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High doses of botulinum toxin effectively treat disabling up-going toe

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Abstract

Involuntary up-going toe can be a disabling consequence of dystonia or spasticity. In this study, we treated eight patients with botulinum toxin (BTx) in the extensor hallucis longus (EHL) and applied objective and subjective outcome measures to determine treatment efficacy. Using 100% higher doses than generally reported, patients noted 62±20% mean benefit and scores on a modified Fahn–Marsden Dystonia Scale decreased significantly by 1.8±0.6 ($p=0.010$). High doses (up to 160 BTx A units) into the EHL were safe and dosage correlated highly and significantly with treatment efficacy ($\rho=0.859$, $p=0.006$).

Keywords: Botulinum toxin; Treatment efficacy; Treatment safety; Dystonia; Muscle; Spasticity; Up-going toe; Striatal toe

1. Introduction

Great toe extension spasms can result in gait imbalance, difficulty wearing shoes, and painful calluses and metatarsal ulcers [1–3]]. The primary muscle involved, the extensor hallucis longus (EHL), can be "overactive" in multiple conditions: dystonia, Parkinson's disease (striatal toe) [4] and spasticity (hitchhiker's toe) [2]. Botulinum toxin (BTx) therapy has been reported as a treatment option with relative success in primary and secondary foot dystonia [5–10]], and a few authors have addressed problematic up-going toe [1,3,11]. In the past fifteen years, the doses generally reported for the EHL are in the 40 Botox® U range [3,8,12]. This is the first case series to analyze BTx dose-response outcomes in treating problematic large toe extension across different diseases.

2. Methods

Subjects receiving injections in the EHL were identified using a database of all BTx treated patients at the Clinical Motor Physiology Laboratory of Columbia University Medical Center (CUMC) between January 1990 and September 2006. The EHL was injected with diluted BTx type A (Botox®) at 10 units/0.1 ml, or type B (Myobloc®) at 500 units/0.1 ml through a hollow core needle under electromyographic guidance approximately every 3 months. A relatively small and easily isolated muscle, the EHL was located using EMG guidance above the bimalleolar line lateral to the tibial crest. For comparative purposes, doses were normalized into "Botox® equivalent units (U)" at 50:1 Myobloc® to Botox®.

All patients receiving EHL injections were selected, evaluated and treated by the same physician (SLP). Severity of involuntary toe extension was scored at the initial visit, and at the time of maximum benefit (6±1 week) once a stable BTx dose was reached; based on a modified Fahn–Marsden Dystonia Scale (0=no spasms; 1=occasional spasms, no significant functional impairment; 2=intermittent spasms, mild impairment 3=frequent spasms, moderate impairment; 4=constant spasms that can be passively overcome, severe impairment). Patients also made subjective assessment of up-going toe improvement based on a visual analogue scale rated in 10% increments (0%=no improvement, 50%=frequency and severity of spasms reduced by half, 100%=maximum benefit, return to baseline). All patients were cognitively capable of evaluating and communicating this response, and participated in accordance

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Table 1
Patient data

Pt	Age at onset (years)	Age started BTx (years)	Gender	Diagnosis	Follow-up (years)	Severity pre-BTx	Severity at max benefit	Subjective treatment response (%)	Initial EHL dose (U)	Stable EHL dose (U)	Duration of effect (months)	Total dose (U)
1	60	62	M	Task specific foot dystonia	11	2	0	90	60	160	7–8	160
2	8	12	M	Generalized dystonia	11	4	1	80	35	160	2.5	400
3	58	60	F	Post-stroke hemiparesis	1	4	1	80	100	100	2.5	300
4	74	79	F	Post-stroke hemiparesis + late-onset dystonia	1	4	2	60	60	80	3	400
5	67	69	F	Post-stroke hemiparesis	7	3	1	60	60	75	3	400
6	55	58	M	Parkinson disease: off dystonia	3	3	1	50	50	50	3	200
7	7	48	M	Generalized dystonia	13	2	1	50	40	40	3	240
8	12	36	M	Generalized dystonia	2.5	4	3ß	30	50	75	3.5	400

Pt = Patient; U = Botox® equivalent units.

with established practice guidelines. Data were analyzed using the Wilcoxon Signed Rank test and Spearman's rho correlation for nonparametric data.

3. Results

Eight patients (3 women), average ± SD age: 53 ± 20 (range: 12–79 years), treated with BTx into the EHL were analyzed (Table 1). Some had dystonia (1 adult-onset task specific, 1 Parkinson disease "off", 3 childhood-onset generalized) and 3 patients had post-stroke hemiparesis. They were all on optimal oral medications throughout their follow-up of 6.2 ± 4.9 years. The average impairment severity was 3.3 ± 0.9. In one patient, the EHL was the only target; the others had foot and toe posturing with regimens involving additional muscles.

Mean initial BTx doses in the EHL averaged 56 ± 20 U, and were increased in 6 patients. Final stable BTx doses averaged 93 ± 46 U, ranging from 40–160 U. All patients reported substantial benefit, with 62 ± 20% improvement (ranging from 30–90%) while severity scores decreased by 1.8 ± 0.6 ($p = 0.01$). Average positive effect lasted 3.4 ± 1.5 months. There were no reported adverse effects.

The three patients (2 dystonic, 1 spastic) receiving highest BTx doses (100–160 U) reported 80–90% improvement in their up-going toe symptoms. Two of the three patients injected with intermediate doses (75–80 U) reported 60% improvement, one reported 30% benefit. The two cases receiving lowest doses (40–50 U) reported 50% improvement. BTx dose had a high and positive significant correlation with subjective treatment response ($\rho = 0.859$, $p = 0.006$) and showed similar trends with objective improvement ($\rho = 0.689$; $p = 0.059$). Subjective and objective responses correlated significantly with each other ($\rho = 0.707$; $p = 0.050$).

4. Discussion

Muscles controlling foot and toe movements require higher BTx doses compared to functionally similar muscles for the hand and fingers [13]. We found that patients benefited from an average EHL dose of 93 U, ranging up to 160 U. This is more than double the generally reported doses, and compares favorably with two studies in post-stroke spasticity where, high doses in the EHL, up to 100 U, showed notably good results [1,2]. Two patients (3 and 4) had unsuccessful BTx injections into the EHL (10–50 U) prior to coming to CUMC. They showed marked improvement with higher doses. Five patients did not receive optimal EHL treatment due to dose-limiting factors: patients 4, 5 and 8 were on maximal BTx regimens (400 U) reducing BTx availability to the EHL; patients 6 and 7 had great toe extension and flexion spasms. They required balanced injections into antagonists so low doses into the EHL (40–50 U) were used to prevent excessive toe flexion. None of our patients reported adverse effects and weakness of great toe extension was without functional significance. Probably due to the anatomical location of EHL, there was no evidence of BTx spread to other muscles.

We found that there was a highly positive correlation between BTx dose and treatment efficacy across a number of conditions and varied injection regimens. Although our study is limited by its retrospective, open-label nature, and small heterogeneous sample size, the results are significant and clinically relevant. These preliminary observations suggest that injecting the EHL with higher than currently reported BTx doses is safe, effective, and results in excellent relief of great toe extension spasms. A larger, blinded, placebo-controlled study is required to investigate further whether BTx dose to the EHL is a predictor of treatment efficacy, independent of underlying etiology or clinical complexity.

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