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A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis

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Objective – To assess the efficacy and safety of low-dose topiramate in migraine prophylaxis vs propranolol. *Patients and methods* – A randomized, double-blind, clinical trial including 62 patients with frequent migraine headaches (≥ 3 attacks per month) was performed for a period of 8 weeks. The patients were randomly divided into two treatment groups – treated by topiramate 50 mg/day and propranolol 80 mg/day, respectively. The patients were assessed at 0, 4, and 8 weeks of the study. *Results* – The topiramate group showed a reduction in the mean (±SD) of monthly migraine frequency from 6.07 (±1.89) to 1.83 (±1.39) episodes per month, headache intensity from 7.1 (±1.45) to 3.67 (±2.1) based on the Visual Analog Scale, and headache duration from 16.37 (±7.26) to 6.23 (±5.22) hours ($P < 0.001$). In the patients treated with propranolol, the mean (±SD) of monthly headache frequency declined from 5.83 (±1.98) to 2.2 (±1.67) per month, headache intensity lessened from 6.43 (±1.6) to 4.13 (±1.94) and headache duration decreased from 15.10 (±6.84) to 7.27 (±6.46) h ($P < 0.001$). *Conclusion* – This study demonstrated that both low-dose topiramate and propranolol could significantly reduce migraine headache frequency, intensity, and duration. However, compared with propranolol, low-dose topiramate showed better results.

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Background

Migraine headache is a common episodic condition that can significantly impair the lives of otherwise normally functioning people. Population-based studies suggest that about 5.6% of men and 17% of women and 5–10% of children experience migraine headaches. According to previous studies, 25.7% of migraine patients met criteria to receive prevention, but just 13% were reported as regularly using daily preventive migraine medications (1, 2).

Pharmacologic options for migraine prophylaxis include beta blockers, calcium channel blockers, antidepressants and anticonvulsants (3, 4); all of which have varying degrees of adverse effects that may potentially limit their use.

Balancing drug efficacy vs its side effects, patients' expectations and compliance and sensible improvement should all be taken into account for successful migraine prevention (3).

Available guidelines commonly recommend beta blockers as the first choice for migraine prophylaxis, yet, it is not clear how exactly beta blockers decrease the frequency of migraine attacks. It is assumed that beta blockers may affect the central catecholaminergic system and brain serotonin receptors (5, 6).

Among the many different beta blockers, propranolol is one of the most commonly prescribed drugs for migraine prophylaxis. While propranolol is well tolerated in general, it is associated with a variety of adverse effects such as bradycardia, hypotension, bronchospasm, gastrointestinal complaints, and vertigo. This wide range of side effects, however, may limit its prescription for some patients (5).

It has been hypothesized that migraine is a disorder resulting from neuronal hyperexcitability (7) which has led to the introduction of new antiepileptic drugs in the prophylaxis of this pathology (8). Recent studies have suggested that topiramate could help as monotherapy in migraine prevention.

Topiramate has numerous effects on the central nervous system. It enhances the inhibitory effect of GABA and blocks the excitatory effect of glutamate. It also stops the repetitive firing of sodium channels, thus reducing calcium channel activity, and inhibits carbonic anhydrase (CA) (9–11). Such mechanisms may possibly explain its effect in pain relief.

Several studies indicated the role of high-dose (100–200 mg/day) topiramate in migraine prophylaxis (12). However, with such high doses, there are usually significant side effects like paresthesia, fatigue, memory difficulties, loss of appetite, and weight loss, nausea, diarrhea, and taste perversion. As a result, many patients do not tolerate high-dose topiramate (13–15).

The present study was planned and performed to evaluate the efficacy of low-dose topiramate in migraine prophylaxis and compare it with propranolol.

Patients and methods

In a period of 8 weeks, a randomized, double-blind clinical trial was carried out to compare the effects of low-dose topiramate and propranolol on migraine headache prevention.

Our cases were selected from the patients with alleged diagnosis of migraine admitted to Al-Zahra Hospital Neurology Clinic; affiliated to Isfahan University of Medical Sciences, Iran, from November 2003 through October 2004.

The diagnosis was confirmed according to the International Headache Society (IHS) (16) and a migraine checklist including demographic and clinical details of the patients such as frequency, duration, and intensity of headache was filled for each. The patients were included based on the following inclusion criteria after obtaining an informed written consent, conforming to the current revision of the Declaration of Helsinki. The Ethical Review Committee of Isfahan University of Medical Sciences approved the study protocol.

The inclusion criteria of our study were as follows:

1 Diagnosis of migraine (with or without aura) according to the IHS criteria.
2 Duration of at least 1 year.
3 Frequency of three or more migraine headache attacks per month during a 3-month period before entry.
4 A pain-free interval of at least 48 h between attacks.
5 Age at onset < 50 years.
6 Age at entry 18–65 years.
7 The concomitant migraine prophylactics withdrawn 1 month prior to entry into this trial.
8 Patient's ability to fill a reliable headache diary successfully.

Women who were pregnant or breast-feeding and patients with concomitant medical problems such as renal stones, cardiac, liver, or neoplastic diseases were excluded. Patients with neurologic diseases were also excluded.

A total of 62 patients met the inclusion criteria. A general evaluation and physical examination was performed in the first visit and patients were asked to complete a Migraine Disability Assessment questionnaire at the same visit.

Headache intensity was rated on a 10-point Visual Analog Scale where 10 represented the most severe pain. The frequency, intensity, and duration of all headaches were logged by each patient in a diary book, which was then transcribed into the patient's case record form at clinical visits, 4 and 8 weeks after the beginning of management. Each patient was also asked to record the side effects of drugs. The 62 patients were randomized on a 1:1 basis to receive either topiramate (50 mg/day) or propranolol (80 mg/day).

Topiramate was administered at 25 mg/day during the first week and was increased to 50 mg/day the following week. Propranolol was started at 40 mg/day and was increased to 80 mg/day respectively.

Patients and clinicians were blinded to study medications with preprinted medication code labels. Sealed envelopes containing the code labels with a tear-off label concealing the randomization number were provided. The patients continued receiving these doses for an 8-week period.

Statistical analysis

The demographic and clinical data were recorded on a predesigned checklist and passed into a Microsoft Excel worksheet. They were analyzed with SPSS version 13. Headache characteristics between groups were compared with an independent sample t-test. Repeated-measures ANOVA was applied to compare values between and within groups. Results are expressed as mean ($\pm$SD) and $P < 0.05$ was considered as statistically significant.

Results

Sixty-two patients who met the inclusion criteria were enrolled in the study. One of the patients in the topiramate group discontinued the drug due to severe paresthesia and another patient did not tolerate propranolol for hypotension. Ultimately 60 patients completed the course of study.

Patients in the two groups were not significantly different regarding age, gender, and other characteristics. The mean age of the topiramate and propranolol groups were 31.7 (±8) years and 29.93 (±9) years, respectively.

Twenty-six (86.7%) cases in the topiramate group and 23 (76.7%) cases in the propranolol group were female. Mean (±SD) number of monthly headache frequency at the beginning of the study with topiramate and propranolol was 6.07 (±1.89) and 5.83(±1.98), respectively. Mean (±SD) duration of each episode of headache at the baseline in topiramate and propranolol groups were 16.37 (±7.26) and 15.10 (±6.84) h, respectively. Mean headache intensity at the beginning of the study was 7.1 (±1.45) and 6.43 (±1.6) in the topiramate and propranolol groups, respectively.

There were no statistically significant differences between the two groups according to baseline headache characteristics (Table 1). Frequency, intensity and duration of migraine headaches decreased significantly between repeated follow-up visits of each patient in both groups according to repeated measurement test (Table 1). After 8 weeks, topiramate was more effective than propranolol compare with 4 weeks management (Figs 1–3).

Although in both groups monthly headache frequency, intensity, and duration decreased, in the topiramate group the mean value of reduction was significantly more than in the propranolol group (Table 2). The baseline parameters of headache were more severe in the topiramate group and this may indicate more improvement in that group compared with the propranolol group.

The most common side effects of topiramate were paresthesia (seven patients), weight loss (five patients), somnolence (four patients) and dizziness (three patients) that were mild to moderate. In propranolol-treated patients, common side effects were bradycardia, hypotension, and dizziness.

Table 1 Comparison of headache parameters at baseline and after 4 and 8 weeks of treatment

	Frequency of migraine (per month), mean (SD)	Headache intensity (VAS), mean (SD)	Duration of each episode (h), mean (SD)
Topiramate			
Baseline	6.07 (1.89)	7.10 (1.45)	16.37 (7.26)
After 4 weeks	4.13 (1.17)	5.23 (1.78)	15.63 (7.19)
After 8 weeks	1.83 (1.39)	3.67 (2.1)	6.23 (5.22)
P-value (within group)	<0.001	<0.001	<0.001
Propranolol			
Baseline	5.83 (1.98)	6.43 (1.6)	15.10 (6.84)
After 4 weeks	3.83 (1.82)	4.87 (2.1)	14.47 (6.49)
After 8 weeks	2.20 (1.67)	4.13 (1.94)	7.27 (6.46)
P-value (within group)	<0.001	<0.001	<0.001
P-value (between groups)	0.889	0.669	0.773

VAS, Visual Analog Scale.

Discussion

The results of this study show that though both low-dose topiramate and propranolol decreased

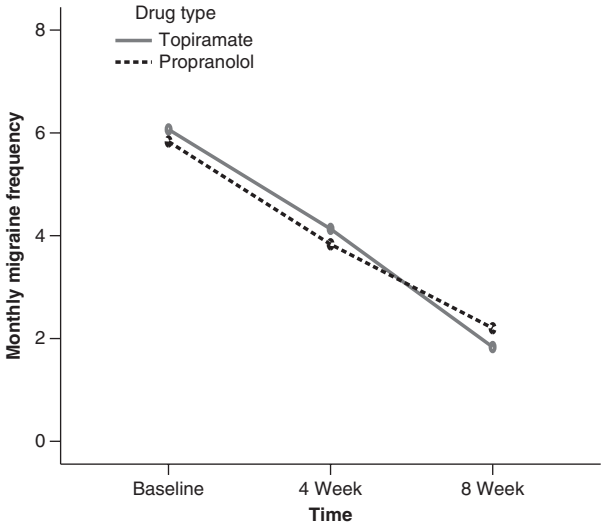

Figure 1. Reduction in headache frequency in both groups.

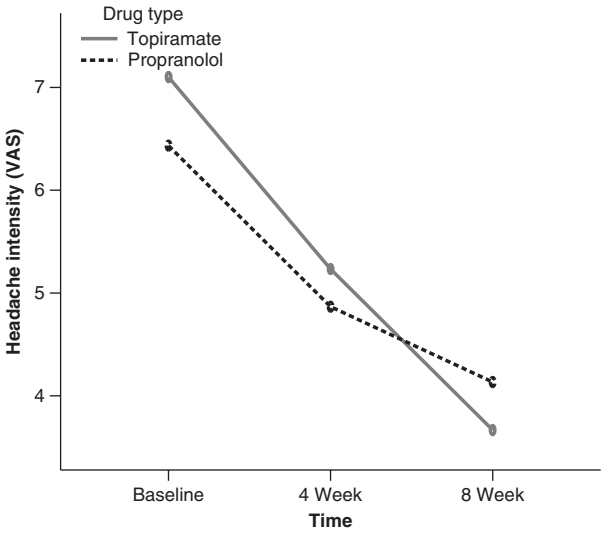

Figure 2. Reduction in headache intensity in groups.

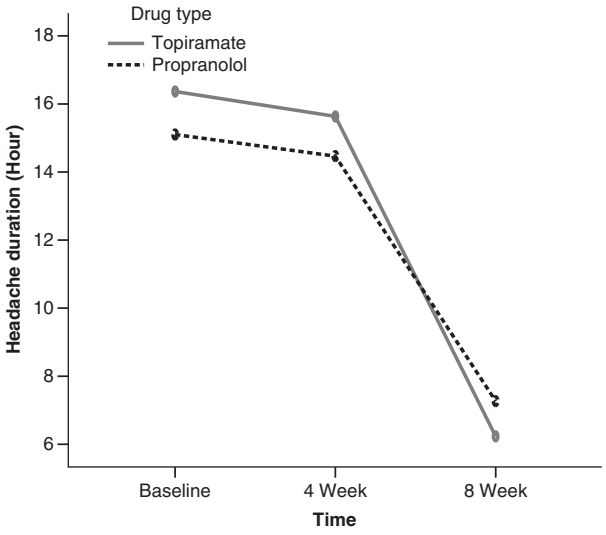

Figure 3. Reduction in headache duration in groups.

Table 2 Comparison of mean reduction of frequency, intensity, and duration of headache in groups after 8 weeks of treatment

	Drug type			95% Confidence interval of the difference	
	Topiramate (n = 30)	Propranolol (n = 30)	P-value	Lower	Upper
Decrease in frequency (mean ± SD)	4.23 ± 1.2	3.63 ± 0.96	0.036	0.039	1.16
Decrease in intensity (mean ± SD)	3.43 ± 1.38	2.30 ± 1.2	0.001	0.46	1.8
Decrease in duration (mean ± SD)	10.1 ± 4.3	7.83 ± 4.5	0.048	0.017	4.6

monthly headache frequency, intensity and duration, topiramate (50 mg/day) proved to be more effective than propranolol (80 mg/day). Moreover, low-dose topiramate was well tolerated.

Propranolol is commonly used as a preventive drug for migraine prophylaxis and can be particularly useful in patients with coexisting hypertension and anxiety, but it is contraindicated in some disease such as asthma and many patients cannot tolerate its high dose (5).

Topiramate is an antiepileptic used for preventive therapy of migraine. Reports from previously conducted trials showed its statistically significant benefit as a prophylactic agent for migraine (17). It was also said to be cost effective (18). These results are consistent with the study of Bussone et al. who demonstrated an effective and generally well-tolerated migraine prevention with topiramate in adults (12).

Two large trials by Brandes and Silberstein et al. evaluated 50, 100, and 200 mg doses of topiramate on migraine patients. These studies showed significant benefits for 100 and 200 mg doses of topiramate with respect to primary endpoints and no benefits for 50 mg dose of topiramate (13, 15).

In another study by Gupta, low-dose topiramate was compared with lamotrigine. This study demonstrated that low-dose topiramate was more effective than lamotrigine (19).

In a study evaluating the efficacy and safety of two doses of topiramate (100 and 200 mg) vs placebo and propranolol, it was shown that topiramate 100 mg/day was superior to placebo as measured by reduction in monthly migraine frequency with an overall 50% responder rate and reduction in monthly migraine days. Topiramate 100 mg/day was better tolerated than topiramate 200 mg/day, and was generally comparable to propranolol. Topiramate 100 mg/day and propranolol 160 mg/day exhibited similar efficacy profiles (12, 20).

Topiramate showed adverse effects like paresthesia, fatigue, nausea, taste alteration, and diarrhea. Cognitive abnormality was another side effect of topiramate (14) these side effects may be more sensible with high doses.

In pivotal topiramate-migraine clinical trials, paresthesia occurred in 35% of subjects in topiramate 50 mg/day group and in 51% of those in topiramate 100 mg/day group, denoting that these adverse effects may be dose dependent (13). As a result, many patients may discontinue high-dose topiramate.

In the present study, mild to moderate acroparesthesia was the most common side effect that was well tolerated. In another study evaluating the efficacy, safety, and tolerability of topiramate as adjunctive prophylactic therapy for migraine, it was shown that the most common side effects were acroparesthesia, weight loss, sleepiness, and worsened headaches (21). Pascual et al. suggested that response to topiramate as a combination therapy was excellent but discontinuation due to adverse effect happened in one out of every six patients (22). However, in our study tolerance to 50 mg topiramate was reasonably good. Our study highlighted the efficacy of low-dose prophylactic topiramate similar to a study in the Chinese population (23).

Conclusion

The results of this study suggest that low-dose topiramate seems effective and relatively safe for migraine prophylaxis; moreover, topiramate showed greater improvement when compared with propranolol.

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