ORIGINAL ARTICLE

Comparing Prophylactic Effect of Levetiracetam, Sodium Valproate, and Propranolol in Pediatric Migraine: A Randomized Clinical Trial

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Abstract

Objectives

Epidemiologic studies point to an increased prevalence of migraine in children in recent decades. Migraine treatment involves acute and prophylactic therapy. Recently, such anti-epileptic drugs as Levetiracetam have been used to treat adult migraines. The present study aimed to compare the efficacy of Levetiracetam, Sodium Valproate, and Propranolol in preventing migraine headaches in children.

Material & Methods

In this clinical trial, children with migraine were randomly divided into three groups. Each group consisted of 13 children. Two groups were treated with Propranolol and Sodium Valproate, respectively. Another group (the case) was treated with Levetiracetam. The patients were assessed based on headache score, PedMIDAS, and headache frequency before and three months after the intervention. Finally, the data was analyzed using descriptive and analytical statistical methods.

Results

Levetiracetam significantly reduced the headache severity (P=0.026), frequency (P=0.024), and PedMIDAS score (P=0.001) in children with migraine. However, no significant difference was found between the three groups. The percentage of patients who experienced pain relief was detected as 69.24%, 92.31%, and 30.76% in the Propranolol, Sodium Valproate, and Levetiracetam groups, respectively.

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Conclusion

This study concluded that Levetiracetam can be used as a migraine prophylaxis drug in children.

Keywords: Levetiracetam, Propranolol, Sodium Valproate, Migraine, Children, Prophylaxis

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Introduction

Migraine disorders are the leading cause of disability in children (1). Approximately 10% of children between the ages of 5 and 15 have migraine (2). Up to 18% of children in the pediatric emergency room have migraine-related symptoms (3). Children with migraine have a genetic predisposition activated by an environmental or physiological stimulus. The brain of people with migraines is genetically more sensitive to the neurochemical changes which can cause symptoms. These neurochemical changes reduce the threshold of trigeminal nerve excitability and neuronal inflammation (1).

Roughly 25% of Children with migraines have one attack a month or less, but about 61% of patients experience more than four serious headache attacks a month requiring prophylaxis treatment (5).

Migraines in children are different from adults. Migraine in children is often without aura and bilateral. The duration of headaches in children is less than in adults (6). Migraine headaches are often severe and cause severe functional impairment during attacks. Students with migraine headaches are often absent from school, suffer from academic failure, and drop out of sports due to recurrent headaches (7). Recurrent migraine headaches also reduce individual communication and affect the quality of life and daily activities (8). The effect of headaches on success in academic achievement, memory, personality, interpersonal relationships, and school attendance depends on the etiology, frequency, and severity of the headaches in children (9). Early diagnosis and intervention improve long-term migraine outcomes in childhood (10, 11). Two main approaches exist to migraine headache treatment: acute and prophylactic therapy. Prophylactic therapy is used for cases where the severity of headache attacks affects daily activities, with two or more migraine attacks per month, with long-lasting headaches, not mentally able to endure the headache attacks, that standard therapies were not practical for acute migraine attacks (12). Treatment of migraine prophylaxis includes non-pharmacological and pharmacological treatment (13). Non-pharmacological therapies include sleep patterns, diet, physical activity, stress management, and avoidance of stimulants (14).

Various compounds such as beta blockers, antidepressants, calcium blockers, anti-epileptic drugs, and Antihistaminic drugs were used to prevent migraine headaches (15, 16, 17, 18).

Recently, Levetiracetam has been used as a prophylactic therapy for migraine (19). As an anti-epileptic drug, Levetiracetam is rapidly and almost completely absorbed after oral ingestion. It rarely binds to proteins compared with other anti-epileptic drugs (20). Metabolism of Levetiracetam is through enzymatic hydrolysis of the acetamide

group and independent of the hepatic cytochrome P450 system. This drug and its metabolites are excreted from the urine and have a half-life of about 6-8 hours. Some studies have shown that Levetiracetam significantly reduced the frequency of migraine headaches in the same dose used to treat epilepsy (19, 20, 21).

Comparative studies have addressed some drugs' positive effects in preventing migraine attacks. However, no consensus exists on a drug's superiority over another (22, 23). Given the materials mentioned above, the present study aimed to compare the efficacy of Levetiracetam, Sodium Valproate, and Propranolol in preventing migraine headaches in children with migraine.

Materials & Methods

The statistical population consisted of all the patients who visited the Be'sat Pediatric Neurology Clinic and Imam Khomeini Clinic in Hamedan during 2017 (12 months). Inclusion criteria were migraine headache based on ICHD-3 criteria (Table) in patients aged 5 to 15, eligible for prophylactic therapy, and with their parent's consent. The patients with secondary headaches, the incidence of serious adverse drug reactions, uncooperative patients, and those with irregular visits were excluded from the study. Those with at least one of the following criteria were eligible for prophylactic therapy: a) more than one headache attack per week; b) more than three headache attacks per month; c) more than one-day school absenteeism per month due to headache; d) a score higher than 20 score in PedMIDAS (Table2).

The patients were randomly divided into three groups (using a random number table). Each group consisted of 13 children. The first group (case) was given 50 mg/kg/day Levetiracetam tablet for one month. The second group (control) was assigned 15 mg/kg/day Sodium Valproate tablet for one month. The third group (control) was given 1 mg/kg/day Propranolol tablet for one month.

These three groups were treated for at least one month. If prophylactic treatment was effective (less than three headache attacks per month and PedMIDAS score less than 10), the drug was continued for four to six months. Other drugs were selected to continue the treatment in case of exacerbated symptoms, no response to the drug, and serious side effects. The efficacy of these drugs was assessed based on the headache severity, headache frequency (per week), and disability. Headache severity was measured using a headache score. Headache frequency (per week) was measured by asking the parents, and headache disability was measured using PedMIDAS (three months before and after the intervention). The patient was identified as a headache-free case if PedMIDAS<10, headache score < 2, and 1 < headache frequency (per week) < 2 after three months. Headache Score was given based on the patient's responses (0 = painless, 1 = mild pain that does not interfere with daily activities, 2 = moderate pain that interferes with some daily activities, 3 = severe pain that disrupts all daily activities). The overall PedMIDAS score was calculated by the number of days the patient did not function properly. Headache frequency was measured in a weekly manner, and headache severity was measured in a monthly manner. However, PedMIDAS was measured three months before and after the treatment. The treatment continued after a month if the headache frequency and severity did not increase and the patient could tolerate the drug.

The required data was collected using a

questionnaire, phone interviews, and patient visits. Demographic data included age, gender, and family history of headaches. These data were recorded in a questionnaire on the first visit. The qualitative data was described with frequency and percent, and the quantitative data was described with mean and standard deviation. The data was analyzed using SPSS version 16, Kolmogorov-Smirnov, Chi-square, the paired t-test, Wilcoxon, the independent t-test, and Mann-Whitney statistical tests. P<0.05 was considered as the significant level in all statistical tests.

Informed consent forms were collected from all the patients' parents before the study. This project was confirmed and registered with the IR.UMSH.REC.1396.532 ID number at the Research Ethics Committee of Hamadan University of Medical Sciences and IRCT20160802029171N3 ID number at the Iranian Registry of Clinical Trials.

Results

Of seventy-five children referred to the Pediatric Neurology Clinic with headaches, thirty-nine were selected. The patients were 17 males (43.58%) and 22 females (56.31%) with an average age of 9.83 ± 2.9 years old. The results of statistical tests showed no significant difference between the three groups in terms of age, gender, and family history of headache (P<0.05). No significant difference was found between the three groups in the headache severity and frequency before the treatment (P<0.05).

Of 13 patients in the group treated with Propranolol, nine completed the treatment (the type of treatment was altered to Sodium Valproate for two patients since no change was detected in the headache parameters. After one month of treatment with Propranolol, one patient died due to an accident, and one did not respond to treatment due to irregular drug use, arbitrary discontinuation of medication, and lack of cooperation). The headache severity, frequency, and disability significantly decreased in the children treated with Propranolol (Pvalue < 0.01) (Table 3).

Twelve patients completed treatment in the group treated with Sodium Valproate (the type of treatment changed to Propranolol for one patient due to a minimal change in the headache parameters after one month). The headache severity, frequency, and disability significantly decreased in the children treated with Sodium Valproate (Pvalue < 0.01) (Table 3). Six people completed the treatment in the group treated with Levetiracetam (the type of treatment changed to sodium valproate in five cases due to exacerbations of symptoms and no change in the headache parameters after one month and two cases due to side effects including agitation, aggression, and severe drowsiness). The headache severity, frequency, and disability significantly decreased in the children treated with Levetiracetam (Pvalue<0.05) (Table 3).

Table 4 shows no significant difference in the mean headache parameters after the treatment between the three groups (Pvalue<0.05). Statistical analysis showed no significant difference in variations in headache parameters between the three groups (Pvalue<0.05).

cases was significantly higher in the two Propranolol (Pvalue = 0.015) and Sodium Valproate groups (Pvalue = 0.001) than in the Levetiracetam group. Table 6 shows that more cases did not respond to Levetiracetam than the other two groups and fewer cases did not respond to Sodium Valproate than the other two groups. Although no significant difference was found between the three groups in response to treatment (Pvalue<0.05), the P-value

Table 1. Comparison of headache parameters in the three groups before and after treatment

	After treatment	**Before Treatment**		
0.006=PValue	0.52 ± 0.44	0.66 ±2.22	Propranonlol	Headache Score
0.002=PValue	0.51 ± 0.42	0.60 ± 2.00	Sodium Valproate	
0.026=PValue	0.51 ± 0.33	0.40 ± 2.17	Levetiracetam	
0.008=PValue	0.32 ± 0.19	1.94 ±3.44	Propranonlol	Frequency (per week)
0.002=PValue	0.45 ± 0.25	0.55 ±2.00	Sodium Valproate	
0.024=PValue	0.78 ± 0.70	1.83± 4.17	Levetiracetam	
0.000=PValue	0.52 ± 3.33	5.54 ± 16.00	Propranonlol	PedMIDAS
0.000=PValue	2.42 ± 4.67	2.17 ± 13.75	Sodium Valproate	
0.001=PValue	4.21 ± 5.17	4.35 ± 19.17	Levetiracetam	

Table 2. Comparison of headache parameters between the three groups after the treatment

	Levetiracetam	**Sodium Valproate**	**Propranonlol**	
0.912=PValue	0.51 ± 0.33	0.51± 0.42	0.52± 0.44	Headache Score
0.223=PValue	0.78 ± 0.70	0.45 ± 0.25	0.32± 0.19	Frequency (Per Week)
0.547=PValue	4.21 ± 5.17	2.42 ± 4.67	4.00 ± 3.33	PedMIDAS

Table 3 . Comparison of the number of headache-free cases and response to treatment in the three groups

				Propranonlol	
		Levetiracetam	**Sodium Valproate**		
0.002=PValue	(30.76)4	(92.31)12	(69.24)9	Yes	Headache Free (%)
	(69.24)9	(7.69)1	(15.38)2	No	
	(0.00)0	(0.00)0	(15.38)* 2	Uncertain	

*one patient for death and another for disruption of drug .

Table 4. Comparison of severe side effects of the drugs in the three groups

				Propranonlol	
		Levetiracetam	Sodium Valproate		
$0.084=P_{Value}$	2(15.38)	0(0.00)	0(0.00)	Yes	side effects (%)
	11(84.62)	13(100)	11(84.62)	No	
	0(0.00)	0(0.00)	(15.38)*2	Uncertain	

*one patient for death and another for disruption of drug .

was close to the significant level.

The least side effects were reported in the Sodium Valproate and Propranolol groups, and the highest side effects were reported in the Levetiracetam group. Although no difference was observed between the side effects of the drug between the groups (Pvalue<0.05), the P-value was close to the significant level (Table 6).

More cases responded to Sodium Valproate compared to the other two drugs. Two cases with mild gastrointestinal complications and one with hair loss were observed in the Sodium Valproate group. No complications related to menstruation and polycystic ovaries were observed.

Discussion

This study showed 12 headache-free cases in the 13 patients treated with Sodium Valproate (92.30%). No severe side effects were also reported in this group. The headache severity, frequency, and PedMIDAS significantly decreased after treatment in this group. The efficacy of Sodium Valproate was 60% in the first study about the effectiveness of this drug in migraine prevention. Another study obtained the same results several years later (24, 25). More cases responded to Sodium Valproate in this study compared to previous studies. However, genetic background, previous history of prophylactic therapy, and patient assessment methods are involved in the efficacy of this drug.

Nine headache-free cases (69.23%) were reported among 13 patients treated with Propranolol in this study. No serious side effects were reported in this group. The headache severity, frequency, and PedMIDAS significantly decreased after treatment in this group. Various studies have examined the prophylactic effect of Propranolol in adults. The results showed that Propranolol reduced the headache frequency by more than 50% in 60-80% of the patients (26-28). However, some reported that this drug did not prevent migraine attacks (29). The dose of Propranolol used in the former study was half of the one used in this study. Therefore, lower doses of Propranolol may not be effective in preventing migraine attacks.

No serious side effects were reported for Propranolol and Sodium Valproate in this study. Other studies have shown that Sodium Valproate increases the risk of congenital malformation in the fetus in pregnant women (especially young females). These malformations include a 20-fold increase in neural tube defects, cleft palate, cardiovascular disorders, genitourinary defects, delayed growth, endocrine disorders, organ malformations, and autism (30, 31). No significant difference was found between Sodium Valproate and Propranolol in the headache

parameters after the treatment in this study (Pvalue <0.05). Although the number of headache-free cases was higher in Sodium Valproate than in Propranolol, no statistically significant difference was found between the two drugs.

A study by Amanat et al. (2020) compared the effects of Sodium Valproate, cinnarizine, and placebo on the prevention of migraine headaches in children, revealed that Sodium Valproate (66% of patients) and cinnarizine (71% of patients) significantly reduced the severity and frequency of headaches in children. Five of the fifty-three children treated with Sodium Valproate had mild complications (32).

Zamani et al. showed a 50% or more than 50% decrease in the frequency of headache attacks in 60% of the patients treated with Sodium Valproate and 78% treated with Propranolol. These results were consistent with the results of this study (11).

Taghdiri et al. studied the response to treatment and side effects of Propranolol and Sodium Valproate in children with migraine. The frequency of headache attacks decreased in both groups. The headache frequency in the Propranolol group (69.2%) decreased more than the Sodium Valproate group (73.1%). Three patients complained about dizziness in the Propranolol group, and two showed the same symptoms in the Sodium Valproate group in the former study (16).

Four headache-free cases (30.76%) were reported among 13 patients in the Levetiracetam group in this study. The percentage of side effects in this group was reported as 15.38%. The headache severity and frequency and PedMIDAS significantly decreased after the treatment in this group. The efficacy of some anti-epileptic drugs (e.g., Levetiracetam) in preventing migraine was investigated in some studies. Levetiracetam's pharmacological properties and safety made it superior to other anti-epileptic drugs for migraine prevention (22). Although most studies investigated the efficacy of Levetiracetam in migraine in adults, some studies showed that Levetiracetam is safe to be used for the treatment of pediatric epilepsy (including children under two years old) and children with migraine can suitably tolerate this drug (3). Although headache parameters in the Levetiracetam group (those who completed the course of treatment) did not significantly differ from the Propranolol and Sodium Valproate groups (those who completed the course of treatment), the number of headache-free cases in the Levetiracetam group was significantly lower than in Propranolol and Sodium Valproate groups in this study. Some previous studies showed the efficacy of levothyroxine in controlling migraine headaches in adults (34, 35, 36, and 37).

Some previous studies addressed the efficacy of Levetiracetam in children. Those studies showed that Levetiracetam significantly decreased the frequency and severity of migraine headaches in children, which was consistent with the results of this study (22, 38).

This drug's side effects were reported in this study, including agitation, irritability, aggression, and drowsiness. Therefore, the medication was changed for two cases in this study. Although the difference between the three groups was not statistically significant, it was close to a significant level. In other studies, the main side effects of Levetiracetam were drowsiness, behavioral disorders, fatigue, dizziness, and headache (41, 42). There are conflicting reports on the behavioral side effects of Levetiracetam (33), and more studies are needed to determine the optimal dosage of this drug for treating migraine in children to obtain high efficacy and minimal side effects. Most studies did not report

behavioral side effects of Levetiracetam and could be relieved with such interventions as pyridoxine therapy and discontinuation of Levetiracetam (43, 44). Some studies reported no serious side effects requiring immediate discontinuation of therapy in the patients treated with Levetiracetam (45). Miller et al. reported that one patient suffered from dizziness, agitation, drowsiness, and hostile behavior, which led to drug discontinuation (22).

In Conclusion

The findings of this study showed that Sodium Valproate and Propranolol effectively prevent headaches. Additionally, the study results indicated that Levetiracetam is effective in reducing headache severity and frequency in children. However, the efficacy of Levetiracetam is not as acceptable as that of Sodium Valproate and Propranolol. Insufficient evidence supports the prescription of Levetiracetam as the first line in pediatric migraine headaches. However, further studies with larger sample sizes, longer treatment duration, and follow-up are required to generalize the results to the entire population.

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Authors' Contribution

Afshin Fayyazi: literature search; study concepts and design, manuscript preparation

Farzaneh Esnaashari: manuscript editing and review.

Hosein Mansuri: clinical studies, data acquisition, analysis, statistical analysis;

Nasrollah Pezeshki: manuscript editing and review

Conflict of interest

None

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