evaluation of itching (11). All dialysis patients received Nephro-Vite tablet containing 60 mg of vitamin C. Then the intervention group received a 5 mg vial of vitamin C produced by Daroopaksh Co. and for the control group, 5 mg of normal saline is given as placebo. This procedure was intravenous and performed three times a week after each session of dialysis for eight weeks. Both patient and the nurse were unaware of grouping due to make the study double-blind. At the end of the eighth week, questionnaires were given to the patients again by the researcher and results were compared with the ones achieved before intervention.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the ethical committee of Kurdistan University of Medical Sciences (#1395.14.IR.MUK.REC). This paper is extracted from the residential thesis of Minoo Sadat Hajmiri, in the

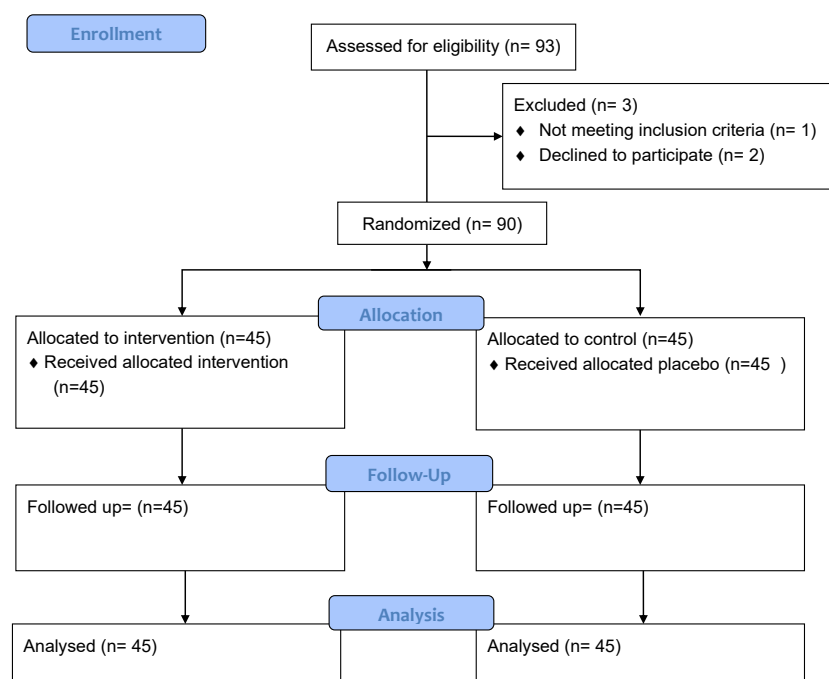


Figure 1. CONSORT flow diagram for the study.

Department of Internal Medicine, Kurdistan University of Medical Sciences. In addition, the Study was registered in the Iranian Registry of Clinical Trials website (identifier: IRCT20141208020249N4; <https://irct.ir/trial/34623>).

Statistical analysis

The collected data was analyzed by the SPSS software and appropriate statistical tests were used to test the hypothesis. Data were analyzed by independent *t* test, paired *t* test, Wilcoxon and chi-square tests. Chi-square test was used to determine a relationship between studied variables from appropriate tests with respect to variable distribution, measurement scale and analysis of nominal qualitative variables.

Results

Ninety patients in total were taken into close consideration for two groups where 45 patients in the first group received vitamin C and others received placebo in the second one. Descriptive results of this study clearly showed that 47.8% of subjects were male (43 patients) and 52.2% were female (47 patients). Additionally, 43.34% of patients were between 32 and 42 years old (51 patients), 80% of subjects were married (72 patients), the most frequent education level was diploma with 34.4% (31 patients) and the most frequent job was house keeping (see Table 1). Around, 26.7% used to smoke cigarette (24 patients) while hypertension and diabetes were the most frequent underlying diseases. Tables 1 and 2 depict the demographic variables frequency in the two groups. Restless leg syndrome and types of sleep disorders were

Table 1. Distribution of demographic variables frequency in the two groups

Demographic variables	Groups		Total No. (%)
	Vitamin C No. (%)	Normal saline No. (%)	
Gender			
Male	22 (48.9)	21 (46.7)	43 (47.8)
Female	23 (51.1)	24 (53.3)	47 (52.2)
Age (y)			
<30	5 (11.1)	4 (8.9)	9 (10)
30-50	14 (31.1)	16 (35.6)	30 (33.3)
>50	26 (57.8)	25 (55.6)	51 (56.7)
Marital status			
Single	10 (22.2)	5 (11.1)	15 (16.7)
Married	32 (71.1)	40 (88.9)	72 (80)
Divorced	3 (6.7)	0 (0)	3 (3.3)
Educational level			
Illiterate	15 (33.3)	10 (22.2)	25 (27.8)
Basic school	11 (24.4)	3 (6.7)	14 (15.6)
Elementary school	5 (11.1)	5 (11.1)	10 (11.1)
High school and diploma	10 (22.2)	21 (46.7)	31 (34.4)
College education	4 (8.9)	6 (13.3)	10 (11.1)
Job			
Unemployed	7 (15.6)	3 (6.7)	10 (11.1)
Self-employed	6 (13.3)	6 (13.3)	12 (13.3)
Employee	7 (15.6)	7 (15.6)	14 (15.6)
Farmer	4 (8.9)	2 (4.4)	6 (6.7)
Labor	2 (4.4)	7 (15.6)	9 (10)
Housewife	19 (42.2)	20 (44.4)	39 (43.3)

Table 2. Distribution of dependant variables frequency in the two groups

Variables	Groups		Total No. (%)
	Vitamin C No. (%)	Normal saline No. (%)	
Background disease			
Diabetes	14 (31.1)	11 (24.4)	25 (27.8)
Hypertension	16 (35.6)	20 (44.4)	36 (40)
Others	15 (33.3)	14 (31.2)	29 (32.2)
Smoke cigarette			
No	30 (66.7)	36 (80)	66 (73.3)
Yes	15 (33.3)	9 (20)	24 (26.7)

considered before itching in this study (Tables 3 and 4).

Results showed a notable difference in the value of itching and restless leg syndrome between the two groups as these values decreased significantly in the intervention group ($P = 0.0001$). There was also a significant difference in sleep disorders including the disorder in subjective sleep quality, sleep latency and daily dysfunction between the two groups and those disorders was significantly lower in the intervention group ($P = 0.0001$). However, some parameters such as lack of sleep, sleep efficiency disorder and usage of hypnotic drugs did not differ statistically in two groups ($P > 0.05$).

Discussion

Hemodialysis is one method of treatment in end-stage renal disease. Several studies have shown that sleep disorders can be seen in 30% to 80% of hemodialysis patients (14). The aim of this study was to evaluate the effect of intravenous vitamin C on the quality of sleep, itching and restless legs syndrome in patients undergoing chronic hemodialysis in Tohid hospital of Sanandaj, Iran in 2015.

In both groups of subjects in this study, there were more females than males and about 80% of subjects were married while the most frequency belonged to patients who are more than 50 years old and at least one belonged to below 30 years old patients. In terms of educational level, 34.4% which is the highest frequency is related to diploma where illiteracy in the group receiving vitamin C and high school and diploma in the group receiving normal saline were the most frequent educational levels. Due to the high proportion of women in the study, 43.3% of subjects in both groups were housewives. Espahbodi et al studied 60 patients in two groups of 30 people where 43.3% in intervention group and 63.3% in the placebo group were males and there was no notable statistical difference between them. Moreover, 93.3% in intervention group and 90% in the control group were married which is consistent with our study in terms of demographic characteristics (12).

Biniyaz et al studied 163 dialysis patients with average

Table 3. Distribution of itching frequency in the two groups before intervention

	No.	%
Itching		
Slight	31	14.4
Moderate	54	60
Severe	23	25.6
Restless leg syndrome		
Rarely	21	23.3
Sometimes	50	55.6
Always	19	21.1
	Negative – No. (%)	Positive – No. (%)
Types of sleep quality disorders		
Subjective sleep quality	29 (32.2)	61 (67.8)
Sleep Latency	29 (32.2)	61 (67.8)
Lack of sleep	37 (41.1)	53 (58.9)
Sleep efficiency	25 (27.8)	65 (72.2)
Usage of hypnotic drugs	30 (33.3)	60 (66.7)
Daily dysfunction	32 (35.6)	58 (64.4)

Table 4. Determining the relationship between itching, restless leg syndrome and sleep disorder in the two groups

		Groups		P value
		Vitamin C No. (%)	Normal saline No. (%)	
Itching	Slight	24 (53.3)	7 (15.6)	0.0001
	Moderate	11 (24.4)	31 (68.9)	
	Severe	2 (4.4)	5 (11.1)	
	Extinct	8 (17.8)	2 (4.4)	
Restless leg syndrome	Rarely	24 (53.3)	8 (17.8)	0.001
	Sometimes	15 (33.3)	28 (62.2)	
	Always	2 (4.4)	8 (17.8)	
	Extinct	4 (8.9)	1 (2.2)	
Subjective sleep quality disorders	Negative	37 (82.2)	9 (20)	0.0001
	Positive	8 (17.8)	36 (80)	
Sleep latency	Negative	36 (80)	9 (20)	0.0001
	Positive	9 (20)	36 (80)	
Lack of sleep	Negative	18 (40)	21 (46.7)	0.523
	Positive	27 (60)	24 (53.3)	
Sleep deficiency	Negative	20 (44.4)	19 (42.2)	0.832
	Positive	25 (55.6)	26 (57.8)	
Usage of hypnotic drugs	Negative	36 (80)	35 (77.8)	0.796
	Positive	9 (20)	10 (22.2)	
Daily dysfunction	Negative	35 (77.8)	10 (22.2)	0.0001
	Positive	10 (22.2)	35 (77.8)	

age of 61.39 ± 12.62 years old. The most frequent gender was male in both groups while most of the cases were married and had the educational level of basic school (15).

In the present study, 26.7% of patients had the background of smoking cigarette while most of them were in the vitamin C group. Sleep quality disorders, 27.8% of the cases suffered from diabetes underlying disease and

405 suffered from hypertension. In the study conducted by Espahbodi et al, 6.7% in the control group and 16.6% in the intervention group had the background of cigarette smoking which is clearly less than the proportion cigarette smoking in our present study. Moreover, in the study by Espahbodi et al for the control group, 36.7% suffered from diabetes as an underlying disease and 40% suffered from hypertension while for the intervention group (20% and 46.7% respectively). It finding is compatible with our study (12). The most common underlying causes of nephropathy in the study of Biniaz et al, hypertension and diabetes where 36% was dedicated to hypertension, 14 percent to diabetes and 21% to both of them together. Additionally, men were more likely to have hypertension, diabetes, and glomerulonephritis than women (15). All above results completely illustrate that hypertension and diabetes are the most important underlying diseases for renal patients and can cause serious dangers.

Different sleep disorders were taken into a close consideration before intervention in the present study. The average total score of sleep quality in the intervention group changed from 7.36 ± 2.58 to 4.005 ± 135.3 . Analytical results of this study showed a notable difference in the amount of itching between two groups ($P = 0.001$), a sharp reduction for patients received vitamin C was detected. Accordingly, only 4.4% of them suffered severe itching while it is 11.1% for patients received normal saline.

Results declared, a significant difference in restless leg syndrome between groups ($P = 0.001$), where a reduction can be seen for patients received vitamin C and only 4.4% of them suffered severe restless leg syndrome while it is 17.8% for patients received normal saline.

Recently, a study by Unruh et al showed that 74% of dialysis patients complain about difficulty in falling asleep (16). Results of the present study indicate that intravenous vitamin C will improve reduced the time of falling asleep. However, this could happen due to other factors such as reduction in restless leg syndrome or hyperphosphatemia in vitamin C receiving group.

There is a remarkable statistical difference in subjective sleep quality, sleep latency and daily disfunction between patients in two groups ($P = 0.001$), where 17.8% of patients receiving vitamin C suffered from these disorders while it is 80 percent for patients receiving normal saline. Although a higher percentage of patients receiving vitamin C suffered from lack of sleep, we found no notable difference in this factor between two groups ($P = 0.523$). There is also no significant difference in sleep efficiency and usage of hypnotic drugs between two study groups. Yet, a higher percent of patients receiving normal saline suffered from sleep efficiency disorder. In addition, the percentages of patients required hypnotic drugs in vitamin C receiving and normal saline receiving groups was 20% and 22.2% respectively. The study by Espahbodi et al declared a remarkable difference in subjective sleep

quality, sleep latency, sleep efficiency and sleep disorders in intervention group. They found a steep reduction of subjective sleep quality, sleep latency, sleep efficiency and sleep disorders in the intervention group while sleep time, usage of hypnotic drugs and daily dysfunction did not differ too much between groups. These results are compatible with our findings (12).

Elder et al studied sleep quality in dialysis centers of seven different countries and found, the worst sleep quality score will be found along with different types of cardiovascular problems, diabetes, pulmonary diseases, depression and itching (17).

We found administration of vitamin C as an antioxidant agent causes improvement in the time of falling asleep. This improvement can be due to reduction in other factors such as restless leg syndrome or itching. In the present study, these interventional factors were considered as the main variables and compared with the control group.

Conclusion

This study showed that intravenous vitamin C can effectively decrease dialysis complications such as itching and restless legs syndrome and improve sleep quality in hemodialysis patients. As a result, it can be proposed as a simple and inexpensive solution for these patients.

Limitations of the study

This study was conducted on a limited proportion of hemodialysis population and needs further investigations by larger samples.

Authors' contribution

SD supervised, reviewed and validated the final manuscript. MSH was responsible for conceptualization, validation, writing and editing the manuscript. DR contributed to setting the research methodology, while MSH validated the results; both of them contributed to the manuscript writing, review and editing. Finally, SD was responsible for original draft preparation and writing. All authors read, revised and approved the final manuscript.

Conflicts of interest

There were no points of conflicts to declare.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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