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Original Article

Ophthalmology Section

Evaluation of Ocular Side Effects in the Patients on Topiramate Therapy for Control of Migrainous Headache

OMID HESAMI[1], SEYEDEH SIMINDOKHT HOSSEINI[2], NASIM KAZEMI[3], SEYED-MOSTAFA HOSSEINI-ZIJOUD[4], NAHID BELADI MOGHADDAM[5], FARHAD ASSARZADEGAN[6], SARA MOKHTARI[7], SHAHRZAD FAKHRAEE[8]

ABSTRACT

Introduction: Topiramate, a sulfa-derivative monosaccharide, is an antiepileptic drug which is administered in the control of migraine. It is reported to cause various ocular side effects such as visual field defect and myopic shift. To investigate the alterations in refractive error, properties of the cornea and changes in the anterior chamber in patients that receive Topiramate for migraine control.

Materials and Methods: This is a hospital-based, non-interventional, observational study that is conducted at Imam Hossein Hospital, affiliated to Shahid Beheshti University of Medical Sciences, Department of Neurology, in collaboration with the department of Ophthalmology.

Thirty three consecutive patients with the diagnosis of migraine that were candidate for Topiramate therapy were recruited. Patients with history of ocular trauma or surgery, keratoconus, glaucoma, congenital ocular malformations and any history of unexplained visual loss were excluded. After thorough ophthalmic examination, all the patients underwent central corneal thickness (CCT) measurement, and Pentacam imaging (Scheimpflug camera) at the baseline. Various parameters were extracted and used for analysis. Anterior chamber volume (ACV), anterior chamber depth (ACD), and anterior chamber angle (ACA) measurement was performed. These measurements were repeated on day 30th and 90th after the initiation of Topiramate therapy. According to the normality tests, parameters with normal distribution were analysed using the repeated measures test and the remaining parameters (with non-normal distribution) were analysed using the non-parametric k-sample test. A p-value< 0.05 was considered statistically significant, according to Bonferroni post hoc correction.

Results: There were 66 eyes of 33 patients under the diagnosis of migrainous headache, that Topiramate was initiated for headache control, included in the study. The mean value of refractive error had a statistically significant myopic change, from –0.23 diopters (D) at the baseline to –0.61 D at the 90th day of follow-up period (p-value < 0.001). Mean CCT was 531.43 µm at the baseline and increased to 534.72 µm at the 30th day, and 537.51 µm at the 90th day after the administration of Topiramate (p-value=0.001). Mean value of other parameters, ACV, ACD, and ACA, did not reveal statistically significant change.

Conclusion: Myopic shift and gradually increasing CCT in the patients after Topiramate administration should be considered before any refractive surgery. We found no gradual change in the anterior chamber and angle parameters in our patients in the 90 days of follow up. More studies with a longer duration of follow-up are needed to elucidate dose-dependent ocular manifestations.

Keywords: Anterior chamber depth, Central corneal thickness, Myopic shift

INTRODUCTION

Topiramate (Topamax, Ortho-McNeil Pharmaceuticals, Raritan, NJ), a sulfamate-substituted monosaccharide, has been approved as an add-on therapy or monotherapy, in resistant partial and generalized seizures. This antiepileptic medication is also used in the management of migraine, depression, and neuropathic pain. It is used as a preventative for atypical migraine. It has a vasodilator effect in the brain, which constrict in response to increased serum serotonin levels [1].

Topiramate is rapidly absorbed after oral intake; it crosses the blood-brain barrier and is excreted in urine with a half-life of almost 24 hours. Its antiepileptic activity is attributed mainly to sodium channel blockade, activation of GABA A receptors and weak anti-carbonic anhydrase activity [2,3].

Now-a-days, with the expanding spectrum of indications for the administration of Topiramate, the range of various adverse effects of the drug is increasing. The most common systemic adverse effects are psychomotor slowing, fatigue, somnolence, cognitive dysfunction, and nephrolithiasis [4].

Ophthalmologic side effects are also important because of their variety and severity [5]. Ocular adverse effects reported as attributable to Topiramate are: acute angle closure glaucoma, ocular pain, headache, hyperaemia, mydriasis, uveitis, visual field defects, acute onset myopia, suprachoroidal effusions, blepharospasm, oculogyric crisis, scleritis, and retinal haemorrhage [5].

There are some published papers describing ocular side effects of Topiramate [6,7]. Banta et al., presented a case of uveal effusion and secondary angle closure glaucoma associated with Topiramate use [8]. In 2001, Ortho-McNeil Pharmaceuticals sent out a statement indicating that 21 cases of acute angle closure glaucoma had been reported to its safety division [9,10]. Topiramate-associated glaucoma with the evidence of high-frequency ultrasound revealing ciliary process swelling and forward displacement of the lens iris diaphragm has been reported [11]. Kerimoglu et al., reported a Topiramate induced myopic shift (TiMS) and an increased central corneal thickness [12]. Frauenfelder et al., reviewed 115 spontaneous reports of ocular side effects associated with Topiramate use. They classified the ocular side effects in 3 groups: a) side effects know to be associate with Topiramate: shallow anterior chamber with angle closure, elevated intraocular pressure, abnormal vision, acute myopia (up to 8.75 diopters {D}), diplopia (at high doses), and nystagmus (at high doses); b) probable side effects: blepharospasm, myokymia, oculogyric crisis and suprachoroidal effusions; and c) possible side effects: congenital ocular abnormalities, periorbital oedema, and scleritis [13].

Since many case reports of ocular side effects of Topiramte therapy has been published [7], these complications should be taken seriously and be subjected to ophthalmic counseling.

These side effects are considered idiosyncratic by some of the researchers. Recent investigations demonstrated that efflux transporters in cornea-like multidrug resistance-associated protein (MRP)-1 and-5, which interfere with drug delivery, might play a role in the presentation of these side effects. However, the pre-treatment findings of affected patients and the effect of Topiramate on the ocular structures in patients that do not present with any side effect clinically, have yet to be understood [14].

In an attempt to elucidate any predisposing factor or early signs of presentation of the ocular side effects of Topiramate, we conducted a prospective study on patients who were administered Topiramate for control of migraine, at Imam Hossein Hospital, Affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. We monitored the precise effect of Topiramate treatment on refractive error, intraocular pressure, and anterior segment ocular structures, including the cornea and anterior chamber.

MATERIALS AND METHODS

The current study was a hospital-based, non-interventional, observational study that was conducted at Imam Hossein Hospital, affiliated to Shahid Beheshti University of Medical Sciences, department of Neurology, in collaboration with the Department of Ophthalmology.

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study to be in accordance with the tenets of the Declaration of Helsinki and the declaration of Iranian Medical ethics Committee group. Consecutive patients that were administered Topiramate for migraine control, were fully informed about the potential side effects of Topiramate, and the aim of the study, and those that were eligible to participate, were recruited and signed a consent form. All patients with previous history of ocular trauma or surgery, keratoconus, glaucoma, congenital ocular malformations, and any history of unexplained visual loss were excluded in this step.

The study included 66 eyes of 33 patients from the Neurology outpatient clinic. The initial Topiramate dose of 25 mg d^{-1} was initially administered and was increased to 50 mg d^{-1} after 1 week. Dose modification and increase to 100 mg d^{-1}, was considered upon the efficacy of the drug in controlling the migraine symptoms after 30 days.

The baseline ophthalmological examination was conducted preceding the use of Topiramate in order to exclude any history or finding of ocular disease. A thorough ophthalmic examination was performed, including best-corrected visual acuity (BCVA), cycloplegic refraction, intraocular pressure (IOP) measurement using a Goldmann applanation tonometer, and anterior segment and fundus examination including gonioscopy. Patients with abnormal IOP or angle structure were excluded in this step.

Additionally, patients underwent measurement of central corneal thickness (CCT), anterior chamber volume (ACV), anterior chamber depth (ACD), and anterior chamber angle degree(ACA) using a Scheimpflug camera (Pentacam; Oculus, Wetzlar, Germany).

Follow-up visits were scheduled for 30, and 90 days after the initiation of Topiramate therapy [7].

During the follow-up sessions, the patients were first asked to complete a questionnaire concerning the ocular side effects including symptoms of like ocular pain, headache, blepharospasm, blurred vision, and red eye. Presence of mydriasis, uveitis, visual field defects, acute onset myopia, suprachoroidal effusions, oculogyric crisis, retinal haemorrhage, and scleritis were checked in the ophthalmic examination that included thorough slit lamp examination, IOP measurement, funduscopy, BCVA measurement, and cycloplegic refraction. Results were recorded in the patient's profile.

Pentacam was performed and the ocular anterior segment structural parameters were calculated in each follow up visit as it was performed before the initial dose of Topiramate.

To reduce the various types of biases, the initial and follow-up examinations were performed at the same time in the morning by the same ophthalmologist (OH).

STATISTICAL ANALYSIS

The statistical analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, Illinois, USA). According to the normality tests, parameters with normal distribution were analysed using the repeated measures test and the remaining parameters (with non-normal distribution) were analysed using the non-parametric k-sample test. A p-value< 0.05 was considered statistically significant, according to Bonferroni post-hoc correction.

RESULTS

The current study included 66 eyes of 31 female patients and 2 male patients that began to use Topiramate for migrainous headache control. The mean age of the participants was 34.53 ± 8.65 years (range: 23–52 years).

One female patient reported acute glaucoma attack in 2 weeks and discontinued the drug due to this adverse event and was excluded before the first follow up session. There were 32 patients that participated in the entire baseline, and the 30th and 90th day examinations.

The initial Topiramate dose of 25 mg d^{-1} was increased to 50 mg d^{-1} after 1 week in all patients and only three patients required a dose increment to 100 mg d^{-1} due to insufficient control of migraine symptoms after 30 days. BCVA measured at the baseline and at all follow-ups was 20/20 in all eyes.

Mean CCT was initially 531.43± 44.83 µm, and increased significantly to 534.72± 53.83 µm and 537.51 ± 42.51 µm at the 30-day follow-up and at the 90 day follow-up, respectively (p-value < 0.001).

The initial Mean value of ACV increased slightly during the 30th and 90th day follow-ups; these increase were not found statistically significant (p-value= 0.55).

The baseline ACD and ACA mean values changed slightly during the follow-up, though not significantly (p = 0.67 and p-value= 0.73, respectively) [Table/Fig-1].

At baseline, the median refractive error was –0.23 D that increased to –0.58 D at the 30th day of follow-up and to –0.61 D at the 90th day [Table/Fig-2]. Statistical analysis showed that there was a significant change in refractive error at the 30, and 90 day follow-ups, as compared to the baseline examination (both p-values<0.001).

	Baseline	30th day	90th day	p-value
CCT (µm)	531.43 ± 44.83	534.72 ± 53.83	537.51 ± 42.51	0.001
ACV (mm^3)	203.56 ± 28.34	207.65 ± 26.73	208.12 ± 26.67	0.55
ACD (mm)	3.56 ± 0.33	3.52 ± 0.30	3.55 ± 0.31	0.67
ACA (°)	40.23 ± 2.90	39.77 ± 4.40	37.83 ± 5.12	0.73

[Table/Fig-1]: Change of the follow-up parameters measured with a Pentacam Scheimpflug camera at baseline, 30th and 90th days of follow-ups (n=32).
CCT: central corneal thickness; ACV: anterior chamber volume; ACD: anterior chamber depth; ACA: anterior chamber angle degree.

		Baseline	30th day	90th day	p-value
Refractive error (Diopter)	Mean±SD	-0.62 ± 1.18	-0.81 ± 1.30	-0.93 ± 1.17	<0.001
	Median	–0.23	–0.58	–0.61	
IOP (mmHg)	Mean±SD	15.1 ± 2.88	14.44 ± 3.02	14.28 ± 2.23	0.35
	Median	14.90	15.10	14.50	

[Table/Fig-2]: Change of the refractive error and intraocular pressure (IOP) at baseline, 30th and 90th days of follow-up (N=32).

There was not any notable abnormality found in the anterior segment, funduscopic, or gonioscopic examinations during the follow-up sessions. The baseline Mean IOP was decreased at the 30th and 90th days of follow-up [Table/Fig-2]. These IOP changes were not statistically significant (p-value= 0.35).

DISCUSSION

Adverse drug reactions and side effects, affect the clinical uses of various pharmacological agents in different indications. Visual symptoms and signs are one of the noticeable side effects that may present in many drugs including some of neurological agents. Visual field defect is one of them. Neurological agents implicated in the causation of visual field defects are Vigabatrin, Tiagabine, Gabapentine, Diazepam, Phenytoin, Carbamazepine and Topiramate [15,16].

Topiramate is a sulfa-derivative monosaccharide with several mechanisms of action, including blockage of voltage-gated sodium channels, hyperpolarization of the cells by influencing potassium currents, enhancement of postsynaptic gamma-aminobutyric acid receptor activity, suppression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainite receptor, and mild inhibition of some carbonic anhydrase isoenzymes. Moreover, it affects sodium and chloride movement, and can therefore interfere with the ionic concentration in various tissues, including the ocular environment [9,17,18].

The literature contains many case reports of ocular side effects of Topiramate therapy. Of the published reports of Topiramate-induced side effects, Kerimoglu et al., presented a TiMS patient whose central corneal thickness had increased. Topiramate was suspected as being the cause, and so was ceased. Over the ensuing 3 weeks, the thickness of the patient's cornea gradually decreased. They postulated that weak carbonic anhydrase inhibitor activity of Topiramate and its Prostaglandin-mediated effect might have been responsible for this phenomenon [12]. In accordance with this finding, we observed a statistically significant increase at the 30th day of follow-up that persisted until 90th day of follow-ups. Carbonic anhydrase isozymes are demonstrated in the corneal endothelium as well as in the pigmented and non-pigmented epithelium of the ciliary body [19].

In addition, Ozturk et al., in their prospective study on the ocular side effects of Topiramate, declared possible alterations in the mean central corneal thickness (from 570 μm at initiation to 574 μm at the end of 3 months). However, the difference between these values was not statistically significant [7].

In the current study, patients demonstrated a slight but statistically significant shift toward myopia as another side effect of Topiramate therapy. As demonstrated in [Table/Fig-2], the pre-treatment median refractive error of - 0.23 D increased to - 0.63 D of myopia at 90th day of follow-up (p-value< 0.001). Though none of the patients reported any complaints concerning their vision, this significant change in the refractive error may lead to blurred vision or frequent changes of eyeglasses. A shift in refractive error toward myopia is a known side effect of sulfur-containing medications, such as Acetazolamide, Sulfamethoxazole, Trimethoprim, Indapamide, Promethazine, etc. As Topiramate is a sulfamate-substituted monosaccharide, it also induces myopia [20,21].

The exact mechanism of myopia is not fully understood, although lens osmotic disturbance and subsequent swelling that results in anterior chamber shallowing was previously postulated. Craig et al., declared that the changes occurring in the lens, accounted for only a small amount of the observed anterior chamber depth decrease (9–16%). Ultrasound studies indicated that acquired myopia is predominantly due to ciliochoroidal effusion, which results in displacement of the lens [22]. Levy et al., reported that rechallenging at low doses does not cause recurrence of myopia, thus allergic hypersensitivity is unlikely [23].

In the present study, evaluation of various parameters such as anterior chamber depth, angle, and volume at the 30th, and 90th days after the initiation of Topiramate showed that there were no significant alterations found [Table/Fig-1], despite a significant shift toward myopia, which may be related to the recruitment of normal patients in the study or low-dose Topiramate use. It is unknown whether the previously reported cases, had any anatomical predisposition for the reported side effects.

IOP was reported to be elevated due to angle closure in many case reports. Symptoms related to angle closure glaucoma have been reported to occur between 3 and 21 days after starting to use the drug [24,25]. In this study, we scheduled ophthalmologic evaluation at the first follow-up for 30 days after the initiation of treatment; however, there were no statistically significant changes in IOP found, at any of the two subsequent follow-up sessions compared to the baseline IOP (p-value= 0.35). As mentioned above, no decrease in anterior chamber depth that could result in angle closure and IOP increase was observed. Immunohistochemical changes characterized by a severe accumulation of GABA in the inner retina has been observed that can be supposed as the mechanism of damage to the retina and field defect [26], but it was not an investigative goal in our study but perimetry is performed every 6-12 months in the patients under Topiramate therapy, routinely in our center.

The present study represents a preliminary effort to determine the changes in intraocular anterior segment parameters contributed to Topiramate use. The observed increase in CCT suggests that all patients are at risk of minor changes in cornea; however, randomized studies with larger cohorts are needed to determine the effects of long term and higher doses of Topiramate. This was one of the current study limitations, which we just observed patients and did not do any intervention. And also, because of difficulties in follow-up and concerning about the likely side effects we had limitation to survey more patients.

CONCLUSION

Due to the expanding spectrum of indications of Topiramate use, neurologists and ophthalmologists should be aware of the diverse ocular side effects of this valuable drug. It is imperative that any visual complication be taken seriously and followed closely by an ophthalmologist. Based on our brief review of the literature, the effects of Topiramate on vision are not only a simple category of side effects, but necessitate a joint effort on the part of practitioners and researchers to address this issue.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Neurology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.
2. Ophthalmologist, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran.
3. Neurologist, Dezful University of Medical Sciences, Dezful, Iran.
4. Social Development and Health Promotion Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.
5. Assistant Professor, Department of Neurology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.
6. Assistant Professor, Department of Neurology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.
7. Optometrist, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.
8. Assistant of Neurology, Department of Neurology, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Nasim Kazemi,
Dezful University of Medical Sciences, Dezful, Iran.
Postal code: 7461715765.
E-mail : nasim.kazemi@gmail.com

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