BOTULINUM TOXIN

Botulinum toxin is a protein neurotoxin that is produced by the bacterium Clostridium botulinum. There are seven serotypes (A-G); only types A and B are manufactured for clinic use. The most commonly used brand is BOTOX® by Allergan, which is a type of onabotulinumtoxin A. BOTOX® was first approved by the Food and Drug Administration (FDA) in 1989 for blepharospasm and strabismus. The current FDA-approved indications of botulinum toxin injections in the head and neck are currently limited. These include chronic migraine, cervical dystonia, blepharospasm and strabismus. The other indications mentioned in this article are all off-label, but studies show promising uses and are standard of care in some disease processes such as spasmodic dysphonia.

Onabotulinumtoxin A is used more commonly throughout the world than type B. There are multiple brands made by multiple companies. Some have studied the ratios of the doses that can be used and attempted conversion tables are in the literature. This is not recommended by the companies that manufacture the product. BOTOX® comes in a 100 unit (U) vial as a freeze-dried powder which needs to be reconstituted for use with sterile saline.

Botulinum toxin type A works by preventing presynaptic release of acetylcholine (Ach). It is made up of a heavy chain and a light chain domain. The heavy chain domain mediates specific and irreversible binding to cholinergic receptor sites on the presynaptic membrane of motor axon terminals. The toxin is internalized, and then the disulphide bond is cleaved allowing the light chain domain to translocate across the endosomal membrane. This light chain then cleaves SNAP-25 (synaptosome associated protein), preventing exocytosis-mediated Ach release. Botulinum toxin type B cleaves the protein VAMP; this causes type B to have a shorter duration but earlier onset of action. In the peripheral nervous system, the action of botulinum toxin occurs in the neuromuscular junction of motor neurons and skeletal muscle cells. In the autonomic nervous system, the action is targeted on myoepithelial cells in sweat glands and salivary glands.
Botulinum toxin can have adverse effects. With the target being mostly skeletal muscles, there can be over-weakening of the targeted muscle. Diffusion of the toxin into surrounding muscles can have negative consequences in the head and neck including ptosis, asymmetry of the face, dysphagia and dyspnea. For ptosis, apraclonidine ophthalmic drops (0.5 – 1%) can be used to ameliorate this. It is an alpha-2-adrenergic agonist that works on Muller’s muscle. There can be local reactions including pain, edema, erythema, numbness and ecchymosis. There can be systematic effects including flu-like symptoms, headache, nausea and most seriously anaphylaxis secondary to sensitivity to the toxin. Pyridostigmine, a reversible acetylcholinesterase inhibitor has been used to ameliorate adverse effects. Some patients may develop an antibody to the toxin causing resistance. This may cause increased doses of the expensive drug to reach therapeutic levels.

There are contraindications to the injection of botulinum toxin. Infection at the site of injection should be taken into consideration. It is contraindicated in pregnant females and in breastfeeding as it is a category C drug. It is contraindicated in neuromuscular diseases such as myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, etc. Concurrent aminoglycoside treatment potentiates the toxin.

HEAD AND NECK CONDITIONS

Botulinum toxin injection has been used in various diseases of the head and neck area. The following will be the utility of injection on the specific conditions cited in the literature.

Voice and swallowing disorders

To understand the effect of botulinum toxin injection in various voice and swallowing disorders, one must have a mastery of laryngeal anatomy and practice of the various injection techniques. Briefly, the adductors of the true vocal folds include the lateral cricoarytenoid muscle (LCA), thyroarytenoid muscle (TA) and interarytenoid muscle (IA). The main adductor is the posterior cricoarytenoid muscle (PCA). The tensor is the cricothyroid muscle. There are 3 main injection techniques. The quickest and most precise is percutaneous injection with electromyography (EMG) guidance. This requires the lowest therapeutic dose but also has the steepest learning curve. To confirm placement into the thyroarytenoid-lateral cricoarytenoid (TA-LCA) muscle complex, patients are told to sustain “ee” or perform a Valsalva maneuver for vocal fold adduction. Percutaneously, one can choose to go translaryngeal or retrolaryngeal to approach the PCA. For confirmation into the PCA, the patient is told to sniff for vocal fold abduction. One drawback of percutaneous translaryngeal injection is that one must go through the cricoid cartilage which may occlude the needle. Secondly, percutaneous injection with laryngoscopic guidance is less precise but easier to learn. The third technique is supraglottic injection with laryngoscopic guidance. This method allows for smoother onset of action, less severe breathy voice and better preserves singing pitch control, therefore making it preferred in professional voice users. The disadvantage to this is the shorter duration of 6-8 weeks and less predictable results in the beginning.

Spasmodic dysphonia (SD) is a disease treated by the otolaryngologist. It is a focal dystonia of intrinsic laryngeal muscles. A dystonia is a chronic neurological disorder of central motor processing characterized by task-specific, action-induced muscle spasms. There are multiple types including the
adductor type (ADSD), the abductor type (ABSD) and the mixed type. ADSD is by far the most common making over 90% of the diseased population. ADSD causes inappropriate glottis closure resulting in strangled breaks in connected speech. ABSD causes inappropriate glottis opening resulting in breathy breaks and hypophonia.

The standard of care treatment of SD is botulinum toxin injection into the offending muscle. The standard volume of injection per vocal fold is 0.1 – 0.2 cc. The concentration should be adjusted to fit this low amount of volume to reduce the subsequent swelling of the injection site. These injections usually cause an initial period of breathiness for several days followed by a 3-4 month plateau of effect. Adverse effects include dysphagia to liquids, dyspnea and stridor. In ADSD, the treatment is bilateral EMG-guided, percutaneous injection of the TA-LCA muscle complex. Rosow et al. compared initial dosing of 1.25 U versus 2.5 U. Their retrospective cases series showed that the preferred dose was 1.25 U which caused less breathiness days of 10.88 days compared to 15.42 days in the 2.5 U arm. In ABSD, staggered injections of the PCA muscles is recommended. The first PCA is injected with a usual starting dose of 5 U. Since PCA muscles abduct the vocal folds, simultaneous bilateral injections can cause closure of the folds leading to dyspnea and asphyxiation. After 2 weeks from the first injection, the vocal folds area examined to see how much the other side can tolerate.

Essential voice tremor is an age-related disorder of involuntary muscle contraction which causes rhythmic, oscillatory movement of the vocal tract. Treatment is similar to ADSD with injection of botulinum toxin into the TA-LCA complex with additional injection into the supraglottis. Adler et al. performed a randomized, prospective case series in 13 patients with this disease. He injected 1.25 U, 2.5 U, 3.75 U of botulinum toxin A into bilateral TA-LCA complexes with improvements in patient rated functional disability, independent ratings of videotaped speech and acoustic measures of tremor.

Vocal fold granulomas are inflammatory masses caused by chronic irritation secondary to larynopharyngeal reflux disease and chronic cough, most often see in men. They present with a held-back, low, monotone voice with habitual coughing and throat clearing. The primary treatment is treating the underlying cause of irritation with acid reducing medicines and speech therapy. For refractory cases, surgical excision may be indicated. Botulinum toxin has been used as an adjuvant treatment to prevent the chronic vocal cord trauma. There are a couple retrospective case series that have shown good results for cases refractory to traditional conservative therapy.

Other voice conditions have also been treated with botulinum toxin. Functional disorders such as plica ventricularis and paradoxical vocal fold motion have been treated with injections. Other disorders including arytenoid dislocation, vocal fold paralysis and posterior glottis stenosis. The theory behind this is to weaken the TA-LCA complex for better airway caliber. Vocal tics have also been shown to be better controlled with this treatment.

The cricopharyngeus is a target for botulinum injection in the head and neck. Oropharyngeal dysphagia caused by achalasia of the cricopharyngeus can be treated with chemical denervation. However, surgical myotomy is the definitive treatment. In patients status-post laryngectomies with tracheoesophageal punctures, function of the cricopharyngeus can cause failed speech. In a case series by Lewis, 23 patients with failed conversational speech were injected with 50 U with 87% achieving fluent speech after their first injection. Injections of the cricopharyngeus can be done multiple ways. EMG-guided percutaneous injection can be done in awake patients. EMG can be confirmed by asking
the patient to swallow to see an action potential that ceases, avoiding to the PCA muscle. Injections can also be done endoscopically under general anesthesia. This allows closer examination to rule out other causes of the problem and allowing direct visualization of the site of injection.

**Pain Conditions**

Injection of botulinum toxin in headaches have been closely studied. Botulinum toxin injections have been FDA approved in chronic migraine, which is at least 15 headache days per month for at least 3 months without medicinal abuse. Tension-type headaches have also been shown to have benefit. Initially, this treatment for headaches was derived from anecdotal reports from patients receiving botulinum toxin injections for hyperfunctional lines. The mechanism is unclear but some studies have shown that there may be direct antiproprioceptive effects on nerves as well as decreased pain signals. Commonly muscles injected are the corrugator supercilii, procerus, frontalis, temporalis and other neck muscles including trapezius, splenius, semispinalis. The PREEMPT was a large phase III trial that showed significant improvements in frequency of headache days, migraine days and moderate to severe headache days in chronic migraine. Trigeminal neuralgia has also been shown to be benefited by intradermal injections into trigger points.

Temporomandibular joint (TMJ) related pain has also been ameliorated by botulinum toxin injections. Underlying cause of this include malocclusion, masseteric hypertrophy, bruxism and other degenerative conditions of this joint. Muscles commonly injected for this are the masseter, temporalis and lateral pterygoid muscles.

**Facial Conditions**

Dystonias of facial muscles are treated with first line botulinum toxin injections. Blepharospasm which causes increased blinking to visual disturbances usually involving the orbicularis oculi. Botulinum toxin is FDA approved for this purpose. A Cochrane review by Costa showed a 90% benefit overall making it unethical to perform new placebo controlled trials. Oromandibular dystonia (OD) affects the lower face muscles and can cause jaw pain, eating difficulties and social stigma. Different types of OD exist that involve different muscles of mastication and strap muscles. Meige Syndrome is a combination of blepharospasm and OD. Cervical dystonia, also known as torticollis, is commonly treated with botulinum toxin injections. A Cochrane review was performed by Costa and showed that this treatment was effective and safe for cervical dystonia. Other facial conditions that have shown benefit from this treatment include facial nerve synkinesis, hemifacial spasm and palatal myoclonus.

**Autonomic Conditions**

Frey’s Syndrome or gustatory sweating, seen after parotidectomy, has been treated with botulinum toxin. The toxin is injected into the dermis of the areas that sweat. A majority of patients have been treated more permanently with this treatment. Sialorrhea has also been treated with injections into the major salivary glands.
CONCLUSION

Botulinum toxin can be used in many conditions in H&N. Dystonias in the larynx and superficial facial and cervical musculature area are effectively and safely treated with injection of botulinum toxin (off-label). EMG guidance is helpful with injections to locate or avoid skeletal muscle. Autonomic dysfunction involving acetylcholine as a neurotransmitter is also effectively treated with botulinum toxin.

FACULTY DISCUSSION: MICHAEL UNDERBRINK, MD, MBA, FACS

Just to be brief, the indications as they are for Botox in the head and neck area, I would just say this: when you have a hammer, everything seems like a nail. It may seem as if Botox is a great hammer. There is a lot of literature out there; some of the indications are well-studied, even FDA approved which is quite extensive. Others have just got level one randomized prospective controlled studies.

Could you mention a few that are case series or just anecdotal so they’re not as well indicated so that we should be careful with how we use that. We do have some indications in our clinic what we use for voice and swallowing.

A very nice talk, Dr. Son. Thank you.

BIBLIOGRAPHY

7. BOTOX Highlights of Prescribing Information. Allergan 2014.