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Botulinum Toxin Treatment in Blepharospasm: Single-center Experience

Blefarospazm Tedavisinde Botulinum Toksin: Tek-merkez Deneyimi

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Abstract

Objective: Blepharospasm (BS) is a focal dystonia that affects periocular muscles such as the orbicularis oculi, procerus, and corrugator. The disease may occur in isolation or in the course of neurodegenerative diseases, and its first-line treatment is the administration of botulinum toxin. In this study, we aim to analyze the clinical features of patients with BS.

Materials and Methods: In this study, the clinical features and treatment responses of patients with BS were retrospectively analyzed.

Results: Of the 49 patients included in the study, 23 were female and 26 were male. The mean age at administration was 56.8 ± 10.8 (between 35 and 85 years), and the mean age of onset was 52.2 ± 11.9 (between 21 and 82 years). Fourteen patients had a diagnosis of a neurodegenerative disease. Fourteen patients had additional oral treatment for their symptoms. The most common oral treatments were anticholinergic drugs, benzodiazepines, and antiepileptics. The mean unit of botulinum toxin was 32.4 ± 5.8 (15.0–42.5). Treatment response was evaluated in 42 patients. Of these, 36 (86%) had either good or excellent benefit. The mean duration of treatment benefit was 105.35 ± 36.35 (between 30 and 180) days. Pretarsal application was associated with better and more prolonged treatment response than preseptal. Other analyzed clinical parameters showed no effect on the benefit of botulinum toxin. Side effects were observed in seven patients, and the most common were orbicularis oculi weakness, ecchymosis, and xerophthalmia.

Conclusion: Our study demonstrated that botulinum toxin is effective and safe in the treatment of BS. Although pretarsal application has a similar side-effect profile to preseptal application, it was associated with better and longer treatment benefit.

Keywords: Dystonia, focal, Meige syndrome, pretarsal, neurodegenerative

Öz

Amaç: Blefarospazm (BS), orbikülaris oküli, proserus ve korrugator kaslar gibi perioküler kasları da etkileyen bir fokal distonidir. Hastalık, tek başına veya nörodejeneratif hastalıkların seyrinde ortaya çıkabilmektedir. Hastalıkta, birinci basamak tedavi botulinum toksin uygulamasıdır. Bu çalışmada, BS tanısı ile izlenen hastaların klinik özelliklerini incelenmeyi amaçladık.

Gereç ve Yöntem: Çalışmamızda, BS tanısı ile takip edilen hastaların klinik özellikleri ve tedavi yanıtları retrospektif olarak analiz edilmiştir.

Bulgular: Çalışmaya katılan 49 hastanın, 23'ü kadın, 26'sı erkekti. Hastaların ortalama başvuru yaşı 56,8 ± 10,8 (35 ile 85 arasında), yakınmalarının ortalama başlangıç yaşı ise, 52,2 ± 11,9 (21 ile 82 arasında) idi. Hastaların 14'ünde bir nörodejeneratif hastalık tanısı mevcuttu. Hastaların 14'ü semptomları için botulinum toksinine ek olarak oral tedavi almaktaydı. En sık oral tedaviler antikolinerjik ilaçlar, benzodiazepinler ve antiepileptiklerdi. Hastalarda ortalama 32,4 ± 5,8 (15,0–42,5 arasında) ünite botulinum toksin kullanıldı. Tedavi yanıtı 42 hastada değerlendirildi. Bu hastaların 36'sının (%86) botulinum toksin uygulamasından iyi veya çok iyi düzeyde fayda gördüğü öğrenildi. Tedaviden görülen yarar süresi, ortalama 105,35 ± 36,35 (30 ile 180 arasında) gün idi. Pretarsal uygulamanın preseptal uygulamaya göre daha iyi ve uzun süreli yanıt ile ilişkili olduğu saptandı. Analiz edilen diğer klinik parametrelerin botulinum toksin uygulamasından görülen faydaya etkisinin olmadığı dikkati çekti. Yedi hastada botulinum toksinin uygulamasına bağlı yan etki geliştiği gözlendi. En sık gözlenen yan etkiler, orbikülaris oküli kas zaafı, ekimoz ve kseroftalmi idi.

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Sonuç: Çalışmamızda, botulinum toksininin BS tedavisinde etkili ve güvenilir olduğu ortaya konmuştur. Pretarsal uygulamanın, preseptal uygulamaya göre benzer yan etki profiline sahip olmasına rağmen hasta değerlendirmesine dayanan fayda oranına göre daha etkili olduğu ve bu etkinin daha uzun süre devam ettiği saptanmıştır.

Anahtar Kelimeler: Distoni, fokal, Meige sendromu, pretarsal, nörodejeneratif

Introduction

Blepharospasm (BS) is a focal dystonia that also affects the periocular muscles such as the procerus and corrugator, and mainly the orbicularis oculi. Although it was first described in the late 19th century, it was first revealed by Marsden (1) about 40 years ago that the disease was a focal dystonia. The prevalence of the condition varies between countries but is around 20–133/1,000,000. Among focal dystonias, it is more common than laryngeal and extremity dystonias but rarer than cervical dystonia (CD), according to studies in North America and Europe (2). The disease, which is slightly more prevalent in women than in men, is most commonly present in the 6th decade of life. It often results in increased blinking, involuntary closing of the eyes, and difficulty opening the eyes. It affects both eyes symmetrically, but in very rare cases, it can be asymmetrical. Difficulty in eye opening may sometimes be accompanied by apraxia of eyelid opening.

Diagnostic criteria for the disease, which was diagnosed with history and examination findings, were determined as follows (3,4):

1. Bilateral, synchronized, and stereotypical contractions of the orbicularis oculi muscle (MOO), causing closure of the eyelids,
2. At least one of the following items:
   a. Relief of symptoms with sensory trickery,
   b. Increased blink frequency.

Symptoms are often exacerbated by stress and bright light. Although a feeling of discomfort in the eyelids accompanies the disease, pain is almost never observed. The disease may be limited to the eye area, but can spread to the jaw, tongue, and facial area, and this disorder is called Meige syndrome. More rarely, it may spread to the cervical region (5).

When BS is observed in isolation, it is called benign essential blepharospasm (BEB). In addition to this, it can occur in structural lesions of the brain, tardive syndromes, neurodegenerative diseases such as Parkinson's disease (PD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), or demyelinating diseases of the central nervous system such as multiple sclerosis (6,7).

The first-line treatment for the disease, which has also been approved by the United States Food and Drug Administration, is the administration of botulinum toxin (8). Ptosis, dry eye, double vision, and facial injection-related asymmetry, which are among the common side effects associated with this treatment, rarely occur when the treatment is applied by professionals with experience in this kind of procedure. In some cases, despite the presence of sufficient clinical knowledge and experience, treatment response may not be at the desired level in a small number of patients. In this study, the clinical features and treatment responses of the patients followed up with the diagnosis of BS were examined.

Materials and Methods

Patient Selection and Evaluation of Treatment Response

In this study, patients who were followed up with a diagnosis of BS in the Botulinum Toxin Outpatient Clinic of the Neurology Department of Istanbul University, Istanbul Faculty of Medicine, between 1996 and 2021 were analyzed retrospectively. The clinical and demographic characteristics of the patients included in the study were examined, and the degree of benefit from the treatment and the development of side effects were recorded in control examinations one, three, and six months after the first botulinum toxin type A (BoNT-A) injection was administered in our clinic. The treatment benefit was divided into four groups: 1) inadequate, 2) moderate, 3) good, and 4) very good. In addition, the duration of any benefit from the BoNT-A injection was recorded. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from the participating patients or their legal guardians, and it was accepted by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee with file number 2023/403 (date: 31/03/2023).

Injection Method

BoNT-A (Botox®) injection was applied to the MOO by using preseptal or pretarsal application methods as previously stated in the literature (9). Before being injected, the BoNT-A was diluted with 0.2 ml of 0.9% saline in the pretarsal applications and 0.2 or 0.4 ml in the preseptal applications. In case of clinical necessity, injections were also applied to the procerus, corrugator, and nasalis muscles. In patients with other focal dystonias, injections were also made to the affected areas, but only BS findings were taken into account in determining the treatment response in this study.

Statistical Analysis

SPSS version 26.0 was used to compare the data. The Mann–Whitney U test was used to compare the means between groups without a normal distribution. The chi-square test was applied to compare the groups in terms of non-parametric data such as

Table 1. Demographic and clinical characteristics of the patient group (49 patients)

	Pretarsal	Preseptal
Gender	Female: 13 Male: 9	Female: 10 Male: 17
Age of onset of symptoms	53.00 ± 12.25	51.63 ± 11.58
Age at admission	59.59 ± 10.15	54.59 ± 14.06
Neurodegenerative disease	Yes: 5 No: 17	Yes: 9 No: 18
Concomitant dystonia	Yes: 7 No: 15	Yes: 8 No: 19
Prior botulinum toxin injection	Yes: 6 No: 16	Yes: 5 No: 22
Oral therapy	Yes: 8 No: 14	Yes: 8 No: 19

frequency of side effects, demographic data, and application method.

Results

Of the 49 patients included in the study, 23 were female and 26 were male. The mean age at presentation of the patients was 56.8 ± 10.8 (35–85), and the mean age of onset of their complaints was 52.2 ± 11.9 (21–82) (Table 1). The most common complaint, in 42 of the patients, was difficulty in opening the eyes. This was followed by sensitivity to light (three patients), increased frequency of blinking (two patients), and dry eyes (two patients). Fourteen patients had a diagnosis of neurodegenerative disease such as PD, PSP, or CBD. Two of these patients also had oromandibular dystonia (OMD) and CD. Of the 35 patients without a known diagnosis of neurodegenerative disease, 11 had different types of focal dystonia accompanying their BS. The most common type of concomitant dystonia in these patients was OMD (Meige syndrome, 8 patients). This was followed by CD (three patients). Fourteen patients were receiving oral therapy in addition to BoNT-A for their symptoms. The preferred oral treatments were anticholinergic drugs, benzodiazepines, and antiepileptics. Four patients had a family history of BS.

A mean of 32.4 ± 5.8 (15.0–42.5) units of BoNT-A was used on the patients. The mean dose injected into the MOO was 26.7 ± 3.8 (15–35) units. Injections were applied to the corrugator muscle in 34 patients, the procerus muscle in 12 patients, and the nasalis muscle in four patients.

Since seven of the patients did not attend the follow-up examination, the observed benefit from the treatment could not be determined. It was learned that 36 (86%) of the 42 patients whose treatment response could be evaluated benefited well or very well from the BoNT-A injection. It was determined that the pretarsal application was associated with a better response than the preseptal application, although there was no significant difference in terms

Table 2. Analysis of the effect of patient clinical characteristics on the response to treatment of patients (42 patients) whose treatment response was learned. The treatment responses of the patients were scored as (1) inadequate, (2) moderate, (3) good, and (4) very good, and the averages were determined based on these scores

		Mean treatment response	*P* value
Gender	Female (n = 20)	3.60 ± 0.59	0.462
	Male (n = 22)	3.32 ± 0.94	
Neurodegenerative disease	Yes (n = 13)	3.31 ± 0.75	0.244
	No (n = 29)	3.52 ± 0.82	
Concomitant dystonia	Yes (n = 29)	3.41 ± 0.82	0.593
	No (n = 13)	3.54 ± 0.77	
Application method	Pretarsal (n = 18)	3.83 ± 0.38	**0.008**
	Preseptal (n = 24)	3.17 ± 0.91	
Prior botulinum toxin administration	Yes (n = 7)	3.71 ± 0.48	0.435
	No (n = 35)	3.40 ± 0.84	
Oral therapy	Yes (n = 12)	3.33 ± 0.77	0.385
	No (n = 30)	3.50 ± 0.82	

Table 3. Analysis of subgroups according to duration of treatment response

		Duration of treatment response (days)	*P* value
Gender	Female (n = 20)	115.50 ± 32.68	0.052
	Male (n = 22)	95.45 ± 38.04	
Neurodegenerative disease	Yes (n = 13)	99.23 ± 35.46	0.343
	No (n = 29)	107.58 ± 37.40	
Concomitant dystonia	Yes (n = 29)	103.44 ± 33.62	0.840
	No (n = 13)	108.46 ± 43.79	
Application method	Pretarsal (n = 18)	120.83 ± 35.82	**0.006**
	Preseptal (n = 24)	93.32 ±33.02	
Prior botulinum toxin administration	Yes (n = 7)	105.00 ± 35.70	0.804
	No (n = 35)	105.00 ± 37.27	
Oral therapy	Yes (n = 12)	102.50 ± 34.93	0.704
	No (n = 30)	106.00 ± 37.76	

of doses administered (P = 0.09). It was noted that gender, presence of concomitant neurodegenerative disease, presence of a different type of dystonia, and additional oral treatment had no effect on the observed benefit from the BoNT-A injection (Table 2).

The mean duration of benefit from treatment was 105.35 ± 36.35 (30–180) days. It was observed that the treatment response lasted longer in the group of patients who underwent BoNT-A injection with the pretarsal application method compared to the group that underwent BoNT-A injection with the preseptal application method (Table 3).

Side effects from the BoNT-A injection were observed in seven patients. These were ptosis (two patients), difficulty in closing eyes due to MOO weakness (two patients), ecchymosis (two patients), and xerophthalmia (one patient). There was no significant difference in the frequency of side effects between the pretarsal and preseptal methods (P = 0.85)

Discussion

In this study, the characteristics and treatment responses of patients with a diagnosis of BS who were treated with BoNT-A injection in our clinic, which had approximately 30 years of experience in therapeutic botulinum toxin treatment, were examined. Although the age of onset of the complaints of our patients showed similar characteristics to previous studies, it was observed that male patients were more common in our patient group, unlike the literature. It was thought that this could be explained by the fact that in our cohort, apart from patients with BEB, there were also patients with neurodegenerative disease diagnosed as having secondary BS. In studies conducted in different centers in our country, a gender distribution similar to that in our patient group was not observed (10,11).

It was observed that 86% of the patients included in the study benefited well or very well from the treatment, similar to previous studies. In a recently published study conducted on a very large patient group with a follow-up period of 30 years, BoNT-A was shown to be effective and safe even after a number of years (12). Similarly, in a study in which long-term follow-ups of patients who received BoNT-A injections on the face in our clinic were analyzed, it was found that the benefit from the treatment continued for an extended period of time (13). In the patients in our study, it was determined that this period was about 3.5 months on average, and it could be extended up to 5–6 months in 20% of them.

In our patient group, there were also patients with BS seen in the course of neurodegenerative diseases. In previous studies, BoNT-A was shown to be effective and safe in this patient group as well. Similarly, in our study, it was observed that this patient group benefited from BoNT-A just as patients with BEB did (14).

It was observed that the pretarsal application method was associated with better clinical response compared with the preseptal application method, as observed in previous studies (11,15). However, the duration of benefit from treatment was longer in the patient group who underwent BoNT-A injection with pretarsal application method compared to preseptal application method. It was noted that this positive effect was independent of the dose used. In addition, it was observed that there was no difference between the two application methods in terms of side effects. It was noted that other variables such as gender, additional oral treatments, or previous administration of BoNT-A had no effect on treatment response.

Conclusion

In our study, in parallel with the literature, BoNT-A was shown to be effective and safe in the treatment of BS. It was observed that this effect was present both in segmental dystonia types such as Meige syndrome, which included BS, and in patients with secondary BS. Although the pretarsal application method was associated with a similar side-effect profile compared to the preseptal application method, it was determined that it was more effective based on patient evaluation and this effect lasted longer. Although the evaluation of the treatment response without using a validated scale might be deemed a limitation of this study, it was thought that this research reflected the practical situation of botulinum toxin applications in our country in terms of the number of patients included, its use of data covering a long time period, and it being based on patients' self assessment. Since it is a relatively simple treatment that can be applied in outpatient settings and is very effective and safe when performed by experienced physicians, BoNT-A, as the first-line treatment in patients with BS, is important for patients' quality of life.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, it was accepted by the Istanbul University, Istanbul Faculty of Medicine Clinical Research Ethics Committee with file number 2023/403 (date: 31/03/2023).

Informed Consent: Informed consent was obtained.

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Authorship Contributions

Surgical and Medical Practices: A.Ç., B.S., H.H., Y.P., Concept: A.Ç., Y.P., Design: A.Ç., B.S., H.H., Y.P., Data Collection or Processing: A.Ç., B.S., H.H., Y.P., Analysis or Interpretation: A.Ç., B.S., H.H., Y.P., Literature Search: A.Ç., Y.P., Writing: A.Ç., Y.P.

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