A Double Blind Placebo Controlled Parallel Trial of Botulinum Toxin B (Myobloc™) for the Treatment of Sialorrhea in Parkinson's Disease

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Abstract

Background: Sialorrhea (drooling) is a major morbidity in several neurodegenerative diseases, including Parkinson's disease (PD). Injections of botulinum toxin A are often an effective treatment for sialorrhea in PD. Based on the relatively higher rates of dry mouth seen with use of botulinum toxin B (BTX-B), there is reason to suspect that it may be equally or more effective. **Objective:** To determine whether injections of BTX-B (Myobloc™, Elan Pharmaceuticals) into the parotid and submandibular glands are a safe and effective treatment for sialorrhea in patients with PD. **Methods:** We assessed demographics, PD treatments, head posture, the Unified Parkinson's Disease Rating Scale (UPDRS), two questionnaires regarding drooling, visual analogue scales, global impressions, salivary gland imaging, and a dysphagia questionnaire in 16 PD subjects with problematic sialorrhea. Patients were then randomized to receive either BTX-B (1,000 into each parotid gland, and 250 into each submandibular gland), or a pH matched placebo, using only anatomical landmarks. Patient returned one month later to undergo an identical assessment. **Results:** All 16 patients completed the study. The drug and placebo groups were initially identical. Compared to placebo, those randomized to drug reported improvement on the visual analogue scale (p<0.001), global impressions of change (p<0.005), Drooling Rating Scale (p<0.05), and Drooling Severity and Frequency Scale (p<0.001). There was no change in UPDRS, head posture, or the dysphagia scale. Adverse events were mild and included dry mouth (3), decreased gait (2), diarrhea (1) and neck pain (1) in the BTX-B group. **Conclusion:** Anatomically guided injections of BTX-B into the parotid and sub-mandibular glands appear to effectively improve sialorrhea without compromising dysphagia in patients with PD.

Introduction

Sialorrhea (drooling) is a major morbidity in several neurodegenerative diseases including Parkinson's disease (PD). Although relatively little attention has been given to the epidemiology or management of this feature, sialorrhea is experienced by the majority of PD patients and some patients consider it to be their worst problem. [1] Conservative treatments include oral anti-cholinergic and anti-histamine medications, however, little formal data supports their efficacy and they are often poorly tolerated. Invasive procedures such as parotid excision, duct ligation and radiation ablation are occasionally used. [2-5]

Recently, injections of botulinum toxin A have demonstrated efficacy against sialorrhea in open label [6-18] and small controlled studies. [19] To our knowledge, there are no published reports of botulinum toxin B for sialorrhea.

Botulinum toxins are thought to reduce saliva production by inhibiting cholinergic autonomic parasympathetic and postganglionic sympathic acetylcholine release that innervates the salivary glands. Together, the parotid, submandiblar, and sublingual glands produce almost all saliva. [20] Most botulinum toxin A studies have only injected the parotid gland, even though the sublingual glands actually produce the largest amount of saliva, despite their smaller size. [20] Furthermore, the location near the mouth maximizes their contribution to drooling.

Cervical dystonia studies employing botulinum toxin B (Myobloc™) have shown a relatively high incidence of dry mouth. [21] This suggests that botulinum toxin B may have a particular predilection for salivary glands, and thus be more effective against sialorrhea.

Methods

This was a double-blind, placebo controlled, parallel trial of sixteen PD patients recruited from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorders Clinic. The diagnosis of PD was made with standard clinical criteria. All patients had clinically meaningful sialorrhea without meaningful dysphagia. The study was approved by the Baylor College of Medicine Institutional Review Board.

All patients underwent a Unified Parkinson Disease Rating Scale (UPDRS) while on their PD medications. They answered validated questionnaires regarding their subjective drooling and swallowing problems and answered a series of global impression questionnaires. Finally, the angle of forward head tilt and lateral head tilt were measured using a protractor and summated.

Salivary gland imaging was accomplished using a standard method. [22] Approximately 10 mCi (range 9.2-11.0) of Tc-99m pertechnetate was injected intravenously. Continuous imaging of the head and neck was then performed in the anterior view using a standard field of view scintillation camera with an all-purpose parallel-hole collimator. All studies were performed on the same camera system. Data was collected in thirty sequential one-minute segments and stored in an on-board computer. Data from three patients, however, was lost due to computer drive malfunction. Quantitative analysis was performed by summing background-corrected counts from manually drawn regions of interest over the parotid and submandibular/submaxillary salivary glands, and the net counts/mCi-injected was calculated for each study.

Patients were then be randomized (1:1 ratio) to receive either botulinum toxin B or a pH matched vehicle provided by Elan Pharmaceuticals. A total of 2,500 units were injected (1,000 divided into two sites into each parotid gland, and 250 in one site into each sub-mandibular gland). All injection sites were localized with anatomical markers and injected with a 29-guage tuberculin syringe at a depth of one-half inch. We injected two vertically placed locations just dorsal to the palpated masseter muscle (parotid gland), and injected one location just anterior and medial to the genu of the mandible (submandibular gland). All patients returned one month later and underwent an identical assessment. They were all offered a single open-label injection at that visit, or at a later time at their request.

As this was a pilot study, no power analysis was performed. Analysis included paired t-tests, Mann-Whitney U and Wilcoxon W when appropriate. A formula was used to calculate total dopaminergic dose: levodopa/100 + levodopa CR/70 + pramipexole/1 + pergolide/1 + ropinirole/3.5. A corrected total levodopa dose (levodopa*1.1) was used if patients also took a COMT inhibitor.

Figure 1:

Study Schemata

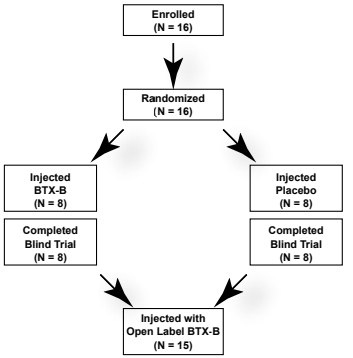

Table 1:

Demographic and Results (N = 16)

	Pre-treatment [a,b]		Post-treatment [b]		
	BTX-B	Placebo	BTX-B	Placebo	p [c]
Age	68.8 ±10.2	72.0 ±13.0	—	—	
Duration of PD	15.9 ±10.3	8.9 ± 6.8	—	—	
Duration of Drooling	2.9 ± 3.9	1.7 ± 1.3	—	—	
UPDRS ADL	24.6 ± 6.1	21.6 ±10.0	24.7 ± 6.2	21.7 ±10.0	ns
UPDRS Motor	38.8 ± 9.3	32.1 ±14.3	37.5 ± 9.7	32.0 ±14.1	ns
Medication Dose	13.6 ± 7.4	9.9 ± 8.5	—	—	
Head Tilt [d]	19.4 ± 8.6	26.3 ±16.0	—	—	
V.A.S. (pre- vs. post.)	70.3 ±16.4	62.1 ±23.0	34.0 ±25.7	78.3 ±14.3	0.001
V.A.S. (change)	—	—	23.0 ±16.7	1.3 ± 2.1	0.01
Drooling Rating Scale	11.4 ± 3.5	11.9 ± 2.0	7.4 ± 4.7	12.3 ± 1.7	0.05
Drooling Severity and Frequency Scale	7.4 ± 0.9	7.4 ± 0.5	5.1 ± 2.1	7.4 ± 0.5	0.001
Scintigraphy (10^3) CT/MCI	30.4 ±18.4	41.0 ±34.8	15.9 ± 9.6	28.5 ±22.5	ns
Dysphagia Scale	2.3 ± 1.6	1.9 ± 1.1	1.9 ± 1.6	1.8 ± 1.2	ns

[a] All pretreatment comparisons, p > 0.05
[b] Each group, n = 8
[c] All comparisons based on pre- and post-treatment delta scores
[d] Degree combined for forward and lateral tilt

Figure 2:

Salivary Gland Imaging Using Tc 99m Pertechnetate

PRE-TREATMENT POST-TREATMENT

Results

All 16 patients (13 male, mean age of 70.4 ± 11.4 and mean PD duration of 12.3 ± 9.1 years) completed the study. [Figure 1] Age, sex, duration of PD, UPDRS scores, initial drooling scores, duration of drooling, head tilt, and medication usage were similar in both the drug and placebo groups. [Table 1] At one month post-injection, compared to placebo, those randomized to drug reported improvement on the visual analogue scale (p<0.001), global impressions of change (p<0.005), Drooling Rating Scale [23] (p<0.05), and Drooling Severity and Frequency Scale [24] (p<0.001). [Table 1] The active drug group subjects reported "dramatic improvement" (4), "marked improvement" (1), "moderate improvement" (2) and "no change" (1). The placebo group reported "no change" (7) and "mild improvement" (1). In the drug group, the latency to "peak response" was 5 ± 5 days [range 1-14]. There was no change in UPDRS sub-scores, angle of head posture, or the dysphagia scale. [25] Adverse events were mild and included dry mouth (3), decreased gait (2), diarrhea (1) and neck pain (1) in the botulinum B group.

Baseline quantified scintigraphy scans varied tremendously, from 2,229 CT/MCI to 100,735 CT/MCI, severely limiting statistical power. [Table 1] Overall, 4/6 subjects on drug improved >33%, whereas only 2/7 on placebo had a similar improvement. (NS) [Figure 2]

The study was not designed to determine duration of effect. Anecdotally, most subjects reported that the clinical improvement lasted between 12 and 20 weeks.

Discussion

Anatomically guided injections of botulinum toxin B into the parotid and sub-mandibular glands appear to effectively improve sialorrhea without compromising swallowing in patients with PD, as determined by a variety of subjective measures. Tc-99m pertechnetate imaging showed too much variance to statistically add to a study this size, but tended to improve more in botulinum B randomized subjects.

The normal individual produces between 0.5-1.0 ml/min of saliva, although this gradually lessons after the age of 30. [20, 26] The larger parotid gland (14-28 mg) produces only serous saliva whereas the smaller submandibular gland (10-15 mg) produces both serous and mucinous saliva. The submandibular gland actually produces the majority of saliva while at rest, whereas the parotid produces the majority when stimulated. [20, 27]

Patients with PD do not make excessive saliva [28], but do have reduced swallowing [29] and forward head posture that likely contributes to sialorrhea. Therefore, the administration of BTX-B does not treat the underlying problem, but does seem to offer effective, non-invasive therapy.

We employed a simple injection technique that did not require any additional equipment, and can therefore, be done efficiently and relatively inexpensively. The parotid and submandibular glands are both large, near the skin, and easily identified anatomically. The cholinergic innervation is equally distributed throughout the gland so we can think of no specific area within the gland to target with ultrasound or electromyography. [30] Prior to the study, we had additionally injected the sub-lingual gland directly under the tongue, but this caused dysphagia in 2/4 patients and did not appear to further reduce sialorrhea.

The mechanism of action by which botulinum toxins reduce saliva production is not known. Both parasympathetic and sympathetic stimulation produce saliva, although acetylcholine mediated muscarinic parasympathetic stimulation predominates. [31] Parotid parasympathetic stimulation originates in the inferior salivatory nucleus, to the otic ganglion, and enters the gland on the auriculotemporal nerve. Submandibular parasympathetic innervation originates at the superior salivatory nucleus, to the submandibular ganglion, and enters the gland via the chorda tympani and lingual nerves. Since both ganglia are near the glands, we can't say whether the toxin affected the ganglia, the nerve-gland junction, or directly impaired fluid secretion from the acini cells.

We have not formally compared the anti-sialorrhea efficacy between botulinum toxin A and botulinum toxin B. It is, however, our clinical impression that type B is more effective in this scenario. This may result from differences in diffusion, differences in receptor binding to the cell, differences in the intracellular proteins that are lysed, or some unknown mechanism.

Potential weaknesses of our study include the small sample size and short duration. We are a tertiary referral center, but do not feel that our PD patients with sialorrhea are intrinsically different than others. We find it unlikely that botulinum toxin B caused the "worsened gait" reported by two subjects, as there were no differences on UPDRS scores, however, this possible AE will need to be further assessed.

Anecdotally in our clinic, botulinum toxin B has produced equally good results when used for sialorrhea in other parkinsonian conditions and in children with static encephalopathy. Definitive recommendations must, however, await controlled trials in these other conditions.

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