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Treatment of blepharospasm with botulinum neurotoxin type A: long-term results

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PURPOSE. *To describe the long-term efficacy and side effects of treatment of blepharospasm with botulinum neurotoxin type A (Botox).*

METHODS. *A total of 178 patients with blepharospasm were treated by injections of botulinum toxin in the Eye Clinic of the University of Naples from 1980 to 2001. The severity of spasm for each patient was graded on a four-point scale. Duration of improvement was assessed and reported in months.*

RESULTS. *Of 178 cases, 10 were lost to follow-up; of the remaining patients, 93% reported improvement after treatments. The mean duration of improvement was 3.6 months. Twelve patients (76%) who underwent more than 14 treatments maintained stable relief. Three patients (1.7%) had a total remission of spasms. Side-effects were local; none of the 168 patients experienced any systemic or toxic reaction.*

CONCLUSIONS. *Botulinum toxin therapy for blepharospasm can provide long-lasting relief and reduction of spasms in the majority of patients. This therapy has the advantages of being safe, simple, and repeatable. (Eur J Ophthalmol 2003; 13: 331-6)*

KEY WORDS. *Botulinum neurotoxin type A, Blepharospasm, Orbicularis oculi muscles*

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INTRODUCTION

Idiopathic blepharospasm is a focal dystonia of unknown etiology characterized by involuntary contractions of the orbicularis muscles of the eyelids that provoke forced eyelid closures. Although its cause is unknown, a defect in neurotransmission appears likely. The median age at onset is approximately 50 to 60 years, and women are more often affected than men, with a 2:1 ratio.

Eyelid closure is usually bilateral, but may be unilateral or asymmetric. Spasms may extend from the orbicularis region to the middle and lower facial muscles. Variability of symptoms is typical and may be influenced by environmental factors. For example, spasms may worsen in some conditions, such as exposure to sunlight, stress, general fatigue and eye fatigue (brought on by watching television, reading, or driving), and may improve when talking or eating.

Variability of responses to botulinum neurotoxin type A (BONT/A) treatment, particularly duration of response, is thought to be associated with clinical and physiologic factors unique to the patient. Burbaud et al (1) found that in 45 patients with blepharospasm and 66

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with hemifacial spasm who underwent BONT/A treatments, there was no correlation between age, sex, cardiovascular disease, cervical trauma, or thyroid disease and the duration of the effect of therapy. However, patients who were clinically anxious or depressed responded less effectively to treatments, suggesting that there may be a psychopathologic basis for differences in response, and that anxiety-depressive disturbances may not be secondary to the spasms.

Ophthalmologic and neurologic examinations are required to make a diagnosis of blepharospasm. There is generally no reason to conduct other medical investigations; in only very rare cases has blepharospasm been associated with brainstem or other structural lesions. If, however, there are other neurologic signs, neuroimaging is indicated.

In the past, control of symptoms had been achieved surgically (using a facial nerve section or a myectomy) to prevent sustained muscular contraction (2-4), or pharmacologically (using anticholinergic drugs, dopamine agonists and antagonists, baclofen, and antipsychotic drugs) (5-7). Although effective in most cases, these treatments had serious drawbacks. Surgery is irreversible and invasive, and the drugs used sometimes have serious side-effects (including dry mouth, blurred vision, confusion, and hallucinations). In addition, some drugs had very low success rates (dopamine agonists and antagonists, baclofen, and antipsychotic drugs) (5-7). The introduction of botulinum toxin injections to treat blepharospasm provided an alternative, and subsequently led to a marked reduction of both surgical and pharmacologic treatments.

Botulinum neurotoxin type A, produced by *Clostridium botulinum*, is a polypeptide dimer consisting of a heavy chain (H chain) and a light chain (L chain) linked by a disulphide bond. The H chain is responsible for the highly selective targeting of the toxin to the cholinergic nerve terminals of the neuromuscular junction. The L chain contains the toxin, which acts by disabling the acetylcholine release mechanism, producing a reversible paralysis of the injected muscle. If used in therapeutic doses in a hyperactive muscle, the muscle is weakened and relaxes (8-10).

Recovery of muscle function is thought to depend on the rate at which the toxin is metabolized by the nerve ends, and the rate at which the nerve is able to replace damaged proteins. Studies show that within 2 days post injection the muscle begins to form new nerve terminals, and within 2 weeks, new synapses, which peak in 5 to 10 weeks (9,10). The effects of the toxin are related to the recovery of muscle function and have a duration on average of 10 to 14 weeks.

Dr. A.B. Scott, from the Smith-Kettlewell Eye Research Foundation in San Francisco, is credited with the first use of neurotoxins to treat eye movement disorders (11). In 1970–71, he injected, under electromyographic control, low doses of various neurotoxin agents into the extraocular muscles of a monkey to reduce the activity of hyperactive muscles. In 1973, he began using botulinum toxin in animal studies to study chemical denervation (12). In 1977, he treated the first human patient with squint using *botulinum* toxin (11). Our studies of the uses of *botulinum* toxin in strabismus began in 1979 (13). Subsequently, because of the success of such treatments, the use of *botulinum* toxin was studied in other ocular motility disorders including nystagmus, hemifacial spasm, spastic entropion, and blepharospasm (14-17).

MATERIALS AND METHODS

Subjects

All patients with blepharospasm presenting in the years 1980 to 2001 underwent an ophthalmologic examination. A total of 178 patients with blepharospasm in whom a secondary cause had been ruled out were identified. Ten of these patients were excluded from the study because they were lost to follow-up after only one treatment, leaving 168 patients in the study. In many cases patients had undergone unsuccessful pharmacologic treatment before inclusion in this study. None had undergone surgery. The severity of the spasms for each patient in the study was graded on a four-point scale (Tab. I) before any *botulinum* treatment.

TABLE I - BLEPHAROSPASM: SPASM INTENSITY SCALE (sec. A.B. Scott)

0 = None
1 = Increased blinking caused by internal stimuli
2 = Mild, noticeable fluttering; not incapacitating
3 = Moderate, very noticeable, mildly incapacitating
4 = Severely incapacitating (inability to drive, read, etc.)

Treatment

Patients were treated with BONT/A. A lyophilized preparation of *botulinum* exotoxin type A in vials containing 100 mouse units (MU) of toxin activity was used.

Each treatment consisted of four injections performed under electromyographic control: two in the lower eyelids in the pretarsal region, one in the lateral canthus, and one in the third lateral part of the upper eyelid. The central part of the upper eyelid was avoided to reduce the risk of ptosis. The initial treatment consisted of injecting 2.5 (5 MU) /0.1 ml at each of the four injection sites of each eye (total dose of 20/40 MU). Treatments was then managed on a case-by-case basis. In no case was a patient treated with more than 80 MU (18, 19).

If subsequent treatments were indicated, they were done after an interval of a minimum of 2 months to allow for the release of bound drug from muscles and plate receptors.

Assessment of treatment

The amount and duration of any improvement was assessed by the patient using a rating scale (Tab. II) or, in the case of patients living close to the hospital, examination by a clinician. Patients were also instructed to record any side-effects.

Treatment was considered successful if there was a reduction in spasm intensity (defined as a reduction of ≥1 point[s] from the baseline described in Table I) lasting at least 2 months. The duration of successful treatment was defined as the time between the last injection and the recurrence of disabling symptoms. Symptoms were considered disabling when they prompted the patient to request additional treatments.

RESULTS

None of the 168 patients experienced any systemic toxic or allergic reactions to the BONT/A injections. A total of 1264 treatments (ranging from 1 to 41 per patient over the course of the study) were done. Nearly all the treatments were considered successful (1100/1264 or 87%). A total of 156/168 patients (93%) reported improvements after treatment. The mean duration of improvement for all patients was 3.6 months (range 0–16 months). Twenty-five patients discontinued therapy after one to three treatments for financial reasons (14%), because they did not respond to treatment (7%), or for unknown reasons (7%). Of 168 patients, 3 (1.7%) had a total remission of spasm 6, 5, and 3 years after his or her last treatment. A total of 116 (69%) of the study participants continue to have *botulinum* toxin treatments.

Twelve of 168 (7%) patients had more than 14 treatments each and were followed in the study for 10 years or more (range 10–18 years). During their therapy, reduction of improvement gained dy treatment was detected (Tab. III).

Side effects as recorded by patients are shown in Table IV.

TABLE II - RATING SCALE TO RECORD IMPROVEMENT AFTER EACH INJECTION (sec. J.S. Elston)

Date:
injection number:

	Months after treatment
Visual function	1 2 3 4 5
Reading Watching television Out alone Driving	
House working or Outside job	1 2 3 4 5
Uncomfortable Difficult Not able	
Side Effects	1 2 3 4 5
Ptosis Double vision Blurred vision Other	

TABLE III - DURATION OF BENEFIT IN 12 PATIENTS RECEIVING AT LEAST 15 INJECTIONS

Patient	**No. of treatments** (both eyes)	**Average dose** (MU)	**Average duration of benefit after first 10 injections** (months)	**Average duration of benefit from 11th to the last injections** (months)	**Follow-up** (years)
RV	34	80	4	4	15
LG	23	80	3	3	10
AA	30	40	5	5	15
IC	32	70	5	6	10
CM	41	80	5	5	18
TV	19	80	6	6	15
TD	25	80	5	5	13
BZ	30	80	3	3	12
BL	21	40	5	5	12
ZP	34	80	3	3	11
LMG	16	70	7	7	11
TV	15	40	6	6	10

DISCUSSION

Our results, which are supported by others (20-24), suggest that BONT/A injections are effective in temporarily treating blepharospasm. Apart from showing its usefulness, our study also addresses some controversial aspects of this therapy; specifically, the duration and amount of reduction of symptoms, the effectiveness of treatment after repeated therapies, the immune response to long-term therapy, and the frequency of side-effects after treatment.

TABLE IV - SIDE EFFECTS RECORDED BY PATIENTS AFTER TREATMENT WITH BOTULINUM NEUROTOXIN TYPE A

Side effects/ complications	**Patient % (n = 168)**	**Treatment % (n = 1264)**
Diplopia	16.6	1.2
Ptosis	9.3	0.7
Lip. orb. paresis	1.3	0.01
Entropion	1.2	0.01

Duration and amount of reduction of symptoms

It is generally agreed that there is a great variability of responses with regard to spasm symptoms among patients with BONT/A therapy and that the duration of the toxin effect is longer in hemifacial spasm than in blepharospasm. Even in the same patient, treatments done at different times may produce different effects. Our results support this and are in accordance with the literature (16, 21, 22). The average duration of relief of symptoms in our patient population was 3.6 months with a range of 4 weeks to 12 months. In some patients, the response to treatment showed a pattern of regression of symptoms which, after reaching a maximum peak, was followed by a progressive recurrence of spasms. In others, the response was unpredictable, with some treatments producing a regression of symptoms and others having little effect.

In our study, the effectiveness of BONT/A injections in reducing symptoms was assessed by patients self-rating their improvement and in a small minority of cases, by clinicial examination. Whereas the patient rating scheme may be considered subjective, we found that patients' ratings closely mirrored those done by the clinician, and for this reason believe that it is a useful way to measure the effectiveness of the BONT/A therapy. Furthermore, we believe that patients, who are generally very sensitive to any changes in treatment efficacy, are in a position to accurately record any differences in the effects of treatment.

The effectiveness of treatment after repeated therapies

There are conflicting reports in the literature regarding the efficacy of BONT/A treatments after long-term use. Although Kraft and Lang (25) found a reduction in the duration of relief of symptoms after serial treatment, most studies find no change (26). Results of our patients who had undergone treatment for over 10 years (n = 12) suggest that, correcting for variability in response within the same patient, the average duration of relief of symptoms does not vary after serial treatments, once an effective dose for the patient has been established (Tab. IV).

The immune response to long-term therapy

Long-term BONT/A therapy is not uncommon and has raised some concerns regarding immune response by patients against BONT/A. The literature has conflicting reports on this subject and comparison of studies is made difficult because of differences in how each study does its antibody titrations (27, 28). Although some patients develop antibodies against BONT/A, it is difficult to predict who will do so, and when antibodies are detected, what effect they will have on the patient's treatment response. In some studies the presence of antibodies is not associated with a reduction in the clinical effectiveness of the treatment (28, 29). In our study, 12 patients had long-term therapy ranging from 10 to 18 years (10 to 41 treatments). None had any reduction in response to treatment. Although the immunoresponse to BONT/A of these patients was not assessed, there is no indication from a clinical perspective that any patients developed antibodies against the toxin. However, given that others (26, 27) have shown that the presence of antibodies may not alter response to BONT/A treatment, it is possible that our patients did develop antibodies that did not interfere with the treatment.

Side effects of BONT/A treatment

The most frequent complications cited after BONT/A treatments in the literature are diplopia and ptosis–both thought to be caused by the diffusion of the toxin to other ocular muscles. Some authors suggest that it is nearly impossible to reduce the percentage of ptosis to below 15%, that the risk of side effects increases with the number of treatments and that nearly all patients who have undergone 15 or more treatments will show at least one side effect (29). In our study a less than average percentage of patients experienced the side effects of ptosis and diplopia (Tab. IV). In part, our low occurrence of ptosis may be because the BONT/A injection was placed as far from the levator muscle as possible. In our study, the percentage of side-effects in relation to the number of treatments (rather than the number of patients) was very low, and in all cases side-effects were temporary. These findings suggest that the use of BONT/A injections for the treatment of blepharospasm is a safe alternative to pharmacologic treatment or surgery.

Twelve of 168 patients (7%) did not respond to BONT/A treatments and the reason is unclear. It is possible that they metabolize the toxin too quickly for it to be effective. In such cases, pharmacologic and surgical options should be investigated. If the etiology of their blepharospasm is somehow different from the others, a different injection site should be considered (30).

CONCLUSIONS

Our results, which are supported by others in the literature, show that botulinum toxin is an effective and safe optional treatment for patients with blepharospasm. In light of the positive results achieved, the duration of results, and the low incidence of side-effects related to treatment, we consider BONT/A therapy as the current treatment of choice. Furthermore, considering the drawbacks, lower success rates, and side-effects of other treatment options, we suggest that BONT/A therapy is the first line of treatment for individuals with blepharospasm.

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