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Long-term stable efficacy of botulinum toxin A in facial movement disorders with no need for increasing dose

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Abstract

Botulinum toxin A is considered an effective treatment for involuntary facial movements. We examined whether treatment efficacy maintained or changed over time with two products, Botox and Dysport, in patients with hemifacial spasm, facial synkinesis and benign essential blepharospasm.

We retrospectively investigated 87 consecutive patients (51 women, 36 men) who had undergone treatment for ≥6 years. Long-term effects, as well as side effects of Botox or Dysport local injections were evaluated. The first three treatments were considered the titration period and not taken into account when testing for dose changes.

Mean treatment duration was 10 years (range 6–11, SD 1.0), 2441 treatments were administered, 1162 with Botox and 1279 with Dysport, the two brands were interchanged as needed. Good to full improvement was seen in 90% of patients both with both brands. Injection doses and treatment responses were consistent during the study with both drugs. No major side effects were reported, and relatively few minor adverse events were reported, with clear reduction from the titration period (6.1%), to the remainder of the study (3.9%).

Botulinum toxin (BTX-A) is a satisfactory long-term treatment without need for dose increase over. Both Botox and Dysport were effective when used interchangeably.

Abbreviations: BEB = benign essential blepharospasm, BTX-A = Botulinum toxin A, FS = facial synkinesis, HFS = Hemifacial spasm, SD = standard deviation.

Keywords: blepharospasm, botox, dysport, hemifacial spasm, long term efficacy, stable dose, synkinesis

1. Introduction

Hemifacial spasm (HFS), facial synkinesis (FS) and benign essential blepharospasm (BEB) are common chronic involuntary facial movement disorders with different etiology and pathophysiology that cause social and communication discomfort and restrict work and daily living capability.[1,2]

Clinical manifestations of HFS include unilateral tonic or clonic contractions of facial expression muscles and orbicularis oculi. Onset is usually after the third decade of life, affecting women more often than men (2:1 ratio). Microvascular compression of the facial nerve root exit zone by posterior circulation arteries or, less common, at the internal auditory canal, has shown to be associated with hemifacial spasm. The condition is usually chronic and progressive and may cause patients significant social embarrassment and sometimes interfere with vision from involuntary eye closure.[3,4] Although there are microsurgery treatment options available, because of potential complications patients may prefer a less invasive treatment modality.[5,6]

FS results from abnormal, involuntary facial muscle contraction during voluntary facial movement of a different group of facial muscles. This phenomenon is seen after recovery from facial nerve injury. The exact cause of synkinesis has not been characterized definitively; the proposed mechanism is believed to be aberrant regeneration and sprouting of new facial nerve axons to facial muscular groups. This aberrant innervation results in unintentional movement in one area of the face during intentional movement in another facial area. For example, while smiling or laughing patients may unintentionally close their eye; or when blinking, mid-face spasms occur. Not only are these aberrant facial movements socially detrimental, patients also complain of pain and facial tightness due to these muscular spasms.[7–9]

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BEB is frequent in the fifth through sixth decade of life, affecting more women than men at a 3:1 ratio. Clinical findings include excessive blinking, photophobia, and persistent eye closure secondary to involuntary spasms and/or contractions of the orbicularis oculi and surrounding muscles. A majority of blepharospasm patients also have involuntary movements of the paranasal muscles, mouth, and jaw. The etiology of blepharospasm not known. Similar movement disorders can pharmacologically produce with levodopa and neuroleptic antipsychotic drugs, both acutely and after long-term therapy. A small number of patients with lesions of the rostral midbrain or caudal diencephalon report having movements akin to those in cranial dystonia. These findings lead to an etiology hypothesis of supranuclear disinhibition of the facial nucleus and brainstem reflexes. However, no specific abnormalities have been found in brain imaging or during autopsies in most patients with blepharospasm.[10]

Botulinum toxin A (BTX-A) local injections into the over-activated muscles have been shown to be effective in treating HFS, FS and BEB and other dystonias.[11–13] Repeated injections that are needed over time raise questions about the long-term efficacy of treatment and the need to increase the dose over the course of treatment. Failure of response to repeated injections of BTX-A has been reported. Findings implicate various reasons for occurrence of such failure, including antibody production against botulinum toxin domains, diversities in immunogenicity of different brands of BTX-A, and a failure of the blocking acetylcholine docking process and release.[14,15] Changing treatments to different formulations of botulinum toxin A has been suggested as one way to overcome primary or secondary treatment failure.[16]

We hypothesized that the continuous, long-term treatment with BTX-A using both products with exchanges between them for HFS, FS and BEB, can maintain efficacy without dose increase needed and with a low incidence of adverse events.

2. Methods

This retrospective cohort study included patients with HFS, FS and BEB, whose treatment and follow up was conducted in our movement disorders clinic between 2003–2015, after the approval of the medical center's IRB committee.

The study's inclusion criteria were:

1. Diagnosis of HFS, FS, or BEB
2. 18 years of age or older
3. Minimum of six years of treatments and follow-up
4. Minimum of two botulinum toxin treatments per year.

Patients were excluded if they had less than six consecutive years of treatment and fewer than two treatments per year.

The injection pattern and frequency of treatments were modified according to the patient response.[16,17] The two-botulinum toxin A brands were interchanged as needed, given that the two products were not always found in the clinic at the same time. Therefore, we had to switch between Botox and Dysport regardless of the clinical response, and according to the conversion ratio of 1:4 Botox:Dysort.

Treatment assessment was evaluated by using a five-points Likert scale (0–4) for treatment response in the following form: point 0= no response; point 1=mild response; 2= moderate response; point 3= good response and point 4= excellent response. These were reported and documented during doctor visits or by telephone. Side effects were also reported and documented by the patients during doctor visits or by telephone.[18,19]

Chi square tests were used to compare the frequency of side effects and treatment response between the treatments and time periods.

Table 1

Demographic data: total of 87 patients, most of them women, with age average onset of illness around 50 years.

Disorder	Patients (%)	Female (%)	Initial mean Age range (yr)
HFS	42 (48)	22 (52)	52
BEB	26 (30)	18 (69)	69
FS	19 (22)	11 (57)	58
Total	87 (100)	51 (59)	59

HFS = Hemifacial spasm, BEB = benign essential blepharospasm, FS = facial synkinesis.

3. Results

Eighty-seven patients, 51 females and 36 males, met the inclusion criteria for the study. There were 42 patients with HFS, 19 patients with FS and 26 patients with BEB. Patient average age was 59.5 (range 18–83, SD 11.5) at initial treatment and 69.8 (range 27–92, SD 11.5) at last treatment (Table 1). The mean number of visits per patient was 28.8 (range 15–48, SD 6.4), and the mean interval between visits was 136 days (SD 45.8). The average duration of treatment was 10 years (range 6–11, SD 1.0). Overall, 2441 treatments were administered during 2503 visits throughout the follow up period, 1162 (47.6%) of them with Botox and 1279 (52.4%) with Dysport.

Eight patients (9.2%) received only Botox and nine patients (10.3%) only Dysport, while 70 patients (80.5%) shifted from one brand to the other as needed, including ten patients with more than one shift (Table 2).

Using the five-point Likert scale for treatment response, none of the patients scored 0, in score 1 there were 24 (2.2%) Botox and 29 (2.5%) Dysport treatments, in score 2 there were 12 (1.1%) Botox and 14 (1.2%) Dysport treatments, in score 3 there were 78 (7.2%) Botox and 76 (6.4%) Dysport treatments, while in score 4 there were 965 (89.4%) Botox and 1061 (89.9%) Dysport treatments. Improvement maintained over time without increasing dosages (Table 3 and Fig. 1). There was no statistical difference in the degree of improvement between the two treatments ($P=.88$).

Side effects decreased from 6.1% during visits 1–3 that was considered the titration period, to 3.9% ($P=.09$) in visit 4 through the end of the study which was considered the follow-up period, with no difference between Botox and Dysport (Table 4)

Table 2

Distribution of Botox/Dysport injections by type of disease.

Disorder	Botox	Dysport	Both	> one shift
HFS	5	4	33	5
BEB	2	3	21	3
FS	1	2	16	2
Total	8	9	70	10

HFS = Hemifacial spasm, BEB = benign essential blepharospasm, FS = facial synkinesis.

Table 3

Treatment response evaluated by the 5 points of Likert scale from 0 to 4.

Treatment response by Likert scale	Botox	Dysport	Total
Point 0	0	0	0
Point 1	24 (2.2%)	29 (2.5%)	53
Point 2	12 (1.1%)	14 (1.2%)	26
Point 3	78 (7.2%)	76 (6.4%)	156
Point 4	965 (89.4%)	1061 (89.9%)	2026
Total	1079	1180	2259*

* (Response was missing for some treatments).

4. Discussion

Botulinum toxin type A (BTX-A) is one of seven neurotoxin serotypes used in the treatment of various types of dystonia include facial dystonia.[20] The onset effect of BTX-A usually occurs several days after injections with 3–4 months duration of clinical improvement thereafter. A small proportion of patients who fail to demonstrate an improvement following BTX-A starting at the onset of treatment are known as 'primary non-responders', while others who show decreased response after repetitive treatments are known as 'secondary non responders'. A possible reason for the latter group's non-response may be partially due to production of circulating antibodies directed against BTX-A along the treatment.[21,22] This reduction in efficacy raises the need for dose increase in order to maintain a good effect over time[23–27], though the frequency of immunogenicity by blocking antibodies was markedly decreased from about 10% when the original Botox was used to frequency of only 1% with current BTX-A products.[22] The antigenicity of BTX-A remains a serious concern and the main reason for the recommendation to avoid frequent injections in intervals shorter than 3 months.

Our retrospective study, showed long term effective response to BTX- A using of one product or the substitute, in which doses did not change over time, during a follow-up period of almost 10 years excluding the titration phase. Excluding this phase of treatment resulting in long-term efficacy of the BTX-A without the need for dose escalation. Czyz et al use this method and found that treatment dosage remained unchanged for a long-term follow up of 19.4 years in 37 patients of facial dystonia.[28] We also found that the long-term clinical improvement percentage is 90% for an average duration of 10 years, which is higher in comparison to the average of 75% found in other studies.[25]

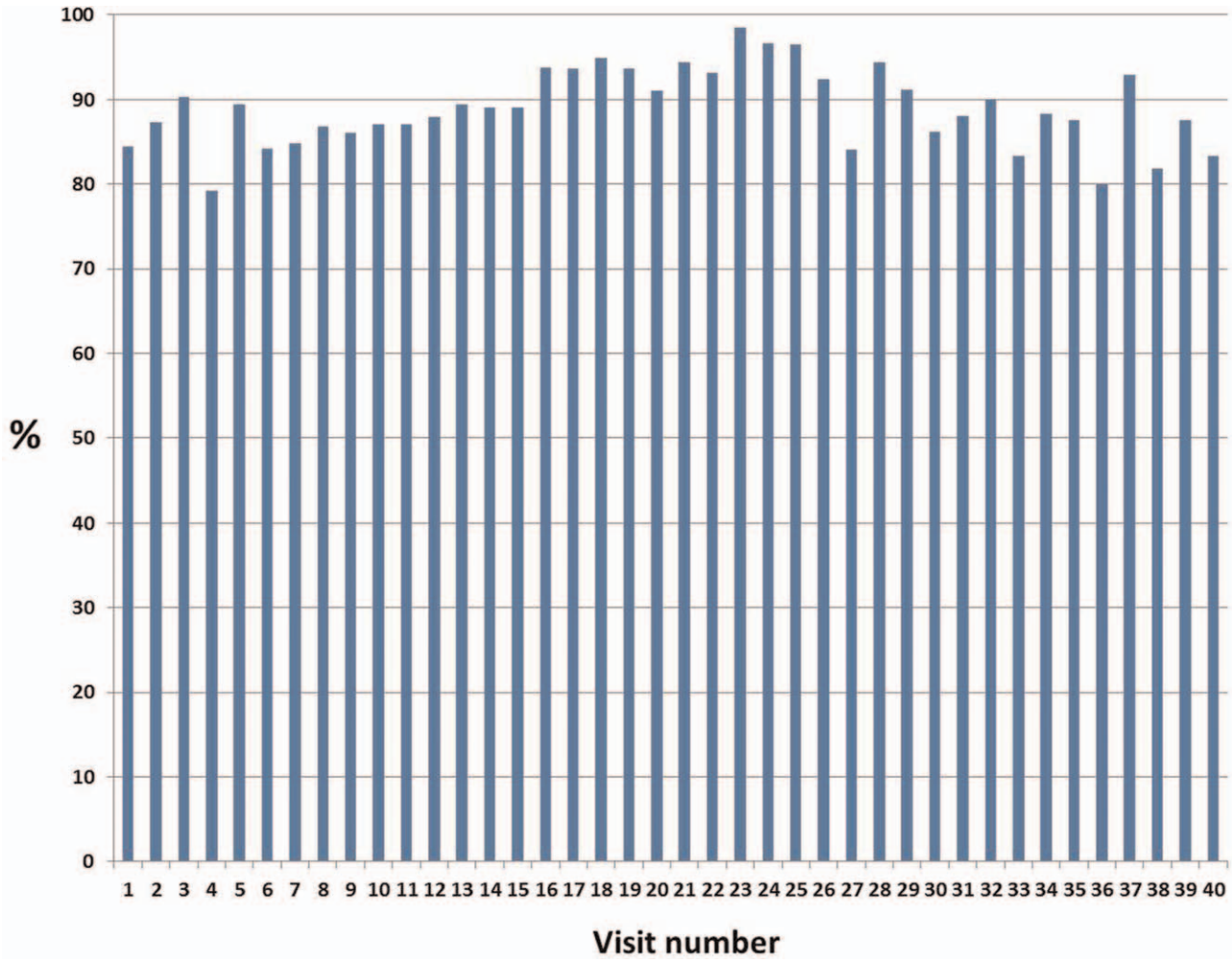

Figure 1. Percent with full improvement by visit number.

Table 4

Side effects of BTX-A decreased from titration period during follow up period ($P = .09$).

Visit number	No. of participants	Any side effect	Specific side effects
1–3 (Titration period)	261	16 (6.1%)	Lacrimation 3 (1.1%) Diplopia 2 (0.8%) Ptosis 4 (1.5%) Hematoma 1 (0.4%) Drooling 1 (0.4%) Over weakness 5 (1.9%)
4-th through end (Follow-up period)	2242	88 (3.9%)	Dry eye 3 (0.1%) Lacrimation 24 (1.2%) Diplopia 7 (0.3%) Ptosis 33 (1.6%) Hematoma 9 (0.4%) Drooling 13 (0.6%) Over weakness 5 (0.2%)

The conversion ratio of 1:4 Botox-Dysort in face dystonia was based on several double-blind studies where it was found that the therapeutic effect and the side effects in this ratio conversion are identical in both products.[29–32]

Switching from one preparation to another can also be effective for clinical improvements and maintaining efficacy of treatment over time, as was found in a previous study where treatment was shifted from Botox to Dysport in patients with blepharospasm and hemifacial spasm when Botox treatment failed.[16]

In this study no serious local or systemic side effects were noted by BTX-A as in the majority of previous studies reported before.[33,34] Patients reported minor adverse events which declined from 6.1% in the titration phase to 3.9% through the long term follow- up, and that is consistent with a previous study focusing on the safety of botulinum toxin therapy and support observations that the highest percentage of side effects occurs during the titration phase of treatment.[26] Transient ptosis, lacrimation and diplopia were the most common adverse events seen in our patients, which is also consistent with previous studies.[9,19,27] Most complications of BTX-A injections, such as ptosis and diplopia, are thought to be due to local effects and unwanted diffusion of the biologic activity neurotoxin into adjacent muscles.

Although BTX-A is one of the most potent toxins, when used by knowledgeable and skilled clinicians it is remarkably safe, even after years or decades of treatments.

In summary, our study showed that BTX-A is a satisfactory treatment for long-term therapeutic response in patients with HFS, FS and BEB, using interchangeable products of both formulations. Long-term treatment was shown to be safe, with a small percentage of minor adverse effects that subside with time, and with efficacy maintained over the years without the need to increase the dose of treatment.

Author contributions

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