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The use of botulinum toxin in patients with sialorrhea

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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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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-

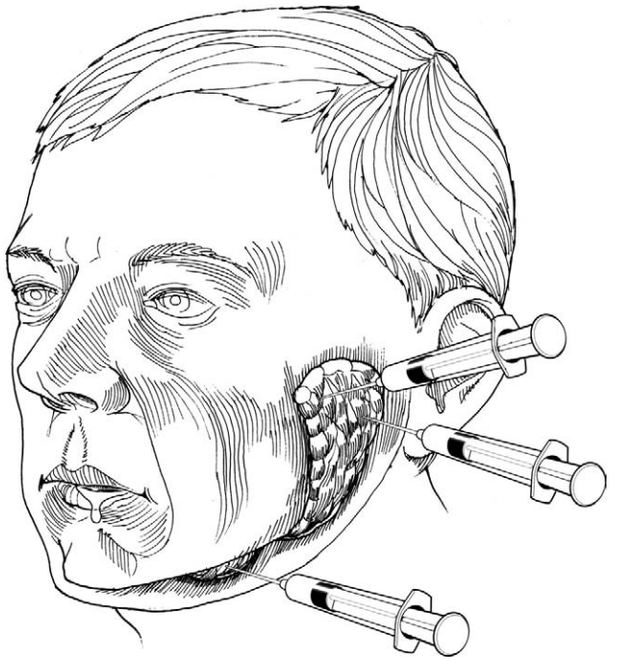

Figure 1 Regions of injection of Botulinum toxin A in to parotid and submandibular glands.

tigators describe injection of both sets of glands, especially in adult patients.[4] Seventy percent of resting salivary flow comes from the submandibular glands and the parotid gland contributes twenty five percent. The parotid glands increase secretions greater than the submandibular glands with oral stimulation.[29] Because of the predominance of submandibular activity, multiple studies have shown injection of only the submandibular glands with success resolution of drooling.[6] One study mentions a greater rate of nonresponders when only the submandibular glands were injected.[15] Thus most studies advocate for both glands to be injected. In our clinical practice, we inject both parotid and salivary glands to obtain the most effective saliva reduction and have never encountered xerostomia.

Image-guided injection versus none

The use of ultrasound allows for accurate gland localization, facilitating targeted injection without significant toxin

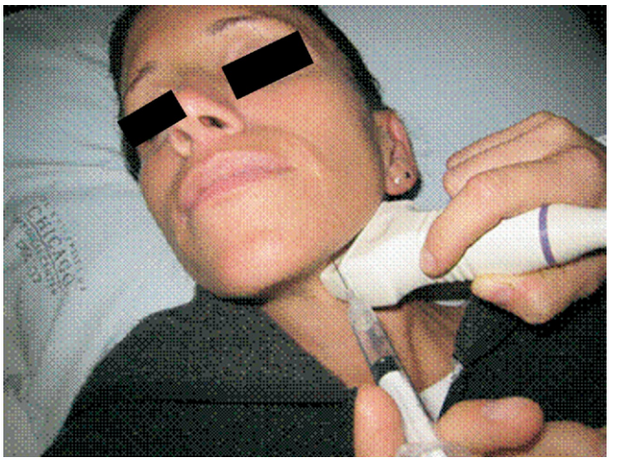

Figure 3 Ultrasound guided injection of the submandibular gland. (Color version of figure is available online.)

spread into surrounding tissue (Figures 2 and 3). This is critical when one considers the proximity of the muscles of swallowing and mastication to the submandibular and parotid glands.[4,5,14] If these muscles are weakened by toxin then dysphagia and difficulty with mastication can occur. Some practitioners elect to perform injections using regional anatomic landmarks, especially in the relatively superficial parotid gland, which can be localized sit between the posterior border of the mandibular ramus and preauricular crease. The submandibular gland can usually be localized by manual palpation. However, one report states significantly greater reduction in sialorrhea when using ultrasound-guided injection compared with "blind" intraparotid injection. However, no mastication related complications were seen in either group.[30] Accurate localization and injection of the submandibular glands may be more challenging especially in those who are not fairly thin.[31]

Dilution/Dosage consideration

The dosage used to inject the glands depends on patient response. Studies in the literature use doses ranging from BoNT-A (Botox, Allergan) 10 U to 100 U and BoNT-A (Dysport, Ipsen) 20U-3000U.[4] Weight-based dose in chil-

Figure 2 Demonstration of ultrasound guided injection of the parotid gland. (Color version of figure is available online.)

dren have been used with BoNT-A (BOTOX, Allergan) 1.4 U/kg for the parotid gland and 0.6 U/kg for the submandibular gland.[17] We start patients at a low dose of Botox at 10 U and increase the dose based on responses to a maximum dose of 70 U.[15] The safest maximum dose is not known, although it could be very low in some situations, particularly in patients with amyotrophic lateral sclerosis, who may be especially sensitive to the toxin. It should be noted that higher doses may lead to dysphagia although we have yet encountered this complication.

Dilution of BoNT-A (Botox, Allergan) stock solution is with sterile, nonpreserved normal saline solution. It is important to handle the stock with care as excessive agitation with mixing and the presence of air bubbles in the solution can denature the toxin, based on manufacturer instruction.[32] Make certain that when reconstituting the saline is drawn into the vial via vacuum; if this doesn't occur, the vial is damaged. However, the authors of one study found that aggressive mixing of toxin had no effect on potency.[33] The manufacturer also recommends using reconstituted BoNT-A (BOTOX, Allergan) within 4 hours of reconstitution; however, there are data that suggest stability from 2 to 6 weeks after reconstitution and storage in a 4°C refrigerator with minimal effect on potency.[32,34,35] We like to use a dilution of Botox 100 U/mL for the submandibular injection. This concentrated solution prevents excess diffusion into surrounding musculature. Our parotid injection is performed with a solution of 50 U/mL.

Author's technique

Our pediatric injections generally take place in the operating room, with the patient under sedation. We dilute the stock BoNT-A (Botox, Allergan) to make solutions of 100 U/mL for the submandibular glands and 50 U/mL for the parotid glands. We often perform injections on multiple patients so as to maximize the Botox used. Ultrasound guidance is used to identify each submandibular gland and perform one to two centrally located injections into the gland using a 25-gauge spinal needle on a one milliliter syringe loaded for the dose that has been predetermined based on patient response. Previously, we performed ultrasound guidance using the Acuson XP Linear Transducer (Mountain View, CA), with a quick clip needle guide that facilitated the injections. We then use regional anatomical landmarks to perform 3 to 5 injections into each parotid gland using a short 25-gauge needle on a 1 mL syringe (Figure 1). The patient is woken and discharged home from the recovery room.

Follow-up

Patient responses to Botox A injection can vary. Average responses begin approximately 3 to 5 days after injections with initial indicators being a "thickening" of saliva. Booster injections are not recommended by the manufacturer because of risk of increased immunogenicity. Maximal effect is seen at four weeks and last about 12 weeks.[2,4,12,15] We typically perform injections in 4-month intervals but have found that intervals may be spaced out longer secondary to longer lasting effects. Be alert to the potential for systemic effects after the administration of botulinum toxins such as: dysphagia, dysphonia, weakness, dyspnea, or respiratory distress. These effects have been reported as early as one day and as late as several weeks after treatment.

Complications

Adverse effects of BoNT injection for sialorrhea include dysphagia and xerostomia. However, these issues are rare and if they do occur are limited to minor complaints that resolve before BoNT effect disappears. Injection site hematomas can occur but are also rare.[4]

Conclusions

Intraglandular injection of BoNT for sialorrhea is an effective therapy and a strong alternative to definitive surgical options that can result in significant complications. This quick, relatively painless procedure can improve quality of life with limited side effects. Because the current literature has small sample sizes and does not clearly identify these issues, more data are needed with regard to a standard dosing regimen, the need for ultrasound guided injections, and which glands to inject. A practitioner must take these issues into consideration to best tailor his practice of BoNT injections.

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