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Pearls of Botox Usage

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■ INTRODUCTION

Our growing experience with Botox over the past 3 decades has led to refined injection techniques, fewer adverse effects, and improved patient satisfaction. The safety and downtime profiles have increased its popularity for a wide variety of cosmetic and functional applications, both "on-label" and "off-label." Successful facial application of Botox requires an in-depth understanding of the underlying functional anatomy and physiology. This article reviews the history, mechanics, and current uses of botulinum toxin to provide the clinician with pearls for successful application of this powerful therapy.

■ HISTORY

In the early 19th century, Justinus Kerner investigated a poison in smoked sausage that interfered with nerve conduction.[1] Seventy years later, Muller characterized the disease *botulus*, meaning sausage in Latin. *Clostridium botulinum* was identified in 1885, and its toxin was identified as the paralytic agent 10 years later. In the 1920s, botulinum toxin type A (BTX-A) was isolated, and it was purified in crystalline form in 1946.[1] Alan B. Scott first used BTX-A in monkeys to treat strabismus in 1973,[2] and the medication won FDA approval in 1979. The US FDA approved its use for the treatment of blepharospasm and hemifacial spasm in 1989; and in 2000, the toxin was approved for treatment of cervical dystonia. Although Botox has been used for cosmetic purposes for almost 20 years, it received FDA approval for treatment of glabellar rhytides only in 2002.

■ MECHANISM

C. botulinum has 8 serotypes that produce 7 serologically distinct exotoxins.[3] Each exotoxin prevents exocytosis of acetylcholine vesicles at the neuromuscular junction of striated muscles and eccrine glands.[3] Neuromuscular junction turnover and axonal nerve sprouting lead to a waning effect 3 to 8 months after injection.[3] Repeated applications may produce a disuse atrophy that can reduce facial rhytides and allow for a greater time interval between treatments.[4] Type A was the first exotoxin purified in a stable crystalline form.[1]

Manufacturers currently produce 5 commercially available preparations. The 4 BTX-A products include Botox (Allergan Inc, Irvine, Calif), Dysport/Reloxin (Ipsen Ltd, Slough, UK/Inamed, Santa Barbara, Calif), Xeomin (Merz Pharma, Frankfurt, Germany), and CBTXA (CBTX-A, Lanzhou Biological Products Institute, Lanzhou, China). Botox is used in the USA and several other countries, whereas Dysport is available mainly in Europe. Myobloc (Elan Pharmaceuticals Inc, San Francisco, Calif) represents the only type B toxin available in the US market. Myobloc does not require reconstitution, causes more pain on injection, takes effect faster, has a longer shelf life, and requires a higher dose to achieve similar effects. Table 1 lists important differences between the 3 most common commercially available forms.

■ RECONSTITUTION

Botox is distributed in a lyophilized form that may remain stable for up to 4 years. Because of its weak polypeptide link, the toxin is easily susceptible to damage by mechanical stress caused by rapid injection, shearing from a narrow gauge needle, or frothing.[5] To avoid mechanical stress during reconstitution, the clinician should gently inject the diluent into the inside wall of the vial; mix the solution without agitation, bubbling, or frothing; and withdraw the solution through a 21-gauge needle. Once reconstituted, the manufacturer recommends keeping the solution refrigerated at 2°C to 8°C and using the material within 4 hours. The manufacturer also recommends reconstitution with preservative-free saline. However, many clinicians use bacteriostatic saline solution preserved with benzyl alcohol to reduce pain and increase shelf life after reconstitution.[6,7] Although BTX-A reconstituted with bacteriostatic saline likely remains sterile and effective

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TABLE 1. *Botox versus Dysport and Myobloc*

	Botox	*Dysport*	*Myobloc*
Botulinum toxin type	A	A	B
Manufacturer	Allergan Inc, Irvine, Calif	Ipsen Ltd, Slough, UK	Elan Pharmaceuticals Inc, San Francisco, Calif, USA
Availability	USA	Europe	USA and Europe
Potency[10,26]	1	3 to 4	50 to 125
Vial	100-U powder	500-U powder	2500-, 5000-, and 10,000-U solution
Storage	−5°C	2°C to 8°C	2°C to 8°C
FDA approval	Strabismus, blepharospasm, hemifacial spasm, glabellar rhytides, axillary hyperhydrosis	None	Cervical dystonia (2000)
Miscellaneous[27]	Contains human hemagglutinin	Lower protein load than Botox	Less appealing for cosmetic application Quicker onset of action (48 h vs 3–7 d for Botox) Shorter duration of action (by 2 wk) More discomfort on injection Larger diffusion pattern May be useful for those with antibodies against Botox More systemic autonomic effects?

for at least 6 weeks,[8,9] most clinicians discard unused material after 1 to 14 days.

Because of the high cost of the product, many practitioners use methods to conserve as much product as possible. Some prefer hubless needles to minimize hub wastage, whereas others add an additional 0.1 to 0.2 mL of diluent to compensate for hub loss. Typical dilutions include 1, 2, or 4 mL of diluent per vial for a final concentration of 10, 5, or 2.5 U per 0.1 mL, respectively. Using the smallest possible injection volume and the largest dose may minimize unwanted diffusion.

Immunogenicity and neutralizing antibodies may potentially lead to a lack of response.[10] Using the smallest possible effective dose, extending treatment intervals, and avoiding enhancement doses may decrease the risk of neutralizing antibody formation. Antibody formation may require more than 300 U injected at 1 session at a frequency of at least every 3 months.[11] The current Botox formulation carries much more potency and less protein than the original formulation, and thus likely carries less immunogenicity. BTX-A resistance using typical cosmetic doses should be very rare. Patients who develop BTX-A resistance may benefit from injections of other serotypes.

■ INDICATIONS

Botox has several FDA-approved functional and cosmetic uses, as well as many off-label applications. Table 2 summarizes current applications to improve functional oculofacial processes. Through chemodenervation, BTX-A weakens muscles to achieve the desired effect.

BTX-A injection addresses only rhytides due to muscle contraction, so the clinician must differentiate these dynamic wrinkles from those caused by gravitational redundancy, intrinsic aging with loss of elasticity, and sleep creases.[4] Treatment is directed not at the

TABLE 2. *Current oculofacial applications of BTX-A for functional processes*

Ophthalmic disorders
Strabismus
Blepharospasm
Apraxia of lid opening
Nystagmus
Lower eyelid entropion
Lagophthalmos
Exposure keratopathy
Aqueous tear deficiency
Dysthyroid upper eyelid retraction
Dysthyroid ocular hypertension
Dysthyroid compressive optic neuropathy
Seventh nerve aberrancy
Nondystonic involuntary muscle disorders
Hemifacial spasm
Tremors, tics
Myokymia
Myoclonus, congenital muscle cramps
Hypersecretion disorders
Gustatory tears
Chronic migraine and tension headache

TABLE 3. *Current cosmetic oculofacial applications of BTX-A*

Upper face
Horizontal forehead furrows ("worry lines")
Brow ptosis
Glabellar rhytides ("frown lines")*
Upper nasalis rhytides or nasal flare ("bunny lines")
Lateral canthal rhytides ("crow's feet")
Palpebral fissure widening
Lower eyelid rhytides
Adjunct to cutaneous resurfacing
Midface
Lower nasalis rhytides
Nasolabial fold
Nasal flare
Short upper lip
Upper gingival show
Perioral rhytides ("smoker's lines")
Facial scars
Lower face
Mouth frown
Melomental folds ("marionette lines")
Downturned labial commissure
Chin dimpling (*peau d'orange*)
Mental crease
Horizontal rhytides ("necklace lines")
Platysmal bands

*Received FDA approval in 2002

rhytides, but at the underlying muscle(s) contributing to their formation. BTX-A may also prophylactically delay the onset and progression of such wrinkles.[4] BTX-A ameliorates wrinkles in many areas of the face and can be used for cosmetic alteration of brow, eyelid, and mouth position. Table 3 summarizes current oculofacial cosmetic applications.

■ CONTRAINDICATIONS

Botox is contraindicated during pregnancy and active nursing, and in the context of preexisting neuromuscular conditions (myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis), interacting medications (aminoglycosides, penicillamine, quinine, calcium channel blockers), allergy to egg albumin, or a history of allergy to Botox.[12]

■ COMPLICATIONS

Most complications result from untoward chemodenervation of unanticipated muscles or greater than desired weakening of the target muscles. The effect depends upon the muscles involved. Overdose, inadvertent diffusion, and incorrect technique often underlie unanticipated weakening. Diplopia occurs with unintended chemodenervation of the superior and inferior oblique muscles. Most cases of blepharoptosis result from diffusion of toxin away from the primary site or using improper injection landmarks. Chemodenervation of the orbicularis oculi may decrease the tear pump to produce epiphora or cause ectropion or lagophthalmos. Overtreatment or mistreatment of the perioral area causes drooling and facial asymmetry. Dysphagia and weakness of the neck flexors can occur after treatment of platysmal bands. Fortunately, unanticipated chemodenervation is self-limited and often requires only temporary supportive care.

Overcorrection can occasionally improve with medical therapy. BTX-A injection of the opposing muscle group may improve cosmesis and asymmetry. For example, brow ptosis caused by frontalis muscle overtreatment may improve with injection of brow depressors. Alpha-2 adrenergic agonist eyedrops such as apraclonidine 0.5% and phenylephrine 2.5% can improve untoward blepharoptosis through Müller muscle stimulation.[13]

Other uncommon complications include nausea, fatigue, headache, flulike symptoms, and rash. More common local effects include pain, edema, erythema, ecchymosis, undercorrection, short-term hypesthesia, lower eyelid edema, and malar bags.[3,14] BTX-A has a wide safety margin;[15] to date, there have been no reported deaths from unadulterated Botox overdose used for cosmetic purposes.

A thorough knowledge of the underlying anatomy and mechanics of injection can significantly limit complications. Small volume injection at each site should minimize unwanted diffusion. Specific bony landmarks may aid the clinician with less experience. Needle placement at least 1 cm superior to the orbital rim for treatment of glabellar rhytides should help prevent blepharoptosis. Avoidance of the central upper eyelid and brow also reduces this risk. Advising patients to stay upright and avoid rigorous exercise for several hours after injection may help minimize unwanted diffusion. During treatment of lower eyelid rhytides, directing the injection toward the lateral preseptal area minimizes the risks of ectropion, festoons, and diplopia. Discontinuation of antiplatelet products, avoidance of visible vessels during injection, and application of very mild postinjection digital pressure and ice minimize the risk of bruising. During correction of lower facial rhytides, the risk of facial asymmetry decreases by injecting the minimal dose and volume and exercising great care when using concomitant lip filler substances.

Several techniques help lower the discomfort of injection, including the use of a 30-gauge needle, changing the needle if it hits the periosteum, and slower injection. Other valuable techniques include applying pressure during injection to capitalize on the "gate theory" of pain

response,[16] using a silicone-coated needle, and verbal reassurance during injection. Although cooling of the skin before injection and topical anesthesia also improve comfort, using the above techniques should obviate the need for topical anesthesia in most cases.

■ TECHNIQUES

Although a detailed description of the underlying anatomy and specific injection techniques for each area of the face is beyond the scope of this text, several general pearls for injection will improve outcomes and patient satisfaction. Choosing the concentration, volume, and exact site and method of injection requires experience and creativity. The dose depends upon the region and characteristics of the specific muscle group, including muscle mass, which is influenced by the patient's sex. Asking the patient to squeeze and relax the muscles in the affected area helps determine the injection site. Along with palpation of the contracting muscle, visualization of the area of maximal skin displacement during contraction aids in determining the location of injection. The medication may diffuse up to 3 cm from each injection site, depending on the volume of injection.[12]

Treatment of essential blepharospasm requires injection of the corrugator/procerus muscles and the orbicularis oculi muscle. Careful superficial injection of approximately 2.5 U centrally within the upper eyelid, just above the lashes, often improves apraxia of eyelid opening without causing ptosis. Because the orbicularis oculi muscle fibers wane medially, high volumes and doses injected in this area risk inferior oblique paresis with little benefit.

BTX-A can temporarily improve lower eyelid entropion[17,18] for poor surgical candidates or in patients who must first discontinue antiplatelet or coumadin therapy before surgery.

For the occasional patient with paralytic brow elevation after ptosis repair, BTX-A injection of the frontalis muscle retrains the brow elevators. Exposure keratopathy due to anterior lamellar insufficiency after eyelid reconstruction or aggressive blepharoplasty can improve with BTX-A injection of the frontalis muscle. The induced brow ptosis may recruit anterior lamella to improve lagophthalmos and protect the cornea.

Symptoms of aqueous tear deficiency may improve with BTX-A injection.[19] Injection of approximately 5 to 10 U in the peripunctal region weakens the orbicularis tear pump to raise the tear meniscus.

Dysthyroid upper eyelid retraction often responds to BTX-A treatment. Patients with active inflammation likely respond better, and subconjunctival injection reduces the risk of lagophthalmos and blepharoptosis.[20]

Although gustatory tears may improve with BTX-A injection within the lacrimal gland by affecting autonomic muscarinic acetylcholine receptors,[21] in our hands, treatment carries a high risk of diplopia.

Horizontal forehead furrows respond very well to BTX-A. These rhytides do not require high doses, and treatment in this area is quite forgiving. Injection of approximately 10 U on each side in a grid pattern or "V" pattern results in improvement. The practitioner should warn the patient about mild brow ptosis after injection. Concomitant injection of the lateral orbicularis oculi muscle may minimize induced brow ptosis.

Mild lateral brow ptosis can improve with BTX-A injection of the lateral orbicularis oculi muscle.[22,23] Injection of approximately 7.5 U superior and lateral to the orbital rim often improves brow position while minimizing the risks of diplopia and blepharoptosis. Immediate discontinuation of injection upon observation of subcutaneous medial spread prevents blepharoptosis.

When evaluating glabellar rhytides, the examiner should spread the tissues digitally and observe improvement in the glabellar rhytides. Those rhytides that do not respond to this digital manipulation may not respond well to BTX-A. Because the medial corrugator fibers originate deeper and the lateral corrugator fibers insert more superficially, injection should occur deeper medially and superficial laterally to maximize efficiency and minimize the dose in this region.

For treatment of lateral canthal rhytides,[24] the practitioner with less experience should consider injecting only lateral to orbital rim to avoid complications. Total doses of approximately 10 to 15 U per side are typical in this region. Laterally extending rhytides of the lower eyelids require conservative injection to avoid malar bag formation from diminished lymphatic drainage.

The clinician should spend extra time counseling patients for perioral BTX-A injection, as a narrower therapeutic window to preserve function exists in this region. Patients must understand that some lip dysfunction will likely result, causing mild difficulty in swishing and spitting, eating soup from a spoon, and saying *p* and *b*. Perioral injection can also lengthen the vertical lip and flatten the vermillion. In general, avoiding this area in patients with a long upper lip seems prudent. Treatment of smoker's lines causes more pain, and patients may desire a topical anesthetic. Success requires only 1 to 2 U per site, injecting along the vermillion and using a maximum dose of 6 U in the upper lip and 4 U in the lower lip. Perioral BTX-A injection may improve the duration of lip filler substances.

Treatment of marionette lines requires only 3 to 5 U, with the needle placed lateral to oral commissure to

avoid depressor labii dysfunction. Injection adjacent to the mandibular margin avoids the orbicularis oris muscle.

Weakening the depressor anguli oris may result in a pleasing upturning of the corners of the mouth, but BTX-A placement requires considerable accuracy in this area. By instructing the patient to pull down corners of the mouth, the practitioner can palpate the belly of the muscle and inject 2 to 3 U approximately 1 cm inferolateral to the commissures.

Platysmal bands respond well to BTX-A treatment.[25] Superficial injections of 2 to 3 U, about 2 cm apart, with a total dose of no more than 50 U should prevent dysphagia.

■ CONCLUSION

Botox represents an ideal therapy to improve cosmesis by offering safe and effective results with little discomfort and no downtime. Success requires a thorough understanding of the underlying anatomy and physiology, experience, and a strong therapeutic bond with the patient. As our knowledge expands, demand and applications will continue to grow.

■ REFERENCES

1. Scott AB. Development of botulinum toxin therapy. *Dermatol Clin*. 2004;22:131–133.
2. Scott AB, Rosenbaum A, Collins CC. Pharmacologic weakening of extraocular muscles. *Invest Ophthalmol*. 1973;12:924–927.
3. Kaltreider SA, Kennedy RH, Woog JJ, et al. American Academy of Ophthalmology; Ophthalmic Technology Assessment Committee Oculoplastics Panel. Cosmetic oculofacial applications of botulinum toxin: a report by the American Academy of Ophthalmology. *Ophthalmology*. 2005;112:1159–1167.
4. Foster JA, Wulc AE, Holck DE. Cosmetic indications for botulinum A toxin. *Semin Ophthalmol*. 1998;13:142–148.
5. Osako M, Keltner JL. Botulinum A toxin (Oculinum) in ophthalmology. *Surv Ophthalmol*. 1991;36:28–46.
6. Klein AW. Dilution and storage of botulinum toxin. *Dermatol Surg*. 1998;24:1179–1180.
7. Alam M, Dover JS, Arndt KA. Pain associated with injection of botulinum A exotoxin reconstituted using isotonic sodium chloride with and without preservative: a double-blind, randomized controlled trial. *Arch Dermatol*. 2002;138:510–514.
8. Hexsel DM, De Almeida AT, Rutowitsch M, et al. Multicenter, double-blind study of the efficacy of injections with botulinum toxin type A reconstituted up to six consecutive weeks before application. *Dermatol Surg*. 2003;29:523–529.
9. Alam M, Yoo SS, Wrone DA, et al. Sterility assessment of multiple use botulinum A exotoxin vials: a prospective simulation. *J Am Acad Dermatol*. 2006;55:272–275.
10. Mannor GE. Practical aspects of cosmetic botulinum toxin. *Int Ophthalmol Clin*. 2005;45:99–106.
11. Jankovic J, Vuong KD, Ahsan J. Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia. *Neurology*. 2003;60:1186–1188.
12. Klein AW. Contraindications and complications with the use of botulinum toxin. *Clin Dermatol*. 2004;22:66–75.
13. Wollina U, Konrad H. Managing adverse events associated with botulinum toxin type A: a focus on cosmetic procedures. *Am J Clin Dermatol*. 2005;6:141–150.
14. Patrinely JR, Whiting AS, Anderson RL. Local side effects of botulinum toxin injections. *Adv Neurol*. 1988;49:493–500.
15. Charles PD. Botulinum neurotoxin serotype A: a clinical update on non-cosmetic uses. *Am J Health Syst Pharm*. 2004;61:S11–S23.
16. Barnhill BJ, Holbert MD, Jackson NM, et al. Using pressure to decrease the pain of intramuscular injections. *J Pain Symptom Manage*. 1996;12:52–58.
17. Carruthers JD. Ophthalmologic use of botulinum A exotoxin. *Can J Ophthalmol*. 1985;20:135–141.
18. Clarke JR, Spalton DJ. Treatment of senile Entropion with botulinum toxin. *Br J Ophthalmol*. 1988;72:361–362.
19. Sahlin S, Chen E, Kaugesaar T, et al. Effect of eyelid botulinum toxin injection on lacrimal drainage. *Am J Ophthalmol*. 2000;129:481–486.
20. Morgenstern KE, Evanchan J, Foster JA, et al. Botulinum toxin type a for dysthyroid upper eyelid retraction. *Ophthal Plast Reconstr Surg*. 2004;20:181–185.
21. Hoffman RJ. Treatment of Frey's syndrome (gustatory sweating) and 'crocodile tears' (gustatory epiphora) with purified botulinum toxin. *Ophthal Plast Reconstr Surg*. 2000;16:289–291.
22. Frankel AS, Kamer FM. Chemical browlift. *Arch Otolaryngol Head Neck Surg*. 1998;124:321–323.
23. Muhlbauer W, Holm C. Eyebrow asymmetry: ways of correction. *Aesthetic Plast Surg*. 1998;22:366–371.
24. Ellis DA, Ran AK. Cosmetic upper-facial rejuvenation with botulinum. *J Otolaryngol*. 1997;26:92–96.
25. Carruthers J, Carruthers A. Aesthetic botulinum A toxin in the mid and lower face and neck. *Dermatol Surg*. 2003;29:468–476.
26. Blitzer A, Binder WJ. Cosmetic uses of botulinum neurotoxin type A: an overview. *Arch Facial Plast Surg*. 2002;4:214–220.
27. Matarasso SL. Comparison of botulinum toxin types A and B: a bilateral and double-blind randomized evaluation in the treatment of canthal rhytides. *Dermatol Surg*. 2003;29:7–13.