1) PROTOCOL TITLE

Comparison of botulinum toxin injections in forearm **FL**exor plus **EX**tensor muscles versus flexor muscles alone for the treatment of **E**ssential hand **T**remor (FLEX-D ET)

2) INVESTIGATORS:

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3) STUDY CENTER:

Cleveland Clinic Center for Neurological Restoration, Cleveland, Ohio

4) STUDY TIMELINES (WITH A PROJECTED ENROLLMENT OF ABOUT 1/WEEK):

-First patient in → September 1, 2016
-1/3 of patients enrolled → September 30, 2016
-2/3 of patients enrolled → October 15, 2016
-Enrollment completed → October 30, 2016
-Last patient out → January 30, 2017
-Analysis of data → February 14, 2017

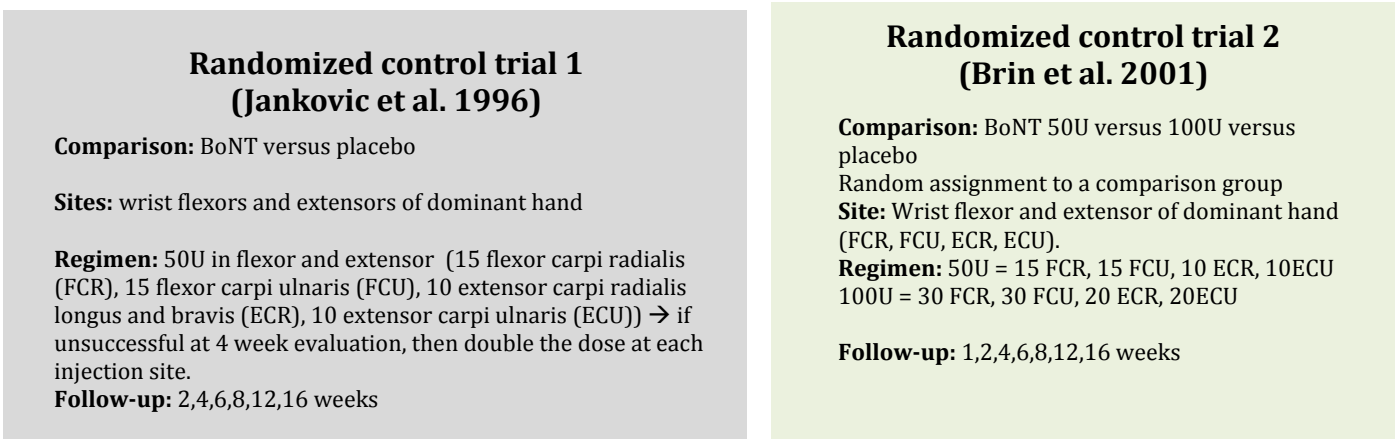
5) BACKGROUND:

ET is one of the most common movement disorders, affecting 4% of adults of 40 years of age and older (Abboud et al. 2011). Although called "benign," ET causes substantial impairment in activity of daily living. ET typically affects both upper extremities, but it can start on one side. Progressive involvement of head, lips, tongue, legs, and voice is also a feature of ET.

Treatment is of ET is symptomatic. Propranolol and primidone are commonly used first-line agents (Simpson et al. 2008). Topiramate, gabapentin and zonisamide are also used as adjunctive or stand-alone treatment (Simpson et al. 2008). Unfortunately, 40-50% of patients do not respond to pharmacotherapy (Sadeghi and Ondo 2010). Pharmacologically refractive ET or patients who are poor candidates for pharmacotherapy often benefit from either botulinum toxin (BoNT) injection or deep brain stimulation (DBS) (Jankovic et al. 1996; Brin et al. 2001; Sadeghi and Ondo 2010). Although DBS is the standard of care for pharmacologically refractive ET, it is invasive, involves the risks of general anesthesia, and produces the side effects of dysphagia, paresthesias, and ataxia in up to 30% of patients (Larson 2014). In addition, 10-20% of patients are non-responders or experience loss of treatment efficacy (Larson 2014). Given these limitations of DBS, the relatively less invasive approach of BoNT injection is a resource that is worth a try.

Two randomized controlled trials (RCT) with somewhat similar study design assessed the efficacy of BoNT in hand ET (Jankovic et al. 1996; Brin et al. 2001) (Figure 1). Both trials used type-A BoNT (Botox®). Both trials investigated injections in wrist flexors and extensors. Injections with two strengths, 50U and 100U, were tested. The dose injected in wrist extensors was always two-third (2/3rd) of that injected in wrist flexors. But there were also some differences in trial designs. Figure 1 depicts the differences.

Figure 1



Both trials reported significant improvement in tremor rating scale and objective assessment using accelerometry (Jankovic et al. 1996; Brin et al. 2001). One study reported that 75% of BoNT treated patients had mild to moderate improvement that reached statistical significance (Jankovic et al. 1996). Objective assessment of ET with limb accelerometry showed a 30% reduction in tremor intensity in 9 of 12 BoNT-treated patients and in 1 of 9 placebo-treated patients ($p < 0.05$) (Jankovic et al. 1996). Similar results were reproduced in a second RCT with much larger (n=133) number of ET patients (Brin et al. 2001). Results of these two RCTs led to the American Academy of Neurology level-B recommendation that BoNT should be considered for treatment of ET in patients who are refractory to oral pharmacotherapy (Simpson et al. 2008).

Both RCTs, however, presented significant caveats. Although patients had significant improvement in tremor rating scales and objective assessments, none had a change in functional rating scales. Most BoNT injected patients in both studies had finger weakness. One RCT reported worse extensor weakness (50% moderate weakness, 42% mild weakness) as compared to flexor (Jankovic et al. 1996), while the other noted "finger drop" in the BoNT injected (Brin et al. 2001). Although claimed "unrelated" in one of the trials, it is possible that lack of subjective sense of improvement evidenced by functional rating scale was related to finger extension weakness. This argument is supported by an open-label study of BoNT injection (Pacchetti et al. 2000). This open-label study electrographically identified the most involved muscles using the surface electrodes placed on the skin overlying extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), brachioradialis, pronator teres (PT), biceps, and triceps. Only muscles that showed significant tremor were injected with BoNT, hence wrist extensors were not injected in all patients (Pacchetti et al. 2000). Although dose and distribution of injected flexor muscles varied amongst patients, only 15% of the patients had finger extension weakness (Pacchetti et al. 2000). Furthermore, there was a significant improvement in both tremor severity and functional rating scales (Pacchetti et al. 2000). It is therefore possible that poor outcome on subjective functional rating scale in both RCTs were related to weakness. In addition, both RCTs had rigid treatment protocol implementing a fixed BoNT dose in predetermined muscles regardless of the disease severity. Lack of subjective improvement in some patients enrolled in these RCTs might be due to the mismatch between administered dose and severity of symptoms; for example, higher dose for mild tremor might exaggerate weakness, while low dose for moderate to high severity tremor might lead to under treatment.

In summary, while these studies have demonstrated the potential role of BoNT for ET there remains limitations that have yet to be addressed. It is unclear if the perceived efficacy of BoNT in tremor reduction is diminished by associated extensor weakness. It is also unclear if BoNT injection of flexors alone is equally efficacious as the injection of both flexor and extensor muscles. If injecting extensor muscles is essential, can the ratio between extensor and flexor muscles be adjusted to give efficacy with no weakness? Furthermore, although previous studies have demonstrated significant objective improvement in tremor severity, they did not observe significant improvements in quality of life (QOL), functional improvement, and global improvement.

With these limitations in mind, we propose a pilot, single center, double blind, randomized, parallel, placebo controlled trial comparing 2 BoNT injection patterns for treatment of moderate to severe essential tremor. To minimize the potential for extensor weakness, we will inject the extensor muscles with 1/3 the dose used for the flexor muscles (a 3:1 ratio of BoNT injected for flexor to extensor as compared to the previous studies which used a 3:2 ratio). Our primary outcome and secondary outcomes as detailed below will include patient global impression scale as well as other functional and QOL scales.

6) STUDY OBJECTIVES:

Study aim:

To compare the efficacy of botulinum toxin (BoNT) injections in forearm flexors plus extensor muscles versus flexors alone for the treatment of essential hand tremor (ET).

Hypothesis:

We hypothesize that both patterns of BoNT injection (flexors plus extensors, flexors alone) will be equally efficacious in decreasing tremor, but that patients in the flexors alone group will experience less motor weakness and therefore report greater global improvement in symptoms.

We acknowledge the possibilities that patients in the flexors plus extensors group may perceive greater improvement in tremor severity due to the additional injection of the extensor compartment and that the injection of the extensor compartment may be well tolerated because the injected dose is only 1/3 of the dose for the flexor compartment.

Primary Outcome Measure:

Difference in 6 week post injection on a Patient Global Impression Scale-Improvement Subscale (PGI-I)

Secondary Outcome Measures:

1. *Improvement in 6 week post injection in tremor rating scale.*
2. *Difference in the mean Quality of Life in Essential Tremor Questionnaire (QUEST) at Week 6 from baseline between wrist flexors versus wrist flexors plus extensors group.*
3. *Improvement in 6 week post injection in Clinician Global Impression Scale-Improvement Subscale (CGI-I).*
4. *Difference in grip strength post injection between the two groups at 6 weeks*
5. *12 week post injection patient global improvement scale*

6. *12 week post injection tremor rating scale*

7. *Difference in the mean QUEST score at Week 12 from baseline between wrist flexors versus wrist flexors plus extensors group.*

8. *12 week post injection clinician global improvement scale*

9. *Difference in grip strength post injection between the two groups at 12 weeks.*

Tertiary Outcome Measures

1. *Monitor changes in depression using PHQ-9 at 6 weeks*

2. *Monitor changes in anxiety using GAD-7 at 6 weeks*

3. *Monitor changes in depression using PHQ-9 at 12 weeks*

4. *Monitor changes in anxiety using GAD-7 at 12 weeks*

The scales that will be used in the study are below:

Global assessment graded by patient and clinician (PGIS and CGIS respectively) on -4 to +4 scale

- -4 = severe worsening
- 0 = no change
- +4 = complete abolishment of symptoms

Tremor Rating scale (TRS) at rest, posture and kinetic

- 0 = none perceived
- 1 = slight (barely noticeable)
- 2 = moderate, noticeable, probably not disabling (<2cm excursions from affected part)
- 3 = marked, probably partially disabling (2-4cm excursions)
- 4 = severe, coarse, disabling (>4cm excursion)

Kinetic tremor will be measured using motor tasks including handwriting and pouring. Patients will be asked to write the sentence “Today is a nice day” with their dominant hand. They will also be asked to draw a spiral. Pouring will be assessed by asking the patient to pour water form one cup to another.

QUEST will also be administered at baseline and follow up visits to assess functional impairment of tremor in activities of daily living.

Grip strength will be assessed using dynamometer.

7) STUDY DESIGN/METHODS:

We propose a pilot, single center, double blind, randomized, parallel, placebo controlled trial comparing 2 BoNT injection patterns for treatment of moderate to severe essential tremor.

We will recruit 20 patients with ET. The following inclusion and exclusion criteria will be used during the screening visit.

Inclusion Criteria

1. Age 18 and over, male or female patient with ET involving at least their dominant hand, as diagnosed by a movement disorders neurologist.

2. Having bothersome hand tremor in dominant hand with a hand TRS ≥2

3. On stable medications during last 30 days prior to enrollment.

Exclusion Criteria

1. Presence of secondary causes of tremor, such as dystonia and parkinsonism
2. Any contraindication to botulinum toxin injections (e.g. motor neuron disease, neuromuscular junction disease, etc.)
3. History of surgical treatment for ET.
4. Dementia as defined by DSM-V criteria
5. Patients with suboptimally treated depression and significant depressive symptoms as defined by a PHQ-9 score of ≥15 (PHQ-9 scores 1-4 Minimal depression; 5-9 Mild depression; 10-14 Moderate depression; 15-19 Moderately severe depression; 20-27 Severe depression). Antidepressant medications, prescribed for depression or anxiety, will be allowed if the patient has been on a stable dose for at least 30 days.
6. Patients with suboptimally treated anxiety and significant anxiety symptoms as defined by a GAD-7 score of ≥15 (GAD-7 scores 0–4: minimal anxiety; 5–9: mild anxiety; 10–14: moderate anxiety; 15–21: severe anxiety). Anti-anxiety medications, prescribed for anxiety, will be allowed if the patient has been on a stable dose for at least 30 days.
7. Significant renal, hepatic, cardiac and thyroid disease

At the screening visit, if patient meets inclusion criteria and signs informed consent, patient will be randomized to one of two paradigms. Tremor will be rated based on Tremor Rating Scale (TRS) and Tremor Severity Scale (TSS). We will also obtain baseline evaluation of depression and anxiety, using PHQ-9 and GAD-7 respectively. In addition we will evaluate grip strength using dynamometer. Patients will be randomized to receive either injections of 150 units of abobotulinumtoxinA (Dysport®) in flexor compartment of dominant arm (75 units in flexor carpi radialis [FCR] and 75 units in flexor carpi ulnaris [FCU]) along with placebo in extensor carpi radialis (ECR) and extensor carpi ulnaris (ECU) or 75 units in FCR and FCU and 25 units in ECR and ECU. Injections will be done in dominant arm only. We will reduce dose in extensor by 66% of that given in flexor as opposed to previous RCTs where dose was reduced by 33% (Jankovic et al. 1996; Brin et al. 2001).

- Group 1 – plus Extensors: BoNT 200 units total (75U FCR, 75U FCU, 25U ECR, 25U ECU).
- Group 2 – Flexors alone: BoNT 150 units total (75U FCR, 75U FCU, 0UECR, 0U ECU).

The patients will be seen in follow up at 6 weeks and again at 12 weeks. At these times we will repeat all baseline measures and in addition have patients evaluate treatment response using a patient global impact scale ranging from -4 (severely worse) to +4 (no more tremor) with 0 meaning no change. Clinicians will be asked to complete the same scale. Figure 2 depicts the outline of our study design.

Figure 2: Study Design

Visit	1	2	3
Type	Screening/Baseline (injection)	Post injection week	Post injection week
Time	0	6 weeks	12 weeks
Informed Consent	X		
History and PE	X	X	X
Concomitant Meds	X	X	X
Adverse Events		X	X
TRS	X	X	X
QUEST	X	X	X
PHQ-9	X	X	X
GAD-7	X	X	X
PGIS		X	X
CGIS		X	X
Grip Strength	X	X	X

Procedure/test:

The BoNT injections will take place in a dedicated clinical research space, located in the CNR Movement Disorders clinic in the U ("Mellen") building. No other patient will be present and the door will be closed to protect patient privacy. The patients will come in the morning when tremor will be evaluated clinically. Each patient will receive BoNT injections into dominant upper extremity using protocol outlined above. We will evaluate patients at week 6 and 12 post injection. At baseline visit, the nurse who is mixing the toxin will not be blinded to the treatment arm, but both the patient and PI who will be injecting as well as administering the rating scale will remain blind.

Randomization will be doing using a computer program and each subject will be assigned an envelope which nurse will have access to and open when she is mixing the agent.

Statistical analysis:

Assessment of tremor improvement - We will compare average result of PGIS and CGIS at week 6 and week 12 between two groups. Furthermore we will compute percent change of TRS and QUEST for each follow-up visit as compared to the baseline. Given the small sample size, Mann-Whitney U test will be used for calculations.

Based on the previous studies (Jankovic et al. 1996; Brin et al. 2001), mean change in TRS and PGIS was 1 point (about 25% improvement on a 4-point scale) with a standard deviation of 0.7 points at week 6 post injection. To achieve an alpha of 0.05 and a power of 80%, we estimate a sample of size of 18 total patients with 9 in each treatment group. Accounting for an estimated 10% attrition rate we will recruit 20 total patients into this trial.

We will use the above analysis to answer our primary question: Whether BoNT injections to both wrist flexors and extensors are superior as compared to injections to wrist flexors alone; or vice versa?

Confidentiality of Data:

Identifying information will be severed from study data. Subject numbers will be used to identify all participants. A password protected file linking subject numbers to identifying information will be maintained on a CNR computer. Likewise, electronic study data will be stored in password protected files and folders on a CNR computer. Any data on portable or removable device will be de-identified and protected by encryption. Paper study forms will be maintained in a locking filing cabinet in a secure area. Only the study investigators will have access to study files and folders.

Safety and Data Monitoring:

All adverse events, as reported by the subject during the study, will be documented and reported to the IRB according to the IRB policy. Any unanticipated problems will be reported to the IRB according to the IRB policy as soon as they occur or as soon as they are discovered. Efficacy data will be collected as per study protocol

Budget:

For a total of 20 patients and 3 visits per patient (Baseline, 6 weeks post injection and 12 weeks post injection) including investigator, coordinator, supplies and patient stipend we anticipate a total cost of $48, 423. Funding will be provided by Ipsen, the manufacturer of Dysport®.

Reference List

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Larson, P. S. (2014). Deep brain stimulation for movement disorders. *Neurotherapeutics : The Journal of the American Society for Experimental NeuroTherapeutics*, *11*(3), 465–74. doi:10.1007/s13311-014-0274-1

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Simpson DM, Blitzer A, Brashear A, et al. (2008) Assessment: Botulinum neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 70:1699-1706 doi: 10.1212/01.wnl.0000311389.26145.95

APPENDIX

Scales

FLEXd-ET

Tremor Rating Scale

Subject ID _____

Visit number _____

Dominant Hand _____

Please use below grading for items 1-3

- 0 = none perceived
- 1 = slight (barely noticeable)
- 2 = moderate, noticeable, probably not disabling (<2cm excursions from affected part)
- 3 = marked, probably partially disabling (2-4cm excursions)
- 4 = severe, coarse, disabling (>4cm excursion)

1. At Rest ....._____
2. Posture (arms 90^{o} perpendicular in front of patient) ....._____
3. Action/Intention (Finger to nose) ....._____
4. Handwriting (Please write *Today is a nice day in line below*) ....._____

   0 = Normal
   1 = Mildly abnormal
   2 = Moderately abnormal. Legible, but with considerable tremor
   3 = Marked abnormal. Illegible
   4 = Severely abnormal. Unablet o keep pencil or pen on paper without holding down with other hand
5. Spiral drawings (on back of sheet) ....._____
   0 = normal
   1 = Slightly tremulous. May cross lines occasionally
   2 = Moderately tremulous or crosses line frequently
   3 = Accomplishes task with great difficulty. Many errors
   4 = Unable to complete drawing

6. Pouring ....._____
   0 = normal
   1 = more careful, but no water spilled
   2 = spills a small amount of water (up to 10% of total amount)
   3 = Spills a considerable amount (>10-50% of total amount)
   4 = Unable to pour water without spilling most of the water

FLEXd-ET

Patient Global Impression Scale

Subject ID _____

Visit number _____

Dominant Hand _____

Please circle which number best corresponds to overall improvement in symptoms after injection

Severely worse — No Change — No further symptoms

-4 -3 -2 -1 0 +1 +2 +3 +4

FLEXd-ET

Clinician Global Impression Scale

Subject ID _____

Visit number _____

Dominant Hand _____

Please circle which number best corresponds to overall improvement in symptoms after injection

Severely worse — No Change — No further symptoms

-4 -3 -2 -1 0 +1 +2 +3 +4