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Long Term Follow-up of Botulinum Toxin Therapy for Focal Hand Dystonia: Outcome at 10 or More Years

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Abstract

Background—Prior studies have explored the efficacy and safety of BoNT treatment for FHD, but none have followed a large number of patients for 10 or more years.

Methods—Retrospective study, with benefit and weakness assessed on a 0-4 subjective scale. Demographic, clinical and treatment characteristics were analyzed using t-tests and Pearson correlations.

Results—20 FHD patients had 10 years or longer treatment. Inter-injection intervals were variable. Musicians were more likely to wait longer between injections and had less complex dystonia. There was a trend for larger benefit in women and with shorter intervals. The dose increased over time. Dystonia characteristics did not predict response or side-effects, but benefit magnitude predicted longer compliance. No serious side-effects or antibody-mediated resistance occurred.

Conclusion—This is the longest reported period of BoNT treatment in the largest FHD cohort. BoNT therapy for FHD remains safe and effective after more than a decade of treatment.

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Keywords

botulinum dystonia “focal hand dystonia”

Introduction

Focal hand dystonia (FHD) is a task specific focal dystonia (1). Botulinum neurotoxin (BoNT) injection is an effective treatment (2,3), reducing pathologic neuromuscular junction hyperactivity (4). We previously reported the safety and effectiveness of BoNT injections for FHD in patients receiving injections for up to 6 years (5). We continue to follow a large cohort, with 20 patients now treated for 10 years or longer.

Methods

Patients

Patients were selected from the NIH BoNT clinic database. Diagnosis was established by initial evaluation and confirmed by ongoing observation.

BoNT injections

Subjects returned for repeat treatment when they felt that reinjection was necessary, no more frequently than every 3 months. The initial dose and targets were based on clinical judgment (6), with the starting dose chosen at the lower end of the range and subsequent adjustments. Injections were performed under EMG guidance, as previously described (7), rarely supplemented by ultrasound. OnabotulinumtoxinA (Botox®, Allergan, Inc.) at a concentration of 50-100 U/ml was used for each injection, except one single injection of RimabotulinumtoxinB (Myobloc®, Solstice Neurosciences, Inc.) in one patient.

Patient evaluations

Muscle strength was assessed using the MRC scale. The toxin distribution and dose were adjusted based on report of weakness and benefit from previous injections. Benefit was assessed on a subjective scale from 0 to 4, based on percent restoration of normal function: 0= none, 1= minimal (1-25% restoration of function), 2= mild (26-50%), 3= moderate (51-75%), 4= excellent (76-100%). The patients self-assessed weakness following the previous injection using a similar scale, as 0 (none), 1 (<25% reduction in normal strength), 2 (26-50%), 3 (51-75%), or 4 (76-100%). The rating procedures and treatment guidelines were consistent throughout the study, and all the information was charted in a Microsoft Access database.

Data analysis

Student's t test and Pearson correlations were used, with $p<0.05$ as significance threshold. All averages are presented ± standard deviation.

Results

Out of 440 patients in our database, 214 patients with FHD have been treated at least once; 20 patients continued treatment 10 years or more. Five patients had professional musician's dystonia and 15 were employed in clerical positions. Dystonia types are shown in Fig.1. Demographic and treatment characteristics are presented in Table 1.

The musicians were more likely to wait longer between injections (19.9±12.4 months for musicians vs 7.7±2.3 for non-musicians, $p<0.002$). There was a trend for shorter inter-injection intervals to be associated with higher benefit (Pearson = -0.44, $0.05<p<0.1$).

Most patients (11/20) experienced mild average benefit (grade 2). Weakness was similarly mild with 9/20 reporting an average grade 2 weakness, with no correlation between benefit and weakness. There was a trend towards larger benefit in women (55.9%±15.2 in women vs 37.4%±19.5 in men, $p=0.057$).

The patients received a higher mean dose at the end of the follow-up period compared to the initial treatment (49.9 vs. 24.9 units respectively, $p<0.00005$). Since the first dose is typically purposefully low, we repeated the analysis excluding the first injection, with similar results (49.9 vs 31.0 units, $p<0.002$). The benefit was higher with the last injection compared to the initial (47.3% vs. 26%, $p=0.039$). No significant correlation was found between dose and benefit at each visit, or between dose and weakness.

To evaluate possible outcome predictors, we performed subanalyses looking at the number of muscle groups injected, divided into: supinator/pronator, hand intrinsics, forearm flexors, forearm extensors, and proximal muscles. 18/20 patients had involvement of the forearm flexors, 16 of the extensors, 9 of the intrinsic hand muscles, 6 of the pronators/supinators, and 4 of proximal arm/shoulder muscles. Most patients had involvement of more than one muscle group, average 1.7±0.8 in musicians vs 3.1±0.8 in non-musicians, $p=0.003$. This number did not correlate with either benefit or weakness.

No patients developed immunity over the duration of follow-up. All patients tolerated the discomfort of multiple injections well; none discontinued treatment due to discomfort. There were no serious adverse effects.

Eleven of the 20 patients are still receiving injections in our clinic. 2 patients discontinued treatment due to insufficient response after 5 and 26 visits respectively. Two moved out of the area and 5 were lost to follow-up.

We compared this group with the patients who had less than 10 years of treatment. Among the latter, a higher proportion were professional musicians (58% vs. 25%). The patients who discontinued therapy after less than 10 years had significantly lower benefit with the last injection (32% vs. 47.2%, $p<0.005$), and the most common reason for discontinuation was insufficient benefit (62.5%).

Discussion

This is the largest FHD cohort with the longest follow-up period reported to date. Few prior reports focused on FHD; most included only a few patients in larger dystonia populations and none followed subjects for as long as 10 years (8,9,10,11). We previously published the 6-year outcome in our cohort (5) and Marion et al. reported 9 patients followed for 5 years or more (12). This study extends observation to a larger cohort and longer follow-up.

Our patients were demographically typical of the FHD population, with writer's cramp the most common type. There was large variability in the frequency of treatments, likely reflecting the fact that while FHD makes particular activities difficult or impossible, it is not otherwise disabling or painful. Patients therefore often tolerate the symptoms and arrange their injections based on anticipated activities. Professional musicians often timed treatments to obtain peak effect around scheduled performances. Since BoNT effects lasted on average 3 months, the long interval between injections is not related to an extended duration of action.

There was a trend for higher benefit in patients returning for treatments at shorter intervals. It is possible that earlier re-injection enhances residual benefit from prior treatments. As noted in earlier studies (5,13), we found no correlation between dose and benefit. Accurate selection, localization and dose adjustments are likely more important outcome determinants (14,15).

Our cohort required a gradual increase in dose over time. This is only partly explained by the choice of a low initial dose, since the gradual increase continued over the later years of treatment. As benefit also increased, it is possible that tolerance led to less weakness with a given dose, allowing higher doses and improved benefit. This dynamic has been seen in some previous studies (8), but not in others (5,16).

There is a large range of response to BoNT injections. We were unable to identify factors that predict an individual's response, other than a strong tendency for women to respond better, possibly explained by a smaller muscle mass allowing the toxin to diffuse more readily to the motor endplate in women. Previous studies proposed an inverse relation between dystonia complexity and benefit, with subjects requiring injection of more muscles benefiting less (7,17). We did not confirm this, finding no such correlation.

The professional musicians in our cohort required injection of fewer muscles, possibly reflecting the exquisite task specificity of musician's dystonia. The need to maintain finely skilled motor control and to minimize weakness is crucial for musicians (18,19,20), and the fewer muscles injected might also reflect the need to minimize weakness. We also note a smaller proportion of musicians among the patients continuing treatment more than 10 years compared to the rest of our cohort, which may be indicative of a higher threshold for satisfactory benefit.

None of the patients followed for more than 10 years developed immunity despite exposure to the first Botox (Allergan, inc.) batch, which was associated with antibodies developing in 10% of cervical dystonia treatments. The newer formulation is less immunogenic (21), and immunoresistance tends to develop in the first 4 years of treatment (22). We show that the risk of developing immunoresistance after more than one decade of FHD treatment is low.

Among the patients who stopped BoNT therapy while under our care, the most common reason was insufficient benefit. The average benefit at the last visit before stopping was significantly lower than the average benefit in patients continuing therapy for more than 10 years, suggesting that magnitude of benefit is an important factor determining continuation of therapy.

It is important to analyze the long-term outcome data for FHD separate from other dystonias, since the BoNT response rates differ. FHD has a lower overall response rate, with about 50% of patients receiving at least mild benefit compared to 80% for cervical dystonia and over 90% for blepharospasm (23,24).

This study is limited in that it is retrospective and uncontrolled, which limits the strength of any conclusion. In addition, our primary outcome assessments are self-reported scales of benefit and weakness. All FHD research shares this limitation, as there are no widely accepted rating scales applicable to all FHD types.

Patients continued therapy for over 10 years in spite of only mild benefit, suggesting that even partial improvement may be worthwhile. BoNT injections maintained efficacy for over a decade, with good tolerability and no new side effects emergent with long-term treatment.

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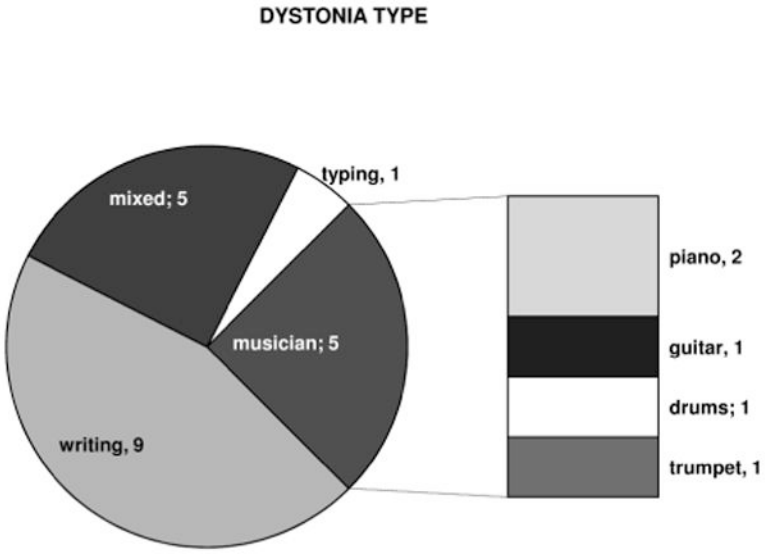

FIG. 1.

Average dosage change of botulinum toxin A used in patients as a percentage of the first-year dose. CD, cervical dystonia; HS, hemifacial spasm; BP, blepharospasm. Error bars represent 95% confidence interval.

Table 1

Variable	Value
Total number of patients	20
Gender, n (%), male/female	15 (75) / 5 (25)
Age at first injection (yrs, avg. +/- STD)	46.6 ± 9.45
Age at dystonia onset (yrs, avg. +/- STD)	37.1 ± 9.8
Duration of follow-up (yrs, avg. +/- STD)	13.6 ± 2.5
Number of visits (avg +/- STD)	19.7 ± 9.9
Average dose (BoNT A units +/- STD)	46.4 ± 24.6
Inter-injection interval (avg +/- STD)	11.3 ± 8.8