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Botulinum Toxin A in Patients with Chronic Migraine: A Single-Center Experience

Kronik Migrenli Hastalarda Bir Kliniğin Botulinum Toksin A Deneyimi

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Abstract

Objective: The Botulinum toxin A (BoNT/A), increasingly used in many fields in recent years, was shown to be effective in chronic migraine (CM) in recent studies. In this study, we aimed to investigate treatment response in our CM patients who underwent BoNT/A therapy.

Material and Method: The study included 41 CM patients (aged 18-65 years). We questioned patients undergoing BoNT/A therapy regarding demographic characteristics, education level, time of diagnosis, migraine triggers, and previous therapies at first visit prior to injection. The patients were assessed together with analgesic use, visual analog scale (VAS) score and Migraine Disability Assessment Score (MIDAS) rating at month 6 after treatment.

Results: There were 36 women (87.8%) and 5 men (12.2%) in the study group. Mean age was calculated as 44.88±10.51 years. Of the patients, 20 patients (48.8%) fulfilled criteria for migraine with aura while no aura was detected in 21 patients (51.2%). Significant decrease was detected in MIDAS rating and VAS scores after BoNT/A therapy ($p<0.001$).

Conclusion: The BoNT/A was found to be effective and safe in the prophylactic treatment of chronic migraine. The BoNT/A is a potent treatment that could be performed by experienced neurologists in eligible CM patients regardless of previous prophylactic treatments.

Keywords: Headache, chronic migraine, Botilinum toxin A

Öz

Amaç: Son yıllarda her alanda kullanımı artan Botulinum toksin A (BoNT/A)'nın yapılan son çalışmalarla etkinliği kronik migrende de (KM) gösterilmiştir. Nöroloji kliniklerinde de uzun yıllardır Fokal Distoniler, Distoni olmayan istemsiz hareket bozuklukları, Spastisite, Otonom Sinir Sistemi bozuklukları gibi kullanımlardan sonra KM de kullanımı hızla yayılmaktadır. Bizde bu çalışmamız ile KM tanısıyla takip ettiğimiz BoNT/A uygulanan hastalarımızın tedavi yanıtlarını incelemeyi amaçladık.

Gereç ve Yöntem: Kronik Migren tanılı, ülkemizdeki ruhsatlı tedavi seçeneklerini kulanmış olmasına rağmen yeterli yanıt alınamayan, 18-65 yaş arası ve ek nörolojik hastalığı olmayan 41 Kronik Migren (KM) hastası çalışmaya dahil edildi. BoNT/A tedavisi alan hastalar enjeksiyon öncesi ilk vizitlerinde demografik bilgiler (yaş,cinsiyet), eğitim durumu, tanı zamanı, migren tetikleyicileri, aldıkları tedaviler açısından sorgulandı ve tedavi sonrası altıncı aylarında analjezik kullanımı, atak sıklığı, VAS (Vizuel Analog Skala) ve MIDAS (Migren Özürlülük Değerlendirmesi) skorları ile birlikte değerlendirildi.

Bulgular: Hastaların 36 (%87.8) kadın, 5 (%12.2) erkekti. Yaş ortalaması 44.88±10.51 olarak saptandı. Migren hastalık süresi ortalama 15.75 yıl idi. Hastaların 25 (%61)'inde birinci derece akrabalarında aile öyküsü varken 16 (%39) hastada yoktu. Hastaların 20 (%48.8)'i auralı migren kriterlerine sahipken, 21(%51.2)'inde aura saptanmadı. Hastaların BoNT/A tedavisi sonrası MIDAS ve VAS skorlarında anlamlı düşme saptandı ($p<0.001$).

Sonuç: Botulinum Toksin A tedavisi KM'nin proflaktik tedavisinde etkin ve güvenilir bulunmuştur. Hastaların migrene bağlı özürlülüğünün azaldığı ve yaşam kalitesinin arttırdığı saptanmıştır.. Tüm proflaksi tedavilerini alan KM'li uygun kriterli hastalarda BoNT/A deneyimli nöroloji uzmanlarınca uygulanacak güçlü bir tedavidir.

Anahtar Kelimeler: Baş ağrısı, kronik migren, Botilinum toxin A

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INTRODUCTION

Chronic migraine is a common neurological disorder characterized by severe headache experienced >15 days per month over 3 months and headache characteristics fulfilling diagnostic criteria for migraine in at least 8 days of a month, which can impair quality of life severely.[1]

According to a population-based epidemiological study from Turkey (2012), migraine is most commonly seen between 20 and 50 years of age with a prevalence of 16.4%. Approximately 10% of patients with migraine suffer from chronic migraine.[2]

The CM prevalence varies from 2.5% to 5.5% in different studies. In a comprehensive study on CM epidemiology from USA, prevalence was estimated as 2%.[3]

The Botulinum toxin A (BoNT/A), increasingly used in many fields in recent years, was shown to be effective in chronic migraine (CM) in recent studies.[4-6] The use of BoNT/A in CM has been rapidly growing following its use over many years in the treatment of focal dystonia, non-dystonic movement disorders, spasticity, autonomic nervous system disorder in neurology clinics.

The prophylactic use of BoNT/A in CM was approved by The United States Food and Drug Administration (FDA) in 2010 and American Neurology Academy guidelines suggest that it is an effective treatment and should be recommend to CM patients in this setting.[7] The National Institute for Health and Care Excellence (NICE) recommends BoNT/A as a prophylactic option in CM patients unresponsive to at least 3 pharmacological prophylactic trials.[8] The botulinum neurotoxin (BoNT) is a protein complex produced by Clostridium botilinum, a gram-positive anaerobic bacterium. Although it has 7 different serotypes, only two are available for clinical use.[9] Mechanism of action involves inhibition of acetylcholine from presynaptic vesicles at neuromuscular junction, resulting dose-dependent, reversible muscle paralysis.[10]

The BoNT exert maximum effect 2 weeks after application and its effect is abolished by axonal budding after 4-6 months. However, it is difficult to explain its effect on pain by this mechanism; it is thought that BoNT/A inhibits peripheral sensitization of nociceptive fibers; thus, decreasing central sensitization.[11] In many studies, it was shown that BoNT/A inhibited substance P, glutamate A and calcitonin gene-related peptide which are among major mediators of inflammatory pain and released from activated sensorial nerve terminals.[12-15] It is thought that such inhibition prevents neurogenic inflammation and peripheral sensitization, resulting in decrease in pain signals transmitted to central nervous system from periphery. Thus, the BoNT/A indirectly blocks central sensitization seen in migraine and other painful conditions.[16,17]

Chronic migraine is a common neurological disorder that adversely influences quality of life, which is most common cause of chronic, daily headache. The effective treatment of disease can improve performance in both professional and personal life. We aimed to demonstrate effectiveness of BoNT/A (with proven effectiveness in pain) on intense pain in CM patients and present treatment responses of our CM patients treated with BoNT/A in our clinic.

MATERIAL AND METHOD

This is a single-center, prospective study. The study included 41 patients without comorbid neurological disorder (aged 18-65 years) who presented to neurology outpatient clinic with headache between January, 2016 and January, 2019 and diagnosed as chronic migraine according to 2004 International Headache Society (IHS) diagnostic criteria and underwent BoNT/A therapy as they did not respond all therapeutic options approved in Turkey (tolerance to agents used or unresponsiveness to prophylactic agent used over 2 months).

Patients with history of head-neck surgery, drug overdose (≥15 simple analgesics or >10 combined analgesics and/or tryptophan use in prior 3 months) and pregnant or breastfeeding women were excluded from study.

As recommended in PREMPT studies[4-6], BoNT/A (5 units per region; overall 155 units) was administered as to 31 points in 7 anatomic regions (corrugator, proserus, frontalis, temporalis, occipital, paraspinal and trapezius muscle groups).

To rule out secondary pathologies, biochemical assays, complete blood count, thyroid function tests, vitamin B12, folic acid and vitamin D levels as well as cranial imaging studies after diagnosis of CM were evaluated.

In our country, the BoNT/A is not in repayment coverage despite approved for use in CM, Off-Label Drug Consent forms were completed as cited in website of Health Ministry. The BoNT/A therapy was given to patients in whom treatment was approved based on defined criteria. The patients were assessed in visits at baseline and on month 6 after BoNT/A therapy. In first visit, the patients were questioned in detail regarding demographic data (age, gender), education level, time of diagnosis, migraine triggers and previous treatments. In addition analgesic use, attack frequency, VAS and MIDAS scores were assessed at baseline and on month 6. All patients gave written informed consent. The study was approved by Ethics Committee of Ankara City Hospital (protocol no: 2019-E-19-083).

Statistical Analysis

All statistical analyses were performed by SPSS (Statistical Package for Social Sciences) for Windows version 20.0. The normal distribution of numerical data was assessed by Shapiro-Wilk test. Continuous variables were defined as mean, standard deviation and min-max. Non-parametric Wilcoxon test was used to compare repeated measurements. A p value<0.05 was considered as statistically significant.

RESULTS

There were 36 women (87.8%) and 5 men (12.2%) in the study group. Mean age was calculated as 44.88±10.51 years ranging from 20 to 64 years (**Table 1**). The family history in first-degree relatives was positive in 25 patients (61%) while it was negative in 16 patients (39%). Of the patients, 20 patients (48.8%) fulfilled criteria for migraine with aura while no aura was detected in 21 patients (51.2%).

Table 1. Age and gender distribution of patients.

Gender	n	%	Age (years)			
			Max	Min	Mean	SD
Male	5	12.2	56	20	43.6	10.5
Female	36	87.8	64	23	45.05	10.5
Total	41	100	64	20	44.88	10.5

Max: maximum, min: minimum, SD: standard deviation

Significant decreases were detected in attack frequency, attack duration, number of painful days, VAS score and MIDAS rating on month 6 after BoNT/A therapy when compared to baseline ($p<0.001$). The mean pain intensity was found as 8.72±1.01 ranging from 5 to 10 before treatment while it was found as 5.85±2.27 ranging from 0 to 9 after BoNT/A therapy (**Table 2**). The MIDAS rating was 1 in 7 patients, 2 in 4 patients, 3 in 8 patients and 4 in 22 patients before BoNT/A therapy while it was 1 in 26 patients, 2 in 11 patients, in 3 patients and 4 in one patient after therapy (**Table 3**).

The main migraine triggers were light, sound and smell found in 32 patients; followed by hunger, stress and insomnia (**Figure 1**). There were 14 patients underwent trial with traditional and complementary medicine interventions which have become popular in Turkey in recent years. Before presentation, 4 patients underwent acupuncture therapy while 10 patients underwent cupping.

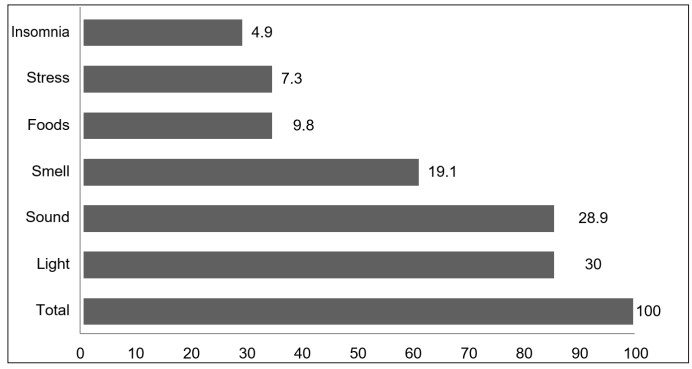

Figure 1. Migraine disease triggers.
Data are presented as percent

DISCUSSION

The effectiveness of BoNT/A, which is first shown to have analgesic effect in patients with spasmodic torticollis, on migraine was detected after its application to facial hyper-functional lines.[18] Subsequently, the BoNT/A was introduced in use in many fields and its effectiveness on patients with CM was established in phase III studies in 2010.[19]

It has been suggested that migraine frequency is approximately 2-folds greater in reproductive women than men and that attacks are more severe in women.[20] In our study, 36 of 41 patients were women. VAS scores before BoNT/A therapy were found to be higher in female subjects in our study.

It has been suggested that there is positive family history in 45-70% of patients with migraine headache.[21] In our study, 25 patients (61%) had positive migraine history in first-degree relatives, 70% of which has diagnosis of migraine.

In the literature, it was reported that aura was observed in about one-third of patients with migraine as visual aura being most common type.[22] In our study, aura was defined in 20

Table 2. Migraine characteristics, attack frequency, attack duration, number of painful days, pain severity and disability degree.

N=41	Before BoNT/A				After BoNT/A				Wilcoxon signed- rank test	
	Mean	SD	Min	Max	Mean	SD	Min	Max	z	p
Monthly Migraine Attack	11.95	6.12	5	30	4.90	4.49	0	20	-4.994	<0.001
Pain duration (hour)	23.66	17.99	6	72	6.34	7.13	0	24	-5.446	<0.001
Number of painful days (month)	17.63	5.80	8	30	5.24	5.31	0	24	-5.515	<0.001
VAS	8.72	1.01	5	10	5.85	2.27	0	9	-5.135	<0.001
MIDAS	24.90	16.08	2	54	4.46	5.13	0	25	-5.513	<0.001

BoNT/A: Botulinum Toxin A, max: maximum, min: minimum, MIDAS: Migraine disability assessment score, SD: standard deviation, VAS: Visual analog scale

Table 3. Migraine Disability Assessment Score (MIDAS) score before and after Botulinum Toxin A (BoNT/A) therapy.

Disability state	Number of patients before BoNT/A therapy (n)	Rate (%)	Number of patients after BoNT/A therapy (n)	Rate (%)
MIDAS-I (0-5 points)	7	17.1	26	63.4
MIDAS-II (6-10 points)	4	9.8	11	26.8
MIDAS-III (11-20 points	8	19.5	3	7.3
MIDAS-IV (≥21points)	22	53.7	1	2.4
TOPLAM	41	100	41	100

MIDAS: Migraine disability assessment score

patients (48.8%). Aura was defined as visual aura in 8 patients (40%); followed by visual-sensorial and visual-vertiginous aura. In a double-blinded, placebo-controlled study by Freitag et al., BoNT/A (n=21) and placebo (n=20) was administered to fixed injection points at fixed doses and it was found that BoNT/A therapy was superior to placebo.[23]

The BoNT/A effectiveness was confirmed in many studies conducted after FDA approval, as our study did. Similarly, it was observed that there were decreases in pain severity, number of days with headache and migraine disability.[24-26]

In a study by Elif Ilgaz et al., in which MIDAS rating and pain scores were assessed at baseline and on weeks 12 and 24 after BoNT/A therapy, it was suggested that MIDAS ratings was improved upon first dose with marked improvement in pain frequency and severity.[27]

Previous studies showed that BoNT/A is well-tolerated by patients with chronic migraine. In addition, it was found that treatment discontinuation due to adverse effects was significantly rare (1.4-3.8%).[28] In our study, there was neck pain in 1 patient and mild pain not requiring analgesic use and lasting less than 24 hours at injection site in 4 patients. No treatment discontinuation was observed. It was shown that treatment discontinuation rate is 12.7% in oral prophylaxis regimes.[29] BoNT/A therapy seem to be a good alternative in this regard.

Some patients with migraine define no trigger for onset of headache. However, stress, light, smell, menstruation, sleep disorders, hunger (skipping a meal), change of air, alcohol (wine and beer in particular) and some foods may trigger migraine.[30] In our study, there was one or more migraine triggers in 78.04% of our patients.

CONCLUSION

It is well-known that migraine is a common neurological disorder that adversely affects social and professional life of individuals. Many drugs and traditional modalities have been used as prophylactic therapy in patients with chronic migraine. The BoNT/A is a novel therapeutic modality in the treatment of migraine which may be triggered by lifestyle, comorbid conditions and eating habits. BoNT/A was found to be effective and safe in the prophylactic treatment of chronic migraine. It was also found that migraine-related disability was decreased with improving quality of life. BoNT/A is a potent treatment that could be performed by experienced neurologists in eligible CM patients regardless of previous prophylactic treatments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by Ethics Committee of Ankara City Hospital (protocol no: 2019-E-19-083).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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