European Journal of Integrative Medicine 28 (2019) 27–32

Contents lists available at ScienceDirect

European Journal of Integrative Medicine

journal homepage: www.elsevier.com/locate/eujim

Clinical trial

Effects of *Melissa officinalis* on anxiety and sleep quality in patients undergoing coronary artery bypass surgery: A double-blind randomized placebo controlled trial

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ARTICLE INFO

Keywords:
Melissa officinalis
Coronary artery bypass surgery
Sleep quality
Anxiety
Traditional Persian medicine
Randomized controlled trial

ABSTRACT

Introduction: Coronary artery disease is prevalent with high morbidity and coronary artery bypass grafting is one of its most important treatments. Anxiety and sleep disorders after surgery are very common and need appropriate control. The current study aimed to evaluate the efficacy of *Melissa officinalis* L. (Lemon Balm) for managing this problem.

Methods: A double-blind randomized placebo controlled clinical trial was conducted with 80 in-patients who underwent coronary artery bypass surgery. The patients were randomized into either the herbal medicine or the placebo group. Capsules containing 500 mg of *Melissa officinalis* L. dried leaf powder as herbal medicine or wheat starch as placebo were administered three times a day. Sleep quality and anxiety measures were the main outcomes and St Mary's Hospital Sleep Quality and Hospital Anxiety Depression Scale were used questionnaires respectively.

Results: At baseline there were no significant differences in the anxiety scores between the two groups. After the intervention, anxiety scores were 7.15 ± 1.2 and 10.18 ± 3.1 in the herbal medicine and placebo groups respectively ($P = 0.001$). Moreover, the mean changes of sleep quality in the herbal medicine group was significantly higher than the placebo group; 14.40 ± 5.1 vs 7.52 ± 4.4 ($P < 0.001$).

Conclusion: The results of current study showed that seven-day treatment with 1.5 g/day dried leaf powder of *Melissa officinalis* appeared to reduce the levels of anxiety and improve the sleep quality in patients after coronary artery bypass surgery, by 49% and 54% respectively.

1. Introduction

Coronary artery disease is a prevalent disease leading to death and disability [1]. Coronary artery bypass grafting (CABG) is the most common surgical procedure used to improve blood supply of the heart in patients with ischemic heart diseases [2]. Sleep disorder and anxiety are typical problems in more than 50% of patients undergoing cardiovascular surgery [3].

Sleep disorder leads to increased mortality, lengthy hospital stay, and short- and long-term physiological disorders including immune system and wound healing disorders and cardiac, respiratory, and nervous consequences [4–6]. In addition, anxiety and depression can cause sleep disorders and even increase the infarct size, arrhythmia, pain, post-operative physical symptoms, and risk of morbidity [7–9].

Various methods are used to reduce anxiety and improve sleep quality in these patients. Medicinal treatments, especially benzodiazepines, have been the preferred method of therapy for sleep disorders and anxiety in hospitalized patients. However, tolerance and dependence on drugs and their adverse effects, such as cognitive impairment, sedation, respiratory depression, and withdrawal symptoms are among the problems of long-term use of these medicines [10–13].

Herbal medicines have been used as alternatives to conventional medicine to treat many diseases. For instance, these medicines have a great effect on neurological disorders such as anxiety, depression, and

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https://doi.org/10.1016/j.eujim.2019.01.010
Received 18 December 2018; Received in revised form 27 January 2019; Accepted 28 January 2019

insomnia [14,15]. Additionally, taking advantage of the experiences of traditional medicine is a suitable approach for achieving effective drugs. Traditional medicine in Iran (Traditional Persian medicine), with a history of about 10,000 years, has suggested they may be effective therapies [16–19]. *Melissa officinalis* (MO) is one of the plants used in Traditional Persian medicine (TPM) with sedative effects and is considered as a tonic for nervous system [20–22]. Moreover, phytotherapy studies have highlighted many effects for MO, entailing relaxant and anti-anxiety effects [23–27]. The properties attributed to MO in traditional medicine resources have been shown in recent studies. Among them are studies showing that MO reduces depression, anxiety, and insomnia; in addition, it may improve benign palpitation and female sexual dysfunction [15,28,29]. The mechanism of anxiolytic effects may be related to a decrease cortisol and an increase in gamma aminobutyric acid GABA [30]. Considering various beneficial effects of *M. officinalis* and the absence of side effects [31–33], and because there was no study which had been conducted on the short-term effects of this herbal medicine on the treatment of anxiety and sleep disorder in patients after CABG, this clinical trial was designed.

2. Methods

2.1. Patients

Participants in this study were volunteer inpatients who underwent coronary artery bypass graft. Patients were selected through a convenience sampling method, and then randomly assigned into two groups, intervention and control. Inclusion criteria were as follows: aged between 30 and 70 years, lack of considerable sleep disorder in the last month prior to the study, which meant a score of less than 28 based on the Pittsburgh Sleep Quality Index and were able to provide informed consent. The exclusion criteria were: psychiatric disorder confirmed by psychologist, sleep disorder within the last month according to Pittsburg Questionnaire scores, a length of stay in the department of open-heart surgery of more than five days, reoperation, discontinued participation, and patient death.

2.2. Herbal medicine

Herbal medicine in this study was Melissa capsules consisting of dried leaves powder of *Melissa officinalis* L. *Melissa officinalis* is the accepted name of a species in the genus Melissa and Family Lamiaceae (www.theplantlist.org). It was obtained from the farm of Zardband Pharmaceutical Co. Gonbad, Iran. The plant was authenticated in the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran (Voucher No. 3380).

2.2.1. Herbal medicine and placebo preparation

In the current study, Melissa capsules consisted of 500 mg powder of dried leaves of *Melissa officinalis* L. in hard gelatin capsules. Every package contained 21 capsules with a label indicating the confidential code as well as the instruction for use. Placebo capsules consisted of 500 mg of wheat starch powder in hard gelatin capsule and their package was similar to herbal medicine.

2.2.2. Herbal medicine assay

The quality of *Melissa officinalis* (MO) as the herbal medicine was assayed by determining the total phenolic and flavonoid content. The tests were performed through the method described by Darvish-Mofrad-Kashani et al. [29].

2.3. Study design and interventions

In this double-blind randomized placebo controlled trial, the volunteers were examined under the supervision of cardiologist and specialist in traditional medicine, and the eligible patients were included in the study. The patients signed the consent form after receiving a complete explanation about the study. Their demographic data were assessed and documented. Then, they were assigned into two groups of intervention and control based on random number tables. The drug and placebo packages were prepared by a pharmacist, who was not informed about the study, who randomly coded the packages 1 to 80. The codes were kept confidential until the end of the study and data analysis. The capsules of the drug and placebo and their packages were completely similar and their contents were unknown for the researchers and patients. The drug and placebo packages were given to the researcher and mixed up. The investigator, cardiologist, and patients were blind to the method of allocation. Additionally, the statistician, who analyzed data at the end of study, was unaware of the status of groups. Medicine administration began one day after surgery. Prior to the intervention, the levels of anxiety and sleep quality of the subjects were assessed using St Mary's Hospital Sleep Questionnaire (SMSHQ) and Hospital Anxiety and Depression Scale (HADS). The medicine was prescribed from the day after surgery, one 500-mg capsule three times a day (morning, noon, and before sleep) for seven days. Each patient received either the drug or the placebo. At the end of the intervention, the questionnaires were completed as well as the side effects form. It should be noted that the patients consumed their routine previous medications prescribed by the cardiologist, according to the hospital protocol.

2.4. Outcomes

Quality of sleep was assessed by St. Mary's Hospital Sleep Questionnaire (SMHSQ). This instrument is available in various languages and is suitable for investigating sleep disorders. The validity and reliability of this scale and its Persian version is shown in numerous studies. SMHSQ has 14 multiple-choice questions, which were scored according to 4-point Likert Scale (1, 2, 3, and 4 scores represent never, rarely, often, much, respectively). The least and highest scores were 14 and 56, which showed lack of sleep disorder and the most severe sleep disorder, respectively [34–37]. Patients' anxiety was evaluated using the Persian version of the Hospital Anxiety and Depression Scale (HADS). In this seven-item subscale of anxiety; each item is scored from 0 to 3. The validity and reliability of HADS was confirmed in several studies [38,39].

2.5. Statistical analysis

The sample size was estimated to be 40 per group based on the results of previous study, confidence interval of 0.95, test power of 80% and 15% sample attrition [26]. Data analysis was performed using descriptive and inferential statistics, Mann–Whitney *U* test with the help of SPSS software (version 16). In all the measurements, P-value less than 0.05 were considered statistically significant.

The practical effect size proposed by the Cohen's d value was considered to be small (0–0.2), medium (0.2–0.8), or large (> 0.8). The effect sizes in every part of the current study were calculated by the mentioned equation [40].

3. Results

3.1. Patients

From the 80 eligible patients who participated in the trial, all of them completed the study. Flow diagram is shown in Fig. 1.

As shown in the diagram, no patients were excluded from the study and no patients died.

Demographic data of the patients are summarized in Table 1. At baseline there were no significant differences identified between patients in the groups regarding age or other demographic data including

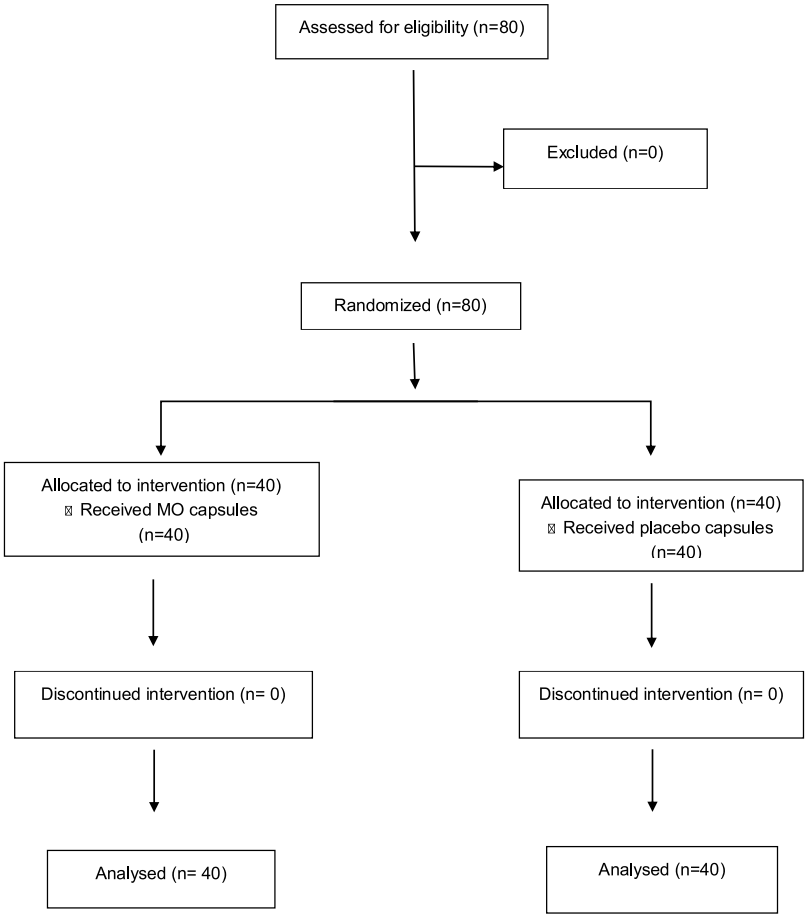

Fig. 1. Flow diagram of study participation.

education, occupation, high blood pressure, pulmonary diseases, history of diabetes, cigarette consumption, history of hospitalization, history of anesthesia, history of surgery, number of the engaged legs and number of the grafts.

3.2. Herbal medicine assay

The phenolic compounds content of MO was determined using Folin-Ciocalteu's reagent and Gallic acid as a standard, was 4.88 ± 0.04 mg GA/g. Also considering **Rutin** as a standard, its flavonoids content was determined as 4.28 ± 0.005 RU/g.

3.3. Intervention

3.3.1. Efficacy of MO for decreasing anxiety

As it is obvious in Table 2, before the intervention, mean anxiety scores in drug and placebo group were not significantly different according to Independent-Samples *t*-test However, after the intervention, there was a significant difference between groups according to Mann-Whitney U test. The related effect size was calculated as 0.97, indicating a large effect [40].

3.3.2. Efficacy of MO for improving sleep quality

Considering the significant differences of scores before and after intervention in both groups (Table 3), mean changes of sleep quality were calculated. As it is obvious in Table 4, there was a significant difference in sleep quality changes between groups and these changes (as a result of the intervention) in drug group is significantly more than placebo group, according to Independent *t*-test (P-value < 0.001).

The results indicated that mean change in the herbal medicine group was 54.46% versus 31.33% in placebo group also, the calculated effect size was 1.62 that is considered large [40].

3.3.3. Adverse effects

MO was well tolerable by the patients and no side effects were observed.

4. Discussion

As mentioned before, *Melissa officinalis* L. (Lemon Balm) is one of the medicinal plants that has been used to treat various diseases for many years in European and Iranian traditional medicine. In addition to TPM that contributes hypnotic effect to *Melissa officinalis*, in Danish folk medicine, this herbal remedy is used to treat insomnia [20,41]. As a part of its effects from TPM point of view, it is known as a "*mofarrah*" that means it is a tonic for brain and nervous system as well as an exhilarant and antidepressant [20–22]. Therefore, the effects observed in the current study as anxiety reduction and sleep quality improvement are expected. Anti-depressant effect also observed according to the results of the HADS questionnaire which was reported elsewhere [42]. According to the recent studies, rosmarinic acid as one of the active ingredients of MO has analgesic effects [43]. Considering the post-operative pain in patients, this medicine can indirectly affect the quality of sleep in patients by relieving their pain. Based on the results of this study, the mean change of sleep quality in the intervention group was significantly higher than the control group. The results of this study were in line with the results of various studies including the Taavoni's study, which showed that the sleep quality improved in 20% of women with menopause who consumed MO [26]. Additionally, Cases et al. demonstrated a 42% reduction in insomnia, 18% in anxiety, and 15% in

Table 1
Demographic and clinical characteristics of the participants.

		Herbal medicine group (n = 40)		Placebo group (n = 40)		*p*
		Mean	SD	Mean	SD	
Age (year)		57.53	4.83	58.2	4.88	0.833
		N	**%**	**N**	**%**	
Gender	Female	11	27.5	11	27.5	1.000
	Male	29	72.5	29	72.5	
Education	Illiterate	14	35	14	35	0.884
	Primary	8	20	11	27.5	
	Intermediate	8	20	5	12.5	
	Diploma	5	12.5	5	12.5	
	University	5	12.5	5	12.5	
Occupation	Housekeeper	11	27.5	9	22.5	0.651
	Occupied	10	25	11	27.5	
	Retried	13	32.5	10	25	
	Miscellaneous	6	15	10	25	
High blood pressure	Yes	30	75	26	65	0.329
	No	10	25	14	35	
Pulmonary disease	Yes	17	42.5	20	50	0.501
	No	23	57.5	20	50	
Diabetes	Yes	18	45	15	37.5	0.469
	No	22	55	25	62.5	
Hospitalization	Yes	36	90	29	72.5	0.045
	No	4	10	11	27.5	
Anesthesia	Yes	13	32.5	13	32.5	1.000
	No	27	67.5	27	67.5	
Surgery	Yes	13	32.5	13	32.5	1.000
	No	27	67.5	27	67.5	
Smoking	Yes	22	55	28	70	0.166
	No	18	45	12	30	
Number of engaged leg	1	32	80	30	75	0.590
	2	8	20	10	25	
Number of grafts	1	2	5	1	2.5	0.841
	2	35	87.5	36	90	
	3	3	7.5	3	7.5	
Cause of CABG	Myocardial infarction	22	55	19	47.5	0.745
	Unstable angina	13	32.5	14	35	
	Stable angina	5	12.5	7	17.5	

anxiety related symptoms in volunteers. In the mentioned study, the standardized extracts of MO, containing 7% rosmarinic acid and 15% hydroxycinnamic acid, was administered as a single dose of 600 mg daily for 15 days [12]. However, in the present study, with seven-day treatment period and the daily use of 1.5 g of *Melissa officinalis* dried leaf powder (without extraction), the levels of anxiety and insomnia reduced by 49% and 54%, respectively. Another study conducted by Cerny et al. revealed the effects of the combination of *Valeriana officinalis* and *Melissa officinalis* in the treatment of mild sleep disorders. In the above study, 33% of subjects in the combined medicine group were reported to achieve sleep quality improvement [44]. In the study performed by Alijaniha et al., 1 g/day of *Melissa officinalis* aqueous extract was administered for 14 days, there was a significant decrease in insomnia and anxiety in the MO group compared to placebo group [28]. In the Cases and Alijaniha studies that used MO extract, while the dose and duration of use were more than the present study, there was less reduction in sleep disturbance and patient anxiety than in this study. Although, despite the lack of uniformity of questionnaires and unequal doses of herbal medicine used in these studies, this comparison is not very accurate; it may be suggested that administration of the completely intact herb would be more effective than its extract. However this hypothesis needs to be investigated in more studies.

Moreover, the results of the present study showed the efficacy of *Melissa officinalis* for anxiety and sleep quality improvement in post-operative CABG patients.

Although, various studies have investigated the efficacy of *Melissa officinalis* alone or in combination with other medicinal plants, none had been performed on patients undergoing CABG. Amongst those studied, Akhondzadeh showed the efficacy and safety of *Melissa officinalis* extract on the cognitive function and agitation of patients with Alzheimer's disease in comparison to placebo [27]. Kennedy et al. showed the anti-anxiety effect of various doses of MO combined with Valerian as well as anti-anxiety and mood enhancer effects of single dose of MO through several studies [45–48]. Heidari et al. showed the antidepressant effects of this medicine in patients admitted after CABG [42]. The findings of the mentioned study indicated the beneficial effects of *Melissa officinalis* on anxiety and mental disorders, which were

Table 2
Comparison of anxiety scores between groups before and after the intervention.

Anxiety score[a]	group	N	mean	SD	SEM	*P*	95% CI[b]	
							Lower	Upper
Before intervention	Herbal medicine group	40	14.03	2.402	0.380	0.204	−0.429	1.979
	Placebo group	40	13.25	2.976	0.471			
After intervention	Herbal medicine group	40	7.15	1.272	0.201	0.001	−4.097	−1.953
	Placebo	40	10.18	3.129	0.495			

[a] Measured by Hospital Anxiety Depression Scale (HADS).
[b] 95% Confidence Interval of difference.

Table 3
Comparison of sleep quality scores between groups before and after intervention.

Sleep quality score[a]	group	N	mean	SD	SEM	*P*[b]	95% CI[c]	
							Lower	Upper
Before intervention	Herbal medicine group	40	26.43	4.987	0.788	0.041	0.102	4.748
	Placebo group	40	24.00	5.440	0.860			
After intervention	Herbal medicine group	40	12.03	1.368	0.216	0.001	−5.919	−2.981
	Placebo group	40	16.48	4.409	0.697			

[a] Measured by Mary's Hospital Sleep Quality Questionnaire (MHSQ).
[b] Mann-Whitney *U* test.
[c] 95% Confidence Interval of the difference.

Table 4
Comparison of sleep quality score changes between groups after intervention.

group	N	mean	SD	SEM	*P*	95% CI[a]	
						Lower	Upper
Herbal medicine group	40	14.4000	5.13809	0.81240	< 0.001	4.74075	9.00925
Placebo group	40	7.5250	4.42016	0.69889			

[a] 95% Confidence Interval of the difference.

in line with our results.

Overview of recent studies concerning the herb-drug interaction indicates no serious interaction for *Melissa officinalis*; however its mild sedative effects have to be considered when barbiturates or other sedative drugs are prescribed [49,50].

No specific side effects were found in this study. This result was consistent with the results of other studies [12,27,28]. Nonetheless, in a case study, it was observed that long-term use of this medicine might be associated with the risk of dependence and may lead to withdrawal symptoms, if it is suddenly discontinued [51].

Considering very few studies conducted for evaluating the herbal medicine after CABG and serious need for controlling psychologic disorders in such patients, the importance of the current study is revealed [52].

4.1. Limitations and implications

Some limitations of this study were the study's short duration, the evaluation of only one dose of MO and the unspecific assessment of disorders and this should be considered in future studies.

Regarding the current study results and other beneficial therapeutic effects indicated for MO, it could be concluded that this herbal medicine may be a good candidate for more comprehensive and detailed studies.

5. Conclusion

The results of current study indicate that seven- day consumption of 1.5 g/day dried leave powder of Melissa *officinalis*, reduces the anxiety, and improves the sleep quality of patients who underwent coronary artery bypass surgery by 49% and 54% respectively.

Considering various efficacy and lack of serious side effects observed in the current study, this herbal medicine might be a candidate for larger studies to be considered as a safe remedy for prevention of undesirable outcomes in CABG patients.

Authors' contribution

All research done by the authors.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

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