Botulinum toxin A in the mid and lower face and neck

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Although once considered a novel concept, the use of botulinum neurotoxins, primarily botulinum types A (BTX-A) and B (BTX-B), to smooth hyperkinetic lines in the upper face has become an accepted and successful procedure in facial rejuvenation. In the mid and lower face and neck, botulinum toxin injections diminish rhytides and sculpt the face into more aesthetically pleasing lines. The doses used in the mid and lower face and neck differ greatly from those in the upper face, however, and only experienced clinicians with a detailed understanding of the underlying muscular anatomy and tissue relationships should inject in areas associated with more risk of potential complications. This article reviews current approaches to botulinum toxins as primary and adjunctive therapies in the mid and lower face and neck.

Botulinum toxins

Botulinum neurotoxins derive from the bacterium Clostridium botulinum and include seven distinct serotypes, identified as A, B, C₁, D, E, F, and G [1]. These serotypes share the ability to block neurotransmission at the neuromuscular junction by blocking acetylcholine release, producing denervation and atrophy of cholinergic skeletal muscles. Because the neurotoxin serotypes differ in their cellular mechanisms of action and in the size of the neurotoxin complex, however, they are not interchangeable and their clinical profiles vary. BTX-A is the most powerful toxin and was the first to be developed for clinical use.

At this time in North America there are two commercially available toxins: Botox (BTX-A) and Myobloc (BTX-B). Botox is the only botulinum toxin currently approved for cosmetic use in North America, although Dysport (BTX-A) is available in Europe and is under consideration for licensing by the US Food and Drug Administration. Because each preparation differs in terms of the C botulinum strain, potency, and manufacturing, the biologic behaviors of each are not interchangeable, and the dosages for each product vary. For most procedures, 1 U of Botox has efficacy equivalent to 3 to 5 U of Dysport. Botox is distributed in a crystalline form with approximately 100 U per vial. The package insert recommends reconstitution with sterile, nonpreserved saline [2]. Recent data, however, suggest that reconstitution with preserved saline does not impair the stability of BTX-A [3,4] and is less painful than nonpreserved saline [5]. The optimum concentration depends on the procedure. Although the package insert suggests that the reconstituted toxin should be used within 4 hours, evidence now indicates that the reconstituted product can be stored refrigerated for a week or longer without any loss of efficacy [6].

Myobloc is available in a liquid formulation containing BTX-B, 5000 U/mL, and is available in 0.5-, 1-, and 2-mL vials containing BTX-B, saline, human serum albumin, and sodium succinate, with a pH of approximately 5.6 (accounting for the stinging sensation reported on injection) [7]. Reconstitution is not required and is hampered by “overfill” of the vials. Clinicians with the desire to add saline are advised to do so in the syringe. The unopened vial is stable for months or years; once opened, the labeling is similar to BTX-A.

Dysport is available as a lyophilized vial containing 500 U of BTX-A and sodium chloride, lactose,
and human serum albumin [8]. In Europe, Dysport is labeled for transport at ambient temperature and storage at 2°C to 8°C, and the guidelines for reconstitution and use are similar to those for Botox.

**Clinical application of botulinum type A**

Intramuscular injections of BTX-A have become the treatment of choice for most forms of focal dystonia. The ability of botulinum toxin to block acetylcholine release from autonomic nerve endings innervating glandular tissue or smooth muscle has led to investigation of its use for other indications including hyperhidrosis [9,10] and gastrointestinal disorders [11–14]. More recently, BTX-A has been reported to have beneficial effects in relieving myofascial pain [15,16] and tension and migraine headache [17–22], and for the treatment of obesity [23]. Because most of the authors’ clinical experience resides with Botox, all references hereafter refer to the Botox or Botox Cosmetic formulations, unless otherwise specified. Clinicians should be aware, however, of the significant clinical differences between the sources of BTX-A and adjust dosages accordingly.

**Contraindications**

Botulinum type A is contraindicated in patients with neuromuscular disease, such as myasthenia gravis and amyotrophic lateral sclerosis [2]. Experience with BTX-A in pregnant and lactating women is extremely limited, so caution is warranted in these cases (the authors believe that use in pregnancy is contraindicated). Other contraindications include infection at the injection site, or a known hypersensitivity to any of the product contents. The possibility of drug interactions exists, and patients taking aminoglycoside antibiotics should receive smaller doses.

**Dosing**

The effects of BTX-A injections begin to appear within 1 to 2 days and typically last for 3 or 4 months or longer. There is a tendency for repeated injections to show a longer duration of effect. Larger muscles require larger unit doses of BTX-A. The volume of the dose should be adjusted according to the desired diffusion of toxin: more concentrated doses diffuse less and should be used to target small muscles. Among cosmetic users, the average volume of diluant has been reported to be 2.5 mL [3], but the authors typically dilute the vial in 1 mL. In general, higher doses of BTX-A delivered in smaller volumes keep the effects more localized and allow for the precise placement of the toxin with little diffusion, whereas smaller doses in larger volumes tend to cause more widespread effects [24].

One of the greatest concerns with the use of BTX-A is the formation of neutralizing antibodies. The total protein concentration and number of units injected are critical in determining potential immunogenicity, and some studies suggest that BTX-A injections at more frequent intervals or at higher doses may lead to a greater incidence of antibody formation [2]. The protein concentration in the current lots of Botox is significantly lower than in previous lots, however, and has been shown to be less antigenic than the original product. The overall risk of antibody formation using BTX-A at recommended doses for cosmetic applications is low, and injecting the lowest effective dose with the longest feasible intervals between injections minimizes the potential for immunogenicity.

**Midface indications**

*Hypertrophic orbicularis*

Widening the palpebral aperture is part of the new “artistry” of BTX-A in facial contouring and sculpting. Hypertrophy of the pretarsal portion of the orbicularis oculi can give a “jelly roll” appearance. In some patients, the act of smiling transiently diminishes the perceived size of the palpebral aperture, especially in Asian patients, who sometimes desire a more round-eyed appearance. Flynn et al [25] injected 2 U subdermally, 3 mm inferior to the lower pretarsal orbicularis, in addition to three injections of 4 U placed 1.5 cm from the lateral canthus, each 1 cm apart and found a mean palpebral aperture increase in 86% of patients of 1.8 mm at rest and 2.9 mm at full smile [25]. One must be careful, however, to select patients who have a good preinjection snap test and who have not had previous lower eyelid ablative resurfacing or infralash blepharoplasties without a coexisting canthopexy to support the normal position of the lower eyelid. Goldman [26] reports one case in which a patient developed festooning of the infraocular area 2 to 3 days following injections of 10 and 2 U BTX-A in the midlateral canthal region and 2 to 3 mm below the ciliary margin in the midpapillary line, respectively.
Bunny lines and nasal flare

Contraction of the muscular fibers of the upper nasalis across the bony dorsum of the nose causes fanning rhytides (bunny lines) at the radix of the nose. Weakening of the underlying mimetic musculature with botulinum toxin effectively and dramatically softens these lines. The authors inject 2 to 4 U of botulinum toxin into the belly of the upper nasalis as it transverses the nasal bone. The injection should be given high on the lateral nasal wall, inferior to the angular vein. Care must be taken to give the injection well above the nasofacial groove to avoid relaxing the levator labii superioris and causing upper lip ptosis. Gentle massage should follow the injection to diffuse the toxin.

Some individuals repeatedly dilate their nostrils in social situations, revealing the sides of the columella and septum. Injecting 5 to 10 U BTX-A bilaterally into the lower nasalis fibers draped over the lateral nasal ala, at the most active area of muscle contraction, can decrease involuntary nostril flare in some patients for 3 to 4 months [24].

Nasolabial folds

Nasolabial (melolabial) folds extend from the lateral nasal ala to a point lateral to the external angle of the mouth. Older individuals who have sustained photodamage or who smile excessively develop a permanent, deep crevice. The most common treatment for these folds has been soft tissue fillers and laser resurfacing. Injecting BTX-A directly into the area of the fold is most likely to produce an asymmetric smile and upper lip ptosis. Weakening the lip elevator muscles and zygomaticus and risorius muscles, tempting although it may be, flattens the midface and elongates the upper lip. In patients who have a naturally shorter upper lip, however, very small doses (1 U) into each lip elevator complex in the nasofacial groove collapses the upper extent of the nasolabial fold but also elongates the upper lip. Because the effect is long lasting (± 6 months), one should select patients carefully and be sure to explain fully the aesthetic result of the procedure.

Perioral rhytides

The orbicularis oris is the sphincter muscle that encircles the mouth, lying between the skin and mucous membranes of the lips and extending upward to the nose and down to the region between the lower lip and chin. Sometimes called the “kissing” muscle, it causes the lips to close and pucker. Overactive orbicularis oris causes vertical perioral rhytides that are commonly labeled as “smokers’ lines” but can also result from heredity, photodamage, playing a musical instrument that requires embouchure, or even whistling. Patients often are disturbed by the increased vertical length of the cutaneous lip and by the radial upper lip lines that can cause lipstick to bleed upward from the lip and blur the outline of the lip. Although multiple fine wrinkles of the upper lip can be treated effectively with fillers, such as collagen, or with ablative or nonablative resurfacing, deeper wrinkles may be resistant to these treatments. Tiny doses (1 to 2 U per lip quadrant) are usually sufficient to result in localized microparesis of the orbicularis oris, especially when used adjunctively with a soft tissue augmenting agent, such as collagen, hylaruronan, or Artecol, and can greatly improve the appearance of the lip without creating a paresis that might interfere with elocution and suction.

To maintain competence of the mouth it is important to be conservative with dosing and to use superficial, rather than deep, injections [24]. Even low doses, however, may result in lip sphincter weakening that affects the ability of the individual to play musical instruments or whistle. Patients should be screened carefully; musicians who play wind instruments, professional singers or speakers, and patients with unrealistic expectations are not ideal candidates for this procedure.

Lower face indications

Botulinum toxin should be used with caution for cosmetic indications in the area of the mouth. Doses are much reduced in comparison with those used for the upper face, and the underlying muscular anatomy varies from patient to patient.

Mouth frown and melomental fold

The frowning expression created when the lateral corners of the mouth are permanently angled downward gives an impression of disapproval and unpleasantness, even in the absence of a discrete melomental fold or “drool groove.” The depressor anguli oris (DAO) pulls down the corner of the mouth in opposition to the zygomaticus major and minor muscles. BTX-A injections can weaken the DAO and reset the muscular balance, allowing the zygomaticus to elevate the corners of the mouth and return them to a horizontal position (Fig. 1) [24]. In the authors’ clinic, 2 to 3 U of botulinum toxin are injected directly into the DAO on each side of the mouth.
Melomental folds (drool grooves or marionette lines) extending from the downturned corner of the mouth to the lateral mentum involuntarily produces a sad expression and reinforces the negative impression produced by the inverted smile. They also give the appearance of advancing age and decrepitude. Traditionally, soft tissue augmentation has been used alone to rebuild the soft tissue support of the lateral mouth corner and the melomental fold, but the effects are short term. Injections of BTX-A are useful adjuncts to soft tissue augmentation, relaxing the muscles and lengthening the duration of the filling-agent effect, such as Zyplast, Hylaform, Restylane, Perlane, or Artecol, by preventing the repeated molding of the implant [27]. BTX-A in combination with laser resurfacing produces the most satisfactory results. The authors inject 2 to 5 U BTX-A into each DAO immediately above the angle of the mandible and 1 cm lateral to the lateral oral commissure.

Caution must be used when placing injections close to the mouth. Injections too medial can cause an ipsilateral weakness of the depressor labii and flattening of the lower lip contour when the mouth attempts to form an “O,” and injections placed too high can interfere with the sphincter function of the orbicularis oris, leading to difficulties with speech and suction. Other possible complications include flaccid cheek, incompetent mouth, difficulty with elocution, and asymmetric smile. Injections are not recommended for singers or musicians, or for patients who use their perioral muscles with intensity.

Mental crease and peau d’orange chin

Contraction of the mentalis produces a deep groove, or mental crease, between the lower lip and the prominence of the chin. Soft tissue augmentation in the mental crease leads to visible beading and poor results. Injections into the mentalis at the bony mentum softens the crease while avoiding an incompetent mouth, which can occur from BTX-A injections at the level of the crease. The authors usually inject 3 to 5 U BTX-A per mentalis band.

The mentalis serves to raise and protrude the lower lip and wrinkles the skin of the chin, producing horizontal or multiple dimple rhytides called the

Fig. 1. Treatment of depressor anguli oris with botulinum type A.
“apple dumpling” or “peau d’orange” chin. Previously treated with soft tissue augmentation and laser resurfacing, chin dimpling responds well either to BTX-A plus soft tissue augmentation or BTX-A alone. The authors inject 5 to 10 U BTX-A into the mentalis at the most distal point from the orbicularis oris, the prominence of the chin. Following the injection, massage of the chin is recommended to aid in the diffusion of toxin.

**Smile lines**

Deep smile lines, produced by contraction of the zygomaticus and often connected to lower crow’s feet lines, are best treated with carbon dioxide laser resurfacing. One to 2 U BTX-A injected into each side of the zygomaticus before resurfacing, however, enhances the effects of the procedure [28].

**Upper gum show**

In some patients, the levator labii superioris alaeque nasi retracts the upper lip and produces excessive upper gum exposure, revealing the gum line, upper incisors, and canines. Injecting 1 to 2 U BTX-A into the levator labii superioris on each side of the bony nasal prominence drops the upper lip enough to correct the upper gum show [27]. Because vertical elongation of the cutaneous lip can occur after injections (a process that occurs naturally with aging), treatment produces optimal results in younger patients. The best results are often obtained when BTX-A is used in combination with soft tissue augmentation in the lip margins.

**Facial asymmetry**

Correction of midfacial asymmetry, which may have bony tissue, soft tissue, or muscular etiology, is another artistic indication for BTX-A that requires a thorough knowledge of muscular anatomy and function. Physicians not comfortable with facial surface anatomy are advised to use the aid of an electromyography system for accurate placement of injections.

In hemifacial spasm, in which repeated clonic and tonic facial movements draw the facial midline over toward the hyperfunctional side, relaxing the hyperfunctional zygomaticus, risorius, and masseter with BTX-A injections allows the face to be centered at rest. Likewise, hypofunctional asymmetry, such as Bell’s palsy, can be alleviated by small injections (1 to 2 U into the zygomaticus, risorius, and orbicularis and 5 to 10 U in the masseter) on the normofunctional side [29].

Botulinum type A can be used to relax the jaw and relieve discomfort in patients who experience asymmetric jaw movements. Injections (10 to 15 U) are placed intraorally into the internal pterygoid on the hyperfunctional side.

Surgical cutting or traumatic lesion of the orbicularis oris or the risorius muscle can result in an off-centered mouth caused by the unopposed action of the partner muscles in the normally innervated side. Correction can be achieved by treatment of the risorius immediately lateral to the corner of the mouth on the normally innervated side. In patients with congenital or acquired unilateral weakness, who cannot depress the corner of one side of the mouth, BTX-A injected into the partner muscle restores functional balance.

**Masseteric hypertrophy**

Preliminary investigations show that BTX-A may be a simple alternative with a short recovery period for facial contouring in patients with masseteric hypertrophy. To et al [30] injected 200 to 300 U of Dysport per side in five patients with unilateral and bilateral hypertrophy of the masseter. All five patients showed a good response, with the maximal effect of a 31% reduction in muscle bulk 3 months after treatment. Three out of nine hypertrophic muscles needed a secondary injection within 1 year to maintain atrophy. Von Lindern et al [31] reported a reduction of the masseter muscles by half in seven patients with unilateral and bilateral hypertrophy of the masseter and temporalis muscles treated with an average of 100 U of Dysport. Four patients considered the result satisfactory after a single injection. More recently, Park et al [32] injected 25 to 30 U BTX-A per side in five to six sites in 45 patients. Masseter thickness was gradually reduced during the first 3 months following injection (average change in masseter thickness, 1.5 to 2.9 mm, equivalent to 17% to 19% of the original muscle thickness). Clinical effects lasted 6 to 7 months following injection before the muscle thickness retreated to its initial size; at 10 months, 36 patients expressed satisfaction with the results. Main transient side effects included mastication difficulty, muscle pain, and verbal difficulty during speech and lasted from 1 to 4 weeks.

**Cervical indications**

The platysma is a large muscle arising from upper parts of pectoralis major and deltoid that slants upward along the full length of the neck. Some platysmal
fibers extend to the mandible, whereas others insert into the skin and subcutaneous tissue of the lower part of the face or blend into the muscles of expression above the angle and lower corner of the mouth and lower lip. As with all facial muscles, there is enormous variability from one individual to another. Two types of lines can be produced from the platysma: horizontal “necklace” lines (transverse lines in the neck that run perpendicular to the contraction of the platysma) and vertical platysmal bands.

**Horizontal neck lines**

Horizontal necklace lines of skin indentation, caused by the superficial musculoaponeurotic system attachments in the neck, often grace the chubbier neck. To treat with BTX-A, the authors “dance” along the lines, injecting small doses over multiple sites, for a total of 15 to 20 U per treatment session. Gentle massage following treatment helps alleviate potential bruising. Physicians are advised to use deep dermal, rather than subcutaneous, injections because of deeper venous perforators that can bleed and underlying muscles of deglutition that can bleed.

**Vertical platysmal bands**

When cervical skin loses its elasticity, the anatomy of the submental space changes: more submental fat becomes visible, and the platysma separates into two diverging vertical bands [33]. These bands tighten and become prominent when the patient speaks or otherwise animates the neck.

Botulinum type A injections can soften vertical platysmal bands in some patients [24,34]; however, careful patient selection of those with obvious platysmal bands, good cervical skin elasticity, and minimal fat descent are essential. In necks with jowl formation and bone resorption, treatment with BTX-A may worsen the appearance of the bands. To some, traditional rhytidectomy surgery remains the gold standard treatment for most aging necks [35]. Used as an adjunct to rhytidectomy, BTX-A reduces the residual muscular banding that becomes apparent in the postoperative phase. In addition, some patients may prefer to use botulinum toxin treatment as a kind of rehearsal for regular surgery.

Because the platysma is external to the muscles of deglutition and neck flexion, large doses of BTX-A (ie, 75 or 100 U) have been known to cause profound dysphagia [24] and must be used cautiously. The authors typically inject 5 U in three sites for each band (with sites that are 1 to 1.5 cm apart) and no more than 25 to 30 U over multiple sites per treatment session. It is far better to undertreat; additional touch-up treatments can always be given if necessary during a subsequent treatment session.

**Side effects and complications**

Side effects that may occur with BTX-A injections include transient swelling or bruising at the injection site, mild headache, and flu-like symptoms. To minimize ecchymosis, patients are instructed to avoid aspirin, nonsteroidal anti-inflammatory drugs, and vitamin E. Smaller doses of BTX-A are less likely to cause problems than larger doses, which supports a conservative approach in most patients. Most complications are relatively uncommon and are related to poor injection techniques [36].

Most side effects result from undesired muscle weakening caused by diffusion of the toxin to adjacent muscles and can be avoided by using concentrated doses. No long-term adverse effects have been reported, and no other systemic safety problems have been associated with botulinum toxin treatment.

Studies of the lower face report complications, such as effects on muscle function and facial expression, usually caused by overenthusiastic use of BTX-A in large doses [36]. Starting with low doses and injecting more superficially rather than deeply limits the potential for complications (such as drooling and asymmetry), and injections should be symmetric to ensure uniform postinjection movement. Avoid injections in singers, musicians, or other patients who use their perioral muscles with intensity. When injecting the DAO, avoid areas too close to the mouth, injection into the mental fold, and interaction with the orbicularis oris, all of which can result in a flaccid cheek, incompetent mouth, or asymmetric smile. Large doses (> 100 U) of BTX-A in the platysma have resulted in reports of dysphagia and weakness of the neck flexors.

**Summary**

Botulinum toxins have been smoothing hyperkinetic lines in the upper face for over 15 years. More recently, their use has widened to include applications in the mid and lower face and neck to smooth, shape, and sculpt, blurring the line between science and art. Their use in the lower face, however, requires a thorough and detailed knowledge of not only facial and cervical anatomy, but also the complex interac-
tions of muscles and the aesthetic and implications of a misplaced injection. Although proper patient selection and injection techniques do not guarantee optimal results, poor selection and techniques almost certainly guarantee disappointing results. In addition to its use as primary procedure, botulinum toxin is also an effective adjunct to other cosmetic procedures, enhancing and prolonging the benefits of surgery, soft tissue augmentation, and laser resurfacing.

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