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## **INTRODUCTION**

*Clostridium Botulinum* is a spore forming obligate anaerobic bacillus. It displays Gram + characteristics in young cultures. *Clostridium botulinum* species produce potent neuroexotoxins that cause the disease botulism. There exist 4 separate groups of *C. botulinum*, I-IV, based on physiologic properties. These four groups produce seven different serotypes of botulinum toxins. The seven types are A, B, C, D, E, F and G. Group I organisms produce types A, B, and F. Group II organisms produce types B, E, and F. Group III produces types C and D, while group IV produces type G.

The serotypes are antigenically distinct, but do have conserved regions of amino acid homology. The toxins are of similar molecular weight, about 150 kilo Daltons. The active molecule is a dichain molecule, consisting of a light and a heavy chain. The molecule has three functional domains: a binding domain at the C terminus of the heavy chain, a translocation domain at the N terminus of the heavy chain, and a catalytic domain at the C terminus of the light chain. The catalytic domain is a zinc metalloprotease.

Toxin-mediated paralysis by botulinum toxin is accomplished in three steps: First, the toxin binds irreversibly to the presynaptic terminal of the motor end plate. Next, the toxin is internalized into the axon by endocytosis, followed by cleavage of SNARE proteins resulting in the inhibition of neurotransmitter release. SNARE proteins are a family of proteins that facilitate the docking of the neurotransmitter vesicle to the presynaptic membrane. The SNARE protein family, N-ethylmaleimide-sensitive factor attachment protein receptors, consist of three main members. These include synaptobrevin, SNAP-25, and syntaxin. Synaptobrevin is incorporated into the neurotransmitter vesicle membrane, while syntaxin is incorporated into the post synaptic membrane. SNAP-25 forms a complex with syntaxin. As the vesicle approaches the presynaptic membrane, this complex binds to the synaptobrevin. Once all three proteins complex together, the vesicle is 'docked' to the axon terminus. Neurotransmitter is released across the synapse by exocytosis. The SNARE proteins are each degraded by different serotypes of botulinum toxin. Synaptobrevin is cleaved by serotypes B, D, E, and G. The SNAP-25 protein is cleaved by serotypes A, C, and E. Syntaxin is cleaved by serotype C. Presence of just

one of the toxins is sufficient to prevent vesicle docking, thereby depleting the neurotransmitter at the synapse. This results in flaccid paralysis of the corresponding muscle fiber. Paralysis is seen 24-48 hours after injection, with return of synaptic function of the neuromuscular junction at about 90 days. Return of muscle function is usually present by 3-4 months. Duration of neurotransmitter inhibition varies with the various serotypes. Inhibition lasts longest with Type A. Duration of type C is approximately equal to A, but there is no clinical application for type C thus far. Type B is of moderate duration and types F and E are of short duration.

Potency of botulinum toxin is determined by *in vivo* mouse assays. One unit of botulinum toxin type A is equivalent to the median intraperitoneal lethal dose (LD50) in female Swiss Webster mice. The estimated LD50 for humans is 2500-3500 units.

## **USES OF BOTOX IN THE LARYNGOPHARYNX**

### **Stuttering**

Stuttering is an involuntary break in the vocal fluency. It affects both children and adults, with approximately 1% of the adult population affected. These patients are often teased and stigmatized. The larynx, lips, oral cavity and pharynx are all thought to contribute to stuttering. Botox injection into the thyroarytenoid muscles decreases the laryngeal contribution. Symptoms tend to return in 12 weeks.

### **Vocal Tics**

Vocal tics are dyskinetic movements of the larynx that result in grunts, abrupt breaks in fluency, and complex formations like screams, loud talking, repetitive words or vowel sounds and coprolalia. Vocal tics are a common finding in Tourette's syndrome and are often accompanied by uncontrolled movements of the eyes, facial muscles, neck and oral cavity. Botox injection into the thyroarytenoid muscles has shown some clinical benefit in treatment.

### **Puberphonia**

Puberphonia, also known as mutational dysphonia, affects men and adolescent boys. The fundamental frequency reverts to a higher frequency similar to the prepubertal fundamental frequency. Speech and behavioral therapy are the mainstay of treatment with botox injection into the cricothyroid muscles serving as an adjunct to therapy. The injection into the cricothyroid muscles enables the larynx to relax, thereby lowering the pitch.

### **Ventricular dysphonia/Dysphonia plica ventricularis**

Ventricular dysphonia is caused by hyperfunctioning of the supraglottic larynx, with an overadduction of the false vocal folds. The fundamental frequency therefore, comes from the false vocal folds. This results in a wet, gravely, hoarse quality voice that is prone to vocal fatigue. This is usually a compensatory mechanism following trauma, cyst, sulci or anything that allows air escape. Treatment consists of botox injection into the false vocal fold, namely the aryepiglottic muscle.

## **Dysphagia**

Dysphagia may result from cricopharyngeus dysfunction or dyskinesis. Botox injection into the cricopharyngeus results in resolution of the dysphagia. A trial of botox injection may identify patients that would benefit from cricopharyngeal myotomy.

## **Tracheoesophageal speech failure**

Botox injection into the cricopharyngeus muscle facilitates TEP speech following laryngectomy in patients that did not receive cricopharyngeal myotomy. It has also been affective in patients who have delayed failure in their TEP speech.

## **Vocal fold granuloma and prevention of posterior glottic stenosis**

Botox injection into the thyroarytenoid muscle following repair of an interarytenoid cleft prevents recurrent scarring and granulation by decreasing the strength of the vocal fold closure and allowing for a more abducted position at rest. This same decrease in the strength of vocal fold closure results in less local trauma and is beneficial in preventing and treating vocal fold granulomas.

## **Arytenoid rebalancing**

Arytenoid dislocation usually follows traumatic intubation. The patient awakens from surgery with a hoarse or breathy voice. Exam reveals an immobile cord. Work up must include EMG evaluation as well as operative endoscopic evaluation. This includes manual repositioning of the arytenoid back to its native position. Botox injection into the interarytenoid, the ipsilateral thyroarytenoid, and the lateral cricothyroid muscles weakens the ipsilateral adductory muscles, allowing for ipsilateral abductory muscles to provide traction, keeping the arytenoid in a more physiologic position.

## **Bilateral true vocal fold paralysis**

Botox injection into the interarytenoid and thyroarytenoid muscles weakens the adductory muscles allowing increased patency of the airway at rest and during activity.

## **SPASMODIC DYSPHONIAS**

Spasmodic dysphonia is a laryngeal dystonia that results in altered speech. Spasmodic dysphonia usually occurs in the third decade of life and is slightly more predominant in women (63%). There exist two types of spasmodic dysphonia, adductor dysphonia and abductor dysphonia. The diagnosis can be made with careful history and examination of the glottis with various laryngeal tasks.

### **Adductor Dysphonia**

Adductor dysphonia is the more common of the two types of spasmodic dysphonia. It accounts for 80% of all cases and is characterized by inappropriate glottal closure caused by hyperactivity of the thyroarytenoid muscles. This produces strain, harshness and strangled

breaks in connected speech.

Treatment of adductor dysphonia with botox is recognized as the primary treatment for the disorder by the American Academy of Otolaryngology-Head and Neck Surgery (Policy statement: Botulinum Toxin. Reaffirmed March 1,1999). Treatment consists of EMG-guided transcutaneous injections of the thyroarytenoid muscles using equal amounts of botox. The initial dose is usually 1-1.25U. This can be increased with necessity of re-injection. The patient is placed in a reclined position with the neck extended. Local anesthesia is not necessary and may actually hinder the efficacy of the EMB electrode. The needle is bent at about a 45<sup>0</sup> angle and inserted through the skin and through the cricothyroid membrane, just off midline. The needle is advanced superiorly and laterally and the patient asked to phonate for EMG confirmation of the needle placement in the thyroarytenoid muscle and the botox is injected.

### **Abductor dysphonia**

Abductor dysphonia occurs less frequently than adductor dysphonia and is characterized by inappropriate glottal opening. This opening, caused by hyperactivity of the posterior cricoarytenoid muscles, produces hypophonia and breathy breaks in phonation.

Abductor dysphonia is treated with EMG-guided transcutaneous injection of one posterior cricoarytenoid muscle. This unilateral injection is to prevent airway compromise. The initial injection is with 3.75U of botox. This dose may be increased if re-injection is necessary. Upon re-injection, the contralateral pca may be injected. The posterior cricoarytenoid muscle may be reached in one of two approaches, the anterior or transcricoid approach or the lateral or retrocricoid approach.

The lateral approach is performed by placing the thumb on the posterior aspect of the thyroid cartilage and rotating the entire larynx to expose its posterior aspect. The needle is inserted at the inferior aspect of the thyroid cartilage, transversing the cricopharyngeus, and advanced until the cricoid cartilage is encountered. The needle is pulled back slightly and the patient asked to sniff. The needle placement is confirmed by EMG and the botox injected.

The transcricoid approach is performed by inserting the needle in the midline through the cricothyroid membrane and advancing until the posterior lamina of the cricoid is encountered. The needle is passed through the cricoid, just lateral to midline. Topical anesthetic may be beneficial in preventing the patient from coughing and it will not interfere with the EMG recording, as the muscle is beyond the cricoid cartilage. The needle is advanced and the first electrical signal encountered is the posterior cricoarytenoid muscle. Needle placement is confirmed by EMG by asking the patient to sniff and the botox injected. The transcricoid approach works better in children than in adults as their cricoid cartilage is not calcified.

### **Conclusion**

Botulinum toxin therapy is an extremely useful and versatile tool in the laryngologist's armamentarium. By chemically denervating the various laryngeal muscles, it is possible to effectively diagnose and treat a number of disorders of the laryngopharynx.

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