

Outcome predictors, efficacy and safety of Botox and Dysport in the long-term treatment of hemifacial spasm

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Background and purpose: To review the clinical characteristics and the long-term outcome of patients with hemifacial spasm (HFS) who received botulinum neurotoxin (BoNT) over the past 10 years. **Results:** A total of 108 patients received 665 treatments. Mean latency of clinical effect was 5.4 ± 5.3 days for Botox and 4.9 ± 4.6 days for Dysport ($P > 0.05$). Mean duration of clinical improvement was higher after the injection of Dysport than Botox: 105.9 ± 54.2 and 85.4 ± 41.6 days respectively ($P < 0.01$). The percentage of treatment failures was 6.5% for Botox and 4.6% for Dysport ($P > 0.05$). The doses of Botox significantly increased over time ($\beta = 0.35$, $P < 0.001$) whilst Dysport dose remained unchanged ($\beta = 0.16$, n.s.). The duration of clinical benefit slightly increased with Botox ($\beta = 0.12$; $P < 0.01$), but remained constant for Dysport. Side effects occurred in 17.4% of treatments: 16.7% of patients who had received Botox, and in 19.7% who had received Dysport ($P > 0.05$). The most common side effects were palpebral ptosis and lacrimation; ptosis and lagophthalmos was more common in Dysport treatments ($P < 0.005$). **Conclusions:** Both brands are effective and safe in treating HFS; efficacy is long-lasting. The differences in outcome and side effects confirm that, albeit the active drug is the same, Botox and Dysport should be considered as two different drugs.

Introduction

Hemifacial spasm (HFS) typically presents with unilateral, involuntary, intermittent and irregular clonic or tonic contractions of the cranial muscles supplied by the facial nerve [1]. The twitching movements usually start in the orbicularis oculi, gradually spreads to other ipsilateral facial muscles, frequently involving also the frontalis and the platysma muscles [2]. HFS is frequently attributed to the compression of the facial nerve at the root exit zone by an ectopic anatomical or pathological structure resulting in axo-axonal 'ephaptic' transmission and increased excitability of the facial motor nucleus [2]. Peripheral facial nerve injury or antecedent Bell's palsy can also precede HFS; in such cases, the HFS often coexists with mild ipsilateral facial weakness and synkinesis [3]. HFS is unilateral in most cases, but may rarely occur bilaterally [4].

Hemifacial spasm is a chronic disorder and may have a severe impact on the patient's appearance, moreover as it persists during sleep, it may lead to insomnia. As spontaneous remissions are infrequent [5], most patients need to be treated for many years, if not lifelong. Treatment option is aimed at reducing or stopping muscular twitches, and includes botulinum neurotoxin (BoNT) injections, medications, neurosurgery and, more recently, doxorubicin chemomyectomy [6].

During the last two decades, BoNT injections have emerged as the first-choice option for HFS [7–9]. Two randomized controlled trials [10,11] and more than 30 open studies, encompassing over 2200 patients, have been published. The majority of these studies report on small series of patients, but several long-term observations of large cohorts confirm the safety and efficacy of this treatment [5,7,12–16]. However, a recent Cochrane meta-analysis concluded that future study 'should explore different BoNT formulations, long-term efficacy, safety, and immunogenicity' [17].

The present study was designed to evaluate retrospectively the outcome predictors, the efficacy and safety of the treatments performed with Botox and

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Dysport in a large series of HFS patients during a 10-year period.

Materials and methods

Patients

Amongst patients attending the movement disorders clinic of Gemelli Hospital in Rome from 1986 to 2003, we included all subjects with HFS who received two or more consecutive treatments with BoNT-A. Exclusion criteria were: previous surgical treatment, unavailability of complete clinical data, treatment with neuroleptics or other drugs interfering with eyelids function.

Treatments

At the first visit, patients were interviewed on their medical history and underwent a full neurological evaluation. All treatments were performed by one of the authors (TI, ARB, and AA). Two preparations of BoNT-A were injected: Dysport (Ipsen, Ltd., Slough, Berkshire, UK); Botox (Allergan Inc, Irvine, CA, USA). The manufacturer's instructions were followed. Both toxins were reconstituted into sterile, preservative free 0.9% saline solution and injected within 4 h from reconstitution. About 500 U Dysport were diluted in 2.5 or 5 ml of saline solution to yield toxin in a concentration of 20 or 10 U per 0.1 ml, respectively. Around 100 U Botox were diluted in 2 or 4 ml of saline solution to yield toxin in a concentration of 5 or 2.5 U per 0.1 ml, respectively. Higher dilutions were preferred to enhance the effect of the BoNT with lower doses, whilst a higher concentration was used to avoid side effects due to the diffusion of BoNT (Table 1) [18].

Injections were performed subcutaneously according to standardized procedures; the dose varied according to the severity of patient's spasm. The orbicularis oculi muscle was injected (in orbital or pre-tarsal portion) in three or four point (medial and lateral side of upper and lower eyelids close to palpebral rim) [19]. If hyperactive, the extra-orbicular muscles were also injected. Usually,

in the first treatment session only the periocular regions were injected. Later, if required, additional sites were treated to control the spread of contractions: the medial eyebrow, the procerus, the corrugator, the frontalis muscle or the paranasal portion of the zygomaticus major muscle. If HFS involved the lower face, at least in the first treatment session, BoNT injections were placed only in the upper face, because it has been recognized that this may be sufficient to control lower facial spasms [5,7]. However, if lower facial muscles were very active or if there was residual mouth contraction following periocular treatment, targeting the orbicularis oris, the levator angularis, risorius, buccinator, depressor anguli oris was considered.

The starting dose varied amongst patients and was successively adjusted according to the severity of spasm, the response to previous treatments and the occurrence of side effects. Patients were asked to annotate latency, size, duration of efficacy and the occurrence of adverse events (latency, duration, and severity).

Design and outcome measures

This was designed as a longitudinal retrospective study; all patients who satisfied the inclusion criteria were included. For each treatment, the following data were recorded: date of treatment; brand used (Botox or Dysport); total dose and dilution; sites injected (orbicular/extra-orbicular muscles) and number of BoNT injections. Response to BoNT was inferred on the basis of the patient's interview considering the perception of relief, interview of spouses or next-of-kin.

Response was assessed by two variables: latency, defined as the interval (days) between injection and the first sign of improvement and total duration of improvement, defined as the interval (days) between the first report of improvement (latency) and the last day of reported benefit. Patients were instructed to report the occurrence of side effects: type, duration and severity.

Statistical analysis

Demographical data were expressed as mean $\pm$ SD (range). The analysis of the severity and treatment response scores was performed by means of ANOVA and *t*-test to compare the mean of continuous variables of sample in exam (age at onset, age at last evaluation, years of disease duration and follow up) and between the different treatments, (dose and occurrence of side effects, dilution and occurrence of side effects). Fisher's exact test was used to compare the categorical variables (male to female ratio, occurrence of side effects and occurrence of treatment failure). The Pearson test was

Table 1 Types and directions of shifts from one brand to the other

Number of shifts	Direction	Number of cases
1	B $\rightarrow$ D D $\rightarrow$ B	12 2
2	B $\rightarrow$ D $\rightarrow$ B	5
3	B $\rightarrow$ D $\rightarrow$ B $\rightarrow$ D	10
4	B $\rightarrow$ D $\rightarrow$ B $\rightarrow$ D $\rightarrow$ B	1
5	B $\rightarrow$ D $\rightarrow$ B $\rightarrow$ D $\rightarrow$ B $\rightarrow$ D $\rightarrow$ B $\rightarrow$ D	1

B, Botox; D, Dysport.

used to correlate the continuous variables (dose and dilution versus duration of treatment). The linear regression analysis and the repeated measure ANOVA were used to assess the time course of dose and duration of clinical benefit. In this computing, the first 10 treatments from the whole sample were considered suitable. The test was considered significant when the P value was <0.05 .

Results

Amongst patients with HFS treated with BoNT, 108 patients (37 males and 71 females) had received two or more consecutive treatments, and had complete clinical data. All of them underwent brain magnetic resonance imaging (MRI): in eight cases (7.4%) a neuro-vascular conflict (defined as the compression of the facial nerve at the root exit zone by an atherosclerotic, aberrant or ectatic intracranial artery) was detected. Twenty subjects (18.5%) reported Bell's palsy before the occurrence of HFS. None underwent EMG of facial muscles. Mean age at onset was 54.1 ± 13.9 years (24–86); 52.8 ± 9.8 and 58.9 ± 15.7 respectively in men and in women (ns). The mean disease duration was 7.9 ± 5.4 years (1–26) with a mean follow up of 4.7 ± 3.0 years (0–11). At the last medical evaluation, the mean age of patients was 65.4 ± 14 years (29–92).

A total of 665 treatments were performed; each patient received an average of 6.2 ± 5.5 (2–30) injections. Botox was injected in 492 sessions, Dysport in 173. Almost all patients (99/108) received Botox at the first treatment. At the latest treatment, 28 patients were injected with Dysport, 80 with Botox. Thirty-one patients (28.7%) shifted from one brand to the other due to: (i) unsatisfactory clinical response to the treatment (34.9%), (ii) occurrence of side effects (24.2%), (iii) unavailability of one of the two preparations in the remaining cases (Table 1).

The mean dose used per session was 11.2 ± 4.9 Botox U (1–50) and 46.5 ± 18.9 Dysport U (8–130). The analysis of repeated consecutive treatments revealed an increase of doses for Botox ($\beta = 0.35$, $P < 0.001$) whereas Dysport doses remained unchanged ($\beta = 0.16$, n.s.) (Fig. 1). Different ratios between the mean doses used along the time have been found with a value ranging from 2.8 to 5.2 (Fig. 1). Different dilutions were used (Table 2).

Mean latency of clinical effect after the injection was 5.4 ± 5.3 days (0–40) for Botox and 4.9 ± 4.6 days (0–30) for Dysport (n.s.). The duration of effect was longer for Dysport than for Botox: 105.9 ± 54.2 days (0–480) compared with 85.4 ± 41.6 days (0–330; $P < 0.001$). Forty treatments (6.0%) were unsuccessful whilst a successful outcome was reported in 94% of

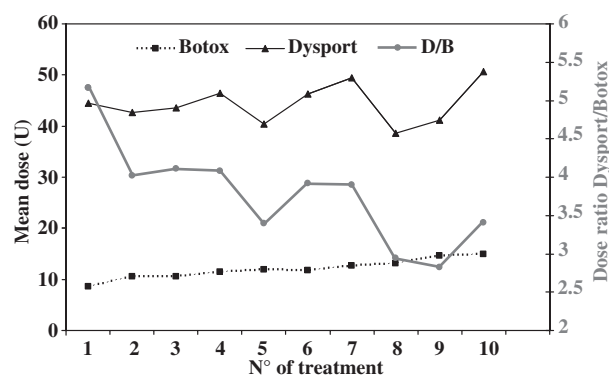


Figure 1 The analysis of 10 consecutive treatment from the whole sample revealed an increase of dose for Botox ($\beta = 0.35$, $P < 0.001$) whilst Dysport dose remained unchanged ($\beta = 0.16$, n.s.). Different ratios between the mean doses used along time ranged from 2.8 to 5.2.

Table 2 Dilutions used

BTX (no. treatment)	Dilution (ml of saline solution)	No. treatment	%
Botox (492)	4	485	98.6
	2	7	1.4
Dysport (173)	2.5	101	58.4
	5	72	41.6

treatment sessions (93.5% with Botox, 95.4% with Dysport, n.s.).

No correlation between dose and duration of benefit was found, nor between BoNT dilution and therapeutic outcome. After repeated treatments, the duration of clinical benefit slightly increased with Botox ($\beta = 0.12$; $P < 0.01$), and remained constant with Dysport (Fig. 2).

Side effects occurred in 116 of 665 sessions (17.4%) with comparable incidence for the two toxins (16.7% of Botox treatments and in 19.7% of Dysport treatments, n.s.). The most common side effects were: palpebral ptosis and lacrimation; ptosis and lagophthalmos were more common after Dysport treatments ($P < 0.005$) (Table 3). No correlation was found between the dose injected or dilution and the occurrence of side effects, either with Botox or with Dysport; however a trend was observed for Dysport dilution and incidence of side effects: we found that 24.6% of treatments using a dilution of 5 ml led to a side effect whilst it occurred in 13.4% of treatments with 2.5 ml. No patient discontinued treatment because of side effects, confirming the safety of BoNT treatment. The most relevant features of treatments performed with Botox and Dysport are summarized in Table 4.

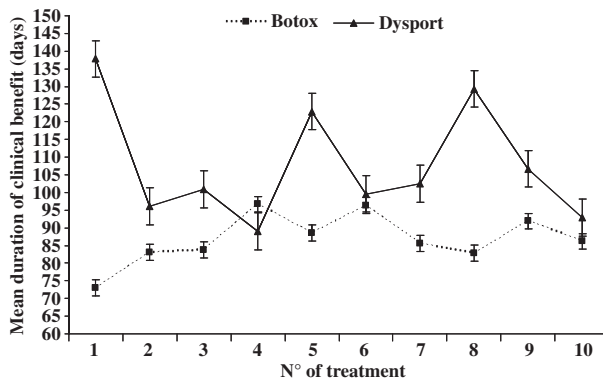


Figure 2 The longitudinal analysis of the mean duration of clinical benefit for 10 consecutive treatments from the whole sample showed that the duration of clinical benefit slightly increased with Botox ($\beta = 0.12$; $P < 0.01$), but remained constant for Dysport.

Table 3 Side effects occurred in 116 of 665 sessions (17.4%) with comparable incidence with the two toxins (16.7% of Botox treatments and in 19.7% of Dysport treatments, P : n.s.)

Side effect	Botox	% (out of 492 treatments)	Dysport	% (out of 173 treatments)
Ptosis	16*	3.2	15*	8.7
Lacrimation	21	4.3	3	1.7
Irritation of conjunctiva	14	2.8	1	0.6
Hematoma	12	2.4	3	1.7
Blurred vision	9	1.8	2	1.2
Lagophthalmos	2**	0.4	8**	4.6
Diplopia	6	1.2	4	2.3
Dry eye	3	0.6	2	1.2
Palpebral edema	3	0.6	1	0.6
Other	1	0.2	1	0.6

* $P = 0.0036$; ** $P = 0.000136$.

Table 4 Features of treatments performed with Botox and Dysport

	Botox	Dysport	P
No. treatments	492	173	–
Patients treated in first session	99/108	9/108	–
Patients treated in last session	80/108	28/108	–
Mean dose used (U)	11.2 $\pm$ 4.9 (1–50)	46.5 $\pm$ 18.9 (8–130)	–
Mean latency (days)	5.4 $\pm$ 5.3 (0–40)	4.9 $\pm$ 4.6 (0–30)	n.s.
Mean duration of benefit (days)	85.4 $\pm$ 41.6 (0–330)	105.9 $\pm$ 54.2 (0–480)	0.0000004
% of sessions failed	6.5	4.6	n.s.
% of adverse reactions	16.7	19.7	n.s.

Discussion

The present study evaluated retrospectively 665 treatments with Botox and Dysport in a series of 108 HFS

patients during a 10-year period. Demographical data and clinical history of the patients are comparable with all previous observations: the percentage of patients with Bell's palsy is comparable to the published rates ranging from 5% [2] to 22.4% [20]. Unintended hemifacial mass contractions can occur as a result of muscle synkinesis in patients with previous Bell's palsy. The spasms reported by these patients may mimic those observed in HFS, but, usually, a careful clinical and neurophysiological examination permits separation of both entities. In HFS, the involuntary twitches of the muscles of one hemiface are not necessarily triggered by voluntary or automatic muscle contraction. This finding is a crucial differential sign with respect to the mass contractions of the postparalytic facial syndrome, which are always started by intended muscular contraction [21]. On the other hand, despite the large majority of patients was diagnosed as primary HFS, the frequency of neurovascular compression as detected by MRI resulted quite low. This could be explained, at least in part, by the outpatient setting, the retrospective design, and different MRI equipments or protocols (e.g. use of angiographic sequences).

In this series, a mean dose of 11.2 Botox U and 46.5 Dysport U was injected. Other authors reported average doses ranging from 10 to 46 Botox U [7,22], and from 53 to 160 Dysport U [23]. Several reports indicate a lack of correlation between the total dose injected and clinical outcome: the effect of treatments in the 'low-dose' Dysport protocol did not differ from standard dosages [24]; furthermore, no significant difference in the response rate and duration of improvement were found in patients receiving 15 or 25 Botox U [25]. Similar discrepancies were reported also by others [26]. In another paradigm, Botox doses were increased to provide a sustained effect with subsequent treatments [15,16]. Alternatively, a slight, albeit not significant (from 17.5 to 15.9 Botox U), dose reduction was reported after 10 years [14]. In two studies using Dysport a dose reduction was observed after the seventh consecutive treatment [27] and a 25% reduction was reported after 5 years [24]. Similarly, in the present long-term series, Dysport dose did not change whilst Botox dose increased by about 73%.

We did not observe any resistance to the treatment: all patients had sustained benefit, some of them up to 11 years. Patients with HFS have the lowest incidence of resistance to treatment, probably due to the low dosages used [28]. No secondary failures were reported in one series [29] and an incidence of 0.9% per year was reported in another series [15]; furthermore, no evidence of immunoresistance was reported in a series of 110 patients [2]. Primary failures were estimated to be 0.02% [27] or 1.4% per year [15], the lowest

amongst different movement disorders treated with BoNT.

No data about dilution of BoNT are available, and in several studies a wide range of dilution was considered. In this series, we used mostly standard dilutions and no clear correlations have been found between BoNT dilution and therapeutic outcome. When comparing the therapeutic proprieties of the two brands we found no difference in latency which, in line with previous reports (from 2.6 [30] to 5.4 days [2]) was about 5 days. In approximately 5% of treatments, patients reported an immediate improvement after the injection, probably due to a mechanical effect of the liquid injected into the muscle or to placebo effect. Most treatments (35%) led a clear benefit within 2 days.

The success rate of BoNT treatment has been estimated between 75% [13] and 100% [7,31], with a reliable estimate around 95%, as reported in two long-term studies [14,15]. The rate in our series (94% of sessions, 93.5% for Botox and 95.4% for Dysport) largely overlaps the most frequently reported rates.

Mean duration of benefit of 106 days (Dysport) and 85 (Botox) is comparable with previous data: 90 days, range 75 [32]–196 days [33]. In our series, the efficacy and duration of clinical benefit increased along time significantly only for Botox probably paralleling the significant increase of dose. From previous studies we learn that benefit duration may increase [14,16,34], decrease [25] or remain unchanged [12,27,29,35,36] with repeated treatments. The benefit generally lasts longer in HFS than in dystonic patients despite the use of smaller doses [15,22,30,35,37]. The longer improvement may be due to a subclinical denervation present in HFS: as a matter of fact, many patients suffering from primary HFS display a mild eyelash sign even before BoNT treatment probably due to neurovascular compression. It has been hypothesized that disuse atrophy may occur in the facial muscles with repeated BoNT injections; but histological studies failed to support this hypothesis [33].

Exceptionally, a few patients reported a very long-lasting benefit (up to 11 – Botox–and 16 – Dysport). The cause of this ‘long-lasting’ effect is unclear, and might be considered a spontaneous remission similarly to those described as uncommon yet possible (3–4% in three different series [5,14,25]).

Side effects complicated 17.4% of treatments. In other series they occur in approximately 30% of patients, mostly consisting of erythema or ecchymosis of the injected region, dry eyes, mouth droop, ptosis, oedema or facial weakness [6]. These complications are transient and usually resolve within 1–4 weeks. Earlier studies reported a high frequency of ptosis (up to 53%) with an overall mean of approximately 12% [35,36],

probably due to diffusion of the toxin to the levator palpebrae superioris muscle. Lagophthalmos and ptosis were more common in Dysport treatments probably due its property of be more diffusible from site of injection than Botox. Mild symptoms of exposure keratitis (lacrimation and irritation of conjunctiva, occurring respectively in 3.6% and 2.3% of all treatments) are presumably an aftermath of decreased blink rate and incomplete eye closure from a partial paralysis of the orbicularis oculi muscles. In several series, the most frequently reported side effect was facial weakness, involving 75% [32], 95% [25] or 97% of cases [11]. In the present series, such side effect was infrequent probably because the injections were rarely performed in mid- and low-facial sites [34]. In another series, 11.6% of the patients with facial weakness had received injections in the lower face, whereas a negligible portion of patients treated in the orbicularis oculi muscle had this complication [35]. As most patients report marked improvement of peribuccal spasms even when lower facial muscles are not directly injected [28,37], caution must be taken before injecting these sites. Despite we did not found any association, a positive correlation between dose and occurrence of side effects has been reported by others [14,24,25].

Comparison between Botox and Dysport

An appropriately powered class II study compared Dysport and Botox in a parallel design without placebo-control or blinded raters with a dose ratio of 4:1. The primary end-point (duration of action) and other end-points (number of booster doses needed, latency of effect, clinical efficacy and frequency of adverse reactions) were similar for the two products [38]. In our experience, it is difficult to compare the two BoNTs used since the study was more powered for Botox; however, when considering the benefit duration and the rate of treatment failure, Dysport provided a longer benefit duration than Botox; on the other hand, Dysport caused more frequently side effects. These statistically significant differences might be related to the low Botox doses injected during the first treatments thus leading to an undertreatment in some patient: as a matter of fact, either doses or duration of clinical benefit significantly increased over time only for Botox. However, no correlation between dose and duration of benefit or occurrence of side effects emerged amongst patients with HFS as well as with blepharospasm (A.R. Bentivoglio, unpublished observations). Both our study and other data support the view that Botox and Dysport are two different drugs.

Although Botox and Dysport namely contain the same chemical substance (confirmed by the observation that the two BoNTs have the same potency given the

identical conditions both *in vivo* and *in vitro* studies [39]), they are different in terms of manufacturing (e.g. methods of extraction, diluents and stabilizers used, volume of injection recommended) [40]. An interesting finding is that Dysport produces intrinsically more swallowing problems than Botox when injected into cervical muscles [41]. According to our data, Dysport has a different spectrum of side effects as it causes more frequently ptosis and lagophthalmos. This might be because of the fact that Dysport is more diffusible than Botox and when injected with an identical technique it reaches more distant (and sometimes unwanted) targets. On the other hand, this may explain the better outcome observed with Dysport. Nevertheless, it should be acknowledged that also the different volumes used to inject Dysport and Botox might have contributed to the differences in outcome and spectrum of side effects between the two toxin formulations.

One limitation of the present study is represented by the fact that three different injectors performed the treatments: it is well known that even slight technical differences may lead to marked differences in the outcome; however, we are confident that the large sample size and the random assignment to one of the injector may partially have solved this bias.

In conclusion, a real bioequivalence between Botox and Dysport might not exist due to the intrinsic difference in pharmacokinetic properties between these products, and a conversion factor should be considered only indicative of a ratio on the magnitude of clinical improvement.

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Conflict of interest disclosure

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