ORIGINAL CONTRIBUTION

Botulinum Toxin A Treatment for Primary Hemifacial Spasm

A 10-Year Multicenter Study

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Background: Botulinum toxin A (BTX) is the currently preferred symptomatic treatment for primary hemifacial spasm (HFS), but its long-term efficacy and safety are not known.

Objective: To assess the long-term effectiveness and safety of BTX in the treatment of primary HFS.

Design: Retrospective review of medical records of the 1st and 10th years of treatment.

Setting: Outpatient clinics of 4 Italian university centers in the Italian Movement Disorders Study Group.

Participants: A series of 65 patients with primary HFS who had received BTX injections regularly for at least 10 years.

Main Outcome Measures: Mean duration of improvement and quality of the effect induced by the preceding treatment (measured using a patient self-evaluation scale) and occurrence and duration of adverse effects in the 1st and 10th years of treatment.

Results: Using a mean BTX dose per treatment session similar to that used by others, we obtained a 95% response rate and an overall mean duration of improvement of 12.6 weeks during year 1. The effectiveness of BTX in relieving the symptoms of primary HFS, as measured by the response rate and average duration of improvement, remained unchanged in the 1st and 10th years. Patients needed statistically similar BTX doses in the 1st and 10th years. The rate of local adverse effects (including upper lid ptosis, facial weakness, and diplopia) diminished significantly in the 10th year of treatment.

Conclusion: Treatment with BTX effectively induces sustained relief from symptoms of HFS in the long term, with only minimal and transient adverse reactions.

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BOTULINUM TOXIN A (BTX) is the currently preferred symptomatic treatment for primary hemifacial spasm (HFS).[1-6] Because HFS rarely remits spontaneously,[7] most patients need to continue treatment for many years, if not throughout life. The long-term efficacy and safety of BTX is therefore an increasingly important question. Few of the numerous published studies[2,5-9] assessing BTX treatment of HFS included patients with serial treatments covering several years, and none had follow-up of more than 5 years. In this multicenter study, we reviewed the long-term effectiveness and safety of BTX treatment in a series of 65 patients with primary HFS who had received BTX injections regularly for at least 10 years.

RESULTS

The 65 patients who completed the 10-year course of continuous BTX treatment received a total of 239 treatments during the first year. On average, each patient received a cumulative yearly dose of 70 U subdivided in 3 to 4 treatment sessions. The mean dose of BTX per treatment session was 17.5 U (range, 7.5-45.0 U). According to patients' subjective impressions, nearly all treatments improved HFS: the response rate was 96%. Although lower face muscles were not directly injected, most patients reported marked benefit in the orbicularis oris. Treatment failures mostly concerned the first injection. In later sessions, when the dose was increased, the symptoms diminished. The mean ± SD duration of effect was 12.6 ± 5.7 weeks. No significant difference was found between treatment variables investigated in the 1st and 10th years of treatment, including number of treatments per patient, number of BTX units per treatment session, cumulative yearly dose per patient, response rate, and duration of effect (**Table 1**).

PATIENTS AND METHODS

Patients with primary HFS attending the outpatient clinics at 4 Italian university centers ("La Sapienza" Rome, Bari, Genova, and Messina) belonging to the Italian Movement Disorders Study Group were enrolled in this retrospective study. All centers used standard methods for recording information, injecting BTX, and assessing treatment effectivness.[10] A total of 86 patients (28 men and 58 women) received a diagnosis of primary HFS according to published criteria[11] and began treatment with BTX between January 1, 1987, and January 1, 1990. Their mean±SD age at first symptoms was 51.0±11.4 years, and mean age at first treatment was 58.0±12.0 years. The intensity and frequency of spasms differed in patients, but all reported marked interference with activities of daily living (reading, eating, talking, watching television, and mental concentration), social tasks, or both. Of the total cohort of 86 patients initially available for study, 21 did not attend follow-up visits for 12 months or more and were thus considered "dropouts." Of the 21 dropouts, 5 had not discontinued BTX therapy but had switched to other treatment centers closer to their homes. The corrected dropout rate was therefore 19% (16/86). Reasons for treatment discontinuation included death from other causes (5 patients), unsatisfactory results (6 patients, 2 of whom underwent surgery), and complete and long-lasting symptom relief (2 patients). Three patients dropped out for unknown reasons. All patients who dropped out discontinued treatment during the second or third year.

The remaining 65 patients (19 men and 46 women) completed at least 10 years of BTX treatment with the same commercial product (Botox; Allergan, Irvine, Calif). Their mean±SD age at onset of symptoms of HFS was 50.0±11.3 years, and mean age at first treatment was 56.0±11.0 years. During the initial months of treatment, patients were continuously monitored and treated when spasms reappeared. Thereafter, they returned only when they needed another injection because symptoms had recurred. Before each injection session, patients were questioned about the results of the previous session. To assess the long-term effectiveness and safety of BTX, we reviewed patients' medical records for the 1st and 10th years of treatment and collected the following information: date of injections, total dose, number and location of injection sites, duration of improvement (defined as the interval between treatment and the recurrence of symptoms severe enough to prompt patients to receive another injection) and quality of the effect induced by the preceding treatment, and occurrence and duration of adverse effects. Because of the lack of reliable clinical methods to assess the severity of HFS, the quality of the BTX effect was measured using a patient self-evaluation scale. At each injection visit, changes in the patient's status were scored as no change (muscle spasms that interfered with activities of daily living or social tasks in such a way that patients continued to be socially embarrassed), moderate improvement (reduction in the frequency and duration of spasms so that they interfered slightly with activities of daily living or social tasks), or marked improvement (spasms in the injected muscle had ceased altogether so that they no longer interfered with activities of daily living or social tasks). Patients who reported no improvement or a short-lasting benefit had their BTX dose increased according to their individual needs. At each session, BTX (10 U per 0.1 mL of isotonic sodium chloride solution final concentration) was injected into 3 or 4 sites in the orbicularis oculi only. We treated HFS by injecting the orbicularis oculi muscle alone rather than both the orbicularis oculi and oris muscles because BTX injection into the latter muscle often causes weakness of the lower facial muscles.[4,6-10] Data were analyzed for statistical significance using the paired t test and the χ^2 test.

Adverse reactions were observed in 24 of 65 patients during the first year of treatment and in 8 of 65 patients during the 10th year ($P=.02$). Likewise, the number of treatment sessions associated with BTX-induced adverse reactions dropped significantly from the 1st to the 10th year (34 of 239 vs 8 of 232 treatment sessions; $P<.001$). The most frequently reported adverse reaction was upper lid ptosis, followed by weakness of lower facial muscles on the side of injection and diplopia (**Table 2**). The reduction from the 1st to the 10th years was significant for upper lid ptosis but not for lower facial weakness on the side of injection and diplopia, probably because of lack of statistical power. Local adverse effects were severe and interfered with daily activities and social tasks in approximately 30% of cases. The mean dose of BTX was slightly but not significantly higher for injection sessions that induced adverse reactions than for sessions that did not (16.4±6.9 U vs 14.2±5.8 U; $P=.23$).

COMMENT

Our multicenter review provided a larger sample of patients with primary HFS receiving BTX treatment than would be possible with one center alone. It also had the advantage of 10-year follow-up. Our study provides evidence of the long-term effectiveness and safety of using BTX to relieve the symptoms of primary HFS.

Although BTX treatment for HFS began in the early 1980s, most available studies[5-9] describe relatively short treatment courses and follow-up. In these investigations, although maximum follow-up ranged from 4 to 8 years, few patients received continuous treatment throughout the study. Elston[5] reported the results of a 7-year study without detailing the results of long-term treatment. In 1995, Van den Bergh et al[8] reported BTX treatment outcome in 40 patients, but they did not provide long-term clinical effects. Mauriello et al[7] reported 47 patients who had been treated for a median of 4.9 years. Jitpimolmard et al[9] conducted a detailed clinical analysis of the effects produced by BTX use, but mean follow-up was 2.4 years, and only 21 patients completed approximately 3 years of treatment.

Until the present study of 65 patients treated for 10 years, data were lacking on longer-term outcome and, most important, on response rate, duration of improvement, and long-term adverse reactions.[5-9]

Using a mean BTX dose per treatment session similar to that used by other researchers,[1-4,6,7] we obtained a 95% response rate and an overall mean duration of improvement of 12.6 weeks during the first year of treatment. This outcome compares well with shorter-term results.[1-4] The

Table 1. Comparison of Findings at the Beginning and End of 10 Years of Botulinum Toxin A Treatment in 65 Patients With Primary Hemifacial Spasm

	1st Year	10th Year	*P* Value*
Treatments, No.			
Total	239	232	
Per patient, mean ± SD	4.00 ± 0.89	3.80 ± 0.97	.22
Botulinum toxin A, units per treatment session, mean ± SD, No.	17.3 ± 7.9	15.9 ± 5.6	.21
Cumulative yearly units per patient, mean ± SD, No.	61 ± 33	58 ± 22	.54
Effect of treatment, %			
None	4	4	
Moderate	65	61	.83
Marked	31	35	
Duration of effect, mean ± SD, wk	12.6 ± 5.7	13.5 ± 5.0	.11

*Paired *t* test and χ^2 test (2 × 3).

Table 2. Comparison of Adverse Events at the Beginning of 10 Years of Botulinum Toxin A Treatment in 65 Patients With Primary Hemifacial Spasm

Adverse Events	1st Year	10th Year	*P* Value*
Upper lid ptosis			
Patients, No. (%)	15 (23)	5 (8)	.03
Treatment sessions, No. (%)	21/239 (9)	5/232 (2)	.003
Duration, mean ± SD, wk	3.0 ± 2.0	2.6 ± 0.5	.07
Facial weakness on the side of injection			
Patients, No. (%)	7 (11)	3 (5)	.30
Treatment sessions, No. (%)	10/239 (4)	3/232 (1)	.10
Duration, mean ± SD, wk	3.5 ± 1.1	3.2 ± 0.5	.66
Diplopia			
Patients, No. (%)	2 (3)	0	.47
Treatment sessions, No. (%)	3/239 (1)	. . .	.28
Duration, mean ± SD, wk	4 ± 0	. . .	NS†

*Paired *t* test and χ^2 test.
†NS indicates not computable.

effectiveness of BTX treatment in relieving the symptoms of primary HFS, as measured by the response rate and average duration of improvement, remained unchanged in the 1st and 10th years. Hence, BTX use seems to induce substantial, sustained relief over time. Further support for its prolonged efficacy comes from the statistically similar doses our patients needed in the 1st and 10th years. Although other researchers reported variable dose reduction during follow-up, despite an unchanged duration of benefit,[5,8,9] they used a higher initial dose than we did.

Consistent with previous studies,[1-9] our patients' most frequent adverse reaction was upper lid ptosis, followed by weakness of lower facial muscles on the side of injection, probably due to spread of the toxin from the lower eyelid. The overall rate of BTX-induced adverse reactions diminished significantly in the 10th year of treatment. Because the mean number of BTX units per treatment session remained practically unchanged throughout the study, we attribute the reduction to optimization of the injection technique.

A potential limitation of our study may be that to rate the quality of the effect of BTX treatment on HFS we used a patient self-evaluation scale rather than an observer-based rating. Valid and reliable clinical methods of assessing the severity of HFS are lacking, however. In addition, no direct relationship may exist between the intensity and frequency of facial spasms and interference with activities of daily living or other social tasks. Thus, a patient self-evaluation scale may express the impact of treatment on HFS in the long term better than 4- or 5-point severity scales based on an observer's subjective assessment of eyelid spasms.[12]

This study provides valuable information regarding the long-term effectiveness and safety of using BTX to relieve the symptoms of primary HFS. Injection of BTX into the orbicularis oculi muscle is a safe and effective treatment for the symptoms of HFS and effectively induces sustained relief from symptoms in the long term (10 years in this study), with only minimal and transient adverse reactions.

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