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The effect of supplementation with intravenous vitamin C on fatigue in patients undergoing hemodialysis

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ABSTRACT

Aims: Fatigue is one of the most common dialysis side effects. It has been among the main nursing diagnosis in hemodialysis patients and can predict cardiovascular events and its mortality in hemodialysis patients as a bioalarm. Considering that decrease in serum level of vitamin C is one of the main causes of fatigue in these patients, this study evaluated the effect of supplementation with intravenous vitamin C on fatigue in hemodialysis patients.

Methods: In a randomized, parallel group, double-blind clinical trial, 177 patients with chronic renal failure who referred to hemodialysis units of Baqiyatallah and Chamran hospitals in Tehran were studied. These patients were distributed randomly into intervention, placebo and control groups. In this study, the multidimensional fatigue inventory (MFI) was used to determine the level of fatigue. Demographic data were also collected with self-report survey. In interventional group three times a week for 8 weeks in a row, 250 mg of vitamin C was injected immediately at the end of each hemodialysis session via the intravenous route. In the placebo group, same term of placebo saline was injected and in the control group, any intervention was performed. To analyze data with SPSS statistical software, test Chi square, T-test, and ANOVA were used. P- Value less than 0.05 was considered significant.

Results: There was complaint of Fatigue in 81/6% of patients. 30/7% of them suffered from severe fatigue before the intervention. The average of dimensions of fatigue showed that loss of activity, physical fatigue, and general fatigue had respectively higher mean compared to the other five fatigue dimensions. The mean of total scores of the five dimensions of fatigue was 65.39±15.92. After the end of intervention there was a significant difference between the three groups. The fatigue mean only decreased in the intervention group significantly.

Conclusion: Vitamin C supplementation can decrease fatigue significantly and be used as a simple, safe and inexpensive way.

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1. Introduction

Incidence and prevalence of chronic kidney disease (CKD) are increasing in the world, including in Iran [1] and now it has become a global health problem and a threat [2]. Although recent improvements in dialysis techniques have increased longevity in patients with chronic kidney failure, chronic dialysis can cause symptoms that preventing them improves the quality of life of the patients [3].

Fatigue is one of the most common side effects of dialysis [4] and is one of the most important Nursing diagnoses in CKD patients [5]. The prevalence of this debilitating symptom that is located at the top of stressors in hemodialysis patients [6] has been reported between 60 to 90% [7, 8]. American Nursing Diagnosis Association, has defined, weakness, lethargy, exhaustion, lack of energy and decreased capacity for physical and mental activity for fatigue Nursing Diagnosis [9]. Exhausted Individuals do not have their previous energy. They work less and make more of an effort to do the least daily activities [10]. This subjective, non-specific, and invisible symptom [11] in hemodialysis patients in addition to having negative impact on their confidence [9], can cause disruption in their family, social and psychological functions [12]. It can also have a significant effect on daily living and quality of life (QOL) [13].

Fatigue is a multidimensional concept [11] consisting of general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. General fatigue indicates the overall functions of the person during the day. Physical fatigue is related to physical feeling of fatigue. Mental fatigue is related to the cognitive symptoms in patients. Reduced activity is lessen physical function related to mental fatigue. Reduced motivation also refers to the lack of motivation to start any activity.

Results of studies in the field of fatigue in hemodialysis patients indicate a significant relationship between fatigue and many demographic, laboratory, clinical and social variables [13] including underlying diseases, especially diabetes , Sedative drug use, poor quality of sleep [4], nutritional deficiencies, physiological changes, abnormal levels of urea, hemoglobin [8] and albumin [4], problems related to hemodialysis (low levels of sodium in dialysate and ultra-filtration at high speed) and psychological factors such as depression [8].

Decreased ability of the cardiovascular system and providing oxygen for the muscles and harvest of metabolic products from them can be one of the reasons of fatigue [14] and therefore fatigue is considered as a bioalarm in the prediction of cardiovascular events and its mortality in hemodialysis patients, especially in patients who are well nourished and seem healthy [4].

Low Serum levels of vitamin C is also a major cause of fatigue in patients treating with dialysis [15]. The natural amount of vitamin C in a non-dialysis individual serum is between 30-60 μM [16]. However, dietary restrictions followed by fear of creating Hyperkalemia [17], fear of creating Unwanted side effects of vitamin C such as oxalate deposition in the kidney [18], hundreds of milligrams of vitamin C loss, during a single session dialysis [19], And high speed of catabolism in hemodialysis patients has caused that a large number of these patients have vitamin C serum levels less than 10 μM and even some of them less than 2 μM [20]. On the other hand, chronic inflammation due to the release of inflammatory mediators in patients with CKD [21] Leads to reduced production of essential antioxidants and increased production of oxidative stress [22] and they are connected to reducing of Vitamin C as an important antioxidant [23]. This Decreasing of antioxidant will lead to the

activation of erythrocyte destruction and hemolysis and eventually renal anemia [24].

Although considering the epidemiological sources, reduction of serum levels of vitamin C related to the increase of mortality [25] fear of causing oxalate has caused a small number of dialysis patients to consume this vitamin routinely and permanently. Around the world, few studies have been done in the field of effect of vitamin C supplementation on fatigue in dialysis patients. Likewise, in Iran just a small sample size study without a placebo group and with oral vitamin C has been done in this regard [26]. Nurse has been one of the key members of the care team of hemodialysis patients that had the most contact with patients compared to the treatment team and is responsible for dialysis process with minimum supervision of a doctor [27]. Hemodialysis patients' experiences show that nursing supportive behavior plays an important role in creating a sense of peace, security and trust in them and this has caused speed up of the process of compatibility with hemodialysis [28]. Considering these points can help us understand the importance of dialysis nurse's supportive role and timely diagnosis and providing necessary cares to reduce fatigue. Considering the number of 25 thousand hemodialysis patients in Iran [29] And the impact of fatigue on the quality of life [13] and their family, job and economical responsibilities [30]. The treatment of fatigue in patients with CKD have a positive impact on well-being [4] it also reduces the risk of cardiovascular events [13]. Significant increase in life expectancy [4] And patient's greater tendency to perform prescribed treatment and feeding instructions well. The aim of this study was to investigate the effect of supplementation with intravenous vitamin C on fatigue in hemodialysis patients.

2. Methods

In a double-blind randomized clinical trial, 177 patients with chronic renal failure referred to the hemodialysis units of Chamran and Baqiyatallah hospitals in Tehran were studied. They were distributed randomly into intervention, placebo and control groups. The sampling frame included all patients with ESRD aged equal or older than 18 years, attended to regular recourse for hemodialysis three sessions per week, received hemodialysis ≥ 3 months, had the level of hemoglobin > 10 g/l and did not take vitamin C at least from 3 months before the study. Exclusion criteria included the patients who had been infected with active infection, caught cancer, transmitted to other dialysis centers, or died. 14 patients out of 177 patients were excluded from the study due to the transmission to other dialysis centers, being infected by active infections, catching cancers, death, or their own refusal, and only 163 patients completed the study (53 persons in the intervention and 55 persons in the placebo and control groups). 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. Ethical approval was obtained from the institutional ethical committee. In this study, the multidimensional fatigue inventory (MFI-20) was used to determine the level of fatigue. Demographic data were also collected with self-report survey.

The MFI-20 questionnaire is a 20-item (5 subscales and every subscale consists of four items) self-report instrument which is planned to measure fatigue. It includes five dimensions: general, physical and intellectual fatigue, reduced activity, and motivation. Each item can be rated between 1 and 5 and each subscale between 4 and 20. A higher score demonstrates a greater level of fatigue. The respondents had to compare each of the 20 declarations on how they had been feeling lately. The MFI-20 has been extensively used and achieved a fine internal constancy with an average α-coefficient between 0.65 and 0.89. The statistical associations ($P < 0.001$) between each of the subscales and the visual analogue scale indicated that convergent validity of the MFI-20 is good. After determining the allowable amount of vitamin C in hemodialysis patients according to National Institute of Health (NIH) guidelines [33], In interventional group three times a week for 8 weeks in a row, 250 mg of vitamin C was injected immediately at the end of each hemodialysis session via the intravenous route. In the placebo group, same term of placebo saline was injected and in the control group, any intervention was performed. Serum levels of Hb and Hct also were assessed at the beginning and the end of the study in the all patients. To analyze data with SPSS statistical software, test Chi square, T-test, and ANOVA were used. P- Value less than 0.05 was considered significant.

3. Result

This study included 163 hemodialysis patients with a mean (standard deviation ±) age (12/62 ±) 61/39 In terms of age, 52/8% of patients were in the middle age group (40 to 65 years)

Table 1. Baseline qualitative characteristics of the respondents

Variable	Group	Interventional group Number (%)	Placebo group Number (%)	Control group Number (%)	χ^2 test
gender	female	22 (13.5)	21(12.9)	20 (12.3)	0.85
	male	31(19)	34 (20.9)	35 (21.5)	
marital status	married	47 (28.8)	43 (26.4)	47 (28.8)	0.28
	single	-	2 (1.2)	3 (1.8)	
	widow	6 (3.7)	10 (6.1)	5 (3.1)	
education	primary	24 (14.7)	24 (14.7)	22 (13.5)	0.94
	secondary	3 (1.8)	6 (3.7)	6 (3.7)	
	diploma	15 (9.2)	16 (9.8)	15 (9.2)	
	academic	11 (6.7)	9 (5.5)	12 (7.4)	
occupation	unemployed	2 (1.2)	3 (1.8)	7 (4.3)	0.34
	employed	4 (2.5)	3 (1.8)	7 (4.3)	
	Retired	27 (16.6)	32 (19.6)	24 (14.7)	
	housekeeper	20 (12.3)	17 (10.4)	17 (10.4)	
income	weak	13 (8)	7 (4.3)	11 (6.7)	0.06
	moderate	31 (19)	44 (27)	30 (18.4)	
	good	9 (5.5)	4 (2.5)	14 (8.6)	

and 37/4% of them were in the elderly group (above 65 years). 19/6% of patients had university education, 64% of them had moderate income and 46% of them had a weight between 50-70 kg. The mean of dialysis duration was (43/84 ±) 37/6 months and the mean of serum hemoglobin levels was (1/67 ±) 11.

intervention, no statistically significant association was found between the three groups. The normality of variables was evaluated by KS test and the similarity of the three groups of interventional, placebo, and control groups related to the qualitative variables was evaluated by the Chi square test and quantitative variables was proved by

Table 2. Baseline quantitative characteristics of the respondents

Group / variable	Interventional group Mean (SD)	Placebo group Mean (SD)	Control group Mean (SD)	ANOVA
age	59.66 (11.94)	62.75(10.85)	61.69(14.75)	0.43
Dialysis vintage	53.33 (60.51)	29.6 (28.82)	30.45 (32.4)	0.06
weight	68.3 (12.03)	71.8(13.33)	68.52(10.3)	0.24

Table 3: Fatigue levels before and after study

Study groups	Fatigue (mean±SD)	
	Before intervention	After intervention
Experimental group	66±14.5	52.3±13.8
Control group	66.6±15.6	63.6±17.5
Placebo group	63.6±17.5	66.5±15.3
ANOVA		
F	0.54	12
Pvalue	0.58	0.03

Respectively most common underlying causes of nephropathy were hypertension and diabetes (hypertension 36%, diabetes 14%, and 29% for both) In this study, men suffer more than women from the complications of hypertension, diabetes, and glomerulonephritis. 43% of the patients with hypertension and 62% of patients with both hypertension and diabetes had primary education and lower. Other demographic data are reported in Tables 1 and 2. Before the intervention, the mean fatigue was (15/92 ±) 65/39. 81/6% of patients complained about some degree of fatigue, but 30/7% of them suffered from extreme fatigue. Before the

independent statistical t test. After the completion of the study, the fatigue mean scores of each dimension and also average of total scores of fatigue five dimensions, just in case group had a significant decrease. Mean changes of fatigue are reported in Table 3.

Before the intervention, 16% of patients in interventional group suffered from extreme fatigue and 30% of them suffered from moderate fatigue, but after the intervention, only 1% of patients in interventional group had extreme fatigue and 33% of them had moderate fatigue. Before the intervention in the control group also 18% of them complained of severe

fatigue and 29% of the moderate fatigue that after the intervention it was changed to 16% severe and 31% moderate.

4. Discussion:

The results of this study showed that vitamin C supplementation can significantly reduce fatigue. According to the results of the studies, the frequency of incidence of CKD is higher in males and age older than 45 years old [8]. Also in this study, males were more frequent (61/3%). Studies show that more than 50% of hemodialysis patients are unemployed or retired [34, 35]. These results were also confirmed in this study because it can be associated with fatigue and lack of energy to do activity.

In terms of etiology, in similar studies, Hypertension and diabetes are the most common underlying causes of CKD [7]. In this study also hypertension with the prevalence of 36% was in the first place.

According to the available sources, there is a direct correlation between the amount of fatigue and duration of dialysis history. The mean of duration of dialysis in this study is close to the average in studies that have reported a similar prevalence of fatigue (37.6 months versus 38.6 months and 3.81 years) [8,26]. Fatigue is one of the main complaints that have been reported in patients undergoing chronic hemodialysis, which can affect many areas of physical, cognitive and emotional. The prevalence of obtained fatigue in this study (65%) is similar to other studies like Parfery (65%), Wissber (69%), Jablonski (77%), Farahani (61%) and Savari (65%) [36].

In 2010, Farahani prescribed 250 mg of orally vitamin C three times a week for 2 months and this helped patients to reduce their complaints of severe fatigue from 64.3% to 32.1% and reduced the mean fatigue from 5.29 to 3.94 [26]. Also in this study, with 250 mg of intravenous vitamin C prescription, fatigue was significantly reduced and fatigue average in the interventional group was changed from 66 to 52.

In Farahani's study, in the control group which no intervention had been done on them complaining of severe fatigue had been changed from 57.1% before the intervention to 60.7% after the intervention and the mean of fatigue had been changed From 5 to 4.93. In the present study, also the mean of fatigue after the intervention in control and placebo groups did not change significantly.

In our study before the intervention, reduction of activity, general fatigue, physical fatigue dimensions had higher average rather than the other five dimensions of fatigue. In The study of Savari, which was done to evaluate the effect of receiving intravenous vitamin B12 on fatigue in hemodialysis patients by using the MFI questionnaire, Frequency of fatigue dimensions have also been reported in the same order [36]. It should be noted that in the Pashandi's study which MFI questionnaire was used to determine the level of fatigue in veterans suffering from respiratory disorders the mean of physical fatigue and reduced motivation were reported more than the average of other dimensions [32]. In this study, after the end of intervention in interventional group, the two dimensions of physical fatigue and reduced activity had higher averages compared to other five dimensions which is similar to the results of Savari's study.

In 2012 also Hadadian designed a study titled the effects of electrical stimulation of acupuncture points on the skin on fatigue in hemodialysis patients Showed that acupuncture can reduce fatigue effects respectively on

walking ability, general activity, mood, normal work, relations with other people, and enjoying life [8] which is almost similar to the results of the present study.

In 2003, Prince attempted to evaluate the effect of antioxidant therapy and vitamin C prescription on reducing fatigue in patients with chronic liver cirrhosis. However, the results of this study indicated that Vitamin C has no effect on reducing fatigue [37]. This could be related to loss of vitamin C during the hemodialysis process and also severe dietary restrictions in thehemodialysis patients leading to a sharp drop of vitamin C in the blood of these patients compared to other chronic patients, including patients with cirrhosis [25].

Until now different ways to treat fatigue in hemodialysis patients has been examined. In 2002, Allan has examined the effect of various biological membranes compatible with biological conditions of body (Biocompatible Membrane) on reducing fatigue after hemodialysis and he did not report it as significant [31]. Different drugs like Applephenon [38] and techniques such as cutaneous electrical stimulation of acupuncture points [8] have also been studied in fatigue reducing that some of them have been reported effective [38], But comparing and evaluating of the impact factor of these methods with vitamin C supplementation in fatigue reducing shows that this vitamin can be prescribed as a inexpensive and successful treatment in hemodialysis patients. At the end it is recommended to design further studies with larger sample size and longer follow-up along with other important consequences of dialysis after supplementation.

5. Conclusion

The results of this study showed that supplementation with vitamin C can significantly reduce fatigue in hemodialysis patients as a simple, safe, and affordable solution.

Considering the prevalence of gastrointestinal problems, large volume of oral medications due to having one or more diseases, lack of adequate oral drug absorption and hemodialysis patients, tiredness of taking drugs, intravenous Vitamin C prescription through a vein at the end of dialysis can be considered as a treatment to reduce fatigue. Considering that each hemodialysis patient spent at least 12 hours per week of his/her time with dialysis nurse, appropriate planning for the efficient use of this time in nursing education in Fatigue reduction and lifestyle modification field is recommended.

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Fatigue assessment questionnaire

Guideline

By using this questionnaire, we want to assess your situation in the recent days. In order to complete the questionnaire, please notice to the below example:
"I have the feeling of calm nerves"
If you think that this sentence is completely true in your case, it means that you had the feeling of calm nerves in recent days, please put a Celtic cross in the first square, it means square number 1, like the answer below:
Yes, it is completely true 1 ☒2 ❑3 ❑4 ❑5 ❑ no, it is completely wrong
Your more disagreement with the considered sentence , according to the disagreement degree, putt he celtic cross in the direction of "no, it is completely wrong", please put the celtic cross for the correct answer for all the sentences and putt he celtic cross just for one answer in every sentence.

1	I have a good feeling and the feeling of being full of energy	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
2	Physically, I have the ability of doing simple works	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
3	I think that I am very active	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
4	I like to do all the Works alone	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
5	I feel that I need to sleep and rest	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
6	I do lots of works in a day	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
7	When I'm doing a work I can concéntrate on that	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
8	Physically I can do lots of works	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
9	I am worried about doing a work	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
10	I think that I do Little works in a day	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
11	I can concéntrate and notice well	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
12	I had a good rest	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
13	I have to try hard to concéntrate on Works	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
14	I think that I,m in a bad condition physically	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
15	I have lots of plans and programms	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
16	I get tired very son	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
17	I have simple and Little actions	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
18	I feel that I do not like to do any work	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
19	My thoughts get distracted very soon	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong
20	I am in a good situation physically	Yes , it's completely right	❑1	❑2	❑3	❑4	❑5	No, it's completely wrong