Botulinum toxin A, a neurotoxic protein produced by *Clostridium botulinum*, is being utilized by clinicians to decrease muscle hyperactivity for a multitude of therapeutic and cosmetic symptoms ranging from cervical dystonia to glabellar rhytids. Its use accounted for more than 25% of nonsurgical aesthetic procedures in the United States in 2008.¹ There are eight serotypes of the toxin, synthesized as a single-chain polypeptide protoxin and “nicked” by proteases to activate binding at nerve terminal receptors. Once bound to synaptic receptor SNAP-25, the toxin inhibits release of acetylcholine, thus causing muscle paralysis.

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At the time of this study, two commercial preparations of botulinum toxin A had been approved by the US Food and Drug Administration (FDA) for cosmetic use. Initially studied for therapeutic uses in animals, BoNT-A was the first FDA-approved neurotoxin. It was originally named Ocullum, but this was later changed to onabotulinumtoxinA (BoNT-ONA; Botox, Allergan, Inc., Irvine, California). It found applications in the treatment of strabismus, blepharospasm, and facial spasm. BoNT-ONA is currently FDA-approved for the treatment of cervical dystonia, severe primary axillary hyperhidrosis, strabismus, and blepharospasm as well as for the temporary improvement in the appearance of glabellar wrinkles. The second compound, abobotulinumtoxinA (BoNT-ABO; Dysport, Ipsen Ltd, Slough, UK), has been approved for the treatment of cervical dystonia and glabellar wrinkles. Several randomized, placebo-controlled, double-blind studies showed its effectiveness prior to approval.

BoNT-ONA and BoNT-ABO differ in the carrier protein attached to the 150-kDa botulinum toxin A protein molecule. Although BoNT-ONA contains a 900-kDa carrier protein attached to the toxin, a 750-kDa carrier exists in BoNT-ABO. Despite the differences in molecular weights, no differences in diffusion times or efficacy have been shown in vivo between the two formulations.

We found few studies comparing the onset of action, duration of action, or efficacy of these two formulations of botulinum toxin A in the literature. We sought to compare the characteristics of the two formulations through side-by-side comparison in the same subject—in effect, using each patient as his or her own control. In this report, we present the results of a randomized, controlled comparison of the onset of action, duration of action, and efficacy of BoNT-ONA and BoNT-ABO in the treatment of forehead, glabellar, and periorbital wrinkles.

METHODS

Study Design and Protocol

This double-blinded, randomized, controlled clinical trial was conducted in a private plastic surgery clinical office setting in Pittsfield, Massachusetts. A multidisciplinary Institutional Review Board at Berkshire Medical Center approved the protocol. Fifty-three subjects were enrolled in the study. Eight were smokers, and 26 had undergone treatment with BoNT-ONA in the past. Both men and women between the ages of 20 and 90 with glabellar and/or periorbital wrinkles (crow’s feet) were eligible to participate in this study. Pregnancy or plans to become pregnant were considered exclusion criteria. Other excluded patients included those with known cardiovascular or neuromuscular disorders, dysphasia, history of recent facial infections, allergies to milk proteins or albumin, or current aminoglycoside therapy. Patients who had undergone BoNT-ONA or BoNT-ABO treatments within the previous six months were also excluded. In addition, patients on any blood-thinning medications were excluded to minimize injection site bleeding complications.

Each study participant attended an initial informational session. At this session, an overview of the study, along with the inclusion and exclusion criteria and other pertinent information, was provided. Each participant was required to have read and understood detailed study consent prior to participation in the study. The patients understood that injections outside of the glabellar region were considered an off-label use. After reviewing and signing the consent, study participants underwent a treatment session, followed by nine subsequent evaluation sessions. The treatment session was considered Day 0 of the study.

At the treatment session, Day 0, pretreatment photos were taken of each patient, and an initial wrinkle analysis was conducted with the Visia complexion analysis system (Canfield Imaging Systems, Fairfield, New Jersey). Digital photos were taken in a studio setting against a standard blue background with uniform flash shots on a Nikon D80 camera (Tokyo, Japan) with a Nikkor lens (Tokyo, Japan) set at a lens angle of 135 mm, exposure of 1/25 of a second, and F-stop of 16. For the Visia analysis, each patient was placed with the chin resting on the bottom of the machine (as opposed to the chin rest, as recommended by the manufacturer) in order to focus on the upper half of the face. Each patient’s head was also slightly angled so as to perform analysis on each half of the face separately.

The two botulinum preparations were diluted with sterile saline so that 1 mL of solution contained either 25 units of BoNT-ONA or 62.5 units of BoNT-ABO. This ratio of 1:2.5 BoNT-ONA:BoNT-ABO was based on the manufacturer’s insert provided with both products; BoNT-ONA instructions recommended 20 units to treat the glabella, and BoNT-ABO recommended 50 units. Therefore, again, a total of 25 units of BoNT-ONA were injected into one side and 62.5 units of BoNT-ABO on the opposite side in standard predetermined areas (Figure 1) in an equal volume of 0.6 mL. This 1:2.5 BoNT-ONA:BoNT-ABO ratio was chosen based on previously published effective doses of these medications. We used equal volumes to negate volume dispersal differences.
Injections were performed after EtOH prep, with BoNT-ONA injected into half of the upper face and BoNT-ABO into the other half. Although in a clinical setting, variable dosing regimens based on muscle mass and depth of wrinkles are most appropriate, for the purpose of this study, we chose a fixed-dosage regimen to eliminate injector variability. All treatments were administered by a board-certified plastic surgeon, with patients randomly assigned to each of two plastic surgeons (BMM, GAC). A coin toss was used to randomly assign the side of the face to receive BoNT-ONA as follows: “heads” meant that BoNT-ONA was injected on the right side, whereas “tails” meant that BoNT-ONA was injected on the left. Patients were blinded to the laterality of treatments. Areas treated on each patient included forehead frown lines, the glabellar area, and crow’s feet. Areas treated were marked on a facial diagram, along with which treatment had been injected into each side of the face (Figure 1).

Each patient was required to return for nine subsequent sessions on posttreatment Days 2, 3, 4, 7, 90, 105, 120, 135, and 150. Digital photographs and wrinkle evaluations were also performed at each session. Each patient was required to complete an evaluation form beginning on Day 7 and every subsequent session thereafter, detailing his or her opinions on observed differences in facial appearance.

Data Collection

Digital photos were uploaded to the Mirror photo analysis software system (Version 7.2; Canfield Imaging Systems). The photos were then graded on the Mirrorphoto system, with pictures taken when the patient was asked to look surprised or frown for facial animation. Forehead wrinkles were graded on the previously-described scale in the frontal view with the face at rest and when the patient was asked to look surprised. Glabellar wrinkles were also graded on the frontal view with the face at rest and after asking the patient to frown. Finally, periorbital wrinkles were graded on a 30-degree lateral view with the face at rest and frowning/squinting. Scores for each photo session were collated into a Microsoft Access database (Redmond, Washington) for subsequent analysis with Microsoft Excel. All patients also underwent Visia facial analysis at each session, and wrinkles detected by the Visia system were recorded as a single score for each half of the upper face. These scores were recorded for each session and also collected in a Microsoft Access database.

Clinical results are shown in Figures 3 to 5.

RESULTS

The 53 patients (one male and 52 females) treated in this study ranged in age from 34 to 65 years (average, 50). Outcomes were measured according to three different methods of assessment with results analyzed in Excel using the XL STAT program.

The eyebrow height for each subject’s right and left facial half was measured in centimeters by blinded evaluators. The change in height over time from Day 1 through Day 150 was not significantly different for BoNT-ABO versus BoNT-ONA, as confirmed by t-test and Wilcoxon signed t-test. There was no difference in the overall height between Day 1 (average, 2.5 cm) and Day 150 (average, 2.5 cm) with maximum effect seen at Day 7 (average, 1.7 cm), illustrating a return to baseline muscle action (Figures 6 and 7). We detected no difference in onset of action or duration between the agents affecting eyebrow motion.

The Fitzpatrick wrinkle grading scale was used to evaluate wrinkles through time in the forehead, glabellar, and periorbital regions. There was no significant difference found between BoNT-ABO and BoNT-ONA in terms of wrinkles. However, the modified Fitzpatrick wrinkle classification system to grade the appearance of wrinkles on a subjective scale as follows: Grade 0 was assigned to the absence of wrinkles, Grade 0.5 described a very shallow yet visible wrinkle, Grade 1 was a visible wrinkle with slight indentation, Grade 1.5 was assigned to a visible wrinkle and clear indentation less than 1 mm in depth, Grade 2 was a clearly visible wrinkle 1 to 2 mm in depth, Grade 2.5 was a prominent and visible wrinkle more than 2 mm and up to 3 mm in depth, and Grade 3 described a deep furrow appearing to measure more than 3 mm in depth (Figure 2). Photo grading was performed by two plastic surgeons and two general surgery residents (BMM, GAC, FNE, AR). All graders were blinded to the laterality of treatments during grading, and grading data were collected separately from treatment data. Patients were randomly assigned to one of the four graders, with each grader scoring all photo sessions for a particular patient. Each grader scored a total of 13 to 14 sets of photos.

Eyebrow height in the frontal view was measured with the Mirrormeasuring tool, with pictures taken when the patient was asked to look surprised or frown for facial animation. Forehead wrinkles were graded on the previously-described scale in the frontal view with the face at rest and when the patient was asked to look surprised. Glabellar wrinkles were also graded on the frontal view with the face at rest and after asking the patient to frown. Finally, periorbital wrinkles were graded on a 30-degree lateral view with the face at rest and frowning/squinting. Scores for each photo session were collated into a Microsoft Access database (Redmond, Washington) for subsequent analysis with Microsoft Excel. All patients also underwent Visia facial analysis at each session, and wrinkles detected by the Visia system were recorded as a single score for each half of the upper face. These scores were recorded for each session and also collected in a Microsoft Access database.

Clinical results are shown in Figures 3 to 5.
Figure 3. This 55-year-old woman is shown (A) with her face at rest on Day 0 (prior to treatment) and (B) at Day 150, when she demonstrates continued effects of treatment with both BoNT-ABO and BoNT-ONA.

Figure 4. The same patient shown in Figure 3 is shown with maximum brow elevation at (A) Day 0, (B) Day 2, (C) Day 3, (D) Day 7, (E) Day 120, and (F) Day 150.
of wrinkle grade (Figures 8-10). A Mann-Whitney two-tailed test was used in place of analysis of variance (ANOVA) to assess significance. There was no difference from Day 2 through Day 150 ($P < .05$) for BoNT-ONA and BoNT-ABO in the forehead and glabellar regions. No difference was seen in the periorbital region through Day 135, with equivocal results at Day 150. Of note, the overall wrinkle grade was less (average, 0.5) than the initial score on Day 1 (average, 0.8-0.9). This indicates a continued effect of BoNT-ONA and BoNT-ABO beyond the 150-day time course expected (Table 1).

The Visia computerized wrinkle grading system measured total wrinkles for the forehead, glabellar, and periorbital regions over time (Figures 11 and 12). There was no statistically significant difference seen in a change from baseline between BoNT-ONA and BoNT-ABO ($P < .05$) from Days 2 through 150, with the average number of wrinkles being 15 and 13 for BoNT-ONA on the respective days and 14 and 15 for BoNT-ABO on the same days. An overall decrease in the number of wrinkles on Day 150 compared to Day 1 also demonstrates the continued effect of BoNT-ONA and BoNT-ABO on wrinkle appearance at Day 150.

Patients were interviewed regarding adverse events. Specifically, patients were asked at each session if they experienced any of the following: flu-like symptoms, headache, pain at injection site, eyelid ptosis, visual field change, or allergic response. No patients reported any adverse events.

**DISCUSSION**

We found no statistically significant difference in the efficacy of BoNT-ONA versus BoNT-ABO in muscle function or wrinkle appearance using multiple methods of observation and measurement through 150 posttreatment days. The same efficacy was demonstrated for BoNT-ONA and BoNT-ABO using the dose ratio of 1:2.5 BoNT-ONA to BoNT-ABO recommended by the manufacturers. With current pricing of BoNT-ONA at $525 per 100 U and BoNT-ABO at $475 per 300 U, BoNT-ABO costs $1.58 per unit, whereas BoNT-ONA is $5.25 per unit. With equal efficacy, there is a clear cost benefit to BoNT-ABO over BoNT-ONA.

The action of BoNT-ONA and BoNT-ABO on muscle function was shown to be statistically similar, with an overall return of muscle height to near-baseline values at the end of the 150-day time course. Both the Fitzpatrick scale and Visia wrinkle grading tools showed no statistical significance between the efficacy of BoNT-ONA and
BoNT-ABO. In fact, a continued measurable muscle weakness and aesthetic effect was demonstrated at Day 150. This indicates that the effects of both BoNT-ABO and BoNT-ONA last longer than the manufacturer-reported duration. Further analysis beyond our chosen end point (which was based on the recommended drug action) could reveal a longer duration of efficacy than previously reported.

Table 1. Percentage of Patients With Continued Aesthetic Effect

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Figure 8. Average forehead Fitzpatrick score over time (days) for BoNT-ABO (Dysport) and BoNT-ONA (Botox).

Figure 9. Average glabellar Fitzpatrick score over time (days) for BoNT-ABO (Dysport) and BoNT-ONA (Botox).

Figure 10. Average periorbital Fitzpatrick score over time (days) for BoNT-ABO (Dysport) and BoNT-ONA (Botox).

Figure 11. Visia (Canfield Imaging Systems, Fairfield, New Jersey) average overall number of wrinkles over time (days) for BoNT-ABO (Dysport) and BoNT-ONA (Botox).
The visual grading systems did demonstrate a continued efficacy beyond Day 150. The difference in the effect on muscle function and wrinkle visibility indicates that the aesthetic effect of each drug outlasts the paralytic effect. The paralytic effects of each drug are demonstrated in many of our eyebrow elevation images, as subjects compensate for their glabellar muscle paralysis by directing their gaze upward. There is potentially a delay between muscle contraction and wrinkle appearance on the skin. This could also be explained by edema from the injection in the skin. Like other authors, we found no differences in diffusion characteristics between the two agents.9

Other authors have noted a persistent aesthetic effect of botulinum toxin in 25% of patients.10 With a similar dosage, we found a much higher rate of persistent effect of both agents in the forehead and glabellar regions. Interestingly, over the same time period, we noted that a number of patients demonstrated worsening of the appearance of wrinkles in the periorbital region. This implies that weakening of the elevators of the forehead leads to some degree of ptosis and consequently compression of the periorbital tissues, causing worsening of wrinkles in some patients.

CONCLUSIONS

BoNT-ABO (abobotulinumtoxinA; Dysport) exhibits the same efficacy as BoNT-ONA (onabotulinumtoxinA; Botox) in reducing the appearance of wrinkles in forehead, glabellar, and periorbital regions at a lower cost to the consumer. Additionally, both drugs exhibit continued efficacy beyond 150 days.

Disclosures

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REFERENCES


Figure 12. Visia (Canfield Imaging Systems, Fairfield, New Jersey) change in wrinkles (number) over time (days) for BoNT-ABO (Dysport) and BoNT-ONA (Botox).