ORIGINAL ARTICLE

Comparing Pregabalin and Sodium Valproate in Pediatric Migraine Prophylaxis: A Randomized Clinical Trial

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Abstract

Objectives

Migraine is a common disorder in children, and its prophylaxis with minimal side effects is momentous. This study aimed to compare the efficacy of Pregabalin and Sodium Valproate in preventing migraine attacks.

Material & methods

Sixty-four children (aged 6-18) with migraines were recruited, as defined by Internation Headache Criteria (ICHD-III). They were randomly assigned to two groups: Sodium Valproate (n=32) and Pregabalin (n=32). The minimum dosage of drugs was prescribed in both groups. The patients were followed for four months. The parameters such as frequency, intensity, duration of migraine attacks, and the number of painkillers that the patients used monthly were recorded. The Spence Children's anxiety scale was also used to evaluate medications' effect on patients' anxiety levels.

Results

Two medications were equally effective in reducing the intensity and duration of attacks. Additionally, their effect on reducing the anxiety level of patients was equal. There was a significant difference between the effect of drugs on the frequency of migraine attacks at the end of the first and fourth months and the number of painkillers used at the end of the fourth month. The frequency of attacks was decreased by more than 50% in twenty-eight patients (90%) of Pregabalin recipients and twenty-one patients (84%) of Sodium Valproate recipients.

Conclusion

Considering the better effect of Pregabalin in the reduction of frequency of migraine attacks and pain-reducing medications consumption, Pregabalin could be a proper substitute for Sodium Valproate for prophylactic migraine treatment in children.

Keywords: Pregabalin; Valproic Acid; Migraine Disorders; Pediatrics
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Introduction

Migraine is a common neurological disorder that affects approximately 10-23% of children and adolescents (1-2). The prevalence of migraine is higher in boys before puberty but increases more rapidly in girls later, leading to a higher frequency among girls after age 11 (3). Migraine attacks are recognized with recurrent moderate to severe headache episodes in frontotemporal regions, which last for several hours and are accompanied by other symptoms such as nausea and vomiting (4).

This disorder is phenotypically similar to adult migraines with slight differences. Headache episodes are shorter in children, and GI complaints, including abdominal pain, nausea, and vomiting, are more prominent. Headaches are bilateral and occur mostly in frontotemporal regions compared to unilateral headache episodes in adults (5-6).

Migraine causes functional disturbances, including school absence and social interaction difficulties. It also profoundly affects the quality of a child's family. When the rates of headache attacks exceed one attack per week or headache episodes lead to severe functional disability, or when the acute treatment is inefficient, prophylactic treatment should be considered to reduce headache frequency and further disability. Pharmacological treatment should include medications with higher efficacy and the most minor side effects. There are currently several pharmacological groups of medications, including antihistamines, calcium channel blockers, antidepressants, and antiepileptic agents for migraine prophylaxis. However, there are no standard and definite guidelines for pediatric migraine prophylactic treatment. Only a few drugs are FDA –approved, and the choice of medications is usually based on adult studies (7).

Migraine and epilepsy have almost the same clinical symptoms and sometimes accompany one another. Therefore antiepileptic drugs are among the main groups of medications used for treating different headaches (8). Antiepileptic agents, including Valproic acid, Topiramate, gabapentin, Levetiracetam, and Zonisamide, are used for migraine prophylaxis (9). Valproic acid has a substantial role in migraine prophylaxis among adults, and several studies approved its efficacy in pediatric migraine (10-12). Pregabalin is an antiepileptic drug that attaches to alpha two delta subunit of voltage-gated calcium channels in the central nervous system and regulates calcium influx at the nerve terminals. It prevents the release of excitatory neurotransmitters, including glutamate, norepinephrine, serotonin, dopamine, and substance P. Considering glutaminergic mechanisms in the pathophysiology of migraine, this drug could be efficient in preventing migraine

attacks by reducing glutamate plasma levels (13-14).

The efficacy of Pregabalin in reducing the frequency and duration of migraine attacks has been proved in limited studies. A study in Iran compared the efficacy of Sodium Valproate and Pregabalin in the adult population and concluded that both drugs were equally effective, just that Pregabalin was not as effective during the first month of treatment (15).

Insufficient data is comparing these drugs in the pediatric population. Furthermore, there is limited data about the advantage of Pregabalin use in preventing pediatric migraine attacks. This study primarily aims to define Pregabalin's efficacy and safety in preventing pediatric migraine attacks and compare Pregabalin's efficacy and safety and widely-used Sodium Valproate. Secondarily it compared the effect of mentioned drugs on reducing anxiety levels in migrainous children.

Materials & Methods

This study was a randomized clinical trial performed between April 2019 and March 2021 in two teaching hospitals affiliated with ShahidBeheshti University of Medical Sciences, Tehran, Iran (Mofid Children's Hospital and Imam Hossein Hospital). Patients (aged between 6 to 18 years) who met the diagnostic criteria for common pediatric migraine based on International Headache Criteria (ICHD-III) were recruited (16). Other inclusion criteria were the following:

- More than two migraine attacks per week
- The attacks lead to severely disabling
- Taking painkillers more than three times a week

Exclusion criteria included other types of headaches, administration of prophylactic migraine treatment, severe psychological disease, and any structural disorders of the brain or degenerative underlying disease. Informed consent was obtained from the patient's parents before entering the study. According to the research criteria, sixty-four patients were eligible for the study. Patients were randomly assigned to two groups: Sodium Valproate (n=32) and Pregabalin (n=32). The minimum dosage of drugs was prescribed in both groups. If the patients did not respond to it, the dosage was increased until receiving a sufficient response. At the baseline, patients' demographic data (age and sex), neurologic exam data, headache frequency (number of attacks per month), and intensity of headache (based on the pain scale), as well as drugs used to relieve headaches, were recorded. Patients were followed for four months. The attacks' frequency, intensity, and duration were recorded at the end of the first and fourth months. In addition, the number of painkillers that patients used monthly was recorded. The Spence Children's anxiety scale was used to evaluate the effect of the received drugs on the anxiety level of the patients (17). It provides an overall measure of anxiety scores on six subscales, each tapping a specific aspect of child anxiety: Panic attack and agoraphobia, Separation anxiety, Physical injury fears, Social phobia, Obsessive-compulsive, and Generalized anxiety disorders. The questionnaires were completed with the cooperation of the parents and a physician at baseline and the end of the fourth month.

All analysis was performed using SPSS version 23. A one-way repeated measure ANOVA was conducted to evaluate the efficacy of Sodium Valproate and Pregabalin. Independent t-test and chi-square have been used for comparing quantitative and qualitative variables between two groups. For all analyses, P-values less than

0.05 were considered statistically significant. The study protocol was reviewed and approved by the Research Ethics Committee at Shahid Beheshti University of Medical Sciences, with the registry number of IR.SBMU.MSP.REC.1398.813.

Results

Sixty-four patients were eligible to enter the study. Patients were 1:1 randomly assigned to Sodium Valproate and Pregabalin groups by the randomizing table. Twenty-five patients on the Sodium Valproate group and thirty-one on the Pregabalingroup completed all trial phases. Figure 1 shows the consort flow diagram of the study.

The two groups had no statistically significant difference in patients' demographic data. Sensitivity to light (66.1%), sensitivity to sound (58.9%), nausea (41.1%), and vomiting (19.6) were the most common accompanied symptoms, respectively. There was no statistically significant difference in the accompanied symptoms of patients in the two groups (Table 1).

The effects of Sodium Valproate and Pregabalin on parameters of attacks (frequency, intensity, and duration of headaches) and the number of painkillers that patients used monthly were evaluated after one and four months of receiving the medications. The patient's anxiety level was evaluated at the baseline and the end of the fourth month. According to repeated measure analysis, two arms had a statistically significant effect on the frequency of attacks (Pregabalin: $F(1,30)=106.55$, $P=0.00$; Sodium Valproate: $F(1,25)=42.81$, $P=0.00$), the intensity of attacks (Pregabalin: $F(1,30)=225.64$, $P=0.00$; Sodium Valproate: $F(1,24)=556.35$, $P=0.00$), duration of attacks (Pregabalin: $F(1,30)=14.17$, $P=0.001$; Sodium Valproate: $F(1,24)=51.85$, $P=0.00$), the number of painkillers (Pregabalin: $F(1,30)=19.57$, $P=0.00$; Sodium Valproate: $F(1,24)=13.01$, $P=0.001$), and the anxiety level of patients (Pregabalin: $F(1,30)=97.04$, $P=0.00$; Sodium Valproate: $F(1,24)=92.87$, $P=0.00$). Figure 2 shows the changes in each parameter over the patients' follow-up process.

According to the analysis, there was a statistically significant difference between the effect of the two drugs on the frequency of migraine attacks at the end of the first and fourth months and the number of painkillers used at the end of the fourth month. The frequency of attacks was decreased by more than 50% in twenty-eight patients (90%) of Pregabalin recipients and twenty-one patients (84%) of Sodium Valproate recipients. In addition, the attacks stopped completely in 13 patients (42%) of Pregabalin and five patients (20%) of Sodium Valproate groups. However, two medications were equally effective in reducing the intensity and duration of attacks. Additionally, their effect on reducing the anxiety level of patients was equal. (Table2)

Table 1. Demographic data and clinical manifestations of patients

	Total	Sodium valproaten=25	Pregabalin n=31	P-value
Age (year)a	10.75±2.58	10.18±2.56	11.25±2.53	0.13
Sex b				
Male	32 (57.1)	16 (64)	16 (51.6)	0.35
Female	24 (42.9)	9 (36)	15 (48.4)	
Accompanied symptoms b				
Nausea	23 (41.1)	10 (40)	13 (41.9)	0.88
Vomiting	11 (19.6)	5 (20)	6 (19.35)	0.79
Sensitivity to light	37 (66.1)	17 (68)	20 (64.5)	0.78
Sensitivity to sound	33 (58.9)	15 (60)	18 (58.1)	0.88

a: mean± standard deviation, b: number (percent)

Table 2. The comparison of study parameters at baseline, first, and the fourth month between two groups**.**

Parameter	Time	Sodium valproate n=25		Pregabalin n=31		P-value
		Mean ±SD	Median (range)	Mean ±SD	Median (range)	
Frequency of attacks (at month)	Baseline	17.56±10.87	12 (4-30)	16.45±9.98	13 (2-30)	0.69
	Month 1	10.24±8.80	8 (0-30)	6.41±4.52	6 (0-15)	0.05
	Month 4	7.00±9.32	4 (0-30)	2.41±2.83	2 (0-8)	0.02
Intensity of attacks	Baseline	88.00±7.07	100 (70-100)	86.77±20.55	100 (40-100)	0.07
	Month 1	64.40±15.76	60 (40-100)	52.74±25.94	50 (0-100)	0.05
	Month 4	38.40±29.28	30 (0-100)	36.45±34.88	40 (0-100)	0.82
Duration of attacks (minute)	Month 1	138.00±117.47	120 (30-600)	111.45±131.63	90 (25-76)	0.42
	Month 4	67.20±46.86	60 (30-240)	65.48±133.35	30 (10-760)	0.94
Number of painkillers (at month)	Baseline	9.16±10.34	8 (4-30)	5.93±6.75	4 (4-25)	0.16
	Month 1	4.96±8.18	3 (0-30)	2.09±3.47	0 (0-11)	0.11
	Month 4	3.68±8.17	0 (0-30)	1.00±2.35	0 (0-10)	0.02
Total anxiety score	Pre-treatment	36.16±17.80	30 (12-89)	37.41±21.15	32 (6-103)	0.81
	Post-treatment	26.00±15.05	21 (1-66)	29.74±17.50	25 (5-77)	0.40

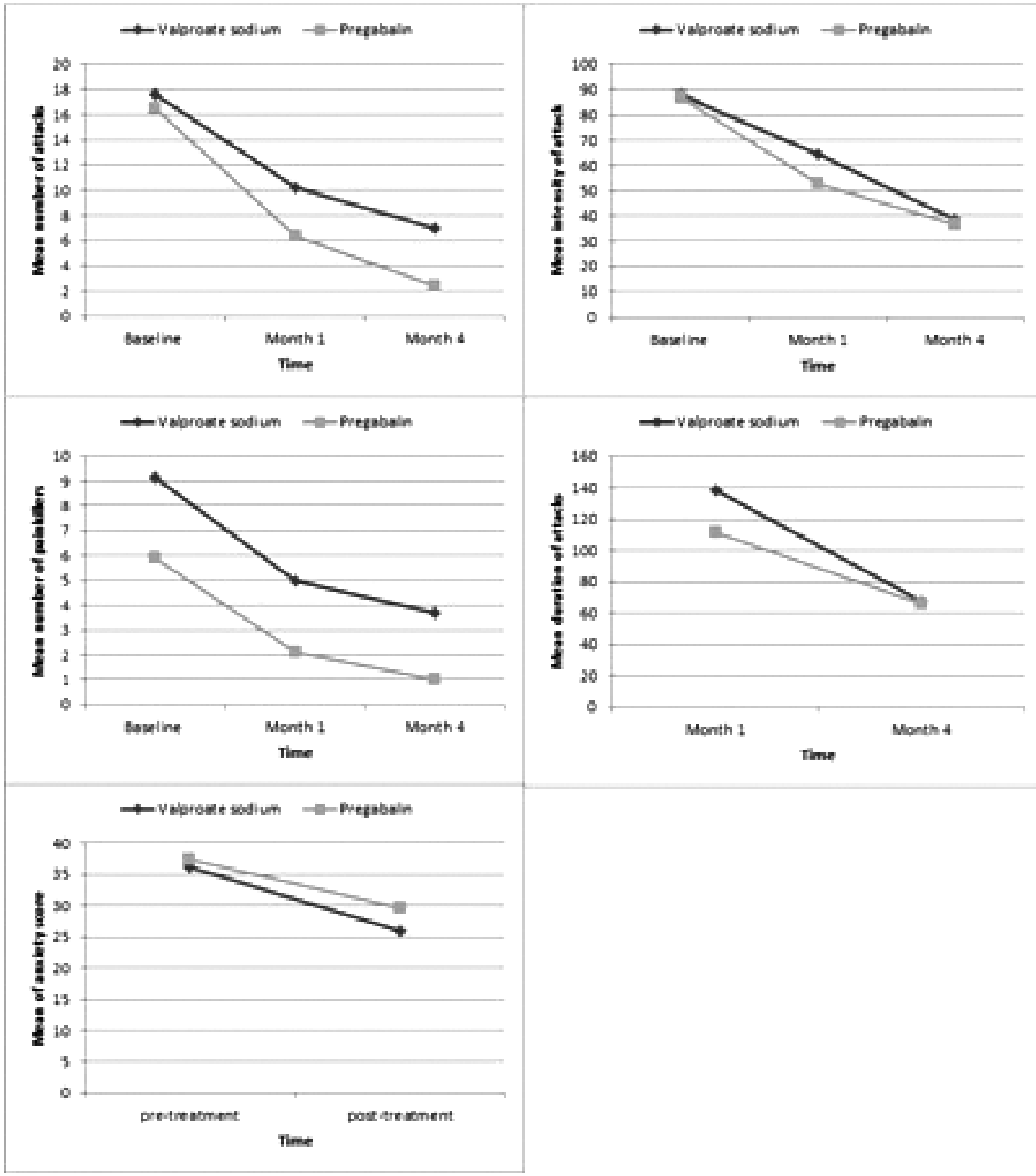

Figure 1. *Consort flow diagram of the study*

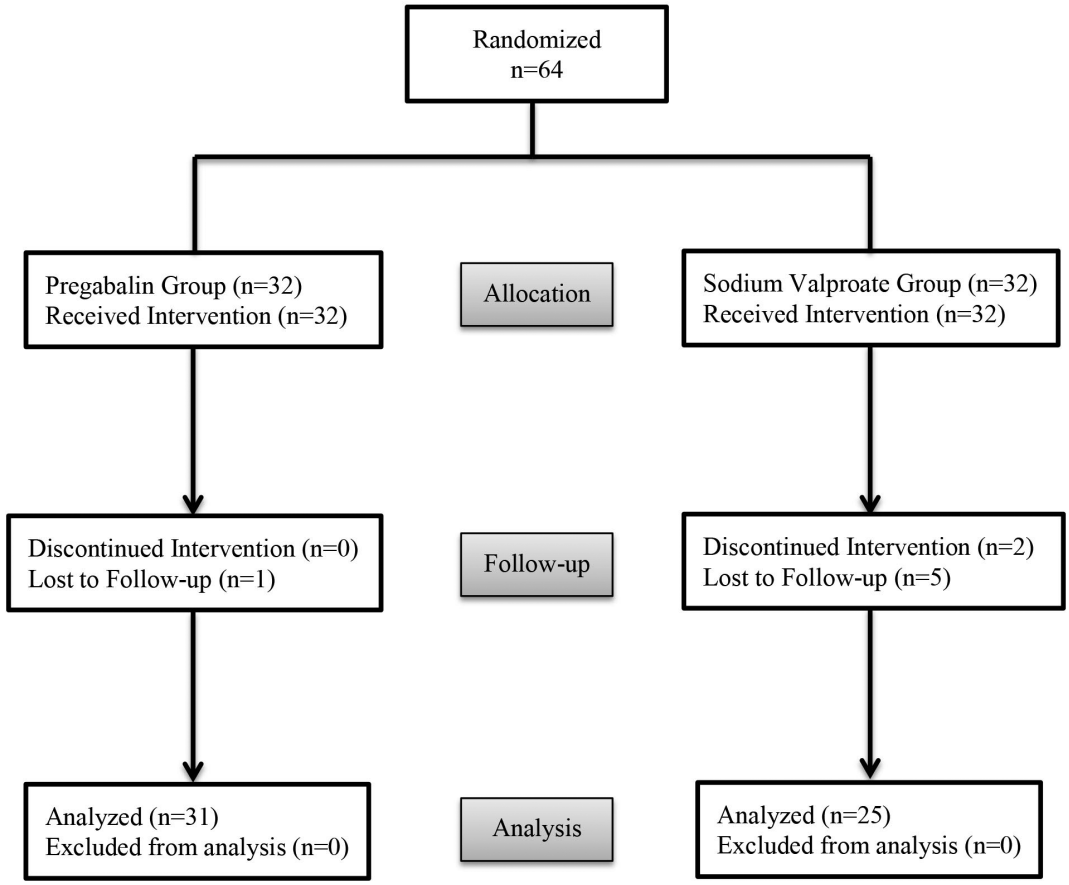

Figure 2. *Change trends of attack parameters (frequency, intensity, and duration of headaches), the number of painkillers taken, and anxiety score of patients in two groups*

Discussion

Treatment of pediatric migraine has always been challenging and requires pharmacological and non-pharmacological interventions. The non-pharmacological approach recommends regular exercise, sleep, proper diet, and stress reduction techniques (18). Pharmacological migraine treatment is often based on prophylactic medications. About half of the children with migraine take prophylactic agents daily (19). Currently, most physicians prescribe prophylactic medications that have been effective in adults for migraine treatment, and adult treatment protocols are the primary principles for reducing the pediatric frequency, intensity, and duration of migraine attacks (20).

Based on the present study, Pregabalin and Sodium Valproate were equally effective in reducing the intensity and duration of migraine attacks. However, Pregabalin has been more effective statistically in reducing the frequency of migraine attacks. Besides, the consumption of pain-reducing medications has significantly been lower in the Pregabalin group than in the Sodium Valproate group. Suppose the reduction of frequency of migraine attacks is considered the main therapeutic effect of prophylactic migraine medications, Sodium Valproate usage lead to at least 50% frequency reduction in 84% of patients, which has been reported between 48 to 78.5% in other studies (21-25). However, this study revealed that Pregabalin reduced the frequency of migraine

attacks in 90% of the patients.

In contrast to the present study, a similar study on migrainous adults showed that Pregabalin and Sodium Valproate were equally effective in reducing migraine attacks' frequency, intensity, and duration (26). Compared with adult studies, Pregabalin seems more effective among pediatric populations. In adults, Pregabalin reduced the frequency of attacks to 4.86±6.46 per month; in this study, Pregabalin reduced attacks frequency to 2.41±2.83 per month. The results of the present study were similar to other pediatric studies. In a study by Bakhshandebali et al., the frequency of migraine attacks has been reduced to 2.2±4.5 and 1.76 ±6.2 attacks per month after four and eight weeks of prophylactic treatment with Pregabalin, respectively, and Pregabalin has been more effective in the reduction of frequency of migraine attacks in comparison with propranolol (27). Ashrafi et al. compared propranolol and Sodium Valproate in 120 patients with migraines. Both drugs were effective in reducing of duration and severity of attacks. More than 50% reduction in headache frequency was reported in 72% of the Sodium Valproate group and 69% in the Propranolol group (21). In another study, Bidabadi et al. compared propranolol and Sodium Valproate in sixty-three children with migraines. According to their findings, 83% of the propranolol group and 63% of Sodium Valproate receivers had more than 50% headache frequency reduction (28).

The present study suggests that in addition to the migraine prophylactic effects of Pregabalin and Sodium Valproate, both drugs are equally effective in reducing anxiety levels in migrainous children. Approximately 29% of the Pregabalin group and 40% of the Sodium Valproate group have experienced some side effects of the drugs. The most commonly observed side effects of Pregabalin were: drowsiness (12.9%), headache intensification (9.67%), vertigo (3.22%), and stress intensification (3.22%). In the Sodium Valproate group, the most common side effects were drowsiness (12%), weight gain (12%), vertigo(8%), and gastrointestinal complaints (8%). All side effects have been well-tolerated. The type and prevalence of side effects have been different in other studies. In the study of Bakhshandebali et al., side effects have been reported in 6.6 % of children treated with Pregabalin (27). The side effects were drowsiness (4.4%), increased appetite (2.2%), and vertigo (6.6%). Mitskostas et al. reported 57.1% side effects in patients treated with Sodium Valproate (29). It seems that the variety of the type and severity of side effects are related to the prescribed dosage of the medication. Naturally, higher doses lead to less tolerance and more side effects.

The present study had some limitations as well. In order to achieve therapeutic goals for the medications, there was no possibility of double blindness, which might have led to undesired results. In addition, this study had no control group to determine the placebo effect. The study was performed in only two pediatric medical centers in Iran. Therefore, further studies with larger sample sizes and the cooperation of other centers are recommended.

In Conclusion

this study revealed that Pregabalin and Sodium Valproate was influential in pediatric migraines' prophylaxis. However, considering Pregabalin's better effect in reducing the frequency of migraine attacks and pain-reducing medication consumption, Pregabalin could be a proper substitute for Sodium

Valproate for prophylactic migraine treatment in children.

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The study protocol was reviewed and approved by the Research Ethics Committee at Shahid Beheshti University of Medical Sciences, with the registry number of IR.SBMU.MSP.REC.1398.813.

Author's contribution

All authors contributed to the study's conceptualization, design, data-gathering process, interpretation, draft writing, revising, and editing.

Conflict of interest

The authors have declared no competing or potential conflicts of interest

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