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Review Article

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Progress in Management of Essential and Parkinson Disease Tremor with Botulinum Toxin Injections-Established Efficacy and Less Adverse Effects

Bahman Jabbari*

Division of Movement Disorders, Department of Neurology, Yale University, New Haven, CT, USA

***Correspondence to:**
Prof. Bahman Jabbari, MD, FAAN
Emeritus Professor of Neurology
Division of Movement Disorders
Department of Neurology
Yale University, New Haven, CT, USA
Tel: 914-482-8542
E-mail: bahman.jabbari@yale.edu

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Abstract

Tremor is a common movement disorder, and in severe cases, often disables the patients. Essential tremor (ET) and Parkinson-related tremor are two of the most common forms encountered. Earlier double blind and placebo-controlled studies had suggested efficacy of BoNT-A injections into the forearm muscles in reducing the hand and forearm tremor in patients with essential tremor (ET). High quality publications over the past two years have established the efficacy of botulinum toxin-A therapy for ET as well as demonstrating probable efficacy of BoNT-A injections in Parkinson disease tremor. These recent publications also describe novel techniques such as the one used in the Yale protocol using EMG screening and a customized approach and the kinematic computerized amplitude analysis of tremor that have substantially reduced the incidence of hand and forearm weakness reported as adverse effects in the previous high quality studies.

Keywords

Botulinum toxin, Botulinum neurotoxin, OnabotulinumtoxinA, IncobotulinumtoxinA, Essential tremor, Parkinson's disease

Introduction

Botulinum neurotoxin (BoNT) injections improve hyperkinetic movement disorders mainly through inhibiting the release of acetylcholine from presynaptic vesicles [1]. Proved efficacious and safe via clinical trials and clinical experience, type A and B of BoNTs are now widely used for treatment of a variety of movement disorders [2].

Tremor is defined as an involuntary, oscillating movement of a body part [3]. Severe tremor can cause functional disability. Essential and Parkinson's disease (PD)-related tremor are two of the most common forms encountered in practice. Pharmacological treatment of severe ET and PD-related tremor is difficult. Approximately 30% of patients with ET do not respond to pharmacological treatment (betablockers or anticonvulsant) and another 25-30% stop the medications due to side effects or dissatisfaction with treatment [4, 5]. Deep brain stimulation of thalamic and subthalamic nuclei and globus pallidus interna (GPI) is currently the most effective mode of treatment for both essential and Parkinson tremor. There is room however, for other modes of treatment since not every patient is willing to undergo a surgical procedure and the DBS carries 3-4% risk of side effects including intracerebral hemorrhage [6].

High quality studies focusing on the treatment of tremor with BoNTs are sparse [7-10]. In the earlier studies, while data showed efficacy, the occurrence of hand and finger weakness following BoNT therapy in a high percentage of patients casted doubt on the utility of this approach in management of limb

tremor [7, 8]. Publications over the past 3 years, however, have provided further support for the efficacy of BoNT therapy in treatment of ET and Parkinson disease tremor; these studies have described newer techniques, the employment of which has substantially reduced the incidence of hand and finger weakness in ET and PD-related tremor following BoNT therapy [9-11].

Research and Results

As of August 1st 2019, the Medline search data showed 316 articles when Mesh terms of "Tremor", "Essential Tremor" or "Parkinson disease tremor" are crossed with "Botulinum Toxin or Botulinum Neurotoxin" (Figure 1). Of these 316 manuscripts, only 17 are specifically related to the subject of this review. Using the criteria of the American Academy of Neurology [12, 13] (Table 1), 4 of 17 articles are considered high quality studies (Class I or II: double blind/placebo-controlled). The data from these four high quality articles and from one other medium quality (prospective, open label, class III) study [11], describing the efficacy of a new technique of injection constitute the focus of this review (Table 2).

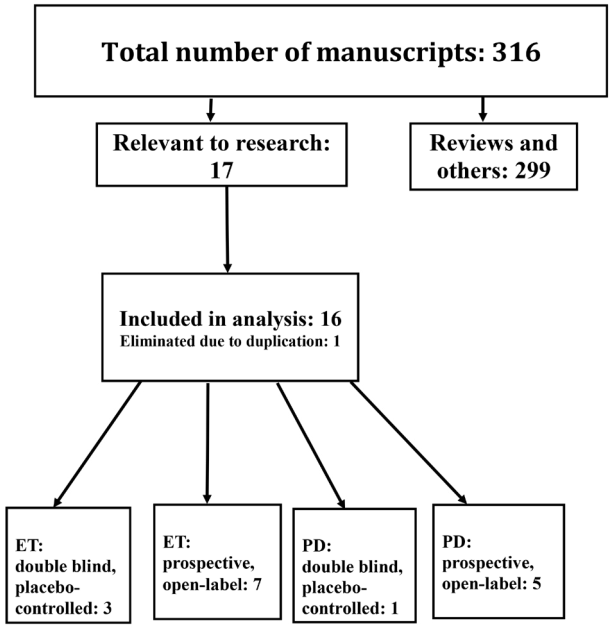

Figure 1: Clinical trials published on botulinum toxin therapy for treatment of essential and Parkinson disease tremor

Jankovic et al. [7], published the first double-blind, placebo-controlled study of botulinum toxin therapy in patients with essential tremor. The authors injected 25 patients with either botulinum toxin-A or saline and compared the results at 4 weeks. A functional grading scale was used for grading tremor in that 0 indicating no tremor and grade 4 meant severe tremor exceeding 4 cm in amplitude. All enrolled patients had a minimum of grade 2 tremor. Patients were injected first with 50 units of type A toxin (onabotulinumtoxinA); if they failed to show improvement, they were reinjected with an additional 100 units several weeks later. Injections were given into 4 forearm muscles: the flexor carpi radialis and ulnaris (FCR, FCU) as well as extensor carpi radialis and ulnaris (ECR, ECU). After the first injection, significant improvement of tremor amplitude was noted in 75% of those who received onabotulinumtoxinA injection compared to 27% of those who received saline ($P < 0.05$). No significant improvement was noted in functional rating scales, although more patients in the toxin group improved compared to the saline group. The positive response of BoNT therapy was noted mainly in the postural tremor. Mild and moderate hand and finger weakness occurred in 50% and 42% of the patients respectively.

Table 1: Class of clinical trials and definition of efficacy level endorsed by the Assessment and Guidance Committee of the American Academy of Neurology*

Study Class
Class I: A randomized clinical trial of the invention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
The following are also required: a. concealed allocation. b. primary outcome(s)clearly defined. c. exclusion/inclusion criteria clearly defined. d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and cross- overs with numbers sufficiently low to have minimal potential for bias.
Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a-d above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-d above.
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.
Class IV: Studies not meeting Class I, II or III criteria including consensus or expert opinion.
Level of Evidence:
Level A (efficacy established, recommended or not recommended), required two class I or one class I and two class II studies.
Level B (probably effective or probably not effective), required one class I or two class II studies
Level C (possible effective or not effective), requires one class II study
Level U (efficacy undetermined): due to contradictory results or lack of quality studies.
Exerted form [12, 13], excluding the criteria for non-inferiority clinical trials

Brin et al. conducted the second double-blind, placebo-controlled study of BoNT efficacy in 130 patients with essential tremor [8]. Injections were directed into the same four muscles of the forearm (FCR, FCU, ECR and ECU). Patients were divided into two groups, high dose and low dose. The low dose group received 15 units into each forearm flexor and 10 units into each forearm extensor. The high dose group received twice that dose in each muscle. The authors noted significant improvement of postural tremor from weeks 4 to 16 post-injection, but observed improvement of kinetic tremor only at week 6. Hand and finger weakness developed in 30% of patients in the low dose and 70% of patients in the high dose group. Authors of both these blinded studies [7, 8], emphasized occurrence of hand and finger weakness as a major drawback of botulinum toxin therapy for ET. Jankovic suggested using a customized rather than fixed pattern of injection for

Table 2: High quality botulinum toxin studies in ET and PD tremor.

Authors, year	Type	Design & Class	pts	Toxin	Muscles injected	Dose Units(u)	Result	Adverse effects
Jankovic et al., 1996	ET	DB-PC II	25	Ona-A	Wrist flexors and extensors EMG guided	Mean dose: 108.6 u	Significant improvement of tremor amplitude and FD at 4 weeks	50% mild and 42% moderate weakness of hand muscles
Brin et al., 2001	ET	DB-PC II	130	On-A	Wrist flexors and extensors EMG guided	Low dose: FCR/ FCU:Each 10u - FCR/FCU:each 15u High dose: dose doubled/ muscle	Postural tremor improved at 4-16 weeks- kinetic tremor only at 4 weeks- no consistent improvement of QOL	Hand weakness in 30% of the low dose and 70% of the high dose
Mittal et al., 2018 Yale protocol	ET	DB-PC I	30	Inco-A	Customized approach: selecting muscles based on detail EMG screening. Mean injected muscles: 9	80-110 u (mean 100)	Significant improvement of NIHCGC & FTM tremor scores and PGIC at 4 and 6 weeks compare to placebo ($p<0.05$)	Subtle hand weakness:6 pts (20%), mod to severe weakness: 1 pt ; 6.6%
Mittal et al., 2019 Yale protocol	ET	DB-PC I	27	Inco-A	Customized approach: selecting muscles based on detail EMG screening. Mean injected muscles: 9	85-110 (mean 100)	Improvement of NIHCGC, FTM scores, PGIC & PDQLS at 4 and 6 weeks compare to placebo. P value less than 0.05 for the first three measures	Subtle hand weakness detected by ergometer in 24%, moderate weakness perceived by patient; 13.5 %
Somotus et al., 2017	ET and PD	OL-Pros III	ET 24 PD 28	Inco-A	kinematic surface measure of tremor amplitude 7 forearm/ 3 shoulder	70-300 u/limb	At 4 weeks tremor amplitude (FTM scale) was reduced by 47% . QOL improved by 26.5% over the period of study.	Bothersome hand and finger weakness ET: 8% PD: 14 %

ET: Essential Tremor; PD: Parkinson, DB-PC: double blind-placebo-controlled; OL: open label, FD: functional disability, NIHCGC: National Institute of Health collaborative genetic , FTM: Fahn Tolosa Marin scale, PDQLS: Parkinson quality of life scale, PGIC: patient global impression of change

treatment of hand tremor and not to inject extensor muscles that developed weakness after BoNT injections.

At Yale University, we investigated the efficacy of BoNT-A injection in 28 patients with ET using a customized approach [9]. The study was randomized, placebo-controlled and double blind with a cross over design (cross over with placebo or vice versa occurred 4 months after the first injection). The protocol was designed on the premise that all major forearm muscles showing evidence of tremor on electromyography (EMG) need to be injected to achieve the best possible response. The 8 major forearm muscles screened by EMG consisted of FCU, FCR, ECU, ECR, flexor digitorum superfecialis (FDS), flexor digitorum profundus (FDP), pronator teres and the supinator. A small, hand-held EMG unit detecting the rhythmic sound caused by tremor in the muscle was used for EMG screening. Only the forearm muscles that clearly demonstrated the typical sound caused by the tremor were injected. When the wrist extensors were injected, the dose was considerably smaller than the one used in the two previously discussed, blinded studies (2.5 units of incoA versus 10 or 15 units of onaA). The units of incoA and onaA are nearly comparable. In addition, since proximal muscles are often involved in ET, in every patient the biceps and triceps were injected with a fixed dose of 20 units as well. All patients also had injection of lumbrical muscles of the hand that often move the metacarpophalangeal joints in tremor. The mean number of injected muscles per patient was 9 and the mean total injected dose was 100 units (Table 3).

Table 3: Doses of incobotulinumtoxinA/muscle administered in the Yale study of ET.

Muscle	Dose of incobtulinumtoxinA (units)
Flexor carpi ulnaris	10
Flexor Carpi radialis	10
Extensor Carpi ulnaris	2.5
Extensor carpi radialis	2.5
Flexor digitorum sublimis	5
Flexor digitorum profondus	5
pronator Teres	10
supinator	10
Lumbricals	12.5 (5 x 2.5)
Biceps	20
Triceps	20

Supinator and wrist extensors were injected only in a few patients

At baseline, the tremor amplitude was evaluated on a scale of 0 to 4 using the National Institute of Health Collaborative Genetic Criteria (NIHCGC) tremor score as well as the Fahn Tolosa Marin scale for writing and spiral drawing. The hand strength was documented by an ergometer. Patient perception of tremor improvement was evaluated at 4 weeks after the first injection by the Patient Global Impression of Change (PGIC). The scores and hand strength were re-evaluated at 4 and 6 weeks after the first injection and then every 8 weeks

for the duration (32 weeks) of the study. The PGIC (0-7 scale) was re-evaluated every 4 weeks. The crossover between toxin and saline (or vice versa) took place at week 16. At 4 and 6 weeks after injection, there was significant improvement of NIHCGC & FTM tremor scores as well as the PGIC score compared to the placebo ($P < 0.05$). Both postural and kinetic tremor, improved. Adverse effects included subtle hand weakness in 6 patients (20%) mostly detected by ergometer and not perceptible by the patient. One patient (6.6%) developed moderate to severe weakness of wrist extensors.

Using the same protocol, our group at Yale conducted another blinded and placebo-controlled, crossover study with incobotulinumtoxinA on 30 patients with Parkinson tremor [10]. The EMG screening and injection schemes were exactly the same as our study for ET [9]. In addition to those indicated in the ET protocol, the evaluation scales included the Parkinson Disease Quality of Life Scale (PDQLS). At 4 and 6 weeks, the toxin group showed statistically significant improvement of NIH score, FTM scores for drawing and writing as well as the Patient Global Impression of Change (PGIC) ($P < 0.05$). In case of resting tremor, the tremor subset of Unified Parkinson's Disease Rating Scale (UPDRS) improved significantly at 4 and 8 weeks ($P < 0.001$). For postural/action tremor, a significant improvement was noted at 8 weeks ($P = 0.01$). The PDQLS improved more in the toxin group compared to the placebo group, but the values did not reach statistical significance. A subtle weakness detected by ergometer was seen in 37% of the patients; two patients (13.5%) developed moderate hand weakness which was limited to finger extensors in one patient. This study is the first double blind, placebo-controlled study investigating the efficacy and adverse effects of BoNT therapy in Parkinson disease tremor.

Recently, Rahimi et al. and Somatus et al. [14, 15], described the kinematic tremor analysis guidance technique that allows careful recording of tremor amplitude from multiple surface sensors placed on different muscles for a more precise identification of affected muscles in ET before BoNT injection. Using the same technique, Jog and his colleagues [11], conducted a prospective open label study of 52 patients (24 with ET and 28 with PD tremor) while screening 7 forearm and 3 proximal muscles for presence of tremor activity. Active muscles were injected with incobotulinumtoxinA. The injections were bilateral with the total dose per session varying from 70 to 300 units. Patients were followed for 3 injection cycles with follow-up every six weeks for 30 weeks. The efficacy of treatment was measured by Fahn-Tolosa-Marin tremor scale, quality of life (QoL) questionnaire, and maximum grip strength. At week 6 after BoNT-A therapy, the tremor amplitude was reduced by 47.7% in both arms. This improvement persisted to the end of the study (week 30). The QoL was improved by 26.5% ($p < 0.005$) over the period of study. A reduction of 30% ($P < 0.005$) was noted in functional interference due to tremor from weeks 6 to 30. Bothersome hand and finger weakness was noted in 8% of patients with ET and 14% of patients with PD tremor. The authors concluded that, by using their computer-assisted tremor analysis method, they were able to remove the variability inherent within the clinical assessment and enabled the patients to have improved bimanual upper limb functionality after the first treatment.

Recently, Niemann and Jankovic [16] retrospectively reviewed the results of BoNT treatment of various forms of tremors at Baylor University Hospitals between years 2010 and 2018. The studied group consisted of 91 patients, of whom, 53 had ET and 6 had PD tremor. Patients had multiple injections with a mean follow-up period of 2.5 years. In 94.6% of the patients, muscles were selected for BoNT-A injection based on anatomical localization. Injections were given mainly into the FCR and FCU with few patients receiving injections into pronator teres, flexor digitorum superfecialis, biceps or triceps muscles. The authors reported significant improvement of the tremor although sustenance of efficacy required 15-20% increase in the dose of BoNT-A over time. Approximately 12% of the patients developed notable weakness of hand and finger muscles; it is not clear what proportion of the 12% had ET or PD tremor. The authors reported a patient dropout rate of 40% after the first injection. Avoiding injection of wrist extensors and using mainly anatomical localization, the authors claim that anatomical localization may be sufficient for attaining a response comparable to that of Yale protocol (using EMG screening) or the kinematic tremor analysis technique for BoNT treatment of tremor. They emphasized the advantage of anatomical localization which includes lower expense and economy of time. As the authors acknowledged however, retrospective data are not hard evidence and need to be supported by careful blinded studies.

Discussion and Conclusion

The efficacy criteria set forward by the Assessment and Guidance Committee of the American Academy of Neurology requires publication of either A) two class I, or B) one class I and two class II studies for acceptance of "established efficacy" for a certain indication (Table 1). With the recent publication of one class I study on ET with positive results [9], and the two previous class II studies [7, 8], there is now established efficacy for BoNT-A therapy in ET. In the case of Parkinson disease tremor, the recent publication of one class I study from Yale group [10], qualifies BoNT therapy as a "probably" effective mode of therapy for this indication (one class I study). Botulinum toxin therapy is now recommended by movement disorder experts for treatment of ET and PD tremor when patients are not satisfied with pharmacotherapy, do not wish to have or cannot have the DBS procedure [16, 17]. The new techniques of EMG screening of 8 forearm muscles before injection combined with injection of two proximal muscles and hand lumbricals (Yale protocol) [9, 10] as well as the technique of computerized Kinematic screening of 7 forearm and three proximal muscles [11, 14, 15] have substantially reduced the incidence of hand and finger weakness following BoNT therapy for ET and Parkinson disease tremor. The importance of a customized injection approach instead of a fixed dose-fixed muscle technique has been emphasized recently, in a review published by Baylor Medical College in collaboration with Cleveland Clinic investigators [18]. In another recent open label study of 31 patients with ET [19], bilateral upper limb injections using computer-assisted tremor

analysis, significantly improved (P < 0.005) tremor amplitude (on FTM scale) and the quality of life (P < 0.005) between 6 weeks to 30 weeks post-injection. The authors concluded that bilateral injections with a personalized approach effectively improves ET and removes the clinical variability inherent in clinical assessment. Whether sole anatomical localization with injection of fewer muscles using a special customized injection approach as suggested by the Baylor group [16] can produce the level of efficacy and the low adverse effect profile similar to the two above mentioned, newly described techniques requires confirmation by future, prospective, double blind, placebo-controlled studies on this subject.

Conflict of Interest

Dr. Jabbari has no targeted conflict of interest.

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