

A comparative study on the effectiveness of topiramate and propranolol in patients with migraine with aura

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Keywords

Migraine Disorders; Aura; Topiramate; Propranolol; Antiepileptic

Abstract

Background: Migraine is considered as one of the most common and disabling diseases of the nervous system that has a great impact on quality of life (QOL) and a little risk of neurologic complications such as stroke. Migraine aura is known to be the result of cortical spreading depression and is associated with higher risk of this complication. Thus, the present study was conducted with the aim to compare the effects of topiramate as an antiepileptic, and propranolol in patients with migraine with aura.

Methods: The present randomized clinical trial was conducted on patients with migraine with aura referred to the neurology clinic of Golestan Hospital, Ahvaz, Iran, in the period of 2019-2020. The patients were randomized into two groups and received either topiramate or propranolol. The Migraine Disability Assessment Scale (MIDAS) score was evaluated before and at the end of

three months after initiating the treatment.

Results: Reduction in the MIDAS score in patients taking topiramate (-16.94) was greater than that in the propranolol group (-14.5), but this difference was not statistically significant ($P > 0.005$). No significant relationship was found between gender and changes in the MIDAS score after the treatment of both groups ($P > 0.050$). However, the changes in the MIDAS score were greater in younger patients, and this relationship was statistically significant ($P < 0.050$).

Conclusion: There was no significant difference in the efficacy of topiramate and propranolol in patients with migraine with aura. No significant relationship was found between gender and changes in the MIDAS score after the treatment in both groups, but the reduction in the MIDAS scores was significantly higher in younger patients of both groups.

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Introduction

Migraine is one of the most common diseases of nervous system, which is divided into migraines with and without aura given the clinical manifestations.^{1,2} Migraine is more common in females.³ Aura is a focal neurological phenomenon that occurs before or during a migraine attack. Aura manifests commonly as visual, and much less often as sensory, speech, or motor symptoms.⁴ About 20% of patients with classic migraine experience aura symptoms before the onset of the headache.⁵ Studies have suggested a genetic basis for migraine.⁶ Obviously, the role of genetics in migraine with aura is greater than that in the common migraine.⁴ Many studies suggest the relationship between stroke and migraine with aura.⁷⁻⁹ Development of serious and permanent neurological complications in patients with classic migraine highlights the importance of controlling and treating this disease. First-line medications established as effective based on clinical evidence include divalproex, topiramate, metoprolol, propranolol, and timolol.⁴ The results of several studies suggest an increase in the quality of life (QOL) following the use of topiramate as a migraine preventive drug.¹⁰⁻¹⁴ Topiramate is a sulfamate-substituted monosaccharide, derived from D-fructose. The drug reduces excitatory neurotransmission and enhances inhibitory neurotransmission, both probably involved in the pathophysiology of migraine. Topiramate, through a broad profile of action, might act at different levels: reducing nociceptive transmission through trigeminovascular modulation, and inhibiting cortical spreading depression. Topiramate is a class of anticonvulsant drugs prescribed for treatment of seizures and epilepsy in generalized tonic, partial, and tonic seizures in adults and children over 2 years of age, various epileptic syndromes, prevention of migraine attacks and treatment of bipolar disorder, schizophrenia, and stress disorder.¹⁵ Although the exact mechanism of action of this drug is not known, several studies have reported blocking effects on sodium and calcium glutamate receptors, inhibition of the carbonic dehydrase, and strengthening effects on gamma-aminobutyric acid (GABA) receptors.^{12,14} However, some adverse effects such as the risk of kidney stones, cognitive impairment, new onset or exacerbation of depression, increased intraocular pressure, and the risk of teratogenicity in unwanted pregnancy have made some limitations for deliberate using of

this drug for a great number of patients.¹⁶ Beta-adrenergic blockers, such as propranolol, are also the most prescribed drugs for migraine prophylaxis. Recent reports suggested the effects of propranolol in relieving acute and common acute migraine attacks.^{16,17} The effectiveness of antiepileptic drugs in the treatment of common and classic migraine has been reported. However, due to the common mechanism of action of antiepileptic drugs and its pathology, especially its special role on the neurotransmitter glutamate and other pathological events, it is hypothesized that the effect of antiepileptic drugs such as topiramate in controlling the classic migraine is greater than the effect of other drugs.¹⁵ Due to the high prevalence of migraine in different communities, the present study was conducted aiming to evaluate and compare the effects of topiramate as an antiepileptic drug and propranolol on migraine with aura, hypothesizing that the effect of topiramate is higher in patients with aura due to its different mechanism.

Materials and Methods

The present study was conducted on patients aged 18 to 65 years with a history of migraine with aura [in accordance with the International Classification of Headache Disorders (ICHD)] and with the frequency of attacks at least once a week in Golestan Hospital, Ahvaz, Iran, in 2019-2020, after obtaining permission from aura Ethics Committee, Research Deputy, Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1398.932) and registering the project on the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20201031049208N1).

Patients with systolic blood pressure below 90 mm Hg, heart rate below 65 beats per minute, presence of tension-type headache attacks in the past month, previous history of using migraine painkiller or specific drug, history of known allergy to topiramate or propranolol, history of kidney stones, and history of depression were excluded from the study. Before starting the study, the objectives and method of study were explained to all eligible participants and if they were willing to participate in the study, they entered the study after receiving their written consent. The sample size was determined using Morgan table and considering the population referred to the neurology clinic of Golestan Hospital of Ahvaz who had migraine with aura. 32 patients were equally and randomly divided into two

intervention groups (n = 16) based on a simple randomization method using a random number table. In this method, a set of numbers without a pattern was randomly generated and entered to a table. In this way, the even numbers and odd numbers were considered for the intervention group 1 and intervention group 2, respectively. For patients in intervention group 1, topiramate was started at a dose of 25 mg daily and increased to 100 mg daily, depending on the patient's tolerance.^{16,18,19} The duration of taking the drug was considered three months. In addition, patients in intervention group 2 received propranolol at a dose of 20 mg twice a day for three months. The required data were recorded by taking the history and performing a clinical examination in the neurology clinic by the research manager. The first section of the questionnaire included demographic information (including age, gender, etc.) and the second section assessed the degree of disability defined by the Migraine Disability Assessment Scale (MIDAS). The patients completed the MIDAS questionnaire at the beginning of the study (before taking the drug) and after 3 months of taking the drug, and their results were compared with each other.

The MIDAS divides the level of disability from migraine headache according to the defined score ranges and grades (Table 1).²⁰

In the present study, descriptive statistics including mean and standard deviation (SD) were used to describe quantitative variables, and frequency and frequency percentage were used to describe qualitative variables of the study. Parametric and non-parametric statistics were

used to test the study hypotheses. All analyses were performed using the SPSS software (version 22, IBM Corporation, Armonk, NY, USA). The significance level of the tests was considered less than 0.050.

Table 1. Migraine disability assessment (MIDAS) score

Level of disability	Score	Grade
Little or no disability	0 to 5	I
Mild disability	6 to 10	II
Moderate disability	11 to 20	III
Severe disability	21 or higher	IV

Results

There was no statistically significant difference between the two groups in terms of demographic characteristics including age, weight, height, and gender ($P < 0.050$). Moreover, before starting the treatment, patients in the two groups were examined in terms of their distribution based on the type of aura (sensory, visual, motor, and other cases), and MIDAS grade (I, II, III, IV) and no significant difference was found between them ($P > 0.050$) (Table 2).

Although reduction in the MIDAS score was higher in patients taking topiramate compared to the propranolol group, this reduction was not statistically significant in the two groups ($P > 0.050$) (Table 3).

There was no significant relationship between gender and changes in the MIDAS score after the treatment in any of the two groups ($P > 0.050$), but patients' age and changes in the MIDAS score after the treatment were negatively correlated with each other in both groups.

Table 2. Demographic and clinical information of patients in the two groups

Variables	Group T (n = 16)	Group P (n = 16)	P
Age (year) (mean ± SD)	29.81 ± 14.12	30.56 ± 15.09	0.670
Weight (kg) (mean ± SD)	70.06 ± 9.10	69.68 ± 8.21	0.720
Height (cm) (mean ± SD)	169.12 ± 15.64	171.06 ± 14.19	0.690
Gender [n (%)]			
Female	10 (62.50)	8 (50.00)	0.210
Male	6 (37.50)	8 (50.00)	
Kind of aura [n (%)]			
Sensory	6 (37.50)	4 (25.00)	0.450
Vision	6 (37.50)	5 (31.25)	
Motor	2 (12.50)	3 (18.75)	
Other	2 (12.50)	4 (25.00)	
MIDAS grade [n (%)]			
I	1 (6.25)	2 (12.50)	0.080
II	3 (18.75)	2 (12.50)	
III	4 (25.00)	3 (18.75)	
IV	9 (56.25)	10 (62.50)	

The statistical tests used were t-test and chi-square test.

SD: Standard deviation; MIDAS: Migraine Disability Assessment Scale

Table 3. Comparison of mean changes in Migraine Disability Assessment Scale (MIDAS) score before and three months after treatment in patients of both groups

MIDAS score	Group T	Group P	P
Mean difference	-16.94 ± 5.87	-14.5 ± 7.19	0.090

Data are expressed as mean ± SD.

The statistical test used was t-test.

MIDAS: Migraine Disability Assessment Scale; SD: Standard deviation

It means that changes (reduction) in the MIDAS score was greater in younger patients, and this relationship was statistically significant ($P < 0.050$) (Table 4).

Table 4. Relationship between rate of changes in Migraine Disability Assessment Scale (MIDAS) score after treatment and age and gender of patients in the two groups

Group	Variables	Correlation (r)	P
Group T	Gender	0.071	0.310
	Age	-0.728	0.003
Group P	Gender	0.119	0.470
	Age	-0.802	0.002

Discussion

The effects of topiramate on excitatory neurotransmitter receptors and voltage-gated ion channels may explain its mechanism of action in reducing the frequency of migraine attacks. The mechanism of cortical spreading depression and migraine aura are similar in terms of involvement of glutamate neurotransmitter and ion channels. Considering the common mechanisms of action of antiepileptic drugs, including inhibitory effects on glutamate neurotransmitter and regulating the ion channels, it is presumed that antiepileptic drugs such as topiramate might have a better profile in the treatment of classic migraine.¹⁰ The aim of the present study was to evaluate and compare the effects of topiramate as an antiepileptic drug and propranolol on the MIDAS score of patients with migraine with aura. The results of the present study showed that the topiramate group had a greater reduction of the MIDAS score compared to the propranolol group, but this reduction was not statistically significant.

This meaningful reduction of the MIDAS score or frequency of attacks in younger patients with classic migraine might be attributed to the specific mechanism of action of topiramate. Furthermore, this study was performed with 100 mg/day dose of topiramate in 16 patients and for three months of follow-up. The use of higher doses of topiramate, in a greater number of patients, and a longer follow-up

might better show the probable differences.

Topiramate has been approved for the treatment of adult patients with migraine, as a relatively safe drug. Its popularity is somewhat due to the weight reducing effect amongst the alternative medications that cause weight gain. However, side effects such as cognitive decline, renal stone, and psychic effects limit its deliberate use, especially in higher doses. Studies and experience have shown that patients with migraine are particularly sensitive to the side effects of topiramate in higher doses. This has led to the use of lower doses of topiramate by most experts in chronic maintenance treatment of migraine.

Different studies have compared its efficacy in preventive treatment of common and classic migraine. Karadas et al. evaluated the effects of topiramate therapy on cerebral metabolism in patients with migraine with aura. Transcranial doppler (TCD) monitoring showed that topiramate is an effective prophylactic treatment in patients with migraine with aura and appeared to play a positive role in the regulation of cerebrovascular autonomic control.²¹

In a randomized, placebo-controlled, double-blind, 12-week pilot study, Silberstein et al. demonstrated the efficacy and tolerability of topiramate 200 mg/day in the prevention of migraine in adults with/without aura. The results of the study suggested that the mean monthly migraine frequency did not differ significantly between the topiramate and placebo groups.²²

Choudhary et al.²³ compared the effects of topiramate and sodium valproate in the treatment of migraine. Their results revealed that the effectiveness of sodium in reducing the frequency of attacks in patients with migraine valproate was 64.44% and effectiveness of topiramate was 56.55%, and there was a significant difference between the two groups ($P = 0.006$). The results of the above study on the effectiveness of topiramate were consistent with those of the present study, but the difference from the present study was probably related to the drugs compared.

Zain et al.²⁴ compared the effects and safety of topiramate with gabapentin in the prevention of migraine on 80 patients with migraine headache. The reduction in frequency of monthly attacks and severity of migraine in the topiramate group was significantly greater than that in the gabapentin group. Besides, reduction in the mean duration of attacks (hours) in the topiramate group was significantly greater than that in the gabapentin

group. The findings of the above-mentioned study on the effectiveness of topiramate in the frequency of monthly attacks and the severity of migraine according to the MIDAS were consistent with those of the present study, but the difference between their study and the present study was related to the drugs compared.

Reuter et al.²⁵ evaluated and compared the effects of topiramate as a preventive treatment in patients with migraine with and without aura over 6 months. Their results revealed that with the use of topiramate, migraine without aura and migraine with aura decreased by 43.1% and 54.1%, respectively, and its effectiveness was similar in patients with migraine with and without aura. The results of this on the effectiveness of topiramate were consistent with those of the present study. However, the above study only evaluated the effectiveness of topiramate and did not compare its effectiveness with an active group.

References

- Bohm PE, Stancampiano FF, Rozen TD. Migraine headache: Updates and future developments. *Mayo Clin Proc* 2018; 93(11): 1648-53.
- Mayans L, Walling A. Acute migraine headache: Treatment strategies. *Am Fam Physician* 2018; 97(4): 243-51.
- Lagman-Bartolome AM, Lay C. Migraine in women. *Neurol Clin* 2019; 37(4): 835-45.
- Charles A. The migraine aura. *Continuum (Minneapolis)* 2018; 24(4, Headache): 1009-22.
- Weatherall MW. The diagnosis and treatment of chronic migraine. *Ther Adv Chronic Dis* 2015; 6(3): 115-23.
- Sutherland HG, Griffiths LR. Genetics of migraine: Insights into the molecular basis of migraine disorders. *Headache* 2017; 57(4): 537-69.
- Abanoz Y, Gulen AY, Gunduz A, Uluduz D, Ince B, Yavuz B, et al. Migraine as a risk factor for young patients with ischemic stroke: A case-control study. *Neurol Sci* 2017; 38(4): 611-7.
- Spalice A, Del BF, Papetti L, Zicari AM, Properzi E, Occasi F, et al. Stroke and migraine is there a possible comorbidity? *Ital J Pediatr* 2016; 42: 41.
- Malik R, Winsvold B, Auffenberg E, Dichgans M, Freilinger T. The migraine-stroke connection: A genetic perspective. *Cephalalgia* 2016; 36(7): 658-68.
- Ha H, Gonzalez A. Migraine headache prophylaxis. *Am Fam Physician* 2019; 99(1): 17-24.
- Diener HC, Tfelt-Hansen P, Dahlof C, Lainez MJ, Sandrini G, Wang SJ, et al. Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. *J Neurol* 2004; 251(8): 943-50.
- Medrano V, Sempere AP, Morera-Guitart J, Fernandez-Izquierdo S, Espinosa-Martinez J. Preventive treatment with topiramate enhances the quality of life of patients with migraine. *Rev Neurol* 2006; 43(5): 259-63. [In Spanish].
- Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. *Cephalalgia* 2007; 27(7): 814-23.
- Bartolini M, Silvestrini M, Taffi R, Lanciotti C, Luconi R, Capecci M, et al. Efficacy of topiramate and valproate in chronic migraine. *Clin Neuropharmacol* 2005; 28(6): 277-9.
- Diamond M, Dahlof C, Papadopoulos G, Neto W, Wu SC. Topiramate improves health-related quality of life when used to prevent migraine. *Headache* 2005; 45(8): 1023-30.
- Silberstein SD. Topiramate in migraine prevention: A 2016 perspective. *Headache* 2017; 57(1): 165-78.
- Gooriah R, Nimeri R, Ahmed F. Evidence-based treatments for adults with migraine. *Pain Res Treat* 2015; 2015: 629382.
- Brandes JL, Saper JR, Diamond M, Couch JR, Lewis DW, Schmitt J, et al. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 2004; 291(8): 965-73.
- Silberstein SD, Lipton RB, Dodick DW, Freitag FG, Ramadan N, Mathew N, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache* 2007; 47(2): 170-80.
- Zandifar A, Asgari F, Haghdoost F, Masjedi SS, Manouchehri N, Banihashemi M, et al. Reliability and validity of the migraine disability assessment scale among migraine and tension type headache in Iranian patients. *Biomed Res Int* 2014; 2014: 978064.
- Karadas O, Gul HL, Ozturk B, Eroglu E, Demirkaya S. The effects of topiramate therapy on cerebral metabolism in migraine with aura patients. *Turk Neurosurg* 2014; 24(5): 704-9.
- Silberstein SD, Hulihan J, Karim MR, Wu SC, Jordan D, Karvois D, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. *Clin Ther* 2006; 28(7): 1002-11.
- Choudhary MU, Nawaz J, Saddique M, Zameer A. Comparison between Topiramate and Sodium Valproate Efficacy in the Treatment of Migraine. *Pak J Med Health Sci* 2017; 11(3): 1005-7.
- Zain S, Khan M, Alam R, Zafar I, Ahmed S. Comparison of efficacy and safety of topiramate with gabapentin in migraine prophylaxis: randomized open label control trial. *J Pak Med Assoc* 2013; 63(1): 3-7.
- Reuter U, Sanchez Del RM, Diener HC, Allais G, Davies B, Gendolla A, et al. Migraines with and without aura and their response to preventive therapy with topiramate. *Cephalalgia* 2010; 30(5): 543-51.

Conclusion

Based on the results obtained, there was no significant difference in the efficacy of topiramate and propranolol in patients with migraine with aura. No significant relationship was found between gender and changes in the MIDAS score after the treatment in both groups, but the reduction in the MIDAS scores was significantly higher in younger patients of both groups. Further studies in larger scales may better clarify the additional effects of antiepileptic drugs in patients with migraine with aura.

Conflict of Interests

The authors declare no conflict of interest in this study.

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