Diagn Interv Radiol 2013; 19:56–60

INTERVENTIONAL RADIOLOGY
ORIGINAL ARTICLE

US-guided botulinum toxin injection for excessive drooling in children

Türkmen Çiftçi, Devrim Akıncı, Nursel Yurttutan, Okan Akhan

PURPOSE
We aimed to evaluate the safety and efficacy of botulinum toxin A (BTX-A) injections under ultrasonography (US) guidance for children with excessive drooling.

MATERIALS AND METHODS
Between January 2006 and January 2011, 44 BTX-A injections into bilateral submandibular glands were performed in 20 children (mean age, 9.1 years; range, 3–16 years; gender, 15 boys and 5 girls) under intravenous sedation. Efficacy of the injections was evaluated 4–12 weeks after the injection. Severity of drooling was assessed using the Teacher Drooling Scale (TDS). If the patient or the patient's caregiver reported a good initial response, injections were then repeated periodically when drooling reached the preinjection score. If there was no response or suboptimal response, a booster injection of BTX-A was given after one month.

RESULTS
Technical success rate was 100%. No procedure-related major or minor complication was detected. One family (5%) reported intermittent problems with swallowing due to viscous saliva. A successful outcome was defined as a minimum two point reduction in TDS score. This outcome occurred for 8 of 20 patients four weeks after the first injection. After consecutive sessions, clinical success was achieved at the end of the 12 weeks for 16 patients (80%). The mean TDS score decreased from 4.75 to 2.1 at the end of the study for all patients ($P < 0.05$). Four patients did not respond to BTXA injection. Submandibular resection was applied to 3 of 4 unresponsive patients. Two patients had complete remission after surgery, but one patient showed excessive drooling that could not be controlled.

CONCLUSION
US-guided submandibular BTX-A injection is a safe and effective procedure in treating drooling in children. It can be performed under intravenous sedation and does not require general anesthesia.

From the Department of Radiology (T.Ç. ✉ *turkmenciftci@yahoo.com*), Hacettepe University School of Medicine, Ankara, Turkey.

Received 21 April 2012; revision requested 15 May 2012; revision received 27 May 2012; accepted 2 June 2012.

Published online 13 July 2012
DOI 10.4261/1305-3825.DIR.5940-12.1

Excessive drooling (sialorrhea) is commonly observed in children with chronic neuromuscular disorders such as cerebral palsy, severe mental retardation, facial paralysis, and encephalopathy. Cerebral palsy is the most common cause of excessive drooling in children, with an incidence of 10%–38% (1). Excessive drooling adversely affects the quality of life, particularly in children, with consequent negative impacts that include perioral skin breakdown and infections, disturbed speech and eating, and the soiling of clothing from saliva (2). In severe cases, aspiration-related pulmonary complications can occur (posterior drooling). In addition, drooling may cause psychosocial morbidity, as other individuals may be averse to the drooling and refuse close contact (2, 3). All treatment strategies currently used include behavioral, medical or surgical approaches; none of these treatments, however, are satisfactory (4). Anticholinergic drugs taken orally or transdermally may be effective, but produce unacceptable side effects (4–7). Surgical treatments, such as removal or denervation of salivary glands or ligation of the major salivary ducts, are more invasive and carry more risk, including severe and irreversible xerostomia (6, 8–10).

Recently, botulinum toxin A (BTX-A) has emerged as a potential treatment agent for the management of drooling. BTX-A blocks the neuromuscular junction by inhibiting the release of presynaptic acetylcholine, which prevents the secretion of saliva (1–7). Results of BTX-A injections into salivary glands in children are well documented in the pediatric and neurology literature, with many cases showing clinical improvement in drooling and few side effects (2–7, 11–18); the number of reports regarding this procedure in the radiology literature, however, is limited (19).

The purpose of this study was to evaluate the safety and clinical efficacy of BTX-A injections under ultrasonography (US) guidance for children with excessive drooling.

Materials and methods

Data collection

This retrospective study included patients treated in our hospital between January 2006 and January 2011. We included all children who underwent US-guided submandibular BTX-A injections for excessive drooling and who were monitored by follow-ups for at least six months. Clinical information for all patients was collected from our institutional database. The mean age of the 20 patients (15 boys and 5 girls) in the study was 9.1 years (range, 3–16 years). This study was approved by the Hacettepe University School of Medicine Institutional Review Board (B. 30.2.HAC.0.70.00.01/431.10-954).

A total of 44 injections was performed in 20 patients for 88 glands. Responses to treatment in all patients were evaluated with Teacher Drooling Scale (TDS) scores before and 4–12 weeks after the treatment,

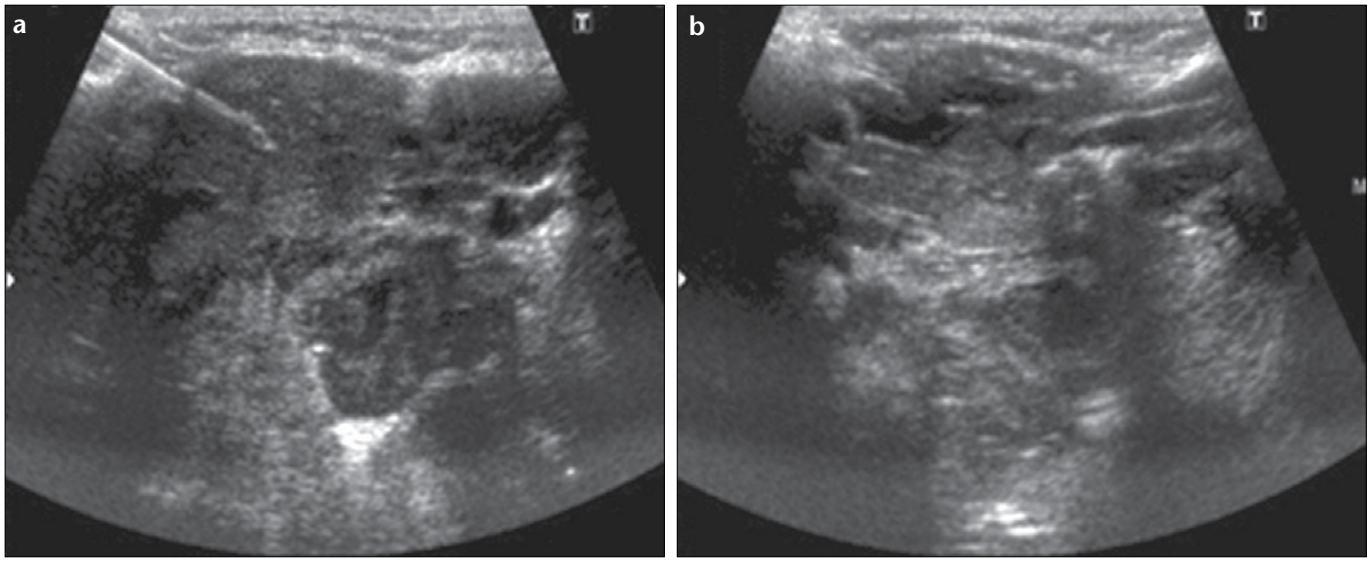

Figure 1. a, b. A seven-year-old girl with mental retardation. Entrance into submandibulary gland with 23 G needle under US guidance **(a)** and BTX-A injection **(b)** are seen.

as done in previous studies (2, 7) (Table 1). TDS scores were obtained by evaluations collected from the patients' caregivers, clinicians, and discharge notes.

Inclusion and exclusion criteria

Injections performed in patients with symptoms of anterior drooling and a score of 3 or higher on the TDS (indicating severe drooling) were included in the study. Injections performed in patients with symptoms such as bronchial aspiration and pneumonia due to posterior (retropharyngeal) drooling were excluded from this study. Patients who underwent salivary gland surgery due to drooling were also excluded from this study.

Procedures

All injections were performed in an interventional radiology suite under US guidance with intravenous sedation. Possible adverse effects and risks related to the interventions or anesthetics were explained to the parents, and informed consent was obtained before the procedure. For sedation, propofol (1 mg/kg) and fentanyl (1 µg/kg) were administered intravenously by an anesthesiologist. US guidance was performed using a system equipped with a 7.5 MHz high-resolution transducer. Only the submandibular glands were injected for each procedure. Before injection, the vascular anatomy of the submandibular glands was carefully assessed with color or power mode of US. A single dose of BTX-A (Botox®, Allergan Inc., Irvine, California, USA) reconstituted with 0.9% sodium chloride solution (1 mL for each gland) was injected bilaterally in the submandibular glands using a 1-mL syringe and a 23 G needle under US guidance (Fig. 1). The needle was inserted into the submandibular gland along the longitudinal axis, and while removing the needle step by step under US control, the toxin was injected; this technique enabled penetration of the toxin into the entire glandular parenchyma. The same procedure was repeated for the contralateral gland parenchyma. The dose of BTX-A was adapted for each child according to body weight (15 U/gland for children <15 kg, 20 U/gland for children 15–25 kg, and 25 U/gland for children >25 kg) (7). If the patient or the patient's caregiver reported a good response, injections were repeated periodically when drooling reached the preinjection TDS score. If there was no response or a suboptimal response, a booster injection of BTX-A was given after one month. The dose of the booster injections was equivalent to the initial dose.

Table 1. Teacher Drooling Scale (TDS) (2, 7)

1	No drooling
2	Infrequent drooling; small amount
3	Occasional drooling; intermittent all day
4	Frequent drooling but not profuse
5	Constant drooling; always wet

Outcome measures

The TDS score served as the primary outcome measure for this study. Assessments of TDS score were performed at baseline and after BTX-A injections (4 and 12 weeks postinjection). A significant response to therapy was defined as a minimum two point improvement on the TDS (7). A commercially available software (Statistical Package for Social Sciences, version 11.5, SPSS Inc., Chicago, Illinois, USA) was used for statistical analysis. A Wilcoxon signed-rank test was used to analyze changes in TDS score. Definitive statistics were presented as mean, standard deviation, and median. Differences were considered statistically significant when $P < 0.05$.

Results

Patients and procedures

Twenty children suffering from excessive drooling due to different

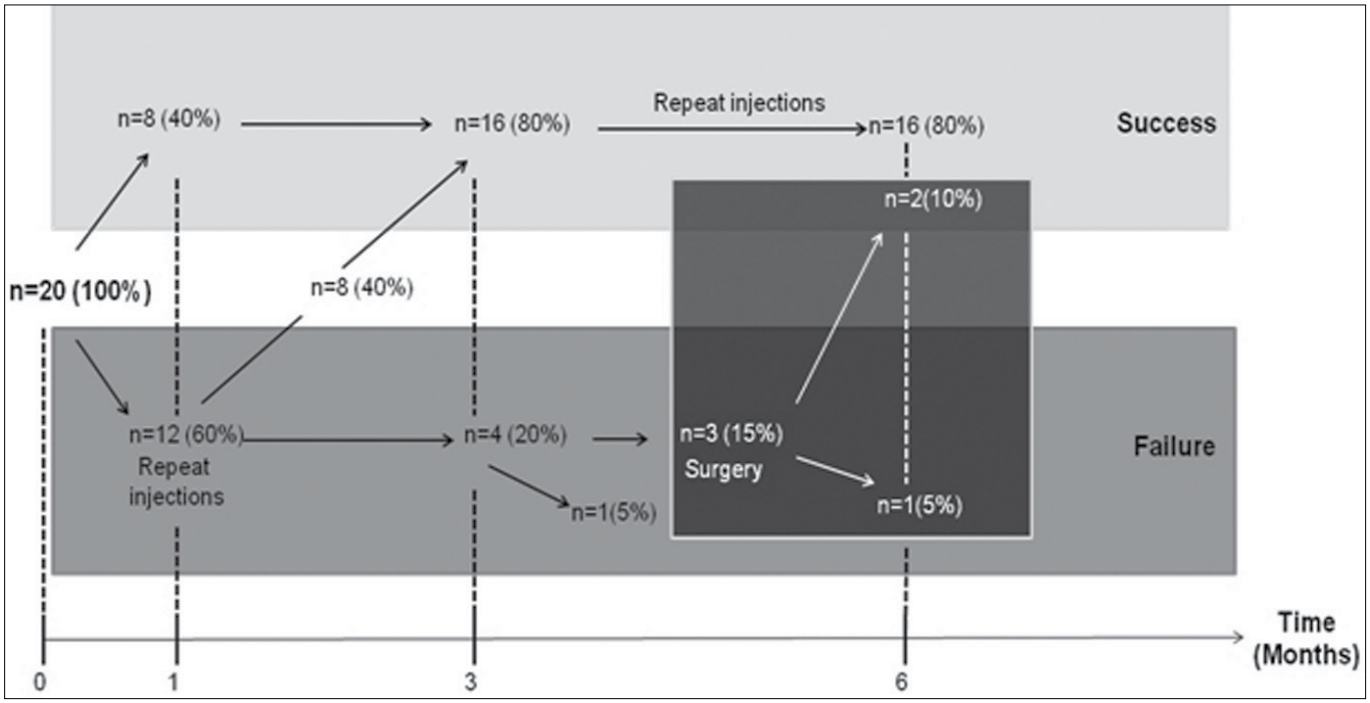

Figure 2. Representative figure showing the clinical outcome of the patients for six months. Light gray box represents the patients who show symptomatic improvement either by BTX-A injections or surgery (success). Dark gray box represents the patients whose symptoms were not improved (failure). Black box summarizes the patients who underwent surgery due to unresponsiveness to BTX-A injections (surgery).

neurological disorders were treated by injection of BTX-A into the submandibular glands under US guidance. Classification of the underlying diseases of the patients is presented in Table 2. Before the procedure, 75% of the patients (n=15) had a TDS score of 5, with the remaining 25% (n=5) having a score of 4 (preprocedural mean TDS was 4.75 for all patients). A total of 44 injection sessions (1–3 per patient; mean, 2.2 sessions) were applied; the technical success rate was 100%. No procedure-related major or minor complications were detected. The dose administered into the submandibular glands ranged from 15 to 25 U/gland (mean, 20 U/gland).

Outcomes

No child had severe or life-threatening events in response to BTX-A treatment. One family (5%) reported intermittent problems with swallowing due to viscous saliva.

A successful outcome was determined by a minimum two point reduction in TDS score. Successful outcome was confirmed in 8 of 20 patients four weeks after the first injection. After consecutive sessions, clinical success was achieved in 16 patients (80%) at the end of the 12 weeks. Re-injections were administered at a median of 3.4 months (range, 1–5 months) and were given if drooling reached the preinjection TDS score. The mean TDS score decreased from 4.75 to 2.1 at the end of the study for all patients ($P < 0.05$). Time until observable change ranged from 5 to 30 days (mean, 15 days); the duration of effect of injection ranged from 8 to 20 weeks (mean, 17 weeks). There was a positive response after BTX-A injection in 16 of the 20 patients, whereas four patients did not show any response. Three of the four unresponsive patients underwent surgical submandibular resection upon the clinician's decision. Two patients had complete remission after surgery, but in one patient, excessive drooling could not be controlled. The remaining one unresponsive patient did not accept further treatment. The outcome of all patients is summarized in Fig. 2.

Table 2. Underlying diseases of the patients

Primary disease	Number of patients (%)
Cerebral palsy	8 (40)
Motor and mental retardation	4 (20)
Hypoxic ischemic encephalopathy	2 (10)
Posterior fossa mass	1 (5)
Congenital *Cytomegalovirus* infection	1 (5)
Myopathy	1 (5)
Apert syndrome	1 (5)
Hydrocephalus	1 (5)
Arthrogryposis multiplex	1 (5)
Total	20 (100)

Discussion

Our study support the findings of previous reports that injection of BTX-A into submandibular glands under US guidance significantly ameliorates the drooling status of children, thus reduces the discomfort of families during care. Previous studies reported success rates between 61.5% and 83% (2, 7, 17–19). Our short-term success rate was 80%, and this result is in line with previous studies.

Mild side effects, such as viscous saliva, chewing difficulties, dry mouth and transient weakness of mouth closure have been reported in the literature (2, 6, 7–19). The majority of these side effects occur due to the muscle weakness that is related to the diffusion of the BTX outside the salivary gland (7). In our study, viscous saliva leading to feeding problems was observed only in one child as minor side effect, and this was resolved as the effect of BTX-A diminished.

In previous studies, a variety of techniques based on either palpation (5, 15) or US guidance (7, 11–14, 16, 18, 19) were used to localize the glands. As it has an evident advantage of visualization over other palpation techniques, US guidance is crucial for avoiding rare but serious complications, such as injection of BTX-A into adjacent muscles. US guidance also allows documenting possible changes of the glandular parenchyma following injection (Fig. 1). No serious adverse effects were observed in this study.

In the present study, we confirmed a positive response after BTX-A injection in 16 of the 20 patients, whereas four patients showed no response to BTX-A injection. The lack of response could not be attributed to a specific reason, as the injection technique was identical and there was not any intercurrent illness. The BTX-A injection procedure was not performed to patients previously for any other reasons, therefore antibody-mediated tolerance may not be responsible for clinical failure. No further investigations were made in these patients. In addition to submandibular glands, parotid gland injections could have been considered as an alternative for unresponsive patients. In previous studies, the reason(s) for different responses to intraglandular BTX-A was not clarified (17–19).

Injections have been successfully administered to the salivary glands, including the parotid glands (5, 15, 16), submandibular glands (7, 11, 13) or a combination of both (4, 12, 14, 18, 19). Submandibular glands are capable of secreting 60%–70% of resting saliva when the individual is not eating (7, 17), while the majority of saliva used during eating and drinking is secreted from the parotid glands (3, 19). Our routine protocol covers only submandibular gland injection, as our approach was designed to not interfere with the necessary activity of parotid glands during eating and drinking. Pena et al. (19) reported no difference in response between only submandibular gland injection and both submandibular and parotid gland injections.

Various doses for BTX-A injection have been reported in the literature, ranging from 10 to 70 U (5, 12). Our adaptation of the injected dose to be based on the weight of child was based on a previous controlled clinical trial (7). The injection procedure and administered toxin dose was well tolerated by all children in this study.

In some studies, procedures were performed using topical anesthetic cream (5) or general anesthesia (18). We performed all of the procedures under intravenous sedation without any complications or side effects.

Previous studies have evaluated the response of BTX-A injection using objective measurements (measurement of saliva flow rate before and after procedure), only subjective measurements, or both (4, 7, 15, 17, 18). However, the use of objective parameters for determining efficacy is not accurate, as the saliva flow rate is not directly dependent on improvement of drooling and patient comfort. Saliva flow rate varies from one individual to another, and its secretion shows circadian fluctuation; therefore, taking objective quantifications into account does not completely reflect the patient's comfort levels. Using subjective methods based on clinical interviews of the patient or the patient's family serves as an appropriate and effective indicator for successful clinical outcome. In this study, instead of evaluating the reduction in saliva flow rate, all patients were evaluated 4–12 weeks after treatment according to their overall satisfaction and their desire to repeat the injection sessions.

Limitations of this study include its retrospective nature, the small groups of patients for statistical analysis, and the heterogeneity of underlying disease in the patient group. Although response to the treatment was evaluated by the scoring method (TDS), these scores were obtained by evaluation of all values collected from patient's caregivers, clinicians, and discharge notes.

In conclusion, US-guided submandibular BTX-A injection is a safe and effective procedure in children to treat drooling. It can be performed under intravenous sedation and does not require general anesthesia. BTX-A injection should be considered as initial treatment for excessive drooling in children before more invasive surgical procedures.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Scully C, Limeres J, Gleeson M, Tomas I, Diz P. Drooling. J Oral Pathol Med 2009; 38:321–327.
2. Wilken B, Aslami B, Backes H. Successful treatment of drooling in children with neurological disorders with botulinum toxin A or B. Neuropediatrics 2008; 39:200–204.
3. Vaile L, Finlay F. Is injection of botulinum toxin type A effective in the treatment of drooling in children with cerebral palsy? Arch Dis Child 2006; 91:862–863.
4. Porta M, Gamba M, Bertacchi G, Vaj P. Treatment of sialorrhoea with ultrasound guided botulinum toxin type A injection in patients with neurological disorders. J Neurol Neurosurg Psychiatry 2001; 70:538–540.
5. Bothwell JE, Clarke K, Dooley JM, et al. Botulinum toxin A as a treatment for excessive drooling in children. Pediatr Neurol 2002; 27:18–22.
6. Benson J, Daugherty KK. Botulinum toxin A in the treatment of sialorrhea. Ann Pharmacother 2007; 41:79–85.
7. Jongerius PH, van den Hoogen FJ, van Limbeek J, Gabreels FJ, van Hulst K, Rotteveel JJ. Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. Pediatrics 2004; 114:620–627.
8. Crysdale WS, Raveh E, McCann C, Roske L, Kotler A. Management of drooling in individuals with neurodisability: a surgical experience. Dev Med Child Neurol 2001; 43:379–383.
9. Mankarious LA, Bottrill ID, Huchzermeyer PM, Bailey CM. Long-term follow-up of submandibular duct rerouting for the treatment of sialorrhea in the pediatric population. Otolaryngol Head Neck Surg 1999; 120:303–307.
10. Panarese A, Ghosh S, Hodgson D, McEwan J, Bull PD. Outcomes of submandibular duct re-implantation for sialorrhoea. Clin Otolaryngol Allied Sci 2001; 26:143–146.

11. Jongerius PH, Rotteveel JJ, van den Hoogen F, Joosten F, van Hulst K, Gabreels FJ. Botulinum toxin A: a new option for treatment of drooling in children with cerebral palsy. Presentation of a case series. Eur J Pediatr 2001; 160:509–512.
12. Suskind DL, Tilton A. Clinical study of botulinum-A toxin in the treatment of sialorrhea in children with cerebral palsy. Laryngoscope 2002; 112:73–81.
13. Jongerius PH, Joosten F, Hoogen FJ, Gabreels FJ, Rotteveel JJ. The treatment of drooling by ultrasound-guided intraglandular injections of botulinum toxin type A into the salivary glands. Laryngoscope 2003; 113:107–111.
14. Ellies M, Rohrbach-Volland S, Arglebe C, Wilken B, Laskawi R, Hanefeld F. Successful management of drooling with botulinum toxin A in neurologically disabled children. Neuropediatrics 2002; 33:327–330.
15. Savarese R, Diamond M, Elovic E, Millis SR. Intraparotid injection of botulinum toxin A as a treatment to control sialorrhea in children with cerebral palsy. Am J Phys Med Rehabil 2004; 83:304–311.
16. Hassin-Baer S, Scheuer E, Buchman AS, Jacobson I, Ben-Zeev B. Botulinum toxin injections for children with excessive drooling. J Child Neurol 2005; 20:120–123.
17. Breheret R, Bizon A, Jeufroy C, Laccourreye L. Ultrasound-guided botulinum toxin injections for treatment of drooling. Eur Ann Otorhinolaryngol Head Neck Dis 2011; 128:224–229.
18. Reid SM, Johnstone BR, Westbury C, Rawicki B, Reddihough DS. Randomized trial of botulinum toxin injections into the salivary glands to reduce drooling in children with neurological disorders. Dev Med Child Neurol 2008; 50:123–128.
19. Pena AH, Cahill AM, Gonzalez L, Baskin KM, Kim H, Towbin RB. Botulinum toxin A injection of salivary glands in children with drooling and chronic aspiration. J Vasc Interv Radiol 2009; 20:368–373.