The Role of Botulinum Injection in Parkinson’s Disease

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Abstract

Botulinum toxin inhibits the release of acetylcholine at the neuromuscular junction, thereby blocking neuromuscular conduction and muscle contraction. The mechanism of action of its various serotypes are similar in respect that all of them cleave the SNARE proteins. It has been successfully used to treat a variety of symptoms related to Parkinson’s disease including cervical dystonia, foot dystonia, focal hand dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm, lid apraxia, camptocormia, hand and jaw tremor, sialorrhea, hyperhidrosis, dysphagia, constipation, and overactive bladder. We did the review of the literature to find out the benefit observed with it, units used, and muscle selected for different indications in various studies done. This might help to determine the important issues related to Parkinson’s disease where its application may be beneficial and also to pave a way for future recommendations.

Keywords: Botulinum; Dystonia; Sialorrhea; Camptocormia; Blepharospasm

Abbreviations: PD: Parkinson’s Disease; BoNT: Botulinum Toxin; FD: Foot Dystonia; FDL: Flexor Digitorum Longus; EHL: Extensor Hallus Longus; CD: Cervical Dystonia

Introduction

Clostridium botulinum is the bacterium that releases the most potent neurotoxin known and is responsible for causing botulism. There are seven different serotypes of C. botulinum (A-G), but only the serotypes A, B, and E cause human botulism via colonization of the lower GI tract after ingestion of contaminated food. Botulism can present as muscle weakness, paralysis, dysarthria, dysphagia, constipation, and urinary retention. Death can occur in up to 10–25% of cases. It has got use in various neurological disorders like spasticity, dystonia, hemifacial spasm, migraine and several non-neurological specialties like cosmetics, GI tract and GU tract disorders and ophthalmology [1]. Parkinson’s Disease (PD) is a progressive, neurodegenerative disorder with pathological hallmark being the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of alpha synuclein-positive neuronal inclusions in several motor and non-motor brain circuits. It is a disorder marked not only by the motor features but also the presence of non-motor symptoms including sleep disorders, fatigue, pain, urinary dysfunction, constipation, sialorrhea, cognitive dysfunction, and depression/anxiety [2-5]. Botulinum toxin (BoNT) has been successfully used to treat a variety of symptoms related to PD including cervical dystonia, foot dystonia, focal hand dystonia, laryngeal dystonia, oromandibular dystonia, blepharospasm, lid apraxia, camptocormia, hand and jaw tremor, sialorrhea, hyperhidrosis, dysphagia, constipation, and overactive bladder. Here overview off its role for various important indications is given below.

Role of botulinum in foot dystonia

Various clinical features of Foot Dystonia (FD) are observed in Idiopathic Parkinson’s Disease (IPD), ranging from simple forms such as inversion or hallux act after ingestion of contaminated food. Botulism can present as muscle weakness, paralysis, dysarthria, dysphagia, constipation, and urinary retention. PD: Parkinson’s Disease; BoNT: Botulinum Toxin; FD: Foot Dystonia; FDL: Flexor Digitorum Longus; EHL: Extensor Hallus Longus; CD: Cervical Dystonia.
muscle. Dystonia was evaluated using a quantitative rating scale and all Patients showed an improvement in their foot posturing [6].

**Botulinum in cervical dystonia in PD**

Cervical dystonia can occur as a manifestation of PD or secondary to levodopa. Anterocollis is the most common dystonia in PD or MSA. Cervical dystonia (CD) is a focal dystonia that causes abnormal postures of the head, neck and shoulders. Class A evidence has established botulinum toxin treatment as an effective means to control the symptoms of CD. Anterocollis in PD may respond to botulinum toxin injections as used for other patterns of cervical dystonia [7]. In a prospective, multicenter, double-blind, placebo-controlled trial, subjects were randomized to one of three arms: placebo, In botulin toxin A 120 U and 240 Units. The primary efficacy outcome measure was change in TWSTRS score from baseline to Week 4. There was continued improvement at Week 8 and at the final visit in comparison to baseline [8]. In another study forty consecutive patients with idiopathic CD were studied. As outcome measures, Tsui scores, VAS scores and patients’ subjective evaluations were assessed at the first visit, after 12 weeks and one year.

Ten patients received injections with Botox and 11 with Dysport with a median (converted) dose of 375 MU. The muscles that were most frequently added to the muscles selected for treatment were the Splenius (SPL), the semispinalis (SESP), the Levator Scapulae (LS) and the trapezius (TPZ) muscles. The mean Tsui score in these patients improved from a baseline score of 11.2 to 10.3 after 12 weeks (8% improvement). After one year of treatment the Tsui scores had significantly improved to 9.1 (18.8% improvement, p <0.01). The subjective scores also significantly improved after 12 weeks (p <0.01) and even further after one year (p <0.001) of treatment [9].

| Author                      | Patients | Duration of cervical dystonia | Total toxin dose per injection cycle | Muscles                          | Response                  |
|-----------------------------|----------|--------------------------------|-------------------------------------|----------------------------------|---------------------------|
| Von Coeln, et al.           | 4        | 1-3 years                      | 1000-3000 Mu abobotulinum toxin A   | Iliopsoas                        | Improved at 2 weeks= 1    |
|                             |          |                                |                                     |                                  | Improved at 6 weeks= 1    |
|                             |          |                                |                                     |                                  | Worsening= 1              |
| Wijemane, et al.            | 1        | 2 years                        | 400 Mu On a botulinum toxin A       | Rectus abdominus, External oblique | Improved= 45              |
| Colosimo, et al.            | 2        | NA                             | 800 MU On a botulinum A             | Bilateral Iliopsoas              | No response               |

Role of botulinum in camptocormia and PISA syndrome: Based on the small studies and variable responses, there is insufficient data for the use of toxin in camptocormia. Summary of studies is given below in Table 1. Interestingly, evidence for efficacy of botulinum toxin in the treatment of axial postural abnormalities in PD is greater for Pisa syndrome than camptocormia shown in Table 2 below [10].

| Author                     | Patients | Duration of Pisa syndrome | Total units of toxin | Muscles                              | Response                |
|----------------------------|----------|---------------------------|----------------------|--------------------------------------|-------------------------|
| Tassorelli, et al.         | 13       | 3.1 years                 | 50-175U xeomin       | Retus abdominis, IL, Paraspinals     | Lateral flexion at 3    |
|                            |          |                           |                      |                                      | months.                 |
| Bonanni, et al.            | 9        | 1-4 years                 | 500 Mu dysport       | Bilateral Paraspinals                | Improvement= 7          |
|                            |          |                           |                      |                                      | No response= 2          |

**Botulinum toxin in sialorrhea in PD**

Sialorrhea occurs in 32 to 74% of PD patients. Sialorrhea is classified as primary or secondary. Primary sialorrhea occurs when there is excessive production of saliva, while secondary sialorrhea is the result of disorders of the coordinated activity of the orofacial and palate lingual muscles decreasing the clearance of saliva. Research has shown that saliva production is lower in PD patients compared to healthy controls and that sialorrhea is of a secondary nature. BoNT as a possible treatment for sialorrhea was first proposed by Bushara, et al. [11]. In a review of 12 studies where the drooling score and drooling frequency score (DS-DF), the Visual Analogue Scale (VAS) and cotton-roll weight were the most frequently used methods of evaluation. BoNT type-A was tested in the range of 64–450 U. BoNT type-B was tested in the range of 1500-3500. For B type the best results were seen at the higher dose (3500 U). Mancini et al. and other several the studies reported a positive effect of BoNT on sialorrhea ranging from 50–100 % of the patients with duration of the effect varied from 1 to 6 months [12].

**Blepharospasm and botulinum toxin**

Blepharospasm is a focal dystonia characterized by involuntary, intermittent, or persistent forceful eyelid closure due to spasmodic contractions of the orbicularis muscles. Benign essential blepharospasm describes the involuntary contractions of only the orbital and periorbital muscles. However, some patients may also have spasm of other facial, oromandibular, pharyngeal, laryngeal, or cervical muscles, which is a form of cranio-cervical dystonia called Meigs syndrome. Blepharospasm typically begins in the fifth to seventh decade of life and is more common in women. It occurs in more advanced stages of PD but can also occur in atypical Parkinsonism and is often associated with apraxia of eyelid opening, defined as an intermittent inability to voluntarily open
the eyelids due to levator inhibition, abnormal contraction of the pretarsal orbicularis oculi, or eyelid freezing. BoNT has a longstanding history in the treatment of blepharospasm and is considered a first-line therapy. In an evidence-based review of the current clinical data available, it was concluded that Onabotulinumtoxin A and Incobotulinumtoxin A are effective in the treatment of blepharospasm (level A recommendation) and Abobotulinumtoxin A is probably effective (level B recommendation). There were no quality studies to confirm the efficacy of Rimabotulinumtoxin B contributing to a level U recommendation. There were no quality studies to confirm and Abobotulinumtoxin A is probably effective (level B recommendation). In an evidenced-based review of botulinum toxin and level of evidence for the safety and efficacy of botulinum toxin use. Evidence of its use for various indications in summarized in Table 3.

Table 3: Summarizing the level of evidence for the use of Botox for various indications in Parkinson’s disease.

| Disorder                         | Level of evidence      |
|----------------------------------|------------------------|
| Cervical dystonia                | Level A recommendation |
| Blepharospasm and eyelid apraxia | Level A recommendation |
| Focal hand dystonia              | Level B recommendation |
| Laryngeal dystonia               | Level C recommendation |
| Lower extremity dystonia         | Level U recommendation |
| Camptocormia                     | Level U recommendation |
| Oromandibular dystonia           | Level C recommendation |
| Sialorrhea                       | Level B recommendation |

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