The Role of Neurotoxins in the Periorbital and Midfacial Areas

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KEYWORDS

• Botulinum toxin • Neurotoxin • Facial rhytids • AbobotulinumtoxinA • IncobotulinumtoxinA • OnabotulinumtoxinA • RimabotulinumtoxinB

KEY POINTS

- Three neurotoxin formulations are approved for cosmetic use in the United States: onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin).
- Selection is dictated by injector and patient preference, patient history, and the presence of allergies, among other considerations.
- No 2 toxins are exactly the same unit for unit, and there is no universally accepted formula for unit conversion.
- Complications of botulinum neurotoxin injection, such as eyelid ptosis, brow ptosis, and double vision, can be reduced with appropriate reconstitution and injection techniques.
- The trend has been toward an individualized, sculpted approach that preserves baseline facial animation and accounts for the gender, ethnicity, individual preference, and professional needs.

Videos of female and male glabellar injections and lateral canthal line injection accompany this article at http://www.facialplastic.theclinics.com/

INTRODUCTION

The concept of therapeutic botulinum toxin (BoNT) injection was ushered in by Dr Allen Scott's landmark study in the late 1970s, which demonstrated safety and efficacy for the treatment of adult strabismus.[1] The US Food and Drug Administration (FDA) approved the first commercial BoNT formulation, onabotulinumtoxinA, for the treatment of strabismus and blepharospasm in 1989. After Carruthers and Carruthers[2] first recognized the dramatic reduction of glabellar rhytids in patients treated for essential for blepharospasm, however, it took more than a decade for the FDA to extend approval to esthetic indications, long after the toxin was already popularized for cosmetic use.

Since the approval of cosmetic Botox in 2002, the number of annual treatments has skyrocketed, making BoNT injections the top nonsurgical esthetic enhancement worldwide for more than a decade. Facial injections were the single most common cosmetic procedure in 2011, accounting for 41% of all esthetic interventions performed in the United States.[3] According to 2013 data from the American Society of Plastic Surgeons, 6.3 million cosmetic BoNT A injections were performed, nearly 3 times the number of dermal filler treatments.[4] Market

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expansion continues at an impressive rate, particularly among men. The number of males seeking cosmetic injections has grown by 268% since 2000.[3] Satisfaction and rates of return for repeat injections are very high, making it both an excellent source of practice revenue and an effective way of introducing patients to other cosmetic treatments.

Seven distinct serotypes of BoNT (A–G) have been isolated from different strains of *Clostridium botulinum*.[5–7] Only BoNT-A and BoNT-B, which function exclusively in cholinergic neurons, have been approved for clinical use.[5] There are currently 4 neurotoxin formulations available for injection in the United States: onabotulinumtoxinA (onaBoNT-A, Botox, Allergan, Inc, Irvine, CA), abobotulinumtoxinA (aboBoNT-A, Dysport, Galderma Laboratories, L.P., Fort Worth, TX), incobotulinumtoxinA (incoBoNT-A, Xeomin, Merz Pharmaceuticals, L.L.C., Greensboro, NC), and rimabotulinumtoxinB (rimaBoNT-B, Myobloc, Solstice Neurosciences, Inc, San Francisco, CA). All 3 BoNT-A preparations are approved for the correction of moderate-to-severe glabellar lines but only onaBoNT-A is approved for lateral canthal lines; all other uses remain off label.[8]

In nature, BoNT consists of a 150-kDa core. With the exception of incoBoNT-A, this core is surrounded by varying amounts of nontoxic complexing proteins.[9] These proteins are thought to stabilize the neurotoxin, protecting it from pH and temperature fluctuations as well as lytic enzymes.[10] Although these accessory proteins confer an obvious advantage to the *Clostridial* bacillus during gastrointestinal transit, the benefits are less clear for therapeutic use. In fact, there is mounting evidence that the presence of complexing proteins merely increases neurotoxin antigenicity without prolonging product shelf life.[11] Accordingly, most manufacturers have worked to reduce the foreign protein load present in each unit of BoNT.

BoNT functions at the level of the neuromuscular junction by blocking acetylcholine release, thus decreasing contraction of the motor unit. It is taken up in the presynaptic terminal via receptor-mediated endocytosis.[9] In the acidic environment of the endosome, a disulfide bond is cleaved, separating the core protein into heavy and light chains, which are the active moieties.[5,9,12] By irreversibly inhibiting components of the SNARE complex, BoNT prevents nontoxic exocytosis; BoNT-A cleaves SNAP-25, whereas BoNT-B cleaves synaptobrevin.[5,13]

With ongoing turnover at the neuromuscular junction, however, contractile function begins to return after several weeks, and usually attains pretreatment strength by 6 months.[13] From a cosmetic and therapeutic standpoint, treatments generally remain effective for 3 to 4 months, and there is no evidence of tachyphylaxis in the majority of patients.[9,14]

TREATMENT GOALS

The superficial facial mimetic muscles insert directly onto the undersurface of the skin; repetitive contraction therefore causes characteristic furrows (rhytids) to form perpendicular to the direction of contraction. Although injection of BoNT does not eliminate static wrinkling, it can reduce dramatically the appearance of hyperdynamic lines in the midface and periocular region via selective chemodenervation.

Since the introduction of cosmetic Botox, treatment goals and therapeutic endpoints have continued to evolve. The trend has been away from a one-size-fits-all 'frozen' appearance, and toward a more subtle, individualized approach. It is important to account for the gender, ethnicity, individual preference, and professional needs of each patient. With careful appraisal of each patient's anatomy, injection can produce a harmonious appearance in which facial animation is preserved. By selectively targeting depressors in preference to elevators, modest lifting and sculpting can also be achieved.

Synergies can be obtained by combining BoNT injection with dermal fillers, cutaneous lasers, retinoids, and facial plastic surgery.[12] Because most rhytids have both static and dynamic contributions, the optimal approach often combines neurotoxin and dermal filler injections. A number of studies report improved patient satisfaction and more durable results when BoNT and hyaluronic acid treatments are administered in tandem.[15,16]

PREOPERATIVE PLANNING AND PREPARATION

Selecting a Product

Three different formulations of BoNT-A are available for cosmetic injection in the United States. RimaBoNT-B has a demonstrably shorter half-life and is only FDA approved for treatment of cervical dystonia; its use is therefore typically limited to secondary nonresponders.[17–19] Comparing the efficacy of onaBoNT-A, aboBoNT-A, and incoBoNT-A is difficult because available head-to-head trials have enrolled relatively small numbers of subjects and are often industry sponsored. On the whole, these products have more similarities than differences; variations in potency, speed of onset, therapeutic duration, and immunogenicity are relatively minor when compared with BoNT-B.[20] Important factors in product selection, therefore, include physician comfort and familiarity