Zonisamide Versus Topiramate in Migraine Prophylaxis: A Double-Blind Randomized Clinical Trial

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Background: Topiramate is an antiepileptic drug that has been approved for migraine prophylaxis. Despite appropriate efficacy for migraine prophylaxis, some patients cannot tolerate its adverse effects. The aim of this study was to compare the efficacy of zonisamide, another antiepileptic drug, with topiramate in decreasing the frequency and severity of migraine attacks to determine whether it could be used as an alternative for noncompliant patients to topiramate.

Methods: Eighty patients, recruited from referred migraineurs to our neurology clinic, who met the diagnosis and inclusion criteria were allocated randomly to group A (50-mg/d zonisamide, gradually titrated up to 200 mg/d) and group B (25-mg/d topiramate, gradually titrated up to 100 mg/d). Each patient was followed for 12 weeks and was assessed at entrance, in the fourth week and twelfth week for frequency of attacks, headache severity, need for acute medication, migraine disability assessment score, and adverse effects. A $P < 0.05$ was considered as the level of significant difference in all tests.

Results: Both drugs caused a significant decrease in frequency, severity, need for acute medication in migraine attacks, and migraine disability assessment score ($P < 0.05$). Except headache severity that was reduced significantly better by zonisamide ($P < 0.008$), there were no significant difference between the 2 groups in other items. Except for 2 cases of intolerable paresthesia, both drugs were tolerated well during the study.

Conclusion: Our results indicated that zonisamide is as effective as topiramate in migraine prophylaxis and can be considered as an alternative treatment when topiramate is not tolerated well.

Key Words: zonisamide, topiramate, migraine, prophylaxis

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Migraine is one of the most common primary headaches, with an estimated prevalence of 18.2% in women and 6.5% in men.[1] Its nature of sustaining for several hours and repeating multiple times in a month, in severe forms, makes it a disabling headache. Absence from school and work or at least reduction of functional ability is common in migraineurs and leads to decreased social and economical productivity.[2] Therefore, a successful and easy-to-tolerate prophylactic treatment can increase the quality of life and reduce the need for acute medication and its relevant costs by decreasing the frequency and severity of migraine attacks and increasing the probability of response to symptomatic therapy.[3,4] Selection of a prophylactic regimen is dependent on the type of headache, drug efficacy, adverse effects, and patient's tolerance. Among prophylactic regimens, anticonvulsants are widely used.[5] Topiramate is an antiepileptic drug and an effective migraine prophylactic drug[6,7] that has been approved for migraine prophylaxis by the Food and Drug Administration (FDA) in 2004.[8] By blocking voltage-activated sodium and calcium channels, inhibiting of excitatory effect of glutamate and facilitating of inhibitory effect of γ-aminobutyric acid, topiramate reduces cortical hyperexcitability and modulates nociception.[9] According to 2 large randomized, double-blind, placebo-controlled clinical trials, the best result would be achieved at the 100-mg/d dosage.[6,7] Zonisamide is another antiepileptic drug that not only has a similar effect on the glutamate and γ-aminobutyric acid neurotransmitters as well as sodium and calcium channels but also reduces nitric oxide (NO) production and scavenges NO free radicals.[10,11] Considering their similar mechanism of action, it seems that zonisamide can be effective in migraine prophylaxis as topiramate. Few uncontrolled studies done to evaluate the efficacy of zonisamide in migraine prophylaxis especially in refractory cases confirmed that it could be effective in prophylaxis of migraine headache.[12–17] However, controlled trial to compare zonisamide with placebo or another approved drug by FDA was not performed up to now.

In this study, we compared zonisamide with topiramate in migraine prophylaxis by evaluating their effect on frequency and intensity of migraine headaches, need for acute medication, and headache-induced disability by measuring migraine disability assessment (MIDAS) questionnaire score.

METHODS

Study Design

This study was a single-center, randomized, double-blind clinical trial. Subjects were recruited among referrals to our neurology clinic that met both international headache society criteria for diagnosis of migraine headache and our inclusion criteria and gave a personal consent for participating in the study.

Except one member of trial team (F.A.), who did not contribute in outcome rating, other participants (ie, all active assessors and patients) were completely blinded about the groups that patients were allocated. Applied dosage form of both drugs was capsule, and to ensure allocation concealment, an independent pharmacist packaged the drugs into numbered containers that were dispensed on the day of randomization. The dosages of drugs were elevated subsequently to the ultimate dose of 200 mg/d of zonisamide and 100 mg/d of topiramate within 1 month of entering the study under the supervision of an appointed trial member (F.A.).

The study protocol was approved by university ethics review committee and was registered in Iranian clinical trial registration system (IRCT), representative of World Health Organization trial registration, under ID number IRCT201011075117N1.

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The inclusion and exclusion criteria are listed below.

Inclusion Criteria

1. History of classic or common migraine that met International Headache Society criteria, since at least 1 year ago;
2. Migraine attack frequency between 4 and 15 times per month, or occur less than 4 times per month but are so prolonged and debilitating that require preventive treatment;
3. In the cases of postmenopausal women, it should be passed at least one year from their menopause;
4. Patients should have a negative pregnancy test, and appropriate contraceptive method must be used during the study;
5. History of unsuccessful prophylactic treatment with one or more of first-line migraine prophylaxis regimens;
6. No history of topiramate or zonisamide consumption for any cause; and
7. Written informed consent obtained from the subject.

Exclusion Criteria

1. The presence of any other primary headaches, for example, tension headache, cluster headache, etc; and
2. The presence of any other cause of pain that needs medications regularly, for example, neuropathy, arthritis, etc.

Outcome Measures

The primary efficacy end points were changes in the headache frequency (number of attacks per month) and response to treatment (good response to treatment was defined as decrease in frequency by more than 50%), headache severity (according to a visual scale of 1–10 points) and the times of need for acute medication. These end points were measured at entrance, the fourth week, and the twelfth week of drug initiation.

Secondary efficacy end points were patient's MIDAS score that was assessed for each patient at entrance and after the third month of drug initiation. Adverse effects of the drug and the necessity to inform the investigators if any occurred were clarified to the participants. All subjects were advised to avoid foods that precipitate headache episodes, consumption of simple sedatives more than 2 times per week, sleep deprivation, and any other factor suspected to exacerbate their headache.

Statistical Analysis

The data analyses were performed by Statistical Package for Social Sciences (SPSS) version 13. Kolmogrov-Smirnov Z was used to check whether variables are normally distributed. Baseline variables were compared using a 2-group t test and Mann-Whitney U test (for headache severity) for continuous variables, and χ^2 test for categorical variables. For efficacy variables, comparisons were made between baseline and the end of treatment for each group by using paired t test and sign test, and then among 2 groups by comparing the improvement in variables by the 2-group t test and the Mann-Whitney U test. Improvement was calculated by numerical difference between the baseline and the end of study for each variable. A $P < 0.05$ was considered the level of significant difference in all tests.

RESULTS

Subject Flowchart

Among 130 screened patients, 80 were enrolled in the study: 40 patients received zonisamide and the other 40 received topiramate (Fig. 1). Finally, 75 patients completed the study, 37 in the zonisamide group and 38 in the topiramate group. Two patients in the zonisamide group and 2 patients in the topiramate group were lost to follow-up owing to adverse events. One patient in the zonisamide group was reported to be noncompliant. Because change in baseline is the primary outcome, a per-protocol analysis was done.

Baseline Characteristics

The zonisamide and topiramate groups had similar baseline characteristics (Table 1). The age, sex, baseline headache frequency, headache severity, mean of the times of need for acute

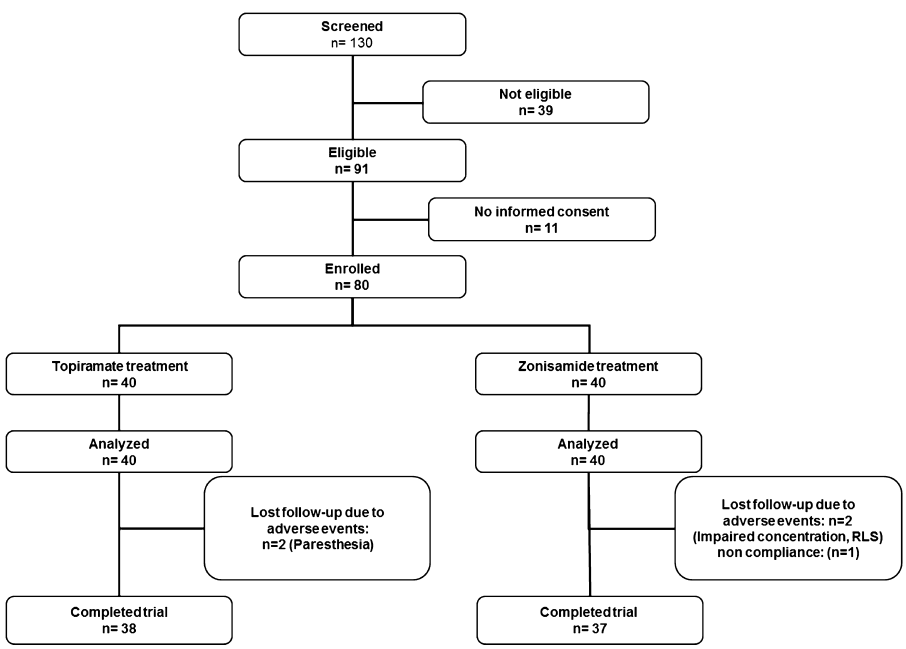

FIGURE 1. Subjects' flowchart.

TABLE 1. Baseline Participant Characteristics

Characteristics	Zonisamide n = 40	Topiramate n = 40	*P*
Demographics			
Age, y	35.5 ± 9.5	33.0 ± 9.2	0.227
Sex			0.785
Male	9	8	
Female	31	32	
History of migraine, mean, y	10.9 ± 5.4	8.9 ± 5.5	0.118
Average number of previous migraine prophylactic drugs	2.9	2.8	0.114
Headache Details			
Frequency per month	7.5 ± 2.9	7.2 ± 3.1	0.622
Severity	6.6 ± 1.1	6.9 ± 1.2	0.313
Need for acute medication	8.2 ± 3.2	7.7 ± 3.8	0.605
MIDAS	39.8 ± 9.8	37.3 ± 10.0	0.814

treatment, and the mean of the MIDAS score did not differ significantly between the groups.

Efficacy Result

Primary End Points

The frequency of migraine attacks and the times of need for acute medication were decreased significantly in both groups ($P < 0.001$) after the fourth week and the 12th week of drug initiation (Table 2). Nevertheless, the improvement difference between the 2 groups was not significant (Table 3). Good response to treatment, defined as decrease in headache frequency by more than 50%, was attained in 37.5% and 40% of the participants in the zonisamide and the topiramate groups, respectively ($P = 0.81$).

The score of headache severity was decreased significantly in both groups (Table 2), but a better improvement was achieved in the zonisamide group in comparison to the topiramate group ($P = 0.008$; Table 3).

TABLE 2. Comparison of Variables With Baseline for Each Group at Fourth Week and 12th Week

	Zonisamide		Topiramate	
Characteristics	n = 37	*P**	n = 38	*P**
Headache Frequency (per month)				
Fourth week	4.4 ± 2.2	<0.001	3.9 ± 1.9	<0.001
Twelfth week	3.9 ± 2.0	<0.001	3.4 ± 1.8	<0.001
Headache Severity				
Fourth week	4.2 ± 1.0	<0.001	4.8 ± 1.0	<0.001
Twelfth week	3.8 ± 0.7	<0.001	4.6 ± 0.9	<0.001
Need for Acute Medication				
Fourth week	5.2 ± 2.2	<0.001	4.0 ± 1.9	<0.001
Twelfth week	4.6 ± 1.8	<0.001	3.3 ± 1.8	<0.001
MIDAS				
Twelfth week	13.8 ± 4.4	<0.001	12.5 ± 4.7	<0.001

Values are presented in mean ± SD.

*Comparisons were made between the fourth and 12th weeks' outcomes with the baseline.

TABLE 3. Outcome Result Showing Improvement by 12th Week in 2 Groups

Characteristics	Zonisamide n = 37	Topiramate n = 38	*P**
Headache frequency improvement†	3.6 ± 1.42	3.7 ± 1.89	0.71
Headache severity improvement†	2.7 ± 0.79	2.2 ± 0.57	0.015
MIDAS improvement†	26 ± 5.9	24.9 ± 6	0.40

*Comparison of improvement between the 2 groups.

†The improvement was calculated by numerical difference between the score at baseline and the one at twelfth week. Values presented are means ± SD.

Secondary End Point

The mean of MIDAS score in the zonisamide and topiramate groups before treatment were 39.9 ± 9.8 and 37.4 ± 10.1, and after 3 months of treatment initiation, these were reduced to 13.8 ± 4.4 and 12.5 ± 4.7, respectively ($P < 0.001$). However, the difference between the 2 groups was not significant ($P = 0.404$; Table 2).

Adverse Events

Reported complications in the zonisamide group were dizziness, tiredness and then drowsiness, impaired concentration, paresthesia, and symptoms of the restless leg syndrome. One patient left the study owing to impaired concentration, and another left owing to unbearable restless leg syndrome. One subject left the study because of noncompliance but did not report a special complaint. The most common complication of topiramate was paresthesia (22.5%), and 2 patients left the study owing to intolerable paresthesia. Other complications in the topiramate group were fatigue, nausea, drowsiness, and changes in the sense of taste. No other adverse events were reported, and both drugs were tolerated well eventually.

DISCUSSION

Proven efficacy in migraine prophylaxis are limited to some specific classes such as β-blockers, antidepressants, calcium channel blockers, neuroleptics, and antiepileptics.[18] Whereas a notable number of patients experience failure of treatment owing to the drug's adverse events,[19] the choice of a regimen is limited more when the physician should regard other important factors such as patient's compliance, the presence of comorbid situations, and various headache profiles. Considering these facts, antiepileptics by appropriate pharmacologic profile and less interaction are regarded as effective tool especially in refractory migraine cases.[12] Although the efficacy of topiramate has been showed in reliable trials and is one of the approved preventive medications for migraine, its use can be limited because of adverse effects in long-term treatment. Blurred vision, intolerable paresthesia, gastrointestinal upset, and cognitive adverse effects are common in long-term treatment of topiramate.[20] As mentioned before, zonisamide has a similar mechanism of action to topiramate, but it has the ability to control headaches that are refractory to topiramate.[12,13] Our results are in line with previous studies that report appropriate efficacy of zonisamide in migraine prophylaxis. Moreover, we found a better control in headache severity by zonisamide in comparison to topiramate. This advantage may be explained by

its effect on inhibition of T-type calcium channels and scavenging NO products.[11] However, both drugs tolerated well during the study; zonisamide, with the ability of being used as single dose in 24 hours because of longer half-life, is expected to show a better tolerability in long-term treatment.[21] As a recent observational study confirmed, responsive but intolerant patients to topiramate could achieve acceptable migraine prophylaxis with a better compliance by using zonisamide.[17]

Baseline disability due to migraine, according to mean of MIDAS (Table 1), for both studied groups was categorized as grade IV (severe) before trial initiation. After the 12th week of treatment, both drugs caused improvement in the migraine-associated disability to grade III (moderate; Table 3). These partial improvements indicate that although both of them are efficient, their usage as single therapy may not provide desirable relief from migraine-induced disability, and perhaps, these medications should be regarded as add-on therapies for prophylaxis, at least in patients with refractory headaches.

The main limitation of previous studies was the lack of control group. In this trial, the results confirmed the efficacy of zonisamide in comparison to topiramate as control, but the main limitation was the small size of participants. Now, it seems that zonisamide has the appropriate pharmacological basis and clinical background to be proposed as a suitable alternative prophylactic drug for migraine. In this phase, larger-size studies are needed to prepare the possibility of starting the approval process for this drug.

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