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Original Article

Evaluation of the Effect of *Melissa officinalis* L. on Cognitive Impairments in major Depressive Disorder Patients Treated with Electroshock Therapy: A Randomized Clinical Trial

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Abstract

Background and aims: Cognitive disorders are among the most common complications of electroconvulsive therapy (ECT) in patients with major depression. The present study aimed to evaluate the effect of *Melissa officinalis* L. (lemon balm) capsules on cognitive impairments in depressed patients treated with ECT.

Methods: This randomized clinical trial was conducted on 70 patients with significant depression undergoing ECT. Intervention groups were treated with medicinal capsules containing 500 mg of dried *M. officinalis* leaf powder administered three times a day, and the control group received wheat starch capsules as a placebo administered three times a day. Data were analyzed using independent t-tests, repeated measures ANOVA, and Bonferroni post-hoc tests with SPSS version 24.

Results: There was no statistically significant difference between demographic variables between groups ($P>0.05$). The MMSE score before the intervention was 24.46±2.11 and 24.86±2.14 in the intervention and control groups, respectively. After the intervention, the MMSE scores were 24.21±2.12 and 24.10±2.26 in both groups, respectively. The MMSE score at the follow-up in the intervention and control groups was 24.66±2.09 and 25.71±1.97, respectively. Moreover, there was no significant interaction between the group and MMSE before the intervention, after the intervention, and at the follow-up ($P=0.356$).

Conclusion: The administration of dried M. officinalis leaf powder demonstrated no significant effect on improving cognitive impairments after ECT. Therefore, the use of the M. officinalis leaf extract capsule for cognitive impairments after ECT in more extended treatment periods should be examined in future studies.

Keywords: Medicinal herbs, Cognitive impairments, Major depression, Electroshock therapy

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Introduction

Major depressive disorder (MDD) is one of the most common, costly, and debilitating mental disorders across the world (1). MDD is a highly prevalent mental health condition that presents interregional differences in its prevalence and sociodemographic correlates. Additionally, it is highly comorbid with other physical and mental health issues (2). MDD impairs the quality of life, and older age, lower education status, poor economic situation, unemployment, worse subjective perception of health, overweight, and mental health struggles are attributed to lower quality of life (3). Symptoms of this disease include discomfort, lack of interest in daily activities, decreased energy levels, feelings of guilt, decreased self-confidence, lack of concentration and cognitive impairment, anxiety, sleep disorders, and sexual dysfunction (4, 5). Depression has adverse impacts on health levels. It increases smoking and alcohol consumption, decreases adherence to diet and healthy lifestyle, and adversely affects health behaviors. It also has harmful consequences for the lives of affected people; thus, most affected people have problems performing daily activities, work, and social activities. In these patients, the risk of suicide is high, which has a tremendous economic burden on the healthcare system (6).

Given that MDD is a debilitating disease with a high risk of suicide and relapse, appropriate and effective treatment is essential. Medication and electroconvulsive therapy (ECT) are two treatments of choice for MDD (7). However, more than 30% of patients do not recover with drug therapy, and due to its high effectiveness, ECT is the gold standard treatment for patients with MDD (8). Despite the efficacy of ECT on depression and bipolar disorder, there are concerns about ECT-related side effects and clinical application. Memory impairment is one of the unpleasant experiences of patients (9). After ECT, patients who receive electric shocks express that cognitive impairment is the worst side effect of the treatment (10).

Although various strategies have been implemented to eliminate or reduce this complication, ECT has yet to achieve complete success (11).

Frequently, herbal medicines enhance memory and boost pro-cognitive abilities (12). Lemon balm (*Melissa officinalis* L.) is a plant from the Lamiaceae family (13, 14). It is one of the most popular and widely used medicinal plants in Central and Southern Europe, the Mediterranean, and West Asia. In addition, it is extensively used in traditional Asian medicine to treat numerous psychiatric conditions. Lemon balm can produce anti-anxiety, antidepressant, anti-insomnia, and neuroprotective effects (15, 16). Further, lemon balm extract improves mood, cognitive function, and memory function (14). Due to the side effects of chemical drugs, medicinal plants have received special attention in recent years . The effect of the *Lamiaceae* family on the treatment of neurodegenerative disorders and cognitive disorders has been suggested in these studies (17, 18). Accordingly, this study aims to investigate the association between *M. officinalis* capsule treatment and cognitive status.

Materials and Methods

Trial Design and Setting

This randomized clinical trial was performed on all depressed patients in the age range of 18–65 years admitted to the psychiatric wards of Hajar Shahrekord Hospital, who were treated with electric shock in 2022.

Participants

The participants of this study included MDD patients who were treated with ECT and were experiencing cognitive impairments and referred to Shahrekord Hajar Hospital with a diagnosis of cognitive impairments by a psychiatrist based on Petersen criteria, with a Clinical Dementia Rating (CDR) score of 0.5 (19). Participants would be eligible if they were 18–65 years old, did not have a history of allergy to the *Lamiaceae* family, and had physical illness leading to cognitive disorders, such as head trauma, dementia, mental retardation, and epilepsy, and consumed selective serotonin reuptake inhibitor drugs (according to the opinion of the psychiatrist). However, participants were excluded if they suffered from other mental disorders in addition to depression, withdrew from the study, experienced stressful events affecting the mood of the patient during the study, and used antidepressants (except selective serotonin reuptake inhibitors).

Sample Size and Sampling Method

This study was a double-blind clinical trial. Based on the sample size formula, 80 patients were included in the study. According to the inclusion and exclusion criteria, 10 of them dropped out of the sample size. Finally, 70 patients were evaluated in 2 groups of 35 people (Figure 1).

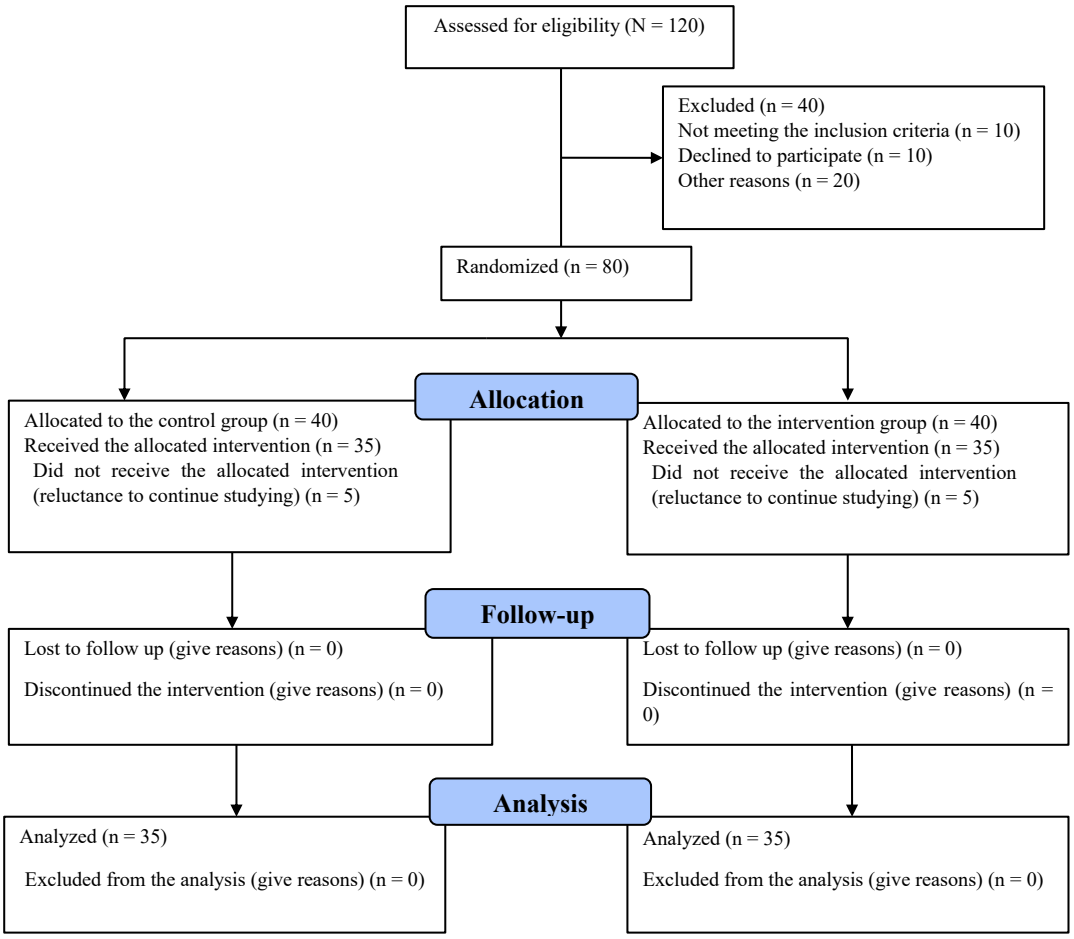

Figure 1. CONSORT Diagram to Illustrate the Flow of Participants Through the Trial

After sampling, the patients were placed in the intervention and control groups, with block randomization and blocks of six .

Randomization

Randomization was performed using block randomization with a fixed block size of 2 to ensure balanced allocation between study groups. In total, forty blocks were created, each consisting of two participants (one assigned to the intervention group and one to the control group). The sequence within each block was randomized independently. Consequently, all 80 participants were allocated in a 1:1 ratio to the intervention and control groups.

Blinding

The trial was double-blind. Participants and study personnel responsible for administering capsules or assessing outcomes were blinded. Capsules (M. officinalis 500 mg or placebo) were prepared and coded by an independent individual.

Preparation of Drug and Placebo Capsules

Lemon balm capsules were prepared from 500 mg of dried, ground, and sifted lemon balm leaf in gelatin capsules. Each package contained 64 capsules with a clear and coded label. The placebo capsule contains 500 mg of starch powder in a gelatin capsule placed in the same packaging as the herbal medicine (20). It should be noted that patients in both groups received common and standard depression-related treatment.

Measurement of Total Phenolic Content

Total phenolic content was measured using the Folin-Ciocalteu assay. The extract was prepared at a concentration of 10 mg/mL. To this end, 0.5 mL of the extract was mixed with 2.5 mL of 0.2 normal Folin-Ciocalteu and stirred for 5 minutes. Then, 2 mL of the 20% sodium carbonate solution at 75 g/L was added. The absorbance of the samples was measured with an ultraviolet spectrophotometer at 760 nm against methanol (as a blank) after they were left at room temperature for 2 hours. The total phenolic content in the extract was determined using a standard curve in mg gallic acid/g of extract.

Measurement of Total Flavonoid Content

The total flavonoid content of the extract was evaluated using the colorimetric method. The extract was prepared at a concentration of 10 mg/mL. Next, 0.5 mL of the extract was dissolved in 1.5 mL of methanol, and 0.1 mL of 10% aluminum chloride was added. Subsequently, 0.1 mL of the 1 M potassium acetate solution and 2.8 mL of distilled water were added to the mixture and left for 30 minutes at room temperature. The absorbance of the resulting mixture was determined at a wavelength of 415 nm using a dual visible-ultraviolet spectrophotometer. Total flavonoid content was measured using the standard curve in mg quercetin/g extract.

Determination of Radical Activity of Hydrogen Peroxide

To determine the ability to inhibit H_2O_2, lemon balm (2 mg/mL) was dissolved in 3 mL of the 0.1 M phosphate solution (pH = 7.4) and mixed with 600 µL of the 43 mM H_2O_2 solution previously prepared in the same buffer. The blank solution was prepared in the same way without the presence of H_2O_2. The absorbance of the solutions was measured at a wavelength of 230 nm to detect the concentration of H_2O_2. Gallic acid was used as the reference. H_2O_2 scavenging activity was calculated using the following equation:

$$H_2O_2 \text{ scavenging activity } \% = \frac{A_1 - A_0}{A_0} \times 100$$

where A0 and A1 denote the absorption of control and the absorption of solution in the presence of extract and gallic acid, respectively.

Measurement of Antioxidant Capacity

The 2,2-diphenyl-1-picrylhydrazyl radical scavenging was utilized to investigate the antioxidant capacity. This method is based on its hydrogenation ability. It is used to evaluate free radical activity, and one of its advantages is the lack of dependence on the sample's polarity.

In addition, 1 mL of the 0.1 mM 2,2-diphenyl-1-picrylhydrazyl solution was added to 1 mL of the extract, and the mixture was shaken gently and left in the dark for 15 minutes. Then, the absorbance of the mixture was read by a UV spectrophotometer at 517 nm against methanol (as a blank). Ascorbic acid was used as a standard.

Intervention and Control Groups

The intervention group was treated with the powder of *M. officinalis* capsules at 500 mg three times a day for one month. To the same extent, the control group received wheat starch capsules.

Although no side effects have been reported for this capsule in previous studies, the drug side effects form was also used. After the intervention and three months after, the cognitive and memory status was measured using the Mini–Mental State Examination (MMSE), and the patient was instructed to take the capsule on time. A follow-up form was given to them to note down the use of medication, and during this time, the patients would be followed up by calling them.

Subjective and Objective Cognitive Assessment

The MMSE, which was developed by Folstein in 1975, is one of the standard tests to evaluate cognitive status and addresses six domains, including orientation, registration, attention, calculation, remembering, language, and design. The highest attainable score on this test is 30. Stores on the scale range between 0 and 30, with lower scores indicating more significant cognitive impairment (21). Foroughan et

al reported its reliability with Cronbach's alpha method of 0.78, and the cut-off point of 21, with sensitivity of 0.90 and specificity of 0.84, was determined as the ideal cut-off point for distinguishing the healthy group from the patients (22).

Data Analysis

Intergroup comparisons were conducted at baseline using an independent t-test, and the ANCOVA test was utilized to compare the groups after the treatment and at the follow-up. Moreover, intra-group comparisons were performed using repeated measures of ANOVA in SPSS (version 24), and the significance level was considered to be less than 0.05.

Results

The results of the herbal drug assay are provided in Table 1.

The antioxidant ascorbic acid was obtained at 91.20 ± 0.29. The inhibition activity of H_2O_2 compared to gallic acid was 16.91 ± 2.86% at a concentration of 2 mg/mL.

The mean age of participants in the intervention group was 40.39 ± 8.91 years, and in the control group, 42.38 ± 11.39, with no statistically significant difference ($P = 0.44$). In addition, the number of ECT sessions in the control group was slightly higher than in the intervention group. Nonetheless, the difference was statistically insignificant (7.66 vs. 9.97, $P = 0.06$, Table 2).

There was no statistically significant difference between the two groups in terms of gender (48.6 vs. 51.4, $P = 0.1$) and occupation (40.6 vs. 48.6, $P = 0.08$).

Likewise, no significant difference was found in the education level ($P = 0.11$), history of hospital admission ($P = 0.80$), family history of disease ($P = 0.22$), and ECT history ($P = 0.40$) between the two groups (Table 3).

The mean scores of MMSE in the intervention and control groups were 24.46 ± 2.11 and 24.86 ± 2.14, respectively, at baseline without any statistical difference. These scores decreased to 24.21 ± 2.12 and 24.10 ± 2.26 in the intervention and control groups after the intervention, indicating no statistical difference between the groups. The MMSE score at the follow-up in the intervention and control groups was 24.66 ± 2.09 and 25.71 ± 1.97, respectively. Moreover, no significant interaction was observed between the group and MMSE before or after the intervention and during the follow-up ($P = 0.356$).

Further, intra-group comparisons showed that the difference was statistically significant in the intervention ($P = 0.001$) and control ($P < 0.001$) groups (Table 4).

The changes in the mean MMSE score during the study in the two groups are illustrated in Figure 2.

Regarding cognitive status dimensions (Table 5), a significant change was found in orientation ($P = 0.001$) and memory 1 after the follow-up ($P = 0.003$) after the intervention. However, the memory improvement was observed after two months ($P < 0.001$).

Discussion

This study investigated the effect of lemon balm capsules on the cognitive disorders of patients with major depression treated with ECT.

Our results revealed that no interaction was noted between the group and the MMSE score before and after the intervention and during the follow-up period ($P = 0.356$), indicating that the lemon balm capsule had no impact on the cognitive disorders of patients with major depression treated with ECT.

In line with our results, the results of a randomized clinical trial of a combined extract of sage, rosemary, and *M. officinalis* on the memory of normal healthy subjects using immediate and delayed word recall demonstrated that there was no significant difference between the case and control groups (23). In addition, in another study, the daily administration of the *M. officinalis* extract containing 500 mg of rosmarinic acid represented no significant differences in cognitive measures in patients with Alzheimer's disease (24).

The findings of our study are consistent with those of a clinical trial conducted by Noguchi-Shinohara et al. The trial evaluated the impact of the *M. officinalis* extract on cognitive function in 323 older adults without dementia. Based on the results of this trial study, no significant variations were found in cognitive measures between the placebo and *M. officinalis*-treated groups from baseline to 96 weeks. Additionally, there were no noticeable differences in physical and neurological actions, vital signs, or hippocampal volume between the two groups (25).

In contrast with the results of our study, those of the clinical trial performed by Taghizadeh et al showed that the total scores of the Wechsler Memory Scale-Revised

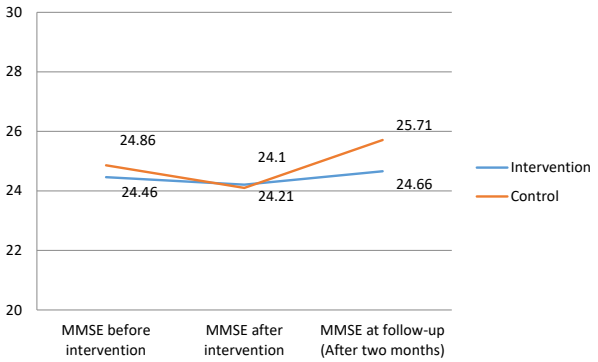

Figure 2. Mean MMSE Score in the Two Intervention and Control Groups During the Study Period
Note. MMSE: Mini–Mental State Examination

Table 1. Results of Herbal Drug Assay

Name of the Plant	Total Phenolic Content	Total Flavonoid Content	Antioxidant Capacity	H_2O_2 Radical Scavenging Activity (%)
Lemon	13.93 ± 0.95	25.41 ± 0.07	68.33 ± 0.48	5.27 ± 0.73

Note. H_2O_2: Hydrogen peroxide.

and subscales, including immediate hearing, immediate memory, immediate vision, and working memory, increased after taking extract tablets containing *M. officinalis* (26). Moreover, in patients with Alzheimer's disease, the *M. officinalis* extract revealed better outcomes on cognitive function than the placebo group (27). In a study conducted by Kennedy et al, cognitive performance was evaluated using the CDR computerized test battery and two serial subtraction tasks. The tests were performed immediately before dosing and 1 hour, 2.5 hours, 4 hours, and 6 hours after dosing. The results indicated that there was no significant difference in any of the criteria of the cognitive score, including individual task scores, cognitive factor scores, serial subtraction scores, and mood scale scores. However, after the administration of 600 mg of *M. officinalis* extract, the accuracy and attention of the participants improved in individual task outcome measures (28). These contradictions may be due to the difference in the *M. officinalis* formation that was applied or the differentiation in the patient population and cognitive function tools. Contrary to our findings, the results of Buchwald-Werner et al reported that the consumption of 300 mg of the lemongrass extract after 1 hour and 3 hours improved cognitive disorders. Cognitive status was evaluated by the Core Battery of CDR, a computerized cognitive assessment system (29).

Previous studies suggested that *M. officinalis* L. can protect the brain against cognitive impairment caused by ECT in MDD patients. This is due to its antioxidant, anti-inflammatory, and neurotransmitter-modulating effects. *M. officinalis* L. is known for its ability to regulate acetylcholine levels, which can improve memory and attention. Lemon balm contains compounds that prevent the breakdown of acetylcholine, a key neurotransmitter involved in learning and memory (30, 31). Enhancing cholinergic activity can improve cognitive functions related to attention and memory. Lemon balm also interacts with the GABAergic system, which regulates mood and cognitive processes. By modulating GABA receptors, lemon balm can have anxiolytic effects and reduce anxiety and stress, indirectly improving cognitive function (32). Although there have been few clinical studies in this field, the differences in the results of the studies can be due to the duration of *M. officinalis* L. consumption. In addition, the method of plant administration may

Table 2. Comparison of Age, Disease Duration, and Number of Electric Shocks Between Groups

Variable	Intervention Mean ± SD	Control Mean ± SD	*P* value
Age (year)	40.39 ± 8.91	42.38 ± 11.39	0.44
Disease duration	9.18 ± 8.18	9.00 ± 3.95	0.20
Number of electric shocks	6.97 ± 1.96	7.66 ± 0.77	0.06

Note. SD: Standard deviation.

Table 3. Comparison of Demographic Variables Between Groups

Variable		Intervention, n (%)	Control, n (%)	*P* value
Gender	Male	17 (48.6)	18 (51.4)	0.1
	Female	18 (51.4)	17 (48.6)	
Occupation	Jobless	17 (48.6)	16 (40.6)	0.08
	Employed	1 (2.9)	2 (5.7)	
	Self-employed	17 (48.6)	17 (48.6)	
Education level	Illiterate	6 (17.6)	15 (42.9)	0.11
	Elementary	14 (41.2)	11 (31.4)	
	High school diploma	13 (38.2)	9 (25.7)	
	Academic	1 (2.9)	0 (0)	
History of hospital admission	Yes	22 (62.9)	23 (65.7)	0.80
	No	13 (37.1)	12 (34.3)	
Family history of the disease	Yes	16 (45.7)	11 (31.4)	0.22
	No	19 (54.3)	24 (68.6)	
ECT history	Yes	28 (80.0)	25 (71.4)	0.40
	No	7 (20.0)	10 (28.6)	

Note. ECT: Electroconvulsive therapy.

Table 4. Comparison of MMSE Scores Between Groups

Variable	Intervention	Control	Interaction Between Group and MMSE
MMSE before the intervention	24.46 ± 2.11	24.86 ± 2.14	df = 1 F = 0.865 *P* = 0.356
MMSE after the intervention	24.21 ± 2.12	24.10 ± 2.26	
MMSE at follow-ups (after two months)	24.66 ± 2.09	25.71 ± 1.97	
Repeated measures ANOVA within two groups	F = 8.96 *P* = 0.001	F = 20.88 *P* < 0.001	

Note. ANOVA: Analysis of variance; MMSE: Mini–Mental State Examination.

Table 5. Comparison of the Orientation, Memory 1, Attention, and Memory 2 Between Groups

Variable	Intervention	Control	*P* value
Orientation before the intervention	6.46±115	8.14±0.96	0.001
Orientation after the intervention	6.46±1.15	7.83±1.10	0.001
Orientation at the follow-up	6.51±1.15	8.34±0.86	0.001
***P*-value**	0.16	0. 06	---
Memory 1 before the intervention	2.71±0.46	2.66±0.50	0.62
Memory 1 after the intervention	2.66±0.54	2.60±0.55	0.66
Memory 1 at the follow-up	2.71±0.46	2.97±0.17	0.003
***P*-value**	0.04	0. 07	---
Attention before the intervention	3.89±1.42	3.71±1.67	0.07
Attention after the intervention	3.79±1.40	3.51±1.77	0.46
Attention at the follow-up	3.89±1.42	3.67±1.67	0.99
***P*-value**	0.23	0.99	---
Memory 2 before the intervention	11.40±0.98	11.34±0.86	0.80
Memory 2 after the intervention	11.31±1.04	10.96±1.18	0.184
Memory 2 at the follow-up	11.54±0.78	11.68±0.54	0.377
***P* value**	0.02	<0.001	---

have affected the results of this study, and better results would have been obtained if the plant extract had been examined at different doses. Contradictions in examining and challenging the results of our study and other research reveal that the effect of *M. officinalis* capsules on cognitive disorders needs further investigation in the future. It is also suggested that studies with another form of *M. officinalis* and more substantial cognitive evaluation be conducted to confirm our findings.

Strengths and Limitations of the Study

Our results support the future replication of this study using the leaf extract instead of the leaf powder of *M. officinalis*, a more extended treatment period, and more powerful tools to investigate cognitive disorders. Neuropsychological evaluation and objective cognitive performance evaluation should be performed as well. Failure to evaluate the effective compounds of *M. officinalis* and inability to investigate different doses and side effects of the plant were among the limitations of this study.

Conclusion

Our findings demonstrated that *M. officinalis* dried leaf powder administration had no significant effect on cognitive impairments after ECT. It is recommended that future studies examine the use of *M. officinalis* capsules from the extract on cognitive impairments after ECT in more extended treatment periods.

Authors' Contribution

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Funding acquisition: Masoud Nikfarjam.
Investigation: Iraj Baratpour.
Methodology: Masoud Nikfarjam, Hadi Raeisi.
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Visualization: Fatemeh Kaviani.
Original draft writing: Masoud Nikfarjam, Iraj Baratpour, Fatemeh Kaviani, Kimia Torabi, Zahra Lorigooini.
Writing–review & editing: Masoud Nikfarjam, Kimia Torabi, Zahra Lorigooini.

Competing Interests

The authors declare that they have no conflict of interests.

Ethical Approval

This study was conducted after the approval of the Ethics Committee of Shahrekord University of Medical Sciences (ethical code IR.SKUMS.REC.1400.074 and IRCT code IRCT20180613040083N1).

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