Treatment of Hyperfunctional Lines of the Face with Botulinum Toxin A

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Since Botulinum toxin A became a mainstay therapy for blepharospasm, its use in treating other dystonic conditions, spasticity disorders, as well as hyperfunctional lines of the face has increased exponentially in recent years. The following article summarizes our experience in establishing a safe and reliable method of administration of botulinum toxin A for treating hyperfunctional lines of the face. *Dermatol Surg 1998;24:1198–1205.*

Over the last 13–14 years we have found an increasing array of medical uses for botulinum toxin. Originally discovered by Scott et al[1] as a treatment for strabismus and blepharospasm, botulinum toxin has become the standard therapy for many dystonic and spastic disorders. Since 1984, thousands of patients with focal dystonias have been treated utilizing botulinum toxin. Published reports by Blitzer and Brin et al[2–13] have reported their experience in treating blepharospasm, torticollis, oromandibular dystonia, adductor and abductor laryngeal dystonia, lingual dystonia, limb dystonia, and hemifacial spasm. A number of years ago, a new use was discovered by Blitzer et al,[14] Keen et al,[15,16] and Carruthers and Carruthers[17] for the treatment of wrinkles and hyperfunctional lines of the face.

Excessively prominent facial lines are often cosmetically displeasing and sometimes misinterpreted as anger, anxiety, fear, fatigue, pain, sadness, or associated with aging. The many different surgical, medical, and cosmetic remedies that emerge and are marketed each year can be confusing to both the patient and the surgeon. Consequently, it is incumbent upon the physician to differentiate and choose the most appropriate treatment for each individual problem and patient. In general, facial rhytids have a myriad of remedies: facelifting, surgical excision, implants, resurfacing procedures using either lasers, acid peels, or dermabrasion, soft tissue fillers such as collagen, fat, dermis, or Gore-Tex®, facial creams, facial massages, and other homeopathic remedies. Therefore, to choose the most appropriate therapy, distinctions must be made between rhytids created by loss of collagen or elastic fibers within the dermis of the skin, wrinkles caused by volumetric loss of fat, redundant folds caused by gravitational pull, and those caused by hyperfunctional facial muscles.

The three primary areas of the upper third of the face associated with hyperfunctional movement such as the glabella frown line, horizontal forehead lines, or crows feet historically have been resistant to most therapies. Even after myectomy via direct or endoscopic brow lift, the corrugator muscles and the secondary frown lines have a high incidence of recurrence. Filler agents such as collagen or fat offer only a partial, short-term solution to fill and smooth out deep lines or folds.[18,19] Direct excision may eliminate the line but, at the same time, also may leave unsightly scars.

In the lower third of the face, a "peau d'orange" effect or excessive wrinkling is often found over the anterior portion of the chin. This is caused by a hyperfunctional mentalis muscle, which is associated with labial incompetence in patients with retrognathia, microgenia, or frequently after chin augmentation. It is also found more frequently in this area in older age groups. We have been able to significantly decrease or eliminate these lines by injecting the mentalis muscle with small amounts of botulinum toxin (approximately 2–4 U). The tensed skin is smoothed out and the effects of skin wrinkling caused by the excessive straining of the mentalis muscle is reduced. In the neck, the platysma muscle bands can also be reduced by a series of botulinum toxin injections into the anterior aspects of the platysma muscle bands. This usually requires approximately 2.5–5 U and three injection sites per side.

The basis for treating facial lines with botulinum toxin must address the etiology of the specific facial line. In hyperfunctional facial lines, such as the brow furrow, crows feet, and horizontal forehead wrinkles, it

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is the tension of the underlying mimetic facial musculature that causes a pleating of the overlying skin. Patients who have Bell's palsy have a functional disability of the facial muscles, but also have smooth skin without the development of deep hyperfunctional lines. In patients treated with botulinum toxin for facial dystonia or hemifacial spasm, we observed a reduction or absence of deep hyperfunctional lines with an improved cosmetic appearance.[5,20]

Botulinum Toxin: Mechanism of Action

Botulinum toxin weakens the overactive underlying muscle contraction, causing a relaxation and flattening of the facial skin, which yields an improved cosmetic appearance, The bacterium *Clostridium botulinum* produces eight serologically distinct toxins designated A, B, C1, C2, D, E, F, and G.[21] Botulinum toxin acts at the neuromuscular junction, inhibiting the release of acetylcholine from the nerve terminal. This causes weakness or a flaccid paralysis of the muscle.

Pharmacologic and morphologic studies suggest the toxin enters the nerve ending via endocytosis and inhibits the release of the vesicle-bound acetylcholine within the nerve terminal itself.[22–24] The therapeutic affect thus is related to the peripheral blockade of neuromuscular activity, which causes muscular weakness. So far there has been no evidence to suggest any permanent degeneration or atrophy of muscles in those patients treated for dystonic or spastic disorders who have been injected with high-dose, repetitive injections of botulinum toxin over a long duration. Muscle biopsies that were taken from patients after injections of botulinum toxin two to five times those used for aesthetic improvement failed to show any long-term evidence of permanent degeneration or atrophy.[25,26]

Safety Issues

There have been no long-term adverse effects or health hazards related to the use of botulinum toxin thus far.[1,27–29] Patients receiving repetitive, high doses of botulinum toxin have been shown to develop antibodies to the toxin. These act as blocking antibodies and may render the patient resistant to further treatment. They do not cause hypersensitivity reactions to the injection of the substance. The factors that predispose patients to the development of antibodies are unknown, but experience has shown that the risk is increased with repetitive dosages above 300 U.[30,31] Dosages for individual sites treated for the purpose of minimizing hyperfunctional facial lines usually require no more than 20–40 U per site. To further minimize the dose and increase the accuracy of toxin placement we often use an electomyographic (EMG)-guided technique. Once familiar with the origin and insertion of the facial muscles, many of these areas can be injected with a 30-gauge needle without EMG guidance. However, in those patients who have shown only partial results from prior treatments, we recommend that the EMG technique be used to assure more accurate deposition of the toxin.

In the informed consent, it must be brought to the patient's attention that botulinum toxin has been approved by the Food and Drug Administration as a safe and effective "on label" therapy since 1989 for use in blepharospasm, strabismus, and hemifacial spasm. The treatment of wrinkles is considered an off-label use. However, the National Institutes of Health consensus conference of 1990 also included botulinum toxin as safe and effective therapy for the treatment of adductor spasmodic dysphonia, oromandibular dystonia, and cervical dystonia.[30] Other "off-label" uses include Meige's syndrome, sphincter dysfunction, tremor disorders, juvenile cerebral palsy, and other spasticity disorders for which patients currently are receiving benefit from botulinum toxin.

Prior Study

In a previous study,[20] we reported the results of a series of 210 injection sites in 162 patients. The patients had preinjection and postinjection photographic documentation and ratings on a four-point qualitative evaluation scale of lines at rest and with action. The patients then had botulinum toxin type A injections, via a monopolar hollow-bore, Teflon-coated EMG needle, into the facial muscles associated with the hyperfunctional lines. The total dose for each region was 1.25–25 U divided into 1.25- to 5-U aliquots representing 0.1–0.2 ml per injection site, depending on the site and the prior experience using toxin on that patient. Ninety-five percent of the patients treated had cosmetic improvement of unsightly facial lines or contractions. The best results were achieved in management of the forehead lines, followed by glabella, crows feet, and nasolabial folds. The dose for forehead lines was 5–25 U (mean 17.3 ± 6.2); glabella lines 5–20 U (mean 11.1 ± 3.1); crows feet 5–15 U (mean 6.2 ± 1.6); nasolabial folds 2.5–5 U (mean 3.12 ± 1.2); and platysma 10–20 U (mean 15 ± 4.0). Effects of the toxin were seen 24–72 hours after injection and lasted 3–6 months, whereupon the increased muscular activity returns, as do the hyperfunctional lines. The improvement in hyperfunctional lines utilized a 0–3 rating scale (0 reflecting no facial wrinkles, 1 signifying mild facial wrinkles, 2 denoting moderate facial wrinkles, and 3 representing severe facial wrinkling at rest and during function).

Patients had their re-evaluation at 2–3 weeks postinjection. Patients returned for additional follow-up when

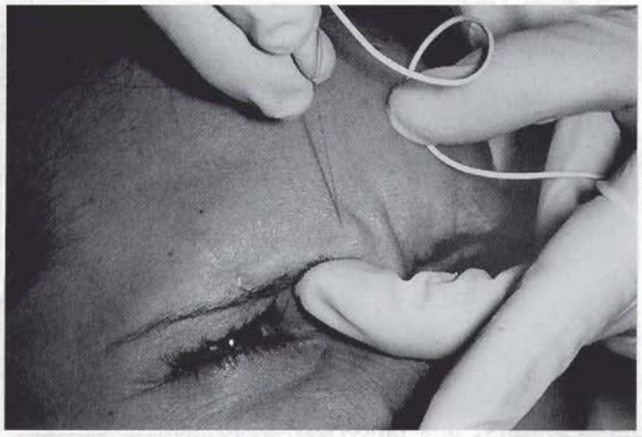
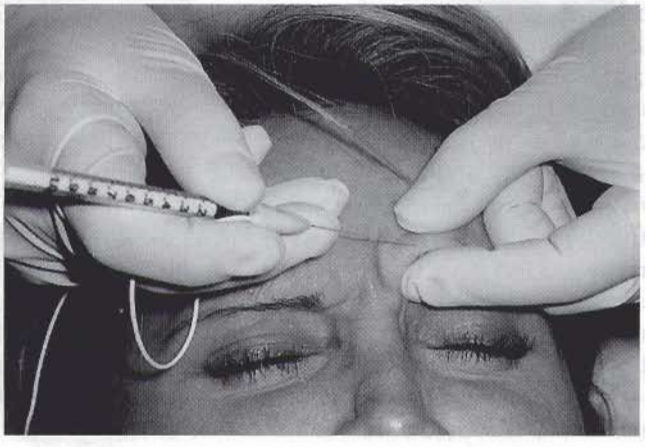


Figure 1. *Injection technique. Mildly compressing the skin with one's finger against the margin of the supraorbital rim further reduces the chances of extravasation of botulinum toxin beyond the intended area of injection site.*

the therapeutic effect diminished. Evaluation by age and site suggested a trend of increased toxin dose with increased age. The only morbidity was related to temporary mild weakness of other adjacent facial muscles. There were no systemic side effects. In addition to the cosmetic benefit, it was noted that several patients who suffered from either migraine or chronic headache pain had relief of their symptoms after the administration of botulinum toxin to the forehead, temporal, and/or glabella regions (Binder, personal communication, 1994). Initially, several nasolabial injections were given. Although they reduced the nasolabial groove, they also diminished the elevation of the lip for smiling, which was not an acceptable cosmetic outcome for most patients and was abandoned.

The adverse effects of the toxin injections were min-

Figure 2. *Injection technique. Mildly squeezing the belly of the corrugator muscle between two fingers and lifting it superiorly assures more accurate placement of the toxin and its confinement to the muscle.*



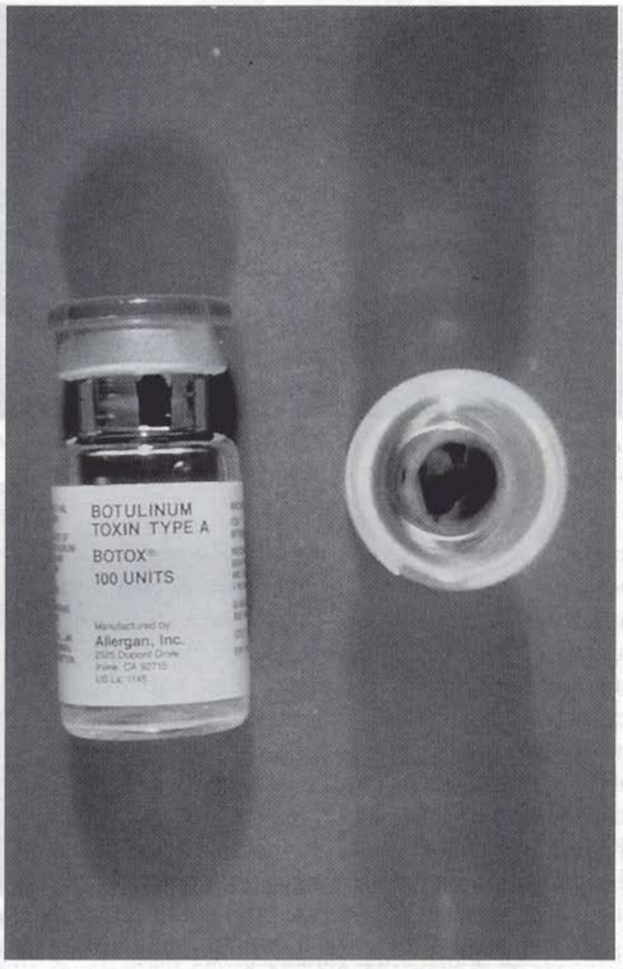
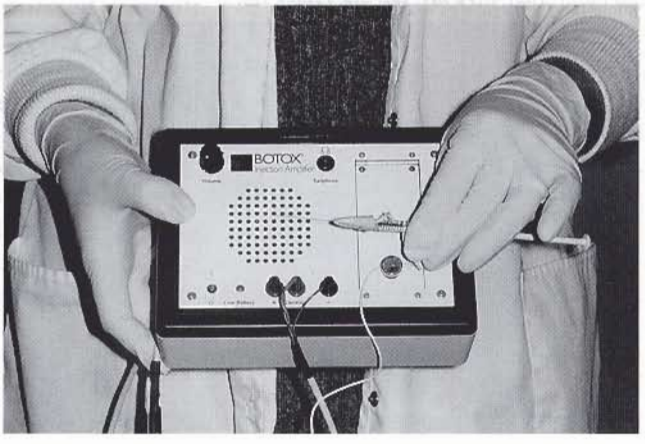


Figure 3. *Botulinum toxin is supplied in 100-U vials as a frozen concentrate that is reconstituted with nonpreservative saline in various concentrations.*

Figure 4. *A Small electromyographic (EMG) machine with ground and reference leads and the Teflon-coated EMG needle with attached syringe consisting of botulinum toxin. The Teflon-coated needle acts as the probe and delivery device.*



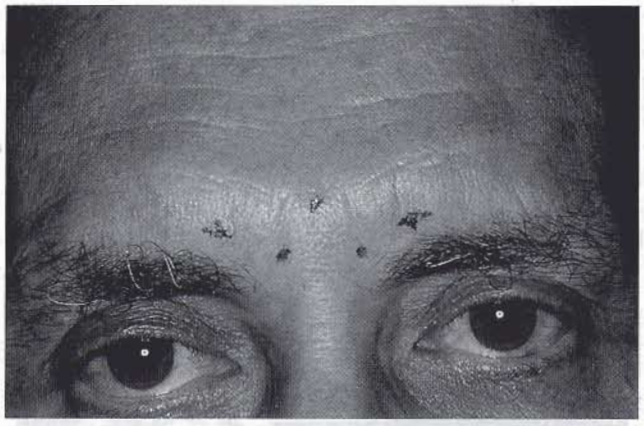
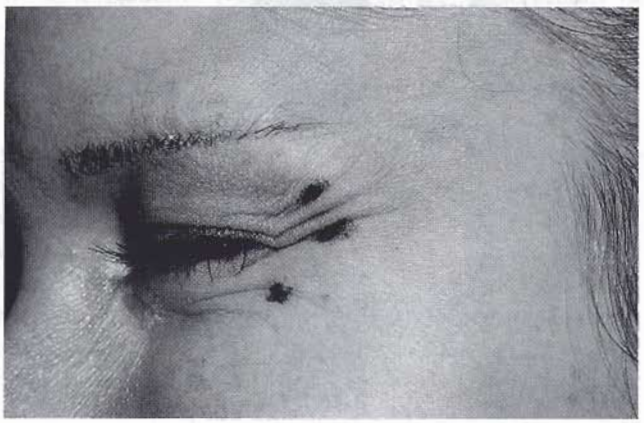


Figure 5. Between 10–20 U of botulinum toxin are injected over five injection sites over the glabella region.

imal and included seven patients who experienced temporary droop of the eyelid or eyebrow, or droop of the upper lip from nasolabial fold injections. No systemic reactions were noted. The effects of the injection lasted an average of 3–6 months, when most patients returned for re-evaluation and treatment. Subsequent to this study, specific techniques of injection utilizing precise placement of small volumes with slow injection of the toxin are important factors in preventing dispersion of the toxin outside the boundaries of the desired effect. In the glabella area, direct pressure at the border of the supraorbital ridge also reduces the potential for extravasation of botulinum toxin, avoiding inadvertent weakening of the levator muscle of the upper eyelid ptosis (Figure 1). In addition, by grasping the mid to lateral portion of the corrugator muscle between two fingers, the deposition of botulinum toxin into this area can be limited further and extravasation prevented (Figure 2). Over the past 4 years, by using these techniques, we have seen no ptosis of the upper eyelid in more than a 1,000 injections.

Figure 6. Between 5–10 U of botulinum toxin are injected over three injection sites per side for crows feet.



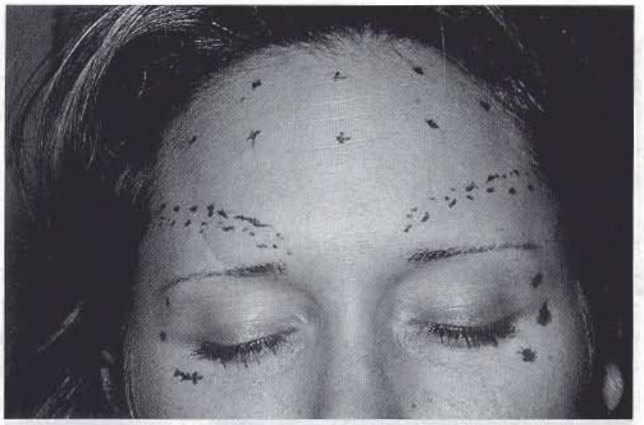


Figure 7. The dosage and number of injections vary depending on the number of forehead lines. This can range between 20–40 U and 5–10 injection sites. Botulinum toxin is usually not injected below an oblique line drawn from the medial brow to a point at least 1 cm above the lateral aspect of the brow.

Current Technique of Botulinum Toxin Injections of Facial Muscles

Lyophilized botulinum toxin (Allergan, Irvine, CA) is obtained in vials containing 100 U of botulinum toxin, which is stored frozen as recommended (−20°C) until reconstitution with sterile nonpreserved saline at the time of injection (Figure 3). One international unit of botulinum toxin is defined as the LD_{50} in mice. The LD_{50} in humans is estimated to be over 3,000 IU.[22]

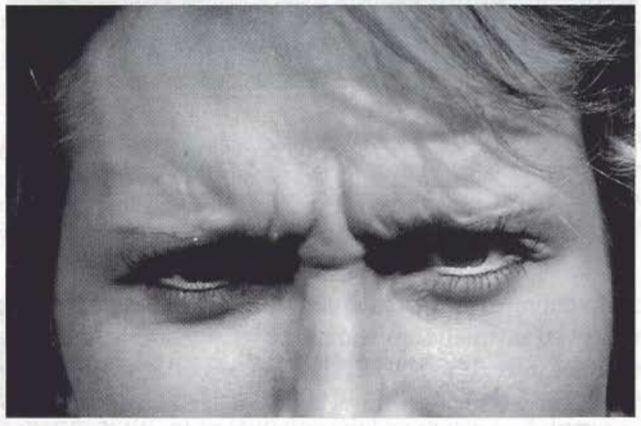
For clinical use, the toxin is reconstituted with normal, nonpreserved saline to a concentration of 2–4 cc (50–25 U/ml). If the EMG technique is used, the toxin is injected via a monopolar hollow-bore, Teflon-coated EMG needle connected to an EMG amplifier (Figure 4). Using previously described technique,[5,6,9,10,12,20] the needle is placed through the skin overlying or adjacent to the facial line and into the hyperfunctional muscle. Before placement of the needle, the patient is instructed to accentuate the specific facial expression, such as frowning, squinting or elevating the eyebrows. Once the needle is inserted in the muscle, it may be moved slightly until it is in the most electrically active part of the muscle complex and produces the maximum EMG signal. The toxin is then injected in 0.1- to 0.2-ml aliquots depending on the dilution used. By using an initial low dose, a graded weakening can be achieved over sequential visits. Small volumes also minimize spread to adjacent muscles, producing unwanted weakness. In the glabella area between 10–20 U are given in five injection points. These are located medially in the right and left glabella folds laterally in the right and left corrugator muscle belly, and a single injection centrally into the procerus muscle (Figure 5). Between 5–10 U of botulinum toxin is injected over three injection sites per side for the crows feet: one site in the upper portion of the crows feet below the lateral corner of the eyebrow,

one site approximately 1 cm lateral to the lateral canthus, and one site approximately 1 cm inferior to the lateral canthus (Figure 6). The dosage and number of injections for forehead lines depend on the depth and number of lines. The dose may range from 20 to 40 U dispersed between 5–10 injection sites. To avoid brow ptosis or prevent the ability of the patient from raising the eyebrow, it is important not to inject the area of the forehead below an oblique line drawn from the medial eyebrow to a point approximately 1 cm above the lateral portion of the eyebrow (Figure 7).

As in all cosmetic surgical procedures, it is important that preinjection photographs be taken of the area being treated during the hyperfunctional and relaxed state. Ideally, it is best to obtain postinjection photographs at approximately 3–4 weeks. Because not all patients will have an "all-or-none" phenomenon that results in complete elimination of the hyperfunctional lines, it is important that an accurate preinjection assessment be made. The patient's expected degree of improvement will depend on this assessment. Calculating the patient's age and skin type into a formula for improvement will help predict the therapeutic effect and provide the patient with a more accurate preoperative informed consent. For example, patients who are in their 20s or 30s with relatively thin, smooth skin will predictably have almost complete elimination of the frown lines (Figure 8). However, in older patients who already have wrinkling of the skin at rest or in patients with thicker, oily skin, only a partial result can be expected (Figure 9). It is important to inform the patient that those wrinkles around and below the lateral canthus caused by passive elevation of the cheek will continue to remain after botulinum toxin treatments. Conversely, these same lines will be prevented from becoming worse during active contraction of these facial muscles.

After successive treatments over prolonged periods

Figure 8. *A) Preinjection photograph of a patient with deep hyperfunctional lines that are formed by active contraction of the corrugator muscles. At rest, however, this patient had smooth skin without glabella frown lines. B) Three weeks after botulinum toxin injection, patient is unable to form any frown lines with attempts at active motion.*



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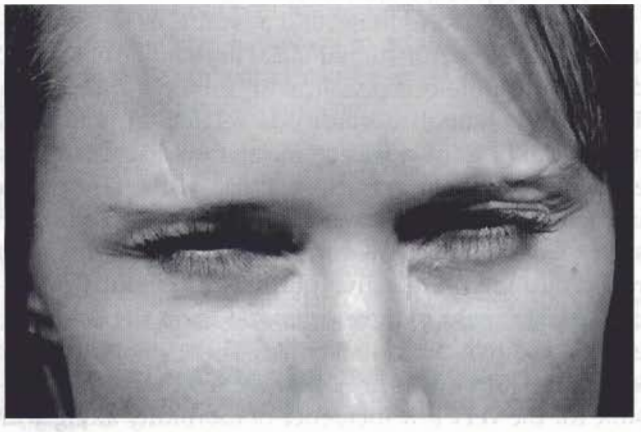

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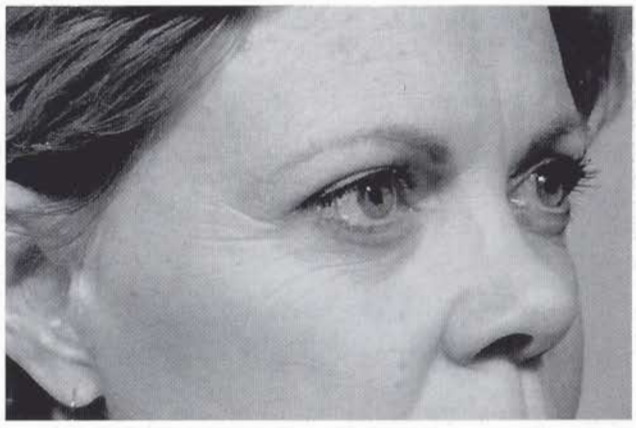

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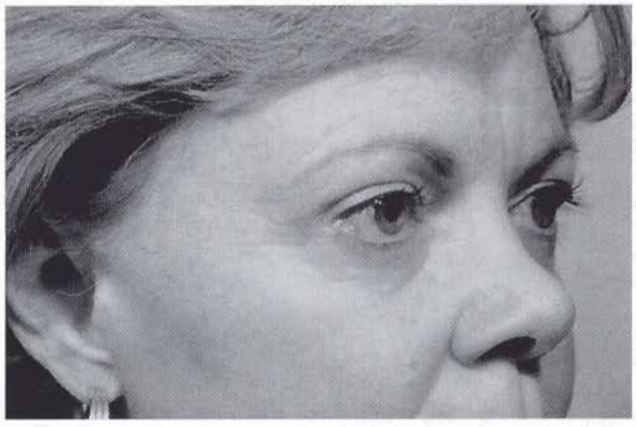

B

Figure 9. *A) Before injection during active contraction. B) After injection during active contraction. A preinjection assessment of this patient indicated that there will be an improvement of the crows feet both at rest and during active contraction of the orbicularis oculi, but the same all-or-none phenomenon that might occur in younger patients could not be expected in this patient.*

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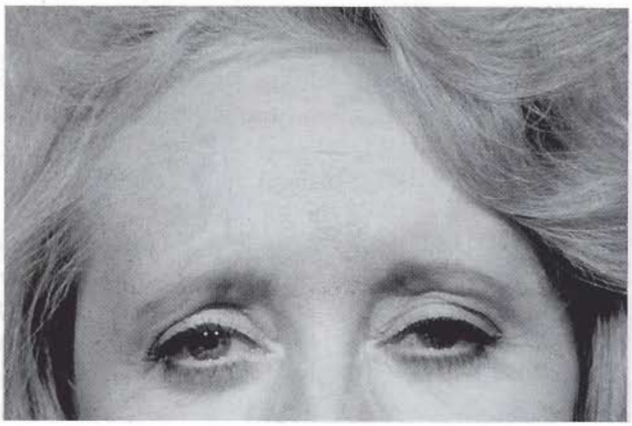

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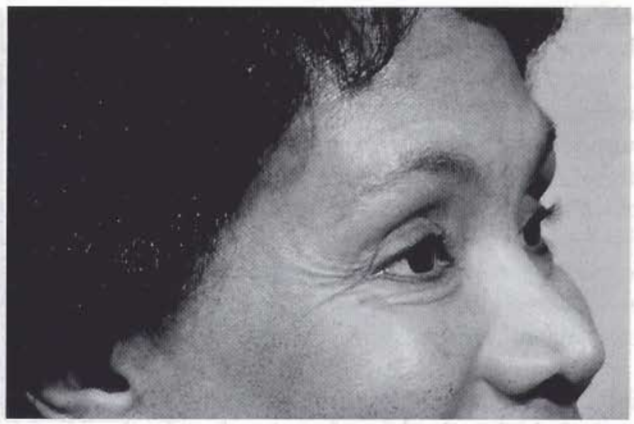
Figure 10. *A) Patient with glabellar frown lines before injection of botulinum toxin. B) The same patient 3 weeks after botulinum toxin injection is unable to actively produce the lines due to corrugator and procerus muscle weakness.*



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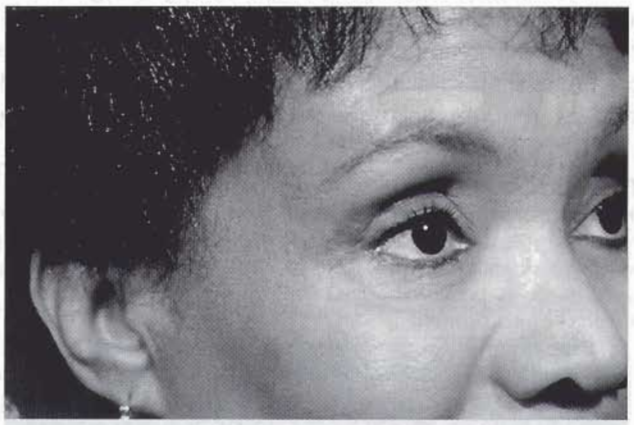


B

Figure 11. *A) Patient with crows feet before injection of botulinum toxin. B) Same patient 2 weeks after botulinum toxin injection unable to produce the lines while actively attempting to squint due to lateral orbicularis oculi weakness.*

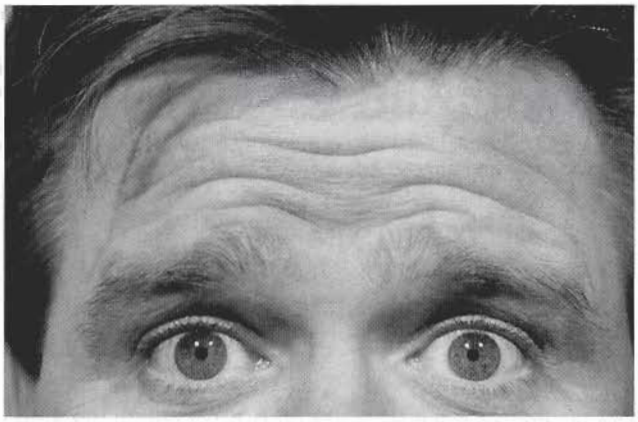
of time, some patients indicated that the effects of botulinum toxin were prolonged. Although there is no scientific basis to support the concept of muscular atrophy, we have observed that perhaps a new behavior modification is developed whereby patients learn to avoid certain undesirable facial movements.

A thorough medical history, including medications and any prior facial plastic surgery, must be obtained before treatment. Any patient who has a history of sensitivity to toxin or has had a neuromuscular disorder such as myasthenia gravis or Eaton-Lambert syndrome should not be treated.

Discussion

Each facial rejuvenation procedure must address the etiology of the cosmetic problem it is trying to correct. Hyperfunctional lines of the face are the result of a functional pull of the underlying mimetic facial musculature. Botulinum toxin weakens the overactive underlying muscle contraction, causing flattening of the facial skin and an improved cosmetic appearance.[1,2,14,20,21,28,29,32] Other facial lines, related to actinic skin changes or age-related loss of dermal elasticity with a laxity of facial skin, may respond incompletely to the toxin and should be treated with other adjunctive modalities.

Botulinum toxin has several advantages in the management of hyperfunctional facial lines and can be used during a routine office visit, with minimal discomfort. The only potential morbidity is related to temporary mild weakness of adjacent facial muscles. Using the electomyograph in refractory cases with the specific injection techniques described, provides additional safety factors that allow for placement of the toxin directly into the more active portions of the muscle. Accurate placement requires minimal toxin deposition to effect a positive clinical response. These small dose and volume requirements are likely factors that are responsible for the very low incidence of morbidity along with a high rate of successful clinical effects (Figures 10–12).



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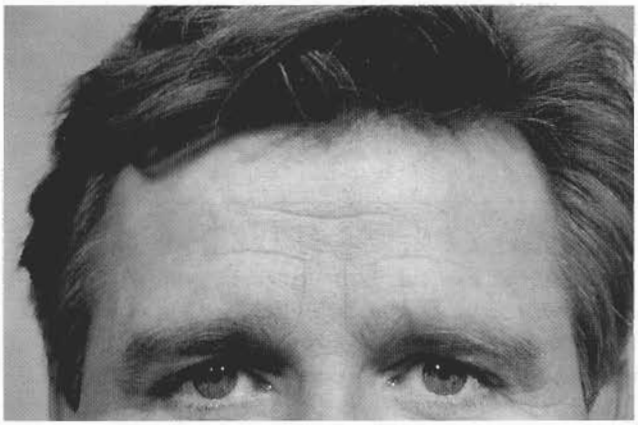

B

Figure 12. A) Patient with forehead creases before injection of botulinum toxin. B) Same patient 3 weeks after botulinum toxin injection unable to produce the forehead lines due to frontalis muscle weakness.

Conclusion

It is our experience that botulinum toxin is a safe and important adjunctive technique for the management of patients with hyperfunctional facial lines. Additional studies and research are necessary to determine the exact mechanism of botulinum toxin on both nerve and the neuromuscular pathways in addition to investigating other adjuvants that can be used concurrently to achieve longer periods of benefit.

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