***Study Protocol***

**A randomized, double-blind crossover controlled study of botulinum toxin treatment in upper limb tremor**

Victor Fung and Morales-Briceno Hugo

Westmead Hospital

Hypothesis and Aims:

To compare clinical, functional, and quality of life measures in patients with upper limbs tremor following treatment with botulinum toxin injections

**Background:**

Botulinum toxin type A (BoNTA) has been widely used in treatment of various movement disorders, such as blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, limb dystonia, adductor laryngeal dystonia, focal tics and tremor[1]. There has been studies suggesting the effectiveness of BoNTA in treating upper limb tremor including two double-blind, randomized, placebo-controlled trial in treating essential tremor[2, 3] and one double-blind randomized, controlled study in multiple sclerosis-related tremor[4]. Despite the significant improvement of tremor severity in the previous studies, functional improvement has been disappointing. Recently, our group published a first retrospective analysis of open-label treatment with BoNTA in 19 patients with proximal tremor and the result of which supported the functional efficacy of customized, BoNTA therapy in the treatment of proximal upper limb tremor with minimal side effects[5]. Further investigation of the treatment efficacy of BoNTA in proximal upper limb tremor regardless of its etiology using a randomized, double-blind, crossover study method is warranted.

**Methods:**

Patient Selection:

*Inclusion Criteria*:

Patients will be selected on the basis of upper limb tremor at the shoulder and/or elbow joint either during action, determined by finger-to-nose task and/or posturing with arms outstretch or in the targeting-nose position.

*Exclusion Criteria*:

1. Patient treated with BoNTA within 6 months before evaluation
2. Changes in any medications that might affect the severity of tremor within 3 months before enrolling or during the 6 months of evaluation.
3. Inability to comply with the study requirements and follow-up period.
4. Patients with cognitive impairment who is unable to complete the assessment
5. Patients in whom consent is unable to be obtained from themselves or next of kin.

Randomization procedure:

Patients will be randomly assigned to 2 groups, A and B.

The design is the 2-sequence, 2-period, 2-treatment crossover design, with sequences AB and BA

The group A will receive BoNTA injection as their first treatment and after a period of 4 months they will be given placebo.

The group B will receive placebo injection as their first treatment and after period of 4 months they will be given BoNTA injection.

Medications:

Onabotulinum toxin A (Merz Pharma GmbH & Co. KGaA) will be used for treatment. Each vial of Xeomin, which contains 100 unit of onabotulinum toxin A will be diluted into 2 mL (5U per 0.1mL) using 0.9% sterile saline. 0.9% sterile saline will be used as placebo. All preparations will be prepared by an unmasked person so that patients can be injected in the same intended volume. The injection dosage will be determined by a blinded, movement disorder specialist.

Muscle Selection:

Muscle selection will be individualized according to tremor characteristics after reviewed by a movement disorder specialist.

Injection techniques:

All patients will be performed with patients sitting on a chair. The target muscles will first be identified by palpation and confirmed with electromyography (EMG). Muscles will be injected only if the EMG bursting are identified.

Data collection, clinical assessment and outcomes:

1. Demographic data will be collected, which includes patient’s age, gender, underlying medical condition, tremor onset age, tremor duration.

2. Patients will be required to present themselves for initial assessment and at 4, 8, 12, 16, 20, 24 weeks for the followings:

* Video recording: A standardized tremor assessment using Fahn, Tolosa, Martin Tremor Rating Scale[6] will be videotaped, renumbered, shuffled and rated by a trained rater. The tremor characteristic will also be recorded, e.g. shoulder abduction/adduction, internal/external rotation, elbow flexion/extension, supination and pronation.
* Patient-specific goal achievement: the Canadian occupational performance or the goal attainment scaling.
* Functional outcome and quality of life: patient-reported Bain and Findley Tremor ADL Scale and Quality of Life in Essential Tremor Questionnaire.
* Muscle strength: Muscles including teres major, teres minor, infraspinatus, supraspinatus, deltoid, pectoralis major, biceps, triceps, finger flexors and extensors will be checked, using the ratings of the Medical Research Council ranging from no contraction of the muscle detectable (0) to full or normal strength (5).

1. Global rating scale[7]:

Global rating for the overall treatment effect, will be obtained at 12 weeks and 24 weeks, by subtracting complication score from peak effect (Peak effect (0-4): 0, no effect; 4, marked reduction in severity and improvement in function; Complication score (0-2): 0, no therapeutic complications; 1, mild complications; 2, severe and disabling complications). The outcome of the treatment was considered to be positive when global rating is equal to or more than 2.

1. Tremor study:

Accelerometry and surface EMG will be used to measure tremor frequency and amplitude. Electrodes will be placed on the four most tremulous muscles of each upper limb (same muscles bilaterally). The electrode placement will be photographed for the reference for follow up study to insure the exact same electrode position in the follow up studies. A standardized protocol including upper limbs at rest, outstretched, at nose-targeting position and when doing finger-nose task will be used. Repeat study will be performed at 1 month and 3 month..

Safety Measures: Patients will be asked to report all the side effects within 24 hours of symptoms onset. Every side effects or complications will be recorded and addressed whenever necessary.

Primary Endpoints:

The Canadian Occupational Performance or the Goal Attainment scaling

Secondary Endpoints:

1. Bain and Findley Tremor ADL Scale
2. Quality of Life in Essential Tremor Questionnaire.
3. Fahn, Tolosa, Martin Tremor Rating Scale
4. Global rating scale
5. Amplitude of the accelerometry and surface EMG

Sample Size:

Total of 30 patients will be recruited with 15 patients in each group.

Proposed Statistical Analysis:

A power analysis will be performed to determine the sample size. The test will be performed with a significance level of 0.05 (two-sided).

The number of participants needed to detect a clinically relevant treatment effect is 30.

A total of 30 patients will enter this two-treatment crossover study. The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 7.498 units. This is based on the assumption that the within-patient standard deviation of the response GAS scaling is 10.

The probability is 80 percent that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 2.999 units. This is based on the assumption that the within-patient standard deviation of the response variable is 4 for the Fahn-Tolosa-Marin Tremor Rating Scale.

References

1. Hallett M, Albanese A, Dressler D, Segal KR, Simpson DM, Truong D, Jankovic J: Evidence-based review and assessment of botulinum neurotoxin for the treatment of movement disorders. Toxicon : official journal of the International Society on Toxinology 2013, 67:94-114.

2. Jankovic J, Schwartz K, Clemence W, Aswad A, Mordaunt J: A randomized, double-blind, placebo-controlled study to evaluate botulinum toxin type A in essential hand tremor. Movement disorders : official journal of the Movement Disorder Society 1996, 11(3):250-256.

3. Brin MF, Lyons KE, Doucette J, Adler CH, Caviness JN, Comella CL, Dubinsky RM, Friedman JH, Manyam BV, Matsumoto JY et al: A randomized, double masked, controlled trial of botulinum toxin type A in essential hand tremor. Neurology 2001, 56(11):1523-1528.

4. Van Der Walt A, Sung S, Spelman T, Marriott M, Kolbe S, Mitchell P, Evans A, Butzkueven H: A double-blind, randomized, controlled study of botulinum toxin type A in MS-related tremor. Neurology 2012, 79(1):92-99.

5. Kim SD, Yiannikas C, Mahant N, Vucic S, Fung VS: Treatment of proximal upper limb tremor with botulinum toxin therapy. Movement disorders : official journal of the Movement Disorder Society 2014, 29(6):835-838.

6. Fahn S TE, Martin C.: Clinical rating scale for tremor, 2 edn. Baltimore: Williams & Wilkins; 1993.

7. Jankovic J, Schwartz K: Botulinum toxin injections for cervical dystonia. Neurology 1990, 40(2):277-280.