BOTULINUM TOXIN TYPE A IN THE TREATMENT OF DERMATOCHALASIS: AN OPEN-LABEL, RANDOMIZED, DOSE-COMPARISON STUDY

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Abstract

Objective: To compare the efficacy and safety of 2 doses of botulinum toxin type A in the treatment of dermatochalasis.

Methods: Forty patients with mild to moderate dermatochalasis were randomly assigned to receive 1 of 2 doses of botulinum toxin type A in the lateral infrabrow—4 U/brow or 6 U/brow—and followed up for 20 weeks.

Results: Investigator assessment showed the proportion of responders (≥1 grade improvement in severity of dermatochalasis on a scale of none, mild, moderate, or severe) at week 2 was 32% with 4 U and 47% with 6 U. Compared with the lower dose group, the higher dose group also reported a greater degree of improvement, significantly higher ratings for feelings of attractiveness and feelings of satisfaction with appearance, and a higher incidence of satisfaction.

Conclusion: Single-site injection of botulinum toxin type A in the lateral infrabrow can offer effective treatment for mild to moderate upper eyelid dermatochalasis.

Introduction

Dermatochalasis is a fold of skin in the eyelid that can develop with age and overhang the lid margin. Resulting from a loss of skin elasticity, weakening of connective tissue in the eyelid, and gravity, dermatochalasis is common in the elderly but can also occur in young adults. The upper eyelids are more likely to be affected than the lower eyelids and, besides affecting appearance, the condition can result in functional problems such as visual field obstruction, ocular irritation, reading difficulties, impairment of peripheral vision, blepharitis, and dermatitis. Upper eyelid dermatochalasis can also contribute to frontal headaches if patients chronically elevate their brows in an attempt to improve their visual field.

Although upper eyelid dermatochalasis can be treated successfully by blepharoplasty, not all patients are suitable candidates for surgery and others may be unwilling to undergo this procedure, especially if their condition is not severe. In recent years, reports have indicated that botulinum toxin type A is effective in elevating the brow in patients who desire a brow lift for cosmetic reasons.14 Botulinum toxin type A is approved by the US Food and Drug Administration for the treatment of moderate to severe glabellar lines,1 cervical dystonia,5 strabismus and blepharospasm associated with dystonia,4 and axillary hyperhidrosis.4 Weakening the brow depressor muscles (eg, the procerus, the corrugator supercilii, the depressor supercilii, and the orbicularis oculi) allows brow-elevating muscles to work unopposed, resulting in brow elevation along with an elevation of upper eyelid skin and a reduction in upper eyelid skin redundancy. Although the efficacy and safety of botulinum toxin type A injections in the periorbital region are already well-documented for the treatment of other conditions (eg, blepharospasm, glabellar lines, and crow's feet13), the clinical potential of botulinum toxin type A for the treatment of dermatochalasis has not been studied extensively. To further evaluate the efficacy and safety of this agent, we performed a comparison of 2 different doses of botulinum toxin type A in patients with mild to moderate upper eyelid dermatochalasis.

Methods

Patients

Patients were eligible to enroll in this open-label, randomized, parallel-group study if they were female and had mild to moderate dermatochalasis (assessed by the investigator on a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe). Patients were required to be 30 to 65 years of age and those of childbearing potential had to have a negative urine pregnancy test at the baseline visit.

Exclusion criteria included: a history of severe anxiety disorders that, in the investigators' opinions, may affect study compliance; a diagnosis of myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disease that may interfere with neuromuscular function; current use of an amnoglycoside antibiotic, curare-like agent, or other agent that might interfere with neuromuscular function; an allergy or sensitivity to botulinum toxin type A; therapy with any serotype of botulinum toxin in the preceding year; prior cosmetic procedures (eg, brow surgery, forehead surgery, or upper blepharoplasty) or visible scars that may affect the evaluation of treatment response or the quality of photography taken during the study; intermittent aesthetic or cosmetic brow treatments; and, if of childbearing potential, pregnancy, breastfeeding, and not using a reliable method of birth control.

The protocol was approved by the relevant institutional review boards and performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided signed informed consent.
Treatment
Patients were randomly assigned to receive treatment with 1 of 2 doses of botulinum toxin type A (Botox® Cosmetic, Allergan, Inc, Irvine, CA)—either 4 U per brow (total 8 U) or 6 U per brow (total 12 U). The 100 U of lyophilized botulinum toxin in each vial was reconstituted according to the manufacturer's recommendations except that 4 mL instead of 2.5 mL sterile non-preserved saline was used to obtain a concentration of 25 U/mL. The appropriate volume of the reconstituted toxin—0.16 mL for each 4-U dose and 0.24 mL for each 6-U dose—was drawn into a 1-cc tuberculin syringe (Becton, Dickinson and Company, Franklin Lakes, NJ) and then injected through a 30-gauge 0.5-inch needle (Becton, Dickinson and Company) into a single site in the orbicularis oculi muscle in each lateral infrabrow. No post-treatment manipulation of the injection site was performed by the physician or the patient.

To identify the correct injection point, patients were first asked to lift their brows maximally so the temporal fusion planes at the lateral margins of the frontalis could be identified. Next, patients were asked to close their eyes maximally so the site of the maximum inward and downward pull of the orbicularis oculi muscle on the lateral brow could be identified. The botulinum toxin was then injected intradermally, with focal superficial placement at the site just inferior to the point of maximum inward and downward pull of the orbicularis oculi muscle (Figure 1). Care was taken to ensure that this point was at least 1.0 to 1.5 cm lateral and inferior to the previously identified most-lateral fibers of the frontalis muscle. The injections were perpendicular to the skin in order to localize botulinum toxin to the superior lateral aspect of the orbicularis and avoid unwanted diffusion to the lateral frontalis fibers superiorly. In order to stay superficial and avoid inadvertent needle trauma to small vessels in the deeper tissue, the injections resulted in a small bleb.

Figure 1. Site of Injection of Botulinum Toxin Type A in the Lateral Infrafrow.

Outcome Measures
Patients were evaluated at baseline and at weeks 2, 8, 14, and 20. Efficacy was evaluated by both the investigator and the patient using the following scale to evaluate the severity of dermatochalasis: 0 = none, 1 = mild (slightly noticeable), 2 = moderate (noticeable), and 3 = severe (distinctive). Patients were considered responders if their score on this scale was at least one grade lower than their baseline score.

Patients evaluated their improvement from baseline on a 9-point scale where +4 = complete improvement (100% better), +3 = substantial improvement (75% better), +2 = definite improvement (50% better), +1 = some improvement (25% better), 0 = unchanged, -1 = slight worsening (25% worse), -2 = moderate worsening (50% worse), -3 = marked worsening (75% worse), and -4 = very marked worsening (100% worse). They also rated their feelings of attractiveness and satisfaction with their appearance on a 7-point scale where 0 = not at all and 6 = extremely. In addition, at their last study visit, patients recorded their level of satisfaction with the treatment on a 6-point scale where 1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, and 5 = very dissatisfied.

Patients were asked about the occurrence of any adverse events 30 minutes after their injections and at each post-baseline visit.

Statistical Analyses
A sample size of 40 was calculated to be sufficient to demonstrate a higher proportion of responders in the 6-U group than the 4-U group at week 20, assuming a power of 0.8 and a drop-out rate of 15%. For all analyses, a P value of ≤.05 was considered to be statistically significant.

Fisher's exact one-sided test was used to test a between-group difference in the proportion of responders. Fisher's exact two-sided test was used to test a between-group difference in the distribution of improvement scores reported by the patients. Wilcoxon rank-sum one-sided test was used to test whether the 6-U group yielded higher median scores for feelings of attractiveness and feelings of satisfaction with appearance than the 4-U group.

Results
Patients
A total of 40 patients were enrolled (20 in each group), of whom 26 (65%) completed treatment. Their mean age was 50 ± 8.3 years in the 4-U group and 44 ± 8.4 years in the 6-U group (overall range: 30 to 63 years). All patients were Caucasian except for one patient in each group who was Hispanic. The 2 groups did not differ significantly in baseline demographic characteristics or baseline dermatochalasis severity.

In each group, 7 patients discontinued prematurely. In the 4-U group, discontinuation was due to loss to follow-up (6) and lack of efficacy (1). In the 6-U group, discontinuation was due to loss to follow-up (6) and breast cancer (1).
Efficacy
Based on the investigators' assessment of the severity of dermatochalasis, the proportion of patients who were responders (i.e., who had at least a 1-point reduction in their severity score) peaked at 32% in the 4-U group and 47% in the 6-U group at week 2 (Figure 2). There were no significant between-group differences in the proportion of responders at this time point or at any later time points. At all later time points, the proportion of responders differed by no more than 4% between groups.

Based on the patients' assessment of the severity of dermatochalasis, the proportion of patients who were responders peaked at 37% in the 4-U group and 24% in the 6-U group at week 2 (Figure 3). There were no significant between-group differences in the proportion of responders at any time point.

The higher dose group tended to report a greater degree of improvement than the lower dose group—the proportion of patients with at least "definite improvement" was consistently larger with the higher dose than the lower dose (Figure 4). Nevertheless, there were no significant between-group differences in the overall distribution of scores.

In terms of feelings of attractiveness and feelings of satisfaction with appearance, patient ratings showed consistently higher mean scores in the higher dose group than the lower dose group. Furthermore, at some time points, median scores were significantly higher with the higher dose than the lower dose (Figures 5 and 6).

At the patients' last study visit, the proportion of patients reporting that they were "satisfied" or "very satisfied" with their treatment was 43% in the 4-U group and 50% in the 6-U group (with 14% and 36%, respectively, reporting that they were very satisfied). Photographic documentation of improvement in dermatochalasis occurring after treatment with botulinum toxin type A is demonstrated in Figure 7.

Adverse Events
Three patients reported adverse events—skin at injection site sensitive to touch (4-U group), right eyelid fasciculations (4-U group), and breast cancer (6-U group). None of these were considered probably or definitely related to treatment although the skin sensitivity and eyelid fasciculations were possibly related to treatment.

Discussion
Several muscles are brow depressors, including the primary muscles of the glabellar complex (the procerus, the corrugator supercili, and the depressor supercili) and the medial fibers of the orbicularis oculi. 7 Paralysis of this musculature in the central brow using botulinum toxin type A can result in medial brow elevation. 8 Similarly, the injection of botulinum toxin type A into the lateral area of the orbicularis oculi can achieve lateral brow elevation. 8, 9 We now demonstrate that lateral brow elevation is possible with just a single injection of botulinum toxin type A in each orbicularis oculi (rather than the 3 injections described previously) 9 and that such treatment offers clinical improvement and patient satisfaction in the treatment of dermatochalasis.

Clinical improvement was evident with both doses evaluated, with up to 32% (4-U dose) and 47% of patients (6-U dose) classified as responders (i.e., achieving at least a 1-grade improvement in the severity of dermatochalasis). Although the between-group difference in the proportion of responders did not reach statistical significance, a higher than anticipated number of patients discontinued prematurely, largely due to loss to follow-up, and this reduced the power of the study to detect such differences. The relatively large number of patients lost to follow-up may be at least partly because, after receiving treatment at the baseline visit, patients had relatively little incentive to attend follow-up visits (i.e., no promise of additional treatment and no financial incentive for attendance).
Younger patients receiving treatment for glabellar lines have also shown a higher rate of response to botulinum toxin type A than older patients. Thus, it is possible that age may also have been a factor influencing the results from this study. However, the 6-U group also reported greater feelings of attractiveness and satisfaction with their appearance than the 4-U group at all time points including baseline, suggesting that this group had more positive self-perceptions even before treatment. Of course, it is possible that their younger age could have contributed to this.

Although other investigators have previously reported the efficacy of botulinum toxin type A in achieving brow lift, these reports involved fewer patients (N = 22), no dose comparisons (7-10 U per injection in all patients), and only patients who desired a brow lift for cosmetic reasons rather than as a result of the diagnosis of dermatochalasis.

In this study, there were no adverse events considered probably or definitely related to treatment. As with other treatments involving botulinum toxin type A, injection technique and selection of a botulinum toxin that minimizes migration outside the target muscle is of great importance in optimizing clinical benefit and avoiding the potential for adverse effects. The rationale for the technique used in this study—a single injection at the lateral aspect of the orbicularis oculi muscle in each brow—was to try to minimize the potential for upward and/or medial migration of botulinum toxin to other muscles. It is important that the injection is far enough away from the frontalis to avoid the potential for the migration of botulinum toxin to cause lateral brow drop and eyebrow ptosis. In addition, it is important that the injection is not too medial so as to prevent migration of the botulinum toxin to the orbital septum area, which could potentially result in eyelid ptosis.

It is important to note that the dosing and results reported in this study are specific to the formulation of botulinum toxin type A manufactured by Allergan, Inc. The Allergan formulation is not interchangeable with other botulinum toxin products and cannot be converted by a dose ratio.
Figure 7. Elevation of the Lateral Brow and Improvement in Dermatochalasis After Injection of 4 U Botulinum Toxin Type A, Bilaterally, in the Lateral Aspect of the Orbicularis Oculi Muscle.

Conclusions
The results from this study demonstrate that single-site injection of botulinum toxin type A can be effective in improving mild to moderate upper eyelid dermatochalasis when injected at a dose of 4 U or 6 U per brow. Treatment with a dose of 6 U may offer greater clinical benefit than a dose of 4 U although this needs to be confirmed in larger studies. There were no adverse events considered probably or definitely related to treatment and the higher dose was at least as well-tolerated as the lower dose. These efficacy and safety data support the further evaluation of the higher dose in future trials.

Although the injections of botulinum toxin type A described here are not an appropriate substitute for blepharoplasty in patients with severe dermatochalasis causing functional impairment, they can offer a valuable alternative to surgery in carefully selected patients with mild to moderate upper eyelid skin redundancy. Such treatment with botulinum toxin type A may allow patients to delay surgery. Although not every patient may respond, the potential clinical benefits, together with the good safety profile and relatively low cost of this approach, merit a trial in suitable candidates. Lateral brow lift with botulinum toxin type A may also be considered for women seeking a more flared brow and for any patient whose brow has descended into a lower position as a result of botulinum toxin over treatment of the frontalis muscle.

Disclosures
This study was sponsored by a research grant from Allergan, Inc (Irvine, CA). Joel L. Cohen MD and Steven H. Dayan, MC FACS are both National Education Faculty members for Allergan. Dr. Cohen is a speaker, national trainer, consultant, and clinical trial participant with Allergan and Medicis.
References

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