OnabotulinumtoxinA (Botox®) and AbobotulinumtoxinA (Dysport®) in Treating Essential Blepharospasm: Long Term Results

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ABSTRACT

Objective: To compare the clinical characteristics and outcomes of patients with blepharospasm who were treated with OnabotulinumtoxinA (Botox®) and AbobotulinumtoxinA (Dysport®).

Methods: A total of 100 eyes of 78 patients who were diagnosed with blepharospasm were evaluated during a retrospective, randomized, parallel group study. The severity of spasm, eyelid closing force, and functional visual status scores were used as quantitative measures of the change in clinical status. Side effects (ptosis, dry eye, ocular foreign body sensation, headache, eyelid edema, pain, and ocular irritation) were collected using a systematic questionnaire.

Results: Both Botox® and Dysport® groups produced similar clinical efficacy and tolerability. Success rates at 4 weeks post-injection were 91.8% in the Botox® group and 90.1% in the Dysport® group. With respect to success rates, no statistically significant difference was detected between groups. In the Botox® group, 2 years of follow-up was completed in 41 eyes. Success was achieved in 36 eyes (87.8%). In the Dysport® group, 2 years of follow-up was completed in 44 eyes. Success was achieved in 38 eyes (86.4%). The difference was not statistically significant ($p>0.05$). There were no clinically relevant differences between Botox® and Dysport® groups with regard to safety parameters. Both Botox® and Dysport® were effective and safe in treating blepharospasm.

Conclusion: This study suggests that both Botox® and Dysport® do not differ from each other in terms of potency and adverse reaction profile. *(JAREM 2016; 6: 110-4)*

Keywords: AbobotulinumtoxinA, botox, essential blepharospasm, dysport

INTRODUCTION

Blepharospasm (BS) is a disabling neurological condition that is characterized by uncontrollable, repetitive eyelid closure because of involuntary contractions of the orbicularis oculi muscles. Although it may sometimes be briefly unilateral at onset, the condition is usually bilateral (1). The most common form of BS, benign essential BS (EBS), is considered to be a result of abnormal functioning of the basal ganglia (1, 2). BS typically insidiously begins in the 5–7th decade of life, and there is a female preponderance (2). The condition generally progresses over several years. In its most severe form, BS results in depression, anxiety, and a substantial negative impact on the quality of life. Furthermore, of all pre-treatment patients, approximately 12% are considered blind because of their illness (3).

Clostridium botulinum produces seven structurally and immunologically distinct botulinum toxin (BTX) forms (A–G). Currently, two of these seven serotypes are commercially available: type A (Botox®, Dysport®, Xeomin®, and CBTX-A®) and B (Myobloc®/NeuroBloc®). BTX development has markedly altered BS treatment (4). When BTX is injected into overactive muscles, acetylcholine release is inhibited at the neuromuscular junction, which results in reduced contractions. Recently, the Therapeutics and Technology Assessment Committee of the American Academy of Neurology concluded that there is level B (probably effective) evidence for the efficacy of BTX type A therapy for BS treatment (5). However, even when different commercially available toxins are from the same class, the potency difference among them may be confusing. Two pharmaceutical preparations are commonly available: Botox® (OnabotulinumtoxinA), of American origin, and Dysport® (AbobotulinumtoxinA), from Britain. Botox® and Dysport® are both serotype A BTXs but carry different characteristics of biological activity (6). Potency of both is expressed in LD50 mouse units; however, the assay differences make the units inequivalent. Head-to-head randomized trials comparing Botox® with Dysport® revealed that these two drugs were not bioequivalent, with a Botox®/Dysport® conversion ratio of between 1:3 and 1:5 commonly used in clinical practice (7).

This study aimed to compare the efficacy and safety of Botox® and Dysport® in EBS treatment.

METHODS

Study Design

This was a prospective, randomized, parallel group comparison study.

This study included 100 eyes that were examined between 2008 and 2015. A written informed consent form, which was approved by the ethical committee of our institution, was collected from all

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participants. The patients were randomly divided into two groups. Of 38 patients in the Botox® group, 49 eyes were included, while of 40 patients in the Dysport® group, 51 eyes were included. We included 100 eyes that were examined between 2008 and 2015. Using computer-assisted randomization, patients with EBS who were treated in our center were randomized to receive an injection of either Botox® (Allergan, USA) or Dysport® (IPSEN, France). A standard SAS® program was used to generate the random allocation sequence and to number the vials, which provided a unique identifier for each subject receiving the administered treatment. Patients who had a confirmed clinical diagnosis of EBS requiring treatment by injection were included in the study. None of the patients had received BTX injections prior to this study. Patients were excluded if they had an atypical variant of BS that was caused by inhibition of the levator palpebrae muscle, myasthenia gravis, Lambert–Eaton syndrome, amyotrophic lateral sclerosis, or any other significant neuromuscular disease. In addition, patients with known alcoholism or other drug abuse, those suffering from severe or uncontrolled systemic diseases, or those who were pregnant or breastfeeding were excluded. Participants were expected to understand and comply with the study requirements and provided written informed consent. This study was conducted according to the Declaration of Helsinki and was approved by the appropriate ethics authority. The patients were evaluated on the first day, after 1 month, and at 3-month intervals after the treatment.

Surgical Procedure

Five min after the injection before the application of povidone iodine with ice application areas marked with cotton applicator with 0.1 mL of a 27 gauge needle. Injections were made. Botox® was injected at 2-mm above the eyelash of the upper eyelid and 1-mm below the eyelash of the lower eyelid, with injection points both on the inner and outer surfaces. The latter injection was administered at the nasoglabellar region that was directed at the corrugator and procerus muscles. Moreover, injections were administered at lateral aspects of the lower and upper eyelids and through the junction between preseptal and orbital parts of orbicularis oculi muscles. Thus, Botox® was injected at two superolateral and two inferolateral injection points, totaling to 10 points. Dysport® was medially injected at 2-mm above the eyelash of the upper eyelid and 1-mm below the eyelash of the lower eyelid. Furthermore, injections were subcutaneously performed lateral to the upper and lower eyelids through the junction between the preseptal and orbital parts of orbicularis oculi muscles. The latter injection was administered at the nasoglabellar region that was directed at the corrugator and procerus muscles. Thus, injections were administered at a total of six points. While administering injections, we took care not to direct the needle toward the levator muscle; a cotton applicator was simultaneously pressed on the skin that corresponded to the margin of the levator muscle. The patients were cautioned against rubbing the eye or any water contact.

The initiative doses were determined as follows: for Botox® a diluent of 4.0 mL 0.9% sodium chloride per vial was added, resulting in a dose of 2.5 IU/0.1 mL; for Dysport® a diluent of 2.5 mL 0.9% sodium chloride per vial, giving a dose of 20 IU/0.1 mL. Total initiative doses for one eye were 25 IU for Botox® and 120 IU for Dysport®. The maintenance doses were determined as follows: for Botox® a diluent of 2.0 mL 0.9% sodium chloride per vial was added, resulting in a dose of 5 IU/0.1 mL; for Dysport® a diluent of 4 mL 0.9% sodium chloride per vial, giving a dose of 12.5 IU/0.1 mL. Total maintenance doses for one eye were 50 IU/3 months for Botox® and 75 IU/2 months for Dysport®.

Outcome Measures

Pre- and postinjection data of biomicroscopic examinations, presence of a corneal defect, eyelid abnormalities (ectropion, entropion, and ptosis), visual acuities based on Snellen scale, Schirmer's test results, and intraocular pressures were recorded. Changes in clinical status were measured using the functional rating scales. Clinical follow-up for both groups was maintained for 2 years. The severity of spasm was clinically graded from grade 0 to 4 (Table 1) (8, 9). The primary efficacy outcome was assessed as the number (%) of patients with an improvement in the severity of spasm of more than one grade at 4 weeks post-injection. Other outcome measures included the eyelid closing force (CF) and functional visual status (FVS) at 4 weeks post-injection (Table 1) (8, 9).

Side effects (ptosis, dry eye, ocular foreign body sensation, headache, eyelid edema, pain, and ocular irritation) were recorded throughout the study.

Table 1. Scoring definition for severity of spasm, eyelid closing force, and functional visual status

Severity of spasm
Grade definition:
0 No spasm
1 Mild spasm at stimulation only
2 Visible spasm without impairment of daily life
3 Visible spasm with impairment of daily life
4 Severe Spasm with impairment of daily life
Eyelid closing force
Grade definition:
1 Flaccid
2 Overcome with minimum resistance
3 Overcome with moderate resistance
4 Normal strength
Functional visual status
Grade definition:
1 Functional blindness
2 Dependent; unable to go out alone
3 Poor function; unable to watch TV, read, or drive
4 Moderate function; unable to read but able to work
5 Inconvenience; intermittent discomfort but able to drive and work
6 Normal

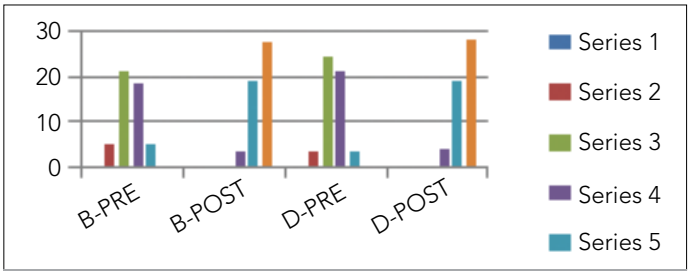

Figure 1. Distribution of severity of spasm scores (grade 0–4) pre-injection and at 4 weeks post-injection in the Botox® and Dysport® groups

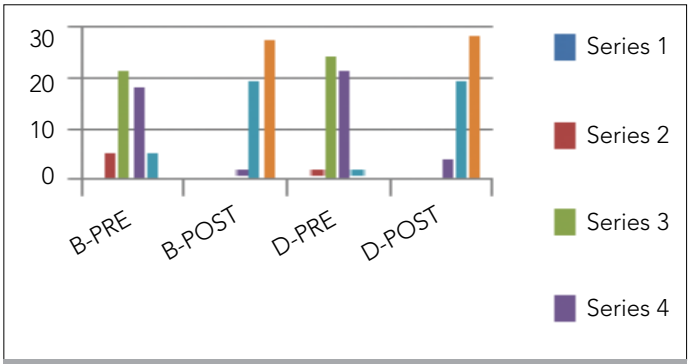

Figure 2. Distribution of eyelid closing force scores (grade 1–4) pre-injection and at 4 weeks post-injection in the Botox® and Dysport® groups

Table 2. Adverse effects in the Botox® and Dysport® groups

	Botox® n=49	Dysport® n=51
Ptosis	1 (2%)	2 (3.9%)
Dry eye	1 (2%)	0
Ocular foreign body sensation	1 (2%)	2 (3.9%)
Headache	1 (2%)	0
Eyelid edema	0	0
Pain	1 (2%)	1 (1.9%)
Ocular irritation	0	1 (1.9%)
Total	5 (10.2%)	6 (11.8%)

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences software (SPSS version 16.0 for Windows Inc; Chicago, IL, USA). All differences that were associated with a probability of ≤0.05 were considered statistically significant. Student t-test, Chi-square test, and Mann–Whitney U test were performed for nominal data.

RESULTS

A total of 100 eyes of 78 patients (41 males, 37 females) with EBS who met the eligibility criteria for the study were randomized for treatment with Dysport® or Botox®. Forty-nine eyes (38 patient) were randomized in the Botox® group, while 51 eyes (40 patient) in the Dysport® group. There were no significant differences between groups with regard to demographic variables (p>0.05).

The patients' mean age was 52.1±9.8 years in the Botox® group and 51.7±10.4 years in the Dysport® group. The mean doses of Botox® per treatment were 27.5 (25–30) U and those of Dysport® were 125 (100–130) U. The effect of Botox® lasted for 12.6 (10–15) weeks, while the effect of Dysport® lasted for 8.3 (7–10) weeks.

At baseline (i.e., before BTX injection), there were no significant differences between groups with regard to severity of spasm, eyelid CF, and FVS scores (p>0.05).

In the Botox® group, the severity of spasm score (pre-injection; mean±SD, 3.8±0.9) significantly improved at 4 weeks post-injection (mean±SD, 1.1±1.2; p<0.001). In the Dysport® group, the baseline severity of spasm score (pre-injection; mean±SD, 3.4±1.3) also significantly improved at 4 weeks post-injection (mean±SD, 1.6±0.8; p<0.001) (Figure 1).

Pre–post eyelid CF scores: The difference in mean scores of eyelid CF at pre-injection and 4 weeks post-injection was 2.6±0.5 and 2.7±0.5 for the Dysport and Botox groups, respectively. No statistically significant difference was detected between groups (p=0.683; Figure 2).

Pre–post FVS score: The difference in mean scores of FVS at pre-injection and 4 weeks post-injection was 0.2±0.9 and 0.1±0.7 for the Dysport and Botox groups, respectively. No statistically significant difference was detected between groups (p=0.498).

Success rates at 4 weeks post-injection were 91.8% and 90.1% in the Botox® and Dysport® groups, respectively. No statistically significant difference was detected between groups with respect to success rates. In the Botox® group, 2 years of follow-up was completed in 41 eyes, with success achieved in 36 eyes (87.8%). İn the Dysport® group, 2 years of follow-up was completed in 44 eyes, with success achieved in 38 eyes (86.4%). The difference was not statistically significant (p>0.05).

There were no clinically relevant differences between Botox® and Dysport® with regard to the safety parameters. Side effects were observed in five of 49 eyes (10.2%) that were treated with Botox® and in six of 51 eyes (11.7%) that were treated with Dysport® (Table 2). Ptosis was observed in one case (2.04%) with Botox® and in two cases (3.92%) with Dysport®. The total number of side effects and the rate of occurrence of ptosis were lower with Botox® than with Dysport®, although the difference was not statistically significant (p=0.432 and p=0.324, respectively) .

DISCUSSION

BTXs continue to be the primary symptomatic treatment for EBS, a disorder for which there is currently no cure. BTXs are biological products that are derived from bacteria and are manufactured using a complex series of steps that may substantially influence their clinical profiles. Consequently, the application of different methods may result in clinical differences with regard to efficacy, adverse events, and/or unit dosing. Both Botox® and Dysport® are serotype A BTXs but differ in their characteristics. In this study, we attempted to compare the clinical characteristics and the outcome of patients with EBS who were treated with Botox® or Dysport®. The results of our study confirm that there is no difference between the two BTX preparations with regard to efficacy, frequency of side effects, and occurrence of ptosis.

Although controlled trials are yet to be conducted, there are many studies that report dramatic improvements in patients with BS when proper dosages and technique are used. Review of available data from 55 studies including >2500 patients and data of the American Society of Ophthalmology have reported an almost 90% success rate (10). Furthermore, several studies report an improvement in the quality of life after BTX treatment (11).

While most physicians consider BTX to be the most effective treatment for BS, a Cochrane review regarding BTX-A did not find any suitable studies that met their criteria for inclusion (12). In 1985, Fahn et al. (13) reported the results of eight patients with BS who were injected with 10 units of BTX-A in one eye and saline in the other. Electrophysiological measurements revealed that patients who received active treatment improved to a greater degree. Sampaio et al. (14) conducted a single-blind, randomized comparison and reported that there were no differences between Botox® and Dysport® in terms of duration of effect (primary endpoint) or adverse events (14). Using a double-blind crossover design, Nüssgens and Roggenkämper (15) studied 212 consecutive patients with BS, comparing Dysport® and Botox®, and stated that the duration of the effect was identical in both groups. The rate of side effects that were caused by Botox®, particularly ptosis, was significantly low. Therapeutic uses of Botox® and Dysport® were also compared in other disease states. Vergilis-Kalner (16) reported that while treating axillary hyperhidrosis, they observed similar effects; however, Botox® exerted a more rapid and prolonged effect. Bentivoglio et al. (17) stated that both Botox® and Dysport® were effective and safe in treating BS. Bihari (18) indicated that Botox® had long-term and reliable therapeutic effects. However, Ranoux et al. (19) reported that Dysport® was more effective with the risk of higher potential for adverse effects (19).

An understanding of muscular anatomy is critical to ensure optimal results. Various injection techniques have been advocated to optimize the response to BTX. In general, BTX is superficially injected over the orbicularis oculi to decrease deeper perfusion. The corrugator and procerus muscles are intramuscularly injected. The orbicularis oculi is commonly injected at five locations, with an initial total dose of approximately 12.5–20 U of Botox® per eye (4, 20). The standard treatment techniques involve injection into four sites around each eye with two in the upper lid, one medially, and one laterally near the canthus. Two additional injection sites in the lower lid, one at the lower lateral canthus, and one near the middle of the lower lid appear to prolong the effects compared with those in the eyebrows, inner orbital, and outer orbital (21). Avoiding injection into the central part of the lower lid also helps decrease entropion and sagging of the lower lid (4). The injection techniques used in this study were selected to maximize efficacy and minimize adverse effects.

Adverse effects with BTX are transitory and include dry eye, ptosis, lagophthalmos, and diplopia with dry eye being the most common (20, 22, 23). Patients with previous blepharoplasty are for times more likely to develop ptosis compared with unoperated patients (4). According to Scott et al. (4), scarring and partial removal of the orbicularis oculi may affect the absorption and diffusion of the drug, thereby possibly weakening the levator palpebrae and resulting in ptosis (4). Accoridng to the findings of a randomized, double-blind study of 26 patients with BS, Frueh et al. (24) suggested avoiding toxin injection in the "medial two thirds of the lower eyelid" to prevent diplopia from inferior oblique weakness. The adverse effects found in this study were similar to those previously reported in the literature (25, 26). No differences were noted in the frequency of adverse effect between the Botox® and Dysport® groups. In a series of Price (21), a 12% incidence of ptosis was reported. In our patient group, post-injection ptosis was observed in one case in the Botox® group and two in the Dysport® group. Two cases who developed ptosis were elderly patients with loose subcutaneous tissues. For the development of ptosis in the last patient, injection directed toward the levator muscle was held responsible. Compression with a cotton applicator on the margin of the levator muscle prevents the entry of the solution into the levator muscle.

Being a randomized, controlled design is the strength of this study. The main limitation of our study is the relatively small size of our series. Another challenge with studies that compare BTXs is the biological nature of these medications. According to the European Medicines Agency, biological medicinal products are typically more complex and difficult to characterize than chemically derived medicinal products. Potency tests are specific to each product, with each manufacturer conducting the test according to its own internal specifications, including the use of different diluents. Thus, any attempt at comparing two products should consider the biological nature of BTXs and their intrinsic differences (27-29). Chundury et al. (30) demonstrated patients that in the treatment of BES was more effective (30).

CONCLUSION

This study suggests that both Botox® and Dysport® do not differ from each other in terms of potency and adverse reaction profile.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Training and Research Hospital (2011).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.E.Ö.; Design - F.N.; Supervision - Z.K.; Resources - F.E.Ö., F.N.; Materials - K.E.; Data Collection and/or Processing - K.E., F.E.Ö.; Analysis and/or Interpretation - F.N., K.E.; Literature Search - K.E., Z.K.; Writing Manuscript - F.E.Ö.; Critical Review - Z.K., K.E.

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