Video Article

Ultrasound-guided Botulinum Toxin-A Injections: A Method of Treating Sialorrhea

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Abstract

Neurological diseases can be complicated by sialorrhea, an excessive flow of saliva. Patients suffering from moderate to severe sialorrhea have an impaired quality of life, often worsened by correlated complications such as aspiration pneumonia, oral infections, dental caries, and maceration of the skin. Diverse therapeutic approaches have been proposed for the treatment of sialorrhea, including surgery and the use of anticholinergic agents, with limited results and the possible occurrence of serious adverse events. Recently, botulinum toxin (BoNT) injection within the major salivary glands has been proposed in patients refractory to anticholinergic therapy, with the aim of inhibiting local acetylcholine release and gland activity.

In order to obtain a better outcome in terms of reduction of saliva production, efficacy, duration, and avoidance of major adverse events, we developed an ultrasound-guided BoNT-type A injection technique accurately described in the text. Here we present a method of treating sialorrhea with bilateral parotid and submandibular gland BoNT-type A injections under ultrasound guidance. Four quadrants of the parotid gland and two quadrants of the submandibular gland are visualized and injected using two accesses and one access, respectively.

The ultrasound-guided procedure provides a simple, non-invasive, real-time visualization of the muscular and glandular tissues and their surrounding structures, optimizing treatment efficacy and safety.

Video Link

The video component of this article can be found at https://www.jove.com/video/54606/

Introduction

Sialorrhea is an excessive flow of saliva representing a common and disabling complication of several neurological disorders, including stroke, cerebral palsy, multiple sclerosis, and neurodegenerative diseases[1]. Patients suffering from moderate to severe sialorrhea have an impaired quality of life, often worsened by correlated complications, such as aspiration pneumonia, oral infections, dental caries, and maceration of the skin[2]. Various therapeutic options are available for the treatment of sialorrhea, ranging from surgery to pharmacological therapy, with the aim of reducing saliva production.

Surgical options include denervation, excision of the salivary glands, and transposition or ligation of the salivary ducts[3,4]. However, despite its efficacy, surgery is by definition an invasive procedure with potentially serious adverse events, such as salivary fistula and cyst formation, infections, loss of taste, loss of hearing, dysarthria, and irreversible effects on salivary gland production[3]. In addition, it has been observed that surgical approaches may have only temporary efficacy due to reinnervation of the salivary glands two or more years after the procedure[2,5]. A more common and less invasive treatment for severe sialorrhea is the use of systemic drugs with anticholinergic properties. However, the chronic use of anticholinergic agents is often associated with systemic side effects such as confusion, memory problems, drowsiness, urinary retention, and paralytic ileus[2,5].

Botulinum toxin (BoNT) salivary injection is an emerging treatment option for sialorrhea. BoNT are proteases (seven, from A to G), produced by the bacterium *Clostridium botulinum*, that are able to halt acetylcholine release from the presynaptic nerve terminals of the neuromuscular junction, blocking muscle contraction and gland activity at the orthosympathetic and parasympathetic postganglionic synapses. BoNT type A (BoNT-A) and type B (BoNT-B) are commonly used for therapeutic management of dystonia and spasticity[6]. Recently, BoNT injection within the major salivary glands proved to be a useful therapeutic option in moderate to severe sialorrhea with suboptimal response to other medical therapies due to a lack of efficacy or the presence of significant side effects[2,7,8].

Human salivary glands are classified into two groups: major and minor. Major salivary glands include a pair of parotid glands, a pair of submandibular glands, and a pair of sublingual glands; the minor salivary glands consist of about 1,000 small glands spread within the sub-

mucosa of the oral cavity[9]. Approximately 0.5 liters of saliva are secreted per day. The three pairs of major salivary glands are responsible for more than 90% of the saliva production, approximately divided as follows: 20% for the parotid glands, 65% for the submandibular glands and 5%, for the sublingual glands[9]. The parotid gland is the largest one and is located below the external acoustic meatus, between the mandible and the sternocleidomastoid muscle; it projects forward on the surface of the masseter muscle[10]. Important structures pass through the gland, such as the facial nerve, external carotid artery, and retromandibular vein, and several other important neurovascular structures are close to the gland. The submandibular gland is a seromucous gland situated behind and below the ramus of the mandible, in the region of the submandibular triangle, between the anterior and posterior bellies of the digastric muscle and around the posterior border of the mylohyoid muscle[11].

BoNT salivary gland injection is a local treatment with the potential to avoid discomfort and/or systemic side effects correlated with the other therapies, such as oral, transdermal, and surgical options. Here, we show a reliable and easily reproducible method to treat sialorrhea with BoNT-A injections in the parotid and submandibular glands under ultrasound (US) guidance in order to obtain a satisfying and long-lasting reduction of drooling while strongly limiting the occurrence of serious adverse events. Data on BoNT-A injection efficacy in sialorrhea in the absence of US guidance are reported in the literature[12]; however, the US-guided identification of glands and their surrounding tissues, along with real-time visualization of the needle position, allows for a reduction in adverse events and a more accurate injection, leading to increased efficacy and outcome reproducibility[7,13].

Protocol

Here, we technically describe the method used for the treatment of sialorrhea in patients with neurological dysphagia. We will not focus on efficacy results, which have been published previously[7]. In this paper, in the results section, we present data from 5 consecutive patients with long-term follow-up (3 treatment sessions) treated from 2014 to 2016. These patients are considered representative of the entire population, which consists of the botulinum toxin service of San Luigi Gonzaga Hospital. The protocol was approved and follows the guidelines of the local ethical standards committee on human experimentation.

1. Patients' Recruitment

NOTE: Patients eligible for this approach are adults suffering from moderate to severe sialorrhea secondary to neurological dysphagia with a history of failure or contraindication to pharmacological treatments such as anticholinergic drugs.

1. Ensure that the patient is evaluated by an experienced neurologist before BoNT injection and that the severity and frequency of sialorrhea is assessed with the Drooling Frequency and Severity Scale (DFSS)[14].
   NOTE: The DFSS score is the sum of the frequency (1 = never, 2 = occasionally/not every day, 3 = frequently/part of the day, 4 = constantly) and severity (1 = never drools, 2 = mild or only lips wet, 3 = moderate or wet on lips and chin, 4 = severe or drool extends to clothes wetting, 5 = profuse or clothing, hands, tray, and objects wet) sub-scores[14]. A score >2 in both of the sub-scores is used as the eligibility cut-off.
   NOTE: The neurologist scores the scale on the basis of objective and anamnestic data provided by the patient and/or caregiver. In addition, the Visual Analogue Scale (VAS) must be administered for the evaluation of the patients' subjective sufferance related to the sialorrhea. The VAS is a self-reported scale represented by a 10 centimeter horizontal line with a statement at each end representing one extreme of the patient's discomfort (from 100 = "no discomfort" to 0 = "extreme discomfort").
2. Collect the number of daily saliva aspirations through a saliva aspirator (when applicable) before BoNT injection, as a useful tool for the evaluation of the therapy efficacy (**Figure 1**).
3. Repeat a neurological evaluation along with the DFSS and a daily saliva aspiration assessment during follow-up, 1, 3 and 6 months after the treatment, or according to the sialorrhea re-occurrence. In particular, retreatment must be taken into account when the number of daily aspirations increases over 50% compared to the 1-month follow-up evaluation.
4. Collect procedure adverse events (local pain, local bleeding, and facial palsy) immediately after the injection. Collect therapy adverse events (local pain, facial palsy, chewing weakness, viscous saliva, and dry mouth) during follow-up assessments.

2. Procedure

1. BoNT-A preparation
   NOTE: The abobotulinumtoxinA is a botulinum toxin type A of the *Clostridium botulinum* complex-hemagglutinin. It is a powder for solution for intramuscular or subcutaneous injection.
   1. For the treatment of sialorrhea in adults, reconstitute 500 IU abobotulinumtoxinA with 2 mL of 0.9% sodium chloride solution for injection in order to obtain a solution containing 250 IU/mL of abobotulinumtoxinA.
   2. Administer a total of 250 IU of abobotulinumtoxinA per patient as follows: 50 IU in each submandibular gland and 75 IU in each parotid gland. In this way treat two patients with a single vial to avoid drug wastage.

2. Patients' preparation
   1. After an adequate explanation of the procedure and of the potential risks and benefits of the treatment, obtain written informed consent from the patient.
   2. Place the patient on the ultrasound table in the supine position and possibly with the neck extended.
      NOTE: Consider that not all neurological conditions leading to sialorrhea allow for the complete extension of the neck.
   3. Disinfect the skin in the area over the parotid and the submandibular glands with an antiseptic. Anesthetize each skin access site with ethylene chloride spray.

3. Ultrasound guidance
   NOTE: An ultrasound-guided procedure with a linear transducer (5 - 10 MHz) is used for gland localization in order to obtain real-time visualization of muscles, glands, bigger vessels or salivary ducts, and other surrounding structures, as well as of the correct needle position within the glandular tissue.

1. Turn on the ultrasound system and press the "Start-end" button to begin the exam.
2. Press the "Probe" button to select the high frequency probe (5 - 10 MHz).
3. Press the "Patient" button and insert the patient's name and surname.
4. Press the "Protocol" button to select the appropriate protocol and sub-protocol (*i.e.*, protocol: "small tissues", sub-protocol: "general").
5. Press the "Depth" button and specify the depth of view to 5 cm.
6. Press the "Focus" button to select the maximum detail of 2 cm.
7. Place the transducer under the mandible, between the anterior and posterior bellies of the digastric muscle, to visualize the submandibular gland, which appears as a hypoechoic area with homogeneous echotexture compared to the surrounding tissues.
   NOTE: Consider the submandibular gland ideally divided into two quadrants, one cranial and one caudal. Identify the widest gland diameter for the lateral needle access.
8. Place the transducer below the external acoustic meatus to visualize the parotid gland, which appears as a hypoechoic area with homogeneous echotexture compared to the surrounding tissues.
   NOTE: Consider the parotid gland ideally divided into four quadrants, two cranial and two caudal. Identify the two access sites for injection midway between the external auditory canal and the mandible angle, one in the cranial part and one in the caudal part of the gland (**Supplemental Figure**).

4. BoNT-A injection
   NOTE: Use a 22 G needle for injections, with needle penetration at least 0.5 cm from the transducer. The transducer must be oriented longitudinally to the needle so that the needle is visible as a bright echoic line. In this way, the penetration of the needle into the soft tissues can be monitored during the procedure as the needle tip proceeds towards the target, preventing injuries to neurovascular structures.
   1. Use a lateral short-access approach at the widest gland diameter to access the submandibular gland.
   2. Inject 25 IU BoNT-A into the upper submandibular quadrant. After the injection, slightly retract the needle and change the direction of the needle tip towards the lower submandibular quadrant, injecting 25 IU BoNT-A for a total of 50 IU to each submandibular gland.
      NOTE: In this way, two submandibular areas (cranial and caudal) are injected, providing a widespread diffusion of the drug within the glandular tissue.
   3. Use two access sites for the parotid gland injection. Identify the two accesses midway between the external auditory canal and the mandible angle, one in the cranial part of the gland and one in the caudal part of the gland.
   4. Using the upper access (in the cranial part of the gland), inject 18 - 19 IU BoNT-A into the medial-cranial quadrant. After the injection, slightly retract the needle, without leaving the site of the cranial part of the gland, and change the direction of the needle tip towards the lateral-cranial quadrant; inject 18 - 19 IU BoNT-A.
   5. Using the lower access (in the caudal part of the gland), inject 18 - 19 BoNT-A IU into the medial-caudal quadrant. After the injection, slightly retract the needle, without leaving the site of the caudal part of the gland, and change the direction of the needle tip towards the lateral-caudal quadrant; inject 18 - 19 IU BoNT-A.
      NOTE: In this way, four parotid areas (medial-cranial, lateral-cranial, medial-caudal and lateral-caudal) are injected with a total of 75 IU BoNT-A, providing a widespread diffusion of the drug within the glandular tissue.
   6. After each injection, dab any bleeding with sterile gauze for 1 - 2 min. Re-evaluate the patient after one hour for any potential adverse events. Administer a nonsteroidal anti-inflammatory drug in case of persisting pain. Schedule a follow-up examination after 1 month.

Representative Results

The US-guided injection is an effective technique to obtain real-time and precise needle visualization for BoNT administration in the salivary glands. This approach provides a reliable sialorrhea treatment, with prolonged efficacy and the absence of serious adverse events. Indeed, the visualization of the glands and of the needle penetration provided by the US-guided approach proposed here allows a widespread administration of BoNT-A within the major salivary glands with significant and long-lasting outcomes. Sialorrhea reduction can be easily observed 1 w after the treatment through the administration of the DFSS and VAS and through the collection of the number of daily aspirations through a saliva aspirator (if appropriate). These data allow a quick follow-up assessment and are useful to evaluate the need for retreatment. We recommend patients for another BoNT-A injection when the number of daily aspirations increases to over 50% of the best efficacy obtained after the previous injection (obtained about 1 month after the treatment). This technique usually allows a treatment interval of 6 months and leads to a significant reduction in severity and frequency of sialorrhea, with a decrease of about 50% in the DFSS. In detail, the DFSS severity score showed a significant reduction from the pretreatment average score of 4.06 ± 0.81 to the average 1-month post-treatment score of 1.73 ± 1.65, and the DFSS frequency score reduced from the pretreatment average of 3.46 ± 0.75 to the average 1-month post-treatment of 1.82 ± 0.56. The VAS score changed from the pretreatment average of 3.01 ± 1.21 to the average 1-month post-treatment of 8.33 ± 1.10. Finally, the need of daily saliva aspirations lowered from the pretreatment number of 11.90 ± .88 to the 1-month post-treatment number of 4.44 ± 1.43. On average, sialorrhea improvement can be observed as soon as 1 w after injection (**Figure 3a, b, c, d**).

The US identification of the different tissues and of the needle route also provides an important reduction in adverse events, avoiding BoNT injection into incorrect targets and needle penetration through neurovascular structures. The most common adverse events observed with this technique are mild and consist local pain, dry mouth, viscous saliva, and local bleeding[7,13,15].

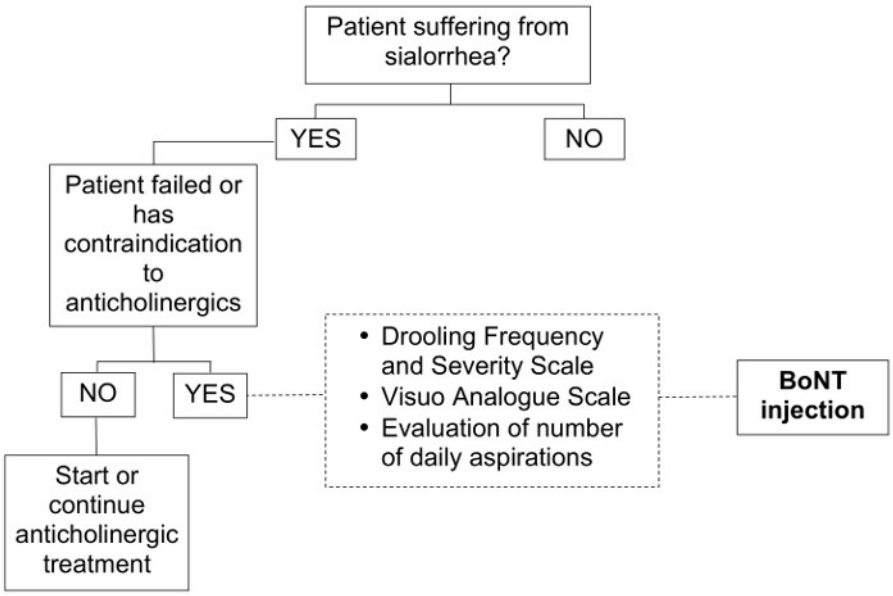


Figure 1: Flow-chart of Patient Selection. Patient evaluation and selection for BoNT-A treatment. Please click here to view a larger version of this figure.

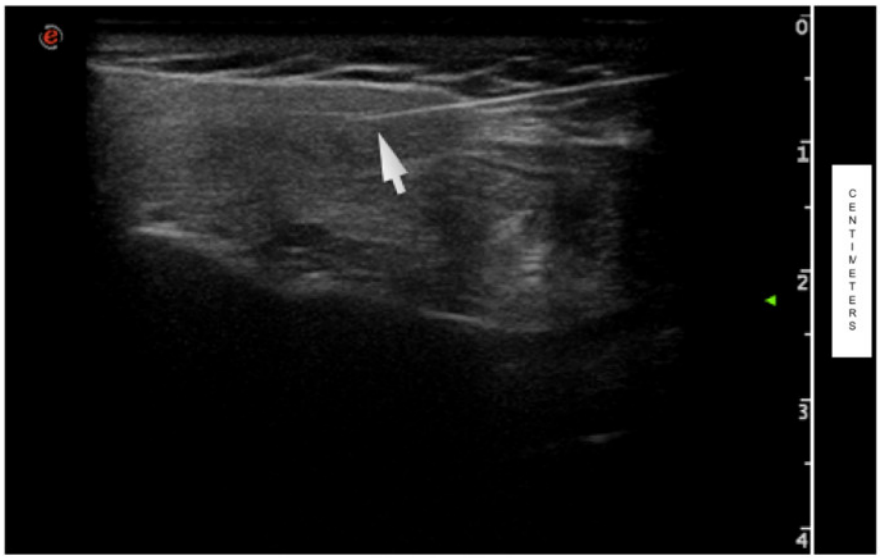


Figure 2: Ultrasound Injection of Parotid Gland. The arrow indicates the needle penetration, visible as a bright echoic line, within the parotid glandular tissue. Unit scale is expressed in cm. Please click here to view a larger version of this figure.

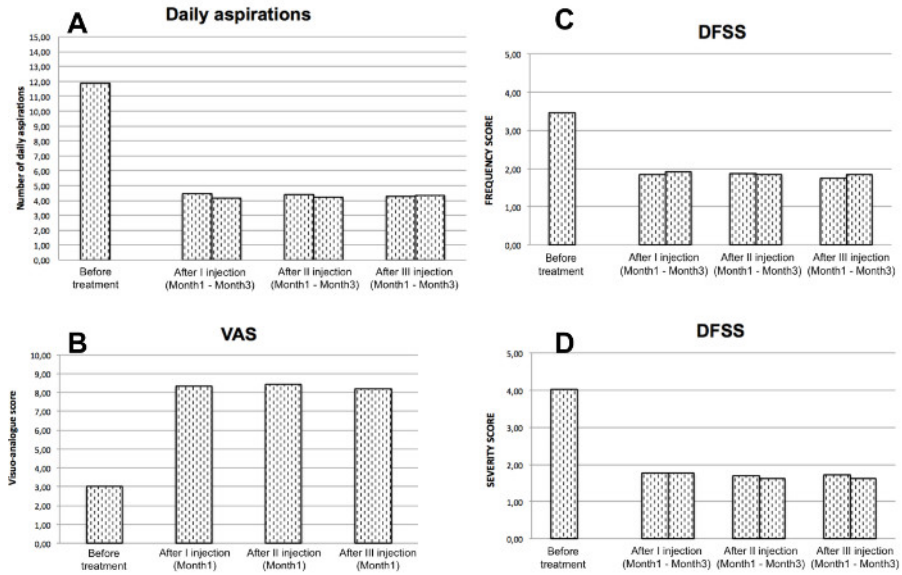
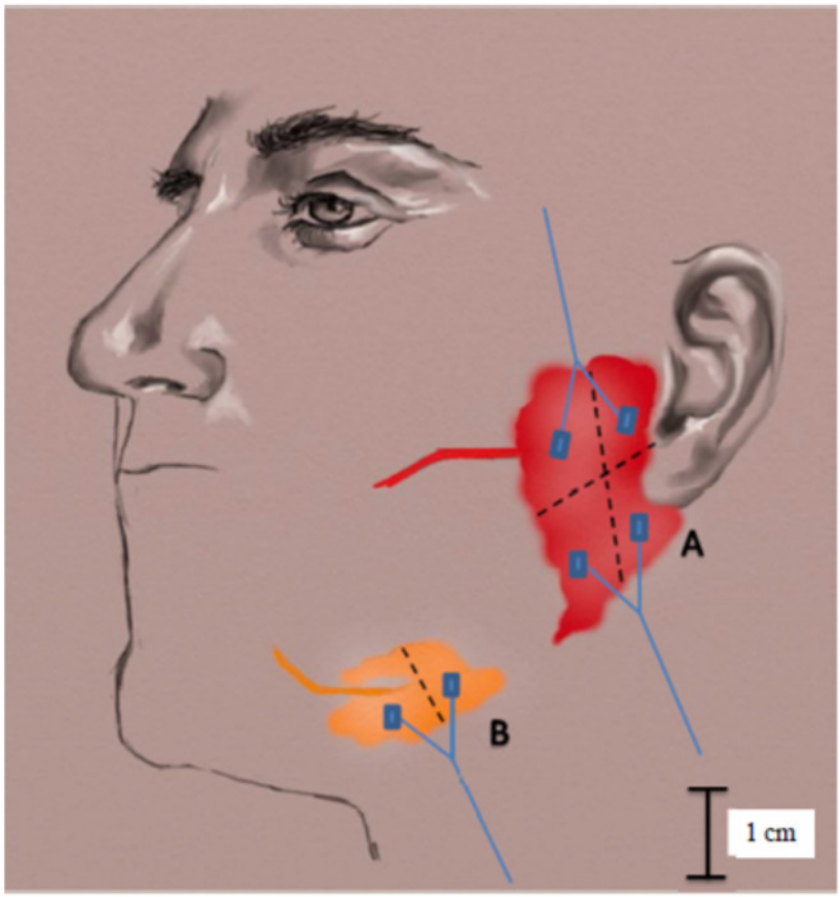


Figure 3: Clinical Outcome of BoNT-A Treatment. Pre = evaluation before therapy; post = evaluation 1 month after therapy; DA = number of Daily Aspirations; VAS = Visual Analogue Scale; FS = Drooling Frequency and Severity Scale - frequency subscore; SS = Drooling Frequency and Severity Scale - severity subscore. Please click here to view a larger version of this figure.



Supplemental Figure: Representation of the Ideal Injection Sites. A) Schematic division of the parotid gland into four quadrants, two cranial and two caudal, for correct injection into four different glandular sites. **B)** Schematic division of the submandibular gland into one cranial and one caudal quadrant for correct injection into two different glandular sites.

Discussion

This protocol describes US-guided BoNT-A injection in the parotid and submandibular glands for the treatment of moderate to severe sialorrhea. Sialorrhea secondary to dysphagia is a frequent complication of the advanced stages of different neurological diseases, and when pharmacological therapy with anticholinergic agents demonstrates scarce efficacy or tolerability, salivary gland BoNT injection represents a useful therapeutic option[2,7]. However, salivary gland BoNT injection guided by anatomical landmarks may be a therapy of low efficacy and possibly burdened with serious adverse events, since the correct injection of the glands is not guaranteed[13]. On the basis of literature data, BoNT salivary injection for the treatment of sialorrhea showed a wide range in success rates, ranging from 30% to 70%. This difference should be attributed to the differences in the published studies in terms of study designs (prospective[17,18] or retrospective[19,20]), sample sizes, injection sites, and techniques. On the other hand, Lakray and collegues[2] recently described a very low complication rate with ultrasound-guided injections of BoNT for the management of sialorrhea, demonstrating a better outcome for the US-guided injection technique compared to the landmarks method. Furthermore, the same review did not evidence the superiority of one therapy brand over another.

As we recently reported[7], ultrasound-guided injections of both the parotid and submandibular glands proved to be an effective technique to obtain real-time and precise needle visualization for correct BoNT administration, providing a reliable sialorrhea treatment with prolonged efficacy and a low rate of serious adverse events. Indeed, the visualization of the glands and of the needle penetration provided by the ultrasound-guided approach allows for the widespread administration of BoNT-A within the glands, significantly reducing the severity and frequency of drooling and improving patient quality of life[7,13,15]. Moreover, our protocol produces long-lasting efficacy in the reduction of sialorrhea, with a treatment-free interval of about 6 months and with a low rate of side effects[7]. The choice of the dose and type of BoNT is based on the clinical practice of our center and is supported by literature data[7,8,16], suggesting that the visual target identification and the ultrasound-guided injection allows for a reproducible and reliable effect with the administration of an identical BoNT-A dose for every patient. Therefore, this technique aims to avoid repeated treatments for the identification of each patient's effective dose, avoiding patient discomfort and reducing costs in terms of time and drug wastage.

The first step for a good outcome is correct patient selection; scales assessing the severity of sialorrhea, such as the DFSS[14], are useful tools for the identification of patients eligible for this treatment. In addition, the evaluation of the number of daily aspirations is of further help in the assessment of subjects with severe sialorrhea; this assessment also represents an objective outcome of the treatment. After patient selection, the critical step of the procedure is the US identification of the targets, specifically the parotid and submandibular glands. The correct visualization of the targets and of needle penetration is crucial to obtain optimal results, since the technique described here allows safe needle tip introduction and widespread BoNT-A distribution within the glandular tissue using multiple injection sites.

Limitations of this procedure include the need for experience in the use of ecographs and for knowledge of the maxillofacial anatomical structures, or for the assistance of a radiologist expert in US procedures. Moreover, the use of this technique in patients with coagulation abnormalities or in those receiving anticoagulant therapy is not recommended due to the high risk of bleeding.

As neurologists, we developed this technique for the treatment of sialorrhea in adult neurological patients, demonstrating its efficacy in subjects with different neurological diseases[7]. However, this approach can potentially be used for the treatment of every subject suffering from moderate to severe sialorrhea, independent of its etiology.

In conclusion, this technique produces a demonstrable and long-lasting improvement of sialorrhea in neurological dysphagia, encouraging the use of BoNT-A injection in the salivary glands and highlighting the role of ultrasound guidance to obtain the best outcomes in terms of efficacy and safety.

Disclosures

The authors have nothing to disclose.

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