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RESEARCH ARTICLE

Botulinum Toxin Treatment on Migraine Patients; Its Effect on Disability, Severity of Migraine and Depression

Gülten Özdemir[1], Çiğdem Çınar[2], Tuğba Şahbaz[3], Kadriye Öneş[4], Yelda Soluk Özdemir[4], Aynur Metin Terzibaşıoğlu[5]

[1]Department of Neurology, Medicana Atasehir Hospital, İstanbul, Türkiye
[2]Department of Physical Medicine and Rehabilitation, Biruni University Hospital, İstanbul, Türkiye
[3]Department of Physical Medicine and Rehabilitation, Beykent University Hospital, İstanbul, Türkiye
[4]Department of Physical Medicine and Rehabilitation, University of Health Sciences, Physical Therapy and Rehabilitation Training and Research Hospital, İstanbul, Türkiye
[5]Physical Medicine and Rehabilitation Private Clinic, İstanbul, Türkiye

ABSTRACT

Objective: Migraine patients have a high risk of developing anxiety and depression, and the relationship between chronic migraine (CM) and depression is believed to be bidirectional. This study aims to evaluate the effects of Botulinum Neurotoxin A (BoNT/A) treatment on migraine-related disability, pain severity, and depression in patients with CM.

Materials and Methods: This study included 24 patients aged between 19 and 55 years who were diagnosed with CM and treated with BoNT/A injections every 12 weeks for six months. Data were collected on demographic characteristics, as well as disability severity, pain severity, and depression levels before and after treatment.

Results: A statistically significant improvement was observed in VAS (Visual Analog Scale), MIDAS (Migraine Disability Assessment Scale), and BDS (Beck Depression Scale) scores after BoNT/A treatment ($p<0.001$). The mean changes in scores were as follows: a 4±1-point reduction in VAS, a 61±23-point reduction in MIDAS, and a 16±9-point reduction in BDS. Patients reported experiencing initial treatment benefits within 12±3 days, with an average duration of effect lasting 93±38 days.

Conclusion: BoNT/A treatment appears to play a significant role in modulating pain perception and emotional responses, particularly in patients with depression and those resistant to conventional migraine treatments. The findings suggest that BoNT/A may be an effective treatment option for reducing migraine-related disability, pain severity, and associated depressive symptoms.

Keywords: Botulinum neurotoxin a, chronic headache, depression, migraine

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INTRODUCTION

Chronic Migraine (CM), according to the International Classification of Headaches (ICHD-3 beta) diagnostic criteria, is defined as the patient having a headache more than 15 days a month for 3 months, having pain on at least 8 days a month, meeting migraine diagnostic criteria, and responding to treatments specific for migraine.[1,2]

The most common psychiatric comorbidities associated with CM are anxiety and depression. Studies have shown that anxiety disorders are 2 to 5 times more common in migraine patients than in the general population and twice as common in individuals with depression.[3] Moreover, migraine-related work loss significantly increases when migraine is accompanied by anxiety and/or depression.[4]

Address for Correspondence: Çiğdem Çınar, Biruni Üniversitesi Hastanesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, İstanbul, Türkiye
E-mail: ccdem.inar@gmail.com **ORCID ID:** 0000-0001-9159-6345

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The relationship between migraine and depression appears to be bidirectional, as the presence of one is thought to increase the risk of developing the other. Depression is also a known risk factor for migraine chronification and is considered an indicator of poor prognosis. Anxiety disorders, depression, and migraine share common triggers such as stress, indicating potential overlapping neurobiological mechanisms.[5,6] Given that depression is a key factor in migraine chronification, identifying and treating depression in migraine patients is of great importance.[7] Consequently, CM often requires a more aggressive treatment approach due to its resistance to multiple individual treatment modalities.[8]

There are limited studies investigating the effect of Botulinum Neurotoxin A (BoNT/A) treatment on depression and anxiety and the relationship between migraine-related disability in CM patients. This study aims to evaluate the effects of Botulinum Neurotoxin A (BoNT/A) treatment on migraine-related disability, pain severity, and depression in patients with CM.

MATERIALS and METHODS

Patients diagnosed with CM based on ICHD-3 beta criteria and resistant to medical treatment at our neurology outpatient clinic between 2015 and 2019 were included in the study. The demographic characteristics of the patients, as well as data on migraine-related disability, attack severity, and depression severity before and after treatment, were recorded. Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Local Hospital Clinical Research Ethics Committee (2018/297).

BoNT/A injection with a diagnosis of CM resistant to single or combination treatments of amitriptyline, propranolol, valproic acid, venlafaxine, duloxetine, verapamil, flunarizine, and topiramate were included in the study. Exclusion criteria were as follows: headaches of non-migraine origin, epilepsy, a history of cranial surgery due to organic brain damage, age below 18 or above 55 years, psychosis, drug-responsive CM, pregnancy, prior surgical or interventional treatments, and neuromuscular system diseases.

A structured form was used to collect sociodemographic characteristics, including date of birth, occupation, educational status, dominant hand, presence of temporomandibular pain, side dominance of migraine pain, disease duration, and medications used. Migraine-related disability was assessed using the Migraine Disability Assessment Scale (MIDAS), pain severity was measured using the Visual Analog Scale (VAS), and depression severity was evaluated using the Beck Depression Scale (BDS).

MIDAS: Assesses the impact of migraine over the past three months through five questions related to work, household tasks, and social activities. Scores range from 0 to 270, with higher scores indicating greater disability. A score of 21 or higher is classified as severe.[9]

VAS: The scale, developed by Price et al.[10] in 1983, is used to determine the severity and level of pain in the patient. This scale is used to convert some values that cannot be measured numerically into numerical values. The patient marks his or her pain on a 10 cm ruler, one end of which indicates no pain and the other end indicates the most severe possible pain.

BDS: Used to assess the severity of depression. It consists of 21 questions, each scored from 0 to 3, with a total score ranging from 0 to 63. Higher scores indicate more severe depressive symptoms. The cut-off score for depression is 17.[11]

BoNT/A Application: According to PREEMPT 1 & 2 studies and treatment guidelines, BoNT/A injections were administered to seven specific head and neck regions (corrugator, procerus, frontal, temporal, occipital, and cervical regions). The standard protocol involved 155 U BoNT/A applied at 31 injection sites every three months. BoNT/A was diluted with 2 cc of physiological saline, and 5 U (0.1 ml) was injected at each site.[2,12,13]

Statistical Analysis

The data were analyzed using IBM SPSS 25.0 (Statistical Package for the Social Sciences). The Shapiro-Wilk test was used to assess the normality of data distribution. Descriptive statistics were presented as frequency (%), mean ± standard deviation (SD), and median (minimum–maximum). The Wilcoxon test was used to compare pre- and post-treatment data. A p-value of <0.05 was considered statistically significant.

RESULTS

Of the 24 patients included in the study, 17 (71%) were female, 7 (29%) were male, and their average age was 41±9 years. The dominant hand of 20 (83%) of the patients was the right, and 4 (17%) had the left. Pain dominance was bilateral in 15 patients (62%), left in 5 (21%), and right in 4 (17%). Temporomandibular joint (TMJ) dysfunction was detected in 6 (25%) of the patients. Patients reported experiencing initial treatment benefits within 12±3 days, with an average duration of effect lasting 93±38 days (Table 1).

Table 1. Demographic data of patients

	n	%	Mean±SD med (min-max)
Age			41±9 44 (19–56)
Gender			
Female	17	71	
Male	7	29	
Dominant hand			
Right	20	83	
Left	4	17	
Pain dominance			
Right	4	17	
Left	5	21	
Bilateral	15	62	
Temporo-mandibular joint dysfunction			
Yes	6	25	
No	18	75	
Side effects			
Yes	1	4	
No	23	96	
Effect start			12±3 12 (7–15)
Effect outcome			93±38 90 (30–150)

SD: Standard deviation

In the clinical evaluations of the patients before BoNT/A injection, the VAS score was 8±1, the MIDAS score was 75±25, and the Beck Depression Score was 27±13. In their evaluation after 6 months, the VAS score was 5±1, the MIDAS score was 14±10, and the Beck Depression Score was 12±8. The mean change in scores was as follows: a decrease of 4±1 points in VAS, a decrease of 61±23 points in MIDAS, and a decrease of 16±9 points in BDS (p<0.001) (Table 2).

When the patients were questioned about the medications they had previously used for migraine, all of them had used NSAIDs; 23 (96%) used tricyclic antidepressants, 22 (92%) used SSRIs or SNRIs, antiepileptics, triptans, neuropathic pain medications, and antipsychotics; 20 people (83%) used calcium channel blockers; 15 people (63%) used beta blockers; and 4 (17%) people had used ergotamine before. When the number of medications used by the patients before BoNT/A injection was questioned, it was found to be 3±1, while the number of medications was found to be 2±1 in the 6th month after treatment. A statistically significant decrease in the number of medications used was detected after treatment (p<0.001) (Table 2).

The rate of patients benefiting from treatment was found to be 100%. Side effects were observed in only one patient (4%), who developed a transient droopy eyelid (ptosis), which resolved spontaneously within a few weeks without the need for additional intervention. No systemic or severe adverse effects were recorded (Table 3).

DISCUSSION

In this study, we evaluated the effects of BoNT/A treatment on migraine-related pain, disability, and depression severity in CM patients. Our results demonstrate a significant reduction in all three parameters following treatment, indicating that BoNT/A is an effective therapeutic option for CM patients who are resistant to conventional treatments. These findings reinforce the clinical relevance of BoNT/A treatment

Table 2. Comparison of pre- and post-treatment evaluations

	Before treatment mean±SD med (min-max)	After treatment mean±SD med (min-max)	Treatment difference mean±SD med (min-max)	p
VAS	8±1 8 (7–10)	5±1 5 (3–6)	4±1 3 (1–5)	<0.001
MIDAS	75±25 75 (35–115)	14±10 13 (2–45)	61±23 60 (20–93)	<0.001
BDS	27±13 22 (10–56)	12±8 8 (3–29)	16±9 12 (6–37)	<0.001
Number of medications used	3±1 3 (1–4)	2±1 2 (0–3)	1±1 1 (0–3)	<0.001

SD: Standard deviation

Table 3. Medication use before treatment and benefit from treatment

	n	%
Before treatment-NSAID		
Yes	24	100
No	0	0
Before treatment-SSRI/SNRI		
Yes	22	92
No	2	8
Before treatment-tricyclic antidepressant		
Yes	23	96
No	1	4
Before treatment-antiepileptic		
Yes	22	92
No	2	8
Before treatment-calcium channel blocker		
Yes	20	83
No	4	17
Before treatment-beta blocker		
Yes	15	63
No	9	37
Before treatment-ergotamine		
Yes	4	17
No	20	83
Before treatment-triptan		
Yes	22	92
No	2	8
Before treatment-neuropathic pain		
Yes	2	8
No	22	92
Before treatment-antipsychotic		
Yes	2	8
No	22	92
BoNT/A benefit		
Yes	24	100
No	0	0

NSAID: Non-steroidal anti inflammatory drug; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin-norepinephrine reuptake inhibitor; BoNT/A: Botulinum Neurotoxin A

in CM patients, not only for reducing pain intensity but also for improving overall quality of life, functional capacity, and emotional well-being.

Migraine and depression share common pathophysiological mechanisms, including serotonergic dysfunction, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and increased inflammatory cytokine levels. Studies suggest that depression is not only a consequence of chronic migraine but may also contribute to its chronification.[14,15] Our findings align with previous research, suggesting that effective migraine management may also alleviate comorbid depression.

In addition, it must be said that these patients need continuous support—not only to discourage the biobehavioral tendency toward compulsive self-medication, sometimes even carried out in anticipation of a migraine crisis, which guarantees them non-exclusion from the social circuit. Therefore, from these considerations, it emerges that the new pharmacological classes of prevention must be applied as an early interdiction to the chronic phase to express their full rehabilitation potential. This increases the importance of examining the relationship between the decline in patients' functioning and increased mood disorders and CM treatment.

In our study, when the medications the patients had previously used for migraine were questioned, all of them used NSAIDs; 23 people (96%) used tricyclic antidepressants; 22 people (92%) used SSRIs or SNRIs, antiepileptics, triptans, neuropathic pain medications, and antipsychotics; 20 people (83%) used calcium channel blockers; 15 people (63%) used beta blockers; and 4 people (17%) had used ergotamine before. While the patients started to benefit from the treatment in 12±3 days, the average duration of benefit was found to be 93±38 days.

In the study conducted by Karadaş et al.,[15] pain intensity, pain frequency, anxiety, and depression were evaluated in a patient group with cervicogenic headache, consisting of 6 men and 12 women. Patients observed a significant reduction in anxiety symptoms with BoNT/A application; they emphasized that BoNT/A has anxiolytic activity as well as anti-inflammatory and analgesic activity through its inhibitory effect on neurotransmitters and neuropeptides.

Yalınay et al.[16] stated that depression and anxiety are closely related in migraine patients and that depression also has a significant relationship with migraine-related disability and migraine frequency. These studies suggest that BoNT/A may affect mood disorders by modulating neurotransmitter release, which may explain the significant decrease in depression scores observed after BoNT/A treatment in our study.

Bigal et al.[17] reported that patients with chronic migraine had significantly higher rates of missing at least 5 days of housework, decreased productivity in housework for at least 5 days, and missed family activities for at least 5 days com-

pared to patients with episodic migraine. It appears that CM causes greater disability than episodic migraine in the population, and although most patients with CM seek medical attention for their condition, many do not receive specific acute or preventive medications. It has been determined that existing migraine preventive treatments generally cannot satisfy patients with CM due to their limited effectiveness, side effects, and drug interactions.

A single-center retrospective study emphasized that poor compliance of patients with treatment is an important problem among patients with CM in real-life settings and may be one of the main reasons for inadequate control of headaches.[18]

An important observation in our study was the low incidence of reported side effects. Only one patient (4%) experienced a mild and transient case of ptosis, which resolved spontaneously. The low rate of side effects observed in our study may be attributed to several factors. Firstly, BoNT/A injections were administered by an experienced clinician following a standardized protocol based on the PREEMPT injection paradigm, which minimizes the risk of complications. Secondly, BoNT/A has a well-established safety profile in chronic migraine treatment, with previous studies reporting mild and transient side effects in most cases. Additionally, our study population consisted of patients without neuromuscular disorders or contraindications to BoNT/A, further reducing the likelihood of adverse reactions. To ensure accurate recording of side effects, patients were closely monitored during follow-up visits, and they were instructed to report any adverse reactions immediately. However, it is important to acknowledge that underreporting of mild or transient side effects by patients is a possibility. Future studies with larger cohorts and systematic adverse event tracking may provide a more comprehensive understanding of BoNT/A's safety profile in chronic migraine patients.

One of the main limitations of our study is the relatively small sample size (n=24), which restricts the generalizability of our findings. A larger cohort would allow for more robust statistical analyses and increase the reliability of the observed effects. Additionally, the absence of a control group prevents us from differentiating the true treatment effect of BoNT/A from potential placebo effects or natural disease fluctuations. Future studies should aim to include a larger sample size with a well-matched control group, such as a placebo-injection group or a group receiving an alternative migraine treatment. Additionally, long-term follow-up studies could provide valuable insights into the sustainability of BoNT/A's therapeutic effects and its impact on migraine-related disability and depression over extended periods.

The strength of our study is that the relationship between disability, depression, and pain was evaluated together. This gave us the opportunity to assess the impact of BoNT/A treatment on migraine-related work loss, pain-related depressive mood, pain frequency, and pain intensity in two ways.

CONCLUSION

As a result of treatment with BoNT/A, patients had significantly fewer migraine attacks and the maximum migraine severity decreased. It was determined that there was a significant decrease in the number of days of using preventive medications and painkillers used in the treatment of acute migraine, and there was a decrease in the incidence of migraine-related symptoms, inability to perform daily life activities, and admission to the emergency clinic. In particular, emotional states such as anxiety and depression due to migraine were significantly improved.

We can say that BoNT/A treatment can reduce work loss due to migraine, depressive mood due to pain, pain frequency, pain intensity, and medication use, and the cost-effectiveness of BoNT/A may be better than other treatments because of the good response to treatment with BoNT/A in CM patients with low compliance to treatment.

Disclosures

Ethics Committee Approval: The study was approved by the Bakirköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (No: 2018/297, Date: 03/09/2018).

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