Botulinum Toxin Use in the Upper Face

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KEYWORDS

• Botulinum toxin • Neurotoxin • Facial rhytids • Brow ptosis • IncobotulinumtoxinA • OnabotulinumtoxinA
• Lateral canthal rhytids

KEY POINTS

- Botulinum toxin is a potent exotoxin that disrupts neuromuscular transmission by inhibiting the release for acetylcholine from the presynaptic membrane resulting in attenuation of muscle contraction.
- There are 3 formulations of Botulinum toxin A approved for cosmetic use in the United States: onabotulinumtoxinA (Botox), incobotulinumtoxinA (Xeomin), and abobotulinumtoxinA (Dysport).
- All 3 products are US Food and Drug Administration approved for the reduction of dynamic glabellar rhytids with the exception of Botox, which is also approved for the treatment of mimetic lateral canthal rhytids. Much of its use is off-label.
- Most complications can be avoided with knowledge of the functional anatomy of the upper face as well as proper injection technique. Some of the more serious complications include brow and/or eyelid ptosis and diplopia.
- The administration of neurotoxin has evolved to become individualized. More sophisticated injection techniques have allowed the clinician to sculpt the brow in a favorable fashion while preserving animation.

Introduction

The nonsurgical treatment of the aging face is centered on identifying the cause of changes to the quality and texture of skin as well as the volume deficiencies in the dermis and underlying tissue. Hyperdynamic rhytids, particularly in the facial upper third, not only can be visually undesirable but, over time, also can result in dermal atrophy and corresponding static facial rhytids. These changes, in concert with dermal photoaging, contribute to the stigmata of the aging face.

Since the introduction of botulinum toxin (BoNT) for the reduction of glabellar rhytids in 1992 and the corresponding US Food and Drug Administration (FDA) approval of the neurotoxin for this therapeutic indication over a decade later, the use of neurotoxins or neuromodulators for cosmetic purposes has seen unprecedented growth.[1] In fact, between 2000 and 2014, there has been a 700-fold increase in the number of annual injections.[2] According to data from the American Association of Plastic Surgeons, there were 6.3 million cosmetic neurotoxin injections performed in the United States in 2013.[2] BoNT injections remain the most common nonsurgical cosmetic treatment for facial rhytids worldwide.

BoNT is an exotoxin, produced by the obligate anaerobe *Clostridium botulinum*, a spore-forming gram-positive rod found in the soil. The toxin causes the disease Botulism, a form of food poisoning that is quite rare today because heating destroys the toxin and because the addition of nitrates to processed meats prevents the growth of the bacteria.[3,4] Several serotypes of the toxin are produced by the bacteria with types A, B, and E being known to cause disease in humans.[3,5] The toxin is a dimeric protein that acts at the neuromuscular junction (NMJ). It binds to the presynaptic membrane of the NMJ and enters the terminal neuron via receptor-mediated endocytosis.[4,5] The acidic environment within the endosome cleaves the complex into its active metabolites.[5] The net effect is irreversible inhibition of acetylcholine release and decreased contraction of the motor unit. With ongoing turnover of the NMJ, however, contractile function returns after several weeks, which correlates with the return of pretreatment muscle strength, 3 to 4 months after injection.[3,4]

BoNT is currently used for several conditions in which the desired result is relaxation or even paralysis of targeted musculature. It has been used to treat a variety of conditions, including strabismus, blepharospasm, hemifacial spasm, dystonia, hyperhydrosis, headache, and facial wrinkling.[1,3,5–8] Novel therapeutic uses are continuously being reported across a spectrum of medical specialties. Its use in cosmetic medicine lies in the denervation of the mimetic muscles of facial expression, thereby reducing the pull of these muscles on the overlying skin. The net effect is temporary reduction in the appearance of dynamic lines.

Preoperative planning and pretreatment assessment

Product selection

There are currently 3 formulations of BoNT commercially available that are FDA approved for cosmetic use: onabotulinum-toxin A (onaBoNT-A, Botox; Allergan Inc, Irvine, CA, USA), abobotulinum-toxin A (aboBoNT-A, Dysport; Galderma Laboratories, LP, Fortworth, TX, USA), and incobotulinum-toxin A (incoBoNT-A, Xeomin; Merz Pharmaceuticals, LLC, Greensboro, NC, USA). All formulations are FDA approved for the treatment of globular rhytids in patients 18 to 65.[9–11] However, onaBoNT

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(Botox) is the only product with additional FDA approval for the treatment of lateral canthal lines.[9] Rimabotulinum-toxin B (RimaBoNT-B, Myobloc; Soltice Neurosciences Inc, San Francisco, CA, USA) is FDA approved for the treatment of cervical dystonia. This product is also used off label in nonresponders to serotype A of the toxin.

Variations between the 3 commercially available products in potency, onset time, therapeutic duration, and immunogenicity are not significant.[12] It should be noted that unit dosing for all BoNT-A formulations is not interchangeable, and therapeutic endpoints are achieved with different unit doses—most notably between aboBoNT-A (Dysport) and the other 2 serotypes.[4,12] Botox and Xeomin are dosed in comparable unit values, whereas Dysport requires 2.5 to 3 times of its own unit value (Speywood units) to achieve the same clinical result.[12]

Product storage

All commercially available BoNT-A products are stored as a lyophilized powder in a vacuum-sealed container. Both Botox and Dysport are shipped in dry ice and require storage in temperatures between 2°C and 8°Cwith a stable shelf life at this temperature of 2 to 3 years.[9,11] Xeomin, however, has a stable shelf of 3 years at temperatures ranging from −20°C to 25°C and therefore does not require refrigeration for shipment.[10] All 3 products, however, require refrigerated storage between 2°C and 8°Cafter they are reconstituted, for use in patients. Although all neurotoxin vials are marketed and labeled for single use within 24 hours of reconstitution, most clinicians store reconstituted product for significantly longer periods of time. In fact, a general consensus exists that product refrigerated at 2°C to 8°C can be effective for up to 6 weeks.[13,14] There are some investigators who advocate freezing the product after reconstitution to allow it to retain its potency for up to 6 months.[13]

Product dilution

Product dilution is an area of frequent controversy. Toxin concentrations vary among treating clinicians, area used, and indication. Patient preference also has some impact on the concentration of neurotoxin used. The author prefers a more dilute mixture and corresponding decreased dose of neuromodulator for cosmetic use because it provides what is thought to be a softer look. For treatment of dystonias and in patients with more pronounced dynamic rhytids, the author uses more concentrated product. Theoretically, a less concentrated (greater diluent) product carries with it a greater risk of diffusion or more appropriately spread, and the potential for complications, and inadequate therapeutic outcomes. However, this has shown not to be the case.[15,16] Recommended product dilutions are shown in Table 1. All manufacturers recommend reconstitution with preservative-free normal saline; however, most clinicians seem to agree that preserved saline is a preferred diluent because the 0.9% benzyl alcohol appears to impart a mild analgesic effect without compromising the product potency or longevity.[17] Diluent is drawn up in a 3-mL syringe and a blunt-tip needle. The needle is then used to pierce the stopper of the product vial, and most of the saline is taken up automatically by vacuum pressure (Fig. 1), with the need for only gentle pressure to push the remainder of the diluent into the vial. The reconstituted mixture is then rolled to gently dissolve the product. Several investigators advise against vigorously shaking the vial because this could create foaming and decrease its potency. Other investigators have found this not to be true. Because Xeomin is stored as an actual powder, Merz Pharmaceuticals recommends inverting the cap while reconstituting the product to ensure any leftover product under the cap is dissolved.[10] Missing this step in the reconstitution of incoBoNT-A may be a reason for the anecdotal reports of Xeomin having a decreased duration of action when compared with Botox. Indicated volume of product is drawn up using a 1-mm Luer-Lock syringe and a 20-gauge needle, and then a 33-gauge 0.5-inch needle (Sterjet needle; TSK Laboratories, Tochigi-Ken, Japan) is used to inject the product (Fig. 2). Some investigators advocate the use of a 31-gauge diabetic syringe (hubless needle and attached syringe) to both draw up product from vial and inject patients.[3] The author feels that, while this technique ensures less waste of product, for multiple injection sites, the needle on a diabetic syringe blunts quickly, producing more injection site pain. For most injections in the upper face (with the exception of heavy dynamic glabellar rhytids), the author uses a concentration of 2 unit/0.1 mL or 20 units in a 1-mL Luer-Lock syringe. For more pronounced hyperdynamic rhytids and in patients insistent on

Table 1 Type and concentration of botulinum toxin

Product Toxin	Concentration (units/mL)
Dysport 300-unit vial	
1.5 mL	20/0.1
3 mL	10/0.1
Botox 100-unit vial	
2.5 mL	4/0.1
5 mL	2/0.1[a]
Xeomin 100-unit vial	
2.5 mL	4/0.1
5 mL	2/0.1[a]

Sample dilutions of different BoNT products.
[a] Denotes a dilute mixture often used by the author in the forehead and occasionally the glabella to impart a softer look to treatment, resulting in an appreciable preservation of animation while blunting mimetic lines.

Fig. 1 Reconstitution of BoNT with preserved normal saline. The vacuum seal within the vial draws up the diluent automatically.