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Effects of delay in botulinum toxin treatment on patients with hyperkinetic facial disorders

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Abstract

Aim: Hyperkinetic facial disorders include Benign Essential Blepharospasm (BEB) and Hemifacial Spasm (HFS), which involve involuntary facial muscle contractions. Botulinum toxin (BTX) is essential for relieving symptoms. The Coronavirus-19 (COVID-19) pandemic-related restrictions have led to delays in receiving BTX treatment. This study aims to assess the impact of BTX treatment delays in patients with hyperkinetic facial disorders.

Materials and Methods: This study retrospectively examined the data of 84 patients (68 HFS and 16 BEB) whose BTX appointments were delayed due to COVID-19 restrictions. Patient status was evaluated using Jankovic disability rating scale (JRS) scores, and administered BTX doses were documented and compared before and after lockdown.

Results: After the BTX treatment delay, the median JRS scores significantly increased from 2 before the lockdown to 3 after the lockdown ($p<0.001$). Furthermore, there was a noticeable increase in the average BTX treatment dose after the lockdown, from 35 units to 37.5 units ($p<0.001$).

Conclusion: Longer intervals between injections may increase disease severity and the effective BTX doses in patients with HFS and BEB. The COVID-19 pandemic has highlighted the importance of timely BTX therapy in managing hyperkinetic facial disorders.

Introduction

Hyperkinetic facial disorders include a range of neurological motor disorders, each with different diagnostic criteria and treatment algorithms. Benign Essential Blepharospasm (BEB) is a focal dystonia characterized by repetitive contraction of the extraocular muscles with excessive blinking and eyelid closure [1, 2]. Common symptoms include dry eyes, frequent blinking, and photophobia [3]. Although these spasms can seriously affect patients' daily activity, they disappear during sleep [4]. It is more common in women and typically occurs between the ages of 40-60 [5]. Hemifacial Spasm (HFS) is identified by the involuntary, sudden contraction of muscles controlled by the facial nerve. Bilateral involvement is rare. Involuntary contraction affects the orbicularis oculi muscle in the upper part of one-half of the face and the orbicularis oris, platysma, and other superficial muscles in the lower region. HFS is also more common in women than men and usually occurs in the fourth to seventh decade of life [5, 6].

Botulinum toxin (BTX) is a type of exotoxin produced by the spore-forming bacterium Clostridium Botulinum. This toxin causes muscles or glands to become inactive by blocking the release of acetylcholine from cholinergic nerve endings [7, 8]. Various studies have shown that BTX provides symptomatic relief in approximately 85% of HFS patients with relatively low complication risks. Similarly, over 90% improvement in motor symptoms has been observed in patients with BEB following BTX treatment [4].

The Coronavirus-19 (COVID-19) pandemic has severely affected all healthcare systems worldwide. Following the World Health Organization's declaration of COVID-19 as a pandemic, some restrictions were implemented in our country, including the shutdown of some outpatient clinics and the postponement of non-emergency medical interventions. These restrictions have resulted in a delay in the treatment of patients with hyperkinetic facial disorders receiving BTX therapy. This study aims to demonstrate the effects of delay in BTX treatment on patients with HFS and BEB, based on the lockdown during the COVID-19 period.

Materials and Methods

The study was conducted by retrospectively examining the demographic and clinical data obtained from the medical records of the patients who were followed up with the

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diagnosis of HFS and BEB and received BTX treatment in the Neurology Botulinum Toxin Outpatient Clinic of Bezmialem Vakıf University Medical Hospital. Based on the G*Power analysis, the minimum sample size required for the study was calculated to be 80 with a power of 87%, a type 1 error rate of 0.05, and an effect size of 0.3 [9]. The data of 138 patients who were scheduled to receive BTX treatment between June 15, 2020, and October 15, 2020, but had their appointments postponed for more than two weeks due to the pandemic related restrictions or who chose not to come to the hospital due to COVID-19 risk were analyzed. All patients had been regularly treated with BTX before the pandemic, were 18 years or older, and received BTX treatment at average intervals of around three months for over a year before the lockdown. After excluding patients with incomplete medical records, 84 patients were included in the study. The study was approved by the Bezmialem Foundation University Hospital Clinical Research Ethics Committee (Approval No: E-54022451, Date: 06.05.2021), and all procedures followed the Helsinki Declaration.

Demographic data, including age, gender, and risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease), type of hyperkinetic facial disorder, duration of the condition, duration of BTX treatment, mean BTX treatment interval and last BTX treatment date before lockdown, first BTX treatment date after the lockdown, and total delay time of BTX treatment due to the lockdown, the last BTX dose before the lockdown and the first BTX dose after the lockdown were recorded. The Jankovic disability rating scale (JRS) scores [10], used in routine evaluation in our BTX outpatient clinic, were used to determine the rate of benefit from the treatment. On this scale, 0 corresponded to normal function and 4 to no improvement. The last JRS scores before the lockdown, the mean JRS scores for one year before the lockdown, and the JRS scores on the first visit after the lockdown were recorded.

BTX treatment

All patients received BTX treatment with OnabotulinumtoxinA (ONA, Botox®) (100MU in 2.5 ml of 0.9% NaCl/H2O). Injections were administered in 1 to 7.5 units to the orbicularis oculi, procerus, corrugator supercilii, risorius, orbicularis oris, and platysma muscles. The administered dose varied based on the response reported by each patient during treatment, the presence of side effects, and clinical evaluation.

COVID-19 restrictions

In March 2020, Turkey Government ordered all hospitals to stop all non-urgent medical procedures. From June to October 2020, our BTX clinic was operative at %50 capacity.

Statistical analysis

The SPSS package program for Windows version 20 (IBM Corporation, Armonk, NY, USA) was utilized for the statistical analysis. To assess the distribution of data, the Shapiro-Wilk test was performed to determine its normality. To analyze normally distributed data, the arithmetic mean and standard deviation were used. Median and interquartile range were used if the data did not follow a normal distribution. A Mann-Whitney U test was conducted to compare JRS scores and BTX doses of HFS and BEB patient groups. Wilcoxon signed-rank test is used to compare JRS scores and BTX doses before and after the pandemic. The association between parameters was assessed using Spearman's Correlation Analysis. To determine statistical significance, P values less than 0.05 were taken into consideration.

Results

A total of 84 patients (51 female) were included in the study. 68 (81%) patients had HFS, and 16 (19%) had BEB. The mean age of the patients was 62.71±10.42 years. The median disease duration was 11 years, and the median duration of BTX treatment was eight years. Before the pandemic, the median interval between BTX injections was 3.5 months; however, due to pandemic-related restrictions, the median BTX treatment interval increased to 7 months. The median JRS score before the lockdown was 2, which increased to 3 on the first visit after the lockdown. The mean last BTX dose before the lockdown was 35 units, and in the first injection session after the lockdown, the mean BTX dose was 37.5 units (Table 1).

The mean age of the 68 patients (41 females) diagnosed with HFS was 61.59±10.12 years, while for the 16 patients (10 females) diagnosed with BEB, it was 67.50±10.62 years. The median JRS score of HFS patients at the last visit before the lockdown was 2. This median score increased to 3 on the first visit after the lockdown. While the median JRS score was 2 in the last BTX injection session before the lockdown in BEB patients, it was 3 during the first treatment after the lockdown. At the last visit before the lockdown, the median BTX treatment dose administered to patients with BEB was statistically significantly higher than the median dose administered to patients with HFS (55 units, 30.5 units, $p<0.001$, respectively). Similarly, at the first visit after lockdown, the median BTX treatment dose administered to the patients with BEB was found to be statistically significantly higher than the median dose administered to the patients with HFS (57.5 units, 33.5 units, $p< 0.001$ respectively) (Table 2).

When HFS and BEB patients were evaluated together, the median BTX treatment dose of the whole group at the first visit after the lockdown was statistically significantly higher than on the last visit before the lockdown (37.5 units vs. 35 units, $p<0.001$ respectively). The median JRS score on the first visit after the lockdown was statistically significantly higher than on the last visit before the lockdown (3 vs. 2, $p<0.001$ respectively) (Table 3). There was no correlation between BTX treatment delay time, BTX doses, and JRS scores (Table 4).

Discussion

HFS and BEB are two common craniofacial movement disorders. BEB is an adult-onset, focal cranial dystonia characterized by involuntary, repetitive, and progressive eyelid and forehead muscle contractions, resulting in functional

Table 1. Demographic characteristics and botulinum toxin treatment data of patients.

Number of patients(n)	84
Gender (n,%)	
Female	51 (60.7%)
Male	33 (39.3%)
Age (Mean±SD)	62.71±10.42
Indication for BTX-A therapy (n,%)	
HFS	68 (81%)
BEB	16 (19%)
Duration of disorder (years) (Median (IQR))	11 (8)
Duration of treatment (years) (Median (IQR))	7 (6)
Hypertension (n,%)	39 (46.4%)
Hyperlipidemia (n,%)	18 (21.4%)
Diabetes Mellitus (n,%)	11 (13.1%)
Coronary Artery Disease (n,%)	9 (10.7%)
BTX therapy routine interval (months) (Median (IQR))	3.5(1)
Delayed treatment interval due to the lockdown (months) (Median (IQR))	7 (2.5)
The Last JRS* score before the lockdown (Median (IQR))	2 (2)
The first JRS* score after the lockdown (Median (IQR))	3 (2)
The last dose of BTX before the lockdown (units) (Median (IQR))	35 (19.5)
The first dose of BTX after the lockdown (units) (Median (IQR))	37.5 (19)

* Jankovic Disability Rating Scale BTX: Botulinum Toxin, HFS: Hemifacial Spasm, BEB: Blepharospasm.

Table 2. Clinical and demographic characteristics of patients according to hyperkinetic facial disorder.

		Hyperkinetic Fasial Disorder		p[a]
		HFS	BEB	
Number of patients	(n,%)	68 (81)	16 (19)	
Age	Mean ± SD	61.59±10.12	67.50±10.62	
Sex	F (n,%)	41 (60.3)	10 (62.5)	
	M (n,%)	27 (39.7)	6 (37.5)	
BTX therapy routine interval (months)	Median (IQR)	3.5 (1)	3.5 (0.9)	0.045
Delayed treatment interval due to the lockdown (months)	Median (IQR)	7 (2)	5.75 (2)	0.045
The last JRS* score before the lockdown	Median (IQR)	2 (2)	2 (1)	0.669
The first JRS* score after the lockdown	Median (IQR)	3 (2)	3 (2)	0.836
The last dose of BTX before the lockdown (units)	Median (IQR)	30.5 (12.5)	55 (13)	**0.000**
The first dose of BTX after the lockdown (units)	Median (IQR)	33.5 (15)	57.5 (25.5)	**0.000**

[a]Mann-Whitney U Test * Jankovic Disability Rating Scale BTX: Botulinum Toxin, HFS: Hemifacial Spasm, BEB: Blepharospasm.

Table 3. Comparison of JRS scores and BTX doses before and after the lockdown.

		Last visit before the lockdown	First visit after the lockdown	p[a]
JRS* score	Median (IQR)	2 (2)	3 (2)	**0.000**
BTX dose (units)	Median (IQR)	35 (19.5)	37.5 (19)	**0.000**

[a]Wilcoxon signed-rank test * Jankovic Disability Rating Scale BTX: Botulinum Toxin.

blindness and poor quality of life without an underlying cause [11]. HFS is a movement disorder that causes involuntary contraction of facial muscles innervated by the facial nerve [5]. Both diseases are clinically similar, but HFS usually develops secondary to facial nerve compression by vascular structures or irritation of the facial nerve, while BEB results from dysfunction resulting from the involvement of the sensorimotor cortical regions of the basal ganglia-cortical circuits [12].

There have been attempts to use oral medication for the treatment of HFS and BEB, but there is still a lack of evidence-based efficacy data. Historically, drugs that prevent seizures and agents with GABAergic properties such as clonazepam, baclofen, carbamazepine, levetiracetam,

Table 4. Correlation between BTX treatment delay and JRS* scores and doses of BTX.

	BTX treatment delay	
	The Spearman correlation coefficient, rho	p
First JRS* score after the lockdown	-0.079	0.081
The first dose of BTX after the lockdown (units)	0.192	0.477

rho: Correlation Coefficient * Jankovic Disability Rating Scale BTX: Botulinum Toxin.

zonisamide and gabapentin have been used for HFS. In the case of BEB, various oral medications including trihexyphenidyl, benztropine, clonazepam, baclofen, tetrabenazine and mexiletine have been used with suboptimal results. Unfortunately, due to adverse side effects and lack of proven efficacy in evidence-based studies, oral agents have fallen out of favor in clinical practice [4].

BTX treatment is a standard symptomatic approach for both conditions [13]. Beyond providing symptomatic relief, there is evidence that BTX therapy is also effective in providing neuroplastic remodeling in the brain [4]. Numerous reports on the efficacy and safety of BTX treatment in BEB patients have shown that BTX treatment is beneficial, its effect is temporary, and it has a low incidence of side effects [3]. In clinical practice, BTX is considered a first-line treatment option for HFS patients, similar to its use in BEB treatment, and positive outcomes that enhance the quality of life have also been reported in HFS treatment [14]. A study conducted with 27 HFS and 16 BEB patients showed a mean improvement of 3.78+0.64 and 3.29+1.07 in the JRS score after treatment with BTX injections, respectively. BTX-induced clinical benefit lasted an average of 4.46+3.11 months in the HFS group and 2.66+1.37 months in the BEB group. These findings showed that local BTX therapy provided effective, safe, and long-lasting relief of spasms [10].

In a study sharing 15 years of BEB treatment experience, it was reported that the dose of BTX was increased significantly (p=0.0046) over time to achieve continuous benefit [15]. Another study demonstrated a significant increase in the average dose after ten years of treatment in 32 BEB and HFS patients (P = 0.003). It was observed that the dose increased over time in 22 patients, remained stable in six patients, and decreased in four patients. It has been suggested that the increase in dose may be due to the chronic, progressive nature of focal dystonias and the formation of low-titer neutralizing antibodies during treatment [11]. Although concerns exist that more frequent applications might lead to the development of immunogenicity, the injection interval has been set at three months in studies to minimize this risk. However, based on the authors' experiences, the risk of increased immunogenicity with more frequent injections is minimal, and the benefits of frequent injections outweigh this risk [4]. Despite studies showing the positive effect of short application intervals in BTX treatment on therapeutic results [16], few studies investigate the effect of disruption in BTX treatment intervals on treatment response. COVID-19 restrictions, including the closure of BTX outpatient clinics in some countries, have enabled us to observe the effects of delayed treatment intervals on patients.

Santamato et al. [17] applied a questionnaire called CORTOX (CORonavirus TOXin questionnaire) over the phone to 151 patients with spasticity after stroke and traumatic brain injury who were treated with BTX. Approximately 72.2% of the participants reported worsening perceived spasticity and 70.9% worsened quality of life. Furthermore, over half of the patients (53%) highlighted the loss of independence attributed to COVID-19-related problems and disruptions in rehabilitation services. In another study by Dressler et al. [18] involving a total of 45 patients receiving BTX treatment for various indications (including cervical dystonia, BEB, spasticity, pain condition, and HFS), a standardized questionnaire was applied. The findings revealed that pandemic-related restrictions led to a mean delay of 6.6 ± 2.3 weeks in BTX treatment. This delay resulted in a 93% increase in muscle spasms and an 82% increase in pain, subsequently contributing to a 40.2 ± 19.5% reduction in overall quality of life. This rate was found to be 33.3% ± 15.3% in 3 patients with BEB and 27.5% ± 17.1% in 3 patients with HFS. Restrictions due to the pandemic have highlighted the importance of BTX therapy in treating dystonia, spasticity, hemifacial spasm, and various pain conditions. Samadzadeh et al. [19] aimed to evaluate the delay in treatment time and symptom severity during COVID-19 restrictions in a study involving 100 patients. Among the 94 patients who could attend the clinic, 48 experienced delays in their scheduled treatment, with 44 reporting exacerbation of symptoms during the delay period. The mean duration of treatment delay was 23 days, and the mean worsening compared to the previous visit was 26%. A significant correlation was found between the delay time and the degree of worsening of the patients. Similar to these studies, we observed that the mean time between BTX injections increased from 3.55±0.47 months to 6.90±1.62 months after lockdown, and this delay in treatment led to a decline in the clinical condition of patients, as evidenced by the deterioration in their JRS scores.

Erro et al. [20] conducted a study involving a total of 137 patients who were receiving BTX treatment for conditions such as spasticity, dystonia, migraine, or other indications. Among these patients, 94 missed their BTX appointments due to the lockdown and were included in the case group, while 43 patients who attended the BTX clinic at their regular appointment times were included in the control group. The researchers asked the patients to assess the worsening perception during the delayed treatment period using a visual analog scale and a standardized two-component questionnaire. The study revealed that the average treatment delay in the case group was approximately 73 days. Notably, the case group exhibited a significant deterioration

in their conditions compared to the control group (5.16 ± 3.09 vs 1.83 ± 3.34, respectively). However, there was no significant difference in the BTX doses administered between the case and control groups (659.54 ± 197.11 vs. 673.49 ± 193.76 IU; t = 0.03). Unlike these findings, our study observed a significant increase in the required BTX doses after the lockdown. However, BTX treatment delay time, BTX doses, and JRS scores were not correlated.

Conclusion

This study showed that the mean severity scores according to the Jankovic Rating Scale (JRS) increased after the treatment delay of BTX, indicating a worsening of symptoms in both HFS and BEB patients. Additionally, the mean BTX treatment dose administered after the lockdown was statistically higher compared to the doses administered before the lockdown. The COVID-19 pandemic-induced restrictions shed light on the critical role of timely BTX therapy in managing hyperkinetic facial disorders.

Ethical approval

The study was approved by the Bezmialem Foundation University Hospital Clinical Research Ethics Committee (Approval No: E-54022451, Date: 06.05.2021).

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