Original Research Article

The effectiveness of *Valeriana officinalis* on sleep disturbance in patients with chronic heart failure

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Abstract

Background: Sleep disturbances are common problems in patients with chronic heart failure (CHF) and are a significant contributing factor to fatigue and poor quality of life. The aim of the present study was to evaluate the effectiveness of *Valeriana officinalis* on sleep disturbance in patients with CHF.

Materials and Methods: A randomized, controlled trial design was used for this study. Eighty patients with CHF experiencing insomnia were designated to intervention and control groups. The patients in the intervention group went through conventional treatment while taking 12cc *V. officinalis* syrup, 1 h before sleeping every night for 4 weeks. The control group received routine medication such as alprazolam. A demographic data form and the Pittsburgh Sleep Quality Index were used to collect data. Questionnaires were completed by all participants before and after the intervention.

Results: The results indicated that regarding the duration of waiting for falling into sleep, there was a significant difference after intervention so that it was less in intervention groups compared to that of the control group ($P = 0.001$). In view of the hours during which the participants were fully asleep, there was a significant difference after the intervention between control and intervention groups, considerably higher among three intervention groups compared to that in the control group ($P < 0.05$).

Conclusions: *V. officinalis* improves the quality of sleep in patients with CHF who experience insomnia. The findings from this study support the reported effectiveness of *V. officinalis* in the clinical management of insomnia.

Keywords: Chronic heart failure, sleep disturbance, *Valeriana officinalis*

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INTRODUCTION

Insomnia is the most frequent sleep disorder.[1] It consists of the inability to fall into sleep and stay asleep and/or to obtain the adequate duration and quality of sleep to restore normal states of energy and wakefulness.[2] The prevalence of general sleep disturbance experienced by people over 1 year is estimated at approximately 85%, while the estimation of diagnosed chronic insomnia is considered at around 10%.[3] Other studies have found this to be higher, with the United States National Health Interview Survey in 2002 revealing a 12-month prevalence of 17.4% of adults with self-reported insomnia or having trouble in sleeping.[4] Around 30% of the population worldwide suffers from insomnia.[5]

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Sleep disturbance is a common problem in patients with chronic heart failure (CHF) and a significant contributing factor to fatigue and poor quality of life.[6] The pathophysiology of CHF often leads to fatigue, due to nocturnal symptoms causing sleep disruption, including cough, orthopnea, paroxysmal nocturnal dyspnea, and nocturia. Only about 10% of those receive adequate treatment.[1,7]

Conventional approaches to the treatment of chronic insomnia usually involve either pharmacotherapy or psychological interventions. Pharmaceutical hypnotics are the primary first-line pharmacotherapy used to treat chronic insomnia. Benzodiazepines are the most effective and utilized drugs used to combat insomnia.[7] The use of these drugs has the potential to cause serious adverse effects.[8] The prolonged use of benzodiazepines produces adverse effects such as dependence, rebound insomnia, bad sleep quality, negative repercussions on cognitive functions,[9] and decreased effectiveness[1] which has brought about the search for safe, alternative treatments among herbal products.[10-12]

Complementary and alternative medical (CAM) therapies may be useful for the management of insomnia in older adults. The 2003 National Sleep Disorders Research Plan recognized as a priority the importance of studies evaluating CAM therapies for sleep disturbances.[13]

Interest in the use of alternative therapies and products for insomnia has grown over the past two decades due to a range of motivational factors.[14]

Many patients prefer "natural remedies" for the treatment of insomnia because they think their adverse effects and interactions are not considerable, they do not require a medical prescription, and do not cause alterations in the sleep state.[8]

Despite evidence on widespread interest, research evidence is lacking on the efficacy of many CAM therapies, especially in older adults. One of the herbal medicines with sedative effect is *Valeriana officinalis* that has been recognized since the 18th century in Europe and has been used for sleep disorders.[15]

V. officinalis contains a variety of chemical compounds, including valerenic acid and derivatives (hydroxyl-valerenic acid, acetoxy-valerenic acid, and valerenal) that may act synergistically to exert sedative effects.[8] Similar to conventional sedative-hypnotic medications, constituents of *V. officinalis* are believed to activate gamma-aminobutyric acid (GABA) receptors that are involved in sleep promotion and regulation. Constituents of *V. officinalis* have also been shown through *in vitro* and animal studies to affect other receptors, adenosine and glutamine (an amino acid that is metabolized into GABA), involved in the regulation of sleep and waking.[16]

Taibi *et al.* review[17] concluded that *V. officinalis* is no more effective than the placebo in the majority of insomnia cases and that this result is deduced above all from the most recent methodologically rigorous clinical trials; however, the meta-analysis by Bent *et al.*[18] showed a statistically significant greater measure of effect (sleep-quality improvement) in the *V. officinalis* treated group in comparison to the placebo group. Nevertheless, they recommend further trials with greater methodological rigor to arrive at a more definitive conclusion. Sleep disturbances are a common problem in patients with CHF. The aim of the present study is to evaluate the effectiveness of *V. officinalis* on sleep disturbance in patients with CHF.

MATERIALS AND METHODS

A clinical trial was conducted in two groups. Cardiac disease patients of Cardiovascular Clinic of Shahrekord University of Medical Sciences having inclusion criteria comprised the study's sample population.

The study participants were patients who were conscious, communicable, and had agreed to participate, were suffering from CHF confirmed by the patient's physician and older than 40 years old.

Patients were excluded from this study if they were unwilling to continue participating in the study or exhibiting sensitivity or physical problems pertinent to medicines during the study.

The protocol and informed consent document were reviewed and approved by the Ethics Committee of Shahrekord University of Medical Sciences and IRCT201204042289N2 was issued for the study by Iranian Registry of Clinical Trials.

All patients provided written informed consent at study screening before receiving any study medication. First, interviews were held by the researcher to complete questionnaires to select those with scoring at least 6. Then, their disorder (i.e., heart failure) was approved by a physician and finally other criteria for inclusion were ensured. Regarding statistical calculations, the number of population was 40 for each group; totally, 80 cases

were selected for pursuing investigation. In the first step, purposeful sampling was adopted. However, the patients were randomly divided into two study groups. At the end of each sampling day, each patient with inclusion criteria was characterized by one and two to be included in groups one and two, respectively. The patients in the first group went through the conventional treatment while taking 12cc *V. officinalis* syrup (Mina, Pharmaceutical and Cosmetics Laboratory, Tehran, Iran), 1 h before going to bed every night within 1 month. The control received the routine medicine such as alprazolam. Regarding that it was rare to have access to the total sample population within 24 h, we had to do sampling within subsequent days and go to the clinic to complete the sample population. Data were collected through a questionnaire comprised two section of demography and sleep quality questionnaire.

The questions specified for sleep appraised included Petersburg Sleep Quality Investigation (PSQI) questionnaire, with 89.6% sensitivity and 86.5% specification. The questionnaire has been developed for investigating patient's attitude toward sleep quality within 4 weeks and bears seven scales of general description of sleep quality by individual, delay in falling into sleep, useful sleep duration, sleep adequacy (ratio of useful sleep duration to the total time spent in bed), sleep disorders (nightly getting up), the amount of soporific medicine taken, and finally daily performance (i.e., the difficulties due to insomnia experienced by an individual during the day).

The review of the literature indicates an acceptable consistency between the questionnaires results and laboratory sleep investigation by means of polysomnography (PSG). The score for each scale is 0–3, representing the natural condition and moderate to mean and severe difficulties, respectively. The summation of 7-fold scales comprises total score, ranging from 0 to 21. The total score of 6 or more was considered as sleep quality unacceptability.[19] Questionnaires were completed by all participants before and after the intervention.

Standardization of the drug

To standardize the syrup, total flavonoid and phenolic compounds as well as antioxidant activity of the syrup were determined as follows:

The amount of total flavonoid compounds in the syrup was determined using the colorimetric method as previously described by Asadi *et al.*[20] One mL of the extract or routine (standard flavonoid compound) was added to 1.5 mL of methanol (60%), 1 mL of 2% aluminum chloride, and 6 mL of 5% potassium acetate and the mixture was left at room temperature for 35 min. Then, the absorbance of the mixture was measured at 415 nm with a double beam spectrophotometer (Unico UV-2100, USA). Standard solutions (Rutin) were prepared at concentrations of 25, 50, 100, 250, and 500 ppm in methanol and the calibration curve was prepared. The experiments were repeated three times. Total flavonoids were expressed regarding routine equivalent (mg/g), which is a common reference compound.[21]

Total phenolic compounds in the syrup were determined colorimetrically using Folin–Ciocalteu reagent.[22,23] Half mL of the extract or standard phenolic compound (gallic acid) was mixed with the Folin–Ciocalteu reagent (1:10 dilution with distilled water) and aqueous Na_2CO (0.4 ml, 7.5%). The mixture was left at room temperature for 30 min, and the amount of total phenolic compounds was determined by spectrophotometer (Unico UV-2100, USA) at 765 nm. The standard curve was prepared using gallic acid at concentrations of 12.5, 25, 50, 62.5, 100, and 125 mg/L in methanol and water (60:40, v/v). The experiment was repeated three times and the amount of total phenols were expressed regarding gallic acid equivalent (mg/g), which is a common reference compound.[24]

Total antioxidant activity of the syrup was evaluated using the previously described method of Shirzad *et al.*[25] A stock solution of β-carotene (0.5 mg) in one mL of chloroform, linoleic acid (25 µl), and tween-40 (200 mg) was prepared. The chloroform was evaporated using a vacuum evaporator at 50°C. Then, 100 mL of oxygenated water (30 min 100 ml/min) were added and 2500 µl aliquots were added to test tubes and 350 µl of the extracts (prepared at 2 g/L concentration) or butylated hydroxy toluene (BHT) (as a positive control) were added and incubated for 48 h at room temperature. The absorbance of the solutions was measured at 490 nm. Antioxidant capacities of the extracts were compared with those of BHT and blank.[26]

Statistical analysis

Data were analyzed using SPSS software 17 (SPSS Inc., Chicago, IL, USA) software. In all analyses, P - 0.05 was considered as statistically significant. We used independent and paired t-tests to compare mean scores between the experimental and control groups at pre- and post-tests.

RESULTS

Total phenol and flavonoid compounds were measured to be 60.04 and 27.7 mg/ml syrup, respectively. The antioxidant activity of the syrup was 40% of routine equivalent.

In this study, 85 participants were initially included in the study. However, five people were subsequently set aside, two because of death and three due to unwillingness to take medicine, finally leaving 80 people divided into two groups of 40 each. The mean age was 58.1 ± 10 years. About 37.5% were male while the rest 62.5% were female ($P > 0.05$). Before the intervention, the mean time to fall into sleep was 1.47 ± 1.06 and after intervention 0.74 ± 0.61 h. Besides, the time duration in which an individual was fully asleep during the night was 0–10 h, with mean 4.54 ± 1.74, and 2–8 h, with mean 5.38 ± 1.05 before and after intervention, respectively ($P < 0.05$). The results obtained by statistical analysis before intervention indicated that there was no significant difference regarding the time of falling into sleep, time duration of waiting for falling into sleep, and the number of hours during which the participants were fully asleep as well as sex and age distribution ($P > 0.05$). Besides, the samples were normally distributed among the two groups.

Regarding the time duration of waiting for falling into sleep, there was a significant difference after intervention so that it was less among intervention groups compared to that of the control group ($P = 0.001$). Given hours during which the participants were fully asleep, there was a significant difference after intervention between control and intervention groups, and this score was significantly higher in the intervention group ($P < 0.05$).

In addition, before intervention, there was no significant difference between two groups regarding total score ($P = 0.239$). However, after intervention, control group had lower quality of sleep in comparison to intervention group ($P = 0.001$).

Finally, the intervention group showed a better sleep quality compared to the control group.

DISCUSSION

This study tested the effects of *V. officinalis* on sleep quality in patients with CHF. Findings showed improvement of sleep quality in intervention group compared to control group. Scientific evidence relative to the efficacy of *V. officinalis* is inconclusive. The current study is one of the few randomized placebo-controlled trials evaluating herbal treatment of insomnia among CHF patients. Some systematic reviews on the efficacy of *V. officinalis* on insomnia have been performed; however, they reach different conclusions.[1]

In a previous study, Wheatley found that stress decreased significantly after the daily taking of 600 mg *V. officinalis* for 6 months. Besides, the patient's insomnia was considerably improved.[27] In another study, Donath *et al.* found that the patient's sleep improved significantly after *V. officinalis* taking for several days.[28] Moreover, there was a significant decrease in sleep latency time in the intervention group in the recent study. The same result was achieved by Leathwood and Chauffard that demonstrated the group taking *V. officinalis* achieved an improvement in sleep quality compared to the placebo group. In addition, the sleep latency time, as well as nightly getting up frequency was decreased.[29]

The use of 450 mg *V. officinalis*, at bedtime in improving sleep in patients who were undergoing treatment for cancer in a study of Barton, could not improve sleep as measured by the PSQI.[30]

Morin in a clinical trial study assessed *V. officinalis*-hops combination and diphenhydramine for treating insomnia. The result showed that *V. officinalis* produced a nonsignificant reduction in sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and a significant reduction in comparison to the placebo group at the end of 28 days of treatment.[31]

Although some studies have reported improvement in sleep quality with *V. officinalis* administration over time, there are few studies mentioning significant improvement in any of the sleep outcomes when *V. officinalis* is compared with a placebo.[32] Despite evidence from *in vitro* studies of *V. officinalis* effect on neuropeptide systems involved in sleep mechanisms,[33] Vitiello *et al.* reported moderately disrupted sleep on PSG recordings in older healthy women who had no complaint of sleep problems; however, this pattern was not observed in healthy older men.[34]

Recently, Shinomiya *et al.* reported that a significant shortening in sleep latency without any significant effects on the total times of wakefulness was observed with *V. officinalis* extract.[35] Although GABA is present in *V. officinalis* extracts, its brain bioavailability through oral administration is uncertain. The action of *V. officinalis* on the central nervous system might be due in part to GABA involvement through a number of mechanisms, including an inhibition of GABA uptake into synaptosomes.[36] *V. officinalis* constituents inhibit the enzymatic breakdown of GABA and enhance benzodiazepine binding.[37] The other potential mechanisms for the pharmacological activity of *V. officinalis* have been proposed, including partial agonistic activities on 5-HT5a receptor.[38]

The results of this study support the hypothesis that *V. officinalis* can improve sleep quality in patients with

CHF. Due to less side effect of herbal medicines,[39] these products could be taken as a safe substitute for synthetic medicines.[10]

CONCLUSIONS

V. officinalis has been demonstrated to have antioxidant activity, and therefore, its beneficial effect on insomnia might be, at least in part, due to its antioxidant activity.

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Conflicts of interest

There are no conflicts of interest.

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