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The effect of Vitamin B_{12} supplemention on fatigue in hemodialysis patients

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ABSTRACT

Aims: Fatigue is a frequent symptom in hemodialysis patients that impairs the quality of life and like pain and fever; it is an important biological warning for human health. So far, despite the many interventions to reduce fatigue in hemodialysis patients, still this phenomenon is reported with high prevalence. The aim of this study was to determine the effect of vitamin B_{12} supplementation on fatigue in patients undergoing hemodialysis.

Methods: It was a semi experimental study with the method of before-after, which has been done on 86 hemodialysis patients with a Purposive sampling method within three months in 2011 in one and two chosen hospitals. The intervention was an intravenous injection of 100 mcg/ml of vitamin B_{12} after dialysis process which has been done three times a week, within two months and by the end of the intervention in order to assess sustainability of the effect of vitamin B_{12} there was no interventions for one month. Fatigue measurement questionnaire was completed by participants and it was analyzed by using SPSS18 software and descriptive statistic tests, paired t-test and analysis-variance of the repetitive measures.

Results: Fatigue after a month of interfering (p=0.001) and with further reduction after two months (p=0.0001) and one month after the end of intervention (p=0.021) has been significantly reduced.

Conclusions: The results indicate the effectiveness of vitamin B12 on the reduction of fatigue in hemodialysis patients. Thus intravenous injection of 100 mcg/ml of Vitamin B12 weekly after dialysis is recommended for hemodialysis patients.

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1. Introduction

According to the latest statistics provided, the number of patients with end-stage renal disease in our country is about 25 thousand people [1]. About 53.7% of renal failure patients are undergoing permanent hemodialysis and 45.5% have had transplantation [2]. Statistics show increasing 15% of hemodialysis (HD) patients per year [3].

Among the behavioral and psychosocial factors, such as fever and pain, fatigue is an important

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biological warning for human health [4]. The North American Nursing Diagnosis Association defined fatigue as a feeling of weakness and decreased capacity for physical and mental activities. They had not their previous energy, do less work and make more effort for the least daily activities, so this issue will impact on their quality of life and self-esteem. Moreover, family and social and psychological functioning of hemodialysis patients may be affected by fatigue [5], it can predict cardiovascular accidents in patients with end-stage renal disease [4].

Fatigue is a frequent symptom in dialysis patients which impairs the quality of life and its prevalence from 60% to over 97% in patients with end-stage renal disease who are receiving renal replacement therapy for long-range is variable [6].

The importance of fatigue in patients with renal failure is such that 94% of hemodialysis patients with increased energy levels like to have more frequent dialysis [7]. Hardy and Stevendeski recently reported that only by asking a simple question "Do you often feel tired? The elderly are identified with high risk of mortality [4].

Water-soluble vitamin deficiency in hemodialysis patients is due to inadequate food intake, excessive losses in dialysate or impaired metabolism of vitamin [8], Vitamin metabolism is impaired in uremia [9]. From the early days of dialysis patients with renal replacement therapy, water-soluble vitamin deficiency is diagnosed which this loss may be due to inadequate intakes of vitamin or water soluble vitamins removed by dialysis, in addition, water-soluble vitamins clearance by hemodialysis is variable [10]. Based on the type of filter used in hemodialysis, Vitamin B12 clearance from 78/73 to 156/136 for a QB: 200/300ml/min (pump blood), is variable Vitamin B12 deficiency is common and its prevalence in the general population is estimated between 5.1 to 15 percent. Adequate treatment regarding the role of the vitamin in the production of red blood cells, normal growth and health of the nervous system is essential [11]. A common cause of vitamin B12 inadequacy is in sufficient absorption or receiving [12]. Erythropoietin therapy puts dialysis patients at risk of B12 deficiency in active form [13]. Manufacturers have been using Vitamin B12 clearance to determine the porosity of dialysis membrane [14]. Depression and fatigue are clinical signs of Vitamin B12 deficiency [15].

Despite the importance of fatigue in dialysis patients, nurses are unaware of the presence and severity of this complication [16] and despite the high prevalence of fatigue, it often remains unrecognized and untreated, therefore urgency of research to understand the factors involved in fatigue is needed [6] regarding the role of various factors in fatigue, frequent interventions in reducing this complication has been carried out which some of them were about the effects of supplements on reducing fatigue in hemodialysis patients, and in some cases good results have been obtained. However regarding high prevalence of fatigue, lack of Vitamin B12 cells in hemodialysis patients and the role of vitamin B12 in reduction of abnormal biochemical factors involved in fatigue such as nitric oxide and proxy nitrite, researcher decided to assess the effect of intravenous injection of Vitamin B12 on fatigue in HD patients.

2. Methods

The present study is a quasi-experimental study with before–after method, this study was conducted from January to the end of March of 2011, sample size of the study of Farmihani [5], including α= 5% and β =10% and Power = 90% and using the Altman nomogram, and the least expected difference in the means, 65 people, including the loss of 10% was estimated 70 people.

102 hemodialysis patients from two hospitals (Baqiyatallah and Chamran) in a purposeful sampling method in one group (at least 3 months have passed since their first dose of dialysis [17], minimal literacy, hyper

homocysteinemia) were selected and have been studied. The data collection tools in this study were demographic questionnaire, fatigue measurement questionnaire (Multidimensional Fatigue Inventory MFI-20) and the results of laboratory tests (measuring serum level vitamin B12 and total homocystein). Assessment questionnaire of fatigue consisted of several distinct dimensions of general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. Actually multidimensional fatigue inventory (MFI-20) measures fatigue in a way that a person feels and explains. General fatigue is related to the function of a person in a day, physical fatigue is related to a physical sense that is related to fatigue directly, mental fatigue indicates cognitive symptoms of a person, activity reduction is also after mental fatigue and motivation reduction indicates reduction or lack of motivation for starting every activity. Each dimension includes 4 questions and answers are collected in a variety of five choices. So the total score of each area is between 4-20 and the total score of fatigue which is determined by summing the other areas is between 20-100. In order to have easy calculation and comparison, the total score is divided by five in 4-20 basis and get adjusted. Higher score indicates more fatigue. Validity and reliability of the questionnaire have been determined in English. The questionnaire was also translated into different languages in different studies and it was validated in and it has been used in various diseases, such as chronic fatigue syndrome, cancer, and heart failure. Also it has had acceptable validity and reliability for being used in groups of patients with respiratory disorders [18].

Serum level of vitamin B12 is considered 200-900pg/ml, laboratory diagnosis of vitamin B12 deficiency is usually based on low serum level of B12 vitamin or increase in Serum level of methylmalonic acid and homocysteinin [19]. Low levels of vitamin B12 and folate were not very specific and it has low sensitivity [9]. Normal range for homocysteine is 5-12 µmol/L and Borderline is 12-16 µmol/L and higher values of 16µmol/L are considered as hyper homocysteinin [13]. Increased homocysteinin is a more significant marker of vitamin B12 and folate deficiency [19]. In this study Hyper homocysteinin of patients is considered as a marker for identifying the deficiency of B12 in the cell. Before starting the intervention, Demographic form and fatigue measurement questionnaire were completed by patients and laboratory tests were performed. 102 patients were enrolled who were injected with 100mcg/ml of Vitamin B12 through intravenous line after dialysis process for 2 months and 3 times a week (Finally, 16 patients due to a kidney transplant, death, low hemoglobin levels, and lack of desire to continue participating in the study were excluded during the study). After the first month of intervention, fatigue questionnaire was completed by participants. After the second month of the intervention, questionnaires were filled and laboratory tests were measured again. Then, immediately after the end of intervention, there was no intervention for one month in order to assess the sustainability effects of vitamin B12 (washout phase), and serum level of vitamin B12 and total homocysteinin were measured again and the questionnaire was completed again. Before the intervention, in addition to obtaining written consent from patients for doing the study, they were assured that their information will be kept strictly confidential and the results will be reported to the patients and medical personnel. At last the raw data were analyzed with SPSS14 software and descriptive statistics tests, paired t-test and variance-analysis of repetitive measures.

3. Results

Table 1: Comparison of fatigue means scores at different stages

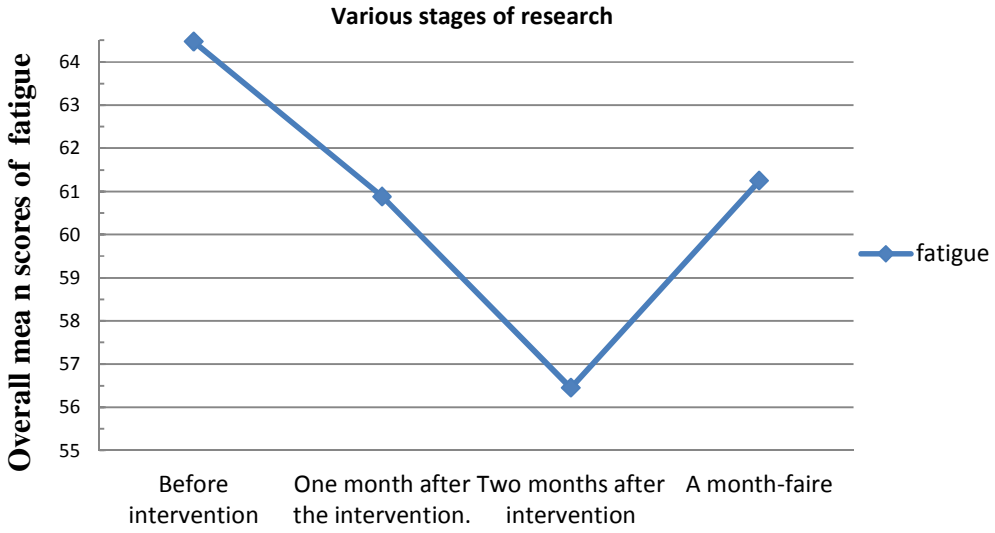
Different stages of research	Fatigue	Paired t-test	
	Average and SD	The significance level	
Before intervention	64047±(17.3)	p=0.001	t=3.331
One month after	60.88± (16.11)		
Before intervention	64.47± (17.3)	p=0.0001	t=6.726
Two months after	56.45± (15.75)		
Before intervention	64.47± (17.3)	p=0.021	t=3.349
Wash out	61.25± (16.84)		

In this study, 86 subjects participated and they were analyzed from demographic and fatigue measurement questionnaire and their serum level of total Hemosistein and vitamin B12 point of view. The mean age of the samples was 62.6 years, 45 patients (52.3%) were male and 41 (47.7%) were female. 68 (79.1%) were married, 1 (1.2%) was single and 17 (8.19%) were widowed or divorced or had deceased spouses. 44 (51.2%) had primary education, 14 (16.3%) had the education under high school diploma and 18 (20.9%) had the high school diploma and 10 (11.6%) had a college education. In terms of employment; 40 (46.5%) were unemployed or housewives, 5 (5.8%) were employed and 41 (47.7%) were retired. In terms of income; 34 (39.5%) were poor, 42 (48.8%) were moderate, 9 patients (10.5%) were good, and 1 (1.2%) was excellent. The mean duration of hemodialysis of patients was 42.4 months. Before the intervention, 61 patients (70.9%) were not taking any B12 vitamin, while 25 patients were taking B 12 vitamin (29.1%). The mean level of total plasma homocysteinin before the intervention was 31.5 with a standard deviation of 19.65 which has been reduced after two months of intervention and the effect of B12 to 22.02 with a standard deviation of 6.67 had been reduced and in the washout phase (one month with no intervention) this level has been reached to 24.83 with a standard deviation of 7.31. Paired t-test in the comparison of the means before intervention in the two months after the intervention (p=0.0001), two months after the intervention and wash out phase (p=0.001);

Table 2: Comparison of serum levels of vitamin B12 in various stages of research

Various stages of research	Vitamin B12 plasma	paired t-test	
	Average and SD	The significance level	
Before intervention	869.43± (565.79)	p= 0.0001	t=17.67
Two months after	1860.76± (249.4)		
Before intervention	869.43± (565.79)	p= 0.0001	t=9.321
Wash out	1355.43± (464.66)		

Figure 1: Comparison of the process of changes in overall mean fatigue scores of patients in various stages of the study



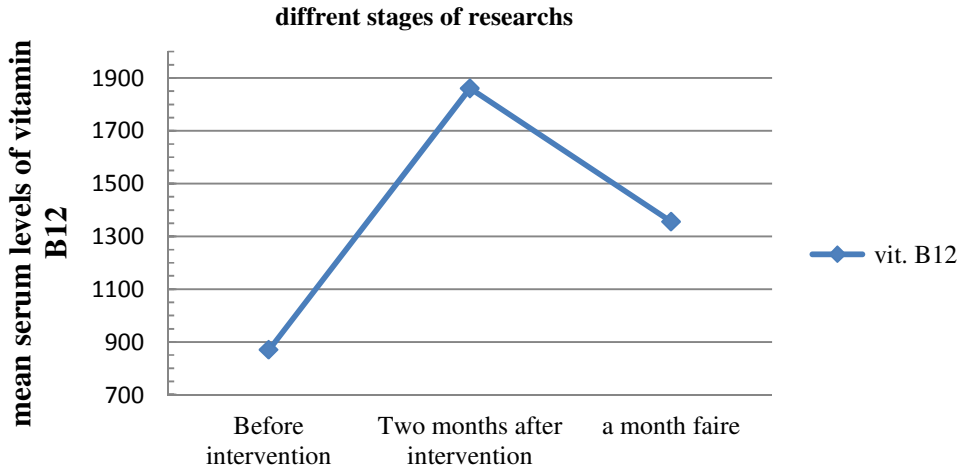
showed significant difference due to injection of vitamin B12in the samples of the study. The serum level of Vitamin B12 before the intervention was 869.43 with a standard deviation of 565.79, and after two months of intervention it was 1860.76 with a standard deviation of 249.4 and in the wash out phase it was 1355.43 with a standard deviation of 464.66 that there was a significant difference according to the paired t test in comparison of the previous means with two months after the intervention p=0.0001, two months after intervention and wash out phase p=0.0001.the mean of fatigue before intervention was 64.47 with a standard deviation of 17.3 that after one month of intervention it had been reduced to 60.88 with a standard deviation of 16.11 and two months after the intervention it had been reduced to 56.45 with a standard deviation of 15.75 and in the wash out it has been reached to 61.25 with a standard deviation of 16.84. Paired t-test in comparison of means one month before intervention with one month after intervention p=0.001, before intervention with two months after the intervention p=0.0001, two months before intervention with wash out phase p=0.021; the samples showed significant difference due to the effect of injection of vitamin B12 ($p<0.05$).

4. Discussion

One of the most common side effects of dialysis is fatigue which is the top in stressors of these patients [20]. Fatigue is common in hemodialysis patients and influence everyday life, it can significantly impair quality of life, it can increase cardiovascular diseases and has a negative impact on survival and it is considered as a debilitating symptom in dialysis patients [21].

Prevalence of fatigue in patients undergoing hemodialysis is from 45% to over 80% and in peritoneal dialysis patients it is 30% to 70% [22]. In several studies of fatigue in Hemodialysis patients the range of fatigue has been measured and reported between 50 to 77 percent [23-25]. Also in the present study, the total fatigue mean was 64.47, according to the Contractual law of one-third it can be stated that the rate of fatigue is lower than the minimum rate and 52.3% of patients complained about moderate fatigue and 27/9%

Figure 2: Comparison of changes in mean serum levels of vitamin B12 in patients at different stages of research



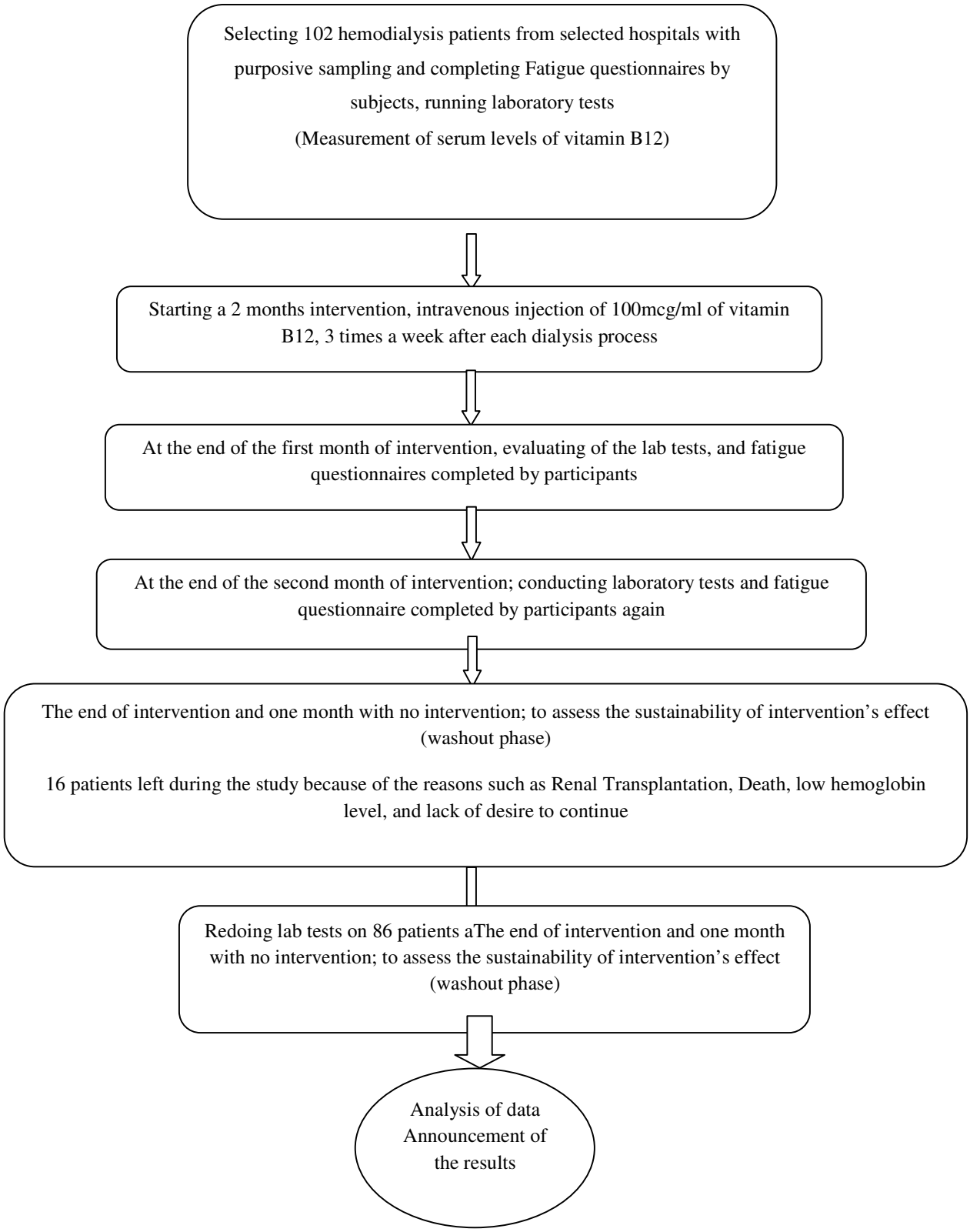
of patients complained about severe fatigue. According to this the results indicate high levels of fatigue in patients undergoing hemodialysis.

Vitamin-Minerals Supplements in chronic fatigue syndrome have been proposed, and it is claimed that fatigue of these people was improved after usage of a high dose of one or more vitamins. Proposed vitamins are vitamin C, vitamins B, vitamin A and beta-carotene [26]. Considering the abnormal biochemical factors involved in the Chronic Fatigue Syndrome, Prof. Martin Pall showed that people who suffer from fatigue have high levels of nitric oxide and its product nitrite proxy; these materials may be directly responsible for many of the symptoms of this condition. Since vitamin B12 is important because it's a powerful absorber of nitric oxide and therefore it reduces symptoms of chronic fatigue without considering its causes [27].

Unfortunately, there are few studies of therapies to prevent or reduce fatigue in dialysis patients and study populations are generally small or that they are not randomized or controlled [21]. In this regard, in the present study with choosing bigger sample size it had been tried to achieve a more reasonable result. To remove the cofounder factor of anemia to induce fatigue in these patients, people with low hemoglobin were excluded from the samples.

results of the study of Hip in 1999 reflect reduced functional status of vitamin B, especially piroxidin in patients with chronic fatigue syndrome, In a double-blind study supplements containing piroxidin, riboflavin and thiamine within 6 weeks of treatment significantly improved fatigue, which is in correspondence with the results of this study, while it is in contrary with other studies which did not show clear benefits in improving the fatigue of folic acid, vitamin B12 or mixture some vitamins [26]. Findings of the study of Jang in patients suffering from fatigue showed that using B-complex with vitamin C intravenously in a month, cause a significant reduction in fatigue from 5.2 to 3.3 [28].

Singer's study showed that daily usage of 250 mg of vitamin C, for 3 weeks has been improving fatigue in patients with kidney failure [29]. The study of Farmihani showed that the usage of 250 mg of vitamin C in hemodialysis patients, 3 times a week for 2



months, significantly decreased fatigue in the case group in compare with the control group, after the intervention [5], also in the current study, vitamin B12 supplementation in

hemodialysis patients with the same duration of the intervention and frequency of usage, significant reduction of fatigue was reported.

Similar to the intervention of this study, the pilot study of vitamin B12 in the Ellis treatment of fatigue, in a double-blind crossover method, 5 mg hydroxy-cobalamin was injected to 28 patients with fatigue, 2 times a week for 2 weeks, and after 2 weeks of rest, placebo was injected for 2 weeks. The patients who had received hydroxy-cobalamin in the second week, had a significant feeling of wellbeing and happiness and it has been recommended that for more effect, Vitamin B12 must be injected at least for 4 weeks [30], that in this study, with doing intervention for two months this recommendation had been considered.

Study of Rooz - Irastor showed that patients with a deficiency of vitamin D, has had more fatigue and most of the studies showed improvement of fatigue after replacement of this vitamin [31]. While in Nirva's study on 29 peritoneal dialysis patients with vitamin D deficiency, and with prescribing 50,000 IU of ergot calcitonin ferrule once a week for 4 weeks, no significant change was seen in fatigue [32].

5. Conclusions

According to the studies it can be concluded that various supplementary are involved in reduction of fatigue.

In the present study with intravenous injection of 100ml/mcg Vitamin B12 to 86 hemodialysis patients, 3 times a week after dialysis process for 2 months and 1 month with no intervention in order to assess the sustainability of the intervention (washout phase), After the intervention, the mean of fatigue significantly reduced. Reduced amount of fatigue in the second month was more than the first month that perhaps one of the reasons for this condition is higher levels of vitamin B12 in the second month rather than the first month of intervention and consequently relative elevated need of the cell and possibly reducing nitric oxide and nitrite proxy.

Also after the washout phase the amount of fatigue significantly reduced, however, after the end of the intervention, we faced slightly increasing of the mean fatigue in the washout phase compared to the mean fatigue of the intervening time and it was probably due to the depletion of vitamin B12 out of patient's serum, At this stage, the patients did not receive supplements of vitamin B12 And considering the mechanisms that have been described previously it Leads to loss of this vitamin and low serum levels in these individuals, At this stage fatigue of patients have increased. Therefore according to the results obtained; taking vitamin B12 as a supplement is inexpensive and available and it can improve fatigue and considering that the reduced amount of fatigue after the second month of the intervention was more than the first month of the intervention and in the washout phase (one month with no intervention), fatigue has increased in compare with the Intervention time, It can be concluded that in order to achieve better results in reducing fatigue, vitamin B12 should be used consistently and in the Long-term.

Therefore, according to the interpretation of the results of this study and the existing evidence in other studies; weekly consumption of vitamin B12 intravenous injection for hemodialysis patients and doing research on a broader level, the more time and on the dimensions of fatigue in these patients is recommended.

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