OnabotulinumtoxinA and Cognitive Behavioral Therapy in Functional Dystonia: A Pilot Randomized Clinical Trial

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ABSTRACT

Introduction: Functional dystonia (FD) is a disabling movement disorder with limited therapeutic options. We aimed to examine the efficacy and safety of chemodenervation with OnabotulinumtoxinA (BoNT) versus placebo prior to cognitive behavioral therapy (CBT) in FD patients.

Methods: FD patients with a Psychogenic Movement Disorders Rating Scale (PMDRS) score ≥ 10 and persistent dystonic posturing for ≥ 1 year were randomized to BoNT or placebo injections prior to 12 weekly individualized one-hour CBT sessions. Clinical assessments included PMDRS, Hamilton Depression Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Katz index of independence in activities of daily living (ADL), and Lawton instrumental ADL (iADL). The efficacy endpoints were the change in clinical assessments at 12 weeks from baseline between and within groups.

Results: Of 18 screened patients, 14 were randomized, and 10 completed the study. All patients showed reductions in PMDRS irrespective of treatment group at the end of the follow-up period. There was no difference in clinical assessments between groups at 12 weeks. Change from baseline in PMDRS score was significantly improved only in the CBT group with prior administration of placebo (mean change -9.0, 95% CI -16.5, -1.5; p=0.02).

Conclusions: CBT yielded robust improvement in FD patients but was unaffected by prior administration of BoNT. These pilot data do not eliminate the potential for examining future BoNT benefit in FD patients with selected topographical involvement, such as face or neck.

INTRODUCTION

Functional dystonia (FD) is among the most common functional (psychogenic) movement disorders [1]. It represents a major diagnostic and therapeutic challenge, where multidisciplinary rehabilitation and physiotherapy are often required [2]. The prognosis remains poor in most patients, particularly when the diagnosis is delayed [3].

Cognitive behavioral therapy (CBT) was successfully used in a 22-year-old woman with a 5-year history of severe dystonic posturing (fixed flexion at the abdomen, hips, elbows, plantar flexion at both ankles, with latero- and anterocollis) [4] suggesting it may be beneficial in other FD patients. Separately, botulinum neurotoxin (BoNT), a well-established treatment for organic focal dystonia, may be beneficial for the functional counterpart. We therefore asked whether the effects of individualized CBT could be altered by a preceding single-administration of BoNT in patients with chronic FD using a randomized trial design.

METHODS

Study design and population. This was a double-blind, placebo-controlled, randomized clinical trial of BoNT versus placebo prior to CBT. Patients with clinically definite FD [5] and persistent dystonic posturing for ≥ 1 year were recruited at the University of Cincinnati's James J. and Joan Gardner Center for Parkinson's disease and Movement Disorders between January 15, 2016 and May 30, 2017. Eligibility included subjects aged 18 to 70 years with FD severity and disability score ≥ 10 as per the Psychogenic Movement disorders Rating Scale (PMDRS) [6]. Exclusion criteria were prior treatment with any BoNT, presence of a clinically unstable medical condition,

comorbid disorders increasing the risk of adverse events to BoNT (e.g., myasthenia gravis or other neuromuscular disorders), and pregnancy.

Interventions. Up to 200 units of OnabotulinumtoxinA (Botox®, BoNT-A) or an equal amount and distribution of normal saline as placebo were injected in selected overactive muscles, with the total number of units based on standard recommendations regarding efficacy and safety for organic focal dystonias [7,8]. When several body regions were affected, the two most affected regions were targeted. Subsequent weekly CBT sessions were conducted for all patients by an experienced therapist (S.R.) for 12 weeks or until symptom remission was achieved, whichever came first.

Randomization and masking. Patients were randomized in blocks (block size = 4) via a random computer sequence. Concealment was achieved using sealed envelopes. All participants, study personnel (R.L.C.), and physician delivering treatment and assessing outcomes (A.J.E.) were blinded to treatment allocation. Injection preparations (BoNT-A or placebo) were conducted following a predetermined randomization scheme by a nurse who had no further involvement in the study.

Clinical assessments. At baseline and at study completion, we administered the following scales: Psychogenic Movement Disorders Scale (PMDRS), which sums severity, duration factor, and incapacitation across body regions, to produce a total score ranging from 0 to 144 (higher means worse) [6]; Hamilton Depression Scale (HAM-D; < 8, normal; 8-16, mild depression; ≥17 major depression) [9,10]; Hamilton Anxiety Scale (HAM-A; ≥17 anxiety disorder) [9,11]; Katz

index of independence in activities of daily living (ADL) [12]; and Lawton instrumental ADL (iADL) [13]. Psychiatric comorbidities were ascertained using a clinically structured interview by the experienced cognitive therapist (S.R.).

Outcome measures. The primary efficacy outcome measures were the change in clinical assessments from baseline to 12 weeks within groups. Secondary outcome measures were the between-group mean differences in clinical assessments at 12 weeks. We recorded frequency, type, and duration of adverse events at the injection procedure and throughout the study period.

Statistical analysis. We hypothesized that changes in clinical endpoints would be similar between groups but greater within the BoNT+CBT group. We anticipated ≥25% improvement [standard deviation (SD) = 15%] from baseline in each group. We calculated that 6 patients per group were required to detect significant differences within each group with 80% power using a paired t-test and $\alpha = 0.05$. Accounting for a 20% dropout rate, a total of 14 patients were required to be included in the study. As a pilot design, we did not adjust for multiplicity in the level of significance and computed sample size to examine for significant changes in each group as opposed to between groups. Descriptive statistics were provided for quantitative (mean and SD) and categorical (count and percentage) variables. For efficacy testing, only subjects who completed the follow-up visit were compared between pre and post-treatments. Semiparametric bootstrap t-test, a powerful test for small-sample studies, which does not require normality assumption [14], was applied to compare the changes between two groups. Within each treatment group, bootstrap paired t-test was used to evaluate change in each clinical measure from baseline. Effect sizes were summarized using mean difference and 95% confidence interval

(CI) in the change from baseline between and within groups computed using two- and one-sample t-distribution, respectively. We further validated the results using traditional parametric tests, permutation t-test, and Wilcoxon rank and signed rank tests, as appropriate. In addition, we carried out a sensitivity analysis by replacing missing points in each group with mean values of the respective variable to validate the findings of the study. P-values <0.05 were considered statistically significant. All data were analyzed using the software program STATA (V15.0; StataCorp LLC, College Station, TX).

Standard protocol approvals, registrations, and patient consents. This study was conducted in accordance with good clinical practice and the Declaration of Helsinki. The study protocol was approved by the institutional ethics committee (University of Cincinnati Institutional Review Board Study# 2015-4496) and written informed consent was obtained from all enrolled individuals. The study was registered at ClinicalTrials.gov, identifier NCT02618889.

RESULTS

Out of a screened population of 18 eligible candidates, 14 subjects were randomized to two groups (Figure). However, one patient from the Placebo+CBT group dropped out after randomization (declined to return for CBT visits). A total of 13 patients either received Placebo+CBT (4 female, 2 male; age 53.7 ± 8.4 years; disease duration 4.4 ± 3.4 years) or BoNT+CBT (6 female, 1 male; age 44.3 ± 15.1 years; disease duration 2.1 ± 3.5 years). Psychiatric comorbidities included depression (n= 5; 38.4%), anxiety (30.4%; n=4), panic disorder with or without agoraphobia (n=3; 23.07%), and obsessive-compulsive disorder (n=2; 5.36%). Depression and anxiety coexisted in 15.4% of the cohort (n= 2). Psychiatric

comorbidities, total number of CBT sessions, dystonia distribution, and other functional movement disorders for each subject are available in the Supplementary Table. There was no difference in age (p=0.20), disease duration (p=0.25), or PMDRS score (p = 0.54) between groups, although two patients in the BoNT+CBT arm, but none in the Placebo+CBT, exhibited fixed limb dystonia (1, hand; 1, foot). Ten patients completed the study, 6 in the BoNT+CBT arm and 4 in the Placebo+CBT arm. The baseline PMDRS severity was similar between completers and non-completers (p=0.23). A total of 121.8 ± 55.2 units of OnabotulinumtoxinA were administered to the BoNT+CBT group.

Efficacy. All patients showed reductions in PMDRS irrespective of treatment group at the end of the follow-up period. However, one patient showed increases (worsening) in HAM-A scores in each group and one increased HAM-D score in the BoNT+CBT group at follow-up. There was no difference in clinical assessments between groups at 12 weeks (Table). Change from baseline was significantly improved only in the Placebo+CBT group for PMDRS score (mean change -9.0, 95% CI -16.5, -1.5; p=0.02). No other significant differences were observed between groups at follow-up or in changes from baseline (Table). After the sensitivity analysis, only the Placebo+CBT group remained significant for PMDRS change from baseline (mean change -7.8, 95% CI -12.3, -3.3; p=0.01) and HAM-D reduction (mean change -13.2, 95% CI - 23.8, -2.6; p=0.02).

Safety. One subject in the Placebo group developed a psychotic episode during the CBT treatment period which required hospitalization and withdrawal from study. Its relationship with

the interventions is impossible to establish, although deemed probably unrelated. No other adverse events were reported.

DISCUSSION

This pilot clinical trial demonstrated that CBT improved FD severity regardless of whether BoNT was pre-administered. While both groups showed benefits, the magnitude of severity reduction from baseline was significant only in the Placebo+CBT group, which was further confirmed in ancillary analyses. Although the sample size was low, the analysis suggests that recruitment of additional subjects in this pilot study would have been futile in changing the outcome in favor of BoNT. However, it is possible that certain topographic subtypes of FD (e.g., facial or cervical) may be more sensitive to BoNT than others (e.g., leg or arm), as suggested by the individual patient data (Supplementary Table).

The prognosis of patients with FD remains poor, with a third of patients worsening and developing additional neuropsychiatric features, and with remission only achieved in 6%, if diagnosed early [3,15]. Psychiatric comorbidity may reduce the success of CBT [16], although it did not seem to affect the efficacy of CBT in our study. Multidisciplinary approach and the combination of treatments, other than BoNT and CBT, may increase the odds of treatment success [17]. Shared pathophysiologic mechanisms in both functional and organic dystonia, such as the reduction of cortical and spinal inhibition and the impairment in somatosensory processing [18,19], justified the choice of testing whether BoNT, an effective treatment in focal organic dystonias, could also reduce the disability in focal dystonia of functional nature.

It is possible that the lack of BoNT efficacy may be partly explained by the inclusion in this arm of two subjects with fixed limb dystonia, a phenotype highly resistant to therapy. Another important consideration is the known placebo effect of injected substances, regardless of the substance used [20]. The efficacy of injecting OnabotulinumtoxinA may be similar as injecting saline solution, but both may be better than injecting nothing at all. An intriguing potential area of future research may be to set up a larger trial of injected saline versus no injection at all (for instance local massage as a control).

Our study had some limitations that temper the strength of our conclusions. First, we examined a small sample size. As a countermeasure, we conducted powerful statistical analyses to validate our results and our attrition rate remained within *a priori* calculations. Our study was primarily powered for comparing pre-to-post changes in PMDRS scores within groups rather than between groups. Our findings should be interpreted cautiously especially for a direct comparison between treatment groups. Second, PMDRS is a "snapshot" measurement of FD severity, which may be highly fluctuating and influenced by factors not captured by the scale (e.g., pain, fatigue). This may explain the post-CBT discrepancy between the improvement in PMDRS and the lack of improvement in ADL. Also, the total score in PMDRS is contributed to by other movements in addition to dystonia; changes in the PMDRS score may reflect changes in comorbid functional movement disorders rather than in FD severity. Third, we did not assess efficacy outcomes at the expected time for BoNT's peak effect (e.g., ~3 to 4 weeks post injection). Indeed, it is possible that major benefits from chemodenervation may have worn off by the study visit in which outcomes were assessed, 12 weeks after, and may have underestimated any independent effects

of BoNT. Finally, we have no data after 12 weeks, which precluded assessment on long-term efficacy.

In conclusion, our data suggest a strong positive effect of CBT in FD but absence of any enhancing effect by BoNT, with the caveats outlined above. Future uses of BoNT efficacy may be examined in selected FD subpopulations with potentially greater susceptibility to this intervention, such as facial dystonia, especially in recent-onset cases with low baseline disability where this limited intervention (even if the mechanism involves the placebo effect) can induce a more rapid remission. In the interim, judicious use of BoNT (e.g., a single session at the outset of treatment) may be considered for use in selected severe focal forms FD to aid other behavioral or physical rehabilitation strategies.

AUTHORS' ROLES

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

J. A. Vizcarra: 1B, 2C, 3A

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All the co-authors listed above gave their final approval of the manuscript version.

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INFORMATION ON AUTHOR ACCESS TO DATA

Drs. Espay, Vizcarra, and Dwivedi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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FIGURE CAPTION AND LEGEND

Figure: Study flowchart. Eighteen patients were assessed for eligibility. Four subjects did not meet eligibility criteria. One subject withdrew consent after randomization in the Placebo+CBT group. One subject was lost to follow-up in the BoNT+CBT group. In the Placebo group, one subject developed a psychotic episode (serious adverse event [SAE]) that required hospitalization and was withdrawn from the study and one patient dropped out from the study. BoNT, OnabotulinumtoxinA; CBT, Cognitive Behavioral Therapy.

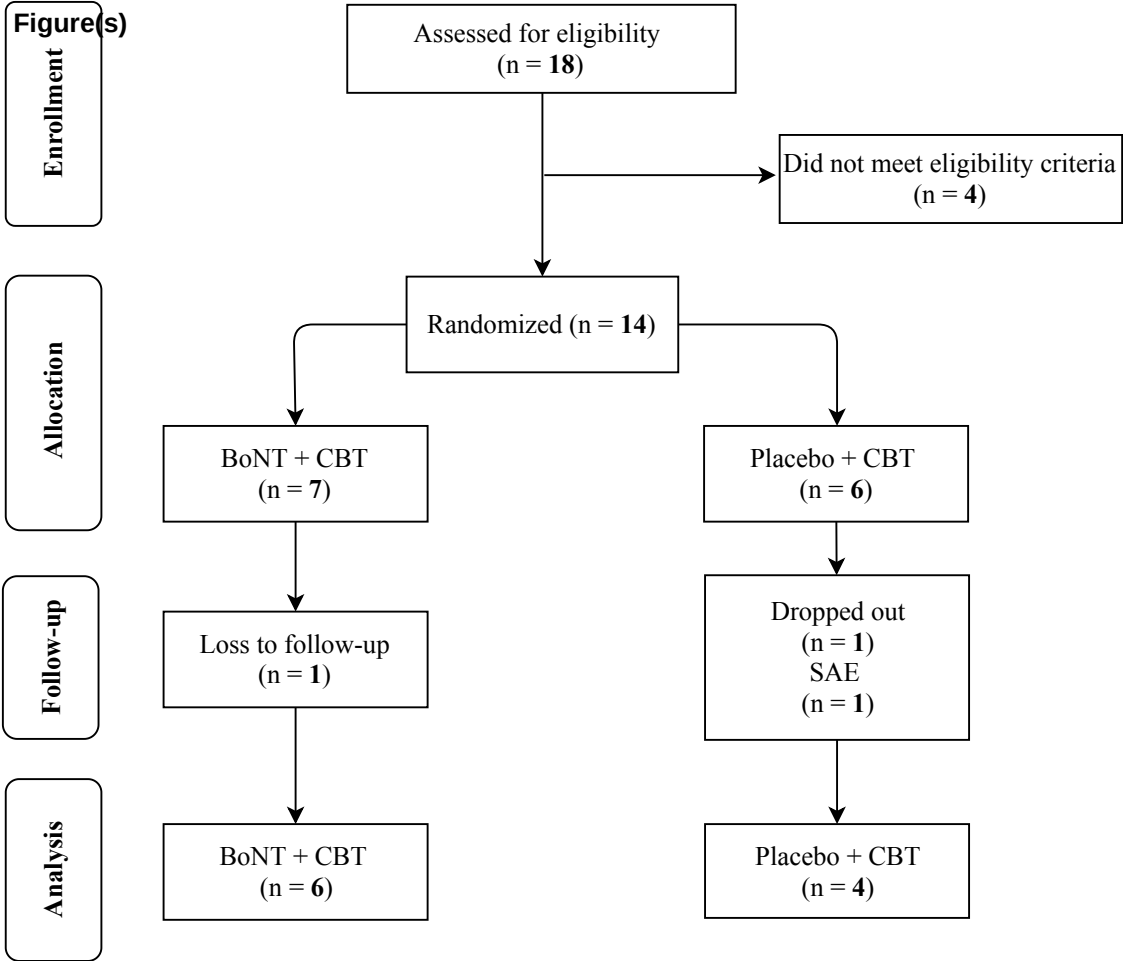
Table(s)

	BoNT+CBT(n=6)				Placebo+CBT(n=4)				Change between groups (95%CI)	P-value
	Baseline	Follow-up	Pre-post change (95%CI)	P-value	Baseline	Follow-up	Pre-post change (95%CI)	P-value		
PMDRS	21.3(13.8)	12(10.3)	-9.3 (-19.9, 1.3)	0.07	15.3(9.6)	6.3(9.9)	-9.0 (-16.5, -1.5)	0.02	-0.3 (-11.4, 10.7)	0.94
HAM-D	17.2(7.2)	10.3(10.1)	-6.8 (-18.2, 4.5)	0.19	16.3(7.1)	6.8(9.1)	-9.5 (-23.5, 4.5)	0.09	2.7 (-11.9, 17.2)	0.69
HAM-A	19.8(10.5)	13.5(9.7)	-6.3 (-12.6, -0.1)	0.05	20(5.4)	14.5(13.7)	-5.5 (-24.8, 13.8)	0.47	-0.8 (-19.0, 17.3)	0.91
ADL	5.5(0.8)	6.2(1)	0.7 (-0.4, 1.8)	0.21	5.8(0.5)	6(0)	0.3 (-0.5, 1.1)	0.81	0.4 (-0.7, 1.6)	0.40
iADL	5.8(1.9)	6.7(2.2)	0.8 (-1.6, 3.3)	0.45	6.3(1.3)	6.5(1.3)	0.3 (-0.5, 1.1)	0.22	0.6 (-1.8, 3.0)	0.57

Table: Clinical assessments and within- and between-group comparisons

Data shown as Mean (SD), unless specified otherwise. SD, Standard deviation; CI, confidence interval; BoNT, OnabotulinumtoxinA; CBT, Cognitive Behavioral Therapy; PMDRS, Psychogenic Movement Disorders Rating Scale; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; ADL, Katz index of independence in Activities of Daily Living; iADL, The Lawton instrumental activities of daily living.

Figure(s)


Enrollment
Assessed for eligibility
(n = 18)
Did not meet eligibility criteria
(n = 4)
Allocation
Randomized (n = 14)
BoNT + CBT
(n = 7)
Placebo + CBT
(n = 6)
Follow-up
Loss to follow-up
(n = 1)
Dropped out
(n = 1)
SAE
(n = 1)
Analysis
BoNT + CBT
(n = 6)
Placebo + CBT
(n = 4)

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