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Research Paper

Safety and Efficacy of Memantine in Improving Cognitive Function of Patients with Epilepsy

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ABSTRACT

Background: The prevalence of cognitive impairment among patients with epilepsy is about 70%. There is still no approved medication for the treatment of this problem.

Objectives: The present study aims to assess the safety and efficacy of memantine in improving the cognitive function of patients with epilepsy.

Materials & Methods: This is a pilot, randomized, double-blind, placebo-controlled, parallel-group clinical trial, conducted in a hospital in Tehran, Iran during 2018-2019. Participants were randomly allocated to receive memantine (5 mg/day in the first eight weeks and 10 mg/day in the second eight weeks) or placebo in a 1:1 ratio. Participants underwent the mini-mental state examination (MMSE), montreal cognitive assessment (MoCA), and frontal assessment battery (FAB) before and after the intervention. The primary and secondary measures were safety and change in the cognitive test scores, respectively.

Results: Out of 53 allocated participants, 33 completed the study. Drug intolerance including headache, somnolence, and dizziness was not significantly different between the two groups. The Intention-to-Treat analyses demonstrated no significant change in MoCA and FAB scores between the two groups after the intervention, but a significant improvement in the MMSE score of the memantine group (P=0.047) was observed. After controlling confounding factors, there was no significant difference in scores of any cognitive tests between the two groups.

Conclusion: Memantine is a safe drug for patients with epilepsy, but it may not exert a beneficial effect on the cognitive function of these patients.

Keywords: Memantine, Epilepsy, Cognition disorders, Seizures

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Highlights

- Memantine may not be useful for treating cognitive impairment in epilepsy
- No serious adverse events were reported after 16 weeks of memantine administration in patients with epilepsy

Introduction

Epilepsy is a serious neurological disease, imposing high psychological and economic costs on patients and health systems. From 1985 to 2013, the prevalence of epilepsy was 6.38 per 1000 persons worldwide [1]. Objective cognitive impairments in attention, executive function, and memory are present in almost 70% of patients with new-onset epilepsy [2]. In chronic epilepsy, cognitive impairment is found in approximately 70-80% of patients, and depression is found in about 60% of patients. Epilepsy can worsen the cognitive functioning of patients [3], and neuropsychological impairment can deteriorate epilepsy by poor drug adherence. Cognitive impairments in patients with epilepsy include deficits in learning, education, attention, memory, executive function, visuospatial skills, and language [4-6].

There is still no approved medication for treating cognitive impairment related to epilepsy. Memantine, a noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist, has been proposed as a possible treatment for cognitive impairment. It is supposed that excitotoxicity by glutamate on hippocampal NMDA receptors leads to hippocampal sclerosis [7]. This may cause more frequent seizures and deteriorates memory function. Blocking this receptor in animal models of epilepsy improved cognitive impairment in spatial learning and memory [8]. Memantine also has antioxidant features and increases the generation of brain-derived neurotrophic factor [9]. Memantine hydrochloride is the available form of memantine, administered orally with an initial dose of 5 mg/day and a maximum tolerated dose of 20 mg/day [10]. Side effects of memantine include dizziness, somnolence, and headache which are rare, mild, and reversible [9, 11]. Memantine has been approved to manage cognitive impairment in Alzheimer's disease, and has a favorable safety, tolerability, and therapeutic profile [12].

The effect of memantine on fatigue and cognitive status of patients with relapsing-remitting multiple sclerosis was evaluated in our previous study, but no significant improvement in fatigue or cognition was found [13]. In a randomized clinical trial, significant improvements in cognitive profile (assessed by Mini–Mental State Examination) and memory (assessed by the Wechsler memory scale) of patients with epilepsy receiving memantine were reported [9]. In another study, authors observed no improvement at the double-blind phase; however, significant improvements in continuous long-term retrieval score, memory-related quality of life, spatial span, and response inhibition were reported using the pooled data analysis at the end of open-label phase [6]. Therefore, we decided to investigate whether memantine can be beneficial for treating cognitive impairment in epileptic patients in Iran.

Materials and Methods

Study design, participants, and intervention

This study was a pilot, randomized, placebo-controlled, double-blind, parallel group, clinical trial conducted in a hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran. Patients diagnosed with epilepsy according to the last version of the international league against epilepsy (ILAE) criteria [14, 15] referred to the Epilepsy and General Neurology Clinics of Imam Khomeini Hospital from August 2018 to February 2019 were assessed for eligibility. The inclusion criteria were age 15-65 years, treatment with anti-epileptic drugs (AEDs) over the past six months, mild to moderate cognitive impairment based on the baseline mini–mental state examination (MMSE) score of 17-23 [16], and subjective complaint of memory or other aspects of cognitive impairment [there are a few participants who have a MMSE score>24 (normal MMSE) but subjective complaint of cognitive impairment], and monthly seizure frequency <4.

Patients had undetermined localization of seizure. Exclusion criteria were: Psychogenic non-epileptic seizures, use of any non-anti-epileptic medications (e.g., antipsychotics and antidepressants) with cognitive side effects, seizure in the past week and during study, progressive neurologic diseases, major psychiatric disorders, mental retardation, severe medical

illnesses, pregnancy or breastfeeding, prior history of drug intolerability, or allergic reactions to memantine. Eligible patients were randomly assigned to memantine or placebo groups in a 1:1 ratio using a random number generator software. Patients and examiners were both blinded to the treatment group. Medications were kept in the same drug container and had similar color, shape, and administration schedule. Patients in the memantine group received 5 mg memantine hydrochloride (Alzixa, Tasnim pharmaceutical Company, Iran) per day orally for eight weeks. Then, the dosage was titrated to 10 mg per day (one 10-mg tablet) which was the administration dose for another eight weeks. The control group received a placebo tablet orally once daily for 16 weeks.

Measurements

All participants underwent the MMSE, montreal cognitive assessment (MoCA), and Frontal Assessment Battery (FAB) at baseline and four months after the intervention. The MMSE and MoCA are general neurologic tests for assessing different aspects of cognition. MMSE is a test that assesses orientation, attention, recall, and language. It is a 30-point test, where a score ≥24 represents normal cognition [17, 18]. We chose MMSE since it was used in a previous study and showed significant improvement after memantine use [9]. MoCA measures memory recall, visuospatial abilities, executive function, attention, concentration, language, and orientation. MoCA score varies from 0 to 30; a score ≥26 represents normal status [19]. MoCA was selected due to higher sensitivity than MMSE in diagnosing mild cognitive impairment [20].

Previous studies have shown that the FAB is a useful tool for evaluating executive function in patients with epilepsy [21]. FAB assesses conceptualization, mental flexibility, motor programming (executive function), sensitivity to interference, inhibitory control, and environmental autonomy. Each sub-test is scored from 0 to 3, and the total score ranges from 0 to 18 [22]. Due to the high prevalence of executive dysfunction in patients with epilepsy [23], we decided to use the FAB as well.

Safety and outcome

The safety evaluation comprised of recording the adverse events. The patients were instructed about possible adverse events, including dizziness, somnolence, and headache. Patients were asked to report any other new symptoms to the caregivers, as well. The incidence of adverse events was compared between the placebo and memantine groups at the end of intervention. We contacted the patients monthly via phone calls to monitor adverse events (self-report) and drug adherence by asking how many pills were left. We also asked them if they experienced increased seizure attacks using a yes/no question as a follow-up session. The primary outcome was safety. The secondary outcome was the change in cognitive status assessed by MMSE, MoCA, and FAB.

Statistical analysis

Descriptive statistics including mean and standard deviation were used for quantitative variables, while absolute frequency and relative frequency were used for qualitative variables to describe them. To analyze the differences between the two groups, the intention-to-treat (ITT) approach was implemented. All subjects who received at least one dose of the allocated medication were included in the analysis to assess the safety and efficacy outcomes. Missing data were managed by the multiple imputation method. Using SPSS software, five datasets were imputed and the results were reported according to the pooled data. We used parametric tests including two-tailed independent t-test and one-way analysis of covariance (ANCOVA) to compare quantitative variables between the two groups, and Chi-square test to compare qualitative variables.

For each cognitive test, the total change in score was calculated by subtracting the mean posttest score (after 16th week) from the mean pretest score. We hypothesized that memantine would improve cognitive test scores after 16 weeks compared to placebo. This hypothesis was examined in two steps. First, the pretest score change was examined using paired t-test, and the mean total change was compared between the two groups using independent t-test. Second, after controlling age, years of education, number of AEDs, and pretest scores, we compared the mean final score in each test between the two groups using ANCOVA. A P-value <0.05 was statistically significant. Data analysis was conducted in SPSS software v. 22 (IBM Corp, Armonk, NY, USA).

Results

A total of 78 patients were assessed for eligibility. Of these, 53 eligible patients were selected and randomly assigned to memantine (n=25) and placebo (n=28) groups (Figure 1). However, two patients were excluded from the placebo group due to the high probability of psychogenic non-epileptic seizure. Finally,

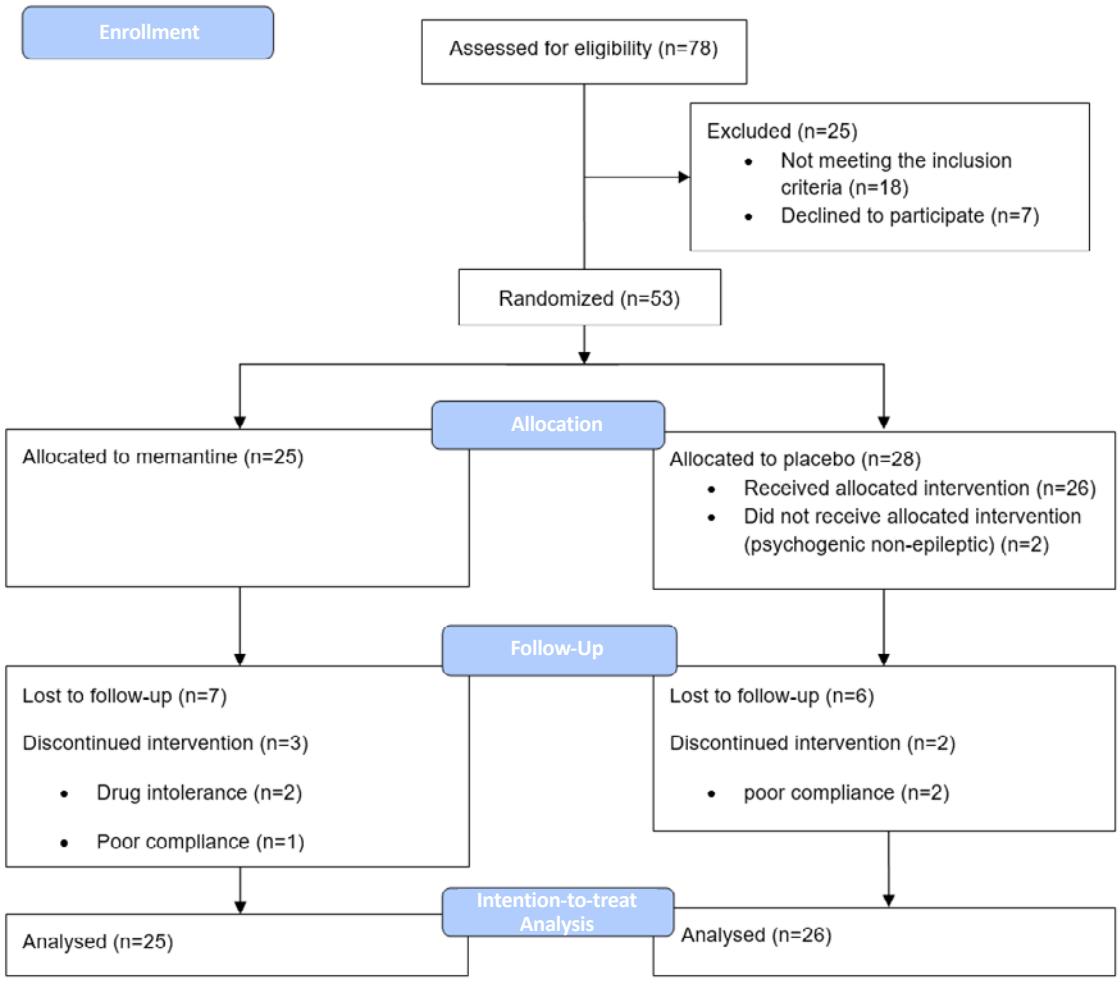

Figure 1. Consort flow diagram

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Drug intolerance and poor compliance are the two reasons of discontinued intervention, as they are shown to be subcategories of discontinued intervention. Therefore, the numbers are correct and 3 patients discontinued intervention (2 of them because of drug intolerance and 1 because of poor compliance).

15 patients in the memantine group and 18 individuals in the placebo group completed the study. Reasons for their exclusion are mentioned in Figure 1. The baseline characteristics of participants are presented in Table 1. We observed no significant differences in baseline characteristics between the two study groups except for last seizure episode ($P<0.05$).

Safety analysis

The study participants reported no serious adverse events. Adverse events were reported in five patients in the memantine group (3 with headache, 1 with somnolence, one with dizziness), and three patients in the placebo group (2 with headache and one with dizziness) ($P=0.406$). Two patients in the memantine group left the study due to adverse events (one due to headache and other due to somnolence), but none of patients in the placebo group left the study because of medication adverse events.

Cognitive status

The pretest and posttest scores of cognitive tests are illustrated in Figure 2. Table 2 provide the results based on the intention-to-treat and per-protocol analyses.

After 16 weeks of treatment, the mean MMSE change in the memantine group was significant ($t_{2472}=4.06$, $P<0.001$), while it was not significant in the placebo group ($t_{28}=0.75$, $P=0.46$). We observed a marginally significant difference between the placebo and memantine groups in mean MMSE change (Mean difference=1.06, 95% CI: 0.02-2.11, $t_{66}=2.03$) (Table 2). After controlling age, years of education, number of AEDs, and pretest score by ANCOVA, no significant difference was found

Table 1. Demographic characteristics of participants

Characteristics		Mean±SD/No. (%)		P
		Memantine (n=15)	Placebo (n=18)	
Age (y)		33.27±10.48	36.50±11.82	0.417**
Male		8(53.3)	10(55.6)	0.898*
Years of education		12.73±2.74	12.44±2.62	0.759**
Number of AEDs	Monotherapy	7(46.7)	10(55.6)	0.759*
	2	5(33.3)	6(33.3)	
	≥3	3(20.0)	2(11.1)	
Last seizure Episode	Between last 8-30 days	9(60.0)	4(22.2)	0.027*
	>30 days	6(40.0)	14(77.8)	

*Chi-square test; ** t-test.

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Figure 2. Mean scores of cognitive tests in Memantine and Placebo groups at baseline and 16 weeks after intervention
Mean MMSE and FAB scores significantly improved after 16 weeks of memantine administration.

Table 2. Comparing cognitive tests scores between memantine and placebo groups (per-protocol and intention-to-treat (ITT) analyses) (P<0.05)

Cognitive Tests		Per-protocol			ITT		
		Mean±SD/95% CI					
		Memantine (n=15)	Placebo (n=18)	Mean Difference	Memantine (n=25)	Placebo (n=26)	Mean Difference
MMSE	Pre-test	23.33±1.80	22.67±2.30	0.67 (-0.82 to 2.15)	23.04±2.50	22.73±2.18	0.30 (-0.98 to 1.59)
	Post-test	24.6±1.91	23.16±2.33	1.43 (-0.10 to 2.97)	24.40±0.62	23.03±0.57	1.37 (-0.28 to 3.02)
	Mean difference	1.27 (0.39 to 2.14)	0.5 (-0.20 to 1.20)	0.77 (-0.30 to 1.83)	1.36 (0.70 to 2.02)*	0.30 (-0.51 to 1.11)	1.06 (0.02 to 2.11)
MoCA	Pre-test	15.27±5.31	17.17±3.94	-1.90 (-5.19 to 1.39)	16.12±4.99	17.07±3.86	-0.96 (-3.4 to 1.48)
	Post-test	16.60±4.10	17.16±4.24	-0.57 (-3.54 to 2.41)	17.03±0.92	17.14±0.88	-0.10 (-2.66 to 2.45)
	Mean difference	1.33 (-0.01 to 2.68)	0.00 (-0.3 to 0.38)	1.33 (-0.05 to 2.72)	0.92 (-0.15 to 1.98)	0.06 (-0.91 to 1.04)	0.85 (-0.65 to 2.35)
FAB	Pre-test	13.87±5.26	12.33±2.91	1.53 (-1.42 to 4.49)	12.92±4.85	13.15±3.31	-0.23 (-2.5 to 2.04)
	Post-test	15.20±4.84	12.72±3.06	2.48 (-0.35 to 5.30)	14.45±0.96	13.57±0.68	0.88 (-1.43 to 3.19)
	Mean difference	1.33 (0.31 to 2.35)	0.39 (-0.18 to 0.95)	0.94 (-0.18 to 2.07)	1.53 (0.5 to 2.56)	0.41 (-0.3 to 1.14)	1.11 (-0.16 to 2.39)

between the study groups in the final MMSE score (Mean difference=0.86, 95% CI: -0.18-1.90).

After 16 weeks of treatment, the mean change in MoCA score was not significant in any groups (t_{44}=1.73, P=0.09 in the memantine group; t_9=0.15, P=0.88 in the placebo group). The difference between the two groups in mean MoCA change was not statistically significant (Mean difference=0.85, 95% CI: -0.65-2.35, t_{16}=1.20) (Table 2). After controlling confounding factors, the difference was not significant in the final MoCA score between the two groups (Mean difference=0.670, 95% CI: -0.77-2.11).

In contrast to the placebo group, there was a significant improvement in FAB score in the memantine group after 16 weeks (t_{53}=1.16, P=0.25 vs. t_{49}=3.00, P=0.004, respectively) (Table 2). However, the mean FAB score change was not significantly different between the two groups (t_{44}=1.76, P=0.08). The adjusted mean difference was not significant for the final FAB score between the two groups (Mean difference=0.923, 95% CI: -0.35-2.20).

Discussion

This study revealed that off-label use of memantine could possibly be a safe option for the management of cognitive impairment in patients with epilepsy. Although the mean change of MMSE score was significantly different between the two groups, no statistically significant difference was observed between the two groups after controlling confounding factors. Likewise, we found no significant difference in the scores of MoCA and FAB between the placebo and the memantine groups after 16 weeks of therapy. Since cognitive complaints are highly prevalent among patients with epilepsy, and few studies have directly assessed the efficacy of pharmacological interventions on cognitive function of these patients [24], finding a safe and efficient medication for this problem can be clinically beneficial.

Since we found no significant difference between the two groups in age, years of education, number of AEDs, and baseline cognitive tests scores. So those didn't affect our results. Based on previous studies on epilepsy and cognitive impairment, higher age and lower educational level were negatively associated

with the change in cognitive status of patients with epilepsy [25]. One difference between MMSE and other cognitive tests (MoCA and FAB) is that MMSE cannot assess executive function. We hypothesized that the possible beneficial effect of memantine on some aspects of cognition can be neutralized when the effect of memantine on the executive function is measured simultaneously (by MoCA and FAB). The maximum dose of memantine administered in this study was 10 mg/day. A same dosage was also used in a previous study [9]. However, the suggested dose of memantine for cognitive impairment in Alzheimer's disease in one study was 20 mg/day [11]. Therefore, a higher dosage of memantine might have more noticeable effects on the cognitive function of patients with epilepsy.

Memantine was used previously in a few studies to assess the same hypothesis [6, 9]. Marimuthu et al. evaluated effectiveness of memantine in improving cognitive impairment in patients with epilepsy [9]. Consistent to our findings, they found significant improvements in cognitive status ($P<0.001$ for MMSE) and memory ($P<0.001$ for the Wechsler Memory Scale) of patients in the memantine group. However, the probable effect of confounding factors was not examined in their study. The lower mean pretest MMSE score in their study may be due to the results regarding the efficacy of memantine. Furthermore, despite a high prevalence of cognitive impairment in younger patients with epilepsy [26], those aged <18 years were not included in their study. We did not assess seizure frequency in our study, while seizure frequency diminished after memantine administration in their study.

Leeman et al. investigated the effect of memantine on cognitive impairment of patients with focal-onset epilepsy at two phases; double-blind and open-label phases. They found no significant difference in memory and executive function in patients between the memantine and placebo groups at the double-blind phase (13 weeks), but there were some improvements in memory, spatial span, and response inhibition in the memantine group using the pooled data at the open-label phase [6]. However, their results should be interpreted cautiously because of possible practice effects, improvement expectancy, and multiple comparisons. In their study, there were small sample size, insufficient supervision of the patients' compliance, and not controlling the effects of confounding factors. Moreover, the baseline cognitive test score was lower in their placebo group which may have led to significant improvements in some cognitive aspects in the control group. However, in the present study, patients in both groups were not significantly different in terms of age, years of education, number of AEDs, and baseline cognitive test scores. Nonetheless, the short duration of intervention in our study may have affected the efficacy of memantine.

The effect of memantine in comparison with donepezil on the cognitive profile of patients with temporal lobe epilepsy was evaluated in a recent study [27], and it was shown that memantine was superior to donepezil in improving MoCA score, particularly in the time and place orientation. The scores of language, visuospatial/executive, and time and place orientation significantly improved in the memantine group, while only the score of abstraction significantly increased in the donepezil group. However, lack of a control group, lack of a blinded design, and the small sample size compromised their results, and the findings should be interpreted cautiously.

The effect of methylphenidate on the cognitive status of patients with epilepsy was evaluated in a double-blind placebo-controlled clinical trial [28] and in a one-month open-label trial [29]. Both studies showed beneficial effects of methylphenidate on the patients' cognitive function. Symbol Digit Modalities Test and Conners Continuous Performance Test, third edition scores improved in both phases. Both control and intervention groups showed significant improvements in several cognitive tests at the open-label phase; however, the only cognitive improvement that was significantly greater in the intervention group was related to the attention domain.

The limitations of our study were existence of multiple cases that lost the follow-up and the undetermined seizure localization. The study hospital located in Tehran city is a referral center that receives patients across the country; high number of patients lived far from Tehran city, which may be the reason for losing the follow-up visits. We did not assess the effect of memantine by considering the seizure frequency. Seizure frequency may be a potential confounding factor in evaluating the efficacy of memantine on the cognitive profile of patients with epilepsy. Similar to prior studies, medication adherence was not assessed by objective methods such as pill counting; however, it was controlled subjectively by asking how many pills were left in the containers. The short duration of intervention was another limitation of the present study. In a study [6], memantine had no overall effect after 13 weeks of treatment, but the authors detected some improvements in the cognitive profile of patients after 26 weeks of treatment. However, Marimuthu et al. [9] showed some improvement in the Wechsler Memory Scale score even after the first eight weeks of treatment. Moreover, memantine might improve cognitive status in some subgroups of patients, such as those with different seizure types, age groups, or lower baseline scores that were not assessed in this study. Another limitation was

that no quantifiable measure of adverse events (i.e., Liverpool Adverse Events Profile) was used.

A few studies evaluated the effect of cholinesterase inhibitors such as donepezil on the cognitive profile of patients with epilepsy [27, 30]. Considering the higher positive effect of donepezil combined with memantine rather than donepezil alone on the cognitive function of patients with Alzheimer's disease [31], we recommend that future studies examine the effect of donepezil combined with memantine in comparison with their administration alone on the cognitive status of patients with epilepsy.

Conclusion

Memantine is a safe medication for patients with epilepsy, but it may not have a beneficial impact on the cognitive status of these patients. We recommend more studies using larger sample size, longer intervention duration, and subgroup analysis for different seizure types, age groups, and baseline cognitive tests.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were in compliance with the ethical guidelines of the Declaration of Helsinki 2013. Ethical approval was obtained from the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.IKHC.REC.1397.052) and was registered by the Iranian Registry of Clinical Trials (IRCT) (ID: IRCT20121110011424N5). Informed consent was obtained from all participants included in the study.

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Authors' contributions

Conceptualization: Abbas Tafakhori, Pargol Balali, Seyedeh Sajedeh Marashi; Methodology: Nasrin Rahimian, Sajad Shafiee, Mahdi Shafiee Sabet; Formal analysis: Pargol Balali, Elmira Agah; writing original draft: Pargol Balali, Seyedeh Sajedeh Marashi, Elmira Agah; editing & review: Abbas Tafakhori, Nasrin Rahimia, Sajad Shafiee, Mahdi Shafiee Sabet; supervision: Abbas Tafakhori. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors reported no conflict of interest.

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