The effects of Valerian on sleep quality, depression and state anxiety in hemodialysis patients: A randomized, double-blind, crossover, clinical trial

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Abstract

Objectives: This study was conducted to determine the effects of Valerian on sleep quality, depression and state anxiety in hemodialysis (HD) patients.

Methods: This randomized, double-blind, placebo-controlled, crossover, clinical trial was conducted on 39 HD patients allocated into a valerian and a placebo group. In first phase of the study, group A (n=19) received valerian and group B (n=20) received placebo one hour before sleep every night for a total of one month. Sleep quality, state anxiety and depression were assessed in the patients at the beginning and end of the intervention using the Pittsburgh Sleep Quality Index, the Spielberger State Anxiety Inventory and Beck's Depression Inventory. In second phase, the two groups' treatment regimen was exchanged with each other's after a one-month washout period and the same process was repeated on the crossover groups, i.e. group A received placebo and group B received valerian.

Results: In the first phase, the mean sleep quality, depression and state anxiety scores showed significant reductions in both groups, but the reduction was significantly higher in group A compared to group B (7.63 vs. 3.20; P<0.001; 6.58 vs. 2.35; P=0.013; 14.68 vs.

7.30; P=0.003, respectively). In the second phase, the mean sleep disorder, depression and state anxiety scores showed significant reductions in both groups, but the reduction was significantly lower in group A compared to group B (1.41 vs. 4.65; P<0.001; 1.29 vs. 3.80; P=0.002; 1.53 vs. 6.20; P<0.001, respectively).

Conclusion: Valerian improved sleep quality and the symptoms of state anxiety and depression significantly in HD patients.

Keywords: Depression; Hemodialysis; Sleep Quality; State anxiety; Valerian.

INTRODUCTION

Sleep is one of the most vital physical, mental and emotional needs of human beings, and many hemodialysis (HD) patients suffer from poor sleep quality [1]. Sleep disorders may be an important risk factor for the incidence of mental health disorders such as depression, anxiety [2]. Depression and sleep disorders, are more prevalent in HD patients [3]. The etiology of sleep disorders, and mental health disorders in patients on dialysis to be multi-factorial, including dialysis, metabolic abnormalities, muscle cramps, medications, fatigue, peripheral neuropathy, emotional problems, malnutrition [3,4], and Body Mass Index (BMI) [5].

They therefore have a poor quality of life and a twice-higher risk of mortality [6]. In addition to sleep disorders, anxiety and depression are associated with a low quality of life in HD patients [7]. The prevalence of sleep disorders, anxiety and depression has been reported as 66.7% [8], 67.5% [9] and 62% [10] in HD patients in Iran. These complications can be threat to patients' health and quality of life, but sometimes could be neglected in clinical practice [3].

Sedatives and hypnotic drugs are frequently used to treat sleep disorders. The most common side-effects of these drugs include impairment of natural sleep cycle, reduced nervous system function, remaining sedative effect throughout the day, insomnia, respiratory problems and immunity risks. The regular use of sleeping pills causes tolerance to the pills

and creates symptoms of sleep deprivation and insomnia after the drug is discontinued [11]. The use of complementary medicine is growing in an attempt to improve sleep quality in HD patients [12].

Valerian is one of the medicinal plants used to reduce anxiety and sleep disorders [13]. Valerian contains 150 to 200 different substances, including volatile oils, ketones, phenols, iridoid esters such as valreotriate, alkaloids, valric acid, amino acids like aminobutric acid, arginine, tyrosine, glutamine and noncyclic, monocyclic and bicyclic hydrocarbons [14]. Valerian/Cascade mixture significantly decreased the latency time for sleeping, and increased total sleeping time. The mixture significantly increased the non-rapid eye movement (NREM) sleep time, while rapid eye movement (REM) sleeping time was decreased, in Electroencephalography (EEG) investigation indicated that decrease of awakening and increase of total sleep time [15]. It has also been administered as a sedative-hypnotic herb for many years. Valepotriates and valerenic acid found in valerian root are responsible for the sedative and anxiolytic effects of the plant [16]. Assisting sleep effect of Valerian/Cascade mixture was shown to be due to the upregulation of gamma-aminobutyric acid A (GABA) receptor [15]. The valerenic acid contained in valerian inhibits the enzyme system responsible for the catabolism of GABA [17]. Valerian and its constituents (e.g. valerenic acid) serve as GABA agonists and the effect of the plant on $GABA_A$ receptors is similar to the effect of benzodiazepines (BDZs) on them [18]. The mechanism of action of valerian has been explained by several theories. The constituents of valerian may increase GABA concentrations and decrease central nervous system activity by inhibiting the enzyme system responsible for the central catabolism of GABA [19]. Valerian may also stimulate the release and reuptake of GABA and bind directly to $GABA_A$ receptors [20]. According to the available evidence, valerian may be the most promising agent for assisting sleep [21] that is also considered a partial agonist of the 5-hydroxytryptamine 2A receptor that boosts melatonin release [22].

Antidepressant and mood-stabilizing effects have also been proposed for valerian [23], which could be due to the plant's ability to interfere with noradrenergic and dopaminergic neurotransmitters, especially serotonin and GABA [17]. Over the past few decades, the root extract of valerian has been widely used as a flowering plant for the treatment of sleeping disorders in Europe [24]. Ziegler et al. compared the effects of a six-week treatment with valerian extract (600 mg/day) and oxazepam (10 mg/day) in 202 patients and found that both groups enjoyed an enhanced sleep quality, while valerian was at least equally effective as oxazepam. The effects of valerian and oxazepam were perceived to be very good by 83% and 73% of the patients, respectively [25].

The US Food and Drug Administration lists valerian as a food supplement with no contraindications for its use [26]. Valerian is a perennial herb native to North America, Asia and Europe whose root is believed to possess sedative and hypnotic properties [27]. Today, valerian root extract is an accepted over-the-counter medicine for the treatment of stress and nervous tension, disturbed sleep patterns and anxiety in Germany, Switzerland, Belgium, Italy and France [28]. Results of a study demonstrated Valerian can be effect on sleep quality in Patients with Multiple Sclerosis[29]. The results have indicated that Valerian is effective in the treatment of anxiety and depression in menopausal women[30]. Valerian is a safe herbal remedy in HD [31]. Valerian has also shown evidence of efficacy with few or no adverse effects when used properly and in accordance with expert recommendations [28]. But evidence for natural remedies valerian controversial and weak, and are not suggested for acute or chronic sleep disorders [2]. Therefore, there are tendency to alternative and complementary therapies to assisting sleep disorders [32]. Further research that assisting sleep is required [33]. Also, the use of valerian as an anti-anxiety and anti-depression agent thus requires further investigations [34].

Valerian is a safe herbal medicine for hemodialysis considering the high prevalence of sleep disorders, depression and state anxiety, and their related complications in HD patients

and the contradictory results on the effectiveness of valerian on these issues in this group. Previous studies have examined the effect of valerian on variable and non-hemodialysis patients. In the present study, the effect of valerian on the three variables including sleep quality, depression, and state anxiety was explored in HD patients. The aim of this study was determine the effects of Valerian on sleep quality, depression and state anxiety in HD patients.

METHODS

Study Design and Sample

This randomized, double-blind, placebo-controlled, crossover clinical trial was conducted on HD patients in Mehdishahr and Kowsar hospitals in Semnan, Iran. The randomization began by flipping a coin, where a head indicated allocation to group A for the first patient and a tail indicated allocation to group B. The next patient, who was similar to the first patient in terms of gender and age (difference of ±5 years), was assigned to the opposite group. Owing to the crossover design, both groups received both the valerian and placebo capsules. Also, the grouping of patients was performed by a nurse was blinded to other aspect of the study.

Sample size calculation

At the beginning of the study, we estimated the sample size using 15 data from each group. Since no changes were made to the study, the data of these 30 individuals were used in the final analysis. It is emphasized that no changes were made in any of the study components. For both valerian and placebo groups, respectively, the mean and standard deviation (SD) of changes were as follows: sleep quality score before and after intervention:

7.63 ± 3.15 and 3.20 ± 1.79, state anxiety scores: 14.68 ± 7.31 and 7.30 ± 5.12, and the depression score: 6.58 ± 5.86 and 2.35 ± 3.34.

The following equation was used to calculate the sample size. Considering a 95% confidence interval and 80% power, the sample size for each group in terms of sleep quality, state anxiety, and depression was estimated to be 6, 12, and 20, respectively. Therefore, 15 people were allocated to each group to evaluate the three variables.

$$n = \frac{\left(S_1^2 + S_2^2\right) \times \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2}{\left(\overline{X}_1 - \overline{X}_2\right)^2}$$

Data Collection

To assess the neuropsychiatric status, data were collected using a demographic questionnaire, the Pittsburgh Sleep Quality Index (PSQI), Beck's Depression Inventory (BDI) and the Spielberger Anxiety Inventory (STAI). Cigarette smoking, drinking tea per day and respiratory disorders which may have an effect on sleep, were entered in the demographic questionnaire.

The PSQI is a self-report questionnaire that evaluates quality of sleep over a one month time interval [35]. The PSQI consists of seven components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disorders, use of sleeping medication and daytime dysfunction. The total score of the PSQI ranges from zero to 21 and scores greater than five indicate a poor sleep quality [36]. The validity of the Persian version of the questionnaire was confirmed with a sensitivity of 100%, a specificity of 93%, and a Cronbach's alpha of 0.89 [12].

The BDI is a 21-item tool and uses 0-3 Likert scales for determining the severity of depression. The total scores in this scale range from zero to 63 and higher scores indicate

higher severity of depression (scores 11-16 show mild, 17-29 moderate, and 30-63 severe depression), it has been used in both the general and CKD population [37]. BDI Intra-class Correlation Coefficient (ICC) has been found 0.85, and by using Spearman-Brown equation, the validity of the scale was reported 0.81 [38].

The STAI is an instrument with two 20-item subscales for the measurement of state and trait anxiety. All the items in this inventory are scored based on a four-point Likert scale. The items in the state anxiety subscale assess the intensity of feelings “in the moment”. In this study the STAI was used to measure state anxiety [39]. The scores of state anxiety range from 20 to 80, that is classified as mild (20-39), moderate (40-59), and severe (60-80).

Inclusion Criteria

The inclusion criteria consisted of age over 18 years, undergoing HD three times a week for three hours or more, and history of HD for at least three months [12], full consciousness, hearing and speech ability, and lack of sensitivity to plants.

Exclusion Criteria

The exclusion criteria consisted of physical disability, mental disorder, drug addiction, cancer, hearing or a visual impairment, recent experience of stressful events, history of kidney transplantation, liver disease, hepatitis, cirrhosis or acute illnesses, BMI over 30 kg/m^2, traveling or death.

Intervention Design

The researchers visited different wards of the HD department of the select hospitals and evaluated the patients undergoing HD in different shifts (morning, evening and night) in order to select the eligible candidates. The patients were fully briefed on the research

objectives and methods. A sample of HD patients who experienced poor sleep quality as per their self-reported symptoms and had no medical or psychiatric conditions leading to sleep disorders was finally recruited. The PSQI was completed to assess the patients' sleep quality in the past month. The eligible patients with PSQI scores equal to or greater than five participated in the study and sign consent forms. The participants completed the PSQI at the beginning of their hemodialysis sessions, and the demographic questionnaire, STAI, and BDI were completed later. The use of valerian and placebo capsules was examined by a nephrologist informed of the type of intervention given to each participant. As the study was double-blind, participants, researchers, and statisticians were blind to the study groups until the analysis was completed.

The valerian capsules (Sedamin, Goldaru Co., Iran) contained 530 mg dried root of Valeriana officinalis (IRC 1228022753). The participants were randomly allocated to two groups to receive either valerian or placebo capsules (groups A and B, respectively).

The placebo capsules contained 50 mg of starch and had a coating similar to the valerian capsules. Both groups were instructed to take the capsules 60 minutes before bedtime for one month. After a one-month washout period, each group's medication regimen was exchanged with the others, and the procedure was repeated. Sleep quality, state anxiety, and depression were assessed using the questionnaires at the beginning and end of the two intervention phases (Figure 1). The participants were asked to report any problems they faced that were linked to the drugs. The researchers followed up on the patients' regular consumption of the capsules and possible side-effects every week through a phone call and by visiting the HD ward.

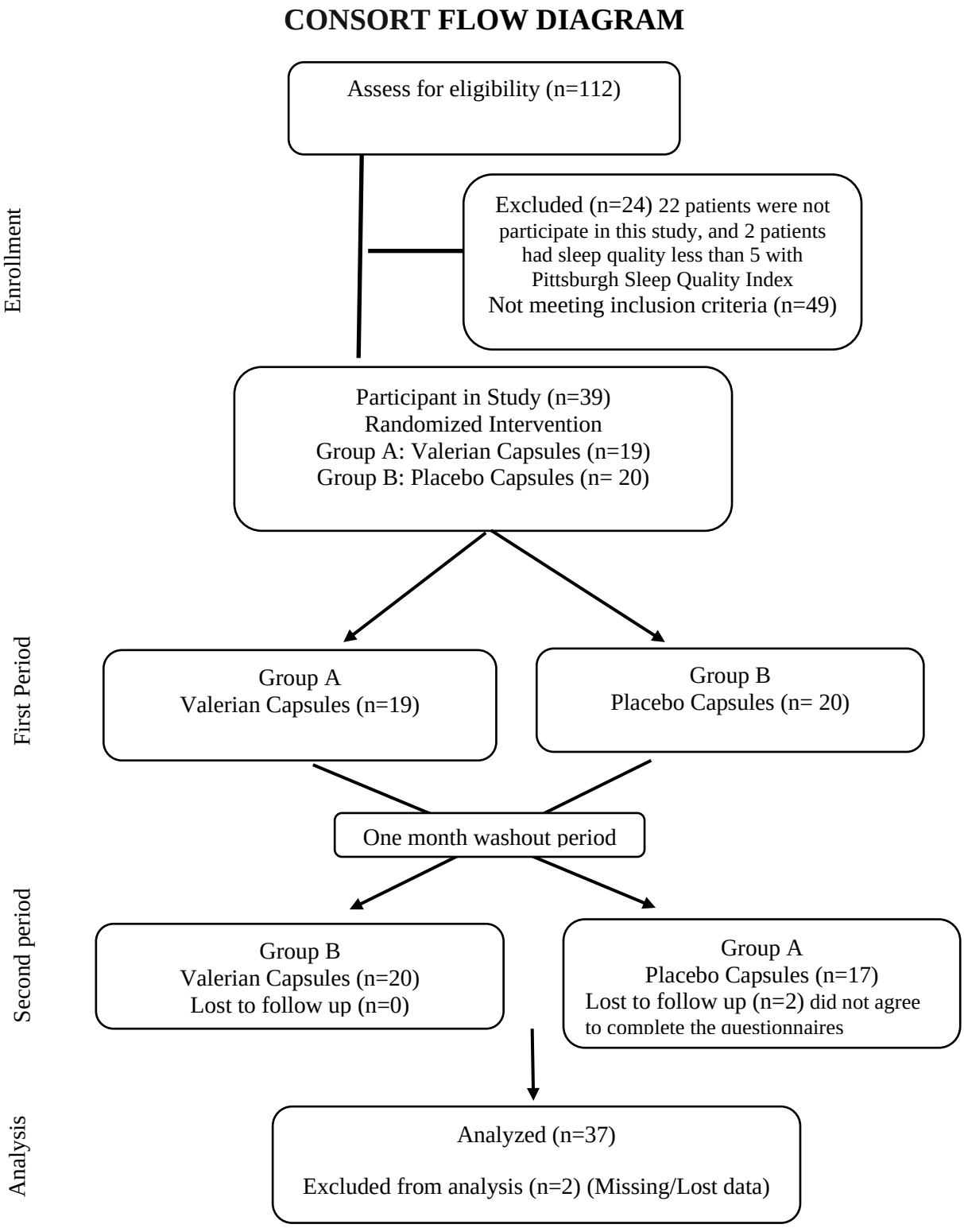

Fig 1. Flow chart of the study design, enrollment, randomization, follow-up and analysis of study participants.

Ethical Approval

The ethical considerations of this research included obtaining the approval of the Ethics Committee of Semnan University of Medical Sciences IR.SEMUMSREC1394.145-2016-01-18, registration of the trial at the Iranian Registry of Clinical Trials IRCT201601286318N5-2016-02-04. The Declaration of Helsinki assured patients that the data gathered has been kept confidential, obtaining informed written consent, and ensuring the confidentiality of the data. The participants were also ensured of their right to withdraw from the study at any time and that their participation would not affect their care process.

Statistical Analysis

Data were first analyzed using the Shapiro-Wilk test for checking the normality assumption. If the normality assumption was met, the comparison of the mean of the two independent groups was carried out using a t-test; otherwise, Mann-Whitney's U-test was used. Further, Paired t-test was applied to the comparison of the mean before and after concerning normality assumption, while Wilcoxon's test was used for lack of normality in the data gathered. Also, in case of nominal variables found in the qualitative findings, Chi-square along with Cohen's *d* for effect size was employed. All the analyses were performed in SPSS-18.0 (SPSS Inc., Chicago, IL, USA) and P-values less than 0.05 were considered statistically significant.

RESULTS

Sample Characteristics

The mean age of the patients was 66.4±14 years (range: 35-88) in group A and 65.6±12.4 years (range: 41-86) in group B. The two groups had no significant differences in

terms of their mean age (P=0.857) using the student t-test. A total of 52.6% of group A and 45.0% of group B were female (P=0.634), using the Chi-square test for nominal variables such as gender. The mean BMI was 23.6±3.3 kg/m^2 in group A and 23±3.1 kg/m^2 in group B (P=0.549). None of the patients were obese in any of the two groups (BMI≥30), the distribution of body mass index was normal in both groups, which made the t-test useful. All the patients in both groups were married and 31.6% in group A and 35.0% in group B were illiterate. The two groups had no significant differences in terms of education level distribution (P=0.588). The level of income was low in 21.1% of group A and 30.0% of group B (P=0.513). Other variables such as the level of education and income were ranked using the Mann-Whitney test. Diabetes was the most common cause of dialysis in both groups (P=0.618), which has been shown in the Chi-square test. The two groups were not significantly different in terms of the number of cups of tea drunk by the patients (P=0.857). Due to the lack of a normal distribution in the two groups, the Mann-Whitney test was used (Table 1). None of the patients in group A was a smoker and only one patient (5%) smoked in group B (P=1.00) using Fisher's Exact test. The duration of HD in each dialysis session was four hours in all the patients in both groups.

Table 1. Distribution of gender, body mass index, education level, income, Dialysis causes, number of cups of tea consumed daily and smoking in both groups

Indexes		**Group**				**p-Value**
		A*		**B**		
		n	**%**	**n**	**%**	
Sex	Female	10	52.6	9	45.0	0.634[a]
	Male	9	47.4	11	55.0	
BMI	<18.5	1	5.3	3	15.0	0.549[b]
	18.5-24.9	12	63.2	12	60.0	
	25-29.9	6	31.6	5	25.0	
Education	Illiterate	6	31.6	7	35.0	

level	Elementary	9	47.4	6	30.0	0.588 [c]
	Diploma or higher	4	21.1	7	35.0	
Income	Low	4	21.1	6	30.0	0.513 [c]
	Average	14	73.7	14	70.0	
	Good	1	5.2	-	-	
Dialysis causes	DM	7	36.8	5	25.0	0.618[a]
	HTN	4	21.1	4	20.0	
	DM,HTN	4	21.1	8	40.0	
	Other	4	21.1	3	15.0	
Number of cups of tea	0	-	-	2	10.0	0.857[c]
	1	5	26.3	5	25.0	
	2	13	68.4	10	50.0	
	≥3	1	5.3	3	15.0	
Smoking	-	19	100	19	95.0	1.00[d]
	+	0	0	1	5.0	

* The group A took valerian capsules in the first therapeutic period of one month and placebo in the second therapeutic period of one month, and vice versa in group B.

[A:] Chi square [b]: t-student [c]: Mann Whitney [d]: Mc Nemar

While none of the patients in group A had a history of lung disease, 10% (n=2) of group B reported a history of lung disease (P=0.487). None of the patients had a history of gastrointestinal diseases in any of the groups (P=0.925). Ten patients in group A (52.6%) and seven in group B (35.0%) took hypnotic drugs (P=0.267). Also, none of the patients used anti-anxiety drugs and antidepressants. There was no significant difference between 52.6% of group A patients and 35% of group B patients using hypnotics. It should be noted that there were no alterations in patients' medications during the study then, no side-effects during and after the interventions were reported. There was no significant difference in dialysis adequacy scores of patients in groups A and B in the first month of treatment, before (P = 0.411) and

after the intervention (P = 0.659). Also in the second month of treatment, the adequacy of dialysis was not significantly different between the two groups, before the intervention (P = 0.565) and also after the intervention (P = 0.605) (Table 2). Table 3 shows the severity of depression and anxiety in patients. In this table, the frequency distribution of depression severity is reported based on the lowest level of depression (scores 11-16).

Table 2. Mean and SD of dialysis adequacy score of patients before and after the intervention in both groups, first and second treatment periods

Group	***First Period***						***Second Period***					
	n	***Before intervention***		***After intervention***		***p-value***	n	***Before intervention***		***After intervention***		***p-value***
		mean	SD	***mean***	SD			***mean***	SD	***mean***	SD	
A*	19	1.52	0.37	1.75	0.45	0.010	17	1.59	0.38	1.57	0.33	0.801
B	20	1.62	0.37	1.68	0.41	0.493	20	1.66	0.38	1.63	0.31	0.537
p-value	-	0.411		0.659		-	-	0.565		0.605		-

* The group A took valerian capsules in the first therapeutic period of one month and placebo in the second therapeutic period of one month, and vice versa in group B.

Table 3. Number (percent) mild, moderate and severe score of state anxiety and depression before and after the intervention in both groups, first and second treatment periods

Index	**Group**	**First Period**			**Second Period**			**First Period**			**Second Period**		
		Before intervention			**After intervention**			**Before intervention**			**After intervention**		
		Mild	Moderate	Sever	Mild	Moderate	Sever	Mild	Moderate	Sever	Mild	Moderate	Sever
State anxiety	A*	2 (10.5)	14 (73.7)	3 (15.8)	15 (78.9)	4 (21.1)	-	10 (58.8)	7 (41.2)	-	11 (64.7)	6 (35.3)	-
	B	1 (5.0)	18 (90.0)	1 (5.0)	8 (40.0)	12 (60)	-	6 (30.0)	14 (70.0)	-	13 (65.0)	7 (35.0)	-
Depression	A*	4 (33.3)	8 (66.7)	-	5 (100)	-	-	4 (80.0)	1 (20.0)	-	4 (80.0)	1 (20.0)	-
	B	7 (58.3)	5 (41.7)	-	8 (72.7)	3 (27.3)	-	12 (80.0)	3 (20)	-	5 (100)	-	-

* The group A took valerian capsules in the first therapeutic period of one month and placebo in the second therapeutic period of one month, and vice versa in group B.

Table 4. The mean score of sleep quality, depression and state anxiety before and after the intervention

Index	Group	First Period n	First Period Before intervention mean	First Period Before intervention SD	First Period After intervention mean	First Period After intervention SD	First Period p-value	Second Period n	Second Period Before intervention mean	Second Period Before intervention SD	Second Period After intervention mean	Second Period After intervention SD	p-value
Sleep quality	A*	19	14.16	2.75	6.53	2.32	<0.001[c]	17	8.49	2.86	7.53	2.55	0.021
	B	20	14.50	3.49	11.30	3.21	<0.001[d]	20	12.15	2.76	7.50	2.24	<0.001
	p-value^		0.496[b]		<0.001[a]		-		<0.001[b]		0.970 [a]		
Depression	A*	19	14.95	7.49	8.37	3.66	<0.001 [c]	17	10.24	4.12	8.94	4.25	0.006
	B	20	13.50	7.10	11.15	4.97	0.005 [c]	20	12.40	4.20	8.60	3.38	<0.001
	p-value^		0.539 [a]		0.055 [a]		-		0.124 [a]		0.787 [a]		
State anxiety	A*	19	51.16	7.96	36.47	5.27	<0.001 [c]	17	39.41	4.87	37.88	5.07	0.042
	B	20	48.70	6.78	41.40	6.26	<0.001 [c]	20	43.90	5.12	37.70	4.39	<0.001
	p-value^		0.305 [a]		0.012 [a]		-	-	0.010 [a]		0.907 [a]		-

* The group A took valerian capsules in the first therapeutic period of one month and placebo in the second therapeutic period of one month, and vice versa in group B.

^ p- value Between groups A, B.

[a]:t-student [b]:Mann whitney test [c]:Paired t-test [d]: Wilcoxon test

Table 5. Mean and SD score of sleep quality, depression and state anxiety before and after the intervention in both groups A and B in the first and second treatment periods

Index	group	First Period			Second Period		
		n	mean	SD	n	mean	SD
Changes in sleep quality scores	A*	19	7.63	3.15	17	1.41	2.15
	B	20	3.20	1.79	20	4.65	2.30
	P-value		<0.001 [a]		-	<0.001 [a]	
Changes in depression scores	A*	19	6.58	6.09	17	1.29	1.69
	B	20	2.35	3.34	20	3.80	2.65
	P-value		0.013 [a]		-	0.002 [a]	
Changes in state anxiety scores	A*	19	14.68	7.31	17	1.53	2.85
	B	20	7.30	5.12	20	6.20	2.53
	P-value		0.003 [b]		-	<0.001 [b]	

* The group A took valerian capsules in the first therapeutic period of one month and placebo in the second therapeutic period of one month, and vice versa in group B.

[a]: t-student [b]: Mann whitney test

Outcomes

Outcomes in the first treatment phase

In the first treatment phase, the mean score of sleep quality decreased significantly in both groups (P <0.001), but the reduction was significantly higher in group A compared to group B (7.63 vs. 3.20; P <0.001; Cohen's d=1.93). Likewise, the mean scores of depression decreased significantly in both groups (P <0.001), but the reduction was significantly higher in group A compared to group B (6.58 vs. 2.35; P =0.013; Cohen's d=0.86). Similar significant reductions were observed in the mean scores of state anxiety in both groups (P <0.001), but the reduction was significantly higher in group A (14.68 vs. 7.30; P =0.003; Cohen's d=1.17).

Outcomes in the second treatment phase

In the second treatment phase, minus two patients in group A, the analysis was performed on 37 participants, the mean scores of sleep quality decreased significantly in groups A (P = 0.021) and B (P <0.001), but the reduction was significantly lower in group A compared to group B (1.41 vs. 4.65; P <0.001; Cohen's d=1.46). Again, the mean scores of depression decreased significantly in groups A (P = 0.006) and B (P <0.001), but the reduction was significantly smaller in group A (1.29 vs. 3.80; P = 0.002; Cohen's d=1.13). The mean scores of state anxiety deceased significantly in groups A (P = 0.042) and B (P <0.001), but the reduction was significantly lower in group A (1.53 vs. 6.20; P <0.001; Cohen's d=1.73). Tables 4 and 5 present the changes in the mean scores of sleep quality, depression and state anxiety before and after the first and second treatment phases in groups A and B.

DISCUSSION

The aim of this study was determine the effects of Valerian on sleep quality, depression and state anxiety in HD patients. The main finding of this study was that valerian improves sleep quality as well as state anxiety and depression symptoms significantly in HD patients. In Spain, Dominguez et al. (2000) concluded that valerian can be used as a supplement to encourage sleep [40]. In Australia, Francis et al. (2002) reported that treatment with valerian accelerates sleep onset and improves sleep quality in children with mental disorders [41]. In the US, Barton et al. (2011) examined the effects of valerian on sleep quality in cancer patients undergoing treatment and observed reductions in sleeping problems and daytime sleepiness following the use of this herbal medicine [42]. In contrast, Jacobs et al. (2005) found that taking valerian cannot improve sleep status significantly [43]. In Norway, Oxman et al. (2007) rejected any significant differences in sleep quality between the valerian and placebo groups [44]. Since the design of these two studies differs, the results of the study

are not generalizable. Likewise, in the US, Taibi et al. (2009) reported that valerian extract has no significant effects on assisting sleep disorders in people with arthritis [45]. Sleeping problems in HD patients differed from other patients. Although the exact mechanism of valerian on sleep disorders is unknown, the plant is believed to have important interactions with the neurotransmitter GABA. Valerian is thought to inhibit the uptake and stimulate the release of GABA [46]. Moreover, this plant has recently been identified as a partial agonist of the adenosine and serotonin receptors [47,48]. These findings may explain the main mechanisms through which valerian enhances sleep quality. Valerian is also accepted as a partial agonist of the 5-hydroxytryptamine 2A receptor that boosts melatonin release [22], which may be another mechanism through which the plant improves sleep quality. Nonetheless, considering the conflicting evidence, further research is required to clarify the effects of valerian on sleep and determine its exact mechanisms of action.

The results of this study showed that valerian decreases state anxiety and depression symptoms significantly in HD patients. In 2003, Müller et al. demonstrated that depressive disorders comorbid with anxiety disorders can be more quickly improved with a combination of St John's Wort and valerian extracts compared to when undergoing mono therapy with St John's Wort [49]. Nevertheless, the evidence regarding the effectiveness of the application of valerian in the treatment of anxiety disorders is currently inadequate [50]. There is no sufficient evidence on the effectiveness of valerian in the treatment of anxiety disorders and sleep problems [51].

The limitation of the study is the small number of participants. Although low sleep quality was a significant and prevalent disorder in HD patients in the studied centers, few people were willing to take the drug and participate in the study. In general, drug adherence was low in HD patients. The reason for some HD patients (n=22) in this study was their reluctance to participate in the study. At the end of the study, two people in group reluctant to

complete the questionnaires. The rate of drug adherence in patients undergoing HD was low. The problem of non-adherence to drug therapy in HD patients can be further addressed in other studies. Appropriate interventions and strategies can be implemented to help enhance the patients' motivation for adherence to medications [52]. Also, sleep was quantified by symptom checklist which is inferior to sleep lab or sleep architecture. Similarly, other checklists (depressive symptoms and anxiety traits) often give the spurious results.

Findings show that, Valerian improved sleep quality, state anxiety and depression significantly in HD patients, therefore the results could help in planning novel non-chemical approaches for decreasing sleep disorders, depression, and state anxiety. Further research are recommended by removing the limitations of this study.

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