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Original Research

The Anxiolytic Effects of *Melissa officinalis* L. on Patients Awaiting Surgery: A Randomized Double-Blind Placebo-Controlled Clinical Trial

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Abstract

Preoperative anxiety is prevalent with up to 80% of patients experiencing this unpleasant feeling. *Melissa officinalis* L. is a famous herb with proposed medicinal activity including anxiolytic effects. Therefore, we aimed to consider the effect of *M. officinalis* in capsule formulation on preoperative anxiety in this clinical study. The plant material was standardized based on its essential oil content using gas chromatography/mass spectrometry apparatus. Then, 45 patients undergoing general surgery with American society of anesthesiology (ASA) physical status I or II were selected. By randomization, 23 and 22 patients were enrolled in treatment and placebo groups, respectively; to receive 500 mg dried powder of *M. officinalis* or placebo capsules, every 6 hours for 24 hours in this double-blind clinical study. They also completed the State Trait Anxiety Inventory for the second time and then proceeded to surgery. After the intervention, results showed a significant difference between the drug and placebo groups. The anxiety scores were 4.73 ± 1.17 and 5.81± 1.22 in the drug and placebo groups, respectively ($p = 0.01$). No adverse event was recorded. The results of this investigation show that *M. officinalis* capsule decreases preoperative anxiety in the patients who are undergoing general surgery and could be considered as a helpful supplement for these patients.

Keywords: Persian medicine; Anxiety; Herbal medicine; Anesthesia

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Introduction

Preoperative anxiety is a prevalent complication in the preoperative period with the incidence of 11-80 percent in adults, depending on the type of surgery, age, and education level [1,2]. It is claimed that preoperative anxiety can be considered as a risk factor for postoperative pain, nausea and vomiting [3]. Therefore, decreasing preoperative anxiety may help improve patient's postoperative outcome. In this regard, sedatives such as benzodiazepines are widely used to help reducing preoperative anxiety [4]. However, they may cause cognitive-psychomotor impairment, withdrawal symptoms and delirium, especially in the elderly and patients with underlying comorbidities [5]. Therefore, finding any new solution is welcomed. Medicinal herbs and traditional systems of medicine are considered as a source of potential hypotheses to find new remedies based on natural products.

In this regard, *Melissa officinalis* L. that is called as Lemon balm and *Badranjbouyeh* in English and Persian, respectively, from Lamiaceae family, is well known for its efficacy on decreasing anxiety, stress and insomnia and also improving patients' cognition and mood [6,7].

There are several components in *M. officinalis* like rosmarinic acid, ursolic acid and oleanolic acid that are responsible for its activities. Current investigations proposed these components act as antianxiety and antidepressant agents by several mechanisms of action including antioxidant activity by scavenging free radicals and decreasing oxidative stress; reduce effect on neuronal excitability by inhibiting GABA-transaminase; prevent oxidative deamination by inhibiting monoamine oxidase A; etc [8].

Furthermore, this plant has been widely used in Persian medicine, as sedative and a tonic for nervous system, with a history of over thousands of years [9,10]. With our understanding, no study has been conducted on the short-term effects of *M. officinalis* capsules on reducing anxiety in the patients undergoing general surgery.

Therefore, it is aimed to evaluate the efficacy of Lemon balm in a randomized clinical trial based on our primary hypothesis dealing with the effect of this plant on decreasing anxiety in the preoperative period. Also, our secondary hypothesis is *M. officinalis* blunts sympathetic response to surgery.

Materials and Methods

Ethical issues

The Ethic Committee of Tehran University of Medical Sciences has approved the study protocol of this clinical study (IR.TUMS.VCR.REC.1396.3806). Also, the study was registered at the Iranian Registry of Clinical Trials (IRCT) with the no. IRCT20141108019860N5. Furthermore, all the participants were informed about the process of the research and signed an Informed Consent Form.

Study design

This study was a randomized double-blind placebo-controlled clinical trial, in which 45 patients undergoing general surgery with American Society of Anesthesiologist criteria (ASA) physical status I or II in the Shariati Hospital of Tehran University of Medical Sciences were enrolled. Randomization was performed via block randomization generated by computer with four size blocks and a random number table assigned into drug and placebo groups. All the researchers, medical staffs, patients and statisticians were blinded about the content of the capsules (drug or placebo).

Formulation and standardization of drug and placebo

The adequate amount of *M. officinalis* dried leaves was purchased from Zargiah Farm of Firoozabad city, Fars province, south of Iran. The leaves were recognized and authenticated by botanist (Gholamreza Amin) at the Herbarium Center of the School of Pharmacy, Tehran University of Medical Sciences Tehran, Iran (voucher number: PMP-1349). *M. officinalis* capsules (hard gelatin capsules) contained 500 mg dried leaves powder of the plant. Each of the 8 capsules were packaged with a label indicating the instruction for use and the confidential code. Placebo capsules were made containing 500 mg of wheat starch powder in the same capsules as the drug's ones and their packaging was completely identical in shape to *M. officinalis* capsules.

For standardization of the content of *M. officinalis* leaves, in advance, the essential oil of the leaves was obtained via Clevenger apparatus method (using 200 g sample of the bulk powder in a 5 lit balloon, for 4 hours operation). Then, a Gass Chromatography apparatus (Agilent 7890) connected to Mass Selective Detector (Agilent 5975C) (GS/MS) was used to analyze the content of the essential oil of *M. officinalis* leaves. In this operation, a fused silica capillary column (Agilent DB-IMS: 30m, 0.25 mm i.d. and film thickness 0.25 μm) and helium as the carrier gas (at 1 mL/min flow rate) were used. Also, the detector was regulated in EI mode (70 eV) and 30-600 m/z mass range with 280°C interface temperature. At the end, libraries including NIST, Willy mass spectra and Adams libraries spectra were used for identification of the components of the essential oil.

Intervention

Inclusion criteria for the patients who enrolled in this study include 20–80 years age for either sex, ASA physical status I or II, clear consciousness, and the

ability to communicate with medical staffs. Exclusion criteria included patients with history of valvular heart disease, congestive heart failure, kidney and liver diseases, psychiatric disorders history, uncontrolled blood pressure, laryngoscopy grade ≥ 3, and also the patients who be scheduled for a nasal procedure or have a major or high-risk surgery.

Demographic data of the participants were assessed and documented. At first, in the enrollment process, patients completed the State Trait Anxiety Inventory (STAI). In the preparation room, they received two capsules of (*M. officinalis*) or placebo every 6 hours for 24 hours and then, they completed the STAI again for the second time. They then proceeded to surgery.

Statistical analysis

Following completing data collection, IBM SPSS statistics version 25 was used for data analysis. The Mann-Whitney test was used to compare age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), visual analogue scale (VAS), oxygen saturation, and anxiety between the two groups. For comparing sex and ASA between the two groups, the Fisher exact test was used. Following analysis of the results, quantitative and qualitative variables are described as mean ± SD [median (min, max)] and frequency (percent). In the reports of the results in all the tests, the *p*-value less than 0.05 was considered statistically significant.

Results

Formulation of the drug/ placebo and standardization

The drug and the placebo were made exactly the same, so that they could not be distinguished from each other for the patients and the research medical team. *M. officinalis* that used to make drug capsules in this clinical study yielded 1% of essential oil. The GC/MS spectra of the analyzing the essential oil of *M. officinalis* is shown in figure 1. Subsequently, the detected and identified components of this essential oil are presented in table 1.

Efficacy evaluation

Flow diagram (CONSORT) of the clinical study enrolling 45 subjects *(drug group;* n = 23 and placebo group; n = 22) is demonstrated in figure 2. Table 2 shows the baseline and demographic characteristics such as age, sex, BMI, ASA, DBP, HR, oxygen saturation and STAI score that were no significant differences between the two groups ($p > 0.05$). After intervention, the mean level of anxiety based on STAI score in the drug and placebo groups were 4.73 ± 1.17 and 5.81± 1.22; respectively which the difference was statistically significant ($p = 0.01$) (Table 3).

Safety

Both drug and placebo were well tolerated and there was no observed or reported side effects by the patients for them in this study.

Discussion

Preoperative anxiety is prevalent with several intraoperative and postoperative complications including delay in healing, higher required doses of anesthetic agents, prolonged hospital lengths of stay and higher need for opioids [11]. Sedatives and anxiolytics are administered frequently before surgery. However,

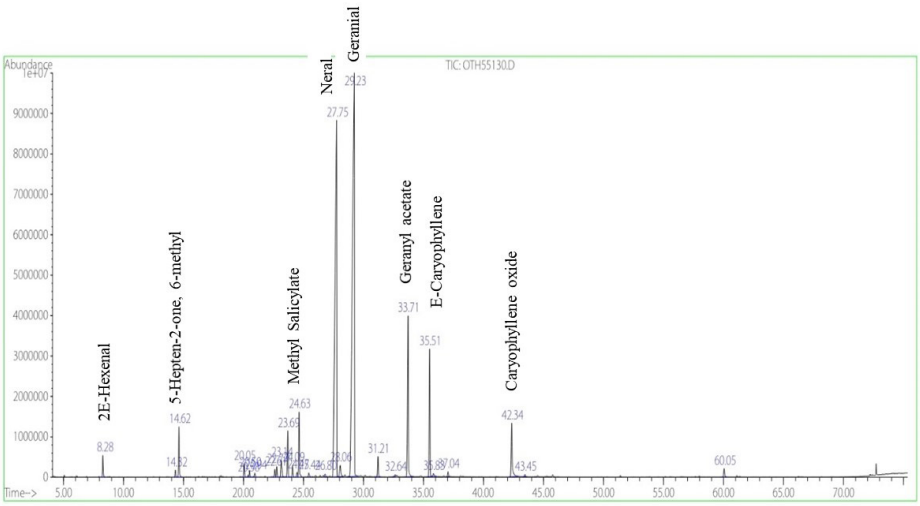

Figure 1. The GC/MS of *M. officinalis* essential oil constituents

Table 1. Chemical composition of essential oils from *M. officinalis* by GC/MS

KI	%	RT	Components	No
860	0.78	8.28	2E-Hexenal	1
987	0.28	14.32	1-Octen-3-ol	2
993	1.93	14.62	5-Hepten-2-one, 6-methyl	3
1106	0.25	20.50	Linalool	4
1159	0.90	23.14	Trans-Chrysanthemal	5
1178	0.47	24.09	Isoborneol	6
1189	2.63	24.63	Methyl salicylate	7
1234	0.16	26.80	Nerol	8
1255	31.64	27.75	Neral	9
1261	0.72	28.06	Geraniol	10
1286	39.76	29.23	Geranial	11
1330	0.77	31.21	Methyl geranate	12
1362	0.08	32.64	Ethyl nerolate	13
1386	6.97	33.71	Geranyl acetate	14
1428	5.20	35.51	E- Caryophyllene	15
1465	0.20	37.04	-Humuleneα	16
1596	2.93	42.34	Caryophyllene oxide	17
	95.66		Total Identified	

they carry risks such as hemodynamic instability and respiratory depression [12]. Therefore, an affordable and safe herbal medicine with anxiolytic effects before anesthesia is favorable. In Persian medicine, *M. officinalis* is a popular medicinal herb that has been widely used for treatment of several psychological disorders including anxiety, depression stress and nervous sleeping disorders [13]. Furthermore, no dangerous or vital side effects of this plant have been reported and US-FDA has put it on the list of Generally Recognized as Safe (GRAS) [14].

There are many studies that show the efficacy of this plant on anxiety. In a clinical trial, *M. officinalis* efficacy on sleep quality and anxiety were studied on patients undergoing coronary artery bypass graft surgery. After 7-days of treatment, 1.5 g/day dried leaf powder of the plant decreased anxiety and improved the sleep quality in the patients, 49% and 54% respectively [9]. In another clinical study on patients with chronic stable angina, taking 3 g/day *M. officinalis* supplement for 8-weeks significantly reduced depression, anxiety, stress, and sleep disorder [7]. In another study a significant decrease in heart palpitation after 14 days of consuming 1 g/day of lyophilized aqueous extract of Lemon balm compared to placebo group was obtained [15]. In a study conducted by Cases et al., 42%, 18% and 15% reduction in insomnia, anxiety, and anxiety-related symptoms was showed, respectively, after 15 days of taking standardized extracts of *M. officinalis* [16]. In a crossover study, performed on 18 healthy volunteers, the effect of two separate single doses of a standardized *M. officinalis* extract (including 300 mg and 600 mg) and a placebo was evaluated on separate days separated by a 7-day washout period. The results demonstrated that the 600-mg dose of the plant extract decreased the negative mood effects of the Defined Intensity Stressor Simulation (DISS), with significantly decreased self-ratings of alertness, enhanced self-ratings of calmness and improved mild-to-moderate anxiety subjects [17].

Although several studies have assessed the efficacy of *M. officinalis* solely or in combination with other ingredients, this study is the first one that has been performed on patients awaiting general surgery. Therefore, this study is the first attempt to evaluate the efficacy of lemon balm to reduce preoperative anxiety. There are three theories about the mechanisms of action of *M. officinalis* on anxiety and relevant neurological disorders. Several experimental investigations including *in vitro* and *in vivo* studies have revealed *M. officinalis* is a GABA-T inhibitor and responsible major active constituents for this activity are rosmarinic acid, ursolic acid and oleanolic acid [7]. Furthermore, in various investigations, *M. officinalis* decreased corticosterone level as main biomarker of stress [18] and demonstrated serotonergic activity [19]. Also, there are no approved important adverse effects for *M. officinalis* and therefore, this plant can be used as a safe treatment compared with the other anxiolytic drugs like benzodiazepines.

The small sample size of this study is the main limitation of this clinical trial. In future studies, more patients should be enrolled to better evaluate the efficacy of this traditional remedy.

Conclusion

The present study demonstrated the clinical efficacy of the capsules containing *M. officinalis* dried powder in decreasing preoperative anxiety. The results support this preparation as a potential anxiolytic natural

Table 2. Comparison of demographic information in two groups of drug and placebo

Parameter		Placebo group	Treatment group	*p*-value
Age		38.04±8.81 [38(25,55)]	40.26±10.10 41(27,77)]	0.60
Sex	1 (male)	11(50%)	12(52.2%)	0.88
	2 (Female)	11(50%)	11(47.8%)	
BMI		24.83±3.72 [23.40 (19.15,31.49)]	24.70±4.96 [24.77 (17.10,37.78)]	0.85
ASA	1	24(77.3%)	25(82.6%)	0.72
	2	11(22.7%)	10(17.4%)	
SBP		138.86±16.52 [145(108,164)]	127.39±14.47 [124(104,154)]	0.02
DBP		96.50±16.18 [97.5(67,127)]	94.52±7.23 [94(82,112)]	0.70
HR		82.18±17.73 [78.5(49,110)]	75.95±13.31 [77(58,103)]	0.20
Oxygen saturation		98.36±1.17 [98(96,100)]	98.39±0.58 [98(97,99)]	0.84
VAS		5.22±0.86 [5(4,7)]	4.52±1.30 [4(2,8)]	0.02

Quantitative and qualitative variables are described as mean ± SD [median (min, max)] and frequency(percent)
ASA, American Society of Anesthesiologist criteria; DBP, Diastolic Blood Pressure; HR, Heart Rate; SBP, Systolic Blood Pressure; VAS, Visual analog scale

Table 3. Comparison of patients' anxiety based on STAI index in two groups of drug and placebo after intervention

Parameter	Placebo group	Treatment group	*p*-value
Anxiety (STAI index)	5.81±1.22 [6 (4,8)]	4.73±1.17 [5(3,7)]	0.01 (for STAI index difference)

Quantitative and qualitative variables are described as mean ± SD [median (min, max)] and frequency (percent)

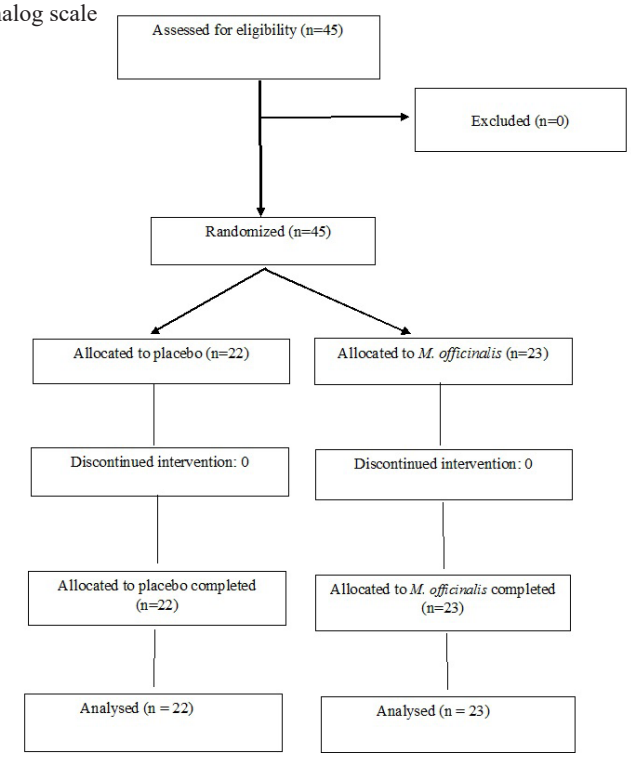

Figure 2. CONSORT Flow Diagram of randomized double-blind controlled clinical

and traditional remedy for patients awaiting general surgery.

Conflict of Interests

None.

Acknowledgments

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