DOI: 10.4274/Tnd.26097

Original Article / *Özgün Araştırma*

Efficacy of Botulinum Toxin Injections in the Treatment of Various Types of Facial Region Disorders

Yüz Bölgesi Hastalıklarının Çeşitli Tiplerinde Botulinum Toksini Enjeksiyonlarının Etkinliği

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Summary

Objective: Local injection of botulinum toxin is a highly effective treatment option for a wide range of movement disorders. There are reliable sources of information on its indications, effects and safety in clinical practice. In this study, we report our experience with botulinum toxin in the treatment of facial region disorders.

Material and Method: Patients followed up at the Botulinum Toxin Outpatient Clinic of the Department of Neurology were retrospectively evaluated. Two preparations of botulinum toxin type A (BT-A) were used. The efficacy of BT-A injections was rated based on the improvement in symptoms and judged as follows; marked: 75-100%, good: 50-74%, moderate: 25-49%, and insufficient: symptom relief below 25%.

Results: One hundred and eighty-two patients (73 male, 109 female) with various facial region disorders were included in the study. Improvement in symptoms was marked and good in subjects treated for blepharospasm, hemifacial spasm, facial synkinesis, and Meige syndrome, and moderate for oromandibular dystonia and hypersalivation. Ptosis was the most common side effect.

Discussion: Based on our results, botulinum toxin is a very effective treatment for blepharospasm, Meige syndrome, hemifacial spasm and facial synkinesis. Moderate efficacy was observed in oromandibular dystonia and hypersalivation. *(Turkish Journal of Neurology 2012; 18:155-161)*

Key Words: Botulinum toxin type-A, facial region disorders, efficacy

Özet

Amaç: Lokal botulinum toksin enjeksiyonu, çok sayıda hareket bozukluğu hastalığı için son derece etkili bir tedavi seçeneğidir ve klinik pratikte endikasyonları, etkileri ve güvenliği ile ilgili güvenilir kaynaklar vardır. Bu çalışmada yüz bölgesi hastalıklarının tedavisinde A tipi Botulinum toksini ile olan deneyimlerimizi bildirdik.

Gereç ve Yöntem: Botulinum toksini polikliniğinde takip edilen hastalar retrospektif olarak değerlendirildi. A tipi Botulinum toksininin iki formu kullanıldı. A tipi Botulinum toksini enjeksiyonlarının etkinliği semptomlardaki iyileşmeye göre aşağıdaki gibi değerlendirildi; %75-100 çok iyi, %50-74 iyi, %25-49 orta, %25 ve altı ise yetersiz.

Bulgular: Çeşitli yüz bölgesi hastalıkları olan toplam 182 hasta (73 erkek, 109 kadın) çalışmaya dahil edildi. Hastalar tarafından "çok iyi" ve "iyi" olarak bildirilen etkinlik oranları blefarospazm, hemifasyal spazm, fasyal sinkinezi ve Meige sendromu grubunda yüksekken, oromandibuler distoni ve hipersalivasyon grubunda orta derecedeydi. En yaygın görülen yan etki ptoz oldu.

Sonuç: Bu sonuçlara göre, Botulinum toksini tedavisinin blefarospazm, hemifasyal spazm, fasyal sinkinezi ve Meige sendromu için oromandibuler distoni ve hipersalivasyon grubuna göre oldukça etkili bir tedavi yöntemi olduğu söylenebilir. *(Türk Nöroloji Dergisi 2012; 18:155-161)*

Anahtar Kelimeler: Botulinum toksini tip A, yüz bölgesi hastalıkları, etkinlik

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Introduction

The use of Botulinum toxin type A (BT-A) was approved by the Food and Drug Administration (FDA) in 1989 for the treatment of strabismus, hemifacial spasms (HFS), and blepharospasm (1,2). Serotypes A and B are now commonly used in clinical practice. Two different preparations of BT-A are used in Turkey: Botox® (Allergan, Irvine, CA) and Dysport® (Ipsen). The present study was designed to evaluate retrospectively, the efficacy of BT-A injections in the treatment of various facial region disorders.

Materials and Methods

All cases presented here were selected among patients admitted to the Facial Movement Disorders Outpatient Clinic between 1996 and 2010. All of the patients filled out and signed an informed consent form. All patients who had received two or more BT-A injections and had been followed for at least one year were included in the study. At least a three-month interval would have to pass before another The BT-A injections were performed with at least a three-month interval.

The distribution of patients according to diagnosis was as follows: Hemifacial spasm (HFS), blepharospasm (BP), facial synkinesis, oromandibular dystonia (OMD), Meige syndrome, hypersalivation, apraxia of eyelid opening, bruxism and masseter hypertrophy, hemimasticatory spasm, chin tremor and others.

At each injection session, patients were questioned about the results of the previous session. Patients' medical charts were reviewed for the treatment sessions and used to collect the following information; mean onset of effect, mean duration of effect, amount of improvement, mean doses of BT-A and side effects. The changes in the level of benefit for the treatment were scored as follows; insufficient (less than 25% symptom relief), moderate improvement (25-49% symptom relief), good improvement (50-74% symptom relief), and marked improvement (75 - 100% symptom relief). Patients who reported no improvement or a short-lasting benefit had their BT-A dose increased according to their individual needs. Two preparations of BT-A (Botox® and Dysport®) were used. Prior to injection, one vial of Botox® was reconstituted with 2 or 4 ml of 0.9% sterile saline solution to yield toxin in concentration of 5 or 2.5 Unit (U) per 0.1 ml, respectively. Similarly, one vial of Dysport® was diluted with 2.5 ml of 0.9% sterile saline solution to yield toxin in a concentration of 20 U per 0.1 ml. Each treatment session consisted of multiple injections into single or multiple muscles. The injections in OMD patients were performed under electromyographic (EMG) guidance.

Results

A total of 182 patients (109 female, 73 male) were enrolled in the study. The mean age was 58±15 (range, 18-88) years. The mean duration of illness was 8±6 years (range, 1-35 years) and the mean follow-up period was 4±3 years (range, 6 months-14 years).

The most common diagnosis was HFS (92 subjects, 50.55% of patients), followed by BP, facial synkinesis, OMD, Meige syndrome and others.

There was a similar movement disorder in the families of 12 patients (6.6%). All subjects had brain magnetic resonance imaging (MRI) or brain computed tomography (CT). Vertebrobasilar dolichoectasia was observed in 17 patients with HFS and lateral bulbar infarction was detected in 1 patient with HFS. There was one patient with facial synkinesis due to multiple sclerosis (MS); MRI demonstrated MS plaques. MRI findings consistent with prior generalized hypoxic-ischemic encephalopathy were detected in one patient with OMD. Bilateral temporal atrophy, more prominent on the left side due to herpes simplex encephalitis, was seen in one patient with hypersalivation.

Fifty-five out of 182 patients (30%) were symptomatic. The essential demographic data are summarized in Table 1. Bilateral HFS was observed in 4 patients. Two patients with blepharospasm had anterocollis, one had writer's cramp, and another one had progressive supranuclear palsy (PSP). In the group of facial synkinesis, one patient had MS. In the Meige syndrome group, one patient also had palatal tremor, whereas another one had anterocollis. Two patients with OMD had also cervical dystonia, and another had generalized dystonia. In the group of hypersalivation, four patients had amyotrophic lateral sclerosis (ALS), two had idiopathic Parkinson's disease (IPD), and one had a history of herpes simplex encephalitis. Out of four patients with apraxia of eyelid opening, one had OMD, two had PSP, and one had IPD. All patients with hemimasticatory spasm also had morphea.

A total of 1494 injections were performed. Botox® was injected in 1423 sessions, and Dysport® in 71. Allmost all patients (181 patients) received Botox® at the first treatment. Nineteen patients (10.4%) shifted from one brand to the other due to either unsatisfactory clinical response to the treatment or the lack of availability of one of the two preparations.

The mean onset of effect after the injection was 8 days (range: 1-60 days). The mean duration of effect was 3.5 months (range: 1-26 months). The mean dose used per session was 33 Botox® U (2-180 U) and 150 Dysport® U (10-400 U).

Benefit rates varied according to the conditions diagnosed, with high rates in the treatment of HFS (88%), BP (91%), facial synkinesis (87%), and Meige syndrome (87%) and moderate in OMD and hypersalivation (65% and 61% of

Table 1. Demographic characteristics of the patients

Diagnosis	N (%)	Age* (year) mean±SD (range)	Gender M/F (N)	Duration† (year) mean±SD (range)	Follow-up (year) mean±SD (range)
HFS	92 (50.55%)	60±12 (29-84)	42/50	8±4 (1-23)	4±3 (1-11)
Blepharospasm	23 (12.64%)	62±13 (33-88)	11/12	9±6 (1-25)	5±4 (1-13)
Facial synkinesis	21 (11.54%)	44±14 (19-64)	4/17	6±6 (2-22)	4±4 (1-14)
OMD	11 (6.04%)	52±12 (31-66)	2/9	10±10 (1-33)	2±2 (1-6)
Meige syndrome	10 (5.49%)	68±10 (55-82)	1/9	12±10 (1-34)	5±4 (1-14)
Hypersalivation	7 (3.85%)	58±22 (18-86)	5/2	4±4 (1-12)	2±2 (1-6)
Apraxia of eyelid opening	4 (2.20%)	59±16 (40-79)	3/1	3±1 (2-4)	1±0 (1-1)
Bruxism and masseter hypertrophy	4 (2.20%)	31±10 (20-41)	2/2	7±4 (3-12)	2±2 (1-4)
Hemimasticatory spasm	3 (1.65%)	38±6 (33-44)	0/3	11±5 (7-16)	4±2 (2-6)
Chin tremor	3 (1.65%)	62±22 (37-79)	1/2	14±18 (3-35)	4±3 (1-6)
Others (tic disorder, essential palatal tremor, musicians' cramp)	2+1+1 (1.09%, 0.55%, 0.55%)	42±18 (24-61)	2/2	10±10 (4-21)	2±1 (1-3)

F= Female; HFS= Hemifacial spasm; M= Male; N= Number of patients, OMD= Oromandibular dystonia; SD= Standard deviation. *Age of the patients at the last visit. †Duration was the period from onset of the symptoms to the last visit

patients, respectively). Treatment results are summarized in Table 2. The efficacy rates were also high in the remaining, rare types of facial movement disorders (Table 3). A total of 169 (11.3%) adverse events were recorded in 1494 sessions. Twenty out of 169 side effects occurred with Dysport®, and the rate of adverse events was higher with Dysport® than Botox® treatment (28% vs. 10.4%). The most common adverse events were palpebral ptosis, weakness of mouth and eye closure and ecchymosis. Details of the adverse events are summarized in Table 4. The highest frequency of adverse events occured in patients with HFS (84 of 92 patients in 109 sessions), followed by patients with BP (19 of 23 patients in 26 sessions), and facial synkinesis (7 of 21 in 11 sessions). There were no serious adverse events.

Sixty-one (33.5%) out of 182 patients did not attend follow-up visits for more than 12 months. In these cases the patient was considered lost to follow-up. Reasons of treatment discontinuation are not known.

Table 1 (Continued). Demographic characteristics of the patients

Diagnosis	Etiology Symptomatic (N/%)	Family history (N/%)
HFS	18 (20%)	6 (7%)
Blepharospasm	3 (13%)	3 (13%)
Facial synkinesis	19 (95%)	0
OMD	1 (9%)	0
Meige syndrome	0	0
Hypersalivation	7 (100%)	0
Apraxia of eyelid opening	4 (100%)	0
Bruxism and masseter hypertrophy	0	1 (25%)
Hemimasticatory spasm	3 (100%)	0
Chin tremor	0	1 (33%)
Others (tic disorder,essential palatal tremor,musicians' cramp)	0	1 (25%)

F= Female; HFS= Hemifacial spasm; M= Male; N= Number of patients, OMD= Oromandibular dystonia; SD= Standard deviation. *Age of the patients at the last visit. †Duration was the period from onset of the symptoms to the last visit

Discussion

Botulinum toxin (BT) has been used in several movement disorders such as dystonia, spasticity, pain and some autonomic disorders (1). The non-cosmetic uses of BT-A play an important role in the management of a wide variety of facial disorders, especially HFS, facial synkinesis, strabismus, nystagmus, oscillopsia, blepharospasm, Meige syndrome, OMD, temporomandibular dysfunction and hypersalivation. Although many systemic drugs have been recommended in the management of movement disorders (1), they were either not effective or had frequent adverse effects. Therefore, BT-A should be considered as the first-choice treatment in patients with various facial movement disorders.

in the present study, we retrospectively analyzed the treatment results of 182 patients with facial movement

Table 2. Treatment data, by patient groups (common types)

Diagnosis	N	Onset of effect* (days) (mean, range)	Duration of effect (months) (mean, range)	Dose (U) (mean, range)
HFS	863	9 (1-60)	3.5 (1.0-12.0)	Botox®: 25 (5-59)
				Dysport®: 135 (10-280)
Blepharospasm	181	6 (1-60)	3.0 (1.0-15.0)	Botox®: 35 (18-87)
				Dysport®: 188 (30-400)
Facial synkinesis	139	6 (1-30)	3.6 (1.0-18.0)	Botox®: 13 (2-43)
				Dysport®: 40 (30-50)
OMD	56	8 (1-30)	3.0 (1.0-4.0)	Botox®: 65 (8-180)
				Dysport®: 240 (150-400)
Meige syndrome	141	6 (1-20)	3.1 (1.0-8.0)	Botox®: 46 (15-120)
				Dysport®: 234 (160-400)
Hypersalivation	25	6 (1-21)	2.5 (1.0-4.0)	Botox®: 79 (30-100)

HFS= Hemifacial spasm, N= Total number of injections, OMD= Oromandibular dystonia, U= Units
*Time until onset of effect

Table 2 (Continued) Treatment data, by patient groups (common types)

Diagnosis	Efficacy (%)	Side effects (%)
HFS	Marked: 67%	13%
	Good: 21%	(12% Botox®, 1% Dysport®)
	Moderate: 5%	
	Insufficient: 6%	
Blepharospasm	Marked: 72%	14%
	Good: 19%	(11% Botox®, 3% Dysport®)
	Moderate: 5%	
	Insufficient: 4%	
Facial synkinesis	Marked: 66%	8%
	Good: 21%	(7% Botox®, 1% Dysport®)
	Moderate: 9%	
	Insufficient: 4%	
OMD	Marked: 27%	13%
	Good: 38%	(9% Botox®, 4% Dysport®)
	Moderate: 11%	
	Insufficient: 25%	
Meige syndrome	Marked: 63%	10%
	Good: 24%	(9 %Botox®, 1% Dysport®)
	Moderate: 9%	
	Insufficient: 4%	
Hypersalivation	Marked: 50%	4%
	Good: 11%	(Botox®)
	Moderate: 6%	
	Insufficient: 34%	

HFS= Hemifacial spasm, N= Total number of injections, OMD= Oromandibular dystonia, U= Units
*Time until onset of effect

disorders and hypersalivation. The patients received a total of 1494 BT-A injections over a 14-year period.

There are many studies in the literature regarding the treatment of various types of facial movement disorders with BT. The total doses used per treatment are reported to be 11.2-46.7 U of Botox® (3-6) and 45-160 U of Dysport® in the management of HFS (3,5-9), while for blepharospasm, the average BT doses ranged from 6.25 to 30 Botox® U (4-6,8,10-12) and from 55 to 120 Dysport® U (5,6,8,9). Treatment of synkinesis with BT-A is described in studies with a limited numbers of patients; the average total doses were 7.5-22.5 U of Botox® and 40-120 U of Dysport® in synkinesis (13,14). The use of BT in patients with OMD is reported in various series; the average doses were 82-200 U of Botox® and 159 U of Dysport® in OMD (4,9,15,16). In previous series, the mean dose of BT used by Van den Bergh and Hsiung et al. to treat Meige syndrome was 110 Botox® U and 241 Dysport® U (9,15). Our findings are similar to those reported in the literature.

Several reports indicate a lack of correlation between the total injected BT dose and the clinical outcome. Van den Berg et al. noted that low-dose Dysport® can be an effective treatment modality for focal movement disorders and may help to avoid adverse effects (9). Furthermore, no differences in the response rate and duration of effect were found in patients with HFS receiving 15 or 25 U of Botox® (17). In two other long-term studies, the authors increased the doses of Botox® to provide a sustained effect with subsequent treatment sessions in various movement disorders (15,18). Bentivoglioa et al. (3) significantly increased the doses of Botox® over time, while the Dysport® dose remained unchanged in 108 patients

Table 3. Treatment data, by patient groups (rare types)

Diagnosis	N	Onset of effect* (days) (mean, range)	Duration of effect (months) (mean, range)	Dose (U) (mean, range)
Apraxia of eyelid opening	18	4 (1-15)	1.5 (1.0-3.0)	Botox®: 40 (25-125)
				Dysport®: 120 (120-120)
Bruxism and masseter hypertrophy	12	13 (1-30)	4.0 (2.0-6.0)	Botox®: 72 (50-120)
				Dysport®: 160 (160-160)
Hemimasticatory spasm	35	9 (1-45)	4.0 (1.0-10.0)	Botox®: 67 (25-110)
Chin tremor	16	11 (2-21)	7.0 (2.0-24.0)	Botox®: 53 (5-100)
Others (tic disorder, essential palatal tremor, musicians' cramps)	8	4 (1-8)	11.1 (1.0-26.0)	Botox®: 34 (10-70)

N= Total number of injections, U= Units. *Time until onset of effect

Table 3 (Continued) Treatment data, by patient groups (common types)

Diagnosis	Efficacy (%)	Side effects (%)
Apraxia of eyelid opening	Marked: 31.25%	No
	Good: 31.25%	
	Moderate: 12.5 %	
	Insufficient: 25%	
Bruxism and masseter hypertrophy	Marked: 33.3%	No
	Good: 55.5%	
	Insufficient: 11.1%	
Hemimasticatory spasm	Marked: 75%	No
	Good: 9.3%	
	Moderate: 9.3%	
	Insufficient: 6.25%	
Chin tremor	Marked: 57.1%	6.25%
	Good: 35.7%	
	Insufficient: 7.1%	
Others (tic disorder, essential palatal tremor, musicians' cramp)	Marked: 100%	No

N= Total number of injections, U= Units. *Time until onset of effect

Table 4. Patient-reported adverse events

Adverse effects	Botox®		Dysport®	
	N	% (out of 1423 treatments)	N	% (out of 71 treatments)
Ptosis	45	3.1	9	12.6
Weakness of mouth closure	31	2.1	7	9.8
Weakness of eye closure	24	1.6	3	4.2
Ecchymosis	21	1.4	0	
Dry eye	13	0.9	0	
Other weakness	11	0.7	0	
Dysphagia	2	0.1	0	
Irritation of conjunctiva	1	0.1	0	
Dry mouth	1	0.1	0	
Diplopia	0	0	1	1.4
Flu-like reaction	-	-	-	-

N= Number of injections

with HFS. In our study, the doses of BT were changed to take into account the individual needs of each patient, such as adverse effects and the degree of efficacy in each treatment session.

The mean duration of effect is reported to be 3-4 months in HFS (3,6,15,19-21), 2-4 months in BP (6,10-12,21-24), 3.5-4 months in synkinesis (13,14), and 3-4 months in OMD (16,20). In our study, the mean duration of effect was between 2.5 and 3.6 months in the common types of patient groups (3.5 months in HFS, 3.0 months in BP and OMD, 3.6 months in synkinesis, 3.1 months in Meige syndrome, and 2.5 months in hypersalivation). In the remainder of the patient groups with rare types, the effect was sustained long term. Our findings are in agreement with previous data. In the present study, the longest duration of action was observed in HFS and facial synkinesis, which may be attributed to the presence of subclinical denervation in HFS (25).

HFS and hemimasticatory spasms have a similar etiology. Based on clinical and electrophysiological studies, it has been concluded that both disorders originate from ectopic excitation due to focal demyelination (26,27,28). However, the site and cause of ectopic excitation are different; HFS is caused by aberrant tortuous blood vessels compressing the facial nerve at its exit from the brainstem, whereas hemimasticatory spasm is caused by compression or stretching of the distal mandibular nerve branch (27). In our three patients with hemimasticatory spasm, the mandibular nerve was affected by morphea.

In this study the success rate of BT-A treatment is between 75% and 100% in HFS, blepharospasm, and facial synkinesis (3,6,10-15,19-24,29). Similarly, the estimated efficacy rates of BT-A treatment for patients who reported marked and good improvement were above 75% for patients with HFS (88%), BP (91%), facial synkinesis (87%), and Meige syndrome (87%).

Numerous studies were published on the efficacy of BT-A in patients with OMD and hypersalivation reporting efficacy rates above 50% in OMD and hypersalivation patients (9,16,18,20,30,31,32). Hsiung et al. observed that the efficacy rate of BT treatment was 100% in jaw-closing dystonia (15). In our study, 65% of OMD and 61% of hypersalivation patients reported marked and good symptom relief. Although our findings are consistent with those published in the literature, the improvement rate was lower in our patients with OMD, possibly due to the relatively short duration of effect reported by these patients. Moreover, because of potential side effects, such as dysphagia and dysarthria, we avoided administering high-dose injections, and this may also be a reason for the lower success rate. There are few published studies reporting that EMG assistance was beneficial in the BT treatment of OMD (9,20,30). On the other hand, Tan et al. noted that BT was a safe and effective long-term treatment for OMD without EMG guidance (16). EMG control was used during the BT injections in OMD patients in our series. Although there is a debate over whether EMG is helpful in the treatment of OMD, we believe that EMG assistance seems to be beneficial in both selecting and targeting the muscles.

Previously, many studies were published on the long-term follow-up of patients who had received BT-A for 5 to 12 years. In some of these studies the authors observed that BT-A was an effective and a safe treatment for patients with HFS (3,19,33,36,35). Other studies showed many patients suffering from various movement disorders benefited from BT-A treatment (9,15,18). In one of them, Hsiung and colleagues showed that BT-A was a safe therapeutic agent and maintained its efficacy after long-term treatment of various types of movement disorders (15). Taylor et al. described that BT-A significantly decreased the symptoms in 235 patients with BP and in 130 patients with HFS during a 5-year period (36).

Our study investigated the clinical efficacy of BT-A in patients with various facial movement disorders and hypersalivation during a 14-year follow-up period. The study group consisted of a heterogeneous patient group and large numbers of patients. The major limitations of this study were the small number of patients in the rare types of movement disorders, overweight in HFS patients, and unequal follow-up periods in the patient groups.

In previous series, adverse effects were reported in approximately 30% of patients and mostly included ptosis, dry eye, facial weakness, diplopia, and weakness of masticatory muscles (15,18,19,26). A total of 169 (11.3%) adverse events were recorded in our series. We observed more adverse events with Dysport® than with Botox®. There are many studies comparing the efficacy of Botox® and Dysport® in clinical trials (29,32,36,37). The previous trials of BT-A preparations suggested that Dysport® tended to have a higher efficacy, a longer duration of effect than Botox®, but may have a higher frequency of adverse events. Dysport® is more diffusible than Botox® and when injected, reaches muscles a much farther distance from the injection site than Botox® (6,36).

Based on our current data, we conclude that BT-A is a safe and effective treatment for various facial region disorders, especially BP, HFS, facial synkinesis, Meige syndrome, and hypersalivation. The implementation of BT-A is easy and fast, and it can be applied in outpatient settings. If appropriate doses of Botox are used, the complication rate and complications in general are of a temporary duration.

Abbreviations

FDA: Food and Drug Administration; BT: botulinum toxin; BT-A: botulinum toxin type A; HFS: hemifacial spasm, BP: blepharospasm, OMD: oromandibular dystonia; EMG: electromyography;; MRI: magnetic resonance imaging; PSP: progressive supranuclear palsy; MS: multiple sclerosis; IPD: idiopathic Parkinson's disease; ALS: amyotrophic lateral sclerosis

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