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Assessment of Botulinum Neurotoxin Injection for Dystonic Hand Tremor
A Randomized Clinical Trial

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IMPORTANCE There is an unmet need for safe and efficacious treatments for upper-extremity dystonic tremor (DT). To date, only uncontrolled retrospective case series have reported the effect of botulinum neurotoxin (BoNT) injections on upper-extremity DT.

OBJECTIVE To assess the effect of BoNT injections on tremor in patients with upper-extremity DT.

DESIGN, SETTING, AND PARTICIPANTS In this placebo-controlled, parallel-group randomized clinical trial, 30 adult patients with upper-extremity DT treated at a movement disorder clinic in a tertiary care university hospital were randomized in a 1:1 ratio to BoNT or saline injection, 0.9%, using a computer-generated randomization sequence. Randomization was masked using opaque envelopes. The participant, injector, outcome assessor, and statistician were blinded to the randomization. Participants were recruited between November 20, 2018, and December 12, 2019, and the last follow-up was completed in March 2020.

INTERVENTIONS Participants received electromyographically guided intramuscular injections of BoNT or placebo into the tremulous muscles of the upper extremity. Injection patterns and doses were individualized according to tremor phenomenologic findings.

MAIN OUTCOMES AND MEASURES The primary outcome was the total score on the Fahn-Tolosa-Marin Tremor Rating Scale 6 weeks after the intervention. Outcomes were assessed at baseline, 6 weeks, and 12 weeks. All patients were offered open-label BoNT injections after 12 weeks and reassessed 6 weeks later.

RESULTS A total of 48 adult patients with a diagnosis of brachial dystonia with DT were screened. Fifteen were ineligible and 3 refused consent; therefore, 30 patients (mean [SD] age, 46.0 [18.6] years; 26 [86.7%] male) were recruited, with 15 randomized to receive BoNT and 15 to receive placebo. In the intention-to-treat group, the Fahn-Tolosa-Marin Tremor Rating Scale total score was significantly lower in the BoNT group at 6 weeks (adjusted mean difference, −10.9; 95% CI, −15.4 to −6.5; $P < .001$) and 12 weeks (adjusted mean difference, −5.7; 95% CI, −11.0 to −0.5; $P = .03$). More participants in the BoNT group reported global improvement on the Global Impression of Change (PGIC) assessment (PGIC 1, 2, and 3: BoNT: 4 [26.7%], 6 [40.0%], and 5 [33.3%]; placebo: 5 [33.3%], 10 [66.7%], and 0, respectively; $P = .047$). Subjective hand weakness (BoNT: 6 [40.0%]; placebo: 4 [28.6%], $P = .52$) and dynamometer-assessed grip strength (mean difference, −0.2 $\log_{10}[\text{kgf/m}^2]^2$/Hz-Hz; 95% CI, −0.9 to 0.4 $\log_{10}[\text{kgf/m}^2]^2$/Hz-Hz; $P = .45$) were similar in both groups.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, botulinum neurotoxin injections were superior to placebo in reducing tremor severity in upper-extremity DT. An individualized approach to muscle selection and dosing was beneficial without unacceptable adverse effects.

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Supplemental content

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Dystonia is a movement disorder characterized by abnormal involuntary sustained posturing of 1 or more body parts.[1] Up to 50% of patients with dystonia have associated tremor, commonly in the upper limbs or the head, a condition known as dystonic tremor (DT).[2] Tremor can be a disabling symptom, affecting multiple domains of daily living. Effective strategies for control of DT are few.[3] Medications used for essential tremor (ET) are commonly used in DT, often with suboptimal results. Anticholinergics, propranolol hydrochloride, and clonazepam had mild to moderate effects on reducing the tremor amplitude in uncontrolled, nonrandomized studies.[3] Deep brain stimulation may be offered to patients with severely disabling DT that is medication refractory, although the results for control of tremor are suboptimal compared with those for ET.[4] Botulinum neurotoxin (BoNT) injections maybe a promising therapeutic option for DT, given their established efficacy in the management of focal dystonia and spasticity and emerging evidence of benefit in other tremor conditions, including ET and Parkinson disease (PD) tremor.[5-9]

A recent evidence-based review[10] classified BoNT injections as possibly useful for ET; however, limited evidence was available for its efficacy in other tremor conditions, including DT. Botulinum neurotoxin injections are efficacious for axial dystonic tremor, such as head and voice tremor. In a systematic review[3] of data from more than 300 patients, BoNT injections improved the symptoms of cervical dystonia and head tremor by 45% to 66%. Case series and isolated reports[3,11] have documented improvement in primary writing tremor, ranging from 66% to 100% with BoNT. In a pilot study[12] of 8 patients with jerky, position-specific upper limb action tremor, BoNT injections reduced the tremor severity. For patients with ET, pivotal randomized clinical studies[6,9] using a fixed-dose approach found improvement in tremor, although the functional benefits were limited because of significant upper-extremity muscle weakness in the injected limbs. Additional studies[7,8,13] using a customized injection approach found significant benefits on tremor without unacceptable hand weakness in patients with ET and PD. No randomized clinical trials have reported the effects of BoNT injections in DT of the hand. We hypothesized that in patients with isolated dystonia and DT of the hand, BoNT injection is superior to placebo injection for control of tremor.

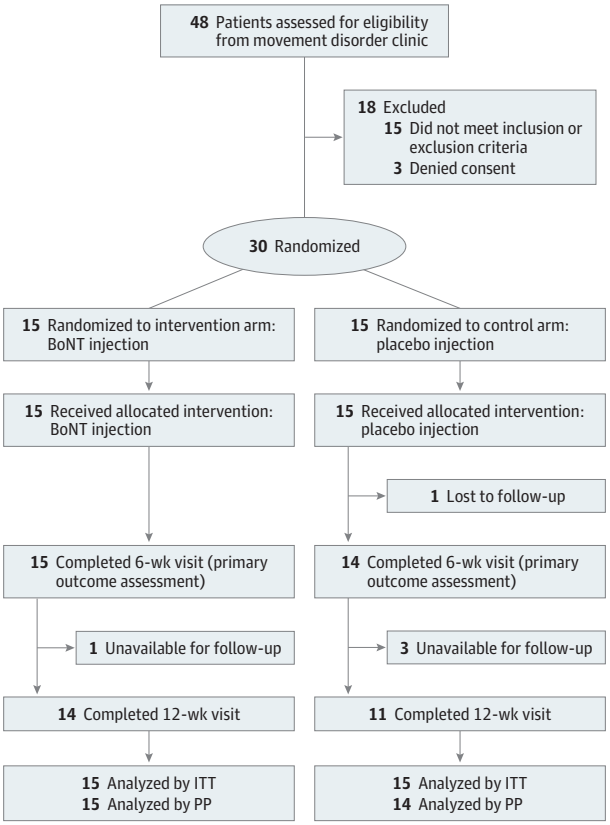
Key Points

Question Are botulinum neurotoxin (BoNT) injections effective in treating upper-extremity dystonic tremor?

Findings In this randomized clinical trial of 30 adults, a mean difference of 10.9 units on the Fahn-Tolosa-Marin Tremor Rating Scale was found between the BoNT and placebo groups 6 weeks after injection, a significant difference in favor of BoNT.

Meaning In patients with upper-extremity dystonic tremor, electromyographically guided individualized BoNT injections were beneficial for achieving tremor control without unacceptable hand weakness.

Figure 1. Study Flow Diagram



BoNT indicates botulinum neurotoxin; ITT, intention to treat; PP, per protocol.

Methods

Study Design

We conducted a placebo-controlled, parallel-group randomized clinical trial with blinded outcome assessment (eFigure 1 in Supplement). This was a single-center study conducted in the movement disorder clinic at the All India Institute of Medical Sciences, New Delhi. All participants gave written informed consent before participation in the study. Data were deidentified and stored according to study identification. The study was approved by the All India Institute of Medical Sciences Ethics Committee and registered at the Clinical Trials Registry of India. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Participants

Between November 20, 2018, and December 12, 2019, consecutive patients with isolated dystonia and DT attending the movement disorder clinic were screened for eligibility. We screened 48 patients and recruited 30 participants; 15 were randomly assigned to each group (**Figure 1**). Patients who met all of the following criteria were included: (1) isolated focal, segmental, multifocal, or generalized dystonia and brachial dystonia with DT as defined by the Movement Disorder Society Consensus criteria for tremor Axis I criteria[14-16]; (2) use of a stable dose of medications for tremor (if any) for the past 1 month before study enrollment; (3) not previously receiving

BoNT for hand DT or last injection at least 4 months before study enrollment; and (4) age older than 18 years. Patients required a consensus diagnosis of DT from 2 movement disorder specialists (any 2 from among R.R., A.K.S., and V.G.) before inclusion. Patients who met any of the following criteria were excluded: (1) clinical evidence of parkinsonism or cerebellar ataxia; (2) hand tremor associated with dystonia in another body part and absent focal hand dystonia; (3) contraindications to BoNT, including concomitant neuromuscular junction disorder or anterior horn cell disorder; or (4) pregnancy.

Randomization and Masking

Participants were randomized to 1 of the 2 arms (BoNT injection or placebo injection) on enrollment. Simple randomization with a 1:1 allocation ratio was performed with a computer-generated randomization sequence. Sequentially numbered, sealed, opaque envelopes were used to conceal allocation. An independent research assistant (A.S.) performed the allocation and reconstituted BoNT or the equivalent volume of placebo (saline, 0.9%) for injection in identical unlabeled syringes. This individual was not involved in administering injections, outcome assessment, or data analysis. The participant, injector (R.R.), outcome assessor (R.A.), and statisticians (A.U. and S.N.D.) were blinded to the allocation until data analysis was completed.

Procedures

Study Assessments

Participants underwent structured videotaped neurologic examination to identify the sites and features of dystonia and tremor. Tremor was assessed with both hands completely supported against gravity (rest); arms outstretched and elbows extended (posture 1); arms outstretched and elbows flexed with fingers pointing toward each other (posture 2); and during finger-nose testing, writing, and pouring tasks. We used the Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) for clinical rating of tremor and the Writer's Cramp Rating Scale for rating of brachial dystonia during writing.[17,18] Both are validated instruments for tremor and writer's cramp, respectively.[19,20] The FTM-TRS consists of 3 parts: part A (tremor severity; range, 0-88, with 0 indicating no tremor and 88 indicating highest severity of tremor), part B (specific motor tasks; range, 0-36, with 0 indicating no tremor and 36 indicating maximum impairment), and part C (functional disabilities; range, 0-32, with 0 indicating no tremor and 32 maximum disability). Parts A and B are objectively rated, and part C is patient reported. The 3 components are combined into a total score that can range from 0 to 156, with higher scores indicating more severe tremor. The Writer's Cramp Rating Scale consists of 2 parts: the Writing Movement Score (WMS; range, 0-28) and the Writing Speed Score (WSS; range, 0-2), with higher values indicating more severe dystonia. Tremor at rest, posture 1, and posture 2 were quantified using combined surface electromyography-accelerometric tremor analysis (Biopac Systems) with the accelerometer placed on the middle phalanx of the index finger. Total power of the tremor spectrum (0-30 Hz) was computed as a surrogate measure of tremor amplitude and the resultant of the 3 axes calculated. Subjective patient-rated improvement was measured on a 4-point Likert scale, the Patient Global Impression of Change scale (1 indicating no benefit; 2, some benefit; 3, significant benefit; and 4, excellent benefit) at the follow-up visits. Self-reported adverse events were documented. Grip strength was measured with handgrip dynamometer (Biopac Systems).

Study Interventions

Participants received the allocated intervention at the injection visit. The BoNT or placebo was injected into the tremulous and/or dystonic muscles of the more affected arm. Muscles were selected by clinical examination and review of videotapes to identify the location of tremor across joints. A single trained injector (R.R.) administered the injections. Injections were electromyographically guided to identify the target muscles and were delivered through injectable electromyographic needle electrodes. The intervention arm received onabotulinum toxin A (Botox, Allergan) reconstituted in a dilution of 50 U per 1 mL in preservative-free saline, 0.9%. The placebo arm received saline, 0.9%. The dose was individualized according to tremor severity and the number and size of muscles involved. Participants could continue their routine medications (including medications for tremor), although no change in the medication was allowed during the study period.

Outcomes

Outcome assessments were performed at baseline and at 6 weeks and 12 weeks after the intervention. The primary outcome measure was the total FTM-TRS score at 6 weeks after the intervention session. The secondary outcomes were (1) FTM-TRS part A score, (2) FTM-TRS part B score, (3) FTM-TRS part C score, (4) Writer's Cramp Rating Scale WMS and WSS, (5) PGIC score, and (6) total power of the spectrum on tremor analysis. Self-reported adverse events were recorded, and dynamometer-assessed grip strength was documented for objective monitoring of grip weakness. At the end of the study period, all participants were offered BoNT injection on an open-label basis and reassessed after 6 weeks.

Statistical Analysis

For the primary outcome (FTM-TRS total score), assuming a minimum clinically meaningful difference of 5 units and an SD of 3.78 as reported previously,[21,22] power of 90%, and $\alpha = .05$, a total of 28 participants were required. The sample size estimation was performed on the web-based platform Free Analysis Research Tool for Sample Size Iterative Estimation (University of Toronto). Assuming 10% unavailability of follow-up, we planned to recruit 30 individuals. Study data were presented as mean (SD) or median (range) and number (percentage). Primary outcome analysis was performed in both the intention-to-treat (ITT) and per-protocol groups. The ITT group included all randomized participants. For those who missed follow-up at 6 weeks, missing data were imputed using the last observation carried forward. Participants who received the intervention and completed the 6-week follow-up were included in the per-protocol analysis. Categorical variables were

compared by χ^2 and Fisher exact tests. For continuous variables, the Shapiro test was used to assess normal distribution, and appropriate transformation (log transformation) was performed for variables not following normal distribution (total power and grip strength). Continuous variables were compared by independent-sample, 2-tailed, unpaired *t* test, and effect sizes with 95% CIs were reported. Variables not following normal distribution were compared by the Wilcoxon rank sum test. Analysis of covariance was used to assess the difference between the 2 interventions after adjusting for baseline values. We performed adjusted analysis for the primary outcome because clinically relevant (although statistically insignificant) changes were detected in baseline covariates after randomization and considering the interindividual variability in tremor. Adjusted analysis was prespecified in the original statistical analysis plan. Within-group change in continuous variables was assessed by the paired, 2-tailed *t* test or Wilcoxon signed rank test. All analyses were performed with Stata software, version 12 (StataCorp), and $P < .05$ was considered as statistically significant.

Results

A total of 48 adult patients with a diagnosis of brachial dystonia with DT were screened. Fifteen were ineligible and 3 refused consent; therefore, 30 patients (mean [SD] age, 46.0 [18.6] years; 26 [86.7%] male) were recruited, with 15 randomized to receive BoNT and 15 to receive placebo. All randomized patients received the allocated intervention and were included in the ITT analysis. One participant in the placebo arm did not complete the 6-week visit; all others completed the primary outcome assessments. One patient in the BoNT group and 4 in the placebo group missed the 12-week assessments. The mean (SD) duration of symptoms was 8.5 (5.8) years. Tremor was present at the onset of symptoms in 20 patients (66.7%) and was reported as a current symptom by 28 (93.3%). Two patients did not primarily report tremor, but tremor was noted during clinical examination. Postural tremor was present in 23 patients (76.7%), action or intention tremor in 20 patients (66.7%), and rest tremor in 12 patients (40.0%). None of the patients had received BoNT injections previously. Baseline characteristics are given in **Table 1**.

Fourteen participants in the BoNT group and 12 in the placebo group received injections in the right upper extremity. The median number (range) of muscles injected per participant was 6 (2-10) in the BoNT group and 6 (4-9) in the placebo group. The mean (SD) dose of BoNT per patient was 63.0 (28.8) U in the BoNT group (median, 50; range, 15-100). The planned mean (SD) dose was 68.3 (31.7) U in the placebo group (median, 50; range, 30-150), and equivalent volumes of saline, 0.9%, were injected. The number of times a specific muscle was injected and the median dose for each muscle are given in eTable 1 in Supplement 2.

In the ITT group, the FTM-TRS total score at 6 weeks was significantly lower in the BoNT group after adjusting for the baseline score (adjusted mean difference, -10.9; 95% CI, -15.4 to -6.5; $P < .001$) (**Table 2** and **Figure 2**). The mean difference

Table 1. Baseline Characteristics of the Study Population[a]

Characteristic	BoNT (n = 15)	Placebo (n = 15)
Age, mean (SD), y	47.9 (18.6)	44 (19.0)
Male sex	14 (93)	12 (80)
Duration of symptoms, mean (SD), y	9.1 (7.1)	7.8 (4.2)
Location of tremor		
Postural	13 (87)	10 (67)
Rest	7 (47)	5 (33)
Action	11 (73)	9 (60)
Location of dystonia		
Upper extremity	15 (100)	15 (100)
Cervical	6 (40)	5 (33)
Lower extremity	0	2 (13)
Trunk	0	2 (13)
Cranial	0	3 (23)
Distribution of dystonia		
Focal	9 (60)	8 (53)
Segmental	5 (33)	3 (20)
Multifocal	1 (7)	2 (13)
Generalized	0	2 (13)
FTM-TRS, mean (SD)/median (range)		
Total score	39.5 (21.6)/37 (11-72)	31.1 (16.5)/25 (11-55)
Part A	8.4 (7.8)/5 (0-24)	6.7 (6.2)/3 (1-19)
Part B	18.5 (10.2)/14 (6-35)	14.9 (7.1)/13 (6-26)
Part C	12.7 (5.7)/12 (3-21)	9.5 (4.8)/10 (2-18)
Injected upper extremity[b]	15.7 (8.5)/14 (5-29)	10.4 (4.9)/10 (4-20)
WMS score, mean (SD)	11.6 (6.9)	11.2 (6.0)
WSS		
0	2 (13)	0
1	7 (47)	13 (87)
2	6 (40)	0
Total power of spectrum, $(g)^2$/Hz-Hz		
Rest		
Mean (SD)	0.0000128 (0.0000242)	0.000544 (0.00135)
Median (range)	7.38×10^{-7} (1.19×10^{-8}-7.71×10^{-5})	1.31×10^{-6} (2.56×10^{-8}-5.00×10^{-3})
Posture 1		
Mean (SD)	0.0000156 (0.00536)	0.000349 (0.000717)
Median (range)	0.0000413 (1.37×10^{-7}-0.0208)	0.0000101 (0-0.002)
Posture 2		
Mean (SD)	0.00567 (0.194)	0.000936 (0.00225)
Median (range)	0.0000278 (5.36×10^{-7}-0.0755)	0.0000261 (4.75×10^{-7}-0.00860)
Grip strength, mean (SD), $\log_{10}(kgf/m^2)^2$/Hz-Hz	6.3 (0.3)	6.2 (0.3)

(continued)

Table 1. Baseline Characteristics of the Study Population[a] (continued)

Characteristic	BoNT (n = 15)	Placebo (n = 15)
Medications		
Propranolol hydrochloride	9 (60)	8 (53)
Trihexyphenidyl	5 (33)	1 (7)
Clonazepam	1 (7)	1 (7)
Levodopa and carbidopa	0	3 (20)
Topiramate	0	1 (7)

Abbreviations: BoNT, botulinum neurotoxin; FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; WMS, Writing Movement Score (range, 0-28, with higher values indicating more severe dystonia); WSS, Writing Speed Score (range, 0-2, with higher values indicating more severe dystonia).

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] The FTM-TRS upper extremity score (range, 0-32, with higher scores indicating more severe tremor) represents a composite of part A items for rest, postural, and action tremor and part B for specific motor task items for the injected upper extremity only.

between the 2 groups remained significant at 12 weeks (adjusted mean difference, -5.7; 95% CI, -11.0 to -0.5; $P = .03$) in favor of the BoNT group. The results were consistent on per-protocol analysis, with an adjusted mean difference at 6 weeks of -11.1 (95% CI, -15.6 to -6.5; $P < .001$) (eTable 2 in Supplement 2). Because 2 patients in the placebo group had a generalized distribution of dystonia, a post hoc sensitivity analysis was performed excluding these 2 patients: the primary outcome remained statistically significant at 6 weeks (adjusted mean difference, -10.2; 95% CI, -14.9 to -5.6; $P < .001$).

At 6 weeks, FTM-TRS part A (adjusted mean difference, -4.7; 95% CI, -6.1 to -3.3; $P < .001$), FTM-TRS part B (adjusted mean difference, -5.0; 95% CI, -7.2 to -2.8; $P < .001$), and FTM-TRS injected upper-extremity scores (adjusted mean difference, -8.1; 95% CI, -13.8 to -2.5; $P = .006$) were significantly lower in the BoNT group (Figure 2). More patients in the BoNT group reported a significant global improvement (PGIC 1, 2, and 3; BoNT: 4 [26.7%], 6 [40.0%], and 5 [33.3%]; placebo: 5 [33.3%], 10 [66.7%], and 0, respectively; $P = .047$) (**Table 3**). There were no demonstrable differences in FTM-TRS part C, WMS, WSS, and accelerometric measures (Tables 2 and 3). At 12 weeks, only the improvements in FTM-TRS total score (adjusted mean difference, -5.7; 95% CI, -11.0 to -0.5; $P = .03$) and FTM-TRS part A (adjusted mean difference, -2.9; 95% CI, -5.4 to -0.3; $P = .03$) remained statistically significant (Table 2).

Eight patients (53.3%) in the BoNT group and 6 (42.8%) in the placebo group ($P = .57$) reported at least 1 adverse effect. The most frequent was hand weakness (BoNT: 6 [40.0%]; placebo: 4 [28.6%]; $P = .52$), followed by pain (BoNT: 5 [33.3%]; placebo: 5 [35.7%]; $P = .47$). Only 1 patient in the BoNT group had severe hand weakness (wrist drop) that affected functionality. Grip strength by dynamometer was similar in both groups at 6 (adjusted mean difference, -0.2 $\log_{10}[kgf/m^2]^2$/Hz-Hz; 95% CI, -0.9 to 0.4 $\log_{10}[kgf/m^2]^2$/Hz-Hz; $P = .45$) and 12 weeks (adjusted mean difference, -0.09 $\log_{10}[kgf/m^2]^2$/Hz-Hz; 95% CI, -0.4 to 0.6 $\log_{10}[kgf/m^2]^2$/Hz-Hz; $P = .72$). Mean (SD) durations of reported weakness (BoNT: 13.6 [10.0] days; placebo: 8.3 [5.3] days; $P = .36$) and pain (BoNT: 15.2 [9.1] days; placebo: 10.8 [9.3] days; $P = .47$) were similar in both groups. Other adverse effects reported include stiffness in the limb (BoNT: 1, placebo: 1), numbness (BoNT: 1), and increased urinary frequency (placebo: 1).

Open-Label Extension

Twenty-four participants received open-label BoNT injection (22 right upper-extremity injections). The median number (range) of muscles injected per participant was 6 (2-9). The mean (SD) total dose of BoNT injected was 69.2 (32.2) U (median, 50 U; range, 20-150 U). The number of times specific muscles were injected and the median doses are shown in eTable 1 in Supplement 2. Follow-up data after 6 weeks were available for 17 participants (eTable 3 in Supplement 2). The mean (SD) FTM-TRS total score was significantly lower at 6 weeks after injection (before BoNT: 34.0 [2.9]; after BoNT: 26.7 [2.8]; $P < .001$) (eTable 3 and eFigure 2 in Supplement 2). Overall, 12 (70.6%) reported some benefit on the PGIC. At least 1 adverse event was reported by 9 patients (52.9%). Transient hand weakness was reported by 5 patients (29.4%) and pain by 3 (17.6%). One patient reported significant extensor weakness of the fifth digit, although it was nondisabling. There was no change in the mean (SD) objective grip strength as assessed by dynamometer (before BoNT: 613.7 [512.6] $(kgf/m^2)^2$/Hz-Hz; after BoNT: 523.6 [571.6] $(kgf/m^2)^2$/Hz-Hz; $P = .11$). The mean (SD) duration of reported weakness was 21.4 (15.9) days. One patient (5.9%) reported numbness, and 2 (11.8%) reported generalized fatigue.

Discussion

In this randomized clinical trial, electromyographically guided BoNT injections with individualized muscle targeting were efficacious in improving upper-extremity tremor in patients with DT. The changes in FTM-TRS scores were driven by changes in both part A and part B scores, suggesting improvement in the severity of tremor and specific motor tasks. Functional disabilities (FTM-TRS part C) did not differ significantly between the groups. Nevertheless, a significantly greater number of patients in the BoNT group reported global subjective improvement despite transient subjective hand weakness reported by 40% in the BoNT group and 28.6% in the placebo group, most of which was mild and nondisabling. As expected for the duration of action of BoNT, maximal efficacy was noted at 6 weeks with a gradual decrease in effect by 12 weeks, although the FTM-TRS score in the BoNT group remained significantly lower. The BoNT effects start to appear 7 to 10 days after injection, and the peak effect is expected to be reached in a few weeks and then maintained for 3 to 4 months after injection. This study measured the primary outcome at 6 weeks to account for all responders, including those who may have a delayed response. Previous studies[6,8,9] have commonly used 4 to 6 weeks as the time point for efficacy assessment, and the largest study[6] on ET found that although postural tremor improved at 4 weeks, the kinetic component of the tremor improved significantly only at 6 weeks.

Table 2. Primary and Secondary Outcomes in the Intention-to-Treat Population

Outcome	Mean (SE)				
		6 wk		12 wk	
	Baseline	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
Primary outcome					
FTM-TRS total score					
BoNT	39.5 (5.6)	26.7 (4.2)	23.5 (1.5)	31.6 (3.8)	28.7 (1.8)
Placebo	31.1 (4.3)	31.2 (4.0)	34.4 (1.5)	31.5 (3.9)	34.4 (1.8)
Mean difference (95% CI)	8.4 (-6.0 to 22.8)	-4.5 (-16.3 to 7.2)	-10.9 (-15.4 to -6.5)	0.1 (-11.1 to 11.4)	-5.7 (-11.0 to -0.5)
P value	.29	.44	<.001	.98	.034
Secondary outcomes					
FTM-TRS part A					
BoNT	8.4 (2.0)	3.7 (1.2)	3.2 (0.5)	4.5 (4.5)	4.1 (0.9)
Placebo	6.7 (1.6)	7.3 (1.5)	7.9 (0.5)	6.5 (1.5)	7.0 (0.9)
Mean difference (95% CI)	1.7 (-3.5 to 7.0)	-3.5 (-7.3 to 0.3)	-4.7 (-6.1 to -3.3)	-2.0 (-5.6 to 1.6)	-2.9 (-5.4 to -0.3)
P value	.45	.07	<.001	.27	.029
FTM-TRS part B					
BoNT	18.5 (2.6)	13.5 (2.4)	12.0 (0.8)	17.1 (2.0)	15.8 (0.7)
Placebo	14.9 (1.8)	15.4 (1.7)	17.0 (0.8)	15.9 (1.5)	17.2 (0.7)
Mean difference (95% CI)	3.7 (-2.9 to 10.2)	-1.9 (-7.9 to 4.2)	-5.0 (-7.2 to -2.8)	1.1 (-3.9 to 6.2)	-1.5 (-3.5 to 0.6)
P value	.34	.53	<.001	.65	.16
FTM-TRS part C					
BoNT	12.7 (1.5)	9.4 (1.1)	8.3 (0.7)	10.2 (1.2)	9.1 (0.8)
Placebo	9.5 (1.2)	8.5 (1.2)	9.5 (0.7)	8.8 (1.2)	9.9 (0.8)
Mean difference (95% CI)	3.2 (-0.7 to 7.1)	0.9 (-2.3 to 4.2)	-1.2 (-3.2 to 0.7)	1.4 (-2.0 to 4.8)	-0.8 (-3.1 to 1.3)
P value	.13	.56	.21	.41	.44
FTM-TRS injected upper extremity[b]					
BoNT	15.7 (2.2)	8.9 (6.3)	6.8 (1.9)	12.3 (5.8)	10.4 (1.9)
Placebo	10.4 (1.4)	12.9 (10.6)	14.9 (1.9)	13.5 (10.6)	15.4 (1.9)
Mean difference (95% CI)	5.3 (0.14 to 10.5)	-4.0 (-10.5 to 2.5)	-8.1 (-13.8 to -2.5)	-1.2 (-7.6 to 5.2)	-5.0 (-10.7 to 0.8)
P value	.04	.22	.006	.70	.09
WMS					
BoNT	11.6 (1.8)	7.7 (1.5)	7.5 (1.0)	7.3 (1.3)	7.2 (1.2)
Placebo	11.2 (1.7)	8.5 (1.4)	8.6 (1.1)	8.8 (1.7)	8.9 (1.3)
Mean difference (95% CI)	0.5 (-4.6 to 5.5)	-0.8 (-5.1 to 3.5)	-1.1 (-4.2 to 2.0)	-1.5 (-5.9 to 2.9)	-1.7 (-5.4 to 1.9)
P value	.93	.71	.49	.49	.34
Grip strength, $\log_{10}(kgf/m^2)^2$/Hz-Hz					
BoNT	6.3 (0.3)	5.8 (0.3)	5.7 (0.2)	6.1 (0.2)	6.1 (0.2)
Placebo	6.2 (0.3)	6.0 (0.3)	6.0 (0.2)	5.9 (0.3)	6.0 (0.2)
Mean difference (95% CI)	0.1 (-0.7 to 0.8)	-0.2 (-1.0 to 0.6)	-0.2 (-0.9 to 0.4)	0.1 (-0.7 to 0.8)	0.09 (-0.4 to 0.6)
P value	.85	.63	.45	.70	.72

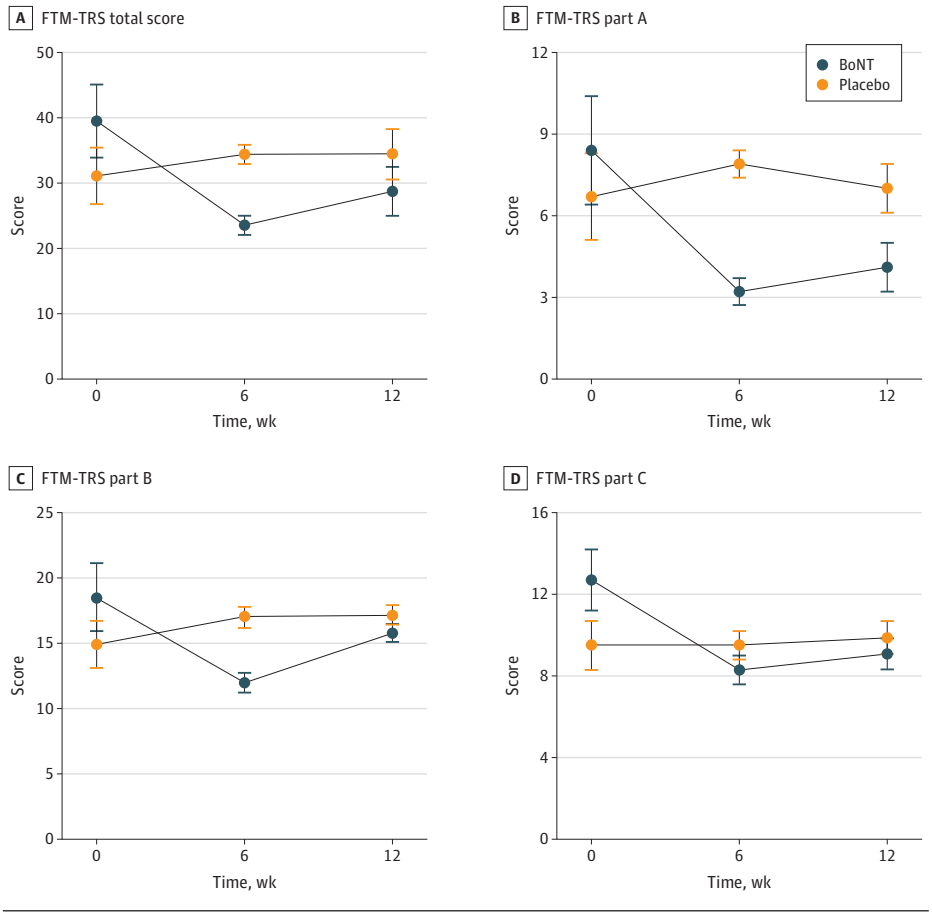
Abbreviations: BoNT, botulinum neurotoxin; FTM-TRS, Fahn-Tolosa-Marin Tremor Rating Scale; WMS, Writing Movement Score (range, 0-28, with higher values indicating more severe dystonia).

[a] Adjusted for baseline values of the same variable. $P < .05$ was considered statistically significant.

[b] The FTM-TRS upper extremity score (range, 0-32, with higher scores indicating more severe tremor) represents a composite of part A items for rest, postural, and action tremor and part B for specific motor task items for the injected upper extremity only.

The results of this study are similar to those previously reported for BoNT in ET and PD.[6-9,13] Compared with the fixed-dose approach in earlier ET studies,[6,9] lower incidence of disabling hand weakness was observed in this study. This finding could be attributable to the individualized selection of muscles and doses according to tremor location, tremor severity, and size of muscles.[23] The mean BoNT dose used in this study falls between the low-dose and high-dose regimens used in fixed-dose BoNT injection studies[6,9] in ET. Furthermore, the extensors of the digits and wrist being particularly sensitive to BoNT-related weakness, this study limited the doses and number of muscles injected in the extensor compartment of the forearm.[24] In general, the following strategy was used. First, finger extensors were injected only in patients with overt extensor dystonic posturing or prominent finger extension movements as part of postural or action tremor. Specifically, the extensor digi-

Figure 2. Fahn-Tolosa-Marin Tremor Rating Scale (FTM-TRS) Scores



Adjusted mean scores are shown for both groups at 0, 6, and 12 weeks. Error bars indicate SEs. BoNT indicates botulinum neurotoxin.

torum communis was altogether avoided in most patients (except 2). For patients who required extensor indicis, extensor pollicis longus, or extensor pollicis brevis injections, no more than 5 U of BoNT was injected into each muscle. Second, wrist extensors were injected in 80% of the patients in the BoNT group, but the mean dose injected into extensor carpi radialis or extensor carpi ulnaris (6.6 U) was nearly half the dose injected into the flexor carpi radialis or flexor carpi ulnaris (11.7 U). Most patients who required wrist extensor injections received no more than 5 to 10 U into each extensor. Despite subjective reports of weakness, objective grip strength remained similar in both groups, suggesting that finger flexors were tolerant to the doses delivered. Pathophysiologic differences between ET and DT may also be hypothesized to be a factor; dystonic muscles may tolerate higher doses of BoNT without weakness and, hence, the threshold for hand weakness may be higher in DT compared with ET.

Only 2 other studies[24,25] have specifically reported the effect of BoNT injections on upper-extremity DT. Both were retrospective reviews of clinical data, and the larger report[24] included 31 patients with DT treated with an individualized approach, limiting the doses to the wrist and finger extensors. Sustained benefit on tremor was reported on a global benefit scale. A recent systematic review[26] on BoNT treatment for tremor identified the need for a randomized clinical trial in this population. In a previous study,[22] a change in the FTM-TRS score greater than 5 was clinically significant, with change of 5 to 10 points corresponding to mild improvement and 10 to 15 points corresponding to moderate improvement. Accordingly, the change in FTM-TRS scores in the BoNT group in the present study suggests moderate clinical improvement. Furthermore, following the approach described by Elble,[27] the improvement in tremor amplitude in the treated upper limb at 6 weeks is estimated to be 69% over placebo, a clinically and statistically significant difference. By 12 weeks, however, the improvement in tremor amplitude in the treated upper limb diminished to 51% over placebo. Although some previous studies[6,27] suggested more improvement in postural tremor than action tremor after BoNT injection, in this study, the estimated improvement in postural (29%) and action or intention (30%) components of tremor in the injected upper extremity were similar using the above-mentioned approach.

Although the primary aim of this study was to assess the effect of BoNT injections on tremor, the effect on dystonia could be surmised through the secondary outcome WMS. No significant difference was found between the groups on this scale; hence, improvement in dystonia is unlikely to have contributed to the subjective benefit reported by patients receiving BoNT. This lack of effect on dystonia could be attributable

Table 3. Additional Secondary Outcomes in the Intention-to-Treat Population[a]

Outcome	No (%)		
	Baseline	6 wk, unadjusted	12 wk, unadjusted
PGIC score for BoNT/placebo groups			
1	NA	4 (26.7)/5 (33.3)	6 (40.0)/7 (46.7)
2	NA	6 (40.0)/10 (66.7)	5 (33.3)/6 (40.0)
3	NA	5 (33.3)/0	3 (20.0)/2 (13.3)
4	NA	0/0	1 (6.7)/0
P value	NA	.047	.71
Total power at rest, median (range), $(g)^2$/Hz-Hz			
BoNT	7.38×10^{-7} (1.19×10^{-8}-7.71×10^{-5})	4.92×10^{-7} (7.52×10^{-9}-6.87×10^{-5})	1.16×10^{-6} (1.06×10^{-7}-4.80×10^{-5})
Placebo	6.84×10^{-7} (2.56×10^{-8}-0.00500)	2.14×10^{-6} (1.28×10^{-7}-0.0160)	3.21×10^{-6} (1.28×10^{-7}-0.001)
P value	.52	.23	.34
Total power at posture 1, median (range), $(g)^2$/Hz-Hz			
BoNT	0.0000413 (1.37×10^{-7}-0.0208)	3.37×10^{-6} (1.39×10^{-7}-0.283)	5.99×10^{-6} (0-0.30901)
Placebo	0.0000166 (0-0.00200)	0.0000108 (0-0.00100)	2.38×10^{-5} (0-7.75×10^{-5})
P value	.89	.54	.91
Total power at posture 2, median (range), $(g)^2$/Hz-Hz			
BoNT	0.0000278 (5.36×10^{-7}-0.07550)	0.0000108 (2.29×10^{-7}-0.491)	1.57×10^{-5} (1.95×10^{-7}-1.472)
Placebo	0.0000201 (4.75×10^{-7}-0.00860)	0.0000244 (1.17×10^{-6}-0.020025)	1.49×10^{-5} (7.11×10^{-7}-0.00283)
P value	.40	.30	.43
WSS for the BoNT/placebo groups			
0	2 (13.3)/0	1 (6.7)/1 (7.7)	0/0
1	7 (46.7)/13 (100)	11 (73.3)/10 (76.9)	10 (66.7)/12 (92.3)
2	6 (40.0)/0	3 (20.0)/2 (15.4)	5 (33.3)/1 (7.7)
P value	.008	.95	.10

Abbreviations: BoNT, botulinum neurotoxin; NA, not applicable; PGIC, Patient Global Impression of Change; WSS, Writing Speed Score (range, 0-2, with higher values indicating more severe dystonia).

[a] Unadjusted analysis. $P < .05$ was considered statistically significant.

to the muscle selection that was based primarily on the tremor phenomenologic findings rather than injection into the muscles responsible for dystonia. The doses required for relief of dystonia may also be higher than the doses used for tremor in this study. Whether an injection strategy guided by overtly dystonic muscles or mirror dystonia would benefit tremor and dystonia without unacceptable weakness needs to be explored in future studies. Similarly, accelerometer recordings did not find significant between-group differences after the intervention. Transducer-based measures, including accelerometry, have a logarithmic correlation with objective clinical rating scales.[28,29] However, the inherent variability in tremor amplitude, sensor positioning, and gravitational artifacts negatively affect the precision and accuracy of accelerometer recordings, and the effect of intervention may not exceed the minimum detectable change.[29] Hence, tremor rating scales are often preferred to assess longitudinal outcomes.

Strengths and Limitations

This study has strengths, including the randomized, placebo-controlled, quadruple-blinded, and parallel-group study design. Particularly, the parallel-group design helped to avoid carryover effects, the duration of which is unpredictable for BoNT and which complicate the analysis in a crossover design.[10,30] Considering the interindividual variability in tremor severity, the study adjusted for this potential confounder in analysis, although statistically the groups were comparable after randomization. This study also has limitations. There is no objective parameter or investigation to detect dystonia, and the interrater agreement for diagnosis of DT is modest.[31] This was addressed by including only patients who were unequivocally classified by 2 raters as having DT. Patients with upper-extremity DT were included regardless of the distribution of dystonia. Although this extends the applicability of the results in practice, whether patients with focal, segmental, or generalized dystonia respond differently needs to be addressed in future studies; however, these results remained robust on a post hoc sensitivity analysis that excluded generalized dystonia. Placebo effects are likely to be significant for interventions such as BoNT. Despite this, objective and global improvement measures had significant effects in favor of BoNT. The possibility of participants' not being truly blinded to the

intervention exists; however, this was considered less likely because none of the participants had previously received BoNT and a comparable number reported hand weakness in the placebo group. The 4-point PGIC scale did not specifically identify those with worsening symptoms after intervention because these participants were included in the category of no benefit. Hypothetically, the secondary outcome of subjective global benefit could yield different results if a scale were used that counted patients with worsening symptoms in a separate category. Nevertheless, the number of patients reporting a significant benefit was unlikely to be changed with the use of an extended scale. Outcomes were not assessed earlier than 6 weeks, which could have led to an underestimation of objective hand weakness. However, patient-reported subjective hand weakness remained mild and not different from the placebo group throughout the initial 6 weeks. The stability of outcomes during multiple injection sessions and functional abilities and quality of life for a longer period need to be explored; the injection strategy for an individual patient may be optimized during multiple visits, which may improve the outcomes further.

Conclusions

This placebo-controlled, parallel-group randomized clinical trial provides level 1 evidence to support the use of BoNT injections for reducing tremor severity in patients with upper-extremity DT. Objective reduction in tremor was accompanied by improvement in specific motor tasks and a larger proportion of patients in the BoNT group reporting a global subjective improvement in symptoms. With an individualized approach to muscle selection and dosing, electromyographically guided injections were safe, with reported rates of hand weakness similar to placebo. Future studies are needed to assess the long-term stability of effects of treatment with BoNT during repeated injection sessions and to identify subgroups who are most likely to benefit from this treatment.

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