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Tremor and Other Hyperkinetic Movements

Articles

Occurrence of Dysphagia Following Botulinum Toxin Injection in Parkinsonism-related Cervical Dystonia: A Retrospective Study

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Abstract

Background: The aim was to compare the occurrence of post-injection dysphagia in parkinsonism-related cervical dystonia (PRCD) versus cervical dystonia (CD) of other etiologies (non-PRCD). A secondary objective was to explore potential clinical differences between PRCD and non-PRCD and their respective responses to botulinum toxin (BoNT).

Methods: A cross-sectional chart review was carried out of patients treated for CD with Onabotulinumtoxin A at the University of Florida. We collected demographic information, dose of BoNT injected, patient-reported presence of dysphagia as a side effect, patient-perceived duration of benefit and efficacy according to the Clinical Global Impression Scale (CGIS).

Results: Of the 144 patients included, 24 patients were diagnosed with PRCD and 120 were diagnosed as non-PRCD. Data analysis showed no significant differences in number of weeks of benefit from BoNT (PRCD 9.1 ± 3.7 versus non-PRCD 9.4 ± 3.7 weeks, $p=0.830$), BoNT dosage (PRCD 235.0 ± 95.6 versus non-PRCD 263.7 ± 101.3 units, $p=0.181$), median CGIS score (median=2 or "much improved" for both groups, $p=0.88$), or the presence of dysphagia after BoNT (PRCD 17% versus non-PRCD 19 %, $p=0.753$, $n=132$). In a subgroup analysis of the non-PRCD group, patients who experienced dysphagia were older than those who did not (63.9 ± 8.9 years versus 58.1 ± 14.4 years, $p=0.02$).

Discussion: Despite an increased baseline risk of dysphagia in patients with PRCD, BoNT appears to be equally safe and equally beneficial in PRCD and non-PRCD patients.

Keywords: Parkinson's disease, parkinsonism, cervical dystonia, botulinum toxin, dysphagia

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Conflict of Interest: None.

Ethics Statement: Data was obtained retrospectively from an IRB approved database at the University of Florida Center for Movement Disorders and Neurorestoration. 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.

Introduction

Cervical dystonia (CD) is the most common type of focal dystonia and consists of sustained muscle contractions leading to abnormal head posture that may be accompanied by tremor and/or pain.[1] CD is commonly a primary (idiopathic) condition, but can occur secondary to other disorders such as parkinsonism. Dystonia of any type occurs in 60% of patients with Parkinson's disease (PD);[2] however, the

prevalence of CD varies in patients with PD and other types of parkinsonism. In general, rates of CD are higher among patients with atypical parkinsonism than in patients with PD, in which CD is more likely to develop as the disease progresses. Among all stages of PD, rates of CD may be as low as 5.8%;[3–5] however, among patients in Hoehn and Yahr stages 4–5, rates of CD have been reported to be as high as 34%.[6,7] In the general PD population, anterocollis is most common;[2] however, in a stage 5 population, 28.4% experience retrocollis, 4.1% experience anterocollis, and 1.4% experience a combination of anterocollis and torticollis.[7] Despite the relatively high prevalence of CD in patients with PD and parkinsonism, little information exists on the safety and efficacy of botulinum toxin (BoNT) therapy in this patient population. Most of the existing body of literature on BoNT for CD is based on primary, idiopathic CD. In primary CD, BoNT injections are an effective and established treatment (class I evidence, level A recommendations),[8] with the advantage of avoiding side effects including sedation, cognitive clouding, and balance impairment that are commonly associated with oral medications. Unlike in primary CD, there is no class I evidence that BoNT is effective in CD associated with PD or parkinsonism. Despite this, it is widely used in this patient population.[2,9]

Dysphagia is the most common treatment-related adverse effect of BoNT therapy, and is believed to occur as a result of regional spread of the toxin to adjacent pharyngeal muscles,[10] particularly after injection of the sternocleidomastoid (SCM) muscles.[2,11] In a large double-blind, randomized, placebo-controlled clinical trial of Onabotulinum toxin A, the average rate of dysphagia as an adverse effect of therapy was 19%;[12] however, reported rates vary from 1.4% to 27.14%.[13–17] PD patients are vulnerable to the occurrence of dysphagia at baseline. One meta-analysis found that 35% of PD patients subjectively report dysphagia, and 82% were found to manifest dysphagia on objective measures.[18] The occurrence of dysphagia in PD increases risk for aspiration pneumonia [21], so minimizing that risk is critical.

The relationship between BoNT and dysphagia in PD and parkinsonism patients is not fully understood. Because dysphagia is already a risk of PD at baseline, we wanted to explore whether PD patients are more likely to suffer from dysphagia as an acute side effect of BoNT injections.

The objectives of the present study were to compare the occurrence of dysphagia post-BoNT injection between PD and parkinsonism-related CD (PRCD) versus CD of other causes (non-PRCD), and explore potential differences in clinical characteristics of CD in these two subgroups.

Methods

This is a retrospective database review from the Institutional Review Board-approved INFORM database at the University of Florida Center for Movement Disorders and Neurorestoration. We included patients who consented to participate in the INFORM database and were treated with Onabotulinum toxin A injections for CD between July 2011 and December 2013. Other BoNT preparations were excluded for consistency of dose comparison. For patients receiving multiple injections during the study period, only their most recent visit was analyzed, and for patients initiating their treatments, we excluded their first two visits as these usually involve gradual titration and dose finding in our practice. Neurologists trained in movement disorders administered the BoNT injections and recorded the total units of BoNT injected per treatment session, potentially including muscles not directly associated with CD when multiple indications were being addressed.

For each patient, we gathered demographic information, including age, gender, and neurologic diagnosis, made by a fellowship-trained movement disorder neurologist. Other measures included patient-perceived efficacy acquired via a Clinical Global Impression Scale (CGIS), a 7-point Likert scale to report CD symptoms as very much improved, much improved, minimally improved, unchanged, minimally worse, much worse, or very much worse compared with the baseline. We also acquired the patient-perceived number of weeks of benefit and the patient-perceived subjective presence of dysphagia as a side effect of the therapy.

We described categorical variables as counts and percentages, and analyzed differences in proportions utilizing chi-square testing, with correction for Fisher's exact test when appropriate. Ordinal variables were displayed as medians and we presented continuous variables as means and standard deviation. We compared means following a normal distribution with the independent samples t-test and non-parametric variables with the Mann–Whitney U test. We assumed $p \leq 0.05$ to be statistically significant and conducted the statistical analysis with SPSS version 22.0.

Results

Clinical and demographical differences between PRCD and non-PRCD

Of the 144 patients included in the study, 120 (83%) were diagnosed with non-PRCD. Within this group, 99 had idiopathic cervical dystonia, five had post-traumatic dystonia, five had tardive dystonia, three had psychogenic dystonia, one had DYT1 dystonia, and six had other secondary cervical dystonias. The remaining 24 (17%) patients were diagnosed with PRCD. Of these, 20 had PD and four had atypical parkinsonism. The mean age of the cohort was 60.34 ± 13.67 years, and 28% of the patients were males. There were no statistically significant differences between the demographics of the PRCD and non-PRCD subgroups, with the exception of an even higher predominance of females in the non-PRCD group ($p=0.003$). Table 1 summarizes the demographic data from both groups.

The reported duration of benefit from the BoNT treatment among all participants was 9.40 ± 3.70 weeks. Subgroup analysis demonstrated no significant difference between duration of clinical benefit between PRCD (9.25 ± 3.63 weeks) and non-PRCD (9.43 ± 3.73 weeks) ($p=0.830$). There was also no difference in the total amount of BoNT administered between PRCD (233.58 ± 93.77 units) and non-PRCD (263.71 ± 101.34 units) ($p=0.181$). The median self-reported benefit from the treatment detected by the CGIS was 2 ("much improved" CD symptoms) for both groups. A Mann–Whitney U test detected no differences between the two groups ($p=0.879$).

Table 1. **Clinical and Demographic Characteristics of Study Participants**

	Non-PRCD (n=120)	PRCD (n=24)	p
Age, years (mean ± SD)	59.6 ± 13.9	64.0 ± 12.1	0.125
Gender, n (%)[a]			
Male	27/120 (22.5)	13/24 (54.2)	0.003
Female	93/120 (77.5)	11/24 (45.8)	
Diagnosis, n (%)			
PD		20/24 (83.3)	
Atypical Parkinsonism		4/24 (16.6)	
Total Onabotulinum toxin A units (mean ± SD)	263.7 ± 101.3	233.6 ± 93.8	0.181
Duration of benefit, weeks (mean ± SD)	9.4 ± 3.7	9.1 ± 3.7	0.830
Peak benefit on CGIS (median)	2	2	0.879
Number reporting dysphagia, n (%)[1,2]	21/108 (19.4)	4/24 (16.7)[3]	1.000

Abbreviations: CGIS, Clinical Global Impression Scale; PD, Parkinson's Disease; PRCD, Parkinsonism-related Cervical Dystonia; SD, Standard Deviation.
[1]Fisher's exact test performed because of small subgroups.
[2]Statistics limited to n=108 subjects.
[3]All PRCD patients who reported dysphagia had PD, not atypical parkinsonism.

Self-reported symptoms of dysphagia in PRCD and non-PRCD

Self-reported occurrence of dysphagia following BoNT treatment was available in 132 out of 144 patients. Eighty-one percent (n=107/132) did not report dysphagia, and 19% (n=25/132) reported dysphagia. Subgroup analysis demonstrated no differences in the percentage of PRCD (17%) and non-PRCD patients (19%) who reported symptoms of dysphagia following BoNT treatment (p=1.000). None of the patients with atypical parkinsonism reported dysphagia following BoNT. Upon performing a post hoc power analysis, the difference between incidences of 17% reporting dysphagia in the PRCD group (n=24) and 19% in the non-PRCD group (n=108) yield to a statistical power of 9% for an alpha error of 0.05. Among the clinical variables, older age had a trend towards statistical significance when comparing means from the groups reporting dysphagia (63.24 ± 8.74 years) and not reporting dysphagia (59.37 ± 14.24 years), (p=0.09). Additionally, in a subgroup analysis including non-PRCD patients, the group reporting dysphagia was statistically significantly older (63.90 ± 8.90 years) than the group reporting no dysphagia (58.05 ± 14.37 years) (p=0.022). In a sub-group analysis including PRCD patients, there was no statistical difference in age between those reporting dysphagia and those not.

Discussion

In this retrospective study we compared the occurrence of post-BoNT injection dysphagia in PRCD versus non-PRCD. As a secondary objective we evaluated for differences in the efficacy of BoNT among these two groups. The demographics of our study population were similar to those reported in the literature when considering age and gender.[14,15] Comparison of the underlying diagnoses of our patient population to the literature was difficult as most studies either included only patients with idiopathic cervical dystonia[16,19] or included cervical dystonia of any etiology without further delineating underlying diagnoses.[12,15,17] In a study by Jankovic et al.,[14] 5.8% of the CD patients also had PD compared with 17% in our sample. We were unable to compare disease severity as our retrospective database did not include severity measures.

The peak response to BoNT in our study was similar to what is reported in the literature.[14,19] The duration of response in our patient population of 9.25 ± 3.63 weeks in PRCD and 9.43 ± 3.73 weeks in non-PRCD was shorter than the 13–16 weeks reported in the literature.[15,17] Our average BoNT doses of 233.58 ± 93.77 units for PRCD and 263.71 ± 101.34 units for non-PRCD were similar to the mean dose of 236 units reported in the clinical trial on the basis of which Onabotulinum toxin A received approval for use in CD.[12] Our average doses also fell within the mid-100s to mid-200s range reported in the literature.[13–17,19] Our rates of dysphagia following BoNT of 17% in PRCD and 19% in non-PRCD patients were similar to the 19% reported in the clinical trial on the basis of which Onabotulinum toxin A received approval for use in CD.[12] Our rate of dysphagia also fell within the range of 1.4–27.14% reported in the literature.[13–17]

The reported doses of BoNT injected for CD varied widely in the literature, ranging from 60 to 374 units.[13] Most studies reported doses in the mid-100s to mid-200s range.[12,14–17] In our patient population,

mean doses for each group were on the higher end of the spectrum. Many factors could contribute to this. In many practices, in order to avoid common side effects such as dysphagia, patients receive gradually escalated doses of toxin until the ideal therapeutic effect is achieved. Some of the studies included patients receiving BoNT for the first time, but we excluded the first two visits, which may have resulted in slightly larger doses than other studies. In addition, we did not exclude patients who received BoNT injections in multiple body regions at the same injection visit, and the addition of doses from other body parts to the total BoNT dosage used contributed to higher average doses in our sample.

The duration of benefit after BoNT in our study was shorter than the standard 12 week dosing interval that most providers adhere to and shorter than the 13–16 weeks of efficacy cited in the CD literature.[15,17] However, recent studies have shown a considerable number of patients do experience recurrence of symptoms before 12 weeks, and nearly half of patients would request another treatment sooner than 12 weeks if possible.[20–22] In addition, disease complexity and severity at our tertiary referral center as well as inclusion of patients who have been chronically on therapy may have contributed to higher than average doses of BoNT and the shorter duration of response; however, severity data were not collected as part of our retrospective study.

Despite our reported rate of dysphagia being similar to the rate reported by the large clinical trial that rendered FDA approval for Onabotulinum toxin A for CD in the United States, some studies reported markedly lower rates of dysphagia.[13,14,16,17] It is possible that our slightly higher rate of dysphagia is directly related to the higher doses of BoNT injected, often including co-occurring injections at other body regions; however, studies correlating BoNT dose with occurrence of dysphagia are limited. Chapman et al.[3] in a large meta-analysis found no correlation between the two.[1] Another possible explanation relates to our instrument for screening, instructing patients to "Please mark any side effects that you may have experienced following the injection of botulinum toxin." In reviewing these items with patients after the course of the study, we have realized that individuals often marked for occurrence of dysphagia that was unrelated to their injections. Also, there was no distinction between transient mild increased awareness of need to swallow versus more significant changes to swallow. Our questionnaire may have encouraged over-reporting, resulting in more positive responses. At the same time, it is critical to note that relying on self-reporting of dysphagia has been shown traditionally to under-report, and future studies could more accurately assess safety by incorporating objective measures.

We did not identify any difference in the rate of dysphagia among our non-PRCD and PRCD groups, rejecting our hypothesis, which to our current knowledge, has not been previously identified in the literature. A possible explanation is that, similarly to patients with PD and parkinsonism who have baseline dysphagia 20–30% of the time,[23] CD patients also experience baseline dysphagia 22.7% of the time, independently of BoNT treatment.[16] Another reason for similar rates of dysphagia may be that we frequently incorporate injections of the SCM muscles in both groups: for anterocollis in the PRCD group and for torticollis in the non-PRCD group. According to the literature, total BoNT dosage injected in the SCM muscles correlates with the occurrence of dysphagia as an adverse effect of BoNT. Borodic et al.[10] showed a direct correlation between BoNT dosing injected in SCM and occurrence of dysphagia, where patients receiving a median dose of 150 units developed dysphagia, whereas patients receiving a median SCM injection of 100 units did not develop dysphagia. Our study was a pilot to look at overall safety, but our database did not capture the pattern of dystonia, muscles injected, and dose per muscle. Examining these data in the future would provide greater depth of understanding of risks.

The strengths of this study are that it addresses an important gap in knowledge about safety and efficacy of BoNT for CD related to PD and parkinsonism. Our results suggest that patients with CD related to parkinsonism can be treated just as safely as those with CD of other etiologies. In addition, the study design allowed for inclusion of patients of CD of any etiology, not just idiopathic CD. This more closely mimics the patient mix cared for in a typical tertiary referral center for dystonia. A few potential limitations of this study exist. The first is that a relatively small and heterogeneous subgroup of PRCD patients (n=24) was enrolled in this retrospective study, prompting the need for larger studies to replicate, confirm, and generalize our findings to the broader population of parkinsonian patients. Some of our null findings could have been influenced by low power associated with small sample sizes. Considering the same proportions as representatives of the total population of these subgroups in order to identify a statistically significant difference between the two proportions at a power level of 80%, a redesigned study would require thousands of patients in each group. This large sample size would be difficult to achieve outside of a multicenter study. A second limitation is that many of the data were based on patient reporting instead of objective measures. No objective method of quantifying the initial severity of CD prior to BoNT was incorporated. The pre-BoNT presence of dysphagia was not assessed and the duration and severity of post-BoNT dysphagia were not assessed with radiographic studies or a formal swallow evaluation. In addition, we did not assess comorbidities that may act as confounders and influence dysphagia risk. Finally, our calculation of total dose of BoNT included all body parts instead of cervical muscles only, and our database does not contain information regarding individual doses for each specific muscle. Therefore, we could not establish correlations between dysphagia and muscle-specific BoNT doses. Additionally, patients who received BoNT injections in other body parts may have inflated the average dose in our results, and despite reflecting "real-world" treatment patterns, this precludes direct comparison with other studies. Though BoNT in PRCD appears to be well tolerated on the basis of self-report, a prospective study involving a larger sample of PRCD patients using objective measures of pre- and post-BoNT dysphagia should be performed to confirm or reject our findings.

In conclusion, this study suggests that patients receiving BoNT injections for PRCD had a similar reported degree and duration of benefit and did not differ in the self-reported occurrence of dysphagia

when compared with patients receiving BoNT for CD of other etiologies. Of the clinical and demographic variables, age seems to correlate with the occurrence of dysphagia, independently of diagnosis; however, the duration of benefit and total BoNT dose administered did not. These results suggest that BoNT is equally safe and effective for patients with PRCD and patients with CD of other causes, based on our retrospective pilot study. Larger studies with attention to cervical dystonia subtypes, specific muscles injected and doses may help further elucidate optimal injection practices.

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