Philadelphia College of Osteopathic Medicine
DigitalCommons@PCOM

PCOM Physician Assistant Studies Student Scholarship | Student Dissertations, Theses and Papers

2016

Do Botulinum Toxin Injections Improve the Freezing of Gait (FOG) Episodes Experienced by Parkinson's Disease (PD) Patients?

Caroline R. Poole
Philadelphia College of Osteopathic Medicine, carolinepo@pcom.edu

Follow this and additional works at: http://digitalcommons.pcom.edu/pa_systematic_reviews

 Part of the Nervous System Diseases Commons

Recommended Citation

Poole, Caroline R., "Do Botulinum Toxin Injections Improve the Freezing of Gait (FOG) Episodes Experienced by Parkinson's Disease (PD) Patients?" (2016). *PCOM Physician Assistant Studies Student Scholarship*. 289.
http://digitalcommons.pcom.edu/pa_systematic_reviews/289

This Selective Evidence-Based Medicine Review is brought to you for free and open access by the Student Dissertations, Theses and Papers at DigitalCommons@PCOM. It has been accepted for inclusion in PCOM Physician Assistant Studies Student Scholarship by an authorized administrator of DigitalCommons@PCOM. For more information, please contact library@pcom.edu.

Do Botulinum Toxin Injections Improve The Freezing Of Gait (FOG) Episodes Experienced By Parkinson's Disease (PD) Patients?

Caroline R. Poole, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences - Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

May 05, 2016

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not botulinum toxin injections improve the freezing of gait (FOG) episodes experienced by patients diagnosed with Parkinson's disease (PD).

STUDY DESIGN: This review is based on three randomized controlled trials published in 2004, 2005, and 2007. All of the studies compared the efficacy as well as safety of using botulin toxin injections to treat FOG episodes experienced by PD patients.

DATA SOURCES: All articles used were published in English, in peer-reviewed journals, and were found using PubMed searches.

OUTCOMES MEASURED: For all studies, the safety and efficacy of botulin toxin injections in the legs of patients with PD who experience FOG episodes was evaluated using clinical assessment as well as questionnaires such as the United Parkinson's Disease Rating Scale (UPDRS). The post-treatment measurements were compared to pre-treatment baseline assessments to determine any improvements.

RESULTS: Leg weakness, skin changes, and increase in number of falls were a few adverse reactions that occurred after treatment with botulinum toxin injections. The three studies completed by Wieler, Fernandez, and Gurevich had statistically insignificant results.

CONCLUSION: All three of the RCTs that were evaluated did not demonstrate a statistically significant difference after the patients received botulinum toxin injections. Botulinum toxin injections are not proven to be effective in the treatment of PD FOG episodes. However, as there were no life threatening or extremely unsafe adverse reactions, further future studies would be warranted in which a larger sample size could be evaluated.

Key Words: Parkinson's disease, botulinum toxin, Freezing of Gait

INTRODUCTION

Parkinson's disease (PD) is a degenerative, chronic and progressive disease that specifically targets and affects the dopaminergic cells of the substantia nigra causing cognitive and movement disorders.[1] The disease is fairly variable from patient to patient.[1] Cognitive impairments range from dementia to mood and sleep dysfunctions to psychosis.[1] Although cognitive dysfunction can be debilitating, this paper focuses on the physical movement disorders experienced by PD patients, including bradykinesia, balance disorders, rigidity, tremors, and freezing of gait (FOG) episodes.[2] It is important to note that PD is not a fatal disease in and of itself, but morbidity is related to PD-related complications including falls, pneumonia, or choking.[1]

Parkinson's disease is the second most common neurodegenerative disease generally diagnosed in patients around 60 years old.[3] It is a growing disease in the United States as the population continues to age.[4] Currently, PD affects 1 million patients in the United States and about 7 to 10 million people worldwide.[4] It is projected that this number will nearly double by the year 2030.[4] An estimated 60,000 Americans are diagnosed each year.[4]

The economic burden associated with PD is expected to increase as the number of patients diagnosed with this disease continues to climb.[3] In the year 2010, it was estimated that the direct costs of PD was around $14.4 billion.[3] Medication costs alone for a single individual battling PD averages to about $2,500 a year and therapeutic surgery is approximately $100,000 per patient.[3] When indirect costs associated with PD, such as lost income due to illness and social security payments are added to the direct costs, it is projected that $25 billion per year is spent just in the United States alone.[3] Although an exact number of health care visits per year due to PD is unknown, patients with PD experience worsening symptoms as their disease progresses,

leading to higher direct costs due to an increase in medications, hospitalizations, office visits, and need for nursing home care.[3] Fifteen percent of PD patients are found in nursing homes, which accounts for about 60% of the direct costs accumulated.[3]

The exact cause of PD is unknown, however, it is thought to be a combination of family history, genetics, and environmental causes. One of the most important risk factors associated with PD is aging.[2] Fifteen percent of patients diagnosed with PD have a family member with PD as well.[2] It has been found that when PD occurs at an early age it is often associated with a gene mutation such as parkin, PINK1, LRRK2, DJ-1, and glucocerebrosidase.[2]

As stated earlier, the presentation and disease progression can vary greatly from patient to patient. The most common presenting symptom is an intermittent resting tremor.[2] Parkinson's disease classically presents with one-sided symptoms that begin to progress over the years and spread to include symptoms affecting the other side of the body as well.[2] PD may be detected by the decreased ability to perform repetitive movements.[2] Another key feature, bradykinesia, is the reason for the stooped, shuffled gait characteristic of a PD patient.[2] Rigidity is commonly seen in PD which causes stiffness and decreased flexibility. Secondary to these motor dysfunctions, patients may experience freezing of gait (FOG). Patients describe FOG as feeling as if their feet are glued to the floor.[2] This sensation is most commonly experienced when patients attempt to take a first step while walking.[2] This sensation greatly increases a patient's risk for falling.[2] Other key features of the disease are micrographia, mask-like expressions, unwanted accelerations of speech and gait, loss of smell, mood disorder, memory difficulties, and orthostatic hypotension.[2]

Parkinson's disease is generally treated symptomatically, as there is no cure. The hope is that by controlling the symptoms, disease progression can be slowed and complications due to

PD can be prevented. The decision to begin treatment is generally made when the symptoms are negatively affecting ability to perform activities of daily living and quality of life.[2]

There are six classes of drugs used to treat PD. The most effective and commonly used medication is Levodopa, which is usually given as a combination pill of Carbidopa and Levodopa called Sinemet.[2] The biggest concern with Levodopa is that over time, motor-fluctuations begin to occur including "wearing off" effect. The "wearing off" effect is when the medication begins to wear off before the next scheduled dose.[2] Monoamine oxidase inhibitors are another group of medications for PD that work to inactivate the breakdown of dopamine.[2] These work to decrease the symptoms of PD by allowing dopamine to remain in the brain for a longer period of time.[2] Other medications include dopamine agonists, Catechol-O-methyl transferase (COMT) inhibitors, and Amantadine.[2] Management of common conditions found in PD patients such as depression, sleep disorders, dementia, psychosis and hallucinations are all treated separately and individualized to each patient.[2]

Currently, there is not a cure for PD and all the above treatments are aimed toward slowing down the disease progression, improving symptoms, and preserving the ability to perform activities of daily living.[2] The method of treatment being proposed is whether or not BTX being injected into the leg muscles of patients with PD may be used to further control the number and severity of the FOG episodes in hopes that patients would experience less falls, less injury, and retain more independence. The use of botulinum toxin (BTX), a gram-positive anaerobe, is currently not a suggested or utilized treatment for PD.[5]

OBJECTIVE

The objective of this selective evidence based medicine review is to determine whether or not BTX injections improve the episodes of FOG in PD patients.

METHODS

Three studies were assessed: a double blind randomized, placebo-controlled pilot study[5], a two period cross over design RCT[7], and a double blind randomized, placebo controlled, parallel-group study[8]. The intervention being used in all three RCTs was BTX injections into the gastrocnemius and soleus muscles of the leg while the comparison group received placebo injections of saline into the gastrocnemius and soleus muscle complex. The studies selected were determining whether or not there was a decrease in the FOG episodes experienced by PD patients after BTX injections.

Data was collected using a detailed search of Cochrane Systematic review as well as PubMed from the years 2004 to present. "Parkinson's disease," "freezing of gait," and "botulinum toxin injections" were keywords that were used in this search. Articles were selected based on their relevance to clinical practice and importance to patient-oriented outcomes. All articles chosen for this review were peer-reviewed and published in well-known journals.

Inclusion criteria for all three RCTs selected for review consisted of RCTs that were peer reviewed and published within the past fifteen years. The studies needed to include PD patients with FOG as a major complaint, that were severe enough to need treatment. Similarly, studies were excluded if they not published in the past 15 years. Studies were also omitted if they did not use UPDRS to measure outcomes.

The three RCTs selected, all reported statistics using mean change from baseline as well as p-values. In the Wieler et al. study, independent T-Tests were used to examine differences between groups and assess for carryover.[6] Paired T-tests were performed to look for pooled group effects without regard to order of treatment.[6] In the Fernandez et al. study, all analyses were performed using the SAS statistical software.[7] Finally, in the Gurevich et al. study, they

used mixed effects models for repeated measures to investigate changes over time in the subject's motor status to handle an unbalanced design where subjects have different number of repeated measures.[8]

Table 1 : Demographics and Characteristics of included studies

Study	Type	# Patients	Age (yrs)	Inclusion criteria	Exclusion Criteria	W/D	Interventions
Wieler (2005)[6]	RCT-Double blind cross-over design	12	Mean age of 77 years (range 53 -79 years)	-Diagnosis of PD with FOG as a major complaint -Good locomotion between freezing episodes -Optimal, stable medical treatment for PD -Ability to keep accurate diaries and attend scheduled visits	If unable to keep a daily diary	0	200-300 U of BTX-A injections into the medial and lateral heads of the gastrocnemius and soleus for a total of six injections.
Fernandez (2004)[7]	RCT-Double Blind, Placebo Parallel-design	14	Mean age of 74 years (range 61–87 years)	-Presence of 3-4 cardinal features of resting tremor, rigidity, bradykinesia, and postural instability, with a significant sustained response to anti-PD therapy -A Hoehn and Yahr stage of 3 -Stable PD medication for at least 30 days -FOG severe enough to need treatment -Optimized on their present anti-PD therapy	None	0	BTX- type B 5,000 U or placebo was injected into 4 areas of the soleus-gastrocnemius complex of the predominantly affected leg.
Gurevich (2007)[8]	RCT-Double blind placebo-design	11	Mean age was 69.4 (Range 56 – 86 years)	-PD patients during the "off" state for at least 3 months. -Diagnosed by 2 independent movement disorders specialist -Disabling FOG -Scored at least a 14 in the FOG questionnaire -FOG episodes with duration of 3 seconds and more every day affecting their ability to walk and their ADLs.	-If unable to walk independently -If had been exposed to BTX-A in the past.	0	BTX 150 IU was injected into both legs (50 IU into medial and lateral heads of the gastrocnemius and 50 IU into the soleus of each leg for a total of 300 IU per patient).

OUTCOMES MEASURED

All outcomes measured for this study were patient oriented outcomes (POEMs) related to the safety and efficacy of the use BTX injections for FOG episodes experienced by PD patients.

These outcomes were measured using United Parkinson's Disease Rating Scale (UPDRS). The UPDRS uses patient questionnaire as well as clinical observation to assess the activities of daily living and motor abilities of PD patients.

RESULTS:

Three studies investigated the impact that BTX injections had on the FOG episodes experienced by patients who had been diagnosed with PD. All three studies were RCTs: the first study was a double blind, two-period cross over design,[6] the second study was a double blind, placebo parallel design,[7] and the third study was a double-blind placebo design.[8]

In Wieler et al., twelve participants were selected, three women and nine men. The sample of patients consisted of 53 to 79 year olds with PD, with the average patient being 77 years old.[6] Patients were selected based on adherence to inclusion and exclusion criteria listed in **Table 1**. The patients were randomly assigned to either a placebo saline injection group followed by a BTX injection group, or a BTX injection group followed by a placebo saline injection group.[6] All participants were assessed at baseline and then received the first set of injections 4 weeks later.[6] At week 8, patients were evaluated for any changes in their condition. At week 16, the groups were switched and the next set of injections were given. At week 20, patients were again assessed for any changes from baseline. The BTX group received 200-300 units, which were injected into the medial and lateral heads of the gastrocnemius and into the soleus muscles for a total of 16.25-25 U/injection into six different injection sites.[6] At the follow up visits, diaries, freezing of gait questionnaires, and UPDRS were used to assess basic mobility.[6] A Parkinson's disease questionnaire (PDQ39 mobility) was used to assess quality of life.[6]

This study demonstrates that after BTX injections, there were no statistically significant differences from the baseline visit to the post-treatment visit that were captured by the FOG-Q

(p>0.18), UPDRS 14 (p>1.0), UPDRS 15 (p>1.0), PDQ39 mobility (p>0.95).[6] The mean change from baseline was 0, representing absolutely no changes post-treatment. **Table 2** is an independent T-test, which demonstrates the differences between the placebo and BTX groups.

There were no evidence of adverse effects, however one subject did report leg weakness that lasted for one week post BTX injection that was described as "my legs felt like jelly for a couple of days."[6] While there was no evidence of improvement, participant's comments alluded to possible improvements after injections.[6] Another patient stated there was a decrease in nocturnal leg cramping after BTX injections for approximately 3 weeks.[6]

Table 2: Mean difference at placebo baseline, placebo week 4, BTX baseline, and BTX week 4.[6]

	Mean difference (SD)	**P value**
UPDRS 14	0 (SD= 0.26)	1.00
UPDRS 15	0 (SD=0.55)	1.00

In the Fernandez et al. study, fourteen participants were selected.[7] The patient's ages ranged from 61 to 87 years old, with the mean age being 74.[7] Participants had an average duration of PD for ten years.[7] Patients were selected based on having idiopathic PD and FOG refractory to medical treatment as well as if they met inclusion criteria listed in **Table 1**.[7] Of the fourteen participants, nine were randomly selected to receive intramuscular BTX injections and five were chosen to receive placebo.[7] This group received 5000 U of BTX-B injections into four areas of the soleus and gastrocnemius muscle of the predominantly affected leg.[7] If both legs seemed to be affected equally, then the side on which the disease process began was selected.[7] This study did not show any statistically significant changes between the placebo and treatment group at baseline and at 1 month post treatment (p>0.15).[7] There was also no statistically significant changes before and after treatment within the group of patients receiving BTX

injections based on the UPDRS ($p>0.80$).[7] The mean change from baseline was -0.6, which proves that this intervention did not have an impact on the patients.[7] **Table 3** illustrates the scores between the BTX and control groups.

The BTX injections were tolerated well by all patients in this study. The only adverse effects that were reported were dry mouth, experienced by two patients, and festination, which is an involuntary quickening of gait, reported by one patient.[7]

Table 3: UPDRS mean scores at baseline, and one month.[7]

UPDRS Score	Baseline score	1 month	P value (1 month)
BTX group	18.7	18.1	0.8
Control group	17.8	17.4	0.8

In the Gurevich et al. study, eleven participants were selected, three females and eight males.[8] The patient's ages ranged from 56 to 86 years old with the mean age being 69.4 years old.[8] Patients were selected based on the inclusion and exclusion criteria listed in **Table 1**. Six patients were randomly selected to receive BTX injections and five patients were assigned to receive saline injections.[8] Baseline assessments were done at four and two weeks before as well as on the day of injection.[8] The participants received 150 IU of BTX injections, 50 IU into the medial and lateral heads of the gastrocnemius as well as 50 IU into the soleus, of each leg for a total of 300 IU of BTX per participant.[8] Post-injection, patients were evaluated at 2, 4, 8, 12, 16, and 20 weeks during which activities of daily living were assessed using UDPRS.[8]

There were insignificant changes found from baseline based on the UPDRS motor scale ($p<0.10$).[8] Mean change from baseline was measured to be +2.0, which is small given the type and size of the population.[8] **Table 4** demonstrates the changes between the placebo and BTX groups.

People participating in this study experienced numerous adverse effects. Of the six patients receiving BTX injections, three patients reported leg weakness, as did two patients who were receiving the placebo, however the leg weakness was not demonstrated by the clinical assessment.[8] Participants in both treatment and placebo group in the two to four weeks post injection reported pain.[8] One patient receiving BTX injections was diagnosed with xerotic dermatitis in the six weeks following injection that lasted throughout the rest of the study.[8] Another adverse affect was an increase in number of reported falls. This seemed to improve by the end of the 20th week study, but overall, falls did increase significantly in the BTX group.[8]

Table 4: UPDRS mean change at baseline, 4 weeks, and 20 weeks.[8]

UPDRS motor	**Baseline**	**4 weeks**	**20 weeks**	**P value**
BTX injections	33.0 (+10.7)	38.2 (+15.2)	43.8 (+8.3)	P<0.10
Control group	35.6 (+11.8)	34.0 (+14.7)	32.0 (+8.0)	Insignificant

DISCUSSION:

Parkinson's disease is an extremely debilitating disease with no imminent cure. Freezing of gait is a common complaint that leads to an increase in number of falls leading to a greater number of injuries and hospitalizations.[4] While treatments are available that can treat symptoms of PD as well as slow the progression, nothing has proven to completely treat and resolve the associated problems of PD.[2] BTX injections did not prove to be a promising addition to the treatment options for PD.

The three RCT's evaluated by this systematic review showed that the use of BTX injections for the FOG experienced by PD patients does not prove to be affective in improving motor abilities or activities of daily living.

BTX acts by binding to sites on cholinergic pre-synaptic nerve terminals and decreases the release of acetylcholine.[5] In doing this, it acts as a neuromuscular blocker.[5] Therefore, BTX,

while most popular for it's cosmetic usages, can be therapeutic for a wide variety of conditions including dystonias, spasticity, strabismus, and chronic pain issues.[5] However, when BTX is used in the wrong dose, dilution, or having been improperly stored, has been shown to have adverse effects.[5] Adverse reaction to BTX is more likely to be seen when being used as a therapy rather than for cosmetic usage.[5] A few commonly reported side effects include respiratory problems, dysphagia, seizures, flulike syndrome, weakness, ptosis, or reaction at site of injection.[5]

There are a few limitations in the RCTs used. Each study was quite small, which may have precluded any ability to detect a significant benefit. A larger group may reveal benefits of BTX injections that was unable to be seen here. Also, there is no known dose of BTX that has been shown to be effective. Because of this, it is unknown if higher doses would have contributed to more significant symptom reduction. Muscle selection is another limitation of these studies as only the gastrocnemius-soleus complex was injected. In the future, other muscle targets could be evaluated, for example, the muscles in the anterior compartment of the leg.

CONCLUSION:

BTX is used to treat a wide variety of disease and neurological symptoms ranging from focal dystonias of the face or limbs to migraine headaches. Its use in the treatment of PD is still nebulous. None of the studies evaluated in this review demonstrated a significant benefit of BTX on the FOG episodes experienced by PD patients. Since no extreme adverse drug reactions were shown to be an issue with this treatment, it may be beneficial to proceed with more studies in order to further evaluate it's safety and efficacy. Future studies should include a larger number of subjects. The reviewed studies do not show extreme promise in any major developments in the treatment for PD.

REFERENCES

1. Ding W, Ding J. Neurodegeneration and cognition in Parkinson's disease: a review. European Review for Medical and Pharmacological Sciences 2015;19:2275–2281.

2. Chou K. Patient information: Parkinson (Beyond the Basics). Parkinson disease 2014. Available at: http://www.uptodate.com/contents/parkinson-disease-symptoms-and-diagnosis-beyond-the-basics. Accessed November 2015.

3. Hermanowicz N, Edwards K. Parkinson's Disease Psychosis: Symptoms, Management, and Economic Burden. Parkinson's Disease Psychosis: Symptoms, Management, and Economic Burden 2015.

4. Statistics on Parkinson's. - Parkinson's Disease Foundation (PDF) 2015. Available at: http://www.pdf.org/en/parkinson_statistics. Accessed November 2015.

5. Kedlaya D. Botulinum Toxin. :Overview, History, Mechanism of Action 2014. Available at: http://emedicine.medscape.com/article/325451-overview#a9. Accessed 2015.

6. Wieler M, Camicioli R, Jones CA, Martin Wr. Botulinum toxin injections do not improve freezing gait of Parkinson disease. Neurology. 2005; 65(4): 626-628.

7. Fernandez HH, Lannon MC, Trieschmann ME, Friedman JH. Botulinum toxin type B for gait freezing in parkinson's disease. *Med Sci Monit.* 2004;10(7):CR282-4.

8. Gurevich T, Peretz C, Moore O, Weizmann B, Giladi N. The effect of injecting botulinum toxin type a into the calf muscles on freezing of gait in parkinson's disease: A double blind placebo-controlled pilot study. *Mov Disord.* 2007;22(6):880-883.