

The effectiveness of *Melissa officinalis* on sleep problems in Patients with Chronic Heart Failure

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Abstract

Background: Numerous studies have documented high prevalence rate of major depression in patients with heart failure.

Aim: The aim of the present study was to evaluate the effectiveness of *Melissa officinalis* on sleep problems in patients with chronic heart failure.

Methods: In a randomized, controlled trial study eighty patients (40 in each group) with chronic heart failure and experiencing insomnia were allocated randomly into intervention and control groups. The patients in the intervention group, received 12 ml *M. officinalis* syrup in addition to conventional treatment one hour before going to bed for 4 weeks. A demographic questionnaire and the Pittsburgh Sleep Quality Index were used to collect data. Questionnaires were completed by all subjects before and after the intervention.

Results: The time duration of waiting for falling asleep in the intervention group was significantly less than the control group ($p=0.001$). The hours during which the subjects were fully asleep was significantly more than the control group ($p<0.05$).

Conclusion: *M. officinalis* may improve the quality of sleep in patients with chronic heart failure who experience insomnia.

Key words: Heart failure, *Melissa officinalis*, Sleep

Introduction

Sleep problem is a common problem in patients with chronic heart failure (CHF) [1], and is a significant contributing factor to fatigue and poor quality of life. The pathophysiology of CHF often leads to fatigue, due to nocturnal symptoms causing sleep disruption, including cough, orthopnea, paroxysmal nocturnal dyspnea, and nocturia [2].

The presence of insomnia symptoms, despite the stable condition in patients who suffered from heart failure and received evidence-based management, suggests that this management alone is not sufficient to decrease insomnia symptoms [3]. Only about 10% of these patients receive adequate treatment [2].

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 [4].

Benzodiazepines are the most effective and utilized drugs used to combat insomnia [5]. The consumption of these drugs, especially in prolonged use, has the potential of serious adverse effects [6] such as dependence, rebound insomnia, bad sleep quality, negative consequences for cognitive functions [7], and decreased effectiveness [2], which has led to the search for safe alternative treatments among herbal products.

Complementary and alternative medicine (CAM) may be useful for 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 problems [8].

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 [9].

Many patients prefer "Natural remedies" for the treatment of their diseases because they think that remedies have low adverse effects and interactions, and do not require a medical prescription [10].

Despite evidence of widespread interest, research evidence is lacking on the efficacy of many plant-based therapies, especially in older adults [10]. One of the herbal medicines with sedative effect is *M. officinalis* that has been recognized since the 18th century in Europe and has since been used for sleep disorders [11].

Medicinal plants including *M. officinalis* are effective in a wide variety of diseases [12-15]. Recent evidence suggests that *M. officinalis* extract, which contains rosmarinic acid and the triterpenoids oleanolic acid and ursolic acid, inhibits gamma-aminobutyric acid transaminase (GABA-T) activity [16].

Sleep problems are a common problem in patients with CHF, but there are few studies investigating the effects of herbal medicines on sleep disorders in these patients. Thus, it is necessary to conduct more research in this field. The aim of the present study was to evaluate the effects of *M. officinalis* on sleep problems in patients with CHF.

Materials and methods

This was a parallel group, placebo controlled trial study that was conducted in the Cardiovascular Disease Clinic of Shahrekord, Iran, from March 2010 till November 2010. Overall coordination of the trial was conducted by Medical Plants Research Center of the Shahrekord University of Medical Sciences. Participants in the study were male and female outpatients aged older than 40 years. The study participants were patients with CHF who were conscious and communicable, and had agreed to participate in the study. All participants were examined by a cardiologist, who took a patient history and performed a clinical examination. Doppler echocardiographic examinations were performed to assess left ventricular ejection fraction (LVEF). Prior to formal inclusion in the study, participants underwent a screening interview to determine the nature and history of sleep difficulty. In addition, the researcher completed PSQI questionnaires in order to select the people with a score of at least 6.

Patients were excluded if they were unwilling to continue participating or had allergy or physical problems to medicines during the study.

The protocol and informed consent were reviewed and approved by the Ethics Committee of the Shahrekord University of Medical Sciences. The protocol was registered in the Iranian Registry of Clinical Trials (no.: IRCT 201204042289N2).

The participants were informed about the study method and assured of confidentiality and anonymity. They

gave written consent and it was made clear that they could withdraw from the study at any time. Regarding statistical calculations, the number of population was 40 for each group; totally 87 cases were selected for pursuing investigation. In the first step, purposeful sampling was adopted. However, patients were randomly divided into 2 study groups. At the end of each sampling day, each patient with inclusion criteria was characterized by 1 or 2 to be included in groups one or two, respectively. The patients in the intervention group received conventional CHF treatment while taking 12 ml, *Melissa officinalis* syrup (produced by Mina-Pharmaceutical and Cosmetics Laboratory, Tehran, Iran), an hour before going to bed every night for one month. The control group received conventional CHF treatment and Alprazolam as a hypnotic drug. Data were collected through a questionnaire comprising two sections of demography and sleep quality questionnaire.

The questions specified for sleep appraisal included Petersburg Sleep Quality Investigation (PSQI) questionnaire, with 89.6 percent sensitivity and 86.5 percent specification. The questionnaire was developed for investigating patient's attitude toward sleep quality within 4 weeks and has 7 scales of general description of sleep quality by individuals, delay in falling asleep, 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 questionnaire's results and laboratory sleep investigation by means of polysomnography. The score for each scale is 0-3, representing natural condition, 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 [17].

Questionnaires were completed by all subjects before and after intervention. Data were analyzed by SPSS software 16 and x2, paired and independent t tests and one way ANOVA. $p < 0.05$ was considered significant.

Results and Discussion

In this study, 87 patients were recruited in a cardiovascular disease center in Shahrekord. However, seven people were subsequently excluded, one because of death, three due to unwillingness to take medicine, and three patients did not perform any baseline visit and thus were not eligible for evaluation. Finally, 80 patients were allocated into two groups. There were 60 (38.2%) male patients while the rest (61.8%) were female ($p > 0.05$) with the mean age of 62.4 ± 9.65 years. The mean time to fall asleep was 1.2 ± 0.96 hours before intervention, and 0.74 ± 0.41 hours after intervention. Furthermore, the time duration in which an individual was fully asleep during the night was 0-10 hours, 4.54 ± 1.74 on average,

Table 1: Comparison of total score sleep quality in the two groups

	Before	After	Sig
Intervention	24.10 ± 7.44	5.75 ± 3.93	(p=0.001)
Control	29.9±6.01	21.27±7.9	(p=0.278)

and 2-8 hours, 5.38 ± 1.05 on average before and after intervention, respectively ($P < 0.05$). The results obtained before intervention indicated that there were no significant differences regarding the time of falling asleep, time duration of waiting to fall asleep, and the number of hours during which the subjects were fully asleep, as well as sex and age distribution ($p > 0.05$). Besides that, the samples were normally distributed between the two groups.

The time duration for waiting to fall asleep was significantly less in the intervention group ($p = 0.001$). In addition, the hours during which the subjects were fully asleep were significantly more than those in the control group ($p < 0.05$).

In the present study, before intervention there was no significant difference between the two groups in total score of quality of sleep ($p = 0.239$). However, after intervention, the control group had a lower score in comparison to the intervention group (Table 1).

The most notable finding of the current study was that *M. officinalis* is effective in causing significant improvements in important sleep parameters in patients with CHF. Findings showed improvement of sleep quality in the intervention group compared to the control group. Scientific evidence related to the efficacy of *M. officinalis* is inconclusive. The current study is one of the few randomized placebo controlled trials evaluating treatment of insomnia using medicinal plants among CHF patients. Some systematic reviews on the efficacy of *M. officinalis* on insomnia have been performed, but they reach different conclusions [18].

In a previous study, Wheatly et al. found that stress decreased significantly after daily taking of 600 mg over 6 months. Besides, the patient's insomnia was considerably improved [19]. In another study, Donath and colleagues found that the patient's sleep improved significantly after taking valerian for several days [20]. Moreover, there was a significant decrease in sleep latency time in the intervention group in a recent study. The same result was achieved in Leathwood and colleagues who demonstrated the group taking valerian 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 [21].

The use of 450 mg valerian, at bedtime in improving sleep in patients who are undergoing treatment for cancer in study by Barton could not improve sleep as measured by the PSQI [22].

Morin in a clinical trial study assessed Valerian-hops combination and diphenhydramine for treating insomnia.

The result showed that Valerian produced slightly greater, though non-significant, reductions of sleep latency relative to placebo and diphenhydramine at the end of 14 days of treatment and greater reductions than placebo at the end of 28 days of treatment [23].

Recently, Shinomiya et al. reported that a significant shortening in sleep latency without any significant effects on the total duration of wakefulness was observed with valerian extract [24]. Although GABA is present in *M. officinalis* extracts, its brain bioavailability via oral administration is uncertain. The action of *M. officinalis* on the CNS might be due in part to GABA involvement through a number of mechanisms, including inhibition of GABA uptake into synaptosomes. *M. officinalis* constituents inhibit the enzymatic breakdown of GABA and enhance benzodiazepine binding [25].

Conclusion

The results of this study support the hypothesis that *M. officinalis* can improve sleep quality in patients with CHF. Because of fewer side effects of herbal medicines, these products can be taken as a safe substitute for synthetic medicines.

Acknowledgments

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