



The Experiential Comparison of Levetiracetam Efficacy in Migraine Headache with Sodium Valproate

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ABSTRACT

Background: Migraine and other recurrent headaches are considered a major public health concern. Levetiracetam, a broad spectrum anti-epileptic have been used in migraine prophylaxis.

Objectives: Assessment the efficacy of levetiracetam on migraine in comparison to sodium valproate.

Materials and Methods: This randomized double blind clinical trial was performed on patients with migraine headache, diagnosed based on ICDH-version B criteria. One group received levetiracetam and the other group received valproate sodium. The number of migraine attacks per month, the mean duration of attacks and the intensity of pain (VAS) and disability due to headache (MIDAS) were assessed at first and after four weeks of treatment. Data were analyzed in SPSS 20 by Mann-Whitney-U and Chi-square tests. The significance level was set<0.05.

Results: Thirty patients (28 women and 2 men, mean age of 35.14±7.3 years) remained in the valproate group and 33 patients (31 women and 2 men, mean age of 36.33±6.7 years) in the levetiracetam group. The patients in both groups showed a statistically significant reduction in the frequency of headache ($p=0.0001$); intensity of headache ($p=0.004$); mean duration of attacks ($p=0.0001$) and MIDAS score of disability ($p=0.004$) compared to baseline. There was also a statistically significant difference between the two groups in terms of frequency of attacks ($p=0.0001$), intensity of pain ($p=0.0001$); and MIDAS score ($p=0.0001$), by the end of the treatment with superiority of levetiracetam.

Conclusion: Levetiracetam, compared to valproate, yielded better results in prophylaxis of migraine headache.

Keywords: Levetiracetam; Migraine

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Introduction

Migraine and other recurrent headaches are considered a major public health concern, and are accompanied with considerable suffering, disability and social costs (1). Migraine is a chronic disease which involves both nervous and vascular systems (2,3) and ranks as the sixth cause of disability in the world (4). This disorder is defined as episodic attacks of headache on one side that might be followed by gastrointestinal complaints, photophobia and phonophobia (1,5). The highest frequency of migraine occurs from 35 to 45 years old (6). According to population-based studies, 10-12% of the general population suffers from migraine (7-9), which can be debilitating to a great extent (10).

Medical treatments have been widely examined, with a wide range of treatment options (11) and significant progress in this area (12); however, there is general consensus that better and more flexible treatments are required (13). Medical treatments cover prophylactic and symptomatic treatments. Migraine symptomatic treatment ranges from a simple analgesic like non-steroidal anti-inflammatory (NSAID), or acetaminophen, to triptan or dihydroergotamine which is less used (14). Prophylactic treatment in both migraines with aura and without aura includes beta-blockers, calcium channel blockers, serotonin partial agonists, tricyclic antidepressants and antiepileptic medications such as gabapentin, valproate sodium and topiramate (14-16).

Newer medications are proposed to be effective in prophylactic treatment of migraine. Levetiracetam, a derivative of pyrrolidine, is a broad-spectrum antiepileptic medication and effective on different types of

epilepsy. It has relatively different structure compared to other antiepileptic medications, fewer side effects and higher plasma concentration. The exact mechanism of levetiracetam is not clear; much evidence supports its efficacy in preventing migraine attacks (17-19).

Other studies have suggested that levetiracetam is effective in migraine prevention among elderly (20) and young adults (10,21). It is also shown that levetiracetam is promising in refractory chronic migraines (22) and in migraines with aura (23). The current study was designed and conducted with the aim of investigating the efficacy of levetiracetam and comparing it with sodium valproate in controlling the migraine headache in terms of the frequency of attacks, intensity and duration of attacks and migraine-induced disability in adults.

Materials and Methods

In a clinical trial, 70 patients suffering from migraine presenting to neurology clinic of teaching hospitals affiliated to Islamic Azad University in Mashhad were recruited in the year of 2015.

Inclusion criteria: age 15-65 years old, having migraine headache according to the ICDH-version B definition for at least six months.

Exclusion criteria: history of consuming levetiracetam and sodium valproate during one year prior to the study, pregnancy and lactation, having underlying diseases that hinder taking medications, liver and kidney failures, non-migraine headaches (any headache non-compliant with migraine headache diagnostic criteria in ICDH-version B), drug and alcohol abuse, smoking cigarettes and taking sedative medications.

Patients were examined for inclusion criteria and if qualified, they signed informed consent forms. They were briefed on the objectives and methods of the study and that they were free to withdraw from the study anytime they wished. An approval and a license were also obtained from the ethics committee of the Islamic Azad University. Data were collected through interviews, examinations and questionnaires. In the beginning of the study, patients' demographic characteristics, interview and examination findings like the frequency of monthly headache attacks and the mean length of attack duration and the intensity of attacks as well as consequent disability during six months prior to the examination were registered in the patients' information form. In this study, migraine induced disability was measured using a 5-item questionnaire of Migraine Disability Assessment (MIDAS). MIDAS score less than 5 is considered grade I or no or little disability, score 6-10, grade II or mild disability, score 11-20, grade III or moderate disability and score 21 or higher, grade IV or severe disability (24,25). The intensity of pain in a migraine attack was measured using Visual Analogue Scale (VAS) (26).

The randomization process was as follows: the first patient was randomly placed in one of the groups and then the other patient was placed in another group and this sequence was repeated for the 70 patients during the study. Hence, patients were randomly allocated to two groups of 35. In one group, patients were treated with sodium valproate pills at a dose of 500 mg for four weeks and the other group was treated with levetiracetam for four weeks. Levetiracetam began at a dose of 250 mg/day and reached a dose of 1000 mg/day with an increase of 250 mg per week. Patients were provided with cards so that they

could record any event of headache, the frequency of attacks, intensity, duration, and disability due to headache and the possible side effects of the medication. In the event of any side effects during the treatment period, the patients were examined by neurologist.

Four weeks after the treatment, the patients were interviewed and examined again, and the frequency, duration and intensity of headache attacks and the severity of migraine-induced disability were measured by MIDAS for the second time. Data were entered into SPSS version 20. In order to compare quantitative variables including the frequency of headache attacks, duration of the attack, intensity of the attack, and the disability at baseline and after treatment in each group, normal distribution of data was firstly examined via Kolmogorov-Smirnov test and in case of normal distribution, paired t-test and in case of non-normal distribution, Wilcoxon test was used. To compare the above variables between the two groups at the end of the treatment, independent t-test was used for normal distribution, and Mann-Whitney test was used for non-normal distribution. Chi-square test was used to compare qualitative variables in the two groups. The significance level was set <0.05 for all the tests.

Results

First, 70 patients entered the study and were divided into two groups of 35 by simple random allocation. During the study, five patients in the sodium valproate group and two patients in the levetiracetam group dropped out. In the end, 30 people in the sodium valproate group and 33 people in the levetiracetam group were examined. Patients' demographic characteristics in terms of age,

gender, profession and education are presented in table 1. As seen, no significant

difference was observed between the two groups in terms of demographic variables.

Table 1: Demographic characteristics of the patients in two groups of the study

Demographic variable	Sodium Valproate group	Levetiracetam group	<i>p</i> -value
	Mean (\pm SD)	Mean (\pm SD)	
Age (year)	35.17(\pm 7.3)	36.33(\pm 6.7)	0.51
Duration of disease (year)	6.18(\pm 5.2)	5.68(\pm 5.1)	0.7
Gender	No. (%)	No. (%)	0.65
Woman	28(93.3%)	31(93.9%)	
Man	2(6.7%)	2(6.1%)	
Total	30(100%)	33(100%)	
Education	No. (%)	No. (%)	0.84
High school dropout	3(10%)	4(12.1%)	
High school diploma	17(56.7%)	20(60.0%)	
Associate diploma	9(30%)	7(21.2%)	
Bachelor's	1(3.3)	2(6.1)	
Total	30(100%)	33(100%)	
Profession	No. (%)	No. (%)	0.99
Housewife	17(56.7%)	19(57.6%)	
Employee	9(30%)	10(30%)	
Self-employed	4(12.1%)	4(13.3%)	
Total	30(100%)	33(100%)	

Also, patients in the two groups were compared prior to the onset of the treatment in terms of variables relating to migraine like the frequency of attacks per month and

duration of each headache attack, intensity of headache and MIDAS score at baseline (Table 2), there was no significant difference between the two groups.

Table 2. Comparison of headache variables in the ground state of the study in the two groups

Headache variables	Sodium Valproate group	Levetiracetam group	<i>p</i> -value
	Mean (\pm SD)	Mean (\pm SD)	
Frequency of attacks per month	6.6(\pm 1.75)	6.15(\pm 1.43)	0.27
Duration of the attack	15.63(\pm 6.8)	14.21(\pm 5.4)	0.36
Intensity of headache	7.67(\pm 1.64)	7.64(\pm 1.67)	0.94
MIDAS score	2.67(\pm 1.09)	2.64(\pm 1.08)	0.91

Patients in each group were compared in terms of the frequency of attacks, duration of attacks, and intensity of headache and MIDAS score at baseline and after treatment. These results were also compared between the two groups after the completion of treatment (Table 3).

The frequency of attacks per month significantly reduced in both groups after treatment as compared with the baseline. Furthermore, a statistically significant difference was observed between the two groups at the end of the treatment in that the reduction in the frequency attacks in the levetiracetam group was greater than that in the valproate group ($p=0.0001$).

Both groups experienced a significant reduction in duration of headache attacks after the treatment, but no statistically significant difference was seen between the two groups by the end of the treatment ($p=0.58$).

The headache intensity in any attack was significantly reduced after treatment in both groups and this reduction was more significant in the levetiracetam group ($p=0.0001$).

Migraine-induced disability (the MIDAS score) showed a statistically significant difference in both groups between the baseline and the end of treatment. Furthermore, by the end of the study, a statistically significant difference was seen

between the two groups such that reduction in the MIDAS score was greater in the

levetiracetam group than that in the valproate group ($p=0.0001$).

Table 3. Comparison of headache variables in both groups at baseline and after the treatment

	Sodium Valproate group			Levetiracetam group		
	Ground state	After treatment	<i>p-value</i>	Ground state	After treatment	<i>p-value</i>
	Mean (\pm SD)	Mean (\pm SD)		Mean (\pm SD)	Mean (\pm SD)	
Frequency of attacks per month	6.6(\pm 1.75)	4.1(\pm 1.18)	0.0001	6.15(\pm 1.43)	2.24(\pm 0.88)	0.0001
Duration of the attack	16.63(\pm 6.9)	11.4(\pm 6.09)	0.0001	14.21(\pm 5.4)	10(\pm 5.2)	0.0001
Intensity of ache	7.67(\pm 1.64)	6.73(\pm 2.06)	0.004	7.64(\pm 1.67)	4.33(\pm 2.24)	0.0001
Migraine-induced disability	2.67(\pm 1.09)	1.93(\pm 1.11)	0.004	2.64(\pm 1.08)	1.15(\pm 0.36)	0.0001

In terms of medication side effects, 66.7% of the patients in the sodium valproate group suffered no side effects while the following side effects were reported early in the treatment course: six cases of insomnia, one case of hypotension, two cases of hand tremor and one case of exacerbated headache. Likewise, 75.5% of the patients in the levetiracetam group suffered no side effects, but five cases had insomnia, two cases had irritability and one case had headache radiating to the back of the head. In both groups, side effects improved as the treatment continued and the medication was not discontinued.

Discussion

In present study both groups showed a significant reduction in the said criteria compared to the baseline state as the study ended. Comparing the two groups revealed that levetiracetam more significantly reduced the frequency and intensity of headache as well as disability related to headache compared to sodium valproate; however, the reduction in headache duration was not significant between the two groups.

In recent years, many studies have examined the effects and efficacy of various medications on migraine headaches for both prophylactic and symptomatic treatments. Prophylactic treatments via beta-blockers,

calcium channel blockers, serotonin partial agonists, tricyclic antidepressants and antiepileptics have proved useful for migraine with and without aura (27-29). Existing evidence and studies are not conclusive regarding the efficacy of antiepileptic medications except for sodium valproate, topiramate, gabapentin and pregabalin. In several clinical trials, levetiracetam has proved more effective than placebo in reducing the frequency of migraine attacks (30-32).

In several studies, prophylactic administration of levetiracetam led to a significant reduction in the frequency of attacks and intensity of migraine headaches compared to baseline (17,18, 32). Result of Sadeghian's study illustrated that six months of treatment with levetiracetam and sodium valproate led to a significant reduction in the frequency of attacks compared to the baseline, which is in line with the current study. Meanwhile, there was no significant difference in terms of the frequency of headaches between the two groups, which is inconsistent with the findings obtained (10).

In a clinical trial by Verma *et al.* 65 patients were treated with levetiracetam and placebo for migraine prophylaxis, and a significant reduction was reported in the frequency of migraine attacks compared to the pre-treatment period as well as a reduction

in the pain intensity compared to the placebo group (20). In the current study in which the efficacy of levetiracetam was compared to sodium valproate, as the standard prophylactic medication for migraine attacks, the frequency of migraine attacks (per month) and intensity of pain showed a significant reduction compared to before treatment; of course, as expected, the control group who received sodium valproate experienced such a difference. And as we compare the two groups in terms of these variables, we notice the frequency of migraine attack and intensity of pain reduced more significantly in the levetiracetam group.

In an open label study by Brighina on 16 patients with high frequency migraine with aura, the patients were treated with levetiracetam for six months and the findings suggested that the frequency of attacks, intensity and duration of the headache witnessed a significant reduction, and tolerance with the medication was reported good (23).

In the Pakalnis' study tolerability and efficacy of levetiracetam were investigated. Eighteen children out of twenty were reported to show a significant reduction in the frequency of attacks and PEDMIDAS disability score with the least side effects (33).

In Rapoport *et al.* study titled "Levetiracetam in preventing treatment resistant migraine" on 36 patients, they reported a significant reduction in the frequency of attacks and disability score (34). Results of the said studies suggest the efficacy of levetiracetam in reducing migraine headache attacks, which are consistent with the results of our study.

The efficacy of medication therapy in controlling migraine headache attacks should

be considered along with the emergence of side effects. To this end, the current study evaluated the side effects in addition to treatment efficacy in the two groups. Levetiracetam, as compared to sodium valproate, showed fewer side effects, which did not lead to discontinuation of treatment. This point highlights appropriate tolerability of levetiracetam. In similar studies, emergence of side effects was similar to the current study and no serious side effects that could lead to discontinuation of medications were observed (17,18, 30-32).

Conclusion

According to the findings, it can be concluded that both levetiracetam and sodium valproate have acceptable efficacy for prophylactic treatment of migraine and cause a significant reduction in the frequency, duration and intensity of migraine attacks and the resulting disability compared to the baseline. In our study, levetiracetam, compared to valproate, yielded better results, though a definite conclusion requires more studies with larger sample sizes.

Conflict of Interest

The authors have no conflict of interest.

References

1. Leonardi M, Steiner TF, Scher AT, Lipton RB. The Global Burden of Migraine: Measuring Disability in Headache Disorders with WHO's Classification of Functioning, Disability and Health (ICF). *J Headache Pain* 2007;6:429-40.
2. Ozge A, Aydinlar E, Tasdelen B. Grey Zones in the Diagnosis of Adult Migraine without Aura Based on the International Classification of Headache Disorders-III beta: Exploring the

- Covariates of Possible Migraine without Aura. *Pain Res Manag* 2015;20(1):1-7.
3. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF, et al. Migraine Prevalence, Disease Burden, and the Need for Preventive Therapy. *Neurology* 2007;68:343-9.
 4. Global Burden of Disease Study. Global, Regional, and National Incidence, Prevalence, and Years Lived with Disability for 301 Acute and Chronic Diseases and Injuries in 188 Countries, 1990–2013: a Systematic Analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743-800.
 5. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia* 2013;33:629-808.
 6. Smitherman TA, Burch R, Sheikh H, Loder E. The Prevalence, Impact, and Treatment of Migraine and Severe Headaches in the United States: a Review of Statistics from National Surveillance Studies. *Headache* 2013;53(3):427-36.
 7. Stewart WF, Lipton RB, Celentano DD, Reed ML. Prevalence of migraine headache in the United States. Relation to age, income, race, and other sociodemographic factors. *JAMA* 1992;267:64-9.
 8. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: Data from the American Migraine Study II. *Headache* 2001;41:646-57.
 9. Ghabaee M, Bayati A, AmriSaroukolaei S, Sahraian MA, Sanaati MH, Karimi P, et al. Analysis of HLA DR2&DQ6 (DRB1*1501, DQA1*0102, DQB1*0602) haplotypes in Iranian patients with multiple sclerosis. *Cell Mol Neurobiol* 2009;29:109-14.
 10. Sadeghian H, Motiei-Langroudi R. Comparison of Levetiracetam and sodium Valproate in migraine prophylaxis: A randomized placebo-controlled study. *Ann Indian Acad Neurol* 2015;18(1):45-48.
 11. Goadsby PJ, Sprenger T. Current practice and future directions in the management of migraine: acute and preventive. *Lancet Neurol* 2010;9:285-98.
 12. Goadsby PJ. Incredible progress in migraine for an era of better care. *Nat Rev Neurol* 2015;11:621-2.
 13. Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J, Goadsby PJ. Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine. *Brain* 2016;139(Pt 7):2002-14.
 14. Toldo I, De Carlo D, Bolzonella B, Sartori S, Battistella PA. The pharmacological treatment of migraine in children and adolescents: An overview. *Expert Rev Neurother* 2012;12:1133-42.
 15. Rizzoli P. Preventive pharmacotherapy in migraine. *Headache* 2014; 54:364-9.
 16. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine. *CNS Drugs* 2002;16:611-34.
 17. Eiland LS, Jenkins LS, Durham SH. Pediatric migraine: Pharmacologic agents for prophylaxis. *Ann Pharmacother* 2007;41:1181-90.
 18. Landmark CJ. Antiepileptic drugs in non-epilepsy disorders relations between mechanisms of action and clinical efficacy. *CNS Drugs* 2008;22(1):27-47.
 19. Carreno M. Levetiracetam. *Drugs Today (Barc)* 2007;43:769-94.
 20. Pizza V, Busillo V, Agresta A, Bisogno A, Capasso A. Elderly patients with migraine: An open-label study on prophylaxis therapy with levetiracetam. *Cent Nerv Syst Agents Med Chem* 2011;11:31-4.
 21. Verma A, Srivastava D, Kumar A, Singh V. Levetiracetam in migraine prophylaxis: A randomized placebo-controlled study in a rural medical institute in Northern India. *Clin Neuropharmacol* 2013;36:193-7.
 22. Lionetto L, Negro A, Palmisani S, Gentile G, Del Fiore MR, Mercieri M, et al. Emerging treatment for chronic migraine and refractory chronic migraine. *Expert Opin Emerg Drugs* 2012;17:393-406.
 23. Brighina F, Palermo A, Aloisio A, Francolini M, Giglia G, Fierro B. Levetiracetam in the prophylaxis of migraine with aura: A 6-month open-label study. *Clin Neuropharmacol* 2006;29:338-42.
 24. Kosinski M, Bjorner JB, Ware JE Jr, Batenhorst A, Cady RK. The responsiveness of headache impact scales scored using

- 'classical' and 'modern' psychometric methods: a re-analysis of three clinical trials. *Qual Life Res* 2003;12:903-12.
25. Magnoux E, Freeman MA, Zlotnik G. MIDAS and HIT-6 French translation: reliability and correlation between tests. *Cephalalgia* 2008;28:26-34.
 26. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emerg Med J* 2001;18(3):205-7.
 27. Lampl C, Buzarth A, Klinger D, Neumann K. Lamotrigine in the prophylactic treatment of migraine aura — A pilot study. *Cephalalgia* 1999;19:58–63.
 28. Ayata C, Jin H, Kudo C, Dalkara T, Moskowitz MA. Suppression of cortical spreading depression in migraine prophylaxis. *Ann Neurol* 2006;59:652-61.
 29. Chen WT, Fuh JL, Lu SR, Wang SJ. Persistent migrainous visual phenomena might be responsive to lamotrigine. *Headache* 2001;41:823-5.
 30. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Antiepileptics other than gabapentin, pregabalin, topiramate, and valproate for the prophylaxis of episodic migraine in adults. *Cochrane Database Syst Rev* 2013:CD010608.
 31. Capuano A, Vollono C, Mei D, Pierguidi L, Ferraro D, Di Trapani G. Antiepileptic drugs in migraine prophylaxis: State of the art. *Clin Ter* 2004;155:79–87.
 32. Haria M, Balfour JA. Levetiracetam. *CNS Drugs* 1997; 7:159-64.
 33. Pakalnis A, Kring D, Meier L. Levetiracetam prophylaxis in pediatric migraine — an open-label study. *Headache*. 2007;47(3):427-30.
 34. Rapoport AM, Sheftell FD, SJ Tepper, ME Bigal. Levetiracetam in the preventive treatment of transformed migraine: A prospective, open-label, pilot study. *Curr Ther Res Clin Exp* 2005;66(3):212-21.