Botulinum A Toxin Injection as a Treatment for Blepharospasm

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• **Thirty-nine patients with blepharospasm were treated with injections of botulinum A toxin into the lid and brow. The maximum number of injections in one patient was 16 over a period of 24 months. A reduction of abnormal movement occurred in all patients, lasting up to 170 days. Both the amount and the duration of effect were dose dependent. Reinjection for recurrence had effects similar to the original injection. Tearing, dry-eye symptoms, or transient ptosis occurred in 20% of injections, especially in patients who had had previous eyelid surgery.**

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Essential blepharospasm is an involuntary spasmodic closure of the eyelids, typically occurring in individuals of middle to older age. It frequently progresses to the point where reading, driving, and pursuing ordinary occupations are impossible. Pharmacologic treatment with agents such as tetrabenazine, clonazepam, trihexyphenidyl hydrochloride, and lithium carbonate have been tried with some success.[1] Surgical treatment consists of removing the orbicularis itself or transsecting the facial nerve branches to the eyelid region. Success with one orbicularis removal is reported to range from 50% to 78%.[2-4]

Botulinum A toxin is known to have great muscle paralytic effect in humans.[5] It was hoped that local use of this agent around the eye would weaken orbicularis oculi contractions and so improve symptoms of patients with essential blepharospasm.

We report herein the safety and efficacy of botulinum A toxin injection in the treatment of essential blepharospasm.

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PATIENTS AND METHODS

All patients included in this study were volunteers and entered after giving informed consent. The protocol was approved by the Joint Council on Human Research at Pacific Medical Center, San Francisco. The diagnosis was made on the basis of history of progressive difficulty with eyelid opening and on the clinical finding of bilateral involuntary spasmodic closure of the eyelids. Dystonic movements of other facial muscles were often noted (Meige's syndrome). Four patients also had hand apraxia, four had overt cerebrovascular disease, and one had parkinsonism. Others were remarkable for their good health. Twenty patients with follow up of less than six months were excluded, as were those with hemifacial spasm and orbicularis myokymia.

Botulinum A toxin was injected into the orbicularis oculi muscle and other facial muscles of patients with blepharospasm. One unit of the drug is equal to the amount of toxin found to kill 50% of a group of 18- to 20-g female Swiss-Webster mice (LD_{50}). The dosages, placement, and solution quantity were varied to establish optimal effects. A 27- or 30-gauge (less pain!) needle was used. No anesthetic was used. Preinjection and postinjection video recording of eye blinking and electromyographic monitoring were done in some patients. The isometric force of eyelid closure was measured in most patients before and after injection with a modified calibrated spring-loaded speculum or other force gauge.

In four patients, only one periocular area was injected with the drug and the other with saline. The side injected with the active agent was unknown to the patient. This

Table 1.—Botulinum A Toxin Treatment Summary*

	Mean	Minimum	Maximum
No. of units of botulinum given during treatment of eye	21.3	5.0	50.0
No. of puncture sites used during treatment of eye	4.5	1.0	8.0
No. of units of botulinum given per puncture site	5.1	1.0	15.0

*Thirty-nine patients (124 treatment visits).

method of control was abandoned after each of these patients showed a dramatic response to the drug and no response to the saline. We still occasionally inject only one eye as a demonstration of the drug effect to patients who prefer to risk only one eye.

In six unoperated-on patients with bilaterally symmetrical blepharospasm, we compared the effect and duration of injection of an identical dose in 0.5 mL on one side (five sites, 0.1 mL each) with that of 4.0 mL on the opposite side (five sites, 0.8 mL each). Duration of effect, intensity of effect, and side effects were the same. The only difference noted by patient or investigator was greater injection discomfort with the larger volume.

Following injection, patients were seen or contacted twice the first week, at weekly intervals for the next three weeks, and at monthly intervals thereafter. Patients were reinjected when the debilitating symptoms recurred.

RESULTS

The results of the study are summarized in Tables 1 through 4.

There were 39 patients treated a mean of 2.9 times each (Table 1). At each visit, approximately 21 units of drug were given to the treated eye in 124 visits. The drug used in each treatment was divided among multiple (usually five) puncture sites. Total follow-up ranged from 24 weeks to a maximum of 96 weeks. The interval between treatments for both eyes varied, the mean being 9.9 weeks.

Table 2.—Interval Between Botulinum A Toxin Treatments, as Related to Dosage*

Dose in Units to Each Eye	Weeks Between Injections, No. of Cases (n = 47) ≤8	>8	Totals
20	16	10	**26**
20	6	15	**21**

*χ^2 uncorrected = 5.07; $P < .025$.

Table 3.—Pretreatment Eyelid Closure Force in Patients With Blepharospasm

Eyelid Force, g	No. of Eyes
>100	19
81-100	16
40-80	8
20-39	2

The variables of dose, patient's age at injection, injection number, and duration of condition at the time of first injection, were examined by stepwise multiple regression analysis for their effects on interval between injections. We found that only dose was significantly related to the interval between injections. Table 2 suggests that patients who were administered doses in excess of 20 units to each eye were much less likely to return for treatment of both eyes within eight weeks than were patients administered small doses ($P < .025$). A moderately strong correlation between actual dose and interval between treatments was found ($r = .313$, $P < .05$); this was seen especially in men ($r = .533$, $P < .06$) and in patients without prior surgery ($r = .613$, $P < .005$).

By our technique, the average eyelid-closure muscle force was 70 g in eight normal adults, aged 30 to 60 years. A consecutive series of these patients showed generally higher forces, possibly due to use hypertrophy (Table 3). Figure 1 shows four examples of orbicularis muscle-force data plotted against time after injection. The return of symptoms always preceded the complete return of muscle force by many weeks. The overall level of electromyographic activity was parallel to the level of muscle force, as one would anticipate. We did not record details of the electromyogram, which allow examination of nerve sprouting or other patterns of changed innervation.

Table 4 shows the effect of previous lid surgery on the rate of occurrence of observed ptosis and strabismus and of reported tearing and dryness. In unoperated-on eyes, this overall complication rate was 8.5%. The rate of complications was higher in eyes that had undergone previous surgery. Tearing and dryness occurred only among patients who had had previous neurectomies or orbicularis stripping. No patient with dry-eye symptoms or tearing had ulceration of the cornea.

Ptosis occurs with higher doses and is a limiting factor on dosage and, thereby, on duration of effect in individual cases. However, the numbers were too small and the variability was too great to allow statistical validation in this overall sample.

Injections in the brow, nasal, upper lip, and chin musculature were made in three individuals with tonic spasm in these areas (Meige's syndrome). These doses were 10 to 20 units in each site and

Table 4.—Risk of Complications After Treatment of One Eye

Complication	No. of Treatments: No Previous Surgery (n = 106)	Blepharoplasty (n = 33)	Neurectomy or Orbicularis Stripping (n = 16)	Total (n = 155)
Observed ptosis	9	7	6	**22**
Reported dryness	0	0	6	**6**
Reported tearing	0	0	5	**5**
Observed strabismus (diplopia)	1	0	1	**1**
Percentage of treatments with 1 or more complications	9.4%	21.2%	87.5%*	19.4%

*Four treatments had more than one complication.

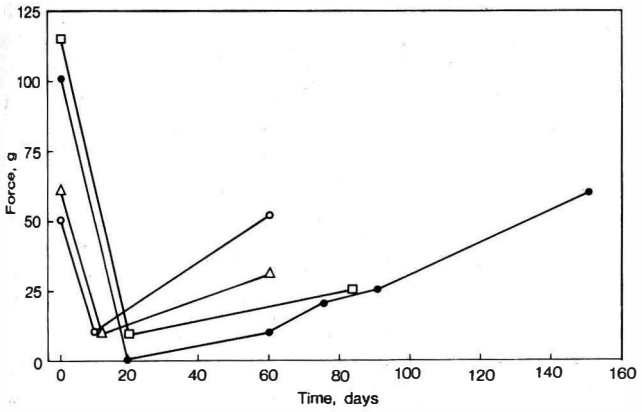

Fig 1.—Eyelid closure force before—and at various times after—initial injection for each of four consecutive patients, who were followed up until reinjection was required because symptoms returned (different symbol for each patient).

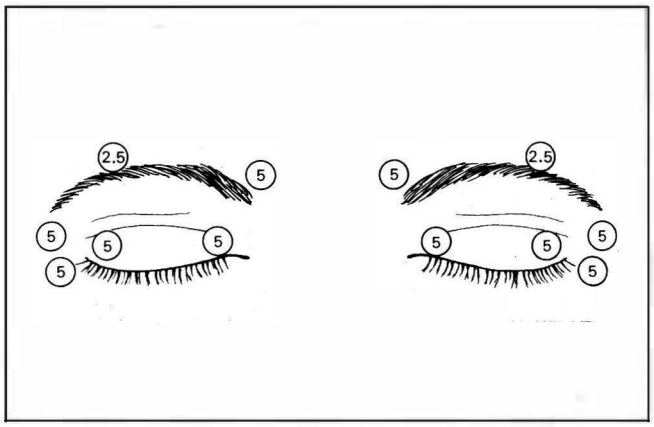

Fig 2.—Present injection strategy for botulinum treatment of blepharospasm. Numbers are units of botulinum toxin.

produced paralysis with symptomatic improvement lasting three to six months (longer than the effect on eyelids).

We were interested in the possibility of axonal transport of the neurotoxin to distal nerve tissue, and we injected only lateral to the eye in two eyes. Local effect occurred without extension of the paralysis to the medical orbicularis. We conclude such transport unlikely. Nerve injection in rabbits had a similar negative result.[6]

COMMENT

These results are comparable with those of Frueh et al[7] and show the treatment to be safe, simple, repeatable, and symptomatically helpful.

We measured orbicularis muscle force during maximum closure as an index of physiologic effect, and we measured the interval between treatments as an indicator of duration of clinical effect. We hoped that repeated injections would lead to prolonged effects from orbicularis denervation atrophy, but our muscle-force measurements and clinical results do not reflect this.

All of the patients injected with botulinum A toxin into the orbicularis oculi experienced some relief from their symptoms of blepharospasm. The duration of beneficial response varied, increasing as we experimented with increasing doses of the drug. We now expect an interval of about three months between injections with our present technique (see below). The interval between injections clearly understated the duration of the actual physiologic effect, as the patients claimed return of symptoms long before full eyelid-closure force had returned, and they were unwilling to allow their problem to return to the pretreatment level of severity (Fig 1).

Our technique for initial injection now consists of multiple, subcutaneous injections in the locations shown in Fig 2, using a solution of 5 units/0.1 mL, given immediately. This was arrived at by trial and error. We avoid the center of the upper lid, as experience showed that this increased the effect on

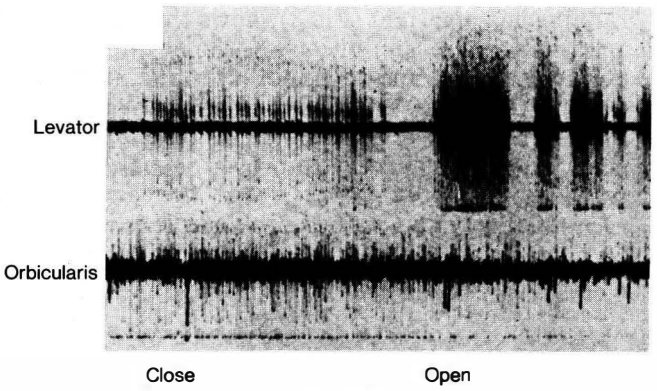

Fig 3.—Patient is unable both to inhibit levator normally (upper trace) during attempt to close eyes and to maintain its normal steady activity during attempt to keep eyes open. Orbicularis is normally active only during closure; in illustration, it is almost steadily active, regardless of attempted eyelid opening or closure.

the levator, causing ptosis, and on the superior rectus muscle, causing hypotropia. When we eliminated injection of the lower lid, this avoided entropion and sagging of the lower lid, with the resulting corneal exposure and tearing symptoms, in patients who had these symptoms on a prior lower-lid injection. Therefore, we avoid injection into the central or medial part of the lower lid. If the spasm-free interval after injection is less than three months, then dosage is increased by 50% on subsequent injections, usually until ptosis begins to occur as a limiting side effect. The effect of minor injection variations on efficacy and side effects are still being studied. We are prospectively comparing the effects of different injection locations and different intervals between injections on the right and left sides of individual patients with symmetrical blepharospasm.

Ptosis was the most common complication, mediated by the effect of the drug on the levator muscle. The ptosis is transient. Ptosis may also occur as part of the blepharospasm disorder[8] and should not be

confused with that induced by the drug. We postulate that the scarring and removal of orbicularis from previous blepharoplasty affects the absorption and diffusion of the drug, allowing access to the motor end-plates of the levator. The chance of ptosis with botulinum A toxin injection in patients with previous blepharoplasty was observed to be four times that of unoperated-on patients. In previously operated-on patients with lid scars, we have the impression that direct infusion of the drug in larger, but more dilute, volume is more reliable in producing and confining paralysis to the orbicularis than is dependence on diffusion through scar tissue. This is not true in previously unoperated-on patients.

Many patients, especially those with associated hand apraxia, parkinsonism, and abnormal facial movements and facial muscle dystonia (Meige's syndrome), have marked apraxia of eyelid opening in addition to orbicularis spasm. In those cases, the treatment is somewhat less helpful. The electromyogram in such a patient (Fig 3) shows this incoordination: the lack of inhibition of the levator during voluntary closure and the inability to maintain levator activity during attempted opening. Even in this patient, however, the removal of the orbicularis spasm allowed markedly improved visual functioning.

A reduction in the effect of subsequent injections was sometimes found by Frueh et al.[7] We agree with this finding both in blepharospasm and in strabismus when doses are closely spaced so that recovery of the injected muscle has not occurred before reinjection. Frueh et al attributed this to possible immune response creating antibodies to the drug. Our experience in patients with multiple injections over 24 months, without decline in dose effectiveness, argues against this mechanism, as does our experience that no such decline in effectiveness occurred in monkeys that received multiple injections over several months with doses of 25 units/kg (20 times our highest dose). In an oral communication (Oct 23, 1984), B. R. Dasgupta, PhD, noted that the large, inactive protein fragment of the toxin molecule can block receptor sites on the nerve membrane against absorption of active new toxin. His finding is another mechanism to explain this reduction of drug effect on early reinjection. It follows that the interval between injections should be made as long as possible, compatible with continued patient function.

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