

# Evaluation of the Efficacy of Topiramate and Botulinum Toxin Injection in the Treatment of Chronic Migraine

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## Abstract

Migraine is one of the most common, life-disabling types of headaches. It receives special attention in therapeutic research aimed at identifying the most appropriate treatment. This study compares the efficacy of oral topiramate and Botox injections in the management of chronic migraine.

It included 215 patients, the average age was  $33.3 \pm 9.3$ , 73.49% of them were females, treated in several centers (Iraq, Syria, Egypt, Saudi Arabia), over a period of five years from January 1, 2019 to January 1, 2024.

Improvement rates were very close, Botox group showed a slight superiority in reducing the frequency of attacks ( $p$  value = 0.0001), while regarding to the severity and duration of attacks, there was a slight preponderance of improvement in topiramate group ( $P$  value = 0.0001) and ( $P$  value = 0.001) in a row. Only about a third of the study patients (35.35%) rely on Botox injections, the majority of whom were female (72%).

Regarding the continued improvement in the modified quality of life questionnaire, the topiramate group recorded an improvement with a statistically significant difference ( $P$  value = 0.001) compared to the Botox group ( $P$  value = 0.054). The occupations most frequently were those who had intellectual jobs (25%).

**Keywords:** Chronic migraine, topiramate, headache, Botox, side effects.

## 1. Introduction

**Migraine** is a multiple factors neurological disorder (vascular, hormonal and genetic) in the sensory processing, the basic symptom is headache. [1] Migraine can be explained by many theories

such as vasodilation,[2] CSDs (Cortical Spreading Depression Syndrome) and be associated with other phenomena and symptoms resulting from the activation of sympathetic system.[3,4] Consequently, it can be defined as a chronic state of family- type trans – headache attacks or focal neurological symptoms or both of them,[5] the severity of pain ranges from moderate to severe pain hindering the patient’s physical ability.[6]

Given the multiplicity of factors, and the overlapping pain mechanisms in migraine [7] considering its effects on all body systems, it has a wide spectrum of symptoms and accompaniments.[8] Regarding to migraine epidemiology, it affects approximately (2.5-6.5%) of general population,[9] more common in females where the ratio of migraine is (1.7-4%),[10] so migraine is the second most common headaches types after Tension headache.[11]

**Chronic migraine** the pain occurrence frequency is 15 days per month with at least 8 episodes that meets migraine standards for 3 months in sequel. [12]

Most likely that chronic migraine is a pathological development of Episodic migraine, as a result of exacerbation of episodes frequency and severity. [13] The incidence rate is (1.4- 2.2%) of general population,[14] and 8% of all migraine patients with an estimating ratio of developing an episodic migraine to chronic migraine of about 3% every year. [15]

Contributing factors to migraine chronicity are: excessive medication treatment,[16] which is the most dangerous factor, futile treatments for episodic migraine,[17] age, female patients, depression and stress, alcoholism, tobacco consumption ,[18] sleep disorders,[19] head trauma or brain injury, atopic patients, obesity, being single and heart diseases. [20]

Botox (botulinum toxin type A) is a neuro toxin has the ability to induce temporary muscular paralysis, secreted by Clostridium Botulinum bacteria, [21] capable when applying to reduce muscular contraction for approximately 3 months. [22] Its effect on chronic migraine discovered by coincidence when cosmetic doctors noticed a decreasing in the severity of headaches attacks in injected patients.

Medicinal uses of Botox are cosmetic uses, hemi-facial spasm, excessive sweating, [23] dentally-related procedures,[24] cervical dystonia,[25] bladder disorders in MS (Multiple sclerosis) patients, chronic migraine, [26] upper limb spasticity, rhinitis,[27] Frey syndrome,[28] phonic tics in Tourette’s syndrome [29] and stuttering[30], drooling in Parkinson’s disease[31], trigeminal neuralgia[32] and spasmodic dysphonia[33]

In 2010, FDA (Food and Drug Administration) allowed Botox to be used as prophylactic treatment, where Botox is applied to treat chronic migraine with recommendations: failure of 3

conservative treatments to treat pain or in the condition of excessive use of medicines and the risk of getting into painkiller's headaches[34,35]

The main goal of injecting Botox procedure is to turnback chronic migraine to episodic migraine, that is to significantly improve life style regarding life style survey, and to reduce headaches attacks frequency.[36]

Most patients need two rounds to establish the efficiency of the treatment, because usually can't determine this efficacy before 4 weeks passes and even more. So, the response to injecting Botox being good when the improvement of the symptoms reaches (30-50%), this proportion ensures an improvement in the patient's life, although, injecting Botox may alleviate symptoms associated with attacks as well, however, the post injecting response is personal differs from one patient to another.[37]

The mechanism by which injecting Botox improves migraine symptoms is still not fully understood, but this can be explained by the fact that Botox inhibits muscular transmission, especially at the level of neuromuscular synapses, as it limits releasing Acetylcholine as a neurotransmitter which may leads to a disruption in pain signals transmission, as well, it works as a prophylaxis treatment preventing the occurrence of initial stimuli of migraine, without risking of rebound headaches that may occur at the administration of oral migraine prophylaxes medications .[38]

In general, Botox can be classified as well-tolerated relatively safe treatment, but it may be associated with side effects such as: redness and mild edema at the site of injection, neck pain, neck stiffness, which is the most common and may last for weeks after the injection, dropping of the eyelid (ptosis), eyebrow and the corner of the mouth, which is temporary because the body is able to get rid of Botox. [39]

Contraindications for Botox injection: It is not applicable in cases of pregnancy and lactation, skin infections at the injection site, the presence of neurological disease such as MG (Myasthenia Gravis), ALS (Amyotrophic Lateral Sclerosis), and Lumbert Eaton Syndrome. Its potential applicability in patients younger than 18 is not adequately evaluated yet.[40,41]

Topiramate is an anticonvulsant drug classified as well-tolerated, its mechanism is complex, this drug has proven efficacy in treating all forms of migraine.[42]

Topiramate rapidly absorbed, reaches its maximum concentration in plasma after two hours, and has a clearance life of 12-25 hours.[43]

Topiramate works in various mechanisms: it blocks voltage-dependent sodium and calcium channels [44,45] and inhibits glutamate-inducing path, [46] enhance GABA levels, Carbonic anhydrase inhibitor [47].

Side-effects of Topiramate are nausea and numbness in the palms and feet, drowsiness, dizziness and fatigue, diarrhea, abdominal pain and dysuria,[48] decreased weight and appetite, blurred vision, orbital pain and red eyes, menstrual changes, depression, back pain.[49]

Contraindications for Topiramate are kidney problems, acute intermittent porphyria,[50] ophthalmic disorders (glaucoma), pregnancy or pregnancy planning period, [51] liver function disorders.[52]

The study aims to compare the effectiveness of topiramate with Botox injections in people with chronic migraine.

## 2. Patients and Methods

A prospective cohort study was conducted on 215 chronic migraine patients in multiple centers and hospitals in four countries: Iraq, Syria, Egypt, and Saudi Arabia from January 2019 to January 2024. Input criteria were patients over 18 years of age with chronic migraine and agree to participate in the study. Exclusion criteria were patients who are contraindicated for the treatment applied or are allergic to the medicinal preparation, patients who have incurable diseases and whose general condition is poor, pregnant and breastfeeding women, alcoholism, malnutrition.

The patients were followed up for six months after being placed on one of the two treatments. The severity of headaches during migraine attacks was assessed by VAS (Visual Analogue Scale), the duration of each attack by hours, the number of attacks during each week, and the change recorded after the end of the follow-up period in the modified quality of life questionnaire QOLQ, the QOLQ was modified to include 20 questions covering all the psychological, physical and health aspects that migraine may affect, so that the best rating is twenty. The degree of migraine's crippling effect on the patient's life before treatment was also assessed using the MIDAS (migraine disability assessment test). 55 patients dropped out before the end of the follow-up period.

Botox is applied by injection with fine needles about 30-39 times in 7 specific spots regarding migraine: round the head and front head, behind the ear and in the neck, and sometimes in what so called trigger point, the injection is either SC (subcutaneous) or IM (intramuscular), considering that the injection will be repeated within 12 weeks (3 months).

For Topiramate, the initial dose is 25mg (oral), then it is increased 25 mg every week until reaching 100mg, divided into two doses every 12 hours.

### 3. Statistical Study

IBM SPSS (version 20) was used for Statistical study. Means, standard deviations (SD), Frequency and percentages were enclosed for basic Descriptive. One-way Anova was used to compare between the three groups. P value <0.05 was appraised as statistically significant.

### 4. Results

The study included 270 patients who met the criteria for chronic migraine in Iraq, Syria, Egypt and Saudi Arabia. 139 patients received oral treatment with topiramate, 76 patients received Botox injections, and 55 patients dropped out during the follow-up period. Patients preferred topiramate if they had the option for reasons related to cost or fear of injections.

The average age of the study patients was 33±9.3, almost two-thirds of whom were female (73.49%),

Gender	Topiramate	Botox	Total	P value
Male (26.51%)	36	21	57	0.0001
Female (73.49%)	103	55	158	
Total	139	76	215	

majority of the patients who underwent Botox injections were female (72.4%).

**Table1: Distribution of the two patient groups (oral topiramate and Botox injections) by gender.**

**Table2: Distribution of the two patient groups (oral topiramate and Botox injections) by countries.**

Country	Number of patients treated with topiramate	Number of patients treated with Botox injection
Iraq	29	15
Syria	45	20
Egypt	41	18
Saudi Arabia	24	23
Total	139	76

**Table 3: The degree to which migraine disrupted patients' lives before the study began.**

Disability from work and daily life	number	Percentage	P-value
No disability	5	2.3%	0.0001
Mild	40	18.6%	
Moderate	28	13%	
Severe	142	66%	

The vast majority of study patients experienced severe impairment in work and activities of daily living due to migraine, and only 2.3% experienced attacks that did not affect their lives married patients.

**Table 4: marital status, occupational distribution of patients**

Occupation	Number	percentage	
Intellectual jobs	54	25.1%	
Housewives	48	22.3%	
Office work	46	21.1%	
Medical staff (doctors, nurses, care givers)	28	13%	
self-employment	27	12.6%	
Jobless	12	5.6%	
Marital status			P value
Single	136	63.26%	0.0001
Married	79	36.74%	

Variable	Pretreatment with topiramate	Post treatment with topiramate	P-value
Headache severity	7.87±1.66	3.75±1.96	0.0001
Frequency of attacks (during the week)	5.27±1.48	2.9±1.97	0.024
Duration of the attack (by hours)	4.42±1.59	1.61±1.46	0.001
Quality of Life Questionnaire	11.27±2.49	15.2±1.74	0.001

As for the occupational distribution of patients, about a quarter of the sample patients were working in intellectual professions, followed with housewives by a small margin. Also, the percentage of single patients was significantly higher statistically than the percentage of

**Table 5: Severity, duration, and frequency of migraine attacks before and after treatment**

In general, the study did not record significant differences in improvement between the two treatment groups.

**Table 6: Undesirable effects of treatment in sample patients**

Botox injection Side effects	Number	percentage
Local symptoms at the injection site (redness, swelling, pain)	59	77.6%
Change in facial features	48	63.2%
Dry mouth	14	18.4%
Dry eye	12	15.8%
fatigue	10	13.2%
Topiramate Side effects	Number	percentage
Digestive symptoms	42	30.2%
Ophthalmic symptom	23	16.5%
Menstrual disorders	17	12.2%
Others	11	7.9%

The most common side effects in patients treated with Botox injections, the reaction at the injection site (77.6%) followed by a change in facial features (63.2) %, while for patients treated with topiramate, the digestive symptoms were the most frequent (30%).

**Table 7: Severity of undesirable effects in both patient groups**

	Barely noticed	Mild	Moderate	Extreme	P value
Botox	29	25	22	0	0.0001
Topiramate	69	42	20	8	

Males showed a better response and tolerance to topiramate, as 86.1% of males treated with topiramate recorded a significant improvement compared to 52.38% for Botox, while the best response among females was recorded with Botox injection , where 90.9% improved compared to 66.99% for treatment

Variable	Pretreatment with Botox	Post treatment with Botox	P-value
Headache severity	7.5 ±2.03	2.75±1.16	0.03
Frequency of attacks (during the week)	5.5 ±2.17	2.3 ±1.33	0.001
Duration of the attack (by hours)	3.4 ± 0.82	2.7±0.92	0.005
Quality of Life Questionnaire	11.4± 2.52	13.66±2.74	0.054

with topiramate.

**Table 8: The relationship between the response to both treatments and the patient Gender.**

Gender	patients who improved significantly with treatment with Topiramate	patients who improved significantly with treatment with Botox
Male	31 (86.1%)	11 (52.38%)
Female	69 (66.99%)	50 (90.9%)

## 5. Discussion

Patients who underwent Botox injections showed a slight advantage in reducing the frequency of attacks ( $p = 0.0001$ ), while for the severity and duration of attacks, the results were slightly better in favor of topiramate therapy ( $P$  value = 0.0001) and ( $P$  value = 0.001) respectively. There was no statistically significant difference in improved quality of life assessed by the adjusted quality of life questionnaire in the group of patients who injected Botox as opposed to patients treated with topiramate.

It is not possible to definitively say that one treatment is superior to the other, as there are factors that depend on the individual response of each patient.

The results of the study are in line with A review study conducted by the University of Arcadia in 2020 showed an estimated improvement of 50% in the frequency and severity of headache attacks, but the data collected were considered insufficient to replace topiramate with Botox and considered it a first line of treatment.[53]

Comparing side effects and their tolerance in patients, 8 patients treated with topiramate reported severe side effects, while side effects in the Botox group ranged from neglected to moderate only. These results are consistent with 2019 study published by the Journal of Head and Face Pain and the American Headache Society, which studied 288 chronic migraine patients, Botox was shown to be superior to topiramate in reducing headache frequency, causing fewer side effects, and greater tolerance in patients.[54].

## 6. Conclusion

Both topiramate and Botox injections are effective treatment options in the case of chronic migraine, but personal differences between patients in terms of improvement, tolerance of side effects and economic cost must also be taken into account in terms of Botox, which can be considered relatively expensive

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