Botulinum Toxin Injection for Hyperfunctional Laryngeal Disorders

Background / Introduction

- Botulinum toxin (BTX) is a naturally occurring neurotoxin produce by the bacteria *Clostridium botulinum*.
- The first use of laryngeal botulinum toxin was reported to be in 1984 by Blitzer and Brin for treatment of spasmodic dysphonia.
- Since then, its use has been described in a wide variety of head and neck conditions.
- References
    - Blitzer A, Brin MF, Fahn S, Lange D, Lovelace RE. Botulinum toxin (BOTOX) for the treatment of ‘‘spastic dysphonia’’ as part of a trial of toxin injections for the treatment of other cranial dystonias. Laryngoscope 1986;96:1300–1301. PMID 3773633
    - Blitzer A, Benson BE, Guss J. Botulinum Neurotoxin for Head and Neck Disorders. 2012, Thieme, New York

Pathophysiology / Mechanism of Action

- BTX inhibits presynaptic release of acetylcholine at the neuromuscular junction, thus weakening the neuromuscular response.
- After internalization at the nerve terminal, BTX works by cleaving proteins in the SNARE complex which facilitates binding of acetylcholine containing vesicles to the presynaptic nerve terminal.
- 7 serotypes of Botox have been identified. Only serotypes A and B are used clinically, cleaving different proteins in the SNARE complex (SNAP-25 (BTX-A) and synaptobrevin (BTX-B)). BTX-A has a longer effect duration than BTX-B.
- Recovery of neuronal activity is thought to be a two-phase process.
    - 1) Early recovery - Functional axonal sprouting from the neuromuscular complex produces temporary reinnervation within the first 4 weeks.
    - 2) Late recovery – New sprouts regress as normal vesicular neurotransmitter release restarts in the original terminals.
- BTX has a longer duration effect upon autonomic neurons (6-9 months) compared with striated muscle neurons (3-4 months).

- BTX also has sensory and anti-inflammatory effects and has been used in neuropathic pain. SNARE proteins are involved in release of glutamate and substance P via c-fiber nociceptive neurons. BTX also downregulates TRPV1 protein levels.
- References

  - Humeau Y, Doussau F, Grant NJ, Poulain B. How botulinum and tetanus neurotoxins block neurotransmitter release. Biochimie 2000;82:427–446 PMID 10865130
  - Walker TJ, Dayan SH: Comparison and Overview of Currently Available Neurotoxins. J Clin Aesthet Dermatol. 2014 Feb;7(2):31-39. PMID 24587850
  - Park J., Park, H.J. (2017). Botulinum Toxin for the Treatment of Neuropathic Pain. *Toxins*, *9*(9), 260. doi:10.3390/toxins9090260 PMID 28837075
  - Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature 1993;365:160–163. PMID 8103915
  - Schiavo G, Benfenati F, Poulain B, et al. Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. Nature 1992;359:832–835 PMID 1331807

Indications and Contraindications

- BTX is established as a treatment for various hyperfunctional disorders of the larynx and pharynx including:
  - Spasmodic dysphonia – Adductor, abductor and mixed variants
  - Other focal, segmental or systemic dystonias involving the larynx
  - Essential tremor of the voice
  - Dysphagia associated with upper esophageal sphincter dysfunction
  - Inducible laryngeal obstruction and other functional laryngeal airway disorders
- References

  - Blitzer A., Brin MF, Stewart CF, Botulinum toxin management of spasmodic dysphonia (laryngeal dystonia): a 12-year experience in more than 900 patients. Laryngoscope, 1998. **108**(10): p. 1435-41 PMID 9778279
  - Gurey LE, Sinclair CF, Blitzer A. A new paradigm for the management of essential vocal tremor with botulinum toxin. Laryngoscope, 2013. PMID 23553653
  - Sulica L, Blitzer A. Botulinum toxin treatment of upper esophageal sphincter hyperfunction. Operative Techniques in Otolaryngology-Head and Neck Surgery, 2004. **15**(2): p. 107-109.
  - Baxter, M., et al., Abnormal vocal cord movement treated with botulinum toxin in patients with asthma resistant to optimised management. Respirology, 2014. **19**(4): p. 531-7 PMID 24655302

- Grillone, G.A., et al., Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. Laryngoscope, 1994. **104**(1 Pt 1): p. 30-2. PMID 8295454
- Ongkasuwan, J., Courey M, The role of botulinum toxin in the management of airway compromise due to bilateral vocal fold paralysis. Curr Opin Otolaryngol Head Neck Surg, 2011. **19**(6): p. 444-8. PMID 21986800

- Other uses reported in the larynx include:
  - Recalcitrant laryngeal granuloma
  - Chronic refractory cough
  - Refractory muscle tension dysphonia
- References

  - Sasieta, H.C., et al., Bilateral Thyroarytenoid Botulinum Toxin Type A Injection for the Treatment of Refractory Chronic Cough. JAMA Otolaryngol Head Neck Surg, 2016. PMID 27367917
  - Nasri S, Sercarz JA, McAlpin T, Berke GS. Treatment of vocal fold granuloma using botulinum toxin type A. Laryngoscope. 1995 105(6) 585-8 PMID 7769940
  - Pacheco PC, Karatayli-Ozgursoy S, Best S, Hillel A, Akst L. False vocal cord botulinum toxin injection for refractory muscle tension dysphonia: Our experience with seven patients. Clin Otolaryngol. 2015;40(1):60-64. PMID 25314339

- **Absolute Contraindications:**
  - Past hypersensitivity to any botulinum toxin preparation
  - Infection at the injection site
  - Pregnancy
- **Warnings / special considerations**
  - The potency and dosage of BTX is not interchangeable between the various preparations. Care must be taken to establish the appropriate dose if/when changing formulations.
  - Lactating / nursing mothers – recommendation against usage
  - Pediatric patients
  - Patients with neuromuscular junction disorders, including myasthenia gravis and demyelinating conditions, must be monitored carefully due to increased risk of side effects including respiratory depression from typical doses of BTX.
  - Aminoglycosides, muscle relaxants, and neuromuscular junction blockers may potentiate the effects of BTX.

- Antibodies to BTX have been known to develop in a small proportion of patients and the risk seems to be dose related. This may translate as decreased clinical effectiveness. Consideration of an alternative BTX preparation (with alternate protein complex) may be necessary if this occurs.
- Recent evidence suggests that the clinical effectiveness of laryngeal botulinum toxin may be reduced in the presence of active infection / inflammation (Blitzer paper).

- Reference - BOTOX (onabotulinumtoxinA) Medication Guide and Full Prescribing information. Allergan Pharmaceuticals Ireland (2010) https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5236lbl.pdf

Treatment Method

- **OnabotulinumtoxinA (Botox TM, Irvine CA) is the most commonly used preparation and the doses recommended below are specific to this preparation.**
- Treatment is directed at the desired hyperfunctional target muscle / muscle group.
- Expected duration of treatment effect is 12 weeks.
- Electromyography (EMG) guidance is recommended to ensure accurate localization of target muscles in an office base setting with an awake patient.
- Visual guidance can also be employed as an adjunct or alternative to EMG.
- The laryngeal adductor complex is the usual muscle target for adductor spasmodic dysphonia, essential voice tremor, inducible laryngeal obstruction, and recalcitrant laryngeal granuloma.
    - The adductor complex can be approached transcutaneously (cricothyroid or thyrohyoid approach), transorally, or via channeled endoscope.
    - Initial dosing can be unilateral or bilateral and ranges from 1 to 5 units depending upon condition and desired effect.
- The posterior cricoarytenoid (PCA) muscle is the usual target for abductor spasmodic dysphonia.
    - The PCA can be approached transcutaneously using EMG guidance (lateral rotational or trans-cricothyroid approach). Endoscopic access is also possible.
    - Initial unilateral dosing of 3.75-7.5 units is recommended.
    - Synchronous bilateral dosing has been described, however the risk of airway embarrassment increases.

- Supraglottic botulinum toxin injections under endoscopic guidance have been used in adductor spasmodic dysphonia and recalcitrant muscle tension dysphonia.
- The cricopharyngeal muscle can be approached transcutaneously (EMG guided) or endoscopically with direct muscle exposure.
    - Typical dosing varies significantly from 20 to 100 units.
- After initial BTX treatment, clinical reassessment of effect and side-effects should occur at 2-4 weeks. Subsequent dosing should be adjusted to the individual patient depending on response to previous treatment.
- References

    - Blitzer, A., Spasmodic dysphonia and botulinum toxin: experience from the largest treatment series. Eur J Neurol, 2010. 17 Suppl 1: p. 28-30. PMID 20590805
    - Simpson CB., et al. Botulinum toxin treatment of false vocal folds in adductor spasmodic dysphonia: Functional outcomes. Laryngoscope, 2016. 126(1): p. 118-21 PMID 26467807.
    - Sulica L, Blitzer A. Botulinum toxin treatment of upper esophageal sphincter hyperfunction. Operative Techniques in Otolaryngology-Head and Neck Surgery, 2004. **15**(2): p. 107-109.

Management of complications

- Hypersensitivity may manifest as anaphylaxis, urticaria, soft tissue edema and dyspnea. Appropriate medical therapy should be administered if allergic reaction is suspected.
- Localized pain, erythema, tenderness, and bruising may occur at the injection site and are generally transient and treated with cold packs and analgesia.
- Other side effects are related to the target muscle group or local diffusion to surrounding muscle groups with spread of effect and may be dose related.
- Pyridostigmine has been reported as useful in management of severe side effects.

- Adductor complex and supraglottis
    - Breathiness / weak voice is common and can be a marker for treatment success. 28% of people report a temporary decrease in vocal function after treatment which usually improves at 2-3 weeks.
    - Liquid dysphagia is reported in 10-14% of treatments. Patients should be counselled to drink slowly for the first few weeks to decrease aspiration risk.
    - Phonatory dyspnea is uncommon and is usually transient.

- Abductor Complex
    - Mild transient dysphagia to solids due to diffusion to pharyngeal constrictor muscles can occur in 6% of injections.
    - Mild dyspnea secondary to unilateral abductor paralysis can occur.
    - Severe airway compromise requiring surgical airway can occur due to bilateral abductor paralysis.
- Upper esophageal sphincter
    - Airway compromise can occur as a result of diffusion into the PCA muscles.
    - Dysphagia can transiently become worse.
- References

    - Novakovic, D., et al., Botulinum toxin treatment of adductor spasmodic dysphonia: longitudinal functional outcomes. Laryngoscope, 2011. 121(3): p. 606-12. PMID 21298641
    - Young DL, Halstead LA. Pyridostigmine for reversal of severe sequelae from botulinum toxin injection. J Voice. 2014;28(6):830-834 PMID 25008379

In the event of accidental overdose, the patient should be monitored for symptoms of excessive muscle weakness or respiratory compromise. Early administration of antitoxin may be indicated