Botulinum Toxin Type A Treatment for Parkinsonian Patients with Moderate to Severe Sialorrhea

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Abstract-

Purpose: To investigate the effect of botulinum toxin type A (BTX-A; Botox®) in reducing saliva in patients with Parkinsonism.

Methods: Fifteen patients with clinical diagnosis of idiopathic Parkinson's disease, dementia with Lewy bodies, or multiple system atrophy were enrolled in this open clinical trial. A total of 40-unit dose of Botox® was injected into the bilateral parotid and submandibular glands. Objective measuring of saliva production with dental rods, subjective Drooling Score, personal impression of clinical improvement, and the duration of response were used for the global assessment of sialorrhea after BTX-A treatment.

Results: All patients showed objective reduction in saliva production following BTX-A treatment and the mean production was reduced at a significant level. The severity of sialorrhea assessed by Drooling Score was 5.87±0.92 (range: 5-8) and 3.60±1.18 (range: 2-6) respectively ($p<0.001$) before and after BTX-A injection. The mean duration of BTX-A response extended for 16.3±5.7 weeks (range: 5-24). No severe adverse effect nor worsening of existing dysphagia was observed in all Parkinsonian patients.

Conclusions: Parkinsonian drooling may undermine patient's health and daily activity. BTX-A local injection is a safe and effective measure in counteracting sialorrhea, even in patients associated with moderate dysphagia.

Key Words: Botulinum toxin, Parkinsonism, Sialorrhea, Drooling, Salivary glands

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INTRODUCTION

Sialorrhea or drooling is one of the characteristic manifestations in Parkinsonian patients and may affect about 70% of patients[1]. In addition, the presence of sialorrhea is closely related with the severity of Parkinsonism[1,2]. Clinically, this symptom may not only cause psychosocial embarrassment but also compromise swallowing function which is pertinent to the risk of choking or aspiration. Disordered salivation in Parkinsonism is thought as a hypokinetic phenomenon associated with focal weakness, incoordination of pharyngeal muscles, abnormal posture or impaired alertness rather than hypersecretion of saliva per se[1,3,4]. In certain

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patients, modification of anti-Parkinsonian medication with improved oropharyngeal coordination and decreased oro-facio-lingual akinesia may ameliorate the symptom. In resistant cases, anticholinergic drugs such as atropine, trihexyphenidyl, scopolamine and glycopyrrolate have been used with variable effect. Besides, their use is limited by side effects including blurred vision, constipation, urinary retention, dizziness, irritability, confusion and hallucination, especially in aged patients[5,6].

Application of botulinum toxin (BTX) injection seems to be a new therapeutic promise in patients with sialorrhea. BTX may act at the cholinergic nerve terminals whereby inhibiting transmission of the cholinergic parasympathetic and postganglionic sympathetic nervous systems. Based on this, BTX has been used in treating autonomic nervous system disorders, including overacting smooth muscle and abnormal gland activities[7,8]. Bushara first proposed treating intractable sialorrhea with BTX-type A (BTX-A) in patients with amyotrophic lateral sclerosis (ALS) in 1997[9]. Over the past few years, sialorrhea related to cerebral palsy, strokes, head neck tumor, ALS, Parkinson's disease and other neurodegenerative disorders has been successfully treated with BTX-A[10-21]. Nevertheless, several issues remain to be solved including its dosage, injection site, and outcome measures. The objective of the current study was to evaluate the effect of BTX-A on salivation after injection to the parotid and submandibular glands in Parkinsonian patients.

PATIENTS AND METHODS

Patients

Fifteen patients (9 men and 6 women) with significant drooling attributable to Parkinsonism were recruited from the movement disorder clinic in Kaohsiung Chang Gung Memorial Hospital between June 2003 and June 2005. The patients were diagnosed as having either idiopathic Parkinson's disease (IPD)[22], dementia with Lewy bodies (DLB)[23] or multiple system atrophy (MSA)[24] according to the related clinical diagnosis criteria.

During the study all patients maintained their antiparkinsonian medication and none of them was taking anticholinergic or other anti-drooling medications. The severity of the disease was evaluated with Hoehn and Yahr disability scale (H&Y)[25]. While the associated swallowing disturbance was assessed with Item 7 (swallowing function) of the Unified Parkinson's Disease Rating Scale (UPDRS)[26]. Written informed consent was obtained from every subject before treatment.

Injection technique

BTX-A (Botox®, Allergan Inc., Irvine, CA, USA) was injected into the bilateral parotid and submandibular glands using a 1-ml syringe and a 30-gauge needle. The total dose for each patient was 40 units (15 units for three sites into each parotid gland and 5 units for two sites into each submandibular gland). Under aseptic technique, the toxin reconstituted with 0.9% saline was injected above the mandible angle at the posterior border of the masseter muscle (parotid gland) and at the medial and posterior parts of the mandibular ramus (submandibular gland). After injection, patients and family were asked to record the time to onset of benefit, duration of the response and any possible adverse or side effects in a diary. All patients were monitored once every 2 weeks during the study.

Assessment of drooling

Objective measure of saliva production with dental rods has been used to quantify sialorrhea at baseline (before the BTX-A injection) and four weeks after injection[14,17]. Briefly, patients abstained from drinking and eating one hour before assessment. After mouth cleaning with water and initial swallow of saliva, eight dental rods (dry weight measured using a microbalance up to 0.01g) were placed into the mouth and retained for 10 minutes. Patients remained in sitting position and were instructed not to talk or swallow during the period. The difference in weight between the dry and wet rods was calculated to determine the amount of saliva produced.

Aside from this, subjective Drooling Severity and Frequency scales[14,19,27] were assessed at the same day for quantitative saliva measurement (baseline and 4 weeks after BTX treatment). One subject with IPD (case 10)

and the other with DLB (case 14) were unable to present accurate subjective ratings, thus the results were provided by caregivers. Global impression of clinical improvement and the duration of BTX-A response were also evaluated by the patients or family members at the end of the study. A 75-100% satisfaction was ranked as "marked improvement", followed by 50-75% (moderate improvement), 25-50% (mild improvement) and 0-25% (no change or minimal improvement).

Statistical analysis

Mann-Whitney U test was used to test the comparison between the saliva production and the severity of Parkinsonism (H&Y stage). Besides, we used Wilcoxon signed rank test to analyze changes in the saliva quantity and subjective drooling score after BTX-A treatment. A p value < 0.05 was considered statistically significant.

RESULTS

Demographic data and clinical diagnosis of the patients were summarized in Table 1. Ten patients had IPD, 4 patients had DLB and 1 had MSA. The mean age of the patients was 71.8±7.1 years (range: 60-85) and the duration of Parkinsonism was 9.5±4.9 years (range: 4-21). All patients had been rated on H&Y as 3 or higher (3.27±0.46; range: 3-4). Ten patients had trouble with swallowing problem and the mean dysphagia score was 1.33±1.17 (range: 0-3) according to UPDRS part II. There was a trend toward a less saliva production associated with the severity of Parkinsonism. Saliva production in the patients with H&Y stage 3 was 3.00±1.55g / 10 min and stage 4 was 1.55±0.75g / 10min, (Mann-Whitney U test; $p=0.078$).

Objective reduction in saliva production following BTX-A treatment was observed in every patient (Table 2). Mean saliva secretion on baseline was 2.61±1.51g / 10 min (range: 0.99-5.56g) and on 4 weeks after injection was 1.48±1.08g / 10min (range: 0.37-3.50g), with an approximately 43% reduction in saliva production. The decrease of saliva production was statistically significant ($p<0.001$; Wilcoxon signed rank test).

Thirteen patients (87%) reported clinical benefits after BTX treatment, including marked clinical improvement (5 patients; 33%), moderate (4 patients; 27%) and mild improvement (4 patients; 27%). Excessive drooling did not improve in 2 patients (case 6 and case 12) as reflected by the global assessment. Mean sialorrhea before and after BTX-A injection was 5.87±0.92 and 3.60±1.18 respectively, as assessed by Drooling Score (the sum of Drooling Severity Scale and Drooling Frequency Scale). The decrease of Drooling Score was statistically significant (mean: 2.27±1.49, $p<0.001$; Wilcoxon signed rank test).

In patients with favorable responses, the effect commenced from 3 days to 2 weeks and the mean latency following injection was 5.4±2.7 days (Table 2). The mean duration of response extended for 16.3±5.7 weeks irrespective of disease subgroup (e.g. IPD, DLB, and MSA) or disease severity. No patients suffered from focal facial nor generalized weakness, muscle wasting, breathing difficulty or worsening of dysphagia after injection. One patient had transient chewing weakness and 2 suffered from mild dry mouth for less than 6 weeks.

DISCUSSION

In patients with cervical dystonia treated with BTX local injection, an unexpected high incidence of dry mouth was found, suggesting its anticholinergic effect on the salivary gland[28,29]. Injections of BTX into the submandibular gland in experimental animals led to significant reduction of acetylcholinesterase in the gland followed by marked decrease in saliva production[30,31]. Action on the acceptors for BTX on autonomic nerve terminals blocking acetylcholine release in the postganglionic parasympathetic fibers has been identified[30,31]. Thence clinical trials with BTX have been applied to conditions characterized by excessive parasympathetic activity such as hyperhidrosis[32-34], gustatory sweating[35,36], pathological hyperlacrimation[37,38], rhinorrhea[39,40] and excessive drooling[10-21].

Significant decrease of drooling was observed in this open clinical trial. Overall the objective measure seemed to be sensitive in reflecting reduced drooling in all of our

Table 1. *The demographic and clinical characteristics of patients with sialorrhea*

Case	Age (yrs)	Sex	Diagnosis	H&Y score	Dysphagia*	Duration (yrs)
1	85	M	IPD	3	1	14
2	66	M	IPD	3	1	7
3	72	M	IPD	3	0	12
4	64	M	IPD	3	0	5
5	76	M	IPD	3	2	14
6	68	M	IPD	3	2	10
7	67	M	IPD	4	3	15
8	66	F	IPD	3	2	8
9	68	F	IPD	3	0	9
10	81	F	IPD	4	3	21
11	80	M	DLB (D,F,V,P)	3	1	8
12	74	M	DLB (D,F,V,P)	3	0	5
13	72	F	DLB (D,F,P)	3	0	4
14	78	F	DLB (D,F,V,P)	4	2	4
15	60	F	MSA	4	3	6
Mean	71.8±7.1			3.27±0.46	1.33±1.17	9.5±4.9

H-Y: Hoehn and Yahr scale; Duration: duration of Parkinsonism; M: male; F: female; IPD: idiopathic Parkinson's disease; DLB: dementia with Lewy bodies; D: dementia; F: fluctuating cognition with pronounced variations in attention/alertness; V: visual hallucinosis; P: spontaneous Parkinsonism; MSA: multiple system atrophy; *Dysphagia: Swallowing disturbance was assessed with Item 7 (swallowing function) of the Unified Parkinson's Disease Rating Scale (UPDRS).

patients. Apart from significant objective reduction in saliva, all but 2 noted subjective improvement of drooling. Our study is compatible with several previous reports which have revealed a significant improvement of drooling after BTX-A treatment, as determined by subjective rating of drooling severity or objective measurement of weight of dental rolls[10,11,13-19,21]. On the other hand, discrepancies between subjective impression of the therapy and objective saliva measurement were noticed. Further investigations in the dosage and applied technique should be performed for those unresponsive to the current modality. A review of the literatures found that the dosage for parotid gland ranged from 5 to 40 units of Botox®[11-16,18,21] and for the submandibular gland, a less frequently injected site, from 5 to 25 units[12,16,18,20]. In this study, we adopted a low dose policy with 15 units for parotid gland and 5 units for submandibular gland. Similar to studies administered lower doses[11,14,15,21], our study confirmed that the current doses were sufficient in reducing saliva and ameliorating intractable drooling. In our study, both parotid and submandibular glands (responsible for about 90% of salivary production) were injected, the efficacy was increased compared to previous studies with only parotid gland treatment[10,11,14,15]. Therapeutic modality using ultrasound guided injection demonstrated a higher response rate to BTX-A treatment, which deserves our attention in designing future studies[16,21].

Favorable responses of the current treatment commenced from 3 days to 2 weeks with a mean latency of 5.4 days, similar to that treated for focal dystonia[41,42], spasticity[43] or hyperhydrosis[8,33]. The duration of the beneficial response on drooling approximated 16 weeks that was longer than those with dystonia via muscular injection[41,42]. In conjunction with the prolonged BTX-A effect in treating patients with hyperhydrosis[33] or hyperlacrimation[38], the above observation suggests that BTX-A affects at cholinergic parasympathetic and postganglionic sympathetic nerve synapses with a longer duration than its inhibition in acetylcholine release at the neuromuscular junction[7,8]. No evidence of axonal sprouting with consecutive innervation in autonomic nerve fibers and trophic changes of autonomic innervation on secretory glands have been proposed for the pro-

Table 2. *Outcome after botulinum toxin type A (BTX-A) injection*

Case	Saliva[1] (Pre-BTX)	Saliva[1] (Post-BTX)	Drooling Score[2] (Pre-BTX)	Drooling Score[2] (Post-BTX)	Onset[3] (days)	Duration[4] (weeks)	Response rate5 (%)
1	2.54	1.10	5 (3+2)	3 (2+1)	5	16	70
2	2.49	1.23	7 (4+3)	2 (1+1)	6	12	90
3	3.20	1.39	6 (4+2)	2 (1+1)	3	24	90
4	1.11	0.59	5 (3+2)	4 (2+2)	10	17	50
5	5.56	3.37	7 (4+3)	3 (2+1)	3	18	80
6	4.49	3.50	6 (3+3)	5 (3+2)	5	6	10
7	2.58	1.43	5 (3+2)	4 (2+2)	7	18	70
8	2.25	1.20	6 (3+3)	3 (2+1)	2	24	80
9	3.43	2.50	6 (3+3)	5 (2+3)	5	15	50
10	0.99	0.54	5 (3+2)	3 (2+1)	5	16	50
11	1.00	0.37	5 (3+2)	2 (1+1)	3	20	80
12	1.72	0.72	6 (3+3)	6 (3+3)	10	5	10
13	5.19	3.07	8 (4+4)	4 (2+2)	3	23	70
14	1.63	0.53	5 (3+2)	4 (2+2)	4	18	50
15	1.00	0.73	6 (3+3)	4 (2+2)	10	12	60
Mean	2.61±1.51	1.48±1.08*	5.87±0.92	3.60±1.18*	5.4±2.7	16.3±5.7	61±25%

[1]Saliva: Saliva production within 10 minutes. [2]Drooling Score: The sum of Drooling Severity Scale and Drooling Frequency Scale scores (range: 2 to 9). Drooling Severity Scale: 1= dry: never drools; 2= mild: only lip wet; 3= moderate: wet on lips and chin; 4= severe: drooling causes clothing damped; 5= profuse: drooling causes objects to become moist and wet. Drooling Frequency Scale: 1= never drools; 2= occasionally drools; 3= frequently drools; 4= constantly drools. [3]Onset: Time to the onset of BTX-A effect. [4]Duration: The duration of responsiveness following BTX-A treatment. [5]Response rate: Subjective global assessment in the improvement of drooling after BTX-A treatment.
Pre-BTX: pre-botulinum toxin injection; Post-BTX: post-botulinum toxin injection.
*p<0.001 (Wilcoxon signed rank test).

longed benefit of BTX-A[16].

There was no severe adverse effects occurring to our patients. Most patients and caregivers were satisfactory in terms of the good clinical response and trivial side effects. Although Porta et al[16]. proposed that ultrasound guided injection might diminish the procedure-related side effects, most studies using a blind method also did not demonstrate significant adverse events, except for occasional local pain, and transient facial, masticatory or bulbar weakness. Severe dysphagia[44] or recurrent jaw dislocation[45] following BTX injection documented in ALS patients, was not identified in patients with Parkinsonism.

In conclusion, not every symptom in Parkinsonism responds to the dopaminergic therapy. Sialorrhea, one of the characteristic symptoms of Parkinsonism may jeopardize patient's health status and life quality. In general, BTX-A injection has been used safely and effectively and should be considered in patients resistant to the conventional treatment. Of special note, a low dose BTX-A injection to the parotid and submandibular glands do not cause severe adverse effects, even in those associated with moderate dysphagia. The effect of BTX-A lasts 4 to 5 months and thus repetitive injections are necessary for a long-term control.

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