Received: 1 June 2023 | Accepted: 8 August 2023

DOI: 10.1002/lio2.1164

ORIGINAL RESEARCH

Laryngoscope Investigative Otolaryngology

The effectiveness of ultrasound-guided injection of BTX-A in the management of sialorrhea in neurogenic dysphagia patients

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Funding information
The Third Affiliated Hospital of Sun Yat-sen University Clinical Medical Research Fund, Grant/Award Number: YHJH201909

Abstract

Objective: To evaluate the effectiveness of ultrasound-guided injection of botulinum toxin type A (BTX-A) in treating sialorrhea.

Methods: We recruited 32 sialorrhea subjects and they received an ultrasound-guided injection of BTX-A. The extent of salivation was evaluated according to the Visual Analog Scale (VAS), Drooling Severity and Frequency Scale (DSFS), and Saliva Flow Rate (SFR). Laryngeal secretions were evaluated based on Fiberoptic Endoscopic Evaluation of Swallowing (FEES) rated according to the Murray Secretion Scale (MSS). We assessed the extent of salivation and laryngeal secretions before injection and at 1, 2, and 4 weeks after injection.

Results: The scores for the VAS, DSFS-S, DSFS-F, and DSFS-T decreased significantly at 1, 2, and 4 weeks after injection compared with before injection ($p < .05$). Based on VAS, the efficacy was substantially higher at 2 and 4 weeks after injection than at 1 week after injection ($p < .05$). According to DSFS-S and DSFS-T, the efficacy was significantly higher at 4 weeks than at 1 week after injection ($p < .05$). The SFR and MSS scores at 1 and 2 weeks after injection were superior to those before injection ($p < .05$). Meanwhile, the SFR score 2 weeks after injection was superior to that 1 week after injection ($p < .05$).

Conclusion: The ultrasound-guided injection of BTX-A can effectively reduce saliva secretion in patients with neurogenic dysphagia. Furthermore, it has the advantages of early onset time and lasting curative effects, which indicates that clinical promotion and application of this technique are justified.

Level of Evidence: Level 3.

KEYWORDS
botulinum toxin type A, dysphagia, parotid gland, sialorrhea, stroke, submandibular gland, ultrasound-guided

1 | INTRODUCTION

Sialorrhea, or excessive saliva beyond the margin of the lip, is a common problem in many neurological diseases,[1,2] including cerebral palsy, Parkinson's disease, traumatic brain injury, and stroke.[2–4] Sialorrhea is caused by either increased salivary production[5,6] or reduced oropharyngeal clearance.[6,7] Sialorrhea may lead to skin irritation and infection around the mouth area[4] and potentially coughing and choking, leading to a higher risk of aspiration.[8] These elements can be highly distressing and diminish patients' quality of life.

Generally, the main aim of sialorrhea management is to reduce salivation.[9] Although sialorrhea can be treated by a variety of modalities (such as radiotherapy, surgery, and pharmacology),[1] direct injection of onabotulinumtoxinA (BTX-A) into the salivary glands is known to be a safe, minimally invasive, and effective treatment.[7,10] The primary benefit of BTX-A injection is that it avoids the side effects caused by oral medication and the need for surgical intervention.[11,12]

The mechanism of botulinum toxin involves blocking acetylcholine release at the parasympathetic terminals of the salivary glands.[13] Ultrasound-guided injection into the salivary glands is more accurate and safer than direct injection.[14] In assessing sialorrhea, researchers frequently used observation-based scales and saliva flow volume in previous studies, for example, the Visual Analogue Scale (VAS), Drooling Severity and Frequency Scale (DSFS), scales for daily living activities, and measures of saliva flow rate (SFR).[8,15–17] To gain deeper insight into sialorrhea, however, a more objective and intuitive assessment tool is needed. The Fiberoptic Endoscopic Evaluation of Swallowing (FEES) test is an objective and sensitive means to classify oral and pharyngeal swallowing stages[18] that has been used to evaluate dysphagia. In the associated method, pharyngeal secretions are intuitively evaluated, and stasis of secretions is scored using the Murray Secretion Scale (MSS).[19]

Consequently, we aimed to investigate the effectiveness of ultrasound-guided injection of BTX-A in the management of sialorrhea in patients with neurogenic dysphagia based on the use of comprehensive measurement tools (comprising subjective, objective, and equipment evaluations).

2 | MATERIALS AND METHODS

2.1 | Study design

Our study included a retrospective cohort of patients examined at our institution's Dysphagia Clinic between July 2018 and March 2022. Video-recorded FEES was performed, reviewed, and scored by the same speech-language pathologist, who specializes in swallowing disorders and is experienced in performing FEES. Our institutional ethics committee approved the study.

2.2 | Participants

Inclusion criteria for patients were (1) aged between 18 and 80; (2) dysphagia caused by neurological disease; (3) a diagnosis of dysphagia by speech-language pathologist through videofluoroscopic swallowing study; (4) diagnosis of sialorrhea based on having any one of the following three conditions: (i) total DSFS score ≥ 6, (ii) score ≥ 2 points for drooling severity scale or drooling frequency scale in each category, and (iii) Murray Secretion Scale (MSS) ≥ 2; (5) conscious and able to cooperate with evaluation for sialorrhea and follow-up; (6) agree to receive BTX-A injection and can sign informed consent. Exclusion criteria for patients were (1) accepted BTX-A injection in the last 6 months; (2) botulinum toxin allergy or contraindication; (3) having taken drugs for salivation or drugs causing salivation in the past month; (4) serious diseases or malignant tumors affecting heart, lung, liver, kidney, and other vital organs.

2.3 | Instruments

2.3.1 | Visual Analogue Score (VAS) and Drooling Severity and Frequency Scale (DSFS)

VAS is a subjective scale scored from 0 to 100,[20] where 0 means no drooling and 100 means the most severe drooling. VAS can be rated by patients or their caregivers.

DSFS consists of two subscales: drooling severity scale (DSFS-S) and drooling frequency scale (DSFS-F).[16] The score of DSFS-S ranges from 1 (never drools) to 5 (severely drool that wets the patient's clothes, hands, and whole body). The score for DSFS-F ranges from 1 to 4 (never, occasional, frequent, and constant). Total DSFS (DSFS-T) is calculated by adding the scores for DSFS-S and DSFS-F. DSFS-T ranges from 2 (no drooling) to 9 (the most severe drooling).

2.3.2 | Saliva flow rate (SFR)

Two pieces of 6 cm × 8 cm double-layer medical gauze were rolled into cylinders with a length of 3 cm and a diameter of 1 cm. The dry weight was measured using a special electronic scale (accuracy: 0.001 g) and then placed the dry gauze against the buccal mucosa on both sides of the patient. The patient was instructed not to chew the gauze. After 5 min, the gauze was taken out from the patient, and measured the wet weight of the gauze. Then the SFR was the result of the gauze's wet weight minus dry weight. And repeat this measurement 5 min later, and three times in total. Then calculating the average of the three SFR results to get the average SFR.

2.3.3 | Murray Secretion Scale (MSS)

FEES was performed using an electronic laryngoscope (ATMOS MedizinTechnik GmbH & Co. KG, Lenzkirch, Germany). While the patient

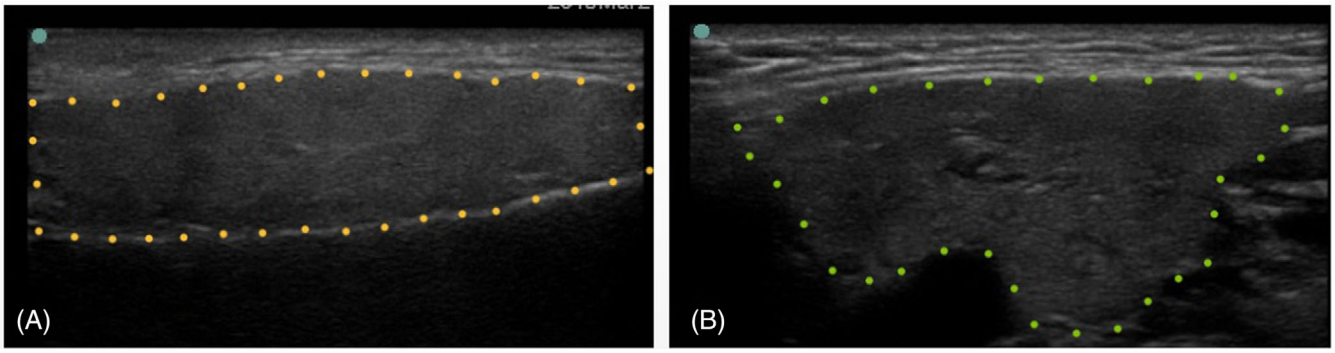

FIGURE 1 Ultrasound images of the parotid and submandibular glands. (A) The parotid gland is inside the yellow dotted line; (B) the submandibular gland is inside the green dotted line.

assumed an upright position, the operator applied lubricant to the end of endoscope and then inserted into the oropharynx via the nasal canal. The accumulation of secretions in the epiglottis valley, piriform sinus, and laryngeal vestibule were evaluated using MSS.[21] For this scale, score 0 means no secretion; score 1 means there were secretion at epiglottis valley and piriform sinus; score 2 means secretion changed from 1 to 3; score 3 was the most severe secretion, secretion could be persistently accumulated at laryngeal vestibule.

2.4 | Procedure

BTX-A (Botox®, Irvine, CA, USA) was used for injection. Before injection, 100 U of BTX-A was diluted in 2 mL of 0.9% sodium chloride to prepare a solution of 50 U/mL concentration. After routine skin disinfection, ultrasound was used to guide the injection of BTX-A into the bilateral parotid and submandibular glands. The parotid gland is located on the external auditory and mandibular angle of attachment. In contrast, the submandibular gland is located under the middle of mandibular angle. The ultrasound probe should be located where the gland tissue was abundant with no neurovascular lines (Figure 1). The unilateral parotid gland had two injection sites, and 15 U of BTX-A were injected into each site. Two sites, one on each side, of the submandibular gland, were each injected with 20 U. In total, 100 U of BTX-A was injected for one patient: 60 U for the bilateral parotid gland and 40 U for the bilateral submandibular gland.

VAS and DSFS were assessed before injection and 1, 2, and 4 weeks after injection. SFR and MSS were evaluated before injection and 1 and 2 weeks after injection.

2.5 | Data analysis

Data analysis was performed using SPSS 26.0. Parametric data are represented as mean ± standard error and analyzed using repeated measures analysis of variance with the *p*-value set at .05. Ranked and non-parametric data was compared using the Friedman test with the *p*-value set at .05. Further pairwise comparison was performed based on the Bonferroni method.

3 | RESULTS

3.1 | Characteristics of participants

We recruited 32 participants who met the inclusion criteria for this study. Diseases included cerebral infarction (15 cases), cerebral hemorrhage (10 cases), cerebral tumor (6 cases), and brainstem encephalitis (1 case). There were 27 males and 5 females, whose average age was 56.41 ± 16.09 years. The average course of diseases was 6.2 ± 5.3 months. All subjects received 100 U of BTX injection (30 U into the bilateral parotid gland and 20 U into the bilateral submandibular gland). DSFS, VAS, SFR, and MSS were scored before and after injection. For detailed information, see Table 1.

3.2 | Changes in VAS

Substantial changes were noticed before injection and 1, 2, and 4 weeks after injection ($F = 78.917$, $p < .0001$). As presented in Figure 1A, the VAS score at 1 week, 2 weeks, and 4 weeks after injection reduced compared with before injection ($p < .0001$). The VAS scores also decreased at 2 and 4 weeks compared with 1 week after injection ($p < .0001$). Compared with the VAS score of 2 weeks after injection, the VAS score of 4 weeks after injection also decreased ($p = .028$) (Figure 2).

3.3 | Changes in DSFS-F

The median values of DSFS-F before injection and at 1, 2, and 4 weeks after injection were 3, 2, 2, and 2, respectively. The scores of the four groups were compared using the Friedman test ($Z = 61.183$, $p < .001$). After post hoc comparisons, the DSFS-F score decreased

TABLE 1 General information on subjects.

Diagnosis	Number of cases	Gender	Age (years)	Course of diseases (months)
		Male/female	(mean ± SD)	(mean ± SD)
Cerebral infarction	15	9/6	59.8 ± 11.5	7.7 ± 6.3
Cerebral hemorrhage	10	10/0	58.1 ± 12.4	3.1 ± 1.9
Cerebral tumor	6	6/0	46.5 ± 28.0	6.5 ± 5.3
Brainstem encephalitis	1	0/1	48	12

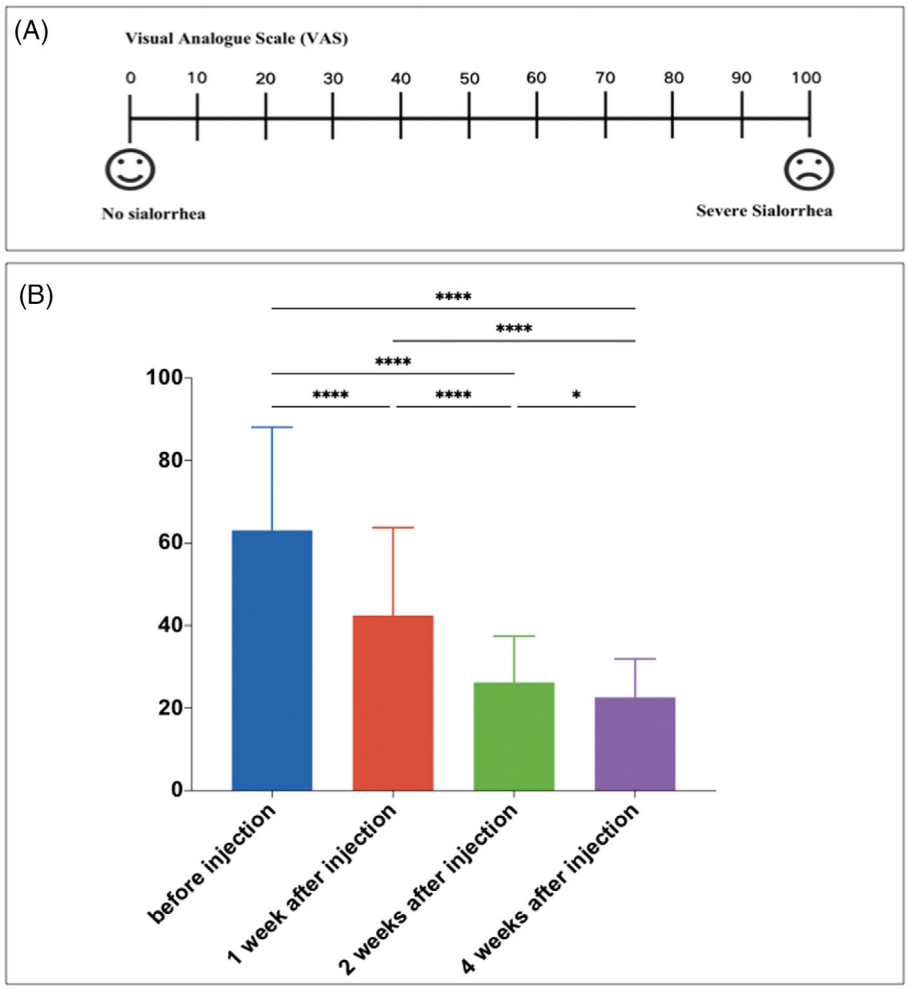

FIGURE 2 VAS score changed before and at 1, 2, and 4 weeks after BTX-A injection. (A) VAS is a subjective scale scored from 0 to 100, where 0 means no drooling and 100 means the most severe drooling; (B) substantial changes among the VAS scores before injection and at 1, 2, and 4 weeks after injection, ****$p < .0001$, *$p < .05$.

1 week after injection compared with before injection ($p = .002$ after adjustment). Meanwhile, the scores from 2 and 4 weeks after injection also differed from that before injection ($p < .0001$). Compared with 1 week after injection, the scores at 2 and 4 weeks after injection had a decreasing tendency, but the difference was not significant ($p > .05$) (Figure 3A).

3.4 | Changes in DSFS-S

The median values of DSFS-S before injection and at 1, 2, and 4 weeks after injection were 3, 2, 2, and 2, respectively. The scores of the four groups were compared using the Friedman test ($Z = 68.916$, $p < .001$). After post hoc comparisons, the DSFS-S score 1 week after injection decreased significantly compared with before injection ($p = .001$). Meanwhile, the scores from 2 and 4 weeks after injection also differed considerably from that before injection ($p < .0001$). Compared with 1 week after injection, the DSFS-S score at 4 weeks after injection was reduced ($p = .030$). Compared with 1 week after injection, the score at 2 weeks after injection had a decreasing tendency, but the difference was not significant ($p > .05$). There was no difference between 2 weeks after injection and 4 weeks after injection ($p > .05$), but it showed a downward trend (Figure 3B).

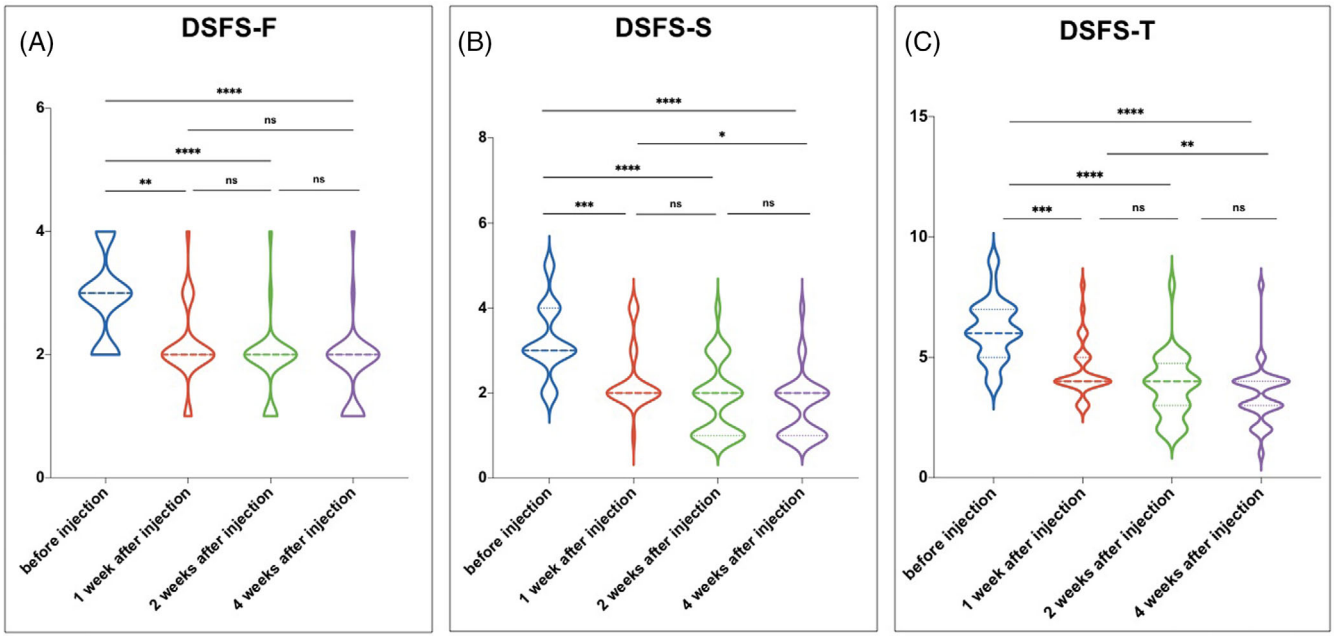

FIGURE 3 DSFS score changes before injection and 1, 2, and 4 weeks after BTX-A injection. (A) The median values of DSFS-F before injection and at 1, 2, and 4 weeks after injection; (B) the median values of DSFS-S before injection and at 1, 2, and 4 weeks after injection; (C) the median values of DSFS-T before injection, 1 week, 2 weeks, and 4 weeks after injection. The scores of the four groups were compared using the Friedman test. ****$p < .0001$, ***$p < .001$, **$p < .01$, ns $p > .05$.

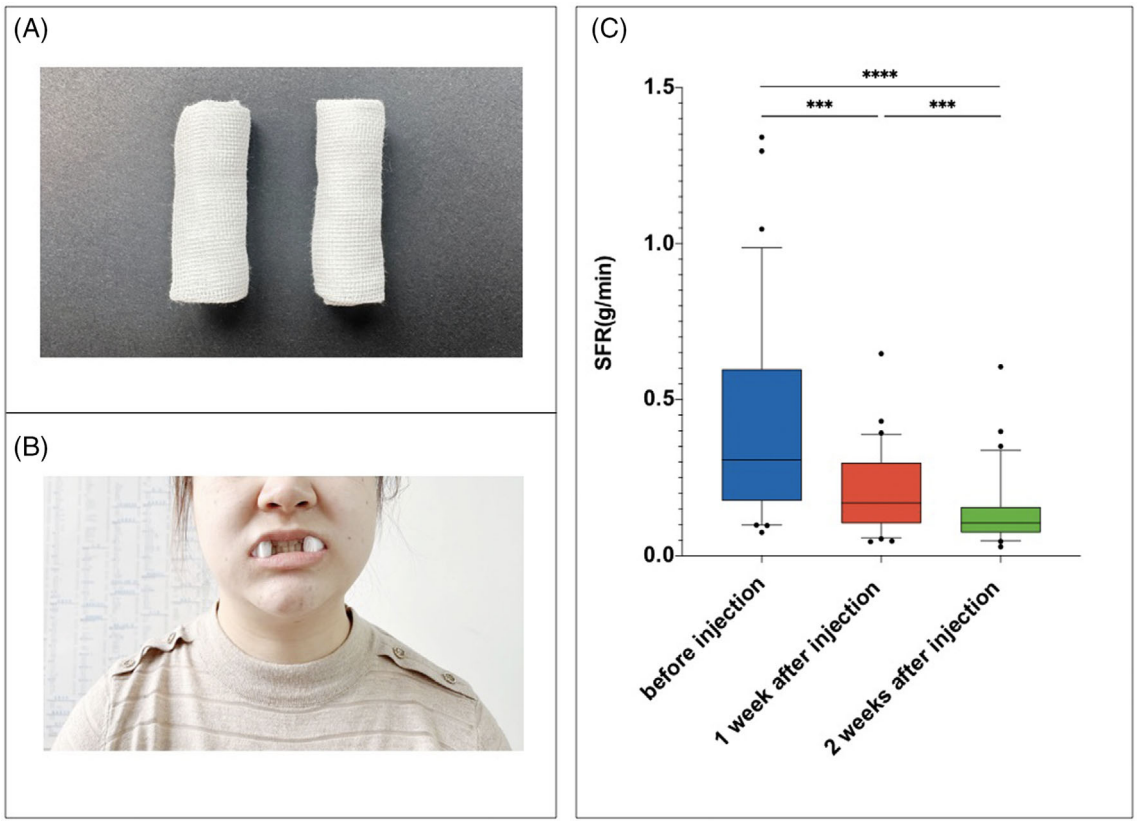

FIGURE 4 The SFR procedures and changes after BTX-A injection. (A) Two pieces of 6 cm × 8 cm double-layer medical gauze were rolled into cylinders with a length of 3 cm and a diameter of 1 cm; (B) the medical gauze was placed against the buccal mucosa insides of the patient; (C) the SFR score changed before and at 1, 2 weeks after BTX-A injection, ****$p < .0001$, ***$p < .001$.

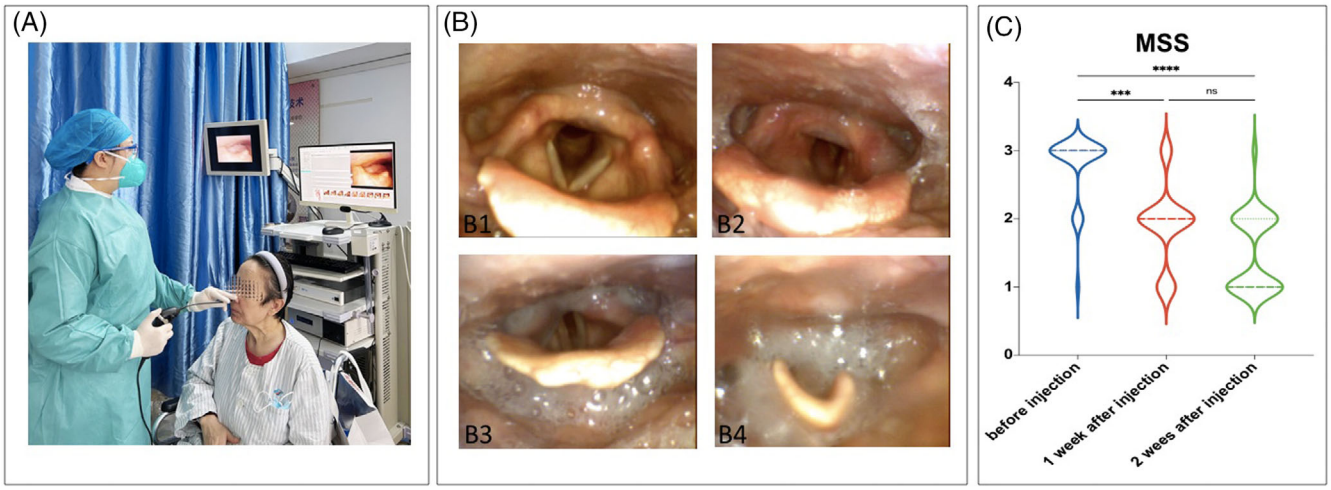

FIGURE 5 The MSS procedures and changes after BTX-A injection. (A) FEES was used to evaluate saliva secretion; (B) MSS scale: B1: score 0 means no secretion; B2: score 1 means there were secretion at epiglottis valley and piriform sinus; B3: score 2 means secretion changed from 1 to 3; B4: score 3 was the most severe secretion; (C) the MSS score changed before and at 1, 2 weeks after BTX-A injection, ****$p < .0001$, ***$p < .001$, ns $p > .05$.

3.5 | Changes in DSFS-T

The median values of DSFS-T before injection, 1 week, 2 weeks, and 4 weeks after injection were 6, 4, 4, and 3, respectively. The scores of the four groups were compared using the Friedman test ($Z = 77.004$, $p < .0001$). After post hoc comparisons, the DSFS-T score at 1, 2, and 4 weeks after injection differed significantly to from before injection ($p < .0001$). Compared with 1 week after injection, the DSFS-T score at 4 weeks after injection was reduced ($p = .004$), and the score at 2 weeks after injection had a decreasing tendency. Still, there was no significant differences ($p > .05$). Compared with 2 weeks after injection, the score at 4 weeks after injection showed a downward trend that showed no significant differences ($p > .05$) (Figure 3C).

3.6 | Changes in SFR

As presented in Figure 4, compared with before injection, the SFR score decreased both at 1 week ($p = .001$) and 2 weeks after injection ($p < .0001$). The scores were also significantly lower at 2 weeks after injection than 1 week after injection ($p = .001$).

3.7 | Changes in MSS

The MSS score was lower 1 and 2 weeks after injection than before injection ($p < .0001$). Though the score had a decreasing tendency, there is no significant difference between 1 week and 2 weeks after injection ($p > .05$) (Figure 5).

4 | DISCUSSION

We found that the VAS, DSFS, SFR, and MSS scores of the neurogenic dysphagia patients decreased after ultrasound-guided BTX-A injection into the parotid and submandibular glands. We used subjective, objective, and instrument evaluations to comprehensively observe the efficacy and safety of BTX-A injection in treating salivation and found that the best effects occurred at 1 and 2 weeks after injection, continuing to be effective 4 weeks after injection.

4.1 | The evaluations for sialorrhea treatment

In our study, we conducted a comprehensive evaluation of ultrasound-guided BTX-A injection for the treatment of sialorrhea. Previous studies have mainly used scales or saliva flow volume,[2,16,22–24] including DSFS, the Sialorrhea Clinical Scale for Parkinson's Disease, Drool Rating Scale, Amyotrophic Lateral Sclerosis Functional Rating Scale, Daily Oral Suction Volume, measuring the amount of saliva production through the weight of a cotton roll, etc. Instrumental assessments are rarely used. Lynch et al.[25] and Langmore et al.[18] indicated that FEES is more sensitive in detecting laryngeal structure, secretions, aspiration, and penetration than other assessment tools and that MSS is a reliable and valid tool to assess the severity of secretion during FEES implementation. Pluschinski et al.[21] investigated MSS and found that it has good intra-rater ($r = .847–.984$) reliability, inter-rater ($r = .951–.961$) reliability, and construct validity. Excessive saliva flows back into the oropharyngeal. Previous research reported that oropharyngeal secretions accumulation was more likely correlated with penetration and aspiration.[19,26] If the MSS score was two or higher, there would be a 13.6 times higher chance of aspiration

than those patients with lower scores.[27] Chronic saliva aspiration eventually leads to pneumonia or even death.[8,24,28,29] After BTX injection, recruited patients in this study tend to have a lower MSS score than before the injection. There were 78% (25 out 32) patients' MSS score decreased from 3 after 2 weeks injection. Thus, with the guidance of instrumental evaluation, we can achieve a more accurate and comprehensive assessment of a patient's sialorrhea and accordingly decide our next steps.

4.2 | The way to locate salivary glands

There are two main ways to locate salivary glands for BTX injection: anatomical and ultrasound-guided. It has been reported that palpation or anatomical landmarks guidance were more convenient than other approaches.[30,31] But Sidebottom et al.[32] found that palpation needs patients' cooperation and had more risks. Moreover, if the needle injects beyond the glands, it might lead to hematoma and affect nerve activity at the intramuscular junction.[32] Previous studies recommended that ultrasound has more advantages than solely manual guidance (such as: visually see the injection structure, needle, blood vessels and nerves that need to be avoided, etc.),[33,34] and there was Level 1 evidence to support this.[33]

In some studies, the success rate for salivary gland injection using anatomical landmarks in the parotid and submandibular glands ranges from 30% to 70%.[14] However, the anatomical position of the salivary glands differs from the proposed landmarks and depends on the individual's age and body weight. Previous studies have compared the accuracy of these two different injection strategies and discovered statistically significant differences between the two procedures when used in submandibular gland injection (non-ultrasound guided vs. ultrasound-guided: 50.00% vs. 91.67%).[35] Based on previous studies, the ultrasound-guided method was recommended as the preferred method. Barbero et al.[13] used an ultrasound-guided injection of BTX-A. Their results showed that this technique resulted in significant and lasting improvements in the treatment of moderate and severe salivary syndrome in patients with neurologic dysphagia and reduced the incidence of adverse events. Our research also used ultrasound-guided injection. No obvious injection complications or adverse drug reactions were observed during the treatment and follow-up. Comparative, randomized studies with large sample sizes showing that ultrasound injection with more advantages is still lacking,[7] future studies are needed.

4.3 | The dose of BTX-A in the sialorrhea treatment

Three types of BTX-A were widely used: abo-, ona-, inco-. Incobotulinum has been approved by FDA, of which the recommend dosage was 100 U and followed the SIAXI protocol.[36] Others have no standard protocol about dosage and frequency of application. To investigate the most effective dose of BTX-A for sialorrhea treatment, Gonzalez-L et al.[37] used 100 U OnaA (25 U each gland) and injected 20 patients, which concluded that BTX injection into saliva glands were effective with no frequent side effect. Weikamp et al.[38] injected 200 U AboA in ALS patients. Although they found that using radiotherapy reduced more that BTX injection, the results shown that BTX injection patients achieved reduction (drooling status-4 weeks versus 12 weeks: 22.5 (5.3) versus 20.8 (6.6); VAS-4 weeks versus 12 weeks: 79 (16) versus 74 (16)). Mazlina et al.[39] injected the parotid and submandibular glands of 30 patients with different dosages of AboA (including 50 U, 100 U, and 200 U) under ultrasound guidance. They found significantly decreased saliva volume for the high-dose group (100 U and 200 U), and no statistical significance between these different dose groups ($p > .05$). For AboA and OnaA dosage equivalence, a ratio of 2:1–3:1 was reported.[40] After considering the results of previous studies and clinical experience, we selected 100 U OnaA (30 U each parotid gland and 20 U each submandibular gland) as the injection dose. According to our results, 100 U had definite curative effects, with improvements to the symptoms of salivary patients. Further studies are needed to determine the efficacy of a higher dosage and the specific distribution ratio of the injection dose into the parotid and submandibular glands.

4.4 | The duration of BTX-A injection's efficacy

Pluschinski et al.[21] injected BTX into the parotid and submandibular glands of 21 neurogenic dysphagia patients using different doses (1500 U in group A, 2500 U in group B, and 0 U in group C) under ultrasound guidance. They found that the saliva volume and salivation symptoms of patients in groups A and B significantly indicated improvements after treatment, with the patients' saliva volume being the lowest after 2 weeks, with the effects lasting 8 weeks. We obtained similar results in our study. The salivation symptoms of patients improved 2 weeks after injection, and the efficacy was ensured until at least 4 weeks after injection. Barbero et al.[41] evaluated the long-term effectiveness and safety of ultrasound-guided BTX-A injection for the treatment of neurogenic dysphagia patients with severe salivation. They found that the efficacy duration was (5.6 ± 1.0) months. This study is still in the follow-up stage, and the follow-up results will be observed and summarized in time.

4.5 | The side effects of BTX-A injection

Botulinum toxin injection into salivary glands was proved to be safe and effective in previous studies and adverse effect were rarely reported.[34,37,39,42] Most treatment-related AEs were mild to moderate in severity and self-limited. The side effect profiles of neurotoxin injections are generally fewer and more tolerable than anticholinergic medication, including dry mouth, saliva thickening, and salivary gland swelling.[43] Diffusion of toxin into adjacent musculature can cause chewing difficulties and transient weakness of mouth closure;

however, this is less common with ultrasound guidance for injection.[44] Due to the severe sialorrhea status of our patients, reasonable dose, and our accurate way to locate salivary glands, we have not found the side effects.

4.6 | Limitation

Some limitation of this study should be noted. First, the observation time of efficacy is insufficient. In this study, 4 weeks after injection was observed, and according to the literature, this tracking time could be extended to 8 weeks or more.[21,39,41] Second, different dosage of BTX-A injection's effectiveness has not been discussed. Future studies could explore whether large doses of botulinum toxin injections work better in patients with severe salivation. Moreover, larger sample size and longer observation time are needed. We plan to address these limitations in a follow-up study.

5 | CONCLUSION

In conclusion, the results of our study indicate that ultrasound-guided injection of BTX-A can effectively decrease saliva flow in patients with neurogenic dysphagia and improve salivation symptoms. The onset time for BTX-A effects is 1 week after injection, with a curative effect of at least 4 weeks.

FUNDING INFORMATION

This work is supported by the (#1 The Third Affiliated Hospital of Sun Yat-sen University Clinical Medical Research Fund) under Grant (YHJH201909).

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

INFORMED CONSENT

All patients gave their informed consent to all the study procedures.

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How to cite this article: He Z, Chen S, Zeng P, et al. The effectiveness of ultrasound-guided injection of BTX-A in the management of sialorrhea in neurogenic dysphagia patients. *Laryngoscope Investigative Otolaryngology*. 2023;8(6): 1607-1615. doi:10.1002/lio2.1164