Levetiracetam in Migraine Prophylaxis: A Randomized Placebo-Controlled Study in a Rural Medical Institute in Northern India

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Objective: Migraine is often a chronic and disabling disorder. The objective of our study was to assess the efficacy and tolerability of levetiracetam (LEV) in adult migraine prophylaxis.

Methods: We conducted a prospective, randomized, placebo-controlled study. A total of 65 patients were randomized in a 1:1 ratio to receive LEV (n = 32) or placebo (n = 33). Twenty-five patients completed the study in the LEV group and 27 patients in the placebo group. Thirteen subjects discontinued early during the trial. After a 1-month run in period, LEV was started at a dose of 250 mg/d (or the matching placebo) and was increased by 250 mg/wk until the final dosage of 1000 mg/d was reached. The titration phase was followed by maintained phase of 3 months.

Results: In LEV group, we found a significant reduction in the frequency (attacks per month) of migraine (from 5.17 [SD, 1.19] at baseline to 2.21 [1.47] in the last 4 weeks) and also in severity of migraine from (2.75 [0.44] to1.29 [0.75]) as compared to the placebo group. Patients treated with LEV also reported a statistically significant reduction in the quantity of symptomatic drugs needed for symptom control as compared to the placebo group ($P < 0.0001$). The percentage of patients on LEV who experienced greater than or equal to 50% reduction in headache frequency was 64% compared with 22% for placebo.

Conclusions: Compared with the placebo group, LEV offers improvement in headache frequency and severity as well as it lowers the requirement for other symptomatic drugs in adult migraine patients.

Key Words: Headache, levetiracetam, migraine prophylaxis

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Migraine has been identified among the world's top 20 leading causes of disability by the World Health Organization.[1] Migraine is a chronic disorder and is characterized by often disabling recurrent attacks of head pain, autonomic dysfunction, and neurological symptoms. Although abortive treatments should be taken only during attacks to reduce the severity and duration of headache, prophylactic treatments have to be taken daily with an aim of reduction in headache frequency and an improvement in functioning and well-being of patients.[2]

The hypothesis that cortical hyperexcitability plays a role in the physiopathology of migraine led to the therapeutic use of some antiepileptic drugs.[3] Antiepileptic drugs including sodium valproate[4] and topiramate[5] have been effective in migraine prophylaxis, although prolonged use is limited due to adverse effects like weight gain, hair loss, and gastrointestinal symptoms in the valproate-treated group and weight loss, paresthesia, and cognitive disturbances in the topiramate group.

Levetiracetam (LEV) is a new antiepileptic with an incompletely understood mechanism of action. It is thought to exert effects on synaptic vesicle protein (SV2A) brain binding site, which differs from the targets of other antiepileptic drugs.[6] Other proposed mechanisms of action include inhibition of Zn^{2+}-associated negative GABA modulation, high-voltage-gated N-type Ca^{2+} channel current, and GABA release.[7] Most studies suggest that it is effective as an adjunctive treatment of partial seizures in adults and children. There are some small open-label trials of LEV suggesting benefit in migraine.[8–10] Its efficacy in migraine prevention is thought to be related to a possible effect on cortical spreading depression, which is an early pathophysiological process in a migraine attack.[11] Levetiracetam has a safe therapeutic profile and is well tolerated with adverse effects usually related to behavioral problems and aggression.[12]

Lack of major contraindications, drug interactions, and better tolerability make LEV one of the most promising options for migraine prophylaxis. Therefore, the aim of this study was to prospectively assess the efficacy and tolerability of LEV in adult migraine prophylaxis.

MATERIALS AND METHODS

We carried out a prospective, randomized, placebo-controlled trial at the UP Rural Institute of Medical Sciences and Research, Saifai, from December 2010 to April 2012. Patients visiting the outpatient service of Neurology Department for evaluation and treatment of headache were recruited after they gave their informed consent for participation in this study. The study was preapproved by the institutional ethics committee.

Inclusion criteria were as follows:

1. Diagnosis of migraine with and without aura was established according to the criteria of the International Headache Society.[13]
2. Frequency of 4 or more attacks per month for at least 3 months.
3. Previous prophylactic treatment with other medication had failed or was discontinued due to adverse events.

Patients who experienced headaches for more than 15 days in a month, affected by headaches other than migraine, experiencing systemic or organic disease, or were pregnant or at risk of pregnancy were excluded. Data collection consisted of baseline headache diaries and history of abortive medication used. The previous migraine preventive medications were tapered off during the washout period of 14 days. Most of the patients in our study were drug naive, whereas 6 patients in the LEV group and 5 patients in the placebo group had responded inadequately to previous prophylactic medications. Of the 11 patients on pervious prophylactic medications, 5 were on propranolol (80–120 mg/d for 3–4 months), 2 on tricyclic antidepressant

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(amitriptyline 75 mg/d for 2 months), 2 on flunarizine (10 mg/d for 6 months), and 2 were on combination of propranolol and flunarizine (80 and 10 mg/d for 3–6 months).

The study began with a 1-month run-in period, the inclusion criteria being reexamined at the end of this period. Sixty-five patients were randomly allocated to treatment with LEV or placebo (ratio, 1/1) in balanced blocks of 2 using a computer-generated random number scheme. The randomization and medication distribution was done by an investigator (D.K.) and the clinical diagnosis and evaluation of outcome by another (A.V.). Packets containing LEV or placebo were identical.

All the eligible patients were subjected to neurological examination, physical examination, and brain computed tomographic scans. Levetiracetam was then started at a dose of 250 mg/d (or the matching placebo) and was increased by 250 mg/wk until the final dosage of 1000 mg/d was reached or placebo (calcium, 500 mg BID) kept in an identical looking packet was administered. The titration phase was followed by 3-month maintenance phase (LEV, 500 mg BID). Patients were free to take their usual abortive medication if needed.

Patients were instructed to return for monthly follow-up. Migraine frequency (attacks/month), severity (rated as follows: 0, no pain; 1, mild; 2, moderate; and 3, severe), clinical disability (1, normal; 2, mildly impaired; 3, severely impaired; and 4, requiring bed rest), acute medication taken for severe migraine, and adverse events were recorded daily by the patients by means of specific headache diaries throughout the entire study period (run-in and treatment phases). A comparable percentage of patients from each treatment group completed the total duration of study (52 patients in total). The patient allocation is shown in Figure 1.

Efficacy Measurement

Primary efficacy measures were (1) reduction of the mean migraine headache frequency when comparing the baseline period to the last 4 weeks of the maintenance phase of the study in the groups treated with LEV or placebo; and (2) the proportion of subjects responding to treatment (as measured by a ≥50% reduction in migraine frequency). Secondary end points were decrease in severity, clinical disability, and reduction in the mean number of acute medication use per month.

Statistical Analysis

This study was designed as a superiority trial expecting LEV to be superior to placebo. To detect the difference between the 2 drugs, α risk was taken as 5%, and critical difference 2 and power of study 80. On the basis of this criterion, the sample size was calculated to be at least 25 in each group[14] using the following formula:

$$N = \frac{(z_a + z_\beta)^2 \sigma^2}{(\mu - \mu_0 - \delta)^2}$$

where α, the probability of type I error (significance level) is the probability of rejecting the true null hypothesis (in our study, 0.05); β, the probability of type II error (1 − power of the test)

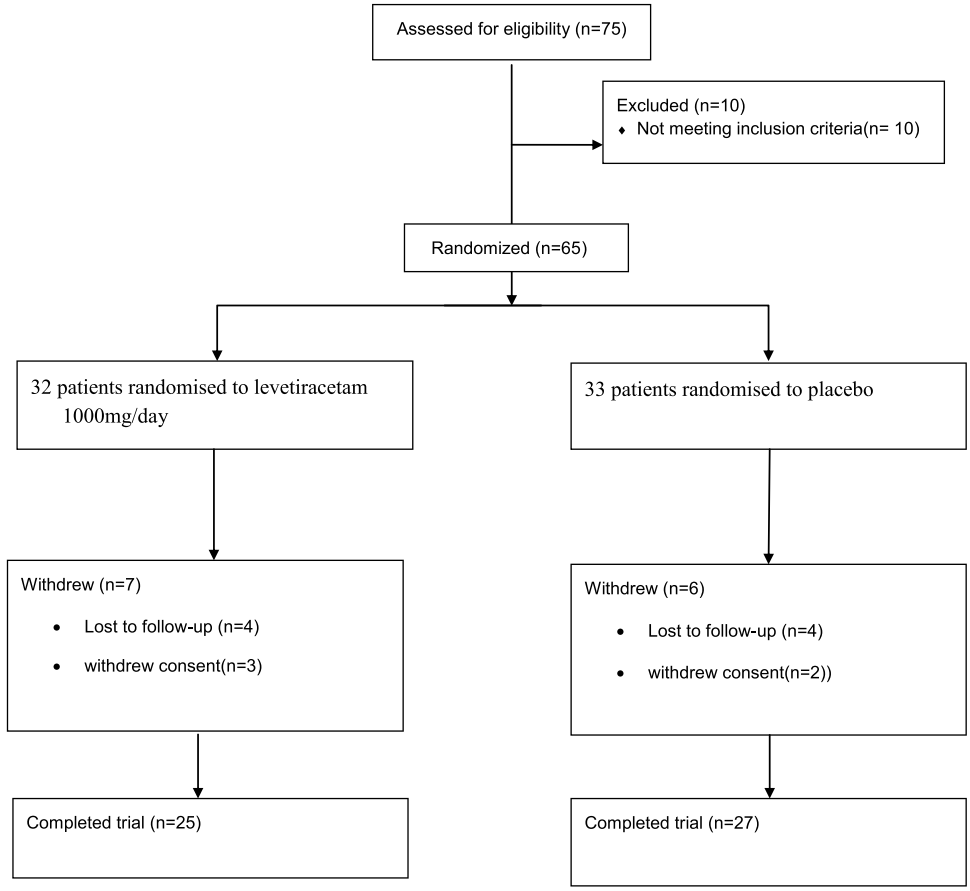

FIGURE 1. Consort diagram showing patients randomization and disposition.

TABLE 1. Patient Demographic and Baseline Characteristics

	LEV (n = 25)	Placebo (n = 27)
Age, mean (SD), y	31.84 (9.57)	30.44 (9.03)
Sex, n (%)		
Male	5 (20)	9 (33)
Female	20 (80)	18 (67)
Patients with migraine with aura, n (%)	5 (20)	4 (15)
Patients with migraine without aura, n (%)	20 (80)	23 (85)
Duration of migraine, mean (SD), y	4.36 (3.92)	4.29 (3.31)
Nausea	19	20
Vomiting	25	26
Photophobia	25	27
Phonophobia	25	27

is the probability of not rejecting the false null hypothesis (in our study, 0.20); δ, the true difference between the 2 mean values at which the power is calculated (in our study, 1); and $\mu - \mu_0$, the value of allowable difference is the difference value between true mean and reference mean (constant value) (in our study, 4).

All variables were continuous; measures met criteria for a normal distribution and statistical analysis relied on parametric measures.

We used Student paired *t* tests to analyze the changes in frequency of headaches, severity, disability, and acute medication use posttreatment compared to baseline values with 95% confidence intervals.

RESULTS

A total of 65 patients were randomized in a 1:1 ratio to receive LEV (n = 32) or placebo (n = 33). Twenty-five patients completed the study in the LEV group and 27 patients in the placebo group. Thirteen subjects discontinued early during the trial. Reasons for withdrawal are outlined in Figure 1. The 2 treatment groups were well matched at the baseline without any statistically significant difference. Our result, therefore, is based on 52 migraine patients whose age ranged between 17 and 46 years (mean, 30.01 years) and 38 of whom were women. The duration of migraine ranged between 1 and 20 years. The demographic and baseline characteristics of migraine patients enrolled in the study are shown in Table 1.

Mean migraine frequency decreased from 5.17 (SD, 1.19) at baseline to2.21 (1.47) in the last 4 weeks of the maintenance phase for patients treated with 1000 mg/d LEV, compared with a decrease from 5.11 (1.27) to 4.40 (1.64) for those treated with placebo. The mean change compared to baseline period was significantly greater for patients treated with LEV ($P < 0.0001$) than for the placebo group ($P = 0.088$) (Fig. 2). The responder rate was significantly better in the LEV group as compared to the placebo group: the proportion of patients treated with LEV responding to treatment (meaning a reduction of ≥50% in migraine frequency) was 64 % compared to 22% of patients in the placebo group.

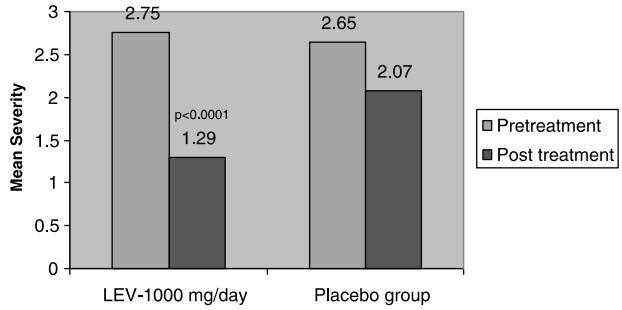

FIGURE 3. Mean change in headache severity from baseline.

The comparison of the severity of migraine between the LEV group and the placebo group is presented in Figure 3. At baseline, the severity was 2.75 (0.44) in the LEV group and 2.65 (0.48) in the placebo group. Patients in the LEV group showed a significant decrease in severity from pretreatment ($P < 0.0001$). There was also a reduction in migraine disability from the baseline in both the LEV (from baseline 3.33 [0.81] to 1.66 [0.76], $P < 0.0001$) and placebo group (from 3.19 [0.94] to 2.38 [0.94], $P < 0.0025$), although the reduction was less in the placebo group (Fig. 4).

Patients treated with LEV reported a statistically significant reduction in the mean quantity of symptomatic drugs taken as compared to the placebo control group: the mean value of symptomatic drugs taken decreased from 5.85 (1.55) to 1.87 (1.39) tablets/mo; this value was significant at $P < 0.0001$ (Fig. 5). Comparing the efficacy between the 2 groups revealed significant improvement in migraine frequency, severity, disability, and acute symptomatic medication use in the LEV group shown in Table 2.

Migraine abortive medications used before and during the study included sumatriptan (50 mg), rizatriptan (10 mg), ibuprofen (400 mg), ketorolac (10 mg), and naproxen sodium (500 mg). We did not find any difference in response rate between migraine with aura and without aura.

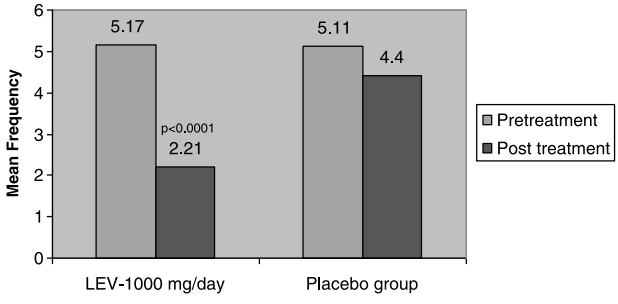

FIGURE 2. Mean change in migraine frequency from baseline.

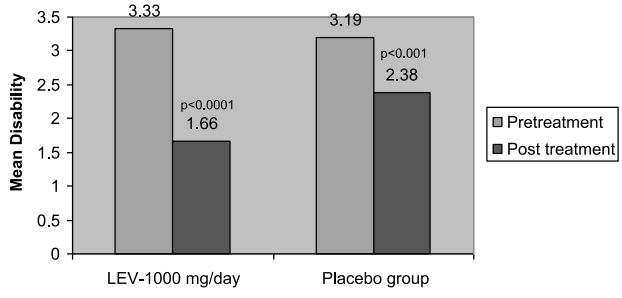

FIGURE 4. Mean change in headache disability from baseline.

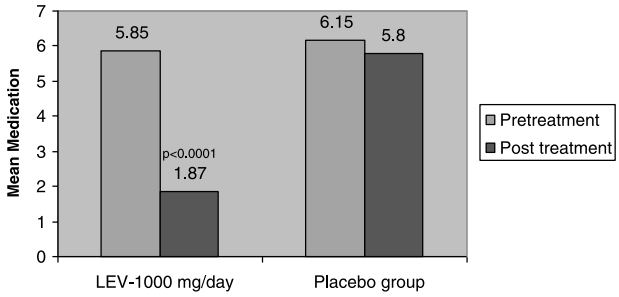

FIGURE 5. Mean change in symptomatic drug taken.

In our study, LEV therapy was well tolerated and only mild and transitory adverse events were reported in 4 patient's somnolence (2), irritability (1), and asthenia (1). No patients discontinued the treatment because of adverse effects.

DISCUSSION

The findings of this randomized placebo-controlled study demonstrate a significant reduction in migraine frequency; the major outcome measure, that is, (attacks/month) in LEV group compared with placebo. The improvement started within 1 month of treatment, maximum benefit observed in the third month followed by plateau in improvement. On LEV, 64% of patients had greater than or equal to 50% reduction in headache frequency and 4 patients became completely attack-free after 3 months of therapy. Levetiracetam was also effective in significantly reducing the other efficacy measures like monthly migraine severity, disability, and rate of acute symptomatic medication use, therefore offering a potential new option for the prophylaxis of migraine in adults.

Although significant reduction in migraine disability was seen in both groups, the effect was higher in the LEV group when compared with placebo. This may be due to small sample size or to the complex confounding effects of placebo in headache trials.[15,16]

Several small prospective open-label and retrospective trials suggest a role for LEV in migraine therapy.[10,17–19] However, these studies lacked placebo control and, in some studies, patients did not fulfill the International Headache Society criteria for clinical trials, making their results difficult to interpret. Our results support the previous findings of Brighina et al, who evaluated LEV in a 6-month-long open-label study in 16 adult patients experiencing frequent migraine attacks with aura. A significant reduction in headache frequency was observed at 1000 mg/d. In 7 (44%) of the 16 patients, the attacks were completely abolished after 3 months of treatment.[20] Adverse effects were minimal, including somnolence and nervousness.

Levetiracetam has also shown good efficacy in reduction of migraine frequency and intensity in elderly patients taking other drugs for concomitant diseases.[21] The role of LEV in preventive treatment of refractory transformed migraine has been reported in an open-label prospective study. In those who completed the study, headache frequency was reduced by 45.2% and the number of moderate or severe headache days per month was reduced by 46.1%.[22] Another multicenter study in chronic daily headache demonstrated a 3.9% increase in headache-free rate with LEV as compared to placebo, although this was not statistically significant.[23]

Our study is limited by relative small sample size and high dropout rate, that is, 21.82% in the LEV group and 18.18% in the placebo group. Most of those who left the study had not even received the initial few dosages of medication. Therefore, including them in the final analysis would have diluted the result with negative impact on the end point result. Thus, in the present study, per-protocol analysis was used as only those patients who completed the entire clinical trial according to the protocol were counted toward the final results.

The high dropout in this study is due to lack of awareness and concern toward health and poor transport facilities in this remote area. Our study was conducted at the tertiary care center and most of the patients enrolled were experiencing moderate to severe headache. Another limitation of our study was that migraine attacks; not the days, were captured from the diary.

As the study was conducted at a single center, there is homogeneity in patient selection and there were no interrater variability.

Levetiracetam presents an attractive prophylactic option for migraine due to lack of hepatic metabolism and minimal drug interactions. Levetiracetam was generally well tolerated in this trial with an incidence of mild-to-moderate adverse events, consistent with the favorable tolerability profiles observed in previous studies, particularly in children.[18,20]

To conclude, our study revealed that LEV at a dose of 1000 mg/d is superior to placebo in relieving migraine frequency, severity, and functional disability. At present, our findings suggest that LEV is a promising drug in adult migraine prophylaxis. Further large randomized double blinded, placebo controlled clinical studies are warranted as the drug has shown good efficacy and tolerability.

TABLE 2. Comparison of Primary Efficacy and Key Secondary Efficacy Values for LEV Versus Placebo

	Pretreatment			Posttreatment		
Parameter	**Study Group**	**Placebo**	***t*, *df* (*P*)**	**Study Group**	**Placebo**	***t*, *df* (*P*)**
Mean migraine frequency (attack) per month, mean (SD)	5.17 (1.19)	5.11 (1.27)	0.18, 50 (0.86)	2.21 (1.47)	4.40 (1.64)	5.13, 50 (0.0001)
Mean headache severity per month, mean (SD)	2.75 (0.44)	2.65 (0.48)	0.01, 50 (0.59)	1.29 (0.75)	2.07 (0.89)	3.84, 50 (0.000348)
Mean headache disability per month, mean (SD)	3.33 (0.81)	3.19 (0.94)	0.57, 50 (0.57)	1.66 (0.76)	2.38 (094)	3.02, 50 (0.0039)
Mean monthly quantity of symptomatic medication, mean (SD)	5.85 (1.55)	6.15 (1.28)	0.76, 50 (0.45)	1.87 (1.39)	5.80 (1.62)	9.42, 50 (0.00001)

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