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Research Paper: Exploring the Therapeutic Effects of Transcranial Direct Current Stimulation on Sleep Quality Among Patients Under Methadone Maintenance Treatment

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ABSTRACT

Background: Patients under Methadone Maintenance Therapy (MMT) are susceptible to several problems, including sleep disturbances and risk of relapse. The present study aimed to assess the effect of transcranial direct current stimulation (tDCS) on sleep quality of addicts under MMT.

Methods: This clinical trial was conducted on 27 male patients who underwent maintenance methadone therapy in MMT clinics of Mashhad City, Iran. They were divided into the experimental and sham groups. The experimental group received seven 20-min sessions of tDCS every other day. In the sham group, the electrical current was delivered for a few seconds, but the electrodes were remained to the end of the session. Sleep quality was measured at baseline, during, and after the intervention by Pittsburg Sleep Quality Index (PSQI). The obtained data were analyzed by descriptive statistics such as mean and standard deviation and inferential statistics, such as t test, Chi-square, Mann Whitney, and Fischer exact test in SPSS v. 25.

Results: The difference between the two groups after tDCS in sleep duration was significant (P=0.04). In the experimental group, the total score of sleep had a reducing trend (P<0.000), while in the sham group, the overall score in 3 phases of evaluation had no significant change (P=0.19). However, the rate of inappropriate sleep quality was not significant between the two groups after the intervention (P=0.12).

Conclusion: This trial demonstrated the positive effect of tDCS on sleep quality in patients under MMT programs. Further studies are needed to confirm our findings.

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1. Introduction

International reports revealed that opioid use has approximately 0.7% prevalence in adults. Opioids are accounted for the second form of the illicit drugs used in the world. Illegal drug use is considered a serious problem in a variety of developed and developing countries such as Iran. These forms of drug use are the main risk factors for social and public health challenges [1-3]. A wide range of therapeutic approaches could be employed to reduce illicit drug use. Among them, Methadone Maintenance Therapy (MMT) has been emerged as an effective therapeutic procedure for decreasing individual and public harms, which are linked to illicit drug use [2, 4].

Despite doing various practical implementation of MMT, several questions and challenges have remained unclear. Sleep problems are common among opioid abusers who were treated with MMT [5]. These problems affect their quality of life and increasing the risk of substance relapse [6, 7]. Therefore, investigating the effective and safe methods seems necessary to relieve sleep problems among these patients.

The specific brain oscillations by applying transcranial electrical stimulation techniques to enhance sleep quality and memory processes have become an intriguing field of research [8]. Modulating brain areas, which are involved in the sleep process, can be effective in sleep dynamics and promote sleep quality [9, 10]. Based on the conducted studies, there is a link between electrical stimulation of the specific areas of cortex and sleep quality [11].

One of these neuromodulatory techniques is transcranial direct current stimulation (tDCS). In this technique, low-intensity electric currents are applied. It is a cost-effective and non-invasive technique without severe side effects, which applies to both healthy subjects and patients with neurologic symptoms [12-16]. Based on Roizenblatt et al. study [17], tDCS increases sleep efficiency via sleep modulation, and in partic-ular, modulation of primary M1 activity in fibromyalgia. Also, the evidence suggests that tDCS might affect sleep quality and neurocognition in euthymia and is useful for relapse prevention [18]. Besides, bilateral anodal tDCS stimulation for 10 sessions (20 min each, 5 per week) demonstrated potential therapeutic effects on depression level improvement and sleep quality in patients with Parkinson disease [19].

In another study, tDCS was applied during REM (rapid eye movement) sleep, with no apparent consolidation benefit for neutral declarative memories [20]. The direct effect of tDCS stimulation and the indirect impact on sleep quality may be favorable in subjects under MMT through bilateral anodal stimulation, over DLPFC (dorsolateral prefrontal cortex), premotor, and M1 areas. Also, tDCS can change the cortical excitability and increases brain excitability by altering the resting potential of cortical neural cells [19, 21]. The safety of tDCS in adults has been well documented and confirmed, and several reported side effects were mild and transient. Most reported adverse effects include headache, and fatigue, and burning sensation and itchiness under the electrodes [22, 23].

These lines of evidence emphasize the importance of tDCS on sleep quality and mental health, suggesting that tDCS may have beneficial effects in patients under MMT programs. Also, it may have a potential impact on nursing care, functional activities, rehabilitation potential, and functional recovery. To our knowledge, data from studies investigating the effects of tDCS on promoting sleep quality in MMT patients are limited. Therefore, this study aimed to evaluate the impact of tDCS on sleep quality among patients under MMT.

2. Materials and Methods

Trial design and participants

This randomized, double-blinded, placebo-controlled clinical trial was registered in the Iranian Clinical Trials website at (http://www.irct.ir: IRCT20180604039979N1). Following the Declaration of Helsinki guideline, all patients gave their informed consent to participate in this study. This trial was conducted on 27 participants undergoing MMT. They were referred to Ibn-e-Sina Hospital in Mashhad City, Iran, from July 2018 to May 2019. A total of 27 patients were selected through convenient sampling method based on the criteria. Then, they were randomly divided into the experimental (n=14) and the sham (n=13) groups (Figure 1).

Observing the ethical considerations, the researchers provided the needed information to all patients, such as the process of treatment, probable side effects of tDCS (such as a sense of mild burning or head-ache), and duration of treatment. Then they asked patients to sign the consent form. All patients received tDCS in 7 sessions (every other day).

Inclusion criteria

The inclusion criteria were being 18-60 years old, at least having a middle educational level, receiving MMT exclusively, methadone taking for less than one year, signing a written consent form, willing to par-ticipate in the study.

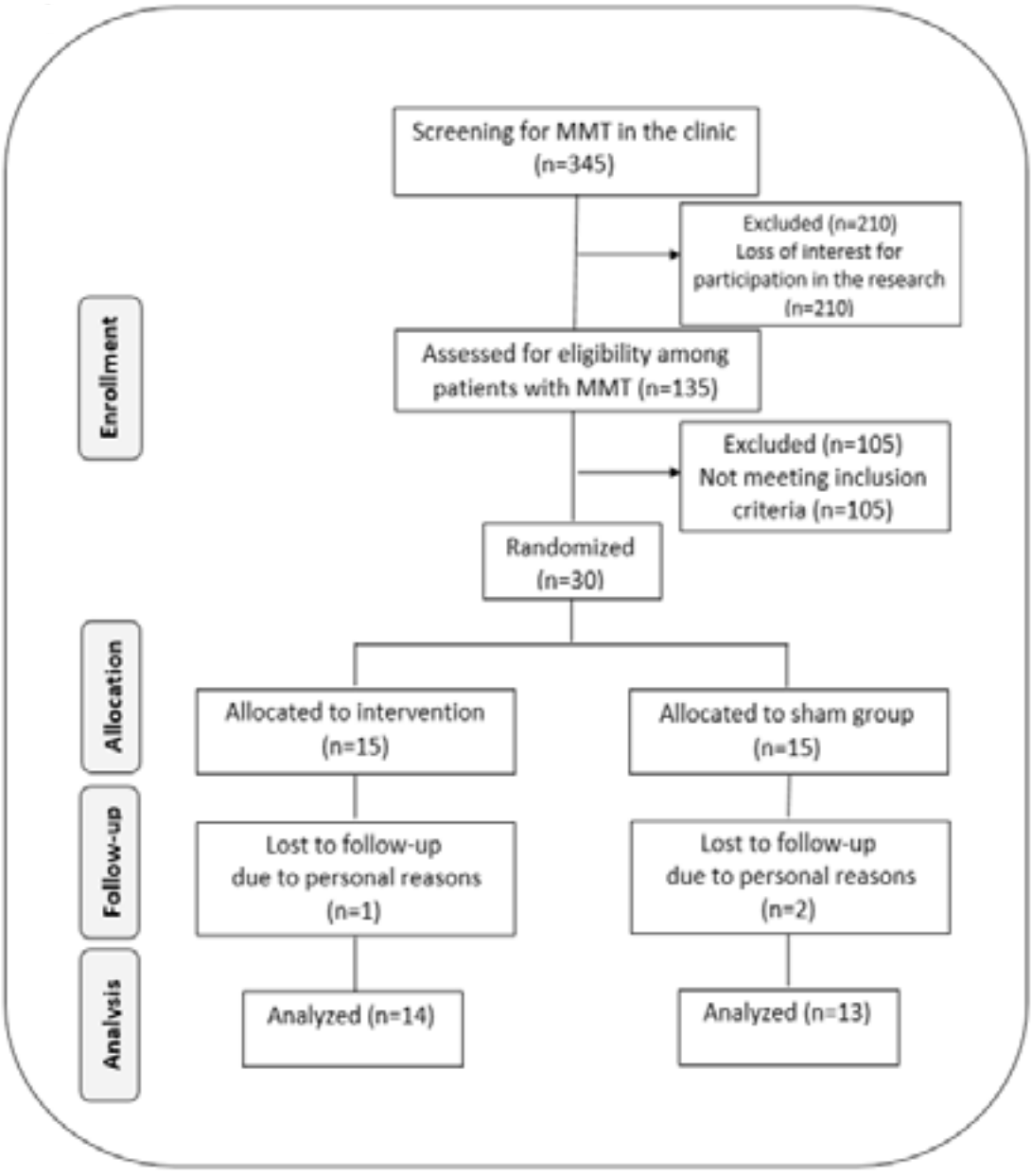

Figure 1. Flow diagram of patients' selection

Exclusion criteria

The exclusion criteria included having diabetes, neurologic disorders, history of head trauma and convulsion, metal subjects, or prosthesis near the site of stimulation, skull shunt, and heart peacemaker. Also, the patients who developed adverse effects due to stimulation were excluded from MMT.

tDCS procedure

In the experimental and sham groups, the electrodes were placed on the head over the indicated points. But the electrical stimulation was discontinued after some seconds in the sham group when the group members felt a burn in the skin, but the electrodes were remained for 20 minutes the same as the experimental group. The electrical stimulation was performed through tDCS for 20 minutes with 2 mA intensity and right anode and left cathode montage using carbonic electrodes on 35 cm 2 of the scalp. The cover of the sponge was filled with saline to provide a better electrical connection between the skull and electrodes. The anode electrode (positive) was placed on the right dorsolateral prefrontal area (F4), and the cathode (negative) was placed on the left dorsolateral prefrontal area (F3) according to the 10–20 international system for EEG [22-25].

Clinical assessments

The clinical measurements included the demographic variables such as age, academic grade, marital status and duration, and amount of methadone use. Also, all patients fulfilled the Pittsburgh sleep quality in-dex (PSQI) in 3 phases: at baseline (at the first session before the intervention), during (at the fourth session), and at the end of the intervention (at the seventh session).

Buysse et al. developed PSQI in Pittsburgh Psychiatric Institute in 1989. The internal consistency of the questionnaire was obtained using the Cronbach α as 0.83. The questionnaire has nine items in its original form, but the fifth question contains 10 sub-items, so the entire questionnaire has 19 items, which are scored based on a 4-point Likert-type scale from 0 to 3. The questionnaire has seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The interpretation of the scores is that 0 indicates a very favorable situation, 1 a relatively favorable, 2 a relatively unfavorable, and 3 very unfavorable. The total score ranges from 0 to 21. The scores between 0 and 5 score are considered as the optimal sleep quality, and the scores between 6 and 21 are regarded as undesirable sleep quality [26].

Statistical analysis

The Kolmogorov-Smirnov test was done to determine the normality of data. The obtained data were analyzed by descriptive statistics such as mean and standard deviation and inferential statistics, including t-test, Chi-square, Mann-Whitney, and Fischer exact tests in SPSS.

3. Results

Table 1 presents the demographic variables of the patients who underwent methadone maintenance therapy. The findings related to sleep quality indexes among two groups of patients treated by tDCS and sham are presented in tables 2, 3, and 4. The difference between the two groups after tDCS in sleep duration was significant, while in the other indexes, there were no significant differences between the two groups. Besides, the results of the inner group evalu-

Table 1. Demographic characteristics of methadone patients

Variables		Experimental Group (n=14)	Sham Group (n=13)
Age (y)		37.36±7.63	36.00±5.69
Educational grade	Intermediate	10 (71.4)	10 (76.9)
	Diploma	4 (28.6)	3 (23.1)
Marital status	Single	3 (21.4)	3 (23.1)
	Married	10 (71.4)	8 (61.5)
	Divorced	1 (7.2)	2 (15.4)
Job	Unemployed	9 (64.3)	4 (30.8)
	Employed	1 (7.1)	0 (0)
	Others	4 (28.6)	9 (69.2)
Psychiatric comorbidity	None	12 (85.7)	11 (84.6)
	Mood disorder	1 (7.1)	0 (0)
	Other disorders	1 (7.1)	2 (15.4)
Use of other drugs	None	12 (85.7)	12 (92.3)
	Benzodiazepine	2 (14.3)	0 (0)
	Antidepressants	0 (0)	1 (7.7)
Methadone dose (mL)		10.15±3.48	10.39±4.17
Duration of MMT (y)		8.93±2.46	8.31±2.78

Data are presented as Mean±SD or No. (%).

Table 2. Results of the Pittsburgh sleep quality index in patients under methadone maintenance therapy

Variables	No. (%)									P
	Experimental Group					Sham Group				
	Intervention	No Problem	Moderate Problem	Severe Problem	Very Severe Problem	No Problem	Moderate Problem	Severe Problem	Very Severe Problem	
Subjective sleep quality	Before	0 (0)	7 (50.0)	7 (50.0)	0 (0)	2 (15.4)	6 (46.2)	4 (30.8)	1 (7.7)	0.519
	During	2 (22.2)	9 (64.3)	3 (21.4)	0 (0)	2 (15.4)	6 (46.2)	5 (38.5)	0 (0)	0.550
	After	6 (42.9)	5 (35.7)	3 (21.4)	0 (0)	2 (15.4)	7 (53.8)	4 (30.80)	0 (0)	0.239
Inner group test			df=2, χ^2=15.200, P=0.001					df=2, χ^2=0.800, P=0.670		
Sleep latency	Before	0 (0)	2 (14.3)	11 (78.6)	1 (7.1)	0 (0)	5 (38.5)	8 (61.5)	0 (0)	0.220
	During	2 (14.3)	3 (21.4)	9 (64.3)	0 (0)	0 (0)	9 (69.2)	4 (30.8)	0 (0)	0.302
	After	5 (35.7)	7 (50.0)	2 (14.3)	0 (0)	2 (15.4)	5 (38.5)	6 (46.2)	0 (0)	0.094
Inner group test			df=2, χ^2=13.378, P=0.001					df=2, χ^2=4.571, P=0.102		
Sleep duration	Before	5 (35.7)	4 (28.6)	3 (21.4)	2 (14.3)	10 (76.9)	1 (7.1)	1 (7.1)	1 (7.1)	0.085
	During	7 (50.0)	5 (35.7)	2 (14.3)	0 (0)	8 (61.5)	3 (23.1)	2 (15.4)	0 (0)	0.685
	After	9 (64.3)	5 (35.7)	0 (0)	0 (0)	2 (30.8)	3 (38.5)	4 (30.8)	0 (0)	0.048
Inner group test			df=2, χ^2=14.966, P=0.001					df=2, χ^2=2.480, P=0.289		
Habitual sleep efficiency	Before	9 (64.3)	5 (35.7)	0 (0)	0 (0)	9 (69.2)	1 (7.7)	3 (23.1)	0 (0)	0.935
	During	12 (85.7)	2 (14.3)	0 (0)	0 (0)	9 (69.2)	2 (15.4)	2 (15.4)	0 (0)	0.430
	After	14(100.0)	0 (0)	0 (0)	0 (0)	9 (69.2)	1 (7.7)	3 (23.1)	0 (0)	0.185
Inner group test			df=2, χ^2=7.600, P=0.022					df=2, χ^2=2.600, P=0.368		
Sleep disturbances	Before	0 (0)	3 (21.4)	8 (57.1)	3 (21.4)	1 (7.7)	7 (53.8)	4 (30.8)	1 (7.7)	0.054
	During	0 (0)	8 (57.1)	4 (28.6)	2 (14.3)	2 (15.4)	7 (53.8)	4 (30.8)	0 (0)	0.280
	After	6 (42.9)	5 (35.7)	3 (21.4)	0 (0)	2 (15.4)	7 (53.8)	4 (30.8)	0 (0)	0.239
Inner group test			df=2, χ^2=21.571, P<0.001					df=2, χ^2=3.800, P=0.150		
Use of sleeping medication	Before	2 (14.3)	1 (7.1)	6 (42.9)	5 (35.7)	10 (76.9)	0 (0)	0 (0)	3 (23.1)	0.022
	During	5 (35.7)	4 (28.6)	4 (28.6)	1 (7.1)	7 (53.8)	3 (23.1)	3 (23.1)	0 (0)	0.350
	After	9 (64.3)	3 (21.4)	1 (7.1)	1 (7.1)	9 (69.2)	2 (15.4)	2 (15.4)	0 (0)	0.905
Inner group test			df=2, χ^2=15.943, P<0.001					df=2, χ^2=0.100, P=0.951		
Daytime dysfunction	Before	3 (21.4)	5 (38.5)	3 (21.4)	3 (21.4)	3 (23.1)	5 (38.5)	2 (15.4)	3 (23.1)	0.905
	During	4 (28.6)	6 (42.9)	4 (28.6)	0 (0)	3 (23.1)	2 (15.4)	5 (38.5)	3 (23.1)	0.141
	After	6 (42.9)	6 (42.9)	2 (14.3)	0 (0)	3 (23.1)	6 (46.2)	2 (15.4)	2 (15.4)	0.220
Inner group test			df=2, χ^2=6.452, P=0.040					df=2, χ^2=4.769, P=0.092		

Table 3. The total score of sleep problems in the patients before and after tDCS

Total Score	Mean±SD		Between-group Test
	Experimental Group	Sham Group	
Before the intervention	08.28±2.7	7.38±4.15	df=25, t=0.476 (independent t-test), P=0.638
During the intervention	6.93±2.76	6.92±3.38	t=0.005 (independent t-test), P=0.996
After the intervention	4.00±2.85	7.00±3.27	z=-2.543 (Mann-Whitney test), P=0.011
Inner group test (difference between before and after the intervention)	df=13, t=4.49 (paired t test), P<0.001	z=-0.483(Wilcoxon), P=0.629	-
Inner group test (difference between before, during and after the intervention)	df=2, Chi-square =16.03 (Friedman test), P<0.000	df=2, Chi-square=3.282, P=0.194	-

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Table 4. The sleep quality in the experimental and control groups before, during, and after tDCS

Sleep Quality	No.(%)		P
	Experimental Group	Sham Group	
Before the intervention Appropriate Inappropriate	1 (7.1) 13 (92.9)	4 (30.8) 9 (69.2)	0.165 (Fischer exact)
During the intervention Appropriate Inappropriate	6 (42.8) 8 (57.2)	5 (38.5) 8 (61.5)	0.816 (Chi-square=0.054, df=1)
After the intervention Appropriate Inappropriate	10 (71.4) 4 (28.6)	5 (38.5) 8 (61.5)	0.128 (Chi-square=2.967, df=1)
Inner group test	df=2, Cochrane Q=13.556, P=0.001	df=2, Cochrane Q=1.000, P=0.607	

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ation showed that sleep quality in the experimental group was improved after tDCS in all indexes.

The results related to the total score of sleep in the experimental and sham groups are presented in Table 3. The difference between the two groups in total sleep score was significant after the intervention. In the experimental group, the total score of sleep decreased while in the sham group, the total score in 3 phases of evaluation has not significantly changed.

Table 4 presents the sleep quality between the two groups of patients before, during, and after tDCS. Based on Cochran's test, the intervention can improve sleep quality while in the sham group, sleep quality had not significantly changed during the study. During the investigation, none of the participants reported the side effects of electrical stimulation.

4. Discussion

In this study, we evaluated the effects of tDCS on the sleep quality of the patients undergoing MMT. We found that the difference between the two groups after tDCS regarding the sleep duration was significant. In the experimental group, the total score of sleep decreased while in the sham group, the overall score has not significantly changed. Although the rate of inappropriate sleep quality was not significantly different between the two groups after the intervention.

Previous studies have demonstrated that sleep disturbances were present in opioid use disorder and MMT [27, 28]. There is no study about the effect of tDCS on the sleep qual-

ity in MMT patients, and it seems that the present study has novelty in this field. Data documenting the effects of tDCS on sleep quality in patients under MMT is limited.

Based on the available evidence, applying tDCS can improve fatigue symptoms and sleep condition among individuals with physical and mental illnesses such as fibromyalgia, Parkinson disease, and bipolar dis-order [17, 29-31]. In a systematic review, Donde and colleagues demonstrated that tDCS could enhance the quality of sleep and neurological symptoms for euthymia patients [18]. Moreover, prefronto-cerebellar tDCS could affect a variety of clinical characteristics that are associated with bipolar disorders development (i.e., neurological symptoms, sleep, and impaired neurocognition).

In this context, prefronto-cerebellar tDCS on neurological soft signs may affect neurocognitive, sensorimotor functions, sleep, and target engagement [31-33]. However, Kim et al. [34] reported that tDCS did not lead to significant changes in sleep quality in patients with diabetic polyneuropathy. In this research, 60 patients were divided into three groups (tDCS, sham, and control). The intervention conducted for five consecutive days. There were no significant differences between the three groups regarding sleep quality.

Given that prefrontal and cerebellar regions play critical roles in the sleep processes, tDCS could target and enhance sleep in a patient with euthymic via engaging the prefronto-cerebellar area [32]. These re-sults may demonstrate that high rates of sleep disturbance during remission contribute to worse outcomes and more mood relapses [35]. Besides, sleep disturbance could be related to relapse into mania or depres-sion, and enhancement in sleep can mitigate these relapses [36, 37].

Taken together, these results suggest that treating sleep disturbance with tDCS can contribute to decreasing mood relapses and treatment resistance [35]. Hence, prefronto-cerebellar tDCS can improve cognitive performance and sleep abnormalities [38]. Although there is no specific mechanism for the effect of tDCS on sleep quality, one of the reasons may be the involvement of the right and left DLPFC in sleep quality. Also, fMRI and source modeling EEG has shown that slow sleep waves are primarily associated with activity in a core set of cortical areas that are mainly located in the left and right prefrontal cortex and DLPFC [29].

Besides, an EEG study identified the cortical topography of local sleep and showed that the prefrontal cortex and DLPFC activities are associated with sleep functions [30]. Therefore, we assume that right anodal and left cathodal tDCS over right and left DLPFC is involved in sleep regulation. More powerful randomized controlled trials are needed to clarify the effectiveness of tDCS.

The present study had some limitations, such as lack of female patients and follow-up periods, to assess the persistency of the effects. Besides, we were unable to evaluate the physical and psychiatric co-morbidities in patients under the MMT program. So, its performance is suggested in other studies. Also, long-term intervention is linked to illustrate better effects. Further studies on male and female patients with larger sample sizes and follow-ups can provide more accurate findings.

5. Conclusion

Our results suggest the positive effect of tDCS to improve sleep quality in the experimental group compared to the sham subjects. So, it can be applied as a safe and effective technique to relieve sleep disturb-ances among patients under MMT. Informed consent was obtained from all individual participants included in the study.

Ethical Considerations

Compliance with ethical guidelines

All procedures performed in studies involving human participants followed the ethical standards of the institutional and or national research committee and complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethics Committee of Kashan University of medical sciences approved the present study (IR.KAUMS.MEDNT.REC.1397.009). This research registered in the Iranian Center for Clinical Trials (Code: IRCT20180604039979N1). All patients signed written consent.

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Author's contributions

Design, conceptualization, statistical analysis: Mohammad Sadeghi Bimorgh and Hamid Reza Banafshe; Supervision: Hamid Reza Banafshe; Collecting data, drafting the manuscript, approve the final manuscript: All authors.

Conflict of interest

The authors declared no conflict of interest.

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