

## CLINICAL NOTE

# Botulinum Toxin Type A Injections to Salivary Glands: Combination With Single Event Multilevel Chemoneurolysis in 2 Children With Severe Spastic Quadriplegic Cerebral Palsy

Heakyung Kim, MD, Yung Lee, DO, Daniel Weiner, MD, Robin Kaye, MD, Anne Marie Cahill, MD, Marc Yudkoff, MD

**ABSTRACT.** Kim H, Lee Y, Weiner D, Kaye R, Cahill AM, Yudkoff M. Botulinum toxin type A injections to salivary glands: combination with single event multilevel chemoneurolysis in 2 children with severe spastic quadriplegic cerebral palsy. *Arch Phys Med Rehabil* 2006;87:141-4.

We describe 2 children with severe spastic quadriplegic cerebral palsy (CP) who have significant drooling and frequent aspiration pneumonia. They underwent simultaneous botulinum toxin type A (BTX-A) injections to salivary glands for drooling and prevention of aspiration pneumonia along with single-event multilevel chemoneurolysis (SEMLC) with BTX-A and 5% phenol for severe diffuse spasticity. There was significant improvement in drooling, frequency of aspiration pneumonia, and spasticity without adverse effect. BTX-A injections into the salivary glands, in addition to SEMLC, for these 2 children with medically complicated severe spastic quadriplegic CP, were safe and highly successful procedures, which improved their health-related quality of life.

**Key Words:** Botulinum toxin type A; Case report; Cerebral palsy; Pneumonia, aspiration; Rehabilitation; Salivary glands.

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**C**HILDREN WITH SPASTIC QUADRIPLÉGIC cerebral palsy (CP) manifest difficulty with motor function, including severe swallowing dysfunction, because of spasticity of the oropharyngeal and esophageal musculature as well as oral sensory dysfunction and poor head control. Excessive drooling is a significant problem in 10% to 37% of affected children.<sup>1-4</sup> The drooling is not secondary to excessive production of saliva,<sup>5</sup> but is the result of pooling of saliva because of neurologic impairment and consequent compromise of swallowing function and/or decreased awareness of saliva spill. Serious medical consequences of excessive drooling include choking, aspiration, diminished coughing ability, other signs of respiratory dysfunction, and pulmonary infections. Drooling also causes social embar-

assment, thereby adversely affecting the quality of social integration and quality of life (QOL).

Management includes feeding programs to increase frequency of swallowing and oral stimulation, behavioral modification programs, medications, and/or surgery. In severe cases, patients require frequent suctioning and pulmonary toilet, neither of which may be sufficient to maintain normal respiratory function. The investment of time and resources that such treatment obliges is very significant.

Effective but noninvasive medical management of drooling requires treatment with anticholinergics. This approach not uncommonly is ineffective and is associated with numerous side effects, including restlessness, irritability, drowsiness, orthostatic hypotension, dizziness, bradycardia, decreased bronchial secretion, urinary urgency and retention, dilation of pupils, loss of accommodation, photophobia, dry mouth, flushing, and dryness of skin. Severe constipation and thickened secretions are common in those cases in which anticholinergics diminish drooling.<sup>6</sup>

Surgical approaches such as salivary gland excision, duct ligation, or rerouting have been used for patients who fail noninvasive strategies. Sialoceles, which is uncommon with modern surgeries,<sup>7</sup> facial nerve paralysis, excessive dryness of the mouth, dental decay, and hypertrophic facial scars<sup>8,9</sup> have been reported as postoperative problems.

Interestingly, acupuncture into the tongue has been tried in Chinese children with neurologic disease. Improvement without complications was noted,<sup>10</sup> but further study is indicated prior to widespread application of this technique.

Recently studies have shown that injection of botulinum toxin type A (BTX-A) into the salivary glands is a safe, minimally invasive and effective treatment for drooling in children and adults.<sup>11-17</sup> Most studies have demonstrated a reduction of drooling, an enhancement in QOL, and minimal side effects. However, there is no documentation that BTX-A treatment improves respiratory status in neurologically impaired patients with frequent aspiration pneumonia and pooling of saliva in the upper airway. Nor has there been a demonstration of the efficacy on QOL of combination therapy with BTX-A injections to salivary glands and single-event, multi-level chemoneurolysis (SEMLC) with BTX-A and phenol to multiple spastic muscles. In this study, we describe improved QOL and respiratory function in children with severe spastic quadriplegic CP who received such therapy.

## CASE DESCRIPTIONS

### Case 1

A 3-year-old girl manifested spastic quadriplegic CP secondary to apparent hypoxic-ischemic encephalopathy (HIE) that occurred at the time of birth due to a nuchal cord and meconium aspiration. Brain magnetic resonance imaging showed abnormal signals within the dorsal putamen, ventral

From the Departments of Physical Medicine and Rehabilitation (Kim, Lee), Pediatrics (Kim, Weiner, Kaye, Cahill, Yudkoff), and Radiology (Kaye, Cahill), University of Pennsylvania, School of Medicine, Philadelphia, PA; and Divisions of Child Development, Rehabilitation and Metabolic Disease (Kim, Yudkoff), Pulmonary Medicine (Weiner), and Radiology (Kaye, Cahill), The Children's Hospital of Philadelphia, Philadelphia, PA.

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Reprint requests to Heakyung Kim, MD, Pediatric Rehabilitation Medicine, Children's Seashore House of The Children's Hospital of Philadelphia, 3405 Civic Center Blvd, Philadelphia, PA 19104, e-mail: kimhk@email.chop.edu.

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Table 1: Summary of Case 1 Before and After BTX-A Injections to Salivary Glands and SEMLC

Variables	Between Birth to 1st Procedure Period 1	Between 1st and 2nd Procedure Period 2	Between 2nd and 3rd Procedure Period 3
Total days of hospitalization/ total days of each period	432/767	29/195	6/153
No. of hospitalization	14	2	1
Indication for hospitalization	Aspiration pneumonia, fever	Aspiration pneumonia, fever	Viral illness without pneumonia
BTX-A injections	NA	Bilateral submandibular glands	Bilateral submandibular and parotid glands
Duration of BTX-A effect on drooling (mo)	NA	4	5
SEMLC therapy: muscles treated	NA	Bilateral brachialis, abductor pollicis brevis, triceps, rectus femoris, right teres major (n=9)	Bilateral brachialis, abductor pollicis brevis, hamstrings (n=6)

Abbreviation: NA, not applicable.

thalami, and medulla. Her management during a 2-month admission to the intensive care nursery was complicated by drooling that was treated with glycopyrrolate and multiple bouts of aspiration pneumonia. After discharge she was rehospitalized repeatedly because of pulmonary infection and respiratory distress. A milk scan revealed multiple episodes of gastroesophageal reflux and a chest radiograph showed right upper lung infiltrates consistent with aspiration pneumonia. During a hospitalization of nearly 4 months, she required a tracheostomy to relieve upper airway obstruction as well as a Nissen fundoplication and gastrostomy tube (G-tube) placement because of her inability to effectively suck or swallow. Feeding was possible only via G-tube. From birth to 24 months of age, she was hospitalized 13 times because of aspiration pneumonia with fever. Total hospitalization was 432 days at 25 months of age with minimal time at home. During the fourteenth hospitalization she had a constant fever despite antibiotic treatment for more than 2 months. A salivagram showed aspiration of saliva into the lungs.

At age 25 months she received BTX-A treatment (1U/kg per gland) into each submandibular gland under ultrasound guidance. She also received SEMLC with BTX-A (total, 170U) and 5% phenol (total, 1.5mL) into 9 severely spastic muscles with a score of 3 on the Modified Ashworth Scale (MAS). SEMLC was done bilaterally to the brachialis, adductor pollicis brevis, and rectus femoris and to the left triceps, right teres major, and right triceps. All procedures were done under intravenous conscious sedation with fentanyl, midazolam, and pentobarbital. A nerve stimulator was used to identify the muscles. At 7 weeks postprocedure, the mother reported no adverse effects. The patient had no more episodes of aspiration pneumonia and fever. Outpatient visits were needed only for 1 episode of otitis media and 1 episode of tracheitis. Her mother reported that postprocedure she required suctioning of her secretions once or twice per hour whereas preprocedure she required suctioning every 15 minutes. Her mother also noted that dressing the patient was simplified because of enhanced flexibility of the elbows and knees. The patient now was able to reach for objects, to sit independently, and to turn from prone to supine. Muscle tone improved from MAS score of 3 to MAS score of 1+ in all 4 extremities. The dose of glycopyrrolate was decreased. The patient was able to remain at home without a need for rehospitalization for nearly 5 months. Increased drooling eventually required repeat BTX-A injections at 6 months after the first procedure. She received bilateral administration of BTX-A (1U/kg per gland) to submandibular and parotid glands

with SEMLC (total, 110U of BTX-A and 3.4mL of 5% phenol) to spastic muscles in both the upper and lower extremities. Within 2 days she became afebrile and had decreased drooling, but an upper respiratory infection led to rehospitalization after 2 weeks. Her mother again reported an improvement in overall condition and a diminished need for suctioning (about once hourly when awake). There were no adverse effects of the procedures. After an additional 5 months she received a third cycle of elective BTX-A treatment (table 1).

### Case 2

A 6-year-old girl with spastic quadriplegic CP secondary to HIE had a complicated course since birth that included 5 separate admissions of several months' duration to the intensive care unit with aspiration pneumonia. At age 5.5 years she received her initial treatment with SEMLC to spastic muscles. Later her mother, an intensive care unit nurse, reported that the child needed continuous suctioning for 550 to 600mL of secretions each day. Glycopyrrolate did not improve pooling of secretions and the patient had severe coughing, choking, and gagging. She was also unable to attend school due to a need for frequent suctioning. One year after the initial SEMLC, she received BTX-A injections into her submandibular glands (1U/kg per gland) along with a second cycle of SEMLC to spastic muscles. Suctioning of saliva declined from about 500 to 250mL/d at 1 week posttreatment and then to 90mL/d at 3 weeks posttreatment (fig 1). The amount of saliva suctioned increased to the basal level at 4 to 5 months after treatment. A

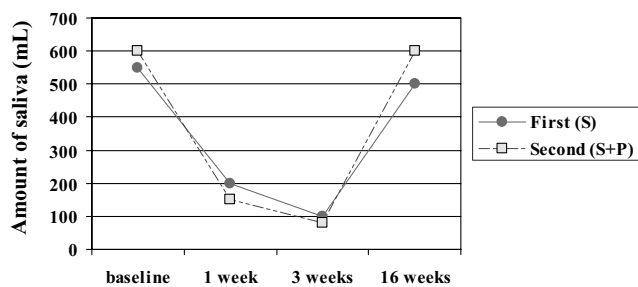


Fig 1. Amount of saliva suctioned after BTX-A injections. Peak effect of BTX-A was at 3 weeks. Production of saliva went back to baseline at approximately 16 weeks. Abbreviations: S, injections to submandibular glands; S+P, injections to submandibular and parotid glands.

second round of BTX-A injections then was done bilaterally to submandibular and parotid glands along with a third cycle of SEMLC to spastic muscles. Within 1 day, saliva suctioning fell from 550 to 200mL/d. A peak effect occurred at 3 weeks when saliva suctioning declined to 80mL/d, but drooling increased to the baseline level after 13 weeks. Thereafter her decreased spasticity led to easier dressing and hygiene and more comfortable sleep. Her QOL was further improved by her new ability to go out with her family as she was liberated from the need for constant suctioning.

### DISCUSSION

Many children with CP have excessive drooling because of poor oropharyngeal motor and sensory dysfunction and dysphagia as well as decreased cognition. Saliva production may be normal. Daily salivary secretion in children is approximately 500 to 600mL, including .32mL/min from sublingual and submandibular glands and .15mL/min from parotid glands.<sup>18</sup> The normal contributions to saliva are: parotids, 20%; submandibulars, 65%; sublinguals, 7% to 8%; and minor glands, 7% to 8%. At higher flow rates, the parotid becomes the dominant gland. Parotid glands provide the bulk of saliva response to the stimulation of taste or smell.

Aspiration of saliva can lead to pneumonia and secondary infection even in youngsters who receive tube feedings. These patients stand to benefit from a relatively noninvasive, localized treatment that would not cause the systemic side effects of anticholinergic therapy.

BTX-A and SEMLC are safe and well-tolerated modalities for relief of spasticity in children with CP.<sup>19</sup> Significant side effects are very rare. Considerable interest focuses on applying these approaches toward the inhibition of salivary gland secretion by local injection of BTX-A in patients with CP and cognate disorders.<sup>15,20-22</sup> Jongerius et al<sup>20</sup> treated 3 children with bilateral injections of the submandibular glands. There occurred a significant reduction of drooling without complication. Bothwell et al<sup>21</sup> administered BTX-A to each parotid gland of 9 neurologically impaired children. Almost all had decreased drooling.

Injection of the parotid glands may traumatize the facial nerve, facial artery, and/or nearby muscles, all of which are near one another. When Bhatia et al<sup>12</sup> injected the posterior margin of the masseter muscle, thereby avoiding the muscle bulk, complications were mild and included chewing difficulties in 2 patients, dry mouth in 1, and dysphagia in another. None developed facial weakness. Three patients considered the response good enough and side effects sufficiently minimal to continue BTX-A treatment at regular intervals. O'Sullivan et al<sup>23</sup> have reported that ultrasound or electromyographically guided injections to assist localization or retrograde injection into Stenson's duct can improve delivery to the parotid gland and minimize diffusion. Porta et al<sup>24</sup> investigated the safety and efficacy of ultrasound-guided BTX-A injections into parotid and submandibular glands of 10 patients with neurologic disorders. All patients had severe dysphagia and speech problems prior to treatment. No serious adverse event occurred. Winterholler et al<sup>25</sup> reported facial weakness after intraparotid injection with BTX-A and severe swelling of salivary glands and tongue when approaching the salivary glands via a catheter through the salivary duct. Jongerius<sup>20</sup> performed BTX-A injection into the submandibular and sublingual glands under ultrasound guidance for children with CP. No complications were found. Based on current reports, ultrasound-guided localization of salivary glands supplemented with electromyographic guidance to avoid complications from BTX-A injections to adjacent muscles, vessels, or nerves is both safe and effective.

Giess et al<sup>26</sup> reported that injection of 30 to 72U of BTX-A into the parotid glands of 5 adults (mean age, 63.8y) with amyotrophic lateral sclerosis (ALS) significantly decreased drooling without side effects. According to Porta,<sup>24</sup> the total dose of BTX-A was calculated based on the rate of salivation before treatment and the patient's body weight. The dose used for the parotid glands was 15 to 40U into 2 injection sites and for the submandibular glands 10 to 15U. The total dosage of BTX-A was 50 to 100U. Patients were followed for up to 1 year. Nine of 10 (90%) patients reported a subjective reduction of drooling. Pal et al<sup>13</sup> was able to control severe drooling in 9 patients with Parkinson's disease after administration of 7.5 to 15U to parotid glands. Both groups concluded that a low dose was probably as effective as the high one. Giess<sup>26</sup> used 32 to 72U to control severe drooling in ALS. An effective decrement of drooling and an improvement in QOL was evident in 85% of patients. Several other studies have used less than 100U without significant complication, although there were occasional complications related to technique. A review of existing literature regarding dosage in children<sup>15,20,21,27,28</sup> reveals no consensus with regard to the dose of BTX-A to use for the salivary gland injection. Our experience using 1U/kg of BTX injection into each salivary gland in these 2 cases suggests that that dose will manage moderate to severe drooling without significant side effects.

An animal study showed that BTX-A injection into the prostate revealed the total volume and weight of the gland in all treated rats (n=30) for 1 to 4 weeks postinjection. Histologically, a generalized atrophy of the glands was observed with the hematoxylin and eosin stain. Such treatment induces selective denervation and subsequent atrophy as well as diffuse apoptosis.<sup>29</sup> Thus it will be important to monitor whether repeated BTX-A injection into salivary glands has permanent effects.

### CONCLUSIONS

Injections of BTX-A to the salivary glands appeared to reduce saliva production and risk of pulmonary complication in our children with spastic quadriplegic CP. Simultaneous BTX-A injections to salivary glands along with SEMLC with BTX-A and 5% phenol treatment of spastic muscles was safe and seemed to improve overall health and QOL. To show validity and applicability of this combined procedure, a study needs to be done with a larger population.

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