Original Article

Comparison of Levetiracetam and sodium Valproate in migraine prophylaxis: A randomized placebo-controlled study

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Abstract

Background: Migraine is a chronic and disabling disorder. Treatment of migraine often comprises of symptomatic (abortive) and preventive (prophylactic) treatment. The current drugs used in migraine prophylaxis include antidepressant drugs (Serotonin Reuptake Inhibitors, Tricyclic antidepressants), and anti-epileptic drugs (valproate, gabapentin, etc). **Objective:** The objective of our study was to assess the efficacy and tolerability of levetiracetam in adult migraine prophylaxis, compared to valproate and placebo. **Materials and Methods:** We conducted a prospective, randomized, placebo-controlled study. A total of 85 patients were randomized to receive levetiracetam 500 mg/d (n = 27), valproate 500 mg/d (n = 32) or placebo (n = 26). The patients were evaluated for treatment efficacy after 6 months. Efficacy was assessed as a more than 50% decrease in headache frequency. **Results:** In levetiracetam group, 17 (63.0%) patients experienced a more than 50% decrease in headache frequency, while this efficacy number was 21 (65.6%) for valproate group and 4 (15.4%) for placebo group. The difference was not statistically significant between levetiracetam and valproate, while it was significant when comparing either levetiracetam or valproate to placebo. **Conclusion:** Compared to placebo, levetiracetam offers improvement in headache frequency in patients with migraine. The efficacy of levetiracetam in migraine prophylaxis is comparable to currently used drugs such as valproate.

Key Words

Efficacy, levetiracetam, migraine, prophylaxis, valproate

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Introduction

Migraine is a common neurological disorder. According to the population based studies, about 10-12% of the general population suffer from migraine.[1-3] It can be highly disabling, and has been estimated to be the most costly neurological disorder in the European Community.[4,5] Classically, it is categorized as migraine with aura (classic migraine) and migraine without aura (common migraine).

Therapeutic options for migraine are widely examined and described. Pharmacological treatment of migraine consists of prophylactic (preventive) treatment and symptomatic (abortive) treatment. The symptomatic therapy of migraine ranges from simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen to triptans or the less commonly used dihydroergotamine.[6] Frequent, severe, disabling and long-lasting migraine attacks require prophylaxis. The prophylactic therapy in both migraine without aura and migraine with aura consists of beta-blockers, calcium-channel blockers, partial serotonin agonists, tricyclic agents and antiepileptic agents such as gabapentin, valproate and topiramate.[6-8]

While these drugs have been shown effective in prophylactic treatment of migraine, newer drugs have also emerged to be effective. Levetiracetam, a broad spectrum anti-epileptic used in many seizure types in children and adults with an excellent tolerability profile, have also been used in migraine prophylaxis.[9] Studies have shown that levetiracetam has been effective in prophylactic treatment of migraine in elderly[10] and adult patients.[11] It has also been shown to be promising in refractory chronic migraine[12] and for migraine with aura with high frequency of attacks.[13]

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Here, we conducted a randomized placebo controlled study in adolescent and adult patients with migraine, comparing the efficiency of levetiracetam and sodium valproate after 6 months of prophylactic therapy.

Materials and Methods

The study duration was from March 2013 till March 2014. The inclusion criteria included:

1. Patients diagnosed with migraine, according to the 2nd edition of International Classification of Headache Disorders (ICHD-II) criteria of International Headache Society (IHS)[14];
2. Presence of an indication for prophylactic treatment (intolerable headache attacks that were either debilitating or resulted in significant loss of daily function, frequent attacks (≥ 4 attacks per month));
3. Adolescent and adult age (age > 12);
4. New untreated patients (no history of proper anti-migraine treatment by a headache specialist (e.g., neurologist, etc.));
5. No concomitant major medical, pregnancy, or psychiatric disorder on first evaluation (e.g. major depression, psychosis, dementia, etc.).

Patients with headache causes other than migraine (cluster headache, headache caused by space-occupying lesions, etc.) were excluded. Women in childbearing age were equally recruited in the study. However, as there exists concerns about the use of antiepileptic drugs during pregnancy, pregnant patients were excluded from the study. During the first visit, a thorough general and neurologic examination was performed. Patients' data including sex, age, occupation, neurologic exam data, symptom duration, headache frequency (attacks per month) were recorded in a computerized database. Patients were then randomly assigned to three groups (based on a computerized selection program that randomly generated a series of 3 characters (V, L, and P) by an equal chance. The patients would then receive the corresponding drug based on the results of the randomizing program):

1. LEV group, in which an initial 250 mg/day of levetiracetam was started, followed by a 250 mg/week increment to a total dose of 500 mg/day after 1 week. The starting dose, total dose and dose escalation was the same in all patients;
2. VPT group, in which 500 mg/day of sodium valproate was prescribed;
3. Placebo group, in which placebo was initiated. Placebo was a white tablet indistinguishable by the patient (provided by Kimidarou, Tehran, Iran).

The study was designed in a double-blinded fashion. All three drugs were contained in anonymous and without label containers, marked by codes provided by the manufacturer and decoded by the completion of the study. The patients were then followed after 1, 3 and 6 months. The headache frequency was recorded in the database. During follow-up visits, a general and neurologic exam was again performed and the patients were also asked about possible side effects. Treatment efficacy was assessed as a more than 50% decrease in headache frequency (per month attacks) in the last visit (after 6 months). This was regarded as a measure of treatment outcome because all patients with a 50% decrease in attack frequency considered this as an improvement in their quality of life.

The study was performed with adherence to the statements of the Declaration of Helsinki and regulations of IRB (Institutional Review Board). All patients gave their consent to participate in the study.[15] Dependent sample and repeated measure ANOVA were used for quantitative variables.[16,17] All analysis was performed with PASW Statistics 18 package (Predictive Analytics Software, SPSS inc, USA).[18,19] For all analysis, *P* values less than 0.05 were considered statistically significant.

Results

Thirty-five patients were assigned to each treatment group by the randomizing program (a total of 105 patients). Among them, 27 (77.1%) completed the protocol in LEV group, 32 (91.4%) in VPT group, and 26 (74.3%) in placebo group. A total of 85 patients finally completed the treatment protocol and participated in all follow-up visits.

The patients' data are presented in Table 1. No patient had an abnormal neurologic examination on either the first or last visit. 77 patients suffered from migraine without aura (90.6%), while 8 (9.4%) had migraine with aura. The number of monthly attacks before and 6 months after initiation of treatment are presented in Table 2. Both levetiracetam and valproate significantly decreased attacks after 6 months. The difference was statistically different for both LEV and VPT compared to placebo (*P* = 0.019 and 0.012, respectively), while the difference was not significance between LEV and VPT themselves (*P* = 0.78). Table 3 shows the number of patients who experienced a more than 50% decrease in headache frequency after 6 months of treatment. The difference was not statistically

Table 1: Patients' data on first evaluation

Age	Mean: 35.3 years, range: 20-52 years
Sex	F = 62, M = 23
Symptom duration	4.6 months, range: 1-13 months
Headache frequency	Mean: 7.3/month, range: 4-13/month

Table 2: Number of headache attacks before and 6 months after treatment

Drug	Baseline attack rate (attacks/month)	Attack rate after 6 months (attacks/month)	*P* value
Levetiracetam	7.9	2.9	0.003
Valproate	8.3	2.8	<0.001
Placebo	7.9	6.9	0.12

Table 3: Number (%) of patients of in each treatment group with 50% decrease in headache frequency after 6 months

Drug	Number (%)	*P* value
Levetiracetam	17 (63.0)	0.028
Valproate	21 (65.6)	0.022
Placebo	4 (15.4)	

significant between levetiracetam and valproate ($P > 0.05$), while it was significant when comparing either levetiracetam or valproate to placebo ($P = 0.028$ and 0.022, respectively).

Twenty-three patients (85.2%) reported no side effects on levetiracetam, while this figure was 22 (68.8%) in VPT group. The most frequent side effects in LEV group were somnolence and dizziness, mild irritability, hostility, moodiness, and hyperactive behavior.

Discussion

Therapeutic options for migraine are widely examined and described. Pharmacological treatment of migraine consists of prophylactic treatment and symptomatic treatment. Both migraine without aura and migraine with aura might benefit from preventive drug therapy with beta-blockers, calcium-channel blockers, partial serotonin agonists, tricyclic agents and antiepileptic agents such as gabapentin, valproate and topiramate.[6-8] In migraine with aura, lamotrigine may also be beneficial.[20-23]

Understanding the role of Cortical Spreading Depression (CSD) as the underlying mechanism in migraine, and hence categorizing migraine as a neuronal rather than vascular disease, have emerged therapies to target this phenomenon.[24-26] This cortical hyperexcitability may play a role in the physiopathology of migraine, and therefore, antiepileptic drugs were used in migraine prophylaxis.[10,27] A variety of causes for hyperexcitability of the brain in migraine have been suggested. These causes include low cerebral magnesium levels, mitochondrial abnormalities, dysfunctions related to increased nitric oxide or the existence of a P/Q type calcium channelopathy.[27,28] Gabapentin, valproate, topiramate, methysergide, amitriptyline, and propranolol have been shown to exert inhibitory effects on CSD, especially if continued beyond 3-4 weeks,[29] while carbamazepine and oxcarbazepine have not been efficient.[25]

However, not all antiepileptic drugs are useful in clinical practice for the prophylaxis of migraine. Linde *et al*., in a review showed that available evidence does not allow robust conclusions regarding the efficacy of antiepileptic drugs other than gabapentin, pregabalin, topiramate and valproate in the prophylaxis of episodic migraine among adults. However, they observed that in some trials, levetiracetam was significantly superior to placebo in reducing headache frequency,[30] a finding supported by two other studies.[31,32]

Levetiracetam is a broad-spectrum anti-epileptic drug that is effective against a variety of seizure types. It has a very favorable pharmacokinetic profile. It has excellent bioavailability, linear kinetics, minimal plasma protein binding and quick achievement of steady state concentrations. It has no clinically relevant drug-drug interactions. Its rapid onset of action, lack of drug-drug interactions and availability as an intravenous solution makes it an optimal drug to treat epilepsy associated with other medical conditions. Moreover, no serious idiosyncratic side effects have been reported for levetiracetam.[9] These characteristics have made it as an interesting option in migraine therapy. Mechanisms of action of this drug remain largely unknown; recently, it has been shown to exert inhibitory effects on neuronal-type calcium channels.[13] As discussed before, calcium channelopathy may be responsible for neuronal hyperexcitability in migraine, and therefore levetiracetam may exert its prophylactic effects through inhibiting these channels. Moreover, along with the proven effect of other antiepileptic drugs on CSD, one other mechanism of action of levetiracetam in migraine prophylaxis may be its probable inhibitory effects on CSD.

Verma *et al*., in a prospective randomized placebo-controlled study in 52 patients (in both drug and placebo groups) showed a significant reduction in the frequency (attacks per month) and severity of migraine in the group receiving levetiracetam (1000 mg/d) as compared to the placebo group. Patients treated with levetiracetam also reported a statistically significant reduction in the quantity of symptomatic drugs needed for symptom control as compared to the placebo group.[11] In another study, it was shown that levetiracetam was well tolerated in 13 elderly patients with migraine. Moreover, levetiracetam showed a good efficacy in frequency and intensity reduction of headache attacks and showed a very good tolerability despite all elderly patients took drugs for concomitant diseases.[10] In the other hand, results of treatment in children are contradictory. While topiramate, valproic acid, and amitriptyline have the most data on their use for prophylaxis of migraines in children, data for efficiency of levetiracetam in this age group is missing.[33,34] However, in some open-label uncontrolled studies, levetiracetam had shown some efficacy in reducing migraine frequency and disability in children.[35,36]

In our study, we prescribed levetiracetam, valproate, or placebo to a group of adolescent and adult patients with non-treated migraine (27, 32, and 26 patients in each group, respectively). Patients who had previously been treated for migraine were excluded from the study in order to omit the effect of previously prescribed anti-migraine drugs on the results of the current study. We used valproate, as it is an accepted standard routinely used treatment in migraine prophylaxis. We followed the patients for a total period of 6 months. After 6 months, both levetiracetam and valproate significantly reduced attacks frequency, compared to placebo (which was inefficient in this regard). They also significantly increased the number of patients with a successful outcome (more than 50% decrease in monthly attacks), compared to placebo. There was no difference between the two drugs regarding these two treatment outcomes, however. Also, an approximate 85% of patients fully tolerated levetiracetam during the treatment course. In most of those who encountered side effects, they were mild and did not discourage the patient from drug discontinuation.

One drawback of this study is its low sample size, which is also seen in other studies evaluating efficacy of levetiracetam in migraine prophylaxis. One reason is that there is still little evidence suggesting levetiracetam as a standard treatment in migraine prophylaxis, and there are a few studies directly assessing efficacy of levetiracetam in migraine.[8,30] Therefore, the first studies addressing this question should recruit smaller sample sizes. Recruitment of large sample sizes can be then performed by observation of promising results in these studies. Moreover, there are very few studies evaluating efficacy

of levetiracetam in migraine prophylaxis with a placebo-controlled design. In this study, we compared the efficacy of levetiracetam to sodium valproate, a standard drug proven to be useful in migraine prophylaxis. However, to address the paucity of placebo-controlled designs, we decided to add a placebo arm to our study. Nonetheless, this has also resulted to a limited sample size in each arm. Considering all these, the comparisons between both drugs and placebo have been statistically significant, indicating that the sample size has not totally decreased the strength and reliability of the results of our study.

Conclusions

Compared to placebo, levetiracetam offers improvement in headache frequency in patients with migraine. The efficacy of levetiracetam in migraine prophylaxis is comparable to currently used standard drugs such as valproate.

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