

Comparable Botulinum Toxin Outcomes between Primary and Secondary Blepharospasm: A Retrospective Analysis

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Abstract

Background: Blepharospasm is a focal cranial dystonia, which could be idiopathic in origin or secondary to an underlying disorder that commonly impairs quality of life. Botulinum toxin (BoNT) injections have become the treatment of choice; however, a less favorable response to BoNT is expected in secondary blepharospasm. No studies have been conducted comparing outcomes between blepharospasm cohorts. We therefore aim to compare BoNT outcomes in primary and secondary blepharospasm subjects.

Methods: A retrospective review of 64 blepharospasm subjects receiving BoNT therapy was conducted. Demographics, BoNT treatment schedules, duration of BoNT therapy, and side effects were recorded. Outcome measures were duration of benefit, peak-dose benefit recorded with the Clinical Global Impressions Scale (CGIS), and related side effects.

Results: No difference was found between the two cohorts regarding duration of benefit from treatment (primary 9.47 weeks vs. secondary 9.63 weeks, $p=0.88$). Perceived peak-dose benefit was more commonly reported as “very much improved” in secondary patients, but this was not significant ($p=0.13$). Higher BoNT dosages were required in both groups over time, with a mean increase of 20.5% in primary and 26.5% in secondary blepharospasm. Ptosis (8%) and diplopia (6%) were the most common reported side effects. Mean follow-up in years was similar between groups, 3.6 years for primary vs. 2.4 years for secondary blepharospasm ($p=0.17$).

Discussion: BoNT injections were effective with comparable benefits seen in both primary and secondary blepharospasm populations. Clinicians should be aware of the similar benefit from BoNT reported in secondary blepharospasm patients. The average duration of benefit in this cohort was comparable with previous reports.

Keywords: Cranial dystonia, botulinum toxin, Parkinson’s, tardive syndromes, Clinical Global Impressions Scale

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Introduction

Blepharospasm is a focal dystonia characterized by involuntary eyelid closure due to overactivity of the orbicularis oculi, the corrugators, and the procerus muscles.¹ The primary or idiopathic form, occasionally referred to as benign essential blepharospasm, is the most frequent subtype.² Blepharospasm may also be a manifestation of another underlying organic disorder. Secondary blepharospasm has been reported most commonly in structural brain lesions,³ tardive syndromes due to medication exposure,⁴ or related to neurodegenerative disorders, in particular Parkinson's disease (PD) and other parkinsonian syndromes.⁵

Blepharospasm is unlikely to be self-limited and may become a lifelong disabling condition requiring long-term treatment.¹ Botulinum toxin (BoNT) injections have become the main treatment for this and other types of focal dystonias⁶ with a reported success rate of 90%.⁷ Studies of BoNT outcomes on secondary blepharospasm are scarce, and there is consensus of a less favorable response to BoNT, with reports ranging from 50% to 60% clinical improvement.^{8,9} No studies have been conducted comparing outcomes between primary and secondary blepharospasm cohorts. We therefore sought to compare the treatment outcomes with BoNT therapy in primary and secondary blepharospasm and to describe the factors affecting these outcomes.

In the following retrospective study, comparable results regarding duration of benefit and perceived peak-dose benefit were observed in primary vs. secondary blepharospasm cohorts.

Methods

Study design

A retrospective review of 275 electronic records at the University of Florida Center for Movement Disorders and Neurorestoration (UF-CMDNR) was conducted from the period of July 2011 to June 2014. Daniel Martinez-Ramirez and Juan C. Giugni performed the chart review. The UF Institutional Review Board (IRB) approved the study.

Population studied

Subjects with a clinical diagnosis of blepharospasm according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM code 333.81), which was made by specialists trained in movement disorders, and who had received or are currently treated in our BoNT clinic were included. Patients with uncertain diagnosis and those with incomplete data on their electronic records were excluded. The studied population was divided into two groups according to the origin of blepharospasm as a primary or secondary blepharospasm. Causes of secondary blepharospasm included tumors, tardive syndromes, or neurodegenerative disorders, such as PD. Data were gathered in a prospective manner into our IRB database and analyzed retrospectively. Demographic information, BoNT treatment

schedules (muscles and units injected) from the first and last (most recent) sessions at the UF-CMDNR, and side effects were obtained from each patient's record, as well as from our IRB-approved database, INFORM-PD.

Description of procedure

Most patients received onabotulinumtoxinA (Botox, Allergan, Irvine, CA). For patients receiving rimabotulinumtoxinB (Myobloc, US World Meds, Louisville, KY; n=3), an approximate ratio of 52.3:1 was used to calculate total dosages.¹⁰ No patients were found to be receiving incobotulinumtoxinA or abobotulinumtoxinA. BoNT was prepared by trained nurses using 1 mL of saline solution for dilution to obtain 10 units in 0.1 mL for onabotulinumtoxinA. Injections were performed by fellowship trained movement disorders specialists experienced in this procedure.

Outcome measurements

The outcomes of the study were to compare 1) the duration of benefit, 2) the perceived peak-dose benefit, and 3) the side effects from BoNT injections from the first and last injections at UF between primary vs. secondary blepharospasm cohorts. Duration of benefit was ascertained by the following question, "How long did the benefit from the botulinum toxin injections last?", which was always asked by the clinician performing injections at each subject visit; it was reported in weeks, and was based on an estimate recall. The perceived peak-dose benefit from BoNT was obtained from the Clinical Global Impressions Scale (CGIS) during each subject's visit. The CGIS is a self-reported seven-point scale covering measures that evaluate change after the initiation of treatment. Subjects answer the question, "How would you describe your peak benefit from botulinum toxin injections?" with the following possible answers: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse.¹¹ Assessment of side effects was performed at each patient's visit. The clinician asked about the following symptoms: bruising, difficulty swallowing, head drop, headache, muscle weakness, drooping of eyelid, or upper respiratory infection.

Statistical analysis

A χ^2 test corrected with an Exact test was used for the following variables: gender, ethnicity, smoker, and muscles injected. Student's t-test was used for age, body mass index (BMI), years since first symptom, years since diagnosis, follow-up duration, dosages, number of injection sites, and side effects. To examine differences in duration of BoNT benefit and CGIS of benefit between primary and secondary blepharospasm, we used the independent samples t-test. *p*-Values <0.05 were considered statistically significant. A univariate general

Table 1. Demographic and Clinical Characteristics of the Studied Population

	Primary Blepharospasm (n=41)	Secondary Blepharospasm (n=23)	p
Female, no. (%)	28 (68.3)	6 (26.1)	0.001
Age, mean (SD), years	69.1 (9.2)	65.9 (10.2)	0.22
Caucasian, no. (%)	36 (87.8)	21 (91.3)	0.32
Smoker, no. (%)	12 (29.3)	10 (43.5)	0.33
BMI, mean (SD)	26.5 (5.5)	29.3 (7)	0.13
Years since first symptom, mean (SD)	14.2 (12.1)	6.2 (4.7)	<0.001
Years since diagnosis, mean (SD)	11 (8.8)	5.7 (4)	0.002
Duration of follow-up at UF, months (SD)	42.8 (39.3)	28.6 (29.5)	0.17

BMI, Body Mass Index; SD, Standard Deviation; UF, University of Florida.

linear model was used to compare outcomes within the secondary blepharospasm cohort. Bonferroni-corrected p-values for multiple comparisons are shown in Tables 1 and 2. Statistical analyses were performed using commercially available statistical software (SPSS, version 22.0; SPSS, Inc., Chicago, IL).

Results

Characteristics of population

Of the 64 subjects included for the final analysis, 64% (41/64) had primary and 36% (23/64) had secondary blepharospasm. Sixty-eight percent (28/41) in the primary blepharospasm group were females compared with 26% (6/23) in the secondary group ($\chi^2=10.5$, $df=1$, $p=0.001$). Mean ages at time of evaluation were 69.1 (± 9.2) years in the primary and 65.9 (± 10.2) years in the secondary group ($t=-1.25$, $p=0.22$). Symptom duration was significantly longer in primary than in secondary blepharospasm 14.2 (± 11.9) vs. 6.2 (± 4.7) ($t=-3.1$, $p=0.003$). Twenty-six primary blepharospasm patients had additional areas (20 patients had oromandibular dystonia (Meige syndrome) and 6 had Meige syndrome plus cervical dystonia) affected, while all secondary blepharospasm patients had other body regions involved. The main causes of secondary blepharospasm included PD 52% (12/23), followed by tardive syndromes in 26% (6/23). Other causes included progressive supranuclear palsy in three out of 23 cases, one case of Tourette syndrome, and one case secondary to radiotherapy. Five patients in the primary cohort had a past history of eyelid plastic surgery but continued to have symptoms requiring BoNT intervention. Four patients with primary blepharospasm, and eight with secondary blepharospasm had deep brain stimulation (DBS) implantation ($df=1$, $p=0.4$). Table 1 describes demographic and clinical characteristics in our population.

The clinical characteristics of the 12 PD patients in our cohort are also described. They had disease duration of 15.8 (± 6.5) years, a Unified Parkinson's Disease Rating Scale-III off-medication (on

stimulation, if the case) score of 39.8 (± 13.1) and an on-medication (on stimulation, if the case) score of 32.8 (± 9.1), Hoehn and Yahr stage 3.25 (± 0.8), and levodopa equivalent dose of 1,367 (± 432.7). Eight patients had DBS, and blepharospasm developed after device implantation.

Characteristics of botulinum toxin injections

The average follow-up at our BoNT clinic was 3.6 years for the primary group and 2.4 years for the secondary group ($t=-1.38$, $p=0.17$). The average dosages used in the first injection were 45.5 (± 28.4) units for the primary cohort compared with 39.3 (± 24.6) units for the secondary cohort ($t=-0.88$, $p=0.38$). The dosages of the last injections were 57.2 (± 21.4) units for primary vs. 53.2 (± 21.1) units for secondary ($t=-0.62$, $p=0.54$). A mean increase in BoNT units of 20.5% in primary and 26.5% in secondary blepharospasm was observed over time. We found that in both cohorts, additional muscles (procerus, corrugators, and frontalis) were included in the treatment plan when comparing the last injection with the initial injection of BoNT therapy. Table 2 summarizes BoNT injections.

“How long did the benefit from the botulinum toxin injections last?”

The primary blepharospasm group reported the duration of benefit to be 9.3 (± 3.6) weeks from the first injection compared with 9.5 (± 3.7) for the last injection at UF. Secondary blepharospasm subjects described the duration of benefit to be 8.2 (± 3.5) weeks from the first injection compared with 9.6 (± 2.3) weeks from the last injection at UF. The analysis revealed a comparable duration of BoNT benefit from the first injections ($t=-1.04$, $df=51$, $p=0.30$) and last injections ($t=0.15$, $df=50$, $p=0.88$) for primary and secondary blepharospasm.

Table 2. Comparison of BoNT Injections between First and Last Sessions at the University of Florida

	Primary (n=41)	Secondary (n=23)	p
First injection			
Dosage in units, mean (SD)	45.5 (28.4)	39.3 (24.6)	0.38
Shots given, mean (SD)	9.3 (2.7)	8.8 (1.8)	0.39
Side effects, no. (%)	10 (25)	1 (5)	0.02
Lateral oculi, no. (%)	41 (100)	23 (100)	1
Pretarsal, no. (%)	30 (73.2)	18 (78.3)	0.65
Corrugator, no. (%)	12 (29.3)	8 (34.8)	0.65
Procerus, no. (%)	14 (34.1)	4 (17.4)	0.15
Frontalis, no. (%)	8 (19.5)	1 (4.3)	0.14
Last injection			
Dosage, mean (SD)	57.2 (21.4)	53.5 (21.1)	0.54
Shots given, mean (SD)	9.9 (2.3)	9.9 (1.9)	0.99
Side effects, no. (%)	6 (16.2)	3 (17.6)	0.89
Lateral oculi, no. (%)	37 (100)	19 (100)	1
Pretarsal, no. (%)	28 (75.7)	18 (94.7)	0.14
Corrugator, no. (%)	18 (48.6)	10 (52.6)	0.78
Procerus, no. (%)	22 (59.5)	6 (31.6)	0.05
Frontalis, no. (%)	9 (22)	2 (10.5)	0.29

BoNT, Botulinum Toxin; SD, Standard Deviation.

Perceived peak-dose benefit from BoNT—CGIS

In the primary blepharospasm cohort, a similar number of patients described the benefit as “much improved” (48.6% vs. 50%) and “very much improved” (27% vs. 30.6%) after the first and last injections, respectively, using the CGIS. In the secondary cohort, 43.8% perceived the benefit as “very much improved” after the initial session compared with 56.3% after the last session. The same number of subjects (31.3%) perceived a “much improved” benefit in both sessions. Figure 1 represents the perceived peak-dose benefit in our populations. The CGIS revealed a similar magnitude of benefit for primary and secondary blepharospasm after the first (2.1 ± 0.9 vs. 1.9 ± 0.9 , $t = -0.73$, $df = 51$, $p = 0.47$) and last injections (1.9 ± 0.8 vs. 1.6 ± 0.7 , $t = -1.56$, $df = 50$, $p = 0.13$). Five primary patients and one secondary blepharospasm patient reported no benefit from the first BoNT injections, with only one primary blepharospasm patient reporting no change after the last injection.

Comparison within secondary blepharospasm cohort

A univariate general linear model was used to compare outcomes within the secondary blepharospasm cohort (neurodegenerative group, $n = 9$, vs. drug-induced group, $n = 5$). No significant differences were observed between groups during sessions. For the first injections at UF, the duration of benefit in weeks was 8.9 ± 2.9 vs. 8.2 ± 2.9 ($df = 1$, $p = 0.68$) and the CGIS was 1.4 ± 0.7 vs. 2.2 ± 0.8 ($df = 1$, $p = 0.1$). Regarding the last injections, the duration of benefit was 8.9 ± 2.2 vs. 11.2 ± 2.1 weeks ($df = 1$, $p = 0.08$) with a CGIS of 1.4 ± 0.8 vs. 1.8 ± 0.8 ($df = 4$, $p = 0.67$).

Side effects

Side effects in our cohort varied from 16.2% to 25% after the first injection and from 5% to 17.6% after the last injection at UF. No significance was found in frequency of side effects between the first ($\chi^2 = 3.6$, $df = 1$, $p = 0.06$) and the last sessions ($\chi^2 = 0.02$, $df = 1$, $p = 0.89$).

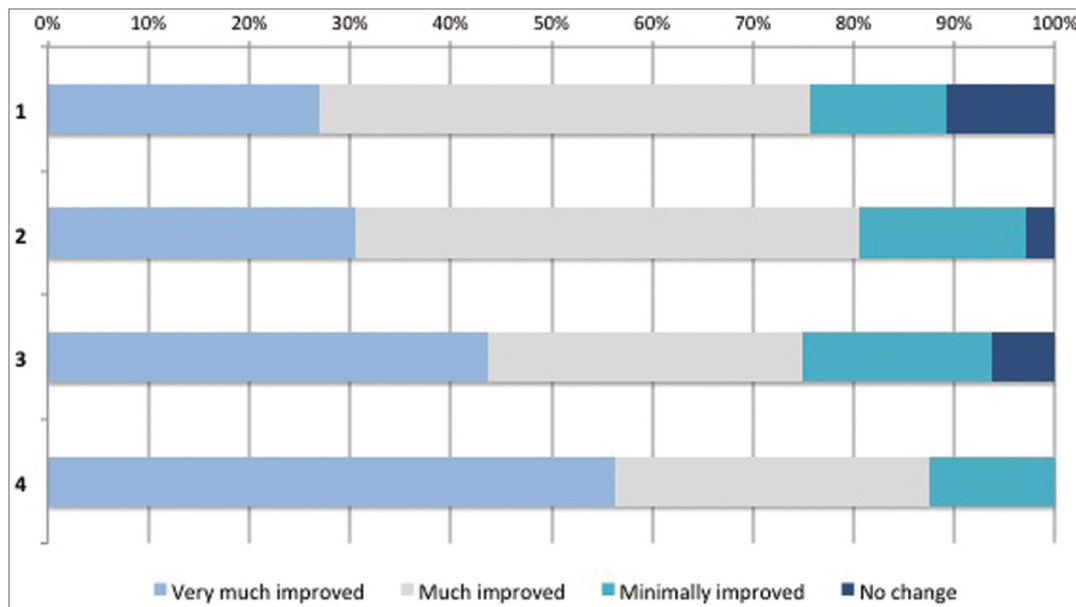


Figure 1. Chart Demonstrating the Clinical Global Impression Scale between Populations at two time points. 1) First session primary blepharospasm; 2) last session primary blepharospasm; 3) first session secondary blepharospasm; 4) last session secondary blepharospasm.

in the blepharospasm cohorts. Reported side effects in the primary blepharospasm group were as follows: first injection, bruising (three out of 10), dry eyes (two out of 10), ptosis (two out of 10), and red eye, diplopia, and pain, one case each; last injection – diplopia (3/6), with bruising, dry eyes, and ptosis one case each. Only one subject in the secondary blepharospasm group reported bruising after the first injections, and three reported bruising after the last injections.

Discussion

In the present study, treatment outcomes of BoNT injections were compared between primary and secondary blepharospasm. Primary blepharospasm was found to be more prevalent in females, whereas secondary blepharospasm was more common in males. These findings are consistent with previous reports,^{5,12,13} where focal cranial dystonias have been reported to be more prevalent in females; since the majority of secondary causes in our cohort were due to PD (52%), which is male predominant, this gender predominance is expected as well. Both populations had a similar mean age of onset for symptoms in the sixth decade of life, which is expected since blepharospasm is known to present as a late-onset disease.^{12–15} Among the etiologies of secondary blepharospasm, PD was found to be the most common, followed by tardive syndrome. This contrasts with other studies,^{5,13} which have reported predominance of atypical parkinsonisms among the causes of secondary blepharospasm. Interestingly, eight of 12 PD patients in our cohort had DBS, with the development of blepharospasm after device implantation, which could also potentially explain the unusual number of secondary blepharospasm cases related to idiopathic PD. Employing different methodologies, which included other cranial dystonias, and a lack of inclusion of patients with apraxia of eyelid opening could explain this difference.

We also observed a significant delay in diagnosis for patients with primary blepharospasm compared with secondary blepharospasm. One possibility could be the fact that patients with secondary causes, particularly patients with PD, would likely be under clinical surveillance by a neurologist with more opportunities for frequent clinical assessments.

The duration of benefit from BoNT injections was comparable between primary and secondary cohorts. More interestingly, the approximate reported benefit in both populations lasted for a mean of 9.5 weeks, which is below the typical 12-week injection schedule. Most studies have reported duration of treatment efficacy ranging from 12 to 18 weeks.^{14–17} However, recent studies have reported lesser duration of benefit as well. In one study of 32 patients with either blepharospasm or hemifacial spasm, for 1.1% of the injections the duration of benefit was reported to be less than 4 weeks.¹⁸ Another study reported that the duration of benefit in nine blepharospasm patients was between 9 and 13 weeks,¹⁹ similar to our findings. A recent study of 288 blepharospasm patients reported a therapeutic effect lasting for about 10 weeks, 2 weeks shorter than the recommended inter-injection interval.²⁰ Most studies have included different types of cranial dystonia, which could also affect the results by incorporating higher cumulative BoNT doses per injection cycle. Our study is the first to compare the duration of benefit in subjects with pure blepharospasm, rather than in a mixed dystonia population.

Comparable with previous studies,¹⁶ a better efficacy of BoNT injections following the last injection was observed in both cohorts when compared with the initial injection. This difference may have been due to the escalation of dose and refinement of muscle distribution of the toxin over time. An alternative explanation is that there may have been a propensity for better benefit when muscles were

repeatedly subjected to treatment, rather than remaining in the native dystonic state. Patients with secondary blepharospasm tended to report a greater level of improvement than primary blepharospasm patients, but this comparison did not reach significance. Furthermore, patients who are responders are more likely to continue with serial injections, so the last injections recorded may select for a pool of better responders, demonstrating improved efficacy. When analyzing the secondary cohort, we observed a shorter duration of benefit in weeks, which was not significant, in the neurodegenerative group when compared with the drug-induced group (8.9 ± 2.2 vs. 11.2 ± 2.1). Although this confirms the consensus of a less favorable clinical outcome in blepharospasm due to neurodegenerative diseases when compared with other secondary causes, studies with a higher number of patients will be required to confirm this observation.

A higher BoNT dose was used in both populations over time (ranging from an increase of 11.7 to 13.9 units over 2.4–3.6 years' follow-up), which is consistent with previous publications. In a study measuring the long-term efficacy of BoNT in several types of dystonia, the dosage was found to have been increased gradually.¹⁶ A recent study of long-term treatment in cranial dystonias reported a higher mean injection dose per visit during the last year than in the first year of injections.¹⁵ However, another study of cranial dystonias reported the dose required for treatment remained unchanged, suggesting that dose changes over time might have been an effect of the "titration" phase, and not of increasing resistance to BoNT.¹⁴ Larger prospective trials will be required to answer whether the increase in dose requirements was due to the methodology employed, to disease progression, or to progressive treatment tolerance.

Side effects in our cohort varied from 5% to 25%, with ptosis (8%) and diplopia (6%) being the most common. This is similar to previous studies that reported side effects ranging from 2% to 35%.^{14–16,18,19} Interestingly, the side effects were more significant during the first injections in primary blepharospasm patients, perhaps because a higher dosage was used in this cohort. The initial dosages in our populations are higher than the recommended initial dosages;²¹ however, a number of our initial BoNT schedules are based on previous treatments received outside our clinic. No previous studies have reported the relationship between the muscles injected and the clinical outcomes. We observed a non-significant difference in self-described benefit from BoNT in patients receiving higher dosages on the first visit and in those receiving injections in the corrugator muscle.

Several limitations should be considered before interpreting our results. It is a retrospective study with a relatively small cohort. Different trained specialists injected patients. In the first session at UF, five different physicians injected the primary blepharospasm cohort while four injected the secondary cohort. Three physicians injected both cohorts in their last session. A variation in techniques could affect the response to BoNT. We did not consider the effect of the initial "titration" phase distinctly from gradual increases over time; however, our follow-up period in both cohorts is over 2 years. We did not use clinical rating scales, such as the Jankovic Rating Scale,²² or the Blepharospasm Disability Index²³ for the assessment of severity or

disability related to blepharospasm. This study did not include obligatory neuroimaging (magnetic resonance imaging or computed tomography angiogram) to rule out structural brain lesions as a secondary cause; however, no signs or symptoms were found during clinical examination that suggested a structural brain lesion in the primary cohort. Finally, medication adjustments could also have affected the results. The doses of neuroleptics were held constant during BoNT treatment for the two patients who were receiving this class of drugs. Three patients received medications to treat tardive dystonia (tetrabenazine or anticholinergics), and five patients had other body regions affected by dystonia (four with cervical and one with generalized dystonia). Doses of dopaminergic medications were modified in five of 12 PD patients during the time of the BoNT injections. All of these factors should be considered when interpreting the results of our study.

In summary, BoNT injections were effective and had similar benefits in both groups of patients, suggesting that the etiology of blepharospasm does not seem to impact the BoNT outcome. However, we need to consider a possible shorter duration of benefit in cranial dystonias, specifically in blepharospasm subjects, compared with a typical 12-week treatment cycle for cervical dystonia.²⁴ These findings should be of interest to practitioners injecting patients who have blepharospasm, especially those injecting patients who have secondary blepharospasm.

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