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PGY 1- Internal Medicine
CRC Presentation

IRB Protcol:
Botulinum toxin as treatment for neck pain and disability in Parkinson's Disease

I. Introduction:

a) Rationale

Parkinson's Disease (PD), the second most common neurodegenerative disorder, manifested by motor and non-motor symptoms that can impair activities of daily living, seriously impacts the quality of life for those afflicted with the disease. Rigidity is one of the cardinal signs of Parkinson's Disease and is clinically assessed by slowly rotating the joint of interest while asking the patient to remain passive and relaxed. It has been hypothesized that hypertonicity of the body axis affects functional performance of tasks involving balance, such as walking and turning (Franzen et al., 2009). Likewise, rigidity in the axial and proximal muscles may contribute to limited functional mobility. Several motor symptoms of PD, such as tremor, bradykinesia, rigidity, and gait instability have been shown to improve with dopaminergic therapeutic options. However, other troublesome symptoms may not respond to conventional treatment strategies, for example cervical dystonia in the form of anterocollis which is commonly noted in PD. The etiology of this forward neck flexure remains unknown and may or may not be related to the rigidity of the neck musculature. Simple activities of daily living (ADLs) can be greatly affected by limited cervical range of motion and subsequent chronic neck pain and disability. Examples of impairment can be found in tasks including dressing, washing, reading, driving, and lifting or moving objects. Treatment options specific to cervical pain and disability in PD are yet to be discovered. The purpose of this study is to consider a treatment alternative in targeting limitations in cervical range of motion as well as associated neck pain in patients with Parkinson's Disease.

b). Review of Literature

Cervical dystonia (CD) is a focal dystonia of the neck and shoulder region that causes head turning (torticollis), tilting (laterocollis), flexion (anterocollis) or extension (retrocollis). Pain is present in 68-75% of patients and can be a disabling feature (Comella, 2008). Botulinum neurotoxin (BoNT) treatment has been studied and used extensively for the treatment of cervical dystonia. In most controlled studies, there is significant improvement following treatment for head posture, pain and disability (Comella, 2008). There are 2 serotypes of BoNT available, type A and B, both have been investigated for the treatment of CD. The first report of efficacy was published in 1985 using a maximal dose of 200 units of BoNTA in 12 CD patients using a single-blinded study design, which showed improvement in 92% of patients that lasted 4-8 weeks (Tsui et al., 1985). These same investigators then conducted a

double blind, placebo controlled crossover study of 21 patients to confirm the early results (Tsui et al. 1986). There are several subsequent prospective, double-blind, randomized controlled clinical trials that have been presented as complete publications meeting the criteria for classification as Class I evidence of the efficacy of BoNTA as a treatment for CD. A controlled study of 20 CD patients assessing differing doses of BoNTA demonstrated subjective improvement in 80% of their subjects that was most apparent in the intermediate dose group of 100-140 units of BoNTA (Gelb et al., 1989).

Over the course of the past 20 years, the therapeutic spectrum of BoNT has been successfully expanding, including uses in the treatment of symptoms in PD. Botulism toxin has shown benefits in the treatment of hypersialorrhea, constipation, and freezing of gait in PD (Truong et al., 2006). Flexion contracture has also been treated with BoNT and may be beneficial, seen in studies treating contractions at the knee level. BoNTA was injected in the hamstring and gastrocnemius muscles with improvement in range of motion around the joint (Truong et al., 2006).

While BoNT has been considered treatment of choice in patients with cervical dystonia, there is no Class I evidence that BoNT is effective in treatment of the anterocollis associated with PD. While patients with PD often have abnormal neck postures, it remains unclear whether this abnormality is due to cervical dystonia, rigidity, a combination of the two or some other mechanism (Jankovic, 2009). Furthermore, anterocollis which is the most common abnormal neck posture associated with PD is often excluded from cervical dystonia trial studies of BoNT. While the side effect of dysphagia is possible, studies by Jankovic have shown that when injecting the bilateral sternocladomastoid (SCM) and scalenus muscles with an appropriate dosage, anterocollis can be successfully treated with minimal or no adverse effects.

Health outcome measures are commonly used in clinical research to determine if treatment has impacted a patient's health status. The Neck Disability Index (NDI) is a commonly used health outcome measure to capture the perceived disability in patients with neck pain (Cleland et al., 2008). The NDI is a survey of ten items that address patients symptoms as they apply to ADLs, pain, and concentration. Each item is scored 0-5 with total scores ranging from 0-50 with 50 points indicating maximal disability and discomfort. The reliability and validity of a self-report measure such as this one, requires a comparison with a construct that indicates a true change has occurred. The reference standard for measuring functional change used in prior studies by Westaway, Stratford, and Cleland have been both the clinician's prognostic rating and a patient global rating of change. From these studies it has been determined that the NDI exhibits moderate to high test-retest reliability in patients with mechanical neck pain (Cleland et al., 2008, Westaway and Stratford, 2009). Two studies have identified the minimal detectable change (MDC), which is the amount of change that must be observed before the change can be considered to exceed the measurement of error for the NDI. Westaway et al. identified the MDC as 5 points in a group of 31 patients with neck pain. Stratford et al. identified the MDC

to be 5 points in a group 48 patients with neck pain. The maximum score for this index which indicates maximum pain and impairment in function is 50 points while the minimum score of a pain free, fully functional patient is 0. Primary data collection from interviewing a patient with PD who has moderate neck pain and disability set a baseline score of 25 to represent moderate severity of symptoms for this study.

In the proposed study, the application of the conventional use of BoNTA in the treatment of CD will be expanded into a trial treatment for painful and disabling anterocollis in patients with PD. The NDI will be used as a tool to assess the perceived pain and disability prior to treatment and the potential improvement after treatment with BoNTA.

II. Hypothesis

The hypothesis for this study is that in patients with PD who experience painful and disabling anterocollis as a symptom that has not been relieved by conventional PD therapies, injection of the bilateral SCM and scalenus muscles with 100 units of BoNTA will show improvement on the patients' neck pain and cervical functional abilities at six weeks post-injection, as measured by the patients' pre- and post-treatment NDI scores, when comparing a treatment group with a placebo group.

The null hypothesis for this study is that in patients with PD who experience painful and disabling anterocollis as a symptom that has not been relieved by conventional PD therapies, injection of the bilateral SCM and scalenus muscles with 100 units of BoNTA will have no affect greater than chance on the patients' pain and functional abilities at six weeks post-injection, as measured by the patients' pre- and post-treatment NDI scores, when comparing a treatment group with a placebo group.

III. Methods

a) Conceptual and operational definitions:

This study will measure the affect of BoNTA injections as a treatment for anterocollis in patients with PD. This will be measured by applying the NDI to the patients at the start of the study with a repeated measurement at six weeks after treatment.

b) Study Design

This is a longitudinal, prospective, interventional study, that will be randomized, placebo controlled and double blinded with parallel arms.

c) Statistical Analysis

An unpaired t-test will be used as a statistical method for analyzing the data gathered from this study.

d) The sample size formula used with an approximation for 80% power, testing at $p = 0.05$ is:

$n = 1 + 16 (\text{std-devn/effect})^2$

The effect was defined as a 5 point improvement in scoring on the NDI in the treatment group as compared to the placebo group. The chosen effect of 5 was based on the minimal detectable change that had been defined at 5 points in prior studies of the reliability and validity of the NDI as tool for measuring neck disability outcomes.

The standard deviation (SD) was found to be 5, based on an average range of 20 in a placebo group. It is assumed that a patient's NDI score during this study period could vary from an increase of 5 points to a decrease of 15 points based on unrelated day-to-day variations in pain and function or based on the placebo effect alone. If it is assumed that this range of 20 represents two standard deviations on either side of the curve, we can set the SD to be 5.

The sample size needed to conduct this study with 80% power, testing at $p = 0.05$ was 32 patients.

IV. Subject Selection

The population of subjects of this study will be patients with PD who present to the neurology clinic with complaints of neck disability leading to pain and impairment of ADLs that have not been adequately treated with conventional PD therapies. These potential subjects will be identified and approached about study enrollment. Informed consent will be obtained by the patient prior to the start of the study. Patients will not be excluded based on age, time since onset of symptoms, or prior and current treatment therapies so long as they continue to complain of symptoms of neck disability at the start of the study. The NDI will be applied to these patients prior to the start of the study over multiple days to keep within subject variability at a minimum. Subjects selected for the study will be those who have a NDI between 25-40 and these patients will be stratified into two groups (25-32 and 32-40) prior to randomization. The population will be randomized into two groups of 18 patients. The treatment group will be injected with 100 units of BoNTA into the bilateral SCM and scalenus muscles while the placebo group will receive injections with normal saline. Both groups will be reassessed at six weeks after treatment initiation and will be asked to complete the NDI again at this time point. A requirement of the study will be that the patients do not have any changes to their prior treatment regimens during the study period of six weeks to avoid confounding variables.

V. Miscellaneous

A potential location for this study could be the neurology clinic at NY Presbyterian Hospital at Columbia. The study questionnaire used is the NDI, a survey of ten items that apply to ADLs, pain, and concentration. Each item is scored from 0-5. Total scores range from 0-50 with 50 points indicating maximal disability and discomfort. It is ethical to include a placebo arm in this study because currently there is no Class I evidence arguing that BoNTA shows improvement in cervical pain and function for patients with PD; therefore, the placebo group is not being denied a known therapy. Likewise there is data available to raise the question that this therapy could be potentially beneficial with low risk. Minimal risks exist, such as hematoma or edema at the injection site. Moderate risks exist in that the treatment group could experience neck muscle weakness or dysphagia; however, this risk is minimized by applying the BoNTA injections to more superficial musculature at appropriate tested intermediate dosages.

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