Received: 2 October 2019 | Revised: 12 January 2020 | Accepted: 8 February 2020

DOI: 10.1002/lio2.363

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

Neurotoxin injection in benign submandibular gland hypertrophy: A first choice treatment

Chrisanthi Karapantzou MD, PhD, MSc[1] | Mark Jakob MD, PhD, Prof.[2] | Martin Canis MD, PhD, Prof.[2]

[1]Facial Rejuvenation Office, ORL Clinic, Ludwigs-Maximillians-University Munich, Munich, Germany

[2]ORL University Department, Ludwig-Maximillians University Munich, Munich, Germany

Correspondence
Chrisanthi Karapantzou, Head of the Facial Rejuvenation Office, ORL Clinic, Ludwigs-Maximillians-University Munich, Marchioninistr. 15, 81377 Munich, Germany.
Email: chrisanthi24@yahoo.gr

Abstract

Background: Various benign clinical entities with a symptomatology of hypertrophic submandibular glands like sialadenitis, sialadenosis, sialolithiasis, or an ageing neck have been described. Botulinum toxin type A is an elegant tool in the management of these conditions.

Methods: This article is an original article, describing the Munich Concept of treating persistent submandibular swelling with Botulinum Toxin Type A from aesthetic and functional aspect. To shrink the affected tissue, 15 Units of Botox or Xeomin are applied in a single injection technique and under ultrasound guidance into the glands. Therefore, the 100 Units vial is being diluted with 3.5 of NaCl.

Results: Intraglandular injections, using a specific dilution and dosage of the neurotoxin preparations, are very effective in the management of these swellings, offering safe and long-lasting results, with a high satisfaction rate. Our working group treated in the last 18 months 23 patients with benign, bilateral submandibular gland hypertrophies, which did not have any major complications.

Conclusion: As there is not yet described an ideal therapeutic strategy for the management of this symptomatology, we suggest, based on our experience, a concept with very promising results from functional and cosmetic aspect.

Several interdisciplinary indications of the head and neck area have been managed effectively with the utilization of botulinum toxin type A, since its first introduction from Scott in 1979.[1] Clinical entities that can be approached with the neurotoxin include facial dystonias, sequelae following facial palsy and other abnormal muscular hyperactivities of the mimic muscles and the platysma. Identifying and understanding its biochemical mechanism of function expanded its application field in the treatment of functional and aesthetic disorders. Botulinum toxin leads to a reversible inhibition of acetylcholine release at the neuromuscular junction, causing a relaxation of the target musculature.

The observation that botulinum toxin could block the acetylcholine release also in the autonomous system, as it affects cholinergic parasympathetic secromotor fibers in sweat and salivary glands, was essential in the development of new, innovative treatments.[2] Frey's syndrome, hypersalivation, hyperhidrosis, and other secretory dysfunctions could be approached in a minimal invasive way. The effectiveness of the toxin use in autonomic disorders is being confirmed and emphasized through the European Approval of incobotulinumtoxin A, for treatments of chronic sialorrhea in adult patients. This announcement in May 2019 made the preparation Xeomin, the first and only to be approved for this indication in the European Union, following the US FDA approval in July 2018.[3,4]

Any botulinum toxin injector might have made the observation that beneath the salivary flow and parenchymal tension, there can

also be a visible reduction in the size of the treated glands. Despite these therapeutic options, there is also another extension in botulinum toxin treatments of salivary glands: the aesthetic aspect. Focusing especially on the submandibularis, there are plenty of patients dealing with benign hypertrophic glands, without having always an underlying pathology, like a sialadenosis or chronic sialadenitis. In addition to that, ageing signs near the mandible and neck, where a bigger size and ptosis of the submandibularis cannot be hidden, play a determinant role in patients' self-perception. Although post neck- and facelift patients are left with visibly improved jawlines, the prominence of the uncoverable submandibular gland on an otherwise lifted and youthful neck causes dissatisfaction and frustration. In these cases, the intraglandular neurotoxin injections offer an elegant and safe solution with long-lasting duration of efficacy[5] (Figure 1).

Physiologically, the daily salivary production in adults has been estimated from 0.75 to 1.5 L. The submandibular glands contribute 70% of the total saliva in unstimulated state, the parotid glands 22%, and the sublingual glands approximately 8%.[6] The stimulation of the submandibular and sublingual glands is from common parasympathetic origin over the submandibular ganglion, whereas one of the parotid glands is from the ganglion oticum, leading to a specific neurotransmitter activation onto the salivary acinar cells. This transmitter is as in the muscular system, acetylcholine, which binds to muscarinic receptors causing an intracellular calcium ion activity increase, inducing this way secretion. A sympathetic muscular contraction follows and enhances saliva expression after its stimulation.[7]

Main anatomic consideration, prior to toxin application, is its localization: under the mandibular bone, beneath the platysma, and in the posterior portion of the submandibular triangle. This triangular appearing anatomical area is formed by the mandible superiorly, the anterior belly of the digastric muscle medially, and the posterior digastric belly infero-laterally.[8] The gland is located 2 to 3 cm posterior to the neck midline and has a subdivision in a superficial and a deep lobe, separated by the mylohyoid muscle. Its excretory duct drains in the oral cavity at the sublingual caruncle.[9] The main role of the gland is the lubrication of the stomatopharynx, to allow adequate swallowing act, initiate digestion, protect the duct epithelium from bacteria, and buffer the pH of the oral cavity.[9]

From histological aspect, it is a branched tubuloacinar gland, due to its synthesis of serous and mucinous acini. Numerically, the serous predominates over the mucous part, but the very active mucous adenomeres lead to a thicker saliva consistency. Saliva not only has organic components including enzymes, proteins (mainly amylase), and immunoglobulines, but also has electrolytes as inorganic components.[9] Scientifically proven is that the neurotoxin reduces the amount of the daily saliva, without having an impact on its composition in organic and inorganic compounds.[9]

Its blood supply comes from external carotid artery branches, the facial, and lingual artery, further divided into submental and sublingual arteries. The facial artery passes from posterior to the gland body. The venous drainage of the submandibularis is supported by the common facial and sublingual vein, flowing into the internal jugular vein.[10]

Various conditions lead to a visible prominence of this gland. Its malignancies make up 2% of all head and neck tumors. Once affected, the possibility of an adenoid cystic and mucoepidermoid carcinoma is with 50% extremely high.[11] Botulinum toxin can be used as a therapeutic tool to control benign hypertrophies of the submandibular tissue, like sialadenitis, sialadenosis, and sialolithiasis. Sialadenitis is a mostly unilateral inflammation disease, caused by obstructive factors like stones, trauma, duct stenosis, or infection with bacteria or viruses. Patients may develop fever, pain, and an enormous glandular edema. Sialadenosis is a typically bilateral noninflammatory hypertrophy of the submandibular glands, having its origin in metabolic disorders like anorexia nervosa, bulimia, and diabetes. Other clinical conditions associated with a high sialadenosis incidence are alcoholism and non-alcoholic cirrhosis. Guggenheimer et al supported that the etiopathological mechanism of sialadenosis is probably an autonomic disruption of the glandular innervation, based on secretory granules accumulation in acinar cells.[12] The last benign condition accompanied with submandibular swelling is sialolithiasis. Regardless the etiology of the tissue swelling, every gland enlargement is associated with pain and superinfection danger, because of the salivary stasis, as the Wharton duct cannot drain the produced seromucous saliva into the oral cavity. This situation offers a great milieu for the development of bacteria.

Every predescribed conditions can be clinically diagnosed, supported by sonography and if needed CT or MR sialography.[9] The initial

FIGURE 1 A 44-year old female patient with benign bilateral hypertrophy of the submandibular glands, associated to a systemic metabolic disorder. Status of the same patient pre (left picture) and after intraglandular injection of 15 units botulinum toxin type A, only 2 weeks after primary treatment

therapeutic treatment is conservative including sialagogues, oral hydration, and antibiotics when inflammation persists or fever occurs. Sometimes salivary stones can be manually palpated when they are localized within the duct and especially near the caruncel. Often small stones can be removed under local anesthesia only with duct distension. In some cases, the stone removal procedure can afford a small papillotomy to prevent future residual conditions. And when conservative treatment fails or a stone lies within the gland body, leading repeatedly to sialadenitis, surgery is the only recommendation. In all these benign clinical entities, botulinum toxin can be used to reduce salivary flow. This quantitative, but not qualitative limitation in the daily produced saliva secretion, helps in the prevention of gland tissue inflammation, as the salivary stasis danger decreases.

1 | METHODS

Technically, botulinum toxin injections into the submandibular glands may be performed using a blind palpation of the glands or under sonographic or electromyographic guidance, to ensure more precise applications into the gland body (Figure 2). In our practice, submandibular glands are treated under ultrasound guided, single injections of 15 Units of Botox or Xeomin. Therefore, we dilute the 100 units vial with 3.5 of NaCl, similar to the 4 mL dilution that was proposed from Prof. Laskawi for sialorrhea treatments and modified by us.[13] To gain on the one hand safe and on the other, possibly longer lasting results, we choose to add into the 100 vial of Botox or Xeomin 0.5 mL less NaCl, as we intend to achieve a little higher toxicity per injection point.

When we treat the gland via sonography assistance, the needle tip is not always visualized. The depth of the treated tissue can be estimated indirectly, through the visible intraglandular parenchymal motion, whereas the substance is being applied. Diffusion phenomena into periglandular muscles can be minimized, when botulinum is placed within the submandibularis and as long as it is injected slowly into the gland. Local anesthesia is never required, as we choose 30-33 Gauge and 12-15 inch long needles, which allow comfortable and well tolerated injections. It is stated that informed written consent was obtained for publication of the patients' images.

2 | DISCUSSION

Having treated 23 patients only in the last 18 months for benign, bilateral submandibular gland hypertrophies, we have not experienced any major complications under the above suggested method and chosen dosage of botulinum toxin type A. Our patients were reviewed after 2 weeks. Further touch-up injections could be administered reaching a botulinum toxin dosage total up to 30 units, but due to a satisfactory response our subjects did not underwent any additional injection. Repeated injections are always necessary for long-term control, typically on the order of every 4 to 5 months. Thirteen patients were treated just for an aesthetic improvement of their appearance, 9 patients because of sialadenosis with submandibular manifestation, and 1 patient for recurrent, bilateral sialolithiasis of the submandibular glands. Minor complications were appeared, where in 15 patients the feeling of tension within the glands was for about 48 hours, which was accompanied by some hypersensitivity in the treated area. Unilateral bruising was reported in six patients. Eight patients complained of sudden, short-lasting pain during injection, probably associated to a contact of the needle with the lingual nerve. Adverse events like diffusion of toxin in neighbored muscles, nerve palsy, tongue dysesthesia, or xerostomia did not occur. Beyond the effectiveness of this procedure, it is remarkable that botulinum toxin has a longer lasting duration on autonomic neurons as on muscles. It is observed that in muscular tone treatments, the toxin acts positive for 3 to 4 months,

FIGURE 2 Demonstration of two different submandibular gland injection techniques with botulinum toxin type A: Sonography-guided application on the left and “blind” palpation technique on the right picture

whereas it lasts from 5 to 12 months in autonomic system indications.[14] Laskawi et al published that the longest duration on an autonomic nervous system dysfunction they treated conservative with botulinum toxin type A was a patient with Frey's syndrome, where the positive results lasted whole 27 months. The exact mechanism behind this phenomenon is subject of further scientific research, although some hypothetic approaches have been documented by some authors.[15] Our patients experienced an improvement in the size of the treated glands from 2 to 10 days post injection, with an average of 8 days. The suggested dosage and dilution of 3,5 mL for the 100 unit vial is turning to be effective. Although experienced injectors might choose dosages up to 30 units of toxin per gland, we could achieve satisfying results also with less injected units, while ensuring safety for our patients. Even the sonographic two-dimensional measurements (length and height) of the glands showed an improvement, especially in the height, meaning a decrease in the volume of the glands, which was estimated from 0.3 to 1.2 cm in some cases. This is a significant result, as the average height of the treated glands reached up to 2.4 cm. The comparison to other alternative and more common approaches for controlling persistent glandular swellings shows why the neurotoxin should replace techniques like oral anticholinergic medication. Scopolamine and glycopyrrolate may work by blocking the parasympathetic nervous system and innervation of the salivary production, which leads indirectly to a shrinking of glandular tissue, but they are associated with side-effects like behavioral changes, severe constipation, etc.[16] Invasive interventions like submandibulectomy might be another option to solve the hypertrophic gland problem, but it is more aggressive as it entails the risk of a ramus marginalis weakness of the mandibular nerve and therefore external incisions are also necessary, which can have a negative impact on the cosmetic outcome of the neck. Complications can be limited, when choosing the proper neurotoxin injection technique and respect the submandibular glands particular anatomic features. Although it is important to note that the ideal dose has not yet been identified, we recommend ultrasound controlled-botulinum toxin type A applications as significant noninvasive methods that can act far from their therapeutic potential on controlling hypersalivation, also as elegant tools in solving aesthetic disturbing conditions of benign submandibular hypertrophies.

CONFLICT OF INTEREST

The authors declare that they have no competing interests. No compensation was received for any work on this study.

ORCID

Chrisanthi Karapantzou https://orcid.org/0000-0002-0182-4832
Mark Jakob https://orcid.org/0000-0002-5068-5218

REFERENCES

1. Scott AB. Botulinum toxin injection into extraocular muscles as an alternative to strabismus surgery. *Ophthalmology*. 1980;87:1044-1049.
2. Drobik C, Laskawi R. Frey-syndrom: Behandlung mit Botulinum-Toxin. *HNO Aktuell*. 1994;2:142-144.
3. Product information Xeomin, May 2019.
4. US Prescribing Information Xeomin, May 2019.
5. Karapantzou C, Karapantzos I, Zarogoulidis P, Karanikas M, Thomaidis V, Charalampidis C. Botulinum neurotoxin for Sialorrhea: a first choice therapy. *Ann Res Hosp*. 2017;1:17.
6. Stuchell RN, Mandel ID. Salivary gland dysfunction and swallowing disorders. *Otolaryngol Clin North Am*. 1988;21:649-661.
7. Blitzer A, Benson BE, Guss J, eds. *Botulinum Neurotoxin for Head and Neck Disorders*. New York: Thieme Medical Publishers; 2012:199-221.
8. Möller I, Janta I, Backhaus M, et al. The 2017 EULAR standardised procedures for ultrasound imaging in rheumatology. *Ann Rheum Dis*. 2017;76(12):1974-1979.
9. Armstrong MA, Turturro MA. Salivary gland emergencies. *Emerg Med Clin North Am*. 2013;31(2):481-499.
10. Holmberg KV, Hoffman MP. Anatomy, biogenesis and regeneration of salivary glands. *Monogr Oral Sci*. 2014;24:1-13.
11. Rapidis AD, Stavrianos S, Lagogiannis G, Faratzis G. Tumors of the submandibular gland: clinopathologic analysis of 23 patients. *J Oral Maxillofac Surg*. 2004;62(10):1203-1208.
12. Guggenheimer J, Close JM, Eghtesad B. Sialadenosis in patients with advanced liver disease. *Head Neck Pathol*. 2009 Jun;3(2):100-105.
13. Laskawi R, Roggenkämper P. *Botulinumtoxin-Therapie im Kopf-Hals-Bereich 2*. Goettingen: Germany, Urban & Vogel; 2004:295-350.
14. Ellies M, Gottstein U, Rohrbach-Volland S, Arglebe C, Laskawi R. Reduction of salivary flow with botulinum toxin: extended report on 33 patients with drooling, salivary fistulas and sialadenitis. *Laryngoscope*. 2004;114:1856-1860.
15. Laskawi R, Drobik C, Schoenebeck C. Up to date report of botulinum toxin type A treatment in patients with gustatory sweating (Frey's syndrome). *Laryngoscope*. 1998;108:381-384.
16. Mier RJ, Bachrach SJ, Lakin RC, Barker T, Childs J, Moran M. Treatment of sialorrhea with glycopyrrolate: a double-blind, dose-ranging study. *Arch Pediatr Adolesc Med*. 2000;154:1214-1218.

How to cite this article: Karapantzou C, Jakob M, Canis M. Neurotoxin injection in benign submandibular gland hypertrophy: A first choice treatment. *Laryngoscope Investigative Otolaryngology*. 2020;5:217–220. https://doi.org/10.1002/lio2.363