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Tremor and Other Hyperkinetic Movements

Brief Reports

A Pilot Study of Botulinum Toxin for Jerky, Position-Specific, Upper Limb Action Tremor

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Abstract

Background: We aimed to investigate the efficacy and safety of botulinum toxin (BT) injections for jerky action tremor of the upper limb.

Methods: We performed an uncontrolled, prospective study of electromyography (EMG)-guided BT injections for jerky, position-specific, upper limb action tremor. The primary outcome was clinical global impression at 3–6 weeks after baseline.

Results: Eight patients with jerky, position-specific action tremor involving the upper limb were consecutively recruited. After a median follow-up of 4.4 weeks (interquartile range [IQR] 3.6–6 weeks), four of them rated themselves as "improved" and two as "much improved." Five of these six subjects reported improvements in specific activities of daily living (bringing liquids to mouth, feeding, shaving, and dressing). Upper limb subscore of the Fahn–Tolosa–Marin Tremor Rating Scale (FTM) significantly decreased from 4.5 (4–6) to 3 (2–5) ($p=0.01$).

Discussion: This pilot, prospective cohort study suggests that EMG-guided BT injections may improve jerky, position-specific, upper limb action tremor. Placebo-controlled studies evaluating larger samples of patients are warranted to confirm these findings.

Keywords: Upper limb tremor, botulinum toxin, action tremor

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Ethics Statement: This study was performed in accordance with the ethical standards detailed in the Declaration of Helsinki. The authors' institutional ethics committee has approved this study and all patients have provided written informed consent. All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

Introduction

The efficacy of pharmacological treatment for upper limb tremors is often disappointing. In this context, use of botulinum toxin (BT) injections has had mixed results. Some studies have described significant improvement of both tremor and function,[1,2] but others have failed to confirm those benefits.[3–5]

More recently, a retrospective study of open-label BT injections for proximal upper limb tremor reported moderate or marked subjective benefit in 63% patients.[6] These encouraging results were related to the application of an individualized injection strategy in accordance with tremor characteristics. However, no details were provided about BT doses and injection sites.

Here we report a pilot, uncontrolled, prospective cohort study investigating the efficacy and safety of BT for jerky, position-specific, upper limb action tremor.

Methods

We recruited consecutive patients presenting with jerky, position-specific, postural and kinetic tremor of the upper limb to a botulinum toxin clinic at the National Hospital for Neurology and Neurosurgery (London), during a period of 10 months. Here we use the term "position-specific" to describe tremor appearance or exacerbation in particular positions of the upper limbs (e.g. tremor worsening while slowly supinating or pronating the forearms with the upper limbs flexed at the elbow). Tremor involved the proximal (i.e. shoulder abduction/adduction or internal/external rotation) and/or distal upper limb (forearm pronation/supination or hand tremor). Participants were naïve to BT and refractory or intolerant to drug therapy, or preferred a trial of BT to trials of medication after balancing the risks and benefits against the alternatives. Non-significant tremor severity and general contraindications to BT were exclusion criteria.

Our primary outcome measure was clinical global impression (CGI) at the follow-up visit (i.e. "much worse," 1; "worse," 2; "no change," 3; "improved," 4; "much improved," 5; as rated by the patient). Secondary outcomes were change in the upper limb tremor subscore of the Fahn–Tolosa–Marin Tremor Rating Scale (FTM),[7] improvement of specific activities of daily living (ADL) (patients were asked specifically about feeding, bringing liquids to mouth, hygiene, dressing, writing and working), and occurrence of adverse events (particularly weakness).

The injection strategy, including muscle selection and dosages, was individualized according to tremor characteristics. Utilization of electromyography (EMG) guidance increased the likelihood of injecting tremulous muscles and sparing non-tremulous ones, thus maximizing efficacy while avoiding muscle weakness as a side effect. Abobotulinum toxin A (Dysport®) was used, in a concentration of 20 units (U) per 0.1 mL. All BT injections were performed by C.C.

Clinical and demographic information was collected during initial assessment by T.A.S. The follow-up visits were performed 3–6 weeks after baseline by T.A.S. and C.C. Baseline and follow-up upper limb FTM subscores were rated by T.T., who analyzed video records blinded for the time point. Ethics approval and the participant's written informed consent were obtained.

Outcome measures were continuous variables, and were expressed as medians (interquartile range). Differences among those variables, before and after treatment, were analyzed using Wilcoxon signed-rank test. The statistical package was STATA version 13 software, and $p<0.05$ was considered significant.

Results

We recruited eight patients with predominantly postural and kinetic, upper limb tremor (five males, three females), with a median age of 70 years (IQR 56–73 years) (Table 1). Tremor was also present at rest in three patients. Tremor was unilateral or asymmetric in all participants. Proximal tremor was predominant, but the shoulder and forearm were involved in most subjects. Tremor was jerky in character in all participants. Moreover, tremor also showed position-specificity in all subjects. Indeed, we observed significant tremor worsening when we asked the patients to slowly supinate or pronate the forearms with the upper limbs flexed at the elbow. Four subjects were non-responsive and/or intolerant to previous drug treatments and another four were treatment naïve. Two patients had head tremor and one had mild cervical dystonia as additional neurological features.

A total of 10 upper limbs were treated, and 14 individual muscles injected. Our approach was to inject, in an individualized fashion, the following muscles according to the clinical presentation: shoulder abduction movement, deltoid (one) and supraspinatus (one); shoulder adduction, pectoralis major (one) and teres major (one) (also arm internal rotation); scapular rotation, trapezius (one); shoulder external rotation, infraspinatus (five) and teres minor (one); arm internal rotation, latissimus dorsi (one) and subscapularis (one); forearm supination, supinator (five); forearm pronation, pronator teres (five) and pronator quadratus (five); wrist extension/abduction, extensor carpi radialis (two); wrist flexion/adduction, flexor carpi ulnaris (one) (Table 1). The median total dosage per participant of Dysport® was 205 IU (190–300 IU) (Table 2).

After a median follow-up of 4.4 weeks (IQR 3.6–6 weeks), four of the eight participants reported themselves to be "improved" and two "much improved." The two other subjects reported no change in tremor. Importantly, five of the six subjects who reported improvement also described functional benefit in specific ADL, including bringing liquids to the mouth (four), feeding (three), dressing (one), shaving (one). FTM upper limb subscores (possible range 0–12) significantly decreased from a median of 4.5 (4–6) to 3 (2–5) ($p=0.01$, Wilcoxon signed-rank test).

Three subjects experienced muscle weakness following injections, but this was only clinically significant in one participant whose weakness affected the shoulder (Table 2). Our sample is too small to correlate efficacy and safety with specific clinical patterns or injection strategies.

Discussion

In this pilot, prospective cohort study we investigated EMG-guided BT injections for jerky, position-specific, upper limb action tremor. Six out of the eight patients reported a beneficial effect. In five of these, it included improvement in one or more ADL, for example bringing liquids to the mouth and feeding. Efficacy was further supported by a significant decrease in the FTM upper limb subscore.

Importantly, BT was well tolerated in our cohort, with significant weakness in only one patient. EMG guidance and an individualized treatment likely contributed to there being limited adverse effects.

Despite the small sample size and the open-label, uncontrolled administration of BT, these results are encouraging. Significantly, this is the first prospective study evaluating BT for jerky, postural, and kinetic tremor of the upper limb. Moreover, our sample included medication-refractory patients with proximal "wing-beating" tremor,

Table 1. **Clinical Characteristics**

ID	Sex	Age	P. Hand	UL Involvement by Tremor			Other	Previous Treatments/Response	Injection Strategy	
				Side (R/L)	Segments Affected	Rest (R), Postural (P), Kinetic (K)			Muscles/Dose	Total Dose
1	F	71	L	L	S, A, H	R, P, K	Head tremor; unsteady gait (stable)	PRO, TPM, GBP, PMD/NR, IT	Left: T min 80, Infraspin 80, L dorsi 80	240
2	M	76	R	R	S, A, F	P, K	Nil	Nil	Right: Infraspin 80, Sup 30, ECR 30, P teres 40, Deltoid 20	200
3	M	71	R	L>R	S, A, F	P, K	Nil	Unknown/NR	Right: Infraspin 50, P teres 50, Sup 50, P quadratus 50	200
									Left: Infraspin 50, P major 50, Subscapularis 100, P teres 50, P quadratus 50, Sup 50	350
4	F	69	R	L>R	S, A>F	P, K	Nil	Unknown/NR	Right: Infraspin 100, P major 100, Trapezius 100	300
									Left: Infraspin 100, P major 100, Trapezius 100	300
5	M	61	R	R>L	S, A, F	R, P, K	Head tremor	PRO/NR, IT	Right: P quadratus 20, Supraspin 40, T major 100, P teres 50	210
6	M	51	R	R>L	F>H, A, S	P, K	Nil	Nil	Right: P teres 60, P quadratus 40, Sup 40	140
7	M	43	R	R=L	H, F>S, A	R, P, K	Nil	Nil	Right: FC ulnaris: 120, EC radialis 40	160
8	F	75	R	R	F>S, A	P, K	Mild cervical dystonia	Nil	Right: Sup 40, P teres 30, P quadratus 40, Infraspin 80	190
Median (IQR)		70 (56–73)								205 (190–300)

Abbreviations: A, Arm; ECR, Extensor Carpi Radialis; F, Forearm; FC ulnaris, Flexor Carpi Ulnaris; GBP, Gabapentin; H, Hand; Infraspin, Infraspinatus; IT, Intolerance; L dorsi, Latissimus Dorsi; NR, Non-response; Other, Other Neurological Problems; PRM, Primidone; PRO, Propranolol; P. hand, Preferred Hand; P major, Pectoralis Major; P quadratus, Pronator Quadratus; P teres, Pronator Teres; S, Shoulder; Sup, Supinator; Supraspin, Supraspinatus; T min, Teres Minor; TPM, Topiramate; UL, Upper Limb.
Dosage is in units of Dysport®.

Table 2. **Outcomes**

ID	Follow-up (weeks)	Side	Global Clinical Impression	Upper Limb CRS for Tremor Subscore		Improvement in Specific Activities of Daily Living	Adverse events
				B	F		
1	3.7	L	3	5	5	None	Marked shoulder weakness
2	3	R	4	2	0	BLM	Mild shoulder weakness
3	6	R	4	5	3	BLM (mild)	None
		L		6	6		
4	6	R	5	3	1	Feeding and BLM	Mild weakness
		L		6	5		
5	5	R	5	6	3	Feeding, BLM, shaving, dressing	None
6	3.6	R	4	4	2	Feeding (mild)	None
7	3.6	R	3	4	4	None	None
8	6	R	4	4	2	None	None
Median (IQR)	4.4 (3.6–6)		4 (3.5–4.5)	4.5 (4–6)	3 (2–5)		

Abbreviations: B, Baseline; BLM, Bringing Liquids to Mouth; CRS, Clinical Rating Scale; F, Follow-up; IQR, Interquartile Range; L, Left; R, Right.
Clinical global impression: much improved (5), improved (4), no change (3), worse (2), much worse (1).

which can be very disabling by interfering with bringing food or liquids to the mouth.[6]

BT injections have a fairly accepted role in managing head tremor, tremulous spasmodic dysphonia, and primary writing tremor.[8,9] However, studies of the effect of BT on other upper limb tremor types have had heterogeneous results in terms of functional disability. Although a placebo-controlled trial in multiple sclerosis-associated tremor[1] and a case report in anti-MAG neuropathy-related tremor[2] described significant improvement of both tremor and function, other studies of BT in essential or parkinsonian tremor failed to demonstrate functional improvement[3,4] and/or to show change in objective tremor measures.[5]

More recently, a retrospective, open-label study of BT for proximal upper limb tremor reported moderate or marked benefit in 63% of 19 patients.[6] The adoption of an individualized injection strategy was most likely to be related to this better outcome.[6] Similarly, we applied an individualized strategy of BT injection, in accordance with tremor characteristics.

Dystonia was present in only one patient in our cohort, and did not affect the upper limb (Table 1). However, upper limb tremor in study participants had clinical characteristics akin to dystonic tremor/tremor associated with dystonia.[10] Tremor was "jerky" in character, position specific, predominantly postural/kinetic, and unilateral/asymmetric. Although dystonic tremor is classically defined by the coexistence of dystonia in the same body part,[11] recent studies suggest that patients can have isolated tremor with dystonic features but without overt dystonia[12,13] and develop dystonia only later in life.[14] In the absence of reliable biomarkers for dystonic tremor, we adopted a descriptive label of "jerky, position-specific, upper limb action tremor," but highlighting the phenomenological similarities between dystonic tremor[10] and that of the patients described here. This is relevant because evidence to guide treatment of dystonic tremor is scarce, and the efficacy of drug treatment generally disappointing.[8] Interestingly, in a previous retrospective study of individually tailored BT injections for upper limb tremor, significant improvements were observed in four out of six patients with dystonic tremor.[6]

We acknowledge that our study has significant methodological limitations. These include a small sample size, the absence of a control group and the open-label nature of the intervention.

Nevertheless, the existence of a common trend among the follow-up clinical global impression of the patients, blinded tremor rating scale scores, and modification of ADL hints at a genuine beneficial effect.

In conclusion, this small, open-label and uncontrolled prospective cohort study suggests that individualized EMG-guided BT injections may reduce tremor and improve function in patients with jerky, position-specific, upper limb action tremor, with few side effects. We believe that these findings should encourage further investigation about the role of individualized BT treatment for upper limb action tremor, through the performance of randomized, controlled, well-powered clinical trials.

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