Botulinum Toxin A in the Treatment of Sialorrhea in Children with Cerebral Palsy

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Sialorrhea is commonly associated with many neurological and systemic conditions. For children and young adults with cerebral palsy, sialorrhea may cause embarrassment and social isolation. Current medical management used for sialorrhea is unsatisfactory. Preliminary studies in adults with sialorrhea have demonstrated that botulinum toxin A as an effective treatment; however, no studies have defined the optimal dose and the duration of botulinum toxin A's effects on sialorrhea in patients with cerebral palsy. We present four patients with cerebral palsy who received botulinum toxin A treatment for sialorrhea. Under ultrasound guidance, body weight-related dosage of botulinum toxin A was injected bilaterally into the parotid glands. All four patients reported distinct improvement within the first 2 weeks following toxin injection. Duration of the toxin's effect varied from 16 to 20 weeks. There were no therapeutic side effects.
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Key words

botulinum toxin A, cerebral palsy, sialorrhea, ultrasound guidance

INTRODUCTION

Sialorrhea is problematic for many neurologically impaired patients. They suffer from excessive salivation because of inadequate oral motor control or swallowing dysfunction [1]. Persistent sialorrhea creates major hygienic and psychosocial problems. Maceration of skin around the mouth and neck may result in secondary bacterial infection. In addition, drooling is not a respectable social behavior and thus contributes to embarrassing and disabling social problems. Children with cerebral palsy are often afflicted with this problem. Lack of control in swallowing coordination may lead to excessive pooling of saliva in the oral cavity. Factors that predispose drooling in children with cerebral palsy include the degree of spasticity, a low swallowing frequency, a diminished intra-oral tactile sensitivity, and constant tongue thrusting [2]. The stigma of drooling further labels them " retarded", which results in both a physical barrier and social isolation [3]. Sialorrhea has been reported to be a significant problem in 10% to 37.5% of patients with cerebral palsy [3].

Salivary glands are controlled by the autonomic nervous system, and are primarily under parasympathetic cholinergic control. There are many treatment options for drooling, including behavioral management [4], oral motor intervention [4], use of oral and intra-oral appliances [5], various medications [3,6] and a range of surgical procedures [7]. However, treatments have limited success [3]. Behavioral modification techniques have limited use in children with intellectual problems [4]. The treatment of drooling with anticholinergic drugs is often ineffective and has side effects including

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constipation, irritability, urinary retention and blurred vision [3]. A recent study reported that 69% of patients treated with glycopyrrolate experienced side effects [6]. Surgical procedures such as gland resection, transposition of the excretory ducts, and tympanic neurectomy and local irradiation of salivary glands are invasive and are therefore often unacceptalce to patients and their families [3,7].

Botulinum toxin targets the neuromuscular junction and blocks the release of acetylcholine from nerve terminals. Botulinum toxin type A (BTX-A) is now widely used in the treatment of disorders characterized by focal muscle hyperactivity, such as strabismus, focal dystonia and spasticity [8]. The toxin also blocks the autonomic cholinergic fibers, including the major secretomotor parasympathetic fibers of sweat and salivary glands. BTX-A has increasingly been used to treat sialorrhea in neurologically impaired individuals [9-11]. These studies have implied that BTX-A may be an effective inhibitor of salivary gland activity. However, the optimal dose, the site of injection and the duration of its effect have not been established for BTX-A as a treatment for children with excessive drooling.

We describe four children with cerebral palsy who underwent BTX-A injection to treat sialorrhea. In contrast to other studies and case-reports, BTX-A was injected into each parotid gland under ultrasound guidance at a dose based on the patient's body weight. The severity and frequency of sialorrhea of all patients were evaluated every 2 to 4 weeks until 20 weeks after injection. This article is the preliminary report of the study.

CASE REPORT

From July 2004 to December 2004, four children with spastic cerebral palsy and sialorrhea were treated with injections of BTX-A. The ages ranged from 5 to 7 years and their data are listed in Table 1. They suffered from severe drooling due to lack of control in swallowing coordination and low swallowing frequency. They were fed orally. Articulation problems due to incoordination of oral motor movement were present in all four patients. According to the "rating scales for drooling severity and frequency" (Tables 2, 3), all patients had very high scores on the scale and were still symptomatic despite rehabilitation. None of them had received botulinum toxin injection for at least 4 months prior to this investigation. Furthermore, none of the patients had ever taken anticholinergic agents or undergone prior surgery to salivary gland. The doses of other medications that might affect drooling, such as tranquilizers or anticonvulsants, were not changed during this study.

One hundred units of BTX-A (BOTOX, Allergen Inc.) was diluted with 2 mL saline. A single dose based on body weight (2 unit Botox/kg body weight) was injected into each

Table 1. Clinical data of the children treated

Case No.	Age	Sex	Body weight (kg)	Diagnosis
1	5	M	18	Spastic diplegic CP
2	7	M	16	Spastic diplegic CP
3	6	M	15	Spastic quadriparetic CP
4	5	M	20	Spastic quadriparetic CP

Table 2. Rating scale for drooling severity

Severity
1 ……dry (never drools)
2 ……mild (only lips wet)
3 ……moderate (wet on lips and chin)
4 ……severe (drool extends to clothes wet)
5 ……profuse (hands, tray and objects wet)

Table 3. Rating scale for drooling frequency

Frequency
1 ……dry (never drools)
2 ……mild (only lips wet)
3 ……moderate (wet on lips and chin)
4 ……severe (drool extends to clothes wet)
5 ……profuse (hands, tray and objects wet)

parotid gland. There were two injection sites in each gland. EMLA® cream (lidocain 25 mg and prilocaine 25 mg) was placed on the skin over the injection site approximately 60 minutes before injection. The parotid gland was located precisely under sonographic guidance (LEMEL, 16 MHz) (Fig. 1) during intraparotid injection. Ultrasound image of the parotid gland revealed a homogenous hyperechoic structure (Fig. 2).

Outcome measurement was assessed by "rating scales for drooling severity and frequency" (Tables 2, 3). Prior to injection and at 2, 4, 8, 12, 16 and 20 weeks after injection, drooling severity and frequency were evaluated. All patients reported a distinct improvement of symptoms within 2 weeks (Figs. 3, 4). The duration of effect was more than 16 weeks in three patients. The longest duration was 20 weeks. No masseter weakness or mouth drying was noted during the follow-up period. Injection of BTX-A into the parotid gland did not alter swallowing and speech function. All patients and their main caregivers were satisfied with the result and were willing to be treated again.

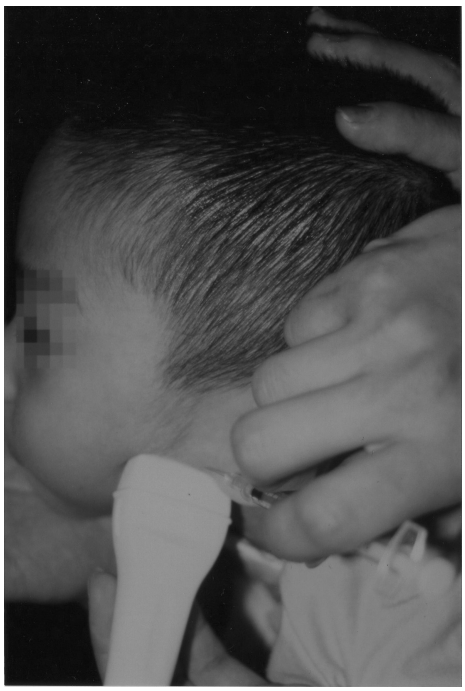

Fig. 1. Ultrasound guidance injection of BTX-A into the parotid glands.

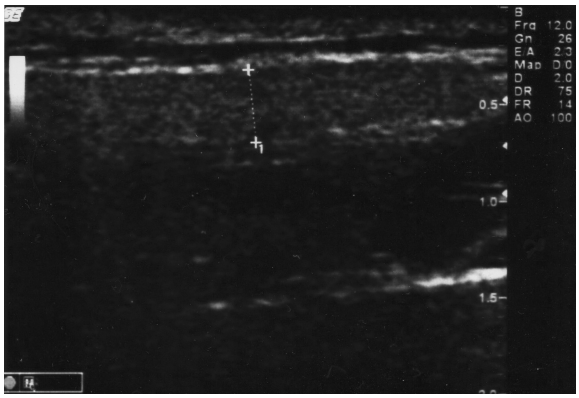

Fig. 2. Ultrasound image shows the parotid gland as a homogenous hyperechoic structure.

DISCUSSION

Of the seven immunologically distinct exotoxins of Clostridium botulinum (A, B, C1, D, E, F, G) [8], only BTX-A is widely known as a therapeutic agent. BTX-A causes paralysis of muscle by binding to peripheral cholinergic nerve terminals, which leads to the inhibition of acetylcholine-release from these terminals. Salivation is mainly driven by parasympathetic cholinergic control. The application of BTX-A blocks the release of acetylcholine, which inhibits neural stimulation of the salivary gland and salivation [9]. BTX-A was first used to treat sialorrhea in patients with Parkinson's disease in 1999 [10]. More recently, studies of the effect of BTX-A on sialorrhea in patients with Parkinson's disease and motor neuron disease have been reported [11,12]. However, few studies on the treatment of sialorrhea in patients with cerebral palsy have been published [13-14]. No consensus has been reached regarding the optimal dose, technique of injection and duration of response sustained.

Three main salivary glands, the parotid gland, submandibular gland and subligular gland, account for up to 95% of total salivation in humans. Three injection sites for treating sialorrhea with BTX-A have been reported: parotid gland alone, submandibular gland alone, both parotid and submandibular gland. Each method was documented to be effective in reducing salivation. Jongerius injected botulinum toxin to the submandibular gland in children with

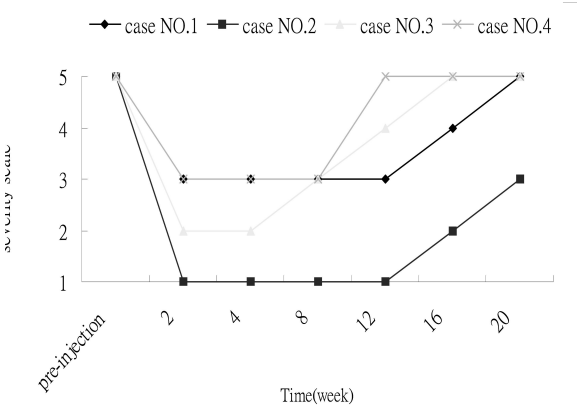

Fig. 3. Scale for drooling severity before and after treatment.

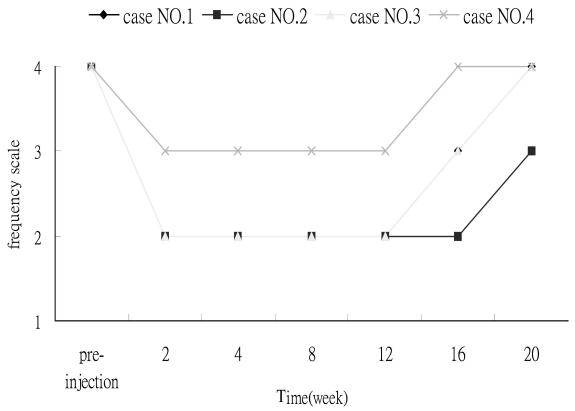

Fig. 4. Scale for drooling frequency before and after treatment.

cerebral palsy under general anesthesia. He reported that it had a positive effect in the majority of patients [15]. Suskind and Ellies injected BTX-A into the submandibular gland in one group of patients, and into both the submandibular and parotid glands in another group of patients [13,14]. They found that only a third of the patients injected in the submandibular gland alone improved, whereas 80% of the patients injected in the submandibular and parotid glands responded well [13,14]. Recent studies have demonstrated significant reduction of salivation after intraparotid injection of BTX-A. For example, Giess treated patients with amyotrophic lateral sclerosis by intraparotid injection. He found reduction of radiotracer uptake in both parotid glands documented by scintigraphy [11]. Savarese found decreased severity and frequency of drooling after intraparotid injection of BTX-A in children with cerebral palsy. The number of bibs used per day also decreased in these children [16]. In our study, to guarantee the basal level of saliva secretion from submandibular and sublingual glands, the parotid glands were chosen. Furthermore, the parotid glands are easily accessible, allowing for intraparotid injection in the outpatient clinic without sedation.

The parotid gland is surrounded by the masseter muscle and facial nerve. Lack of precise localization during intraparotid injection will lead to weakness of the masseter muscle. BTX-A may diffuse into the masseter and produce excessive muscle weakness leading to jaw dislocation after bilateral intraparotid BTX-A injection [17]. Therefore, we injected BTX-A under sonographic localization. There was no weakness of masseter muscle in any patient after injection. In previous studies, Ellies, Suskin and Hassin-Baer also injected BTX-A under sonographic guidance [13,14,18]. However, the fixed dose of BTX-A they chose was not suitable for the different- sized salivary glands in growing children with cerebral palsy [13,14,18]. In our study, under sonographic guidance, body weight dependent dosage was effective in reducing the severity and frequency of drooling. Good responses were observed within 2 weeks after injection and lasted for 3 to 5 months. Jost also demonstrated that the effect of BTX-A injected into the glands lasts for 4 to 7 months longer than that at the muscular level [10]. Dose-related efficacy was suspected by Gutinas-Lichius but it has not been proven [19].

Despite the multitude of approaches to treating sialorrhea, the volume of saliva production has still not be objectively quantified. The amount of saliva production has been assessed by several methods: roll saturation test [2], number of bibs used, salivary scintigraphy [15], sialometry, sialochemistry [14], drool quotient (defined as the number of times when drool was present measured at 15-second intervals over a 10-minute period) [13], rating scales for drooling severity and frequency [20], and visual analog scale. In our study, we used the "rating scales for drooling severity and

frequency" [20] described by Thomas, to evaluate the effect of BTX-A. It is interesting to note that the secretion of saliva may be influenced by weather or the condition of patient. As our fourth patient, the frequency and severity of sialorrhea rebounded 12 weeks after injection, which could have been due to his upper respiratory tract infection at that time.

Under sonographic localization, we injected a single dose of BTX-A, based on the patient's body weight, into the parotid glands. Satisfactory results without complications were observed in all patients. A double blind placebo controlled clinical trial using quantitative measurement, different dosage of injection and injection into different glands should be conducted to determine the optimal method of BTX-A injection to treat sialorrhea.

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以A型肉毒桿菌毒素治療腦性麻痺患者流口水

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過去對於因吞嚥障礙而造成的流口水問題，並沒有令人滿意的治療方法。最近有研究利用A型肉毒桿菌毒素來阻斷唾液腺的神經支配，但目前應用於腦性麻痺患者的研究較少。本文報告四位腦性麻痺患者以A型肉毒桿菌毒素治療流口水，有別於過去研究使用的固定劑量注射，我們首次根據患者的體重給予不同劑量(每公斤體重2單位肉毒桿菌毒素)，並配合超音波定位。經過20週的追蹤，四位患者皆達到滿意的治療效果，療效維持可達16至20週，且無併發症發生。（**中台灣醫誌 2006;11:261-6**）

關鍵詞

A型肉毒桿菌毒素，腦性麻痺，流口水，超音波定位

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