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# A Comparative Study of Topiramate and Botulinum Toxin in Reducing Migraine Disability in Patients with Chronic Migraine

**Erick-Eduardo Solís-Tun**
Department of Internal Medicine, Clínica Hospital Mérida, ISSSTE,
Facultad de Medicina, Universidad Autónoma de Yucátan (UADY),
Mérida, Yucatan, México

**Steven-Andrés Piña-Ballantyne**
General Medicine, Universidad Anáhuac Mayab,
Mérida, Mexico

**Jorge Arceo-Novelo**
Neurology Department, Clínica-Hospital Mérida,
Mérida, Mexico

## ABSTRACT

**Background: Chronic migraine (CM) is a highly debilitating neurological condition that requires effective treatment. Topiramate and botulinum toxin are widely used for management and prevention. However, comparative data on treatment escalation in patients with treatment-resistant CM and incobotulinum toxin A (inco-BTX-A, Xeomin®) remain limited. The Migraine Disability Assessment (MIDAS) questionnaire is a valuable tool for objectively quantifying the impact of migraines on daily functioning. This study aimed to conduct a comparative analysis of topiramate and inco-BTX-A in terms of their effectiveness in reducing disability associated with treatment-resistant CMs. Methods: This comparative, observational study evaluated the effectiveness of topiramate and botulinum toxin in reducing MIDAS scores in patients with CM who had previously failed initial treatments. Patients were divided into three groups: group 1 (topiramate to inco-BTX-A), group 2 (non-steroidal anti-inflammatory drugs/NSADIs to topiramate), and group 3 (NSAIDs to inco-BTX-A). Data collection included demographic features and MIDAS scores before and after treatment. Results: A total of 96 patients were included, with a predominance of female patients (85.41%). Group 1(n=39) showed a significant reduction in MIDAS scores 4.1 ± 2.88, t-statistic = 8.89 ($p < 0.05$). There was no significant difference between Group 2 (n=39) and Group 3 (n=18), with a p-value of 0.0545. Conclusions: Topiramate and inco-BTX-A effectively reduced MIDAS scores in patients with CM, particularly in those with treatment resistance. While groups 2 and 3 showed similar outcomes, inco-BTX-A demonstrated a more significant effect in group 1, suggesting its potential as an effective treatment for treatment-resistant CM.**

**Keywords:** Chronic migraine, topiramate, botulinum toxin, treatment-resistant, incobotulinum toxin A.

## INTRODUCTION

According to the third edition of the International Classification of Headache Disorders (ICHD-3), the diagnosis and definition of chronic migraine (CM) requires specific criteria. These include experiencing headaches for more than 15 days per month for at least three months, having a history of at least five migraine attacks, and at least eight of these headaches must fulfill the criteria for migraines with or without aura. Furthermore, the condition should not be better explained by any other diagnosis [1].

CM affects approximately 1-3% of the global population, with a higher prevalence in women aged between 18 and 44 years [2, 3]. Its pathophysiology is complex and multifactorial, involving central sensitization, neurovascular changes, and dysfunction of pain pathways, which are not fully controlled by traditional acute treatments. Therefore, preventive treatments are critical for managing CM, with topiramate and botulinum toxin emerging as key therapeutic options [4, 5].

Topiramate is a broad-spectrum anticonvulsant with multiple mechanisms of action, commonly used for epilepsy and CM. It modulates voltage-gated sodium and calcium channels, inhibits carbonic anhydrase and glutamate receptors, and enhances gamma-aminobutyric acid activity [5]. These mechanisms contribute to the efficacy of preventing CM by reducing neuronal excitability and central sensitization. However, despite their clinical utility, a significant proportion of patients fail to achieve adequate relief or experience adverse effects, highlighting the need for alternative treatments [4-6].

Botulinum toxin, specifically Botox® (onabotulinum toxin A) and Xeomin® (incobotulinum toxin A), has emerged as an effective option for patients with treatment-resistant CM [6, 7]. Xeomin® works by inhibiting acetylcholine release at neuromuscular junctions, reducing the activation of pain pathways in the trigeminal nerve and the central nervous system. Unlike Botox®, Xeomin® contains only the purified active neurotoxin, without complex proteins, which may reduce the risk of antibody formation and treatment resistance [7-12]. Studies have shown that botulinum toxins can significantly reduce migraine frequency and severity, providing a valuable treatment option for patients with chronic or treatment-resistant forms of migraines [6, 7].

The Migraine Disability Assessment (MIDAS) questionnaire is a key tool for measuring the impact of migraine on daily functioning, helping clinicians to evaluate the efficacy of treatments in real-world settings [13]. This study aimed to compare the effectiveness of topiramate and botulinum toxin in reducing MIDAS scores in patients with CM who had failed previous treatments.

## MATERIALS AND METHODS

### Study Design

This was a comparative, observational study to evaluate the effectiveness of topiramate and Xeomin® in reducing MIDAS scores in patients with CM who had previously failed to respond to initial treatments. Patients were divided into three groups: group 1, patients who switched from topiramate to Xeomin®; group 2, patients who switched from NSAIDs to topiramate; and group 3, patients who switched from NSAIDs to Xeomin®.

Data collection included demographic data from electronic clinical records and the use of the MIDAS questionnaire to quantify the disability associated with CM in each group with pre- and post-treatment assessments. The patients´ responses to topiramate and Xeomin® were compared to determine which treatment was more effective as subsequent therapy after NSAIDs or topiramate.

Inclusion criteria: Patients aged 18–85 years with a diagnosis of CM according to the ICHD-3 criteria were included in the study. Participants were required to have had inadequate or no response to at least one prior preventive treatment. MIDAS scores were available both before and after treatment to assess changes in disability. Exclusion criteria: patients with episodic migraine (fewer than 15 migraine days per month); those with a history of serious neurological, psychiatric, or systemic disorders that could interfere with migraine treatment or assessment; and those who had received botulinum toxin injections within the past 3 months. Additionally, patients who were pregnant, breastfeeding, or had planned pregnancies were excluded.

**Xeomin Information**

Xeomin® (inco-BTX-A; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is derived from the same Clostridium botulinum type A strain (ATCC 502) as Botox®, exhibiting similar biological effects. Unlike Botox®, Xeomin® contains only the purified active neurotoxin, with complex proteins and clostridial contaminants removed during production [8-12]. Xeomin® was administered intramuscularly for CM prevention according to the Research Evaluating Migraine Prophylaxis Therapy (PREEMT) protocol, with a total dose ranging from 155 to 195 units [14-16]. The total dose was divided across seven specific head and neck areas, with each injection delivering five units per 0.1 ml. This resulted in 31–39 injections per session. The injections were administered at predefined sites in the frontal, temporal, occipital, and cervical regions to target the migraine-related pain pathways. The treatment was performed as a single session for each participant.

**Statistical Analysis**

All statistical analyses were performed using the SPSS software (version 22.0; IBM Corp., Armonk, NY, USA). The data were checked for completeness and consistency. Descriptive statistics were used to summarize categorical variables using frequencies and percentages. To compare the differences between groups, Student's t-test for independent variables was used to evaluate the reduction in MIDAS scores between groups 2 and 3, while the paired t-test was applied to assess the changes in group 1. Wilcoxon tests were employed when normality assumptions were violated. The Shapiro-Wilk test was conducted to assess the normality of the data. Statistical significance was set at $p\text{-value} < 0.05$.

**Ethical Statement**

This study was conducted in compliance with the principles of the Declaration of Helsinki. The subjects included in this study read and signed an informed consent form, which specified the objective of the research.

## RESULTS

A total of 96 patients were included, with a predominance of female patients (85.41%). Demographic features are shown in Table 1, with a mean age of 44.91 years. No adverse effects or reactions were reported by patients during the treatment administration and observation



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periods. Table 2 presents the statistical analysis, showing significant reductions in the MIDAS scores in all treatment groups.

**Table 1: Demographic features.**

| Characteristics | All patients (n=96, 100%) | Group 1 (n=39, 40.62%) | Group 2 (n=39, 40.62%) | Group 3 (n=18, 18.75%) |
|---|---|---|---|---|
| Age, years | | | | |
| Mean | 44.91 | 43.02 | 49.64 | 38.77 |
| Range | 67 | 37 | 52 | 48 |
| Sex | | | | |
| Male | 14 (14.58%) | 6 (15.38%) | 7 (17.94%) | 1 (5.55%) |
| Female | 82 (85.41) | 33 (84.61%) | 32 (82.05%) | 17 (94.44%) |

Table 1 legend: Data presented as n (%). Group 1: Topiramate to inco-BTX-A; Group 2: NSAIDs to topiramate; Group 3: NSAIDs to inco-BTX-A.

**Table 2: Statistical analysis.**

| Treatment group | MIDAS score before treatment (Mean ± SD) | MIDAS score after treatment (Mean + SD) | Average reduction (Mean + SD) | T-statistic | P-value |
|---|---|---|---|---|---|
| Group 1 (n=39) | 8.74 ± 2.47 | 4.64 ± 1.58 | 4.1 ± 2.88 | 8.89 | **< 0.05** Wilcoxon test: **< 0.05** |
| Group 2 (n=39) | 14.64 ± 3.27 | 8.08 ± 4.02 | 6.56 ± 4.29 | -1.97 | 0.0545 |
| Group 3 (n=18) | 13.5 ± 4.42 | 4.33 ± 1.57 | 9.17 ± 5.36 | | |

Table 2 legend: Data presented as n (%); SD: standard deviation; Group 1: Topiramate to inco-BTX-A; Group 2: NSAIDs to topiramate; Group 3: NSAIDs to inco-BTX-A.

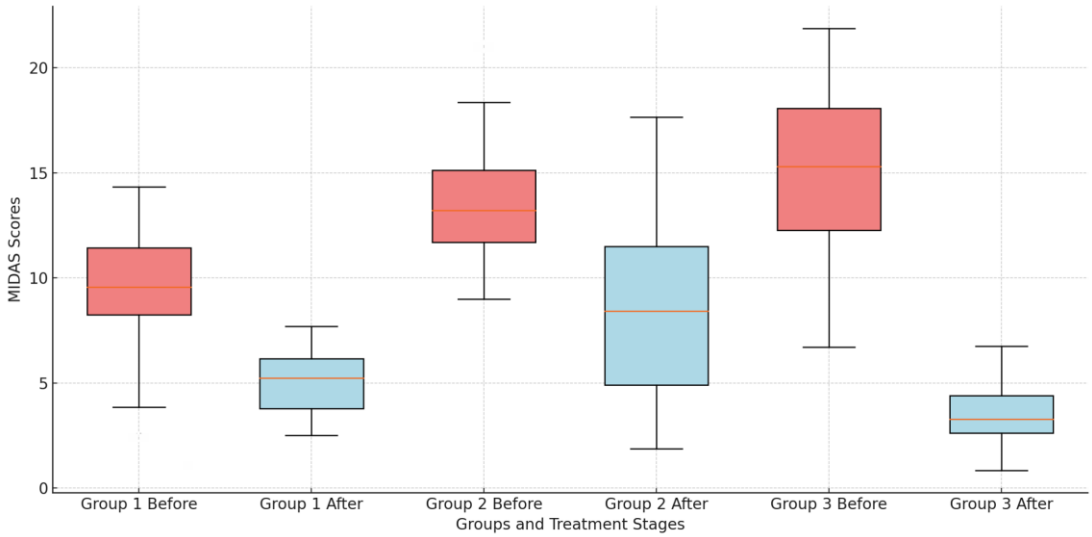


**Figure 1: Comparison of MIDAS scores before and after treatment across groups.**

Figure 1 legend: Group 1: Topiramate to inco-BTX-A; Group 2: NSAIDs to topiramate; Group 3: NSAIDs to inco-BTX-A; MIDAS: Migraine Disability Assessment.

## DISCUSSION

Chronic migraine (CM) is a prevalent neurological disorder that significantly impacts patient´s quality of life and functionality. In the United States, it affects approximately 2% of the population with a female predominance, like the demographic profile of this study [17].

Topiramate has long been considered as a first-line preventive therapy for CM, with multiple studies demonstrating its efficacy in reducing the frequency and severity of migraine attacks [4, 5]. Participants who received topiramate showed a notable reduction in migraine frequency and the associated disability was significantly lower, reinforcing previous evidence.

Despite the growing success of similar formulations, such as Botox®, research on Xeomin® remains relatively limited. A previous study by Ion et al. demonstrated its effectiveness in reducing days and alleviating migraine-related disability, highlighting its therapeutic potential [7]. By inhibiting the release of acetylcholine at the neuromuscular junction, Xeomin® provides a localized and sustained reduction in muscle hyperactivity, which is thought to contribute to the pathophysiology of CM [6, 8, 10]. In our study, patients who received Xeomin® injections reported significant improvement, including reduced migraine-related disability, as evidenced by MIDAS scores and decreased reliance on acute migraine medications. These findings are consistent with the outcomes observed in the study by Ion et al., further validating its importance as a valuable therapeutic option for CM management [7].

Both treatments demonstrated significant reductions in MIDAS scores, although some differences were observed between the groups. In group 1, the average reduction was $4.1 \pm 2.88$, with a t-statistic of 8.89 ($p < 0.05$), indicating a significant improvement, further supporting the efficacy of botulinum toxin (Xeomin®) as an effective treatment for treatment-resistant CM following topiramate use [7]. The p-value in the Wilcoxon test further reinforced the results of the t-test, indicating that the reduction in symptoms was statistically significant. A comparison between groups 2 and 3, with a p-value of 0.0545, suggested that there was no statistically significant difference in the reduction in MIDAS scores. However, the p-value was very close to 0.05, indicating a trend towards a difference, which warrants further investigation into larger studies. Notably, no adverse effects or reactions were reported during the treatment administration or observation periods, indicating good tolerability of Xeomin®.

Although both treatments reduce CM disability, they operate through distinct mechanisms and present different clinical considerations. Topiramate is a daily oral medication that offers convenience but potentially limits adherence due to side effects such as cognitive impairment and paresthesia [5]. In contrast, Xeomin® requires periodic injections, which may provide more sustained effects, especially for patients who struggle with daily medication regimens [7, 15, 16]. The choice between these therapies should be individualized by considering patient preferences, side effect tolerance, and treatment response. For those with suboptimal results from monotherapy, combination therapy could be considered as the pharmacologic action of topiramate, and the neuromodulatory effects of Xeomin® may complement each other, offering a more comprehensive approach to CM management [3, 4, 18].

Study limitations include the small sample size, particularly in group 3. The reliance on MIDAS scores may not fully capture all aspects of treatment efficacy, and the short follow-up period


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restricts the long-term outcome assessment. Potential confounding factors such as comorbidities or concurrent treatments were not included in the analysis.

## CONCLUSION

In conclusion, both topiramate and botulinum toxin (Xeomin®) were effective in reducing MIDAS scores in patients with chronic migraine, particularly in those who had previously failed to respond to other treatments. Although no significant difference was found between groups 2 and 3, both treatments showed similar effects on symptom reduction. However, Xeomin® exhibited a more pronounced effect in group 1, highlighting its potential as an effective treatment for treatment-resistant chronic migraine.

These findings support the use of botulinum toxin as a valuable therapeutic option for patients with inadequate response to topiramate. Further studies with larger sample sizes and longer follow-up periods are needed to confirm long-term efficacy and safety.

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