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C. Pacchetti • F. Mancini • M. Bulgheroni • R. Zangaglia • S. Cristina • G. Sandrini • G. Nappi

Botulinum toxin treatment for functional disability induced by essential tremor

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Abstract This study aimed to improve botulinum toxin's (BTX) efficacy and to reduce its unwanted effects in the treatment of functional disability due to essential tremor (ET) of the hand. Twenty patients with disabling ET, not responding to conventional pharmacological therapy, were enrolled in this open-label study. Activities of daily living self-questionnaire (ADLS) and severity tremor scale (STS) were used to establish patients' functional disability and tremor severity. Accelerometry and surface electromyography were used to identify the arm muscles with tremorogenic activity during impaired positions. Global rating was used to measure treatment efficacy and unwanted effects. BTX type A was injected into the muscles principally responsible for impaired positions. After BTX treatment, there was a significant reduction in both severity and functional rating scales scores (ADLS and STS) and of tremor amplitude as measured with accelerometry and EMG. Adverse effects were limited to a slight third finger extension weakness in 15% of patients. BTX injections are effective and safe in reducing disability due to ET, if based on the criterion of functional selection.

Key words Essential tremor • Botulinum toxin • Functional disability

C. Pacchetti (✉) • F. Mancini • R. Zangaglia
S. Cristina • G. Sandrini
Parkinson's Disease and Movement Disorder Center
Neurological Institute IRCCS C. Mondino
University of Pavia
Via Palestro 3, I-27100 Pavia, Italy

M. Bulgheroni
Milan, Italy

G. Nappi
Neurological Institute IRCCS C. Mondino and
Neurological Institute
University of Rome La Sapienza
Rome, Italy

Introduction

The use of botulinum toxin type A (BTX) for the treatment of hand tremor has now been established [1-5]. Placebo-controlled studies have confirmed that chemodenervation with BTX may reduce tremor, which fails to improve with conventional pharmacological therapy, although no substantial functional improvements were noted [5]. Furthermore, the BTX efficacy may be limited by focal weakness of the injected muscles that masks the functional benefit derived from treatment [4, 5]. The aim of this open-label study was to demonstrate the efficacy and safety of a different procedure of BTX treatment, directed to improve the functional disability due to hand tremor and to reduce the risk of weakness, thus minimizing the side effects and maximizing the tremolytic effect of BTX.

In this view, before BTX treatment, we attempted to identify, in each individual, the most disabled functions and the muscles that were mainly involved in the generation of tremor causing disability. Subsequently, BTX treatment was performed only in those muscles responsible for tremor disability during specific functions.

Subjects and methods

Subjects

Twenty right-handed patients (7 men and 13 women, mean age 66.40 ± 3.77 years, range 60-72 years) with essential tremor (ET)

were enrolled in an open-label study after giving their informed consent.

The inclusion criterion was a diagnosis of ET (according to established criteria [6]) responsible for functional disability which failed to improve with conventional medication. Exclusion criteria were abnormal neurological signs other than tremor, recent exposure to tremorogenic drugs or other known secondary causes of tremor. The mean disease duration was 23 ± 19 years. All patients presented upper limb tremor and 6 also had head tremor. Eighteen patients had bilateral tremor and 2 had right arm tremor. Ten patients were being treated with propranolol (mean dosage 108 mg), 2 with primidone (750 mg) and a further 2 with trazodone (75 mg). These patients continued their usual therapy at a constant dosage for at least 1 month before the trial and throughout the study period. Six patients were drug-free at the time of the study (conventional pharmacological therapy for tremor having previously been withdrawn due to side effects).

The patients enrolled in this study were instructed to abstain from tremor-inducing or alleviating substances for at least 48 hours prior to evaluations.

Methods

The patients enrolled in this study underwent a neurological examination, scales application and neurophysiological assessment before BTX treatment and after 1, 3 and 5 months.

The activities of daily living self-questionnaire (ADLS) total score (0, best; 3, worst rating) [7] was used to assess the degree of functional disability caused by tremor during the performance of several activities of daily living (e.g. eating, dressing, writing, bathing). The severity tremor scale (STS) [8] was used to quantify tremor intensity.

Maximum benefit after BTX injection was defined as peak effect (PE) and rated on a scale of 0-4 (0, no effect; 4, marked reduction in severity and improvement in function). In each patient, a complication score (CS) was recorded (0, no therapeutic complications; 1, mild complications; 2, severe and disabling complications). Thus, the overall response to BTX treatment was expressed by the global rating (GR) obtained by subtracting CS from PE. The outcome of the treatment was considered to be positive when GR ≥ 2 [9].

The most severely affected functions involved the use of the dominant hand. Accordingly, we evaluated the clinical and neurophysiological data involving the right hand.

A priori, we decided to evaluate with accelerometry and surface electromyography (EMG) only the two positions corresponding to the ADLS activities with the highest scores. For example, item 14 of ADLS ("write a letter") was recorded while the patient was writing a short sentence; item 2 ("use a spoon to drink soup") was recorded while the patient was holding a spoon full of water.

Occasionally, when more than two ADLS items had equivalent scores, the patient was invited to choose the two tasks considered to be the most disabled.

Accelerometry and surface EMG were used to measure tremor frequency, and amplitude and pattern of muscle contraction. Eight channels of EMG data were acquired using surface electrodes and a telemetric transmitting unit (TELEMG, B|T|S, Italy). The position of the surface electrodes was carefully recorded to allow their accurate repositioning at follow-up sessions. EMG surface electrodes were placed on the extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), flexor carpi ulnaris (FCU), brachioradialis, pronator teres (PT), biceps and triceps of the right arm. All the muscles that showed an activity pattern synchronous with tremor during the performance of the two most impaired positions were candidates for treatment. Among these, we considered for injection only those muscles that showed tremor during both the impaired positions recorded. In accordance with literature data and our own experience about correlation of BTX treatment of ECR and ECU and unwanted weakness of third finger extension, we decided not to inject ECR or ECU unless they were found to be the only muscles responsible for disability. Applying these criteria, the selected muscles and their number varied from patient to patient depending on individual EMG pattern and most impaired positions.

Accelerometry data were acquired using an ultra-light, uniaxial, piezo-resistive miniature accelerometer (0.65 g), with linear sensitivity of 0.167 mV/ms^2 (Bruel & Kjaer). The accelerometer was placed on the dorsal side of the right hand, between the first and second metacarpal-phalanx joints. The EMG and accelerometry signals were acquired at a sampling rate of 500 Hz. The data were filtered between 2 and 15 Hz to eliminate signal components not related to tremor phenomena. Both the acceleration and EMG signals were amplified, filtered and transmitted to a computer (Pentium processor) for further processing. The EMG data were high-pass filtered (5 Hz) to eliminate cable movement artifacts, rectified and low-pass filtered (100 Hz). Both EMG and acceleration data were processed in order to obtain the power spectrum. The mean power frequency and the average amplitude were computed for each channel [10-12].

BTX (Dysport, Ipsen) was reconstituted with sterile, injectable, preservative-free 0.9% saline at a dilution of 20 U/0.1 ml. The BTX dosages were determined according to the mass of the selected muscles and on the basis of both our experience and literature data [1-4,13]. BTX was injected without EMG guidance.

A non-parametric Wilcoxon's signed-rank test was used to evaluate the efficacy of BTX injections at 1, 3 and 5 months after treatment on the following measures: ADLS total score, ADLS subscores relating to the two most impaired tasks (the mean score of the two most impaired tasks), ADLS subscores relating to all the other tasks (the mean score of all the other tasks) and STS total score. At the same times, we evaluated also power frequency and average amplitude data of the injected muscles. All the statistical tests were at the 0.05 significance level.

Results

All patients completed the study, and all but 1 asked to continue BTX treatment after the end of the study.

The most disabled ADLS were found to be "write a letter" (16 patients), "use a spoon to drink soup" (8 patients), "hold a cup of tea " (8 patients), "unlock your front door with the key" (4 patients) and "pour milk from a bottle or carton" (4 patients).

Among the 160 muscles recorded during the two most disabled functions, 60 showed an activity synchronous with tremor. Of these latter, we treated with BTX injections a total of 28 muscles that we found involved in both the most impaired positions, excluding carpi extensors, unless they

were the only muscles selected. In particular, 8 patients were treated in 2 muscles (6 patients in FCR and biceps and 2 patients in FCR and triceps) and 12 patients in 1 muscle (2 patients in FCR, 4 patients in ECR, 6 patients in biceps). No patients required BTX injections in 3 muscles. Furthermore, triceps was treated in 2 patients, ECR in 4 patients, FCR in 10 patients and biceps in 12 patients.

The mean total dosage of BTX administered to each patient was 95.50 ± 40.58 IU (range, 25-175). The mean dosage injected into each muscle was 68.21 ± 26.29 IU (range, 20-100). In particular, the mean dose injected into the ECR was 43.75 ± 12.50, into the biceps 85.42 ± 16.71, into the FCR 51.00 ± 24.01 and into the triceps 100.00 ± 0.

One month and 3 months after BTX treatment, ADLS total score ($p<0.05$, $p<0.001$) and STS score ($p<0.05$) showed significant improvements in relation to baseline, while at the fifth month they returned to baseline values. In particular, ADLS subscores relating to the two most impaired positions showed significant reduction 1 and 3 months after treatment ($p<0.0001$) while at the fifth-month follow-up, they returned to baseline values (Table 1). Moreover, even ADLS subscores relating to the other tasks showed significant variations 1 and 3 months after treatment ($p<0.001$) (Table 1).

One and 3 months after BTX treatment, but not at the fifth-month follow-up, mean amplitude of contraction of the injected muscles recorded by surface EMG during the two disabled tasks showed significant reduction of amplitude ($p>0.01$ and $p<0.05$) (Fig. 1).

Significant reduction of mean tremor amplitude recorded by accelerometry during the two most impaired tasks were found at 1 and 3 months after BTX treatment ($p<0.001$) (Fig. 2). No significant variations in mean power frequency of tremor recorded by accelerometry were found (data not shown).

Table 1 ADLS total score and subscores (the two most impaired tasks and the other tasks) and STS score before BTX treatment and 1, 3 and 5 months after treatment. Values are mean (SD)

	Baseline	Follow-up		
		Month 1	Month 3	Month 5
ADLS				
Total score	33.10 (14.83)	19.10 (9.55)*	17.70 (8.80)**	32.80 (13.90)
Most impaired tasks	2.60 (0.51)	0.90 (0.73)***	1.20 (0.63)***	2.50 (0.50)
Other tasks	2.10 (0.50)	1.30 (0.50)**	1.30 (0.50)**	1.90 (0.50)
STS	2.80 (0.77)	1.80 (1.11)*	1.80 (1.11)*	2.30 (1.03)

ADLS, activities of daily living self-questionnaire; *STS*, severity tremor scale; ***$p<0.0001$ vs. baseline; **$p<0.001$ vs. baseline; *$p<0.05$ vs. baseline

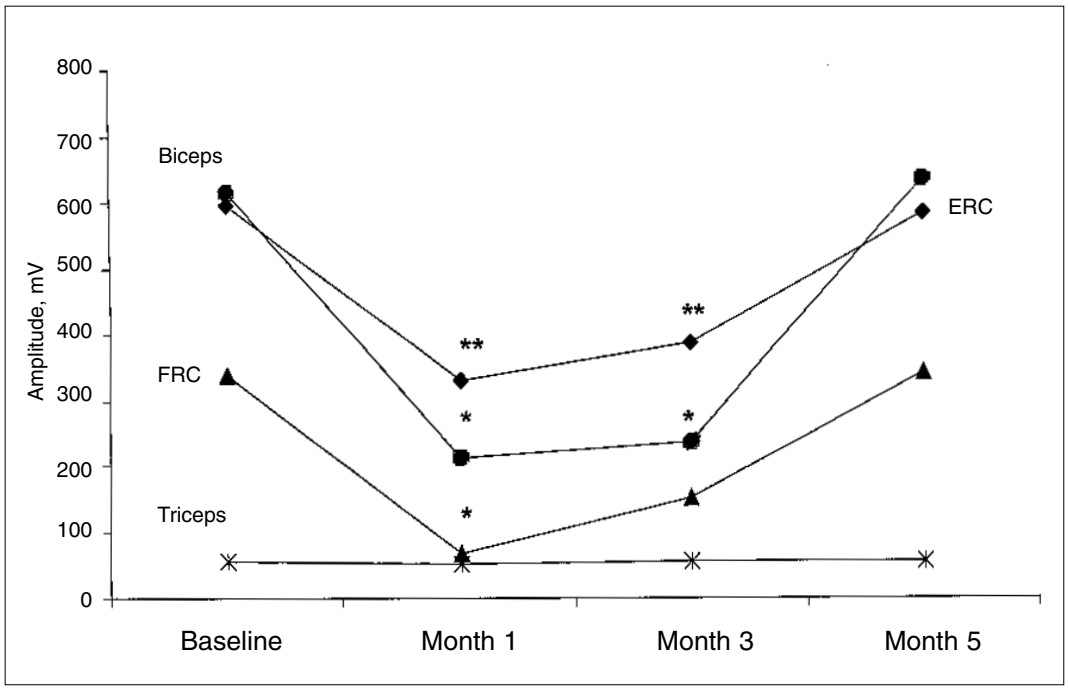

Fig. 1 Mean amplitudes of contraction (mV) of the injected muscles recorded with surface EMG during the two most impaired tasks. *FRC*, flexor carpi radialis; *ERC*, extensor carpi radialis. * $p<0.05$; ** $p<0.001$

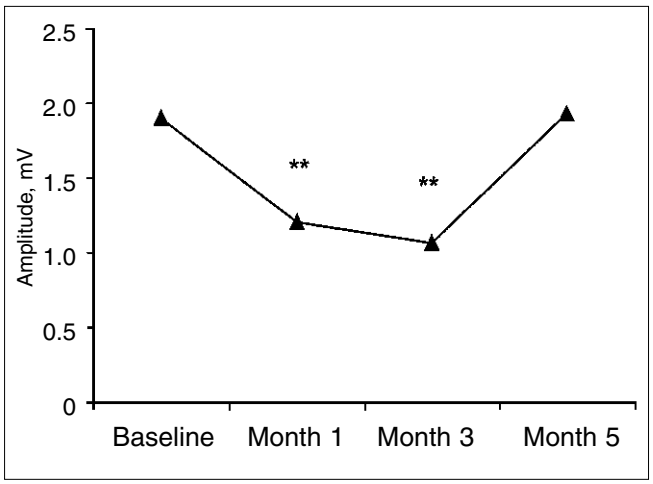

Fig. 2 Mean tremor amplitudes (mV) recorded by accelerometry during the two most impaired tasks before BTX treatment and after 1, 3 and 5 months. $**p<0.001$

The mean PE of the entire sample was 2.7 ± 0.7, the CS 0.3 and the GR 2.4 ± 0.7. In particular, the PE was 4 in 6 patients, 3 in 6 patients, 2 in 6 and 1 in 2 patients while the CS was 0 in 10 patients, 1 in 7 patients and 2 in 3 patients. Eleven patients had a GR of 2, 3 patients had a GR of 3, 2 patients had a GR of 4 while the remaining four recorded a GR of 1.

Adverse effects were limited to a third finger extension weakness (CS 2) in 3 patients (15%) who were administered 50 IU BTX in the ECR. This condition did not interfere with the patients' activities of daily living more than tremor did prior to the treatment. Patients with CS = 1 showed temporary and slight extension weakness of the third and fourth fingers. These patients were administered 50 IU BTX in the ECR. This condition did not interfere with improvement of hand function, as referred by the patients.

Discussion

Only 50%-60% of patients with ET, the most common movement disorder [14], improves functional disability pharmacologically. BTX injections in arm muscles can now be considered a useful but additional therapy for ET patients who fail to respond to standard pharmacological medication.

In previous studies [1-4], with the aim of reducing tremor severity, BTX injections were given in all the muscles involved in the production of tremor, as observed during standard arm positions (i.e. rest, posture, nose/finger). Therefore, the dosages of BTX given (and the sites of injection selected) were often higher than those strictly compatible with patients' functional requirements. In particular, inoculation of ECR was always included in treatment schedules. The high level of focal weakness, in fact, has often been cited as the main and most severe adverse effect of this treatment, capable of reducing its efficacy and ease of application in 45%-50% of patients [2, 3]. Consequently, to minimize the side effects and to maximize the tremolytic effect of BTX, some authors have suggested that "an individualization of site of injection and dosage may provide more optimal results" [3].

In this perspective, the aim of our trial was to test a procedure of BTX administration able to maintain BTX efficacy and, at the same time, to reduce its unwanted effects by limiting the number of treated muscles, excluding, when possible, ECR treatment.

The main goal of our study was to demonstrate that this individualized technique of BTX administration is useful to reduce BTX side effects without reducing its efficacy, which has been previously proved.

We shifted the main goal of BTX treatment from the reduction of tremor severity to the improvement of tremor-related disability that induces the loss of specific functional ability. Accordingly, we selected the two most impaired functions, in each patient's opinion, as emerged from ADLS scale. To reduce disability during these activities, we selected the muscles that increased or first showed their activity in synchronicity with tremor during both the most disabled ADL tasks, i.e. when patients assume the upper limb postures that mimic the most disabled functions. In this way, the individualization of BTX treatment consists in selection and treatment only of those muscles responsible for tremor-related disability during the two selected tasks or positions.

Furthermore, we reduced the number of muscles to be injected and we excluded extensors carpi, unless they were the only muscles responsible for tremor activity during disabled functions. This choice was made on the basis of our previous experience that evidenced the correlation between extensors carpi treatment with BTX and frequent weakness of extension of the third finger.

The exclusion of extensor carpi muscles from most of BTX treatment schedules did not reduce global efficacy of BTX and permitted the reduction of unwanted effects. These results suggest that BTX injections in proximal arm muscles are not associated with unwanted weakness and are helpful in reducing tremor intensity and disability.

In fact, the significant reduction of ADLS subscores relating to the two most disabled tasks indicates that BTX treatment was correctly aimed to the muscles actually responsible for disability during those functions. Moreover, the significant reduction of ADLS total score and subscores relating to the less disabled tasks after BTX treatment indicates a reduction of disability due to tremor also during the performance of activities of daily living in general. The STS also improves after BTX injections. Thus, even treating the muscles selected studying only 2 impaired functions, tremor reduction in these few muscles allowed an improvement of patients' general disability.

By reducing to the lowest level possible the overall quantity of BTX administered to a patient, the risk of toxin diffusion to adjacent non-tremorogenic muscles is reduced [15, 16] and, as a result, unwanted weakness is minimized, even if BTX is injected without EMG guidance.

In our study, only 15% of patients showed third finger

extension weakness due to BTX treatment of ECR. This outcome, supported by the fact that all but one of our patients expressed a wish to continue the treatment when the study was over, underlines the safety of our method of assessment. These results indicate the usefulness and safety of BTX injections in arm muscles to decrease disability due to ET when administered according to individualized schedules.

Sommario *L'obiettivo dello studio è stato quello di migliorare l'efficacia e ridurre gli effetti collaterali della tossina botulinica (BTX) nel trattamento della disabilità funzionale indotta dal tremore essenziale (TE) delle mani. In questo studio in aperto sono stati arruolati 20 pazienti con TE disabilitante, non responsivo alla terapia farmacologica convenzionale.* L'activities of daily living self-questionnaire *e la* severity tremor scale *sono state utilizzate per valutare la disabilità funzionale dei pazienti e la severità del tremore. L'accelerometria e l'EMG di superficie sono state impiegate per identificare i muscoli degli arti superiori con attività tremorigena durante il mantenimento delle posture disabilitate. La* global rating *è stata utilizzata per misurare l'efficacia del trattamento e gli effetti collaterali. La BTX tipo A è stata iniettata nei muscoli identificati come responsabili della disabilità funzionale tremorigena. Dopo il trattamento con BTX, è stata registrata una significativa riduzione del punteggio della ADLS e della STS e dell'ampiezza del tremore, rilevata con l'accelerometria e l'EMG. Gli effetti collaterali consistono in una moderata riduzione della forza nell'estensione del terzo dito, presente nel 15% dei pazienti. Se somministrate in base ad un criterio di selezione funzionale, le infiltrazioni di BTX sono più sicure ed efficaci nella riduzione della disabilità dovuta al TE.*

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