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Long-term efficacy, safety, and side effect profile of botulinum toxin in dystonia: A 20-year follow-up

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ABSTRACT

Most long-term studies of the efficacy and safety profile of botulinum toxin (BoNT) in the treatment of dystonia are limited by lack of objective assessments, relatively small sample size, or short follow-up periods. We present one of the longest follow-up studies of BoNT treatment. This is a retrospective, longitudinal study that analyzes data on 89 patients treated with BoNT for dystonia at our Movement Disorders Clinic for up to 26 years (mean follow-up period of 18.5 years). The mean ages at the time of the first and last injections were 49 and 68 years old, respectively. The most common diagnoses were cervical dystonia (N = 51), blepharospasm (N = 34), and oromandibular dystonia (N = 26). The total number of onabotulinumtoxinA units received during the first injection was 140.3 as compared to 224.5 at the last injection ($p < 0.0001$). The global response effect was 3.18 after the first injection session and 3.57 after the last injection ($p < 0.0001$). The duration of response after the initial injection session and at the last injection was 16.33 weeks versus 19.42 weeks (p 0.0037), respectively. Adverse events, typically related to injection site, were reported in 19% of the visits. This series of dystonia patients with the longest reported treatment with BoNT provide evidence that in selected patients repeated chemodenervation is associated with sustained symptomatic benefit, decreased latency effect, and prolonged duration of therapeutic response. Despite the higher requirement of mean units per visit over time, only 19% of all treatment cycles are associated with adverse, but tolerable, side effects.

1. Introduction

The use of botulinum toxin (BoNT), utilized in our Movement Disorders Clinic since 1981, has dramatically expanded over the next three decades from the initial treatment of blepharospasm and other facial spasms to hundreds of different indications involving nearly all disciplines of medicine (Hallett et al., 2013; Jankovic and 2013). Results from the first double-blind, placebo-controlled trials demonstrated efficacy of BoNT-A in cervical (Tsui et al., 1986) and cranial-cervical dystonia (Jankovic and Orman, 1987) and were used for the initial approval of BoNT by the United States Food and Drug Administration (FDA) for the treatment of blepharospasm and other facial spasms in 1989 and for cervical dystonia in 1990.

The long-term studies on the efficacy and safety profile of BoNT for the treatment of dystonia provide evidence that BoNT products not only exert safe and effective symptomatic relief (Ramirez-Castaneda and Jankovic, 2013) but also long-term benefits, possibly even favorably modifying the natural history of this disease such as prevention of contractures in patients with cervical dystonia (Jankovic,

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2004). However, some of these studies were limited by lack of objective assessments, relatively small sample size, or short follow-up periods. In 2005, we published longitudinal follow-up data on 45 patients who had received BoNT treatments continuously for a mean period of 15.8 years at Baylor College of Medicine Movement Disorders Clinic (Mejia et al., 2005). The most frequent reasons for treatment were cervical dystonia (43%), cranial dystonia (26%), and blepharospasm (11%). Over time, there was no significant change in latency but total duration of response to treatment, dose per visit, peak duration of response, global rating, and peak effect showed incremental improvement over time. One third of patients developed side effects after their initial visit compared with 22% at their most recent visit. These findings suggest that BoNT is an effective long-term treatment with adequate and persistent therapeutic response and mild side effect profile. We present here an even longer follow-up study, concerning the efficacy and safety profile of BoNT for dystonia patients in clinical practice.

2. Methods

This is a retrospective, longitudinal, descriptive study that analyses follow-up data on patients with a primary diagnosis of dystonia who have been periodically followed at the Parkinson's Disease Center and Movement Disorder Clinic (PDCMDC) at Baylor College of Medicine. We used the following inclusion criteria: 1. PDCMDC patients with a primary diagnosis of dystonia; 2. Initial treatment visit between September, 1st 1981 and December, 31st 1996; 3. BoNT treatment administered for at least 10 years; and 4. Patients who continued receiving treatment at least once a year in our center or with their primary neurologist.

The 'Botulinum Toxin Data Form' is the main instrument used at each injection visit which serves the purpose of documenting specific demographic, clinical, and other information about BoNT-related treatment. A qualitative scale (Tsui et al., 1986) was used to rate peak effect dystonia: 0 = no effect; 1 = mild effect, but no functional improvement; 2 = moderate improvement, but no change in functional disability; 3 = moderate change in both severity and function; and 4 = marked improvement in severity and function. To calculate the global response score we subtracted 1 point if non-troublesome side effects followed treatment visit or 2 points if troublesome complications occurred as judged by the injector. Latency of response in days, maximum and total duration responses in weeks, and adverse event type and duration in days were collected for each visit.

3. Statistical analysis

Descriptive statistics were used to analyze data including demographic characteristics, type of dystonia, type of BoNT products used, and side effect profile. Measures of central tendency such as median follow-up time and mean values for age at first and last injections, number of injection visits per diagnosis, dose per session, dose per diagnosis, dose per period of time, total cumulative dose, global and peak effect response per visit and diagnosis, latency response period, maximal and total duration response, and duration of side effects. Corresponding indices of variation (range, standard deviation) and inferential statistics were used with a p-value criterion of $p \leq 0.05$ to test statistical significance.

4. Results

Out of a total of 1636 patients treated with BoNT injection for any type of movement disorder during the selected period of time, 1361 had a therapeutic indication of dystonia from which 89 were identified as having continuous treatment of $\geq$1 injection visit per year for at least 10 years. The male to female ratio was 1:3 (22 male, 67 female) and the mean ages at the time of the first injection and last injection were 49 and 68 years old, respectively. The mean interval follow-up period was 18.5 years, with one third of the patients followed for at least two decades (Table 1). The most common diagnoses were cervical dystonia (51 subjects with a total of 2370 injection visits), blepharospasm (34 subjects with 1646 visits), and oromandibular dystonia (26 subjects with 1235 visits) (Fig. 1). OnabotulinumtoxinA was almost universally the toxin of choice in 95% of the cases (rimabotulinumtoxinB 3.1%, abobotulinumtoxinA 0.44%, incobotulinumtoxinA 0.12%, and other which include research protocol BoNT 1.06%). The mean BoNT injection dose (in onabotulinumtoxinA units) was 180 units per session and the average BoNT units received per dystonia type was 266 for cervical dystonia, 75 for blepharospasm, and 149 for oromandibular dystonia (Table 1). The total number of BoNT units received during the first injection was 140.27 compared to 224.48 received at the last injection ($p < 0.0001$). The global response effect was 3.18 after the first injection session and 3.57 after the last injection ($p < 0.0001$). The peak effect dystonia for the first and last injections were 3.45 and 3.75, respectively ($p < 0.0005$). The response latency decreased from 5.5 days after the first injection to 3.3 after the last injection (p 0.0001). The duration in weeks of total and maximal responses after the initial injection session and at the last injection were 13.45 versus 15.78 (p 0.0084) and 16.33 versus 19.42 (p 0.0037), respectively (Table 2). From a total number of 4133 visits, adverse events were reported in 19% (793) of the visits. The most common side effects reported were dysphagia, ptosis, and neck weakness (Table 3).

Table 1
Demographics of long-term follow-up of 89 patients with dystonia treated periodically with BoNT injections for at least 10 years.

Variable	Mean	SD	Range
Age at first injection (yr)	49.71	12.52	8.3–74.2
Age at last injection (yr)	68.29	12.62	24.6–90.1
Interval follow-up period (yr)	18.58	3.18	9.9–26.3
Number of visits	46.43	13.36	16–86
BoNT units			
per session	180.59	140.65	4–1050
per dystonia type			
Cervical Dystonia	266.18	103.71	
Blepharospasm	75.79	45.91	
Oromandibular dystonia	149.54	92.91	

SD: standard deviation; BoNT: botulinum toxin.

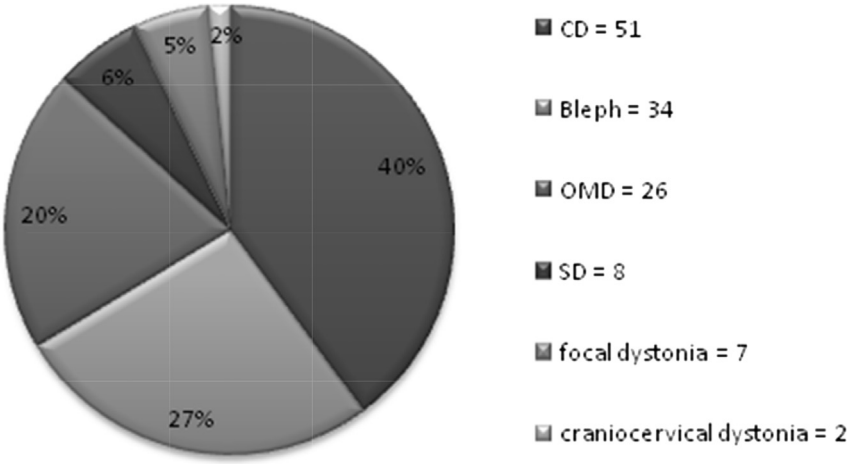

Fig. 1. Type of dystonia diagnoses in active patients treated with BoNT injections for the past two decades. CD: cervical dystonia; Bleph: blepharospasm; OMD: oromandibular dystonia; SD: spasmodic dysphonia; focal dystonia includes: arm dystonia, writer's cramp dystonia, leg dystonia, and foot dystonia.

Approximately 10% (409) of the visits had side effects reported for cervical dystonia, 9.5% (394) for blepharospasm, and 7% (291) for oromandibular dystonia (Fig. 2). A total of 47 BoNT-A antibody tests, using mouse protection assay (Hanna and Jankovic, 1998) were performed in 35 patients, 6 of which were positive and 41 were negative. Lack of response or recurrent decreased response was the most common reason for immunoresistance testing.

5. Discussion

The efficacy and safety profile of BoNT injections for the treatment of dystonia have been demonstrated by many studies (Ramirez-Castaneda and Jankovic, 2013). However, many of the studies have been limited because of relatively short follow-up period, small sample size, lack of objective assessments, or other problems. Our study, with a median follow-up period of 18.5 years, provides the longest follow-up in the largest series of patients. The demographics of our patient population are comparable to those of other long-term studies (Mejia et al., 2005; Lungu et al., 2011; Tan and Jankovic, 1999; Berman et al., 2005; Mohammadi et al., 2009; Bentivoglio et al., 2009; Hsiung et al., 2002). The dose of injected BoNT increased throughout the course of treatment when compared to the first injection (140.27 U versus 224.48 U, $p < 0.0001$). This is partly explained by the conservatively low dose used in initial injection session and also possibly by the need to inject higher doses as the treated disease progresses. Similarly, a fifteen-year follow-up period of 128 patients with blepharospasm treated with onabotulinumtoxinA and abobotulinumtoxinA demonstrated that the dose of both BoNTs was significantly increased over time (Bentivoglio et al., 2009).

In our study, the great majority of patients showed a prolonged sustained therapeutic benefit with repeat injections over the interval follow-up period (10–26 years). There was improved global response effect after the last injection compared with the first injection (3.57 versus 3.18, $p < 0.0001$), and peak effect dystonia was superior following the last injection than after the first injection (3.75 versus 3.45, $p < 0.0005$). Furthermore, there was a faster response latency after the last injection (5.5 days versus 3.3 days, $p < 0.0001$), and the duration of total and maximal responses after the last injection session was longer than after the initial session (15.78 versus 13.45,

Table 2
Long-term follow-up of treatment efficacy of 89 patients receiving periodically BoNT injections for treatment of dystonia.

Parameter	First injection	Last injection	p[a]
BoNT units	140.27 ± 94.18	224.48 ± 173.04	<0.0001
Global rating effect	3.18 ± 0.63	3.57 ± 0.49	<0.0001
Peak effect dystonia	3.45 ± 0.64	3.73 ± 0.45	0.0005
Latency of response (days)	5.3 ± 4.4	3.3 ± 3.16	0.0001
Duration of maximal response (weeks)	13.45 ± 4.14	15.78 ± 6.74	0.0084
Duration of total response (weeks)	16.33 ± 4.50	19.42 ± 7.90	0.0037

[a] $p \leq 0.05$ demonstrates statistical significance.

Table 3
Different type of side effects from BoNT injections from the total number of reported side effects during the entire follow-up period.

Side effects	Total number (793)	Percent (%)
Dysphagia	164	20.68
Ptosis	144	18.15
Neck weakness	71	8.95
Ocular side effects[a]	56	7.06
Injection site muscle weakness[b]	51	6.43
Injection site pain	44	5.54
Injection site hematoma	42	5.29
Flu-like symptoms	40	5.04
Hoarseness	36	4.54
Generalized weakness	31	3.91
Dry mouth	17	2.14
Dysarthria	14	1.76

[a] Includes: blurred vision, diplopia and dry eyes.
[b] Neck weakness not included.

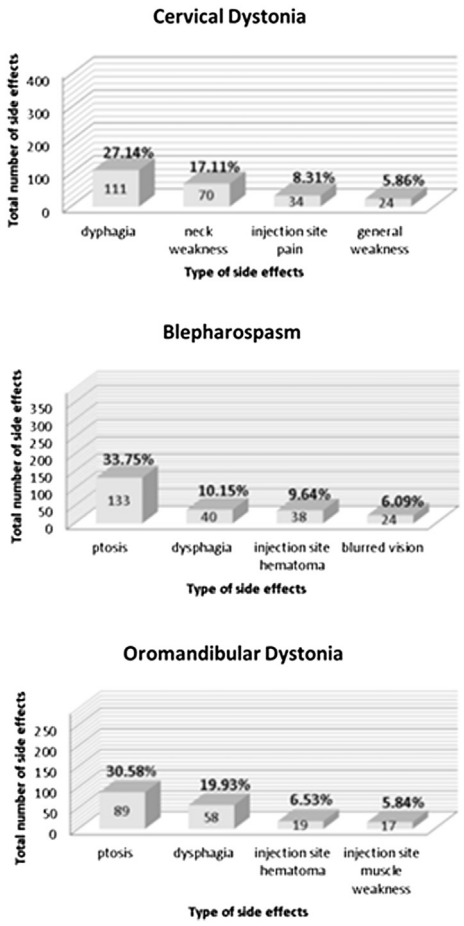

Fig. 2. Most common type of side effects per type of dystonia reported during the entire follow-up period of 89 patients receiving periodic BoNT injections.

$p = 0.0084$ and 19.42 versus 16.33, $p = 0.0037$, respectively). This correlates with results from other long-term studies which have shown similar efficacy outcomes. In one study, the treatment efficacy of 303 cervical dystonia patients with abobotulinumtoxinA showed sustained benefit over a mean follow up period of 3.2 years (Kessler et al., 1999). In another study, 78 cervical dystonia patients treated with onabotulinumtoxinA were followed for a mean period of 5.5 years had an improved median difference of 4.0 on a 1–8 visual analog scale (Skogseid and Kerty, 2005). A retrospective chart review to evaluate the efficacy and safety of BoNT-A injections after more than 10 consecutive years of treatment for blepharospasm and hemifacial spasm showed a higher mean injection dose per visit during the last year compared to the first year (26.8 ± 10.3 vs. 22.5 ± 7.5 units, $p = 0.003$), and the mean duration of effect during the first and last years were 12.4 ± 7.1 and 14.6 ± 7.0 weeks, respectively ($p = 0.076$) (Ababneh et al., 2013 Jul 12).

In our study adverse events were limited to less than 20% of all the visits, and when distributed by dystonia type 10% were reported for cervical dystonia, 9.5% for blepharospasm, and 7% for oromandibular dystonia. Dysphagia (27.1%) and neck muscle weakness (17.1%) were the most common side effects in patients with cervical dystonia in our patient cohort. This is consistent with the side effect profile reported by previous authors (Mohammadi et al., 2009; Hsiung et al., 2002; Kessler et al., 1999; Skogseid and Kerty, 2005; Brashear et al., 2000; Thenganatt and Jankovic, 2013; Haussermann et al., 2004). Ptosis was the most common side effect (33.7%) in patients injected for blepharospasm which correlates with pervious available data (Bentivoglio et al., 2009; Hsiung et al., 2002; Snir et al., 2003; Cillino et al., 2010). Oromandibular dystonia patients reported ptosis and dysphagia, 30.6% and 19.9%, respectively; other studies describe similar findings (Tan and Jankovic, 1999; Colosimo et al., 2012; Erdal et al., 2000). These results, which are consistent with those of other series (Mejia et al., 2005; Lungu et al., 2011; Tan and Jankovic, 1999; Berman et al., 2005; Mohammadi et al., 2009; Bentivoglio et al., 2009; Hsiung et al., 2002; Kessler et al., 1999; Skogseid and Kerty, 2005; Haussermann et al., 2004; Snir et al., 2003; Cillino et al., 2010; Schuele et al., 2005) provide evidence that BoNT exerts not only safe and effective symptomatic relief but also long-term benefits (Jankovic, 2006; Kojovic et al., 2011). The adverse events associated with chronic and periodic exposure to BoNT injections for the treatment of dystonia are usually minor, self-limiting, and decrease over time (Colosimo et al., 2012; Czyz et al., 2013).

Our primary aim was to depict a real-world experience which may be helpful when addressing the frequently asked question raised by patients about their long-term outcome. There are many reasons why patients stop receiving BoNT treatment or are lost to follow-up after a period of time, most of which are not necessarily related to medical issues or side effects but most frequently include financial and logistical (e.g. long distance travel) challenges. Although the long-term studies are open-label and have other limitations, such as high drop-out rate, it would be logistically and ethically impossible to conduct such longitudinal study in a double-blind placebo controlled design. Nevertheless, based on our results from this selected group of 89 patients treated for their dystonia for up to 26 years (mean follow-up period of 18.5 years), we conclude that BoNT treatment can provide a safe and long-term symptomatic benefit.

Author roles

Juan Ramirez-Castaneda, MD.

Research project conception and execution, organization, manuscript writing and review.

Joseph Jankovic, MD.

Research project conception and execution, organization, manuscript writing and review.

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Juan Ramirez-Castaneda, MD: nothing to disclose.

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Ethical statement

Only a retrospective chart review was performed. Patients were not directly contacted in this study. No protected health information is being disclosed to another party. Data obtained from the chart review were stored in a secured, password-protected department maintained server. Only investigators had access to the stored data. No personal information such as names, dates of birth, medical record number, etc. were stored. This protocol does not involve the additional collection of information other than what has already been documented on every single clinical visit. There is no biological sample collection.

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None.

Conflicts of interest

The authors declare no conflict of interest.

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