Botulinum Toxin A: A Novel Method to Remove Periorbital Wrinkles

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Periorbital wrinkles are not adequately corrected by standard blepharoplasty techniques. These lines, which are also known as crow's feet, are caused by the contraction of the lateral fibers of the orbicularis oculi muscles that insert on the undersurface of the skin of the temporal area.[1] Botulinum toxin A is a neuromuscular blocking agent that induces a flaccid paralysis when injected into striated muscles. Selective denervation of the appropriate portions of the orbicularis oculi muscle will weaken the resting tone of these muscles and effectively and physiologically eliminate the crow's feet for up to 6 months.[2]

There are numerous surgical procedures and techniques designed to eliminate periorbital wrinkles—all of these techniques have drawbacks and are not universally accepted. The blepharoplasty excision can be extended laterally and the skin overlying the crow's feet can be excised and resutured. The drawback with this technique is that the scar is quite obvious because the eyelid skin is much thinner and heals much quicker than the skin of the temporal area. A temporal face-lift with orbicularis oculi plication can be effective but carries a significant risk of injury to the facial nerve and it is not a simple office procedure.[3] Silicone and collagen injections can fill in the wrinkles; however, silicone is not approved by the Food and Drug Administration for this indication and collagen is only effective for approximately 6 to 8 weeks.[4] Both have a tendency to appear lumpy in this area. In contrast, botulinum toxin A can safely, effectively, and reliably eliminate periorbital wrinkles with minimal risk of side effects for 6 months at a time.[2,3] The appearance is quite natural and restores a youthful look to this area of the face. Critics have stated that paralysis of the mimetic muscles of the face will eliminate the facial expression and give a stone-face type of facial appearance. This has just not been the case when the toxin has been selectively and judiciously injected. In fact, the procedure, which will be described, has been remarkably free of serious side effects.[3,4]

BOTULINUM TOXIN A

The bacterium *Clostridium botulinum* produces eight serologically distinct toxins that exert their effects at the neuromuscular junction by inhibiting the release of acetylcholine, and this in turn causes a flaccid paralysis.[5] Pharmacological and morphological studies suggest that the toxin enters the nerve via receptor-mediated endocytosis.[6] The binding is selective and saturable.[7] It is the release of vesicle-bound acetylcholine that is inhibited by the toxin.

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Botulinum toxin does not affect the synthesis and storage of acetylcholine. The therapeutic effect is related to the peripheral blockade of neural–muscular activity. One international unit is defined as the median lethal dose (LD_{50}) in mice. The LD_{50} in humans is estimated to be approximately 2730 IU.[8] The toxin is shipped freeze-dried in 100 IU vials (Allergan, Irving, CA). When used clinically, the toxin is reconstituted with normal saline to a concentration of 2.5 to 5.0 U/mL. It should be noted that there have been no long-term adverse effects with the use of botulinum toxin A for blepharospasm and Meige's disease.[9–11] Muscle biopsies taken from patients after repetitive injections have failed to show any long-term evidence of permanent degeneration or atrophy, and those patients have received dosages that were two to five times the dosages that we have utilized for aesthetic improvement.[12,13] Patients also develop antibodies to botulinum toxin when they have had continued exposure to large dosages. The factors that predispose patients to developing antibodies is unknown, but some evidence has shown that the risk is increased with use of more than 300 IU within a 30-day period.[8] Therefore we have developed and utilized an electromyographic (EMG)-guided technique to increase the accuracy of the injection and minimized the dose and antigenic exposure.

INJECTION TECHNIQUE

Botulinum toxin A was freshly diluted to a concentration of 2.5 or 5.0 U/mL and was injected via a monopolar hollow bore Teflon-coated electromyography needle that was connected to an EMG recorder. Using a technique that has been previously described,[1,2,14–20] the needle is placed through the skin overlying the periorbital wrinkles. With the needle in place, EMG recordings commence and the patient is instructed to accentuate the lines with a squint. The needle is then moved to the electrically most active portion of the muscle, once this portion of the muscle is identified, a small aliquot of toxin is injected. By using a small initial dose, a graduated weakening can be achieved. Additional injections can be used to achieve the optimum relaxation of the muscle. If too much weakness is produced, the strength gradually returns with time. Injections need to be repeated on an average of every 4 to 6 months.[21] It takes approximately 72 hours for the injection to take effect. There is no massaging of the injection site for approximately 24 hours to minimized unwanted spread of the drug.

MATERIALS AND METHODS

A total of 80 patients were included in the study. Patients were first evaluated with a thorough review of their medical history, medications, and prior facial plastic surgical procedures. Any patients who had a sensitivity to the toxin or had a neuromuscular disorder such as myasthenia gravis or Eaton-Lambert syndrome or those patients who could not complete the protocol were eliminated from the study. Preliminary photographs were taken for each patient at each injection site both at rest and during function. All photographs were standardized using the same camera, lenses, flash systems, and film. The photographs were obtained at 3 feet with 105-mL lens oriented vertically using Ektachrome 400 slide film and a ring flash. A set of close-up photographs at 2 feet with the camera oriented horizontally were also obtained. The photographs were repeated at 2 weeks and 12 weeks postinjections. The patients were

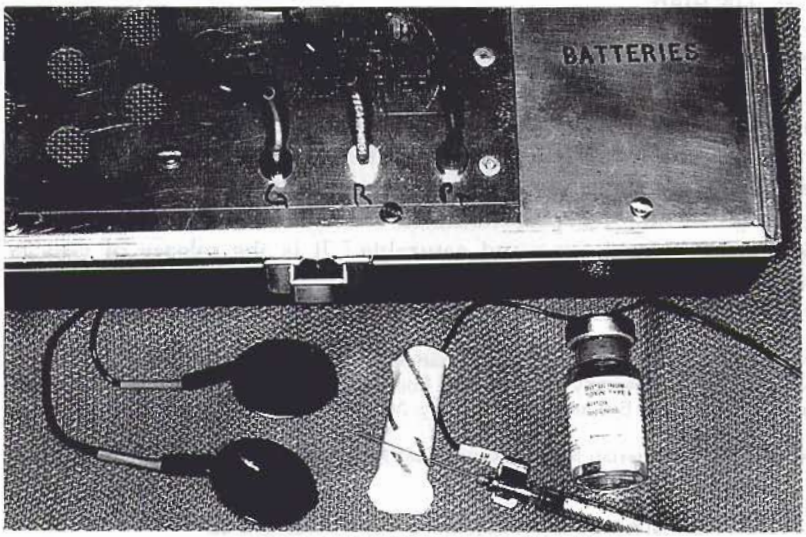

Figure 1. Botulinum toxin A, hollow bore electromyographic needle, and electromyographic machine.

Table 1. Periorbital Wrinkle Grading System

Scale	Wrinkles
0	None
1	Mild
2	Moderate
3	Severe

asked to rate their periorbital wrinkles. We utilized a 0 to 3 rating scale (Table 1). The patients evaluated their wrinkles both at rest and during functioning before injection and at 2 and 12 weeks after injections. The results were tabulated and analyzed (Table 2). There were 16 male patients and 64 female patients, the age ranged from 21 to 78 years old, with a mean of 45 years. The dosage utilized in this study was based on our previous experience and modified during this study, depending on the patient's individual response to the drug. When injecting periorbital wrinkles, a dose of 5 to 15 IU was utilized in three different injection with a mean of 7.5 U. A beneficial response was noted in 95% of all patients. All of the patients had a toxin affect within the first 72 hours of injection. On average, the crow's feet evaluation improved 1.36 rating points, denoting a 34% improvement. Adverse effects of the toxin injections were minimal and included four (5%) patients who experienced a temporary droop of the lateral portion of the lower eyelid. This occurred early in the study; as we gained more experience, we learned not to inject quite that close to the lateral canthus and this complication was eliminated. Three patients (4%) had significant black and blue marks when the needle inadvertently pierced a blood vessel in the temporal area, this resolved within 2 weeks. There were no systemic reactions, the effect of the toxin lasted between 4 and 6 months whereupon the majority of patients (91%) returned and were reinjected.

DISCUSSION

Periorbital wrinkles are common cosmetic deformities. In the past these lines have been treated by surgical excision, yielding unsightly scars, or injected with silicone or collagen, or even the patient's own fat in an effort to blow out the skin and flatten the wrinkles.[2,4,22,23] Face-lifting and temporal extensions of face-lifts are surgical endeavors and can only partially improve these wrinkles and add a significant cost in terms of scarring and healing. These treatments do not adequately address the fact that these periorbital wrinkles are functional and are related to the pull of the underlying mimetic facial musculature. Just as the patient with a facial paralysis does not have a line on their face, the flaccid paralysis that is induced by small quantities of botulinum toxin A effectively eliminates these periorbital wrinkles. The toxin weakens the mimetic muscles and, thereby, physiologically lessen the wrinkles that are caused by the muscular contraction. Not all facial wrinkles are caused by the tension of the underlying mimetic muscles. Laxity of the skin that is related to age-induced change in the dermal collagen can also cause periorbital wrinkles. Indeed, our poorest results were in our elderly patients in whom skin laxity played a significant role in the origin of the wrinkles (Table 3).

The toxin can easily be injected on an ambulatory basis with minimal discomfort by utilizing the EMG-monitored technique. By using small volumes of concentrated solutions, one can precisely localize the injections; this can be accomplished with minimal side effects. A graded weakness can be achieved by utilizing low dosages initially and then repeating the injections if necessary to achieve the desired effect.If too much weakness is achieved, the toxin gradually wears off in 4 to 6 months. By starting with a low initial dose, undesirable side effects can be avoided. The injections need to be repeated every 4 to 6 months to sustain the results. This may be considered an inconvenient drawback to the procedure. However, this represents an improvement over collagen, which lasts only 2 to 3 months, and to silicone, which is not currently legally available for this use. Full function returns without any long-term sequela and side effects were limited to a mild degree of lower lid droop in a few patients early in the study. There were no complaints of adverse or limited facial expression in the patients we injected, nor were there any patients who could not close their eyes.

Table 2. Dose Response for Periorbital Wrinkles

		Delta Rating	
No.	Average Dose	At Rest	Squinting
80	6.22 U	0.92 (23%)*	1.36 (34%)

*Number in parenthesis represents percent improvement.

Table 3. Periorbital Wrinkles: Dose and Response by Decade

			Average Delta Response	
Decade	No.	Average Units Per Side	At Rest	Squinting
2nd	1	5	1	1.0
3rd	29	6.08	0.79	1.5
4th	30	6.08	1.15	1.57
5th	16	6.25	0.71	1.57
6th	3	5.0	1.0	1.0
7th	1	7.0	1.0	1.0

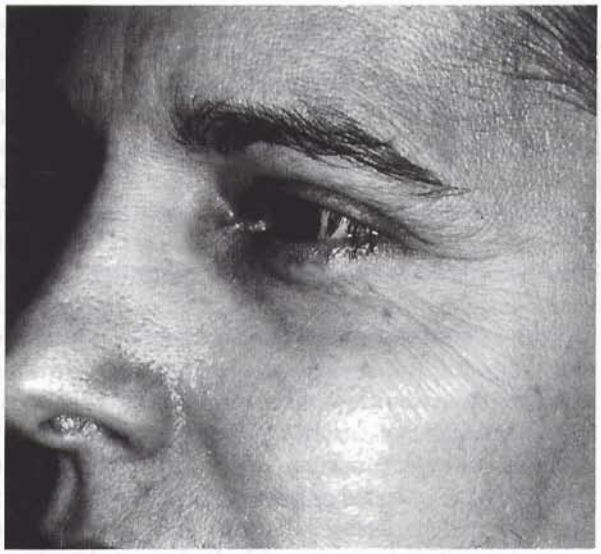

Figure 2. Crow's feet at rest, preinjection.

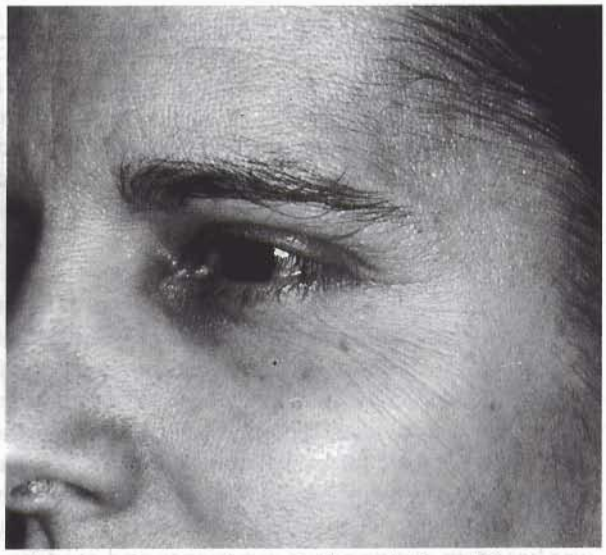

Figure 3. Same patient as in Figure 2. Crow's feet at rest, 1 month postinjection.

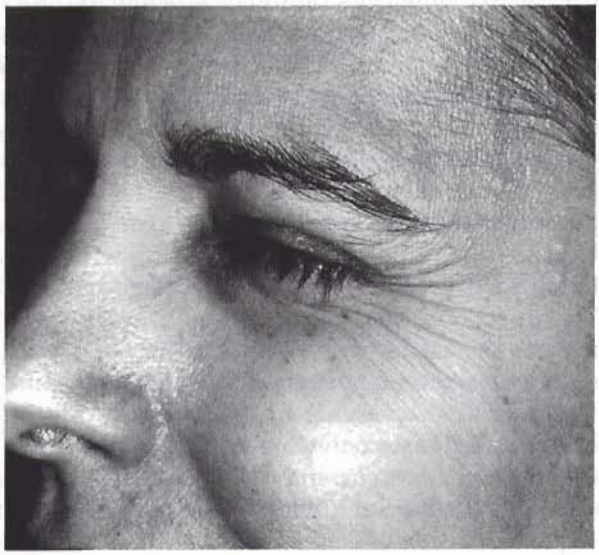

Figure 4. Same patient as in Figure 2. Crow's feet, squinting, preinjection.

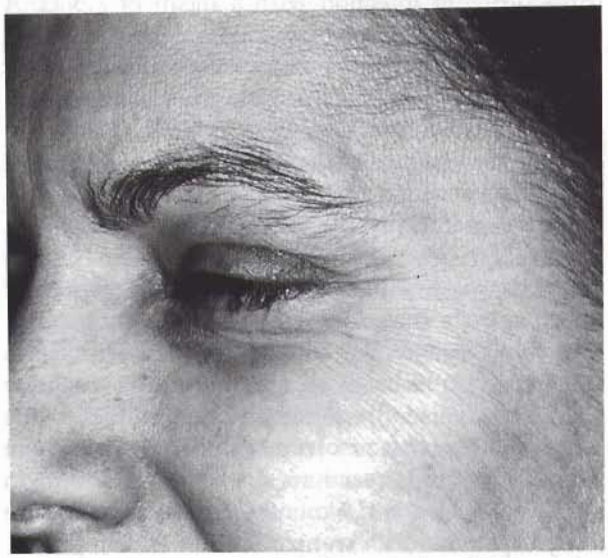

Figure 5. Same patient as in Figure 2. Crow's feet, squinting, 1 month postinjection.

Antibodies to botulinum toxin A have been described in patients receiving much larger dosages, two to five times the dose necessary for aesthetic indications, for longer periods of time.[4,24] These antibodies can render the toxin ineffective but do not harm the patient. No antibody production has ever been described in patients receiving botulinum toxin A for blepharospasm.[12,25,26] Muscle biopsies taken from patients after repetitive injections of botulinum toxin A have failed to show any long-term evidence of permanent degeneration or atrophy, and those patients have received much larger dosage than are utilized for aesthetic indications and have been studied for more than 8 years.[11,12,27] Our experience has demonstrated that the dose for crow's feet is approximately 5 to 15 U in three separate injections placed lateral to the lateral canthus. The response was excellent with greater than 95% of the patients demonstrating a significant improvement with the toxin. Our results reflected a trend that older patients needed a larger dose of toxin to obtain a beneficial effect. Overall, the improvement was more noticeable when the patient was actively squinting than at rest.

A word of caution is necessary to the surgeon who has not had experience with this drug. Although we are recommending relatively low dosages of the toxin, there is a very real danger of injecting too

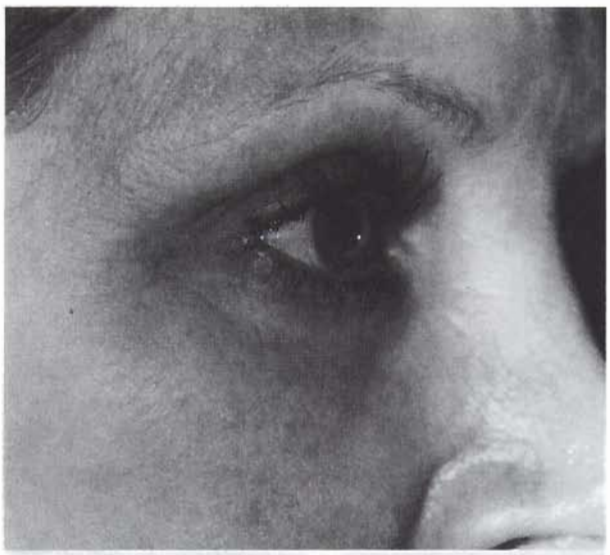

Figure 6. Preinjection at rest.

Figure 7. Same patient as in Figure 6, 1 month postinjection, at rest.

Figure 8. Same patient as in Figure 6, preinjection, squinting.

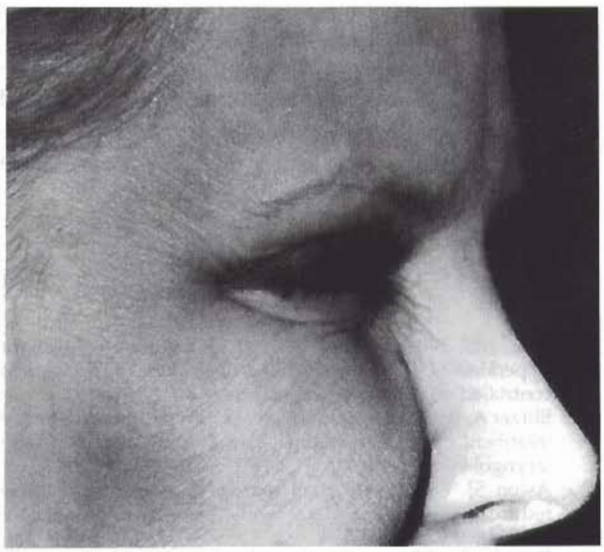

Figure 9. Same patient as in Figure 6, 1 month postinjection, squinting.

much toxin in the wrong areas of the face and achieving an unsightly facial palsy or ectropion. This is because the toxin takes approximately 3 days to give an effect and there is no way to monitor exactly which wrinkles will be eliminated with each specific injection. We recommend the EMG injection technique as a way to ensure the correct placement of the toxin. A week after the original injection a second "touch up" shot may be necessary. Once the surgeon has had experience with the injection technique, the control afforded by EMG monitoring may not be necessary. Since everyone's reaction to the drug is different, it is vitally important to underdose at the first session to ascertain the individual patient's reaction to the medication. Once injected, one must wait for the toxin to be metabolized because there is no medication that can reverse the metabolic effects. Our results seem to indicate that the toxin is most beneficial in patients in the 30- to 50-year-old age group and most effective in eliminating crow's feet during animation of the face.

CONCLUSION

We conclude the botulinum toxin A is a safe and effective method of nonsurgically eliminating crow's feet and periorbital wrinkles, in surgical patients for

Figure 10. Male patient with sun-damaged skin, preinjection, squinting.

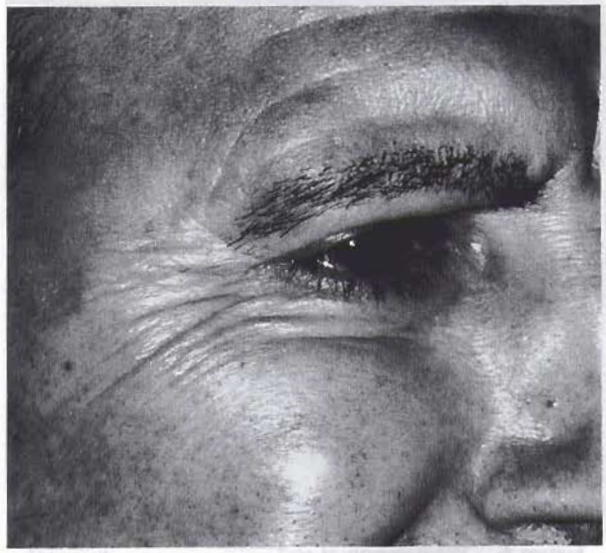

Figure 11. Same patient as in Figure 10, modest improvement, 1 month postinjection, squinting.

a period of 4 to 6 moths. Botulinum toxin A may play an increasingly important role as an adjuvant treatment in cosmetic surgical enhancement of the lateral portion of the aging eye. Botulinum toxin A injections address the need for a short-term reversible therapy to tough up the aging eye.

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