Neurotoxin Treatment of the Upper Face

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Neurotoxin injections have continued to increase in popularity over the last decade. Currently, several different preparations of botulinum toxin type A (BTX-A)(onabotulinumtoxinA [Botox Cosmetic, Allergan, Inc]; abobotulinumtoxinA [Dysport, Medicis Aesthetics Inc]; incobotulinumtoxinA [Xeomin, Merz Aesthetics, Inc]) and botulinum toxin type B (BTX-B)(rimabotulinumtoxinB [Myobloc, Solstice Neurosciences, Inc]) are available in the United States. Although common injection techniques exist for the various muscle groups of the upper face, every patient is unique and should be individually assessed. Evaluating and understanding the muscular anatomy is crucial in mastering injection techniques and avoiding complications. On the horizon are exciting new topical and injectable forms of botulinum toxin (BTX) that will continue to influence the cosmetic art of rejuvenating the aging face.

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In the last decade, botulinum toxin (BTX) has revolutionized the art of cosmetic medicine. In 2011, BTX injections were ranked as the top nonsurgical procedure for the treatment of dynamic rhytides.[1] Neurotoxins produce a temporary and reversible chemical denervation of striated muscles by inhibiting the release of acetylcholine at the neuromuscular junction.[2] This article will focus on the use of neurotoxins for the treatment of upper facial rhytides.

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BACKGROUND

Derived from the spore-forming bacterium *Clostridium botulinum,* there are 7 different strains of toxin (serotypes A–G); the most commonly used serotypes include botulinum toxin type A (BTX-A) and botulinum toxin type B (BTX-B).[3] Preparations of BTX-A that currently are available in the United States include onabotulinumtoxinA (Botox Cosmetic, Allergan, Inc), abobotulinumtoxinA (Dysport, Medicis Aesthetics Inc), and incobotulinumtoxinA (Xeomin, Merz Aesthetics, Inc).

In 2002, the US Food and Drug Administration (FDA) approved Botox Cosmetic for the temporary improvement in the appearance of moderate to severe glabellar lines in patients 65 years of age or younger; Dysport was approved for the same indication in 2009. These preparations consist of a biologically active 150 kDa neurotoxin component within a 300 to 900 kDa protein complex.

Xeomin is the newest formulation of highly purified BTX-A and was granted FDA approval in July 2011 for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients. It is exclusively composed of a purely active neurotoxin and is free from nonactive complexing proteins.[4] Because foreign proteins

can induce neutralizing antibody formation, Xeomin is expected to have minimal immunogenic potential.[3]

RimabotulinumtoxinB (Myobloc, Solstice Neurosciences, Inc) is the only available form of BTX-B.[2] It currently is FDA approved for cervical dystonia but also has been found to be effective in the off-label treatment of dynamic rhytides. Botulinum toxin type B has been shown to produce a greater area of diffusion and more rapid onset of action than BTX-A in the treatment of moderate to severe forehead wrinkles. It also may be effective in the treatment of glabellar rhytides that are refractory to treatment with BTX-A. However, study participants have reported increased burning or stinging at BTX-B injection sites that may be attributed to the slightly acidic liquid formulation (pH 5.6) of BTX-B compared to BTX-A, which is reconstituted at a more physiologic pH of 7.4.[2]

MECHANISM OF ACTION

Botulinum toxin type A exerts its effects by weakening skeletal muscle. Normally the presynaptic neuromuscular nerve ending contains vesicles with the neurotransmitter acetylcholine. Neuronal stimulation initiates a cascade of events facilitated by the soluble *N*-ethylmaleamide sensitive factor attachment protein receptor (SNARE) complex that leads to the fusion of the acetylcholine-containing vesicle with the nerve cell membrane. Following the fusion of the vesicle with the cell membrane, acetylcholine is released into the synaptic cleft where it binds to receptors on muscle, causing muscle contraction.

The principal mechanism of action for BTX-A involves inhibition of vesicular fusion to the cell membrane. The neurotoxin first binds to the external surface of the motor nerve terminal; once bound, it becomes internalized and subsequently cleaves synaptosomal associated protein of 25 kDa (SNAP-25), a component of the SNARE complex. Cleaving SNAP-25 disrupts the synaptic fusion complex, so the vesicles storing acetylcholine cannot fuse with the nerve membrane, thus interrupting the release of acetylcholine into the neuromuscular junction.[5,6] Botulinum toxin type B works in a similar manner but affects synaptobrevin, another component of the SNARE complex and a vesicle-associated membrane protein.

The onset of action is observed 3 days to 2 weeks following administration of BTX-A for cosmetic purposes. The effects may last for 3 to 6 months, though a longer duration of action has been reported.[7] Interestingly, BTX-A may have a persistent effect at rest, even after muscle paralysis has reversed, possibly because of dermal remodeling, slight muscle atrophy, or behavior modification in the patient's muscle use.

INDICATIONS

Currently, BTX is available for the treatment of blepharospasm, cervical dystonia, chronic migraines, moderate to severe glabellar lines, severe primary axillary hyperhidrosis, strabismus, upper limb spasticity, and urinary incontinence due to neurologic disease.[8-10]

CONTRAINDICATIONS

General contraindications for BTX injection include hypersensitivity reactions to any BTX preparation or any of the formulation's components, including human albumin, lactose, and saline.[8] Patients with a history of neuromuscular disorders such as myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or an infection at the proposed injection site should not receive BTX injections. Patients also should be aware that certain medications can potentiate the effects of BTX injections, including aminoglycosides, curarelike nondepolarizing blockers, lincosamides, polymyxins, quinidine, magnesium sulfate, succinylcholine chloride, cyclosporine, and calcium channel blockers. Cholinesterase inhibitors may diminish the effects of neuromodulators.[8]

Botulinum toxin is considered a pregnancy category C drug and should not be administered during pregnancy. It is not known if the neurotoxin is excreted in breast milk; therefore, it should not be administered to a patient who is breastfeeding.

Relative contraindications include patients with unrealistic goals as well as those with a history of psychiatric disease such as body dysmorphic disorder.[7]

METHODS AND TECHNIQUES

Consultation

An initial consultation for BTX treatment is essential to discuss treatment goals and patient expectations. Using a mirror, ask the patient to point out what he/she considers to be his/her problem areas and address any existing facial asymmetry with him/her.

There are many factors that determine treatment sites and doses used, including the brow arch, asymmetry, ptosis, and muscle mass.[11] It recently has been suggested to evaluate patients using an upper face rating scale, which assesses the severity of rhytides and is considered a reliable tool for valid and reproducible assessment of the aging process.[12] These assessments evaluate glabellar and forehead lines and crow's-feet, most commonly utilizing a 5-point rating scale ranging from 0 (no sign) to 4 (very intense or observable signs). These scales can serve as a starting point for patients and dermatologists in identifying problem areas as well as for demonstrating treatment success during long-term follow-up.[12]

Preparation

(This section primarily discusses BTX-A preparations, as BTX-B is not yet FDA approved for cosmetic use.) Currently, Botox Cosmetic, Dysport, and Xeomin are packaged as vacuum-dried powders that must be reconstituted before treatment.[13] Prior to reconstitution, Botox Cosmetic and Dysport must be stored in a refrigerator at 2°C to 8°C, whereas unopened vials of Xeomin do not require refrigeration. Although Botox Cosmetic and Xeomin should be used within 24 hours of reconstitution, it is recommended that Dysport be administered within 4 hours because of concerns regarding decreased efficacy and bacterial growth[8-10]; however, longer reconstitution periods (up to 49 days) have demonstrated no decrease in efficacy or increase of bacterial contamination.[14]

Although dilution amounts often are debated, most dermatologists reconstitute 1 vial of neurotoxin with 1 to 3 cc of saline.[7] Some argue that using bacteriostatic saline can decrease pain and improve the longevity of the reconstituted material. Using a more concentrated solution allows for less pain on injection and more accurate placement of the product. Concentrated solutions also restrict diffusion, thereby decreasing the risk for diffusion-related side effects; however, the greater diffusion observed with less concentrated doses may allow for treatment of a broader area with a given dose of neurotoxin. Regardless of the amount of saline that is used, diffusion of 1.0 to 1.5 cm is common and should be noted while planning placement of injections to avoid denervation of nontarget musculature.[7]

The most common dilution ratios of Dysport units to Botox Cosmetic units are 2.5 to 1 and 3 to 1.[7] One study showed that Xeomin was equally as effective as Botox Cosmetic in a 1:1 ratio.[4]

Administration

For this section, all unit doses given will refer to Botox Cosmetic unless otherwise stated.

Glabella—Treatment of glabellar frown lines is the most common cosmetic application of BTX. The glabellar complex consists of the corrugator supercilii, procerus, depressor supercilii, and orbicularis oculi muscles. Understanding the muscular anatomy and function of each muscle is an essential part of performing neurotoxin injections. The corrugator supercilii muscles lower the eyebrows and form the oblique glabellar skin lines. The procerus muscle draws the medial angle of the eyebrows inferiorly and produces transverse wrinkles over the superior nasal bridge. The depressor supercilii muscle, a superomedial band of the orbicularis oculi, moves the brow inferomedially. Collectively, these muscles move and depress the eyebrows. Weakening these muscles with BTX-A effectively inhibits frowning and elevates the eyebrows.[11] Although mostly indicated for the treatment of dynamic glabellar rhytides, BTX-A also has been shown to effectively improve mild resting rhytides of the glabella.[15]

The neurotoxin should be injected intramuscularly via a syringe using a 30-gauge needle. The patient should be seated in an upright position, and injections should be aimed away from the eye. The product should be administered at 5 injection sites within the glabellar region (Figure 1). The neurotoxin should be injected into the belly of the procerus muscle. Each corrugator should receive 2 injections: 1 into the medial belly and 1 into the lateral tail of the muscle. Medial corrugator injections should be placed 1 cm above the bony supraorbital ridge to avoid ptosis. Injections in the procerus and medial corrugator muscles effectively treat the depressor supercilii muscle secondary to diffusion of the neurotoxin.

If the glabellar complex is treated without subsequent treatment of the brow-elevating frontalis muscle, unopposed action of the frontalis can cause a chemical brow-lift.[3] Additionally, injection at the tail of the eyebrow above the lateral canthus can weaken the inferior pull of the lateral orbicularis oculi muscle, further potentiating the brow-lift.

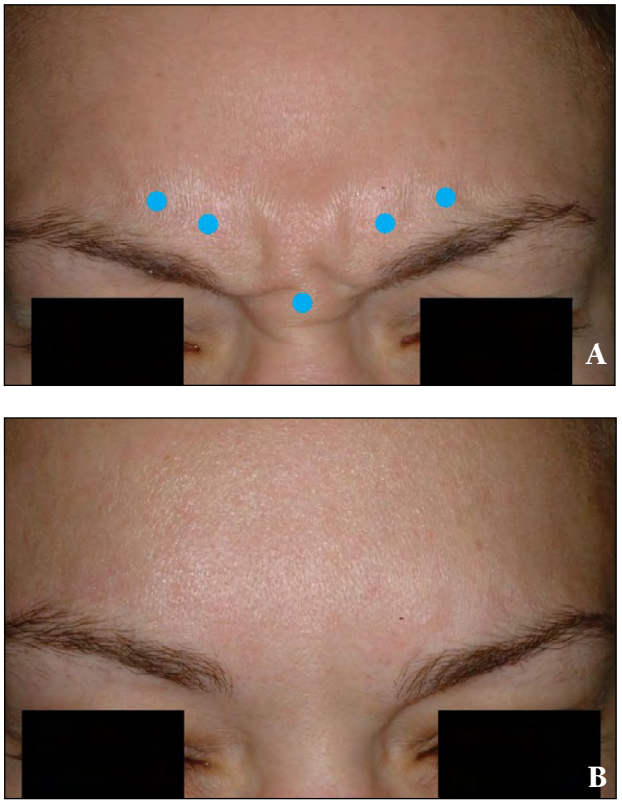

Figure 1. The glabella before (5 injection sites marked with blue dots)(A) and 8 days after treatment with onabotulinumtoxinA (Botox Cosmetic, Allergan, Inc)(B). Photographs courtesy of Mary P. Lupo, MD, New Orleans, Louisiana.

The initial dose for treatment of the glabella is approximately 20 U for Botox Cosmetic and 50 U for Dysport.[7] In one study, an initial dose of 24 U of Xeomin was comparable to the same amount of Botox Cosmetic[4]; however, larger doses may be needed. Using a single standardized dose is not optimal because gender and muscle mass affect the amount of product required for efficacy.

Lateral Canthus—Lateral canthal lines, known as crow's-feet, are caused by the movement of the lateral orbicularis oculi. The recommended dose of Botox Cosmetic for treating lateral canthal lines is 8 to 16 U divided into 3 or 4 injection sites. Injections are placed in a slightly curved arch lateral to the bony orbital rim (Figure 2A).[16] Although it is important to assess the muscle while it is contracted (while smiling), injections should be administered while the muscle is at rest to avoid accidental treatment of the zygomaticus complex, which can result in cheek drooping and upper lip ptosis. Instead of the intramuscular technique used in the glabella, an intradermal technique is most commonly used for injection of the lateral orbicularis oculi to minimize bruising.

The inferior portion of lateral orbicularis oculi also can be weakened to open the palpebral aperture of the eye and to smooth hypertrophy or bunching of the muscle within the inferior eyelid under the eye. This technique involves intradermal injection of 2 to 4 U of Botox Cosmetic 3 mm inferior to the ciliary margin at the midpupillary line. This process eliminates the jelly roll of skin below the eye, creating a smoother, more open aperture (Figure 2B).[17]

Upper Forehead—Contraction of the frontalis muscle causes horizontal forehead rhytides. This muscle is responsible for lifting the eyebrow; therefore, conservative treatment with neuromodulators is recommended. Treating only the medial frontalis muscle allows for unopposed action of the lateral frontalis muscle, enhancing lateral eyebrow lift.

Most dermatologists recommend treating the muscle with 8 to 15 U of Botox Cosmetic divided into 4 or 5 injections and injected into the belly of the muscle at least 2 to 3 cm above the eyebrow[18]; however, more injection sites may be necessary in patients with a larger forehead surface area and/or greater muscle mass (Figure 3).

Dorsal Nose—Contraction of the superior nasalis muscle causes radial rhytides of the lateral nasal root, or "bunny lines." Approximately 2 to 4 U of Botox Cosmetic injected into the belly of each side of the superior nasalis muscle softens these lines.[18]

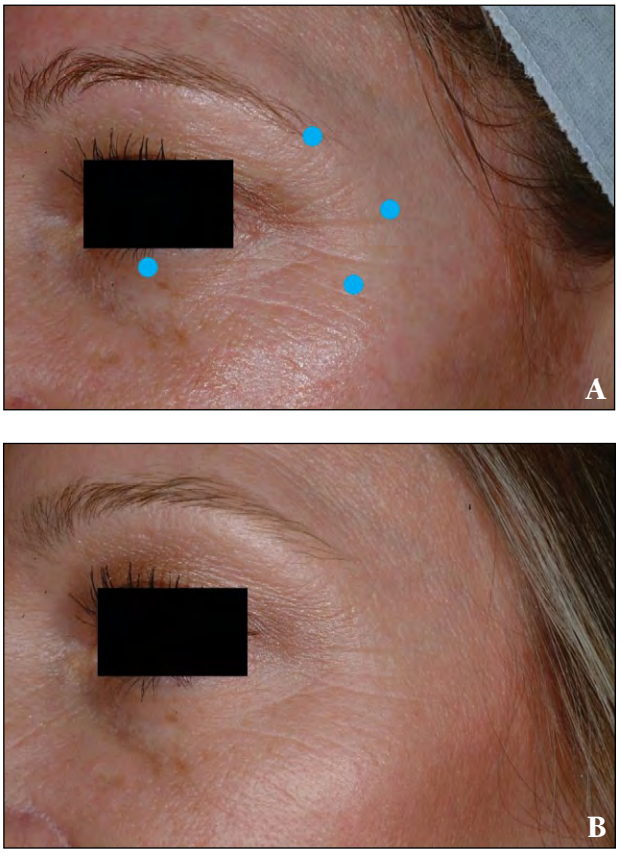

Figure 2. The lateral canthus before (4 injection sites marked with blue dots)(A) and 2 weeks after treatment with abobotulinumtoxinA (Dysport, Medicis Aesthetics Inc)(B). Photographs courtesy of Mary P. Lupo, MD, New Orleans, Louisiana.

COMPLICATIONS

Complications from treatment of rhytides with BTX usually are mild and self-limited.[7] The most common complications associated with BTX-A are injection site reactions including pain, erythema, and edema. Pain can be managed by the application of topical anesthetic preparations 30 minutes before treatment. Reconstituting BTX-A with preserved saline also has been associated with a reduction of pain, possibly because the preservative benzyl alcohol acts as an anesthetic. Ecchymoses also may occur and can be prevented by avoiding aspirin, nonsteroidal anti-inflammatory drugs, and high doses of vitamin E for 1 week prior to treatment. Removing makeup prior to neurotoxin injection allows for a better view of the superficial blood vessels. Headache, forehead rigidity, a heavy feeling in the forehead, and vertigo are not uncommon reactions. Flulike symptoms also have been reported, but the incidence is equal to placebo.[7]

Less common complications include eyelid and eyebrow ptosis. Eyelid ptosis occurs when larger doses or high volumes of neurotoxin are used to treat the corrugator supercilii muscles. Neurotoxin can diffuse through the orbital septum and affect the function of the levator palpebrae superioris muscle. Ptosis can be treated with

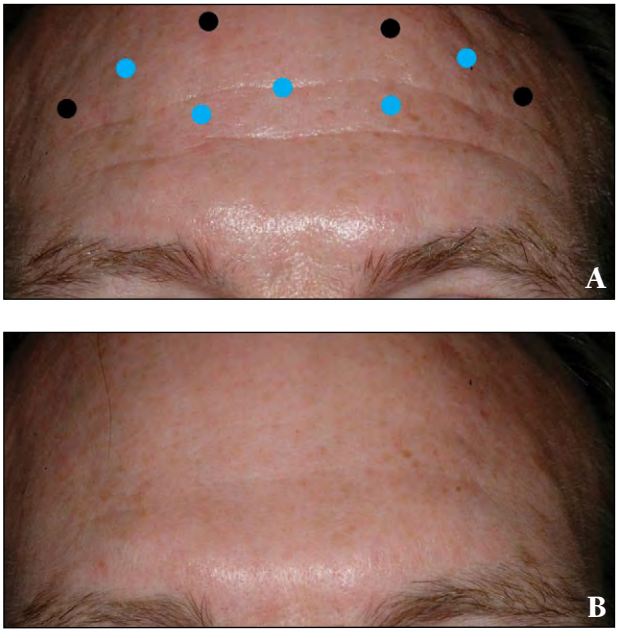

Figure 3. The upper forehead before (5 standard injection sites marked with blue dots; 4 additional injection sites marked with black dots)(A) and 3 weeks after treatment with abobotulinumtoxinA (Dysport, Medicis Aesthetics Inc)(B). Photographs courtesy of Mary P. Lupo, MD, New Orleans, Louisiana.

α-adrenergic agonist (apraclonidine 0.5% or phenylephrine hydrochloride 2.5%) ophthalmic drops twice daily to the affected side. Treatment can result in a 1- to 2-mm temporary elevation of the eyelid. Eyebrow ptosis can result from large doses, inferior injection, or extreme lateral injection of the frontalis muscle. It is important to place injections at least 1 cm above the superior orbital rim. The rate of eyelid and eyebrow ptosis appears to be determined by the skill and experience of the injector.[19] Careful patient selection also is important in preventing adverse outcomes from treatment with neurotoxins, as patients with a history of intermittent ptosis, lazy eye, or tears in the levator palpebrae superioris muscle should not receive BTX injections.[11] Alternatively, a quizzical or cockeyed appearance of the eyebrows can result from undertreatment of the lateral frontalis muscle. Although it is important to inject conservatively in this area to avoid lateral eyebrow droop, 1 to 2 U of Botox Cosmetic injected in each side of the lateral frontalis can soften the appearance of this complication.[18]

Injection of the orbicularis oculi muscle is not without complication. Drooping of the cheeks or upper lip can occur when trying to inject the lateral orbicularis oculi to treat periorbital rhytides. Accidental injection or diffusion of the neurotoxin into the zygomaticus complex is the cause of this complication. Additionally, diplopia can be caused by medial migration of BTX-A from the lateral orbicularis oculi muscle to the lateral rectus muscle. Keratoconjunctivitis sicca, or dry eye syndrome, can occur after injection of the inferior orbicularis oculi muscle. Also, if the lateral and inferior orbicularis oculi muscles are completely weakened, they can create a hallowing of the lower orbit that is not cosmetically pleasing to most patients. Therefore, conservative treatment to weaken the muscle for a natural result is preferred.

A complication of Botox Cosmetic and Dysport injections in general is the development of antibodies to the complexing proteins. Antibody formation has been demonstrated in 4.3% to 11.9% of patients.[3] Risk factors for developing antibodies include receiving large doses of BTX-A at short injection intervals. Currently, "booster injections," defined as minimal doses injected at 2-week intervals, are not recommended.[20] Once a patient has developed antibodies to these BTX-A preparations, it has been hypothesized that treatment with Xeomin can be initiated to recapture response.[3]

ON THE HORIZON

Although neurotoxin treatment of upper facial rhytides has gained popularity exponentially over the last decade, less than 10% of consumers in the target demographic for BTX-A treatments have actually received treatment.[6] It is possible that creating less painful, more affordable BTX products will persuade potential patients to seek treatment. Several topical forms of BTX-A are on the horizon. One preparation by Revance Therapeutics, Inc (RT 001), has been shown to substantially reduce the severity of lines of the lateral canthus.[21] Transdermal Corp has developed an FDA-approved topical BTX-A cream (CosmeTox) that uses ionic nanoparticle technology for transdermal delivery of the neurotoxin.[6] Another topical BTX-A product, Azzalure (Galderma S.A.), was adapted from Dysport and has already been approved in several European countries.[7]

In addition to novel topical BTX-A therapies, new injectable neurotoxins are forthcoming. Purtox (Mentor Corporation) currently is undergoing US clinical trials.

CONCLUSION

Botulinum toxin has become a paramount tool in treating the aging face. It is now common to use neurotoxins in combination with other treatments, such as dermal fillers, chemical peels, and laser resurfacing. Combining treatments facilitates a 3-dimensional approach involving muscle control, volume restoration, and recontouring. An important concept to remember is that each patient is unique and should be approached individually to ensure the best outcome.

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