Operative Techniques in Otolaryngology (2008) 19, 243-247

Operative Techniques in Otolaryngology

The use of botulinum toxin in patients with sialorrhea

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KEYWORDS
Botulinum toxin;
Sialorrhea;
Parotid;
Submandibular;
Neurologic dysfunction;
Drooling;
Botox

Sialorrhea is a common clinical problem in children and adults that can have significant social and medical implications. Multiple treatments exist, with varying degrees of success. The use of intraglandular injection of botulinum toxin is a simple and effective alternative to current treatments. We present issues when considering injection and our technique.

Sialorrhea, or drooling, can have a major impact on an individual's growth. It may act as a social barrier for children and adults, resulting in embarrassment, diminished self-esteem, and subsequent isolation from peers. Clinically, chronic drooling can lead to perioral chapping, dehydration, and salivary aspiration.[1]

Although it may be observed in children until age 4, neurologically impaired children can exhibit sialorrhea until much later in life. Approximately one-third of children with cerebral palsy are affected by drooling, and 75% of adults with Parkinson's disease.[2-4] Drooling is also common in adults with amyotrophic lateral sclerosis and stroke.[5] Secretion of saliva is under control of the autonomic nervous system, which controls both the volume and type of saliva secreted. The presence of drooling is usually not an effect of hypersalivation. It is usually secondary to oral motor discoordination that prevents normal passage of saliva from the oral cavity to the esophagus.[4,6]

Evaluation of the drooling patient includes a complete history to appreciate the possible causes as well as the medical and social effects the condition has on the patient. Physical examination involves assessment of anatomic pathology (eg, dental caries, poor muscle tone, nasal airway obstruction) that may exacerbate chronic drooling.

Treatment of drooling centers on the reduction of salivary flow with preservation of oral hydration. Oral motor and behavioral therapy can improve developing coordination of swallow; however, these treatments are challenging with varying results in the neurologically impaired patients. The treatment goal in neurologically impaired patients is aimed at reducing saliva production because smaller amounts of saliva are easier to keep within the oral cavity and swallow.[7]

Pharmacologic treatments include use of anticholinergic medications (glycopyrrolate, scopolamine) but adverse systemic effects, such as visual disturbances, nausea, urinary retention, and insomnia, limit long-term use.[1,6]

The surgical options to reduce drooling include transposition of submandibular and parotid ducts to oropharynx, parotid duct ligation with submandibular gland excision, and parasympathetic nerve section. All surgeries have varying degrees of success, but severe xerostomia and other complications may result.[7-9]

The introduction of botulinum toxin injection into the salivary glands is a novel therapeutic option with good results and minimal complications. It was first noted to decrease salivation in canine models and has since been applied in more than 20 clinical studies with positive results.[4,10] Recent data have even shown the possibility of using botulinum toxin to reduce placement of tracheotomy.[11]

Botulinum toxins act by cleaving the synaptosome-associated protein of 25 kD (SNAP-25), which normally acts as a fusion complex allowing for the exocytosis of acetylcholine at the neuromuscular junction. Cleavage of SNAP-25 results in decreased release of acetylcholine and subsequent muscle relaxation. The effect of the toxin is temporary as neurons begin to regain the ability to secrete neurotransmit-

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doi:10.1016/j.otot.2008.10.008

ter, which is first seen at one month, and the neuron is fully functional at three months.[12] The salivary glands are innervated by parasympathetic nerve terminals that release acetylcholine to stimulate saliva secretion. By blocking the cholinergic stimulation of the glands, salivary output can be decreased.[4] Botulinum toxin-A has also been used in the treatment of salivary pathology such as sialoceles, Frey's syndrome, and ranulas.[13-16]

Commercially available botulinum toxins are manufactured from *Clostridium botulinum,* which is an anaerobic Gram-positive bacillus that is responsible for botulism, characterized by flaccid paralysis and autonomic dysfunction (ie, dry mouth). It exerts its effects via an exotoxin that exists as 8 different serotypes: A, B, C1, C2, D, E, F, and G. Two BoNT serotypes are available in the United States: BoNT-A (Botox®, Allergan, Inc., Irvine, CA) and BoNT-B (Myobloc®, Solstice Neurosciences, San Francisco, CA). BoNT-A Dysport® (Speywood Pharmaceuticals Ltd, Maidenhead, United Kingdom) is available in Europe and New Zealand for sialorrhea treatment but still is currently under investigation for esthetic use in the United States.[4,12] Other BoNT-A formulations available outside the United States are Prosigne (Lanzhou Institute of Biological Products, Gansu, China) and Xeomin (Merz Pharmaceuticals GmbH, Frankfurt, Germany).[17,18] Another BoNT-A is in Phase 2 studies being developed by Mentor Corp. (Santa Barbara, CA).

BoNT-A was initially used to treat neuromuscular disorders such as blepharospasm, cervical dystonia, and spasmodic dysphonia. This mechanism consists of blocking vesicular release of acetylcholine from the neuromuscular junction which results in weakened muscle contraction. It is also used in facial esthetics to relieve forehead and periorbital rhytids by the same mechanism. Axillary hyperhidrosis, an approved indication of BoNT-A, is clinically treated as the sweat gland function is mediated by the autonomic nervous system, which is innervated by neurons that secrete acetylcholine at the sympathetic nerve endings.

The Food and Drug Administration has approved use of BoNT-B (Myobloc) for cervical dystonia and is noted to cause a greater degree of xerostomia compared with BoNT-A with the speculation it has a higher affinity to autonomic receptors than BoNT-A.[19] Clinical studies have shown effective reduction in sialorrhea in adults with Parkinson's disease and ALS.[20-22] However, one case study in which the authors used BoNT-B in children with drooling showed inactivation of toxin as the result of antibody formation, and one report outlined limitations of its use attributable to its high antigenicity rate.[23,24] Myobloc, Botox, and Dysport are not dosed equally due to differences in potency. The dose equivalent of 1 U Botox is 50 to 100 U Myobloc, and 1 U Botox is 3 to 4 U Dysport.[25]

In our clinical practice, we rely on evidence that has shown a reduction in drooling in children and adults after intraglandular injection of BoNT-A.[3,4,15,18,26] This report illustrates considerations and techniques in the injection of BoNT-A in the drooling patient.

Indications

Botulinum toxin can be used in children and adults who have evidence of chronic drooling with no response to behavioral or medical therapy. A discussion with the patient and his/her family is undertaken to assess the degree of drooling as well as the clinical and social impact on the patient.

Contraindications

The use of botulinum toxin is contraindicated in patients with certain neuromuscular disorders such as myasthenia gravis that may be exacerbated. BoNT-A is pregnancy category C. Patients who have had a prior allergic reaction to injection should not have this treatment. Relative contraindications to this procedure include prior history of dysphagia with aspiration as botulinum toxin can worsen symptoms.[12] Also, concomitant administration of aminoglycoside antibiotics or agents interfering with neuromuscular transmission may potentiate the toxin.

Procedure

After thorough history and physical examination and a complete discussion of therapeutic options, the practitioner has a number of considerations before performing botulinum toxin injection. These considerations include the anesthetic approach, glands to be injected, use of image guidance, and dosage and dilution to be used during injections.

Topical anesthesia versus sedation

The first issue to consider is whether to perform the injection using topical anesthesia, eg, EMLA cream versus sedation. Although most botulinum toxin extremity injections in children with cerebral palsy are done with topical anesthesia, injections in the glandular area may prove to be more challenging. It is important to gauge the patient's ability to tolerate multiple injections despite topical anesthesia. Also, one must consider, especially in children, the potential for lidocaine toxicity because the application of EMLA must cover both the parotid and submandibular gland regions depending on where the injection will take place.[27] There has been one fatal case of BoNT-A-related anaphylaxis reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.[28] We prefer to do the injections of children in the operating room under sedation which allows accurate and efficient localization of the salivary gland. In contrast, adults generally tolerate injections with topical application of EMLA cream alone.[15]

Which glands to inject

A second consideration is which glands to inject; submandibular, parotid or both (Figure 1). The majority of inves-