ORIGINAL ARTICLE

Efficacy of Pregabalin versus Cinnarizine in Preventive Treatment of Children with Migraine Headache: A Randomized Double-Blind Clinical Trial Study

Mohammad Vafaee-Shahi, MD[1]; Helen Vaferi, MD[2]; Mahmoudreza Ashrafi, MD[3]; Aina Riahi, MD[1]; Azar Mohammadzadeh, MD[4,5]; Navid Hadavi, MD[6]; Davood Kheirkhah, MD[7]

[1]Pediatric Child Neurology Department, Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran
[2]Pediatrician, Aliasghar Children's Hospital, School of Medicine, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[3]Pediatric Neurology, Pediatric Growth and Development Research Center, Faculty of Medicine, Teran University of Medical Sciences, Tehran, Iran
[4]School of Dentistry, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[5]Pars Advanced and Minimally Invasive Medical Manners Research Center, Pars Hospital, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[6]Department of Pediatrics, Tehran Medical Sciences, Azad University, Tehran Iran
[7]Infectious diseases research Center, Kashan University of Medical Sciences, Kashan, Iran

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ABSTRACT

Objectives: Different drugs have been proposed to control migraine headaches in children, which have different effectiveness. This study aims to compare the effectiveness of Pregabalin and Cinnarizine in the preventive treatment of children with migraine headaches.
Materials & Methods: In this randomized, double-blind clinical trial, 74 children aged 6 to 17 years with migraine headaches were included. Patients were randomly assigned to Pregabalin (n = 37) and Cinnarizine (n = 37) groups. In the Pregabalin group, one oral capsule (50 or 75 mg) was prescribed at bedtime, and in the Cinnarizine group, patients received oral tablets (25 or 50 mg) at bedtime. The frequency of migraine headaches, the severity of migraine headaches, and the severity of migraine disability were measured and recorded at the beginning of the study, 4, 8, and 12 weeks after initiation of intervention, through the patient's notes, pain scale (VAS), and PEDMIDAS, respectively. The data were analyzed using SPSS version 25, and the significance level for all statistical tests was set at < 0.05.
Results: Three out of 74 patients did not continue follow-up for unknown reasons, and later it was found that all three were in the pregabalin group. Of 71 subjects, 38 (53.5%) were boys: 17 (50%) in the Pregabalin group and 21 (56.8%) in the Cinnarizine group. No significant difference was observed between the two groups regarding gender (P-value = 0.0569). The mean and standard deviation of the patients' ages were 10.24 and 2.51, respectively, and their age range was 6 to 17 years. Headache frequency decreased by 72% in the Cinnarizine group and 58% in the Pregabalin group. Headache intensity decreased by 63% and 35% in the Cinnarizine and Pregabalin groups, respectively. Furthermore, the reduction rate of disability caused by migraine attacks was 89% in the Cinnarizine group and 73% in the Pregabalin group.
Conclusion: The findings revealed that both drugs reduced migraine headaches, but Cinnarizine was more effective than Pregabalin in controlling children's migraine headaches, with this improvement sustained through the third month.

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Introduction

Migraine is the most common type of primary headache in children (1). Prevalence of migraine varies according to age, from 3% in young children (under 12 years old) up to 20% in teenagers (12 to 17 years old) (2). Quality of life studies show that migraine has a significant negative effect on children, adolescents, and their parents because of disruptions in school, family, and extracurricular and social activities, similar to other chronic diseases in children, such as cancer (3).

Corresponding Author:
Aina Riahi
Email: ainariahi@yahoo.com

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Drug therapy for migraine headaches includes two approaches: abortive and preventive. The goal of abortive treatment is symptomatic therapy of headache and other symptoms associated with an acute migraine attack. Preventive therapy reduces the frequency or severity of attacks, improving the patient's performance and increasing the quality of life. This treatment is suitable for patients who have very frequent or severe attacks (more than 3 to 4 attacks per month) or significant disability associated with headache or refractory to acute treatment (4). The purpose of prophylactic treatments is to improve patients' quality of life by reducing the frequency, intensity, and duration of migraine headaches. Therefore, the treatment should have the greatest effect on reducing the migraine severity and the fewest side effects in patients (5). Drugs in the class of beta-blockers, calcium channel blockers (CCBs), antiepileptic drugs, antihistamines, and tricyclic antidepressants (TCAs) are used for the preventive treatment of migraine (6). Consistent evidence regarding the superior preventive efficacy of these drug classes for pediatric migraine management remains elusive. Different countries select different treatment approaches based on cultural and political factors. For example, Pizotifen, used by many pediatricians in the UK, is not available in the US; Cyproheptadine is used in the US but not in the UK; and beta-blockers are favored in Finland (7).

Pregabalin and Cinnarizine are two drugs in the class of CCBs that have recently entered the market. By binding to calcium voltage-dependent channels, Pregabalin reduces the infiltration of calcium into the nerve terminal, and as a result, synapse-stimulating neurotransmitters such as glutamate, noradrenaline, and substance P are reduced. Therefore, Pregabalin restores normal function at nerve terminals (8) High levels of glutamate in migraine patients' plasma and cerebrospinal fluid have been observed. In a study, a significant reduction in serum glutamate levels after treatment with migraine prophylaxis has been reported (9). Cinnarizine, in addition to being a calcium channel blocker, is also an antihistamine drug. This drug destroys calcium currents in vestibular hair cells. Inhibition of these currents reduces nausea, vomiting, dizziness, and motion sickness by decreasing the reactivity of vestibular hair cells that send information about balance and movement to the brain (8,10). Seemingly, both drugs have a preventive effect in children with migraine according to the mentioned mechanisms, but which of these drugs has a better preventive effect is not yet known. Therefore, the present study aimed to conduct a clinical trial to compare the effectiveness of Pregabalin and Cinnarizine in children with migraine.

Materials & Methods

Setting and study design

A double-blind, parallel-group, randomized clinical trial was conducted between March 2021 and September 2022 on pediatric patients referred to the Children's Neurology Clinic at Rasool Akram Hospital, an academic medical center affiliated with the Iran University of Medical Sciences.

Participants

Children aged 6 to 17 years who were referred to the Children's Neurology Clinic were included in the study. Inclusion criteria were consent to participate in the study, boys and girls aged 6 to 17 years with migraine headaches who needed prophylaxis, and not taking Pregabalin and Cinnarizine in the past. Diagnosis of migraine was based on the International Headache Society criteria, includingcases of migraine without aura (5 attacks), migraine with aura (2 attacks), duration of each attack from 1 to 72 hours, pulsating and severe in nature, and be accompanied by nausea or vomiting, photophobia and phonophobia. Patients with other headaches such as headaches caused by brain structural disorders, systemic diseases, chronic daily headaches, focal neurological disorders with migraine, history of sensitivity to calcium channel blocking drugs and antihistamines, use of any drug except supplements and patients suffering from any underlying disease such as diabetes, gastrointestinal, liver and kidney diseases and special diseases such as cancer and hepatitis were not included in the study. Subjects were withdrawn from the study due to intolerance to oral medication (symptoms such as diarrhea, nausea, and vomiting), anaphylaxis, severe dizziness, and severe drowsiness.

Intervention

In the two studied groups, one received a Pregabalin regimen and the other a Cinnarizine regimen. In the first intervention group, a Pregabalin oral capsule 50 or 75 mg (manufactured by Actoverco, Iran) was prescribed at bedtime for three months for those weighing less than 30 kg and more than 30kg, respectively. The second intervention group, received Cinnarizine oral tablets 25 or 50 mg (manufactured by Amin Pharmaceutical, Iran), prescribed at bedtime for 3 months, depending on weight: less than 30 kg or more than 30 kg, respectively.

Randomization, concealment, and masking

The present study used the www.sealedenve-lope.com website to generate random sequences with block randomization (block size of 4). The random list was given to an epidemiologist who had no involvement in selecting drugs. Subjects were then randomly assigned to two groups: Pregabalin and

Cinnarizine. To blind the patients, Cinnarizine tablets were placed into a capsule shell of Pregabalin, so both drugs were identical. To blind the doctor, envelopes were created and given to a researcher who had no involvement in selecting the type of medicine. A unique code (generated by www.sealedenvelope.com) was written on each envelope. After the subjects entered the study and their baseline information was collected, they went to the researcher to receive the medicine, who then gave one of the envelopes to each patient.

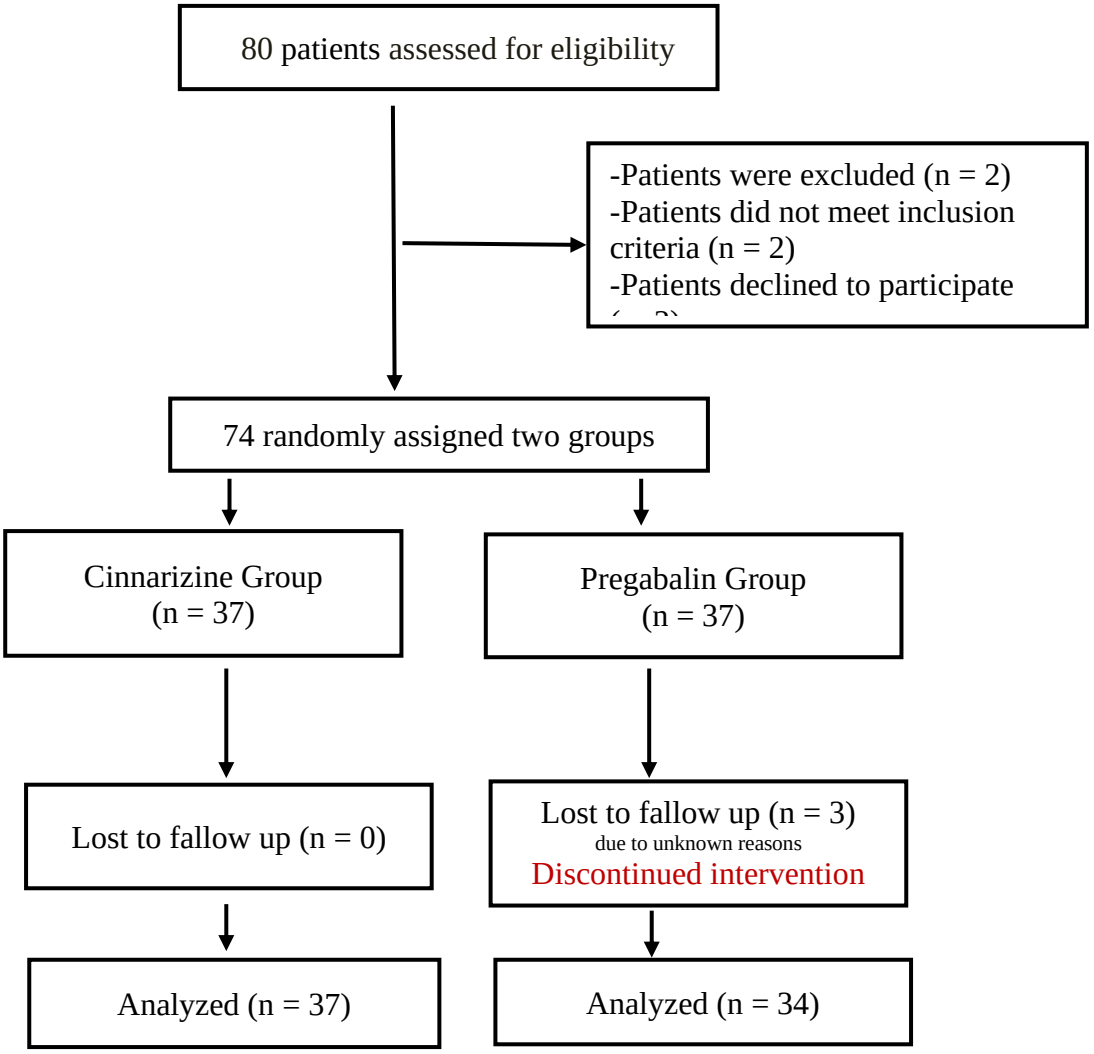


Fig. 1. Participants flow diagram

Primary and secondary outcomes

The primary outcome measure was the frequency of migraine attacks, assessed through patient medical history and longitudinal headache diaries. Participants—or their legal guardians—were required to record the occurrence of each migraine attack throughout the three-month treatment period and report the total count at the study's conclusion.

Secondary outcomes included migraine severity and migraine-related disability. Pain intensity was evaluated using the Visual Analog Scale (VAS). Participants were presented with a series of facial expressions ranging from 0 ("no pain") to 10 ("worst possible headache"). They were asked to identify the face that most accurately represented their current pain level. Migraine-related disability was quantified using the Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire, a validated 5-item scale measuring total days of disability, with possible scores ranging from 0 to 50.

Table 1. Participants baseline characteristics by treatment regimens

Variables		Cinnarizine	Pregabalin	Total	P-value
Age-mean (SD)		10.19 (2.53)	10.29 (2.54)	10.24 (2.51)	0.862
Sex (boy/girl)-no (%)	Boy	21 (56.8)	17 (50)	38 (53.5)	0.569
	Girl	16 (43.2)	17 (50)	33 (46.5)	

Table 2. Comparing the number of headaches in study groups

		First day Mean (SD)	1nd Month Mean (SD)	2nd month Mean (SD)	3nd month Mean (SD)	P-value
Number of headaches	**Cinnarizine**	6.89 (1.712)	4.94 (1.929)	3.57 (2.089)	2.05 (2.767)	0.386
	Pregabalin	7.26 (1.814)	5.44 (1.941)	4.03 (2.879)	3.26 (2.761)	0.439
	Total	7.07 (1.759)	5.18 (1.93)	3.79 (2.489)	2.63 (2.631)	0.052
Severity of headache	**Cinnarizine**	5.24 (1.116)	4.32 (1.156)	2.86 (1.378)	1.95 (1.840)	0.402
	Pregabalin	5.41 (0.857)	4.56 (1.186)	3.68 (1.981)	3.26 (2.416)	0.016
	Total	5.32 (0.997)	4.44 (1.168)	3.25 (1.730)	2.58 (2.221)	0.013
Severity of migraine disability	**Cinnarizine**	9.32 (5.503)	5.30 (3.807)	1.49 (2.815)	1.27 (2.755)	0.802
	Pregabalin	9.32 (4.558)	5.44 (3.518)	2.15 (2.618)	2.12 (2.637)	0.122
	Total	9.32 (8.00)	5.37 (5.00)	1.80 (0.00)	1.80 (0.00)	0.055

Table 3. Comparison of the reduction percentage of headache variables at the beginning and end of the study

	Cinnarizine	Pregabalin	P-value
Number of headaches	-0.72 (0.30)	-0.58 (0.32)	0.068
Headache severity	-0.63 (0.35)	-0.35 (0.42)	0.013
Severity of migraine disability	-0.89 (0.21)	-0.73 (0.34)	0.022

Sample size

The sample size was calculated to be 74 patients, based on a study done by Alebrahim et al. (10) and the mean number of migraine headaches in week 8, assuming alpha = 0.05, beta = 0.2, and an effect size of 0.67. Furthermore, this study considered a drop-out rate of 5%.

Statistical analysis

Statistical analyses were conducted on a per-protocol basis, including only participants who fully adhered to the study protocol. Descriptive analyses were performed for all study variables. To verify the adequacy of randomization, baseline characteristics, including demographic and clinical variables, were compared between the two groups prior to the intervention. For continuous variables, the independent t-test was used for normally distributed data, and the Mann–Whitney U test was used for non-normally distributed data. Categorical variables were compared using the chi-square test. Changes in headache frequency over time within each group were analyzed using repeated measures ANOVA. When significant differences were detected, Bonferroni's post hoc test was applied for pairwise comparisons. A p-value of less than 0.05 was considered statistically significant.

Results

Seventy-four eligible patients were included in the study and allocated to the Cinnarizine (n = 37) and Pregabalin (n = 37) groups. Three out of 74 patients did not continue the follow-up due to unknown reasons, and later it was found that all three were related to the pregabalin group. (Table 2, Fig.1)

The mean and standard deviation of age in patients were 10.24 and 2.51, respectively, and their ages ranged from 6 to 17 years. Thirty-eight (53.5%) subjects were boys. Seventeen people (50%) in the Pregabalin group and 21 people (56.8%) in the Cinnarizine group were boys. No significant difference was found between the two groups regarding gender (P-value = 0.569) (Table 1).

The mean and standard deviation of the number of headaches, headache severity, and disability severity were not significantly different between the two groups at the beginning of the study. However, at the end of the third month, this difference was significant (Table 3). The evaluation of headache frequency, headache severity, and disability severity during the study, using repeated-measures methods, showed that both drugs led to improvements in headache frequency and severity. However, as shown in Figure 2, this improvement is more in the Cinnarizine group and at the end of the third month has been significant (Figure 2).

Comparison of the percentage reduction in headache variables at the beginning and end of the study showed that the reduction in headache frequency was 72% in the Cinnarizine group and 58% in the Pregabalin group. The decrease in headache severity was 63% in the Cinnarizine group and 35% in the Pregabalin group. Furthermore, the rate of reduction in

migraine disability severity was 89% in the Cinnarizine group and 73% in the Pregabalin group (Table 3).

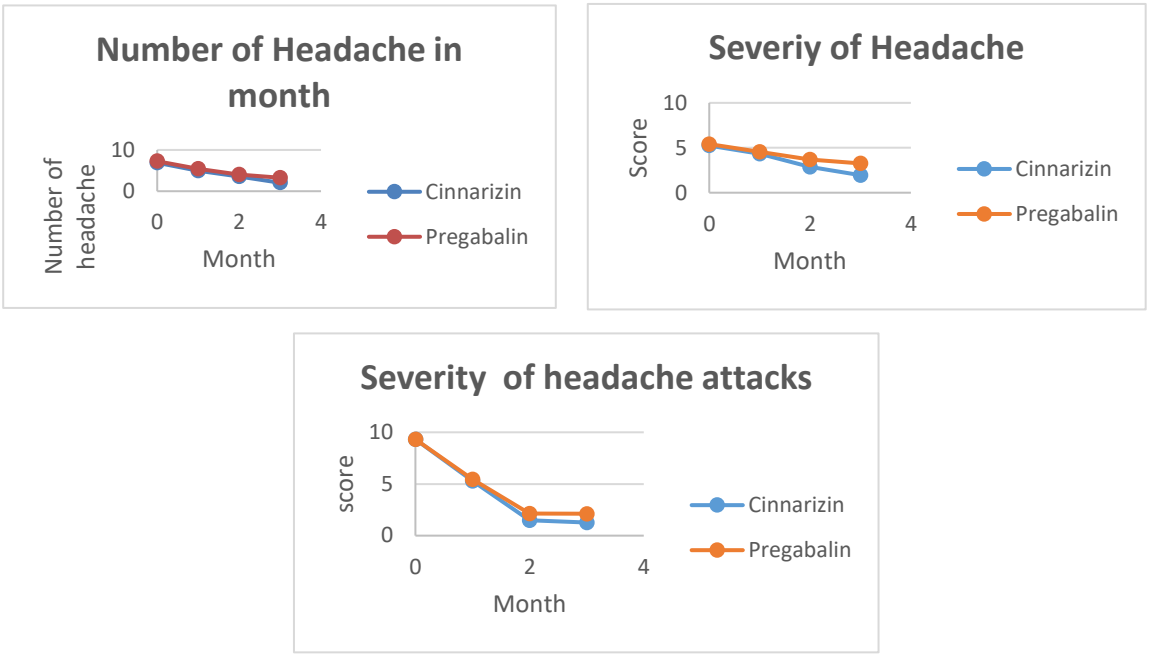


Fig. 2. Changes in the number of headaches, headache intensity, and the degree of disability caused by migraine attacks in the two groups of cinnarizine and pregabalin at the beginning of the study, the first month, the second month, and the third month**.**

Discussion

Several classes of medications may be used for preventive treatment, including antidepressants, antiepileptics, antihistamines, and antihypertensives. These drugs are widely prescribed for other conditions such as depression, anxiety, epilepsy, and other pain disorders, and thus their side effects are well described (11). In recent years, many studies have been conducted on the effect and effectiveness of different drugs on migraine headaches, and Cinnarizine and Pregabalin were among the drugs that have been relatively successful in preventing migraine attacks. Therefore, this study assessed the effectiveness of Cinnarizine and Pregabalin on 71 patients with migraine headache (age range 6-17 years).

In recent years, the use of CCBs drugs in preventing migraine headaches has attracted many researchers (12, 13). In this regard, a study was conducted by Raucci et al. to assess flunarizine in the prevention of migraine headaches in children aged 7-15 years. They showed that this drug had a positive effect in reducing migraine headaches. Given Cinnarizine's pharmacokinetic characteristics , many studies have confirmed its effectiveness in relieving migraine headaches (14). Cinnarizine is an antihistamine and calcium channel blocker from the diphenyl-methyl piperazine group (15).

Morover, several studies in Iran have investigated the effect of Cinnarizine on the control of migraine headaches. In a trial study, Ashrafi et al. investigated the effectiveness of Cinnarizine and topiramate in two groups of children aged 4-15 years with migraine (each group = 20). Their results showed that the group that received Cinnarizine had significantly less severity of migraine headache than the other group, but the difference was not statistically significant (16). In another similar study, Ashrafi et al., in two groups of 34 children with migraine, compared the effectiveness of Cinnarizine with placebo in a randomized and double-blind clinical trial. In this study, Cinnarizine was administered at 1.5 mg/kg/day for children weighing less than 30 kg and 50 mg/ day for children weighing more than 30 kg. Finally, Cinnarizine significantly reduced the number of headaches (60% of the studied children reported a reduction of more than 50% in monthly headaches). Moreover, the severity of migraine headaches decreases from 8 to 6 at the end of the first, second, and third months (17). The Wong-Baker Faces Pain Rating Scale was used to assess headache duration and severity in this study.

In a systematic review and meta-analysis, ten studies, including seven randomized controlled clinical trials and three quasi-experimental studies, showed that Cinnarizine significantly reduces the frequency and severity of migraine attacks compared to placebo. In addition, Cinnarizine has shown better results compared to active control groups, including sodium valproate, topiramate, and propranolol (18).

In the P Calandre study in Spain, the effectiveness of Pregabalin was investigated on 30 patients with chronic migraine headaches, aged 24 to 75 years, for 12 weeks. In this study, prescribed Pregabalin was associated with a significant reduction in headache frequency ($P < 0.0001$) and headache severity ($P = 0.0005$) (19). Pizzolato also observed a significant reduction in migraine frequency after 1 and 3 months of Pregabalin administration in a prospective study in Italy on 47 adult patients (20). Hesami also investigated the effectiveness of Pregabalin compared to valproate in 140 patients in a double-blind clinical trial, and the results showed that both drugs were equally effective. Nevertheless, Pregabalin reduced the number of attacks during the first month of treatment. Comparison with the beginning of the study was not significantly effective (5).

Although many studies have been conducted on controlling migraine headaches, there is not enough evidence regarding the optimal drug. Randomized controlled trial studies of migraine preventive drugs in children and adolescents are limited and often report conflicting results. Considering the safety and efficacy of Cinnarizine and Pregabalin in migraine prophylaxis for children, this study recommends that these two drugs may be suitable for this indication

In Conclusion

In the present study, both Cinnarizine and Pregabalin reduced headache frequency, headache intensity, and migraine-related disability. Nevertheless, this improvement was more significant in the Cinnarizine group at the end of the third month.

Acknowledgment

The Ethics Review Board at Iran University of Medical Sciences approved this study's protocol (approval code: IR.IUMS.FMD.REC.1400.127). This study was conducted in accordance with the CONSORT guidelines to ensure transparent and standardized reporting, and the trial protocol was registered in the Iranian Registry of Clinical Trials (IRCT) under the registration number of IRCT20230415057911N1

Authors' Contributions

Mohammad Vafaee Shahi (MVS) and Mahmoudreza Ashrafi (MA) study conception and design. Helen Vaferi(HV) and Davood Kheirkhah (DKH) data collection. Azar Mohammadzadeh (AM) and Aina Riahi (AR) analysis and interpretation of results. Navid Hadavi (NH) and Azar Mohammadzadeh (AM) draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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