THERAPEUTIC REVIEW

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Botulinum A Toxin (Oculinum®) in Ophthalmology

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Abstract. Botulinum A toxin has been used to treat strabismus and a variety of spasmodic neuromuscular diseases. Botulinum toxin treatment of strabismus is not as definitive and stable as the traditional surgical approach, but it has been found most useful in postoperative overcorrection, small deviations, sensory deviations, and acute sixth nerve palsy. This toxin has been effective in the treatment of essential blepharospasm and hemifacial spasm, for which it produces temporary relief of symptoms. In addition, this treatment has been applied to lower lid entropion, myokymia, aberrant regeneration of the seventh nerve, lid retraction, corneal exposure, nystagmus, spasmodic torticollis, and adductor spastic dysphonia. **(Surv Ophthalmol 36:**28–46, 1991)

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The clinical use of botulinum A toxin (Oculinum®) was pioneered by Dr. Alan B. Scott as an alternative to strabismus surgery. It has since been used in the treatment of various other neuromuscular diseases, because it is considered safer, more effective, and easier than surgical procedures for these conditions. Complications can occur from local spread of the toxin, and the indication for botulinum toxin injection in some diseases is controversial. In this paper we review the results of other investigators, as well as our six-year experience.

I. Historical Review

The idea of injecting a pharmacologic agent into human extraocular muscles with the goal of producing a prolonged or permanent paresis was first conceived by Dr. Conrad Behrens. He tried using alcohol as the agent, but usually it was ineffective or it caused total, permanent paralysis.[44,117,126] In 1972, Dr. Scott and coworkers adopted Dr. Behrens' idea and experimented using various drugs, such as diisopropyl-fluorophosphate (DFP), Bungarus neurotoxin (cobra toxin), alcohol, and botulinum toxin (type A), to paralyze the extraocular muscles of rhesus monkeys. Systemic food poisoning, i.e., botulism, causes ocular symptoms, such as blurred vision and diplopia, by paralyzing intraocular and extraocular muscles.[27,44,126] Dr. Scott appreciated this toxin's properties, and he found that botulinum type A toxin was an ideal drug for producing both transient weakness of ocular muscle and permanent changes of ocular alignment without serious side effects.[117]

After his animal experiments with botulinum A toxin in the early 1970s,[117,126] Dr. Scott began human studies in 1977.[130] His preliminary reports showed that it could be used as an alternative to traditional strabismus surgery.[124,125] Subsequently, botulinum toxin was found useful in treating other conditions, such as blepharospasm, hemifacial

spasm, myokymia, lower lid entropion, Graves' ophthalmopathy, nystagmus, corneal ulcer, and aberrant regeneration of the seventh nerve (Table 1). Botulinum toxin was made available to 292 investigators in academic institutions, clinics, and private practices in the United States and 27 foreign countries (as of Feb. 1989).[1] These investigators acted under the direction of Dr. Scott at the Smith-Kettlewell Institute of Visual Sciences, San Francisco, California; 5725 patients with strabismus, 9983 patients with blepharospasm, and 3571 patients with hemifacial spasm were treated with botulinum toxin (personal communication from Dr. Scott).

On December 29, 1989, botulinum A toxin was released from investigational use for the treatment of blepharospasm and strabismus (in patients 12 years of age and older). The commercial preparation, Oculinum®, is distributed by Allergan Pharmaceuticals, Inc.

TABLE 1

Ophthalmic Indications for Botulinum Toxin Injection

1. Strabismus
   - Horizontal nonparalytic, nonrestrictive strabismus
     - Less than 40 prism diopters of deviation
     - Surgical undercorrection and overcorrection
     - Sensory deviation
     - Preoperative evaluation for intractable diplopia
   - Vertical nonparalytic, nonrestrictive strabismus
   - Acute or chronic third and sixth nerve palsies
   - Restrictive strabismus caused by dysthyroid myopathy
   - Strabismus following retinal detachment surgery
   - Surgical correction contraindicated or refused
2. Acquired nystagmus
3. Essential blepharospasm
4. Hemifacial spasm
5. Aberrant regeneration of the seventh cranial nerve
6. Myokymia
7. Lower lid entropion
8. Corneal ulcer
9. Corneal exposure

II. Pharmacology

The toxins of *Clostridium botulinum* (a large, anaerobic, gram-positive, rod-shaped organism) are classified into eight immunologically distinguishable exotoxins (A, B, C1, C2, D, E, F, and G).[95] Three types (A, B, and E) are commonly associated with toxicity to humans.[27] These toxins are structurally very similar to each other. The type A toxin is easily produced in deep culture and was the first one obtained in a highly purified, stable, and crystalline form.[113,126] The crystalline form of type A toxin is a high-molecular-weight protein (about 900,000 daltons) and consists of two subunits that dissociate in solution. Each subunit (450,000 daltons) consists of three peptide chains of about equal molecular weight (150,000 daltons); one peptide chain is the toxic moiety while the other two are non-toxic peptides. The toxic peptide chain consists of a heavy (H) unit (100,000 daltons) and a light (L) unit (50,000 daltons) held together by -S-S- bonds. One of the two nontoxic chains has hemagglutinating activity.[21]

The kinetics of botulinum A toxin uptake at the nerve terminal proceed in three steps: binding, internalization, and paralysis. Injected toxin is rapidly and firmly bound at receptor sites on the cholinergic nerve terminal. The binding occurs in a saturable fashion to unmyelinated areas of the nerve terminal mediated by the heavy subset of the toxic peptide chain.[95] Internalization of the toxin from the terminal membrane to the intracellular compartment is accomplished through the synaptic vesicle recycling process. Paralysis of muscle is caused by the inhibition of the release of acetylcholine (ACh). This effect is not due to interference with the propagation of nerve impulses or the inhibition of synthesis or storage of ACh. In addition, the toxin does not block the entry of calcium into the nerve terminal.[23,69,72,95] Botulinum toxin does not interfere with nonquantal ACh release, but it specifically blocks quantal ACh release.[139] Therefore, it is assumed that the toxin attaches to the ACh-containing vesicles in the nerve terminal and prevents calcium-dependent exocytosis.[134]

The paralytic effect of botulinum toxin is dose-related, and the peak of the paralytic effect occurs five to seven days after injection.[82,126] Denervated muscle histopathologically shows muscle atrophy and a mild degree of demyelinative changes at the nerve terminal with subsequent regeneration that is characterized by onion bulb formation and newly formed sproutings at neuromuscular junctions.[102,126] It takes six to nine months to recover completely from the effects of the toxin.[44,117] After recovery, the injected muscle may or may not resume the preinjection level of function.[132]

Scott's experiments using rhesus monkeys indicated that: 1) botulinum toxin produced both transient weakness of ocular muscles and permanent changes of ocular alignment without serious side effects; 2) the onset and duration of the denervation was dose-related; 3) the effect of the toxin was reduced with a subsequent (within 0–30 min.) antitoxin injection into the treated muscle; 4) repeated injections of the toxin were not recognized by the immune system; and 5) the toxin's local effect was prevented by prior toxoid immunization.[117,126]

Botulinum A toxin is provided to the physician in a frozen, lyophilized form in which it will remain stable for up to four years;[126] however, once the

TABLE 2

Complications of Botulinum Toxin Treatment of Horizontal Strabismus

1. Ptosis
2. Induced deviations (overcorrection, hyperdeviation)
3. Undercorrection
4. Diplopia
5. Pupillary dilatation
6. Reduced accommodation
7. Hemorrhage (subconjunctival, retrobulbar)
8. Scleral perforation

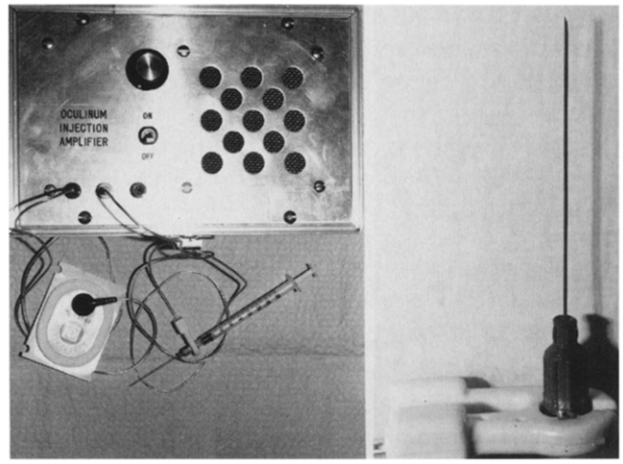

Fig. 1. Electromyographic amplifier (left) and monopolar electrode needle (right).

toxin is placed into a saline solution it will deteriorate within a few hours.[24] The toxin is susceptible to damage by mechanical stress (e.g., rapid injection, frothing) or an inadequate solution (e.g., low concentration, heat, pH, various chemicals).[24,113] Botulinum toxin should be used on the day of dilution.

One vial of Oculinum® contains 100 units. One unit of botulinum toxin (about 0.25 nanograms) is the lethal dose for 50% (LD/50) of mice.[56,115,119] The LD/50 for humans is estimated at about 39 units/Kg.[127,129] In monkeys, the dose that causes systemic toxicity is close to the LD/50.[118] If the toxin is injected locally into a muscle, it binds to the tissues rapidly and firmly, and there is little possibility for systemic effects by its passing into the circulatory system.[126] Sensitivity to botulinum toxin varies with muscle mass. In strabismus, the larger the muscle, the more toxin is needed to produce a desired effect.[127,132]

III. Botulinum Toxin in the Treatment of Strabismus

Botulinum toxin injections seem to produce effects that are not as predictable and stable as traditional strabismus surgery.[7,37] Botulinum A toxin may be effective in treating specific types of strabismus, such as small angle deviations, sensory deviations, transient acute sixth nerve palsies, subacute dysthyroid ophthalmopathies, overcorrections, residual deviations after strabismus surgery, strabismus following retinal detachment surgery, and in cases not amenable to general anesthesia or surgical correction (e.g., history of hyperthermia, terminal cancer).[86,116,131] However, traditional strabismus surgery is still the most appropriate treatment in cases where the deviations are large, involve multiple extraocular muscles, or have an A-V pattern.[86,116] In the authors' experience, we have found botulinum toxin quite helpful in treating blind or limited vision eyes with secondary deviations (sensory deviation). These patients often desire psychosocial improvement, and one to three botulinum toxin injections will accomplish this. Follow-up injections may be required at periodic intervals.

Compared with surgery, the advantages of botulinum toxin injections are: ease of administration if the patient is cooperative (it can be performed in the office), use of a topical anesthesia, little or no postinjection discomfort, and no postoperative recovery period. It takes only a few minutes to inject botulinum toxin, it requires no incision, and it leaves no scars.[81,97] The disadvantages are that it requires repeated injections in 60% of the cases, and the results still may not be permanent.[129] In contrast, strabismus surgery can achieve a satisfactory result in 70–90% of cases with one operation.[82,86] Ocular misalignment tends to recur more easily after botulinum toxin injection than after surgery if fusion is not established.[116] Carruthers et al compared botulinum toxin treatment to the use of adjustable suture surgery in adult strabismus patients without fusion. At six months after the procedure, 50.5% of ocular misalignment was corrected by botulinum toxin treatment; however, 92.7% of ocular misalignment was corrected by adjustable suture surgery.[16] Diplopia, which is induced by the temporary paralysis following botulinum toxin injection, may also be troublesome for patients, but it is essential for a fusional result. Patients who have a fusion response have a more favorable reaction to the treatment than those who do not, but they have difficulties with postinjection disorientation and diplopia for several weeks and often need patching (Table 2).[44,135] The goal in this treatment of strabismus is to create adequate weakness of sufficient duration in the injected muscle so that it becomes slightly atrophied and stretched while the antagonist muscle takes up the slack with some degree of

contracture.[56,124,126] By this process the ocular misalignment is reduced. Therefore, it is desirable to see an overcorrection of the deviation one week following the injection[7,8,44] (the maximum effect is observed in about one week[44,82,135]). This alignment change continues for years after the paralysis is gone.[82,85]

A. TECHNIQUE OF BOTULINUM TOXIN INJECTION FOR STRABISMUS

Botulinum toxin is administered with a 27-gauge monopolar electrode needle on a tuberculin syringe (1.0 cc). This monopolar electrode tip is inserted into the extraocular muscle transmitting the electromyographic response to an amplifier (Fig. 1). Prior to this insertion, topical proparacaine anesthesia or ketamine anesthesia (0.5–1.0 mg/kg) is used. The dosage of injected toxin is adjusted according to the age and weight of the patient. (In adults and children above age 2–3, 2.5 to 5 units is injected. In infants below 12.5 kg, progressively less toxin is used. With a 6 kg infant, 1.2 units are used.[132]) By having the patient gaze in the direction away from the muscle to be injected, or by fixing the globe with forceps, the surgeon can insert the needle into the extraocular muscle. The eye is then turned toward the muscle being injected which activates the motor units of the muscle. As the needle is guided into the muscle, the EMG sound of the muscle activity increases until the needle reaches the largest part of the muscle. The increase in EMG activity heard from the amplifier assists the surgeon by assuring that the tip of the needle is in the appropriate position in the muscle. The needle is advanced until the tip reaches halfway to the origin of the muscle, which is the area where the neuromuscular junctions of the singly innervated muscle fibers are concentrated (about 2.5 cm posterior to the insertion).[125] There the toxin is injected into the muscle (Fig. 2). After the injection, a dilated fundus examination is recommended to check for ocular perforation.

The EMG amplifier plays an important role in guiding the needle into the target muscle. In the event the tip reaches outside the muscle, the sound from the amplifier dies away, warning the surgeon to maneuver the needle so that the toxin is prevented from leaking into other muscles, which can cause problems such as ptosis and unexpected deviations.[24]

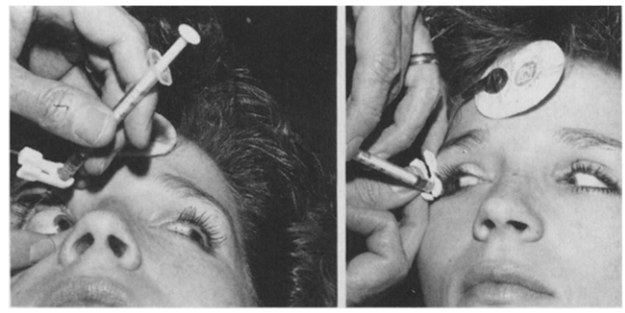

Fig. 2. While the patient gazes in the direction away from the extraocular muscle to be injected, a monopolar electrode needle is inserted into that muscle (left). Then the eye turns toward the muscle being injected. With the guidance of the amplifier, the tip of the needle is advanced about 2.5 cm until it reaches approximately half the distance from the muscle insertion. The toxin is injected when the EMG response is maximum (right).

B. TYPES OF STRABISMUS

1. Nonparalytic Strabismus

a. Nonrestrictive Strabismus: Horizontal

Two methods are generally used to evaluate the effect of the toxin in strabismus. The first method is to calculate the percentage of reduction of the initial deviation after the paralytic effect fades away. The second method is to determine whether or not the deviation improved to within 10 prism diopters of having the eyes straight, or orthophoric. At present, these criteria are not always consistently applied. Although many authors are using a minimum of six months following injection before evaluation, it is not certain that the paralytic effects have completely disappeared by then. In cases of sensory strabismus, the deviation may progress after the muscles have fully recovered from the toxin.

Esotropia vs. exotropia: In horizontal strabismus, it is reported that patients with esotropia are more responsive to botulinum toxin injection than those with exotropia.[24,43] Recent reports from Scott showed that the percentage reduction of preinjection deviation averaged 65% (more than six months after last injections). Achieving 10 prism diopters or less of residual strabismus were 63% of children (2 months–11 years) and 56% of adults (12–90 years). Overcorrection occurred in less than 1% of patients.[129] Children with exotropia were the most undercorrected category of the patients with horizontal strabismus.[129] To obtain desirable effects, more than half of the patients required repeated injections (three injections on average).[1,129]

This treatment has also demonstrated beneficial effects in the adjustment of overcorrection or residual deviation after surgery (fine tuning).[7,54,57,92,116] McNeer's report showed that the results in treating consecutive exophoria in adults by botulinum toxin injection was not as stable as the results in treating consecutive esophoria. Older patients with

consecutive exophoria have typically undergone multiple previous surgical procedures, which cause cicatricial changes and render the patients less responsive to botulinum toxin injections.[92]

In our clinic the reduction of deviation for six adults with sensory exotropia was 66% on average, ranging from 17% to 100%. The patient in Fig. 3 had a sensory exotropia from dense optic atrophy. He had had previous muscle surgery and wanted to try botulinum toxin injection. He has since had botulinum toxin injections four times over the last five years. Although the patient's deviation has recurred somewhat, he is quite satisfied with his appearance. Biglan et al reported that fourteen patients who had deviations caused by decreased vision received botulinum toxin injections, and 50% of the patients achieved satisfactory alignment.[7] Sensory deviations often drift back after surgery. Botulinum toxin can be repeatedly injected and produces effects similar to those obtained from the surgical procedures.

Occasionally, adults with congenital strabismus request psychosocial surgery to straighten their eyes. These patients are at risk for intractable, postoperative diplopia. Botulinum toxin may be injected to see whether realigning the eyes will produce diplopia. If it develops, the deviation will gradually return to its preinjection status, allowing previous suppression patterns to return. The patient and surgeon will be forewarned that, after corrective surgery, diplopia may persist and become troublesome.

There are many reports of strabismic infants and children treated by botulinum toxin injection; however, it is still controversial whether or not this method should be used for these patients.[7,24,43,54,81,84–86,116,120] Scott reported that 61% of patients with congenital esotropia improved to 10 prism diopters or less, and the average reduction from initial deviation was 65.3%.[120] Magoon and Scott reported that, in their series, reinjection was necessary in 85% of infants and children to achieve improvement.[81] Biglan et al reported that patients with congenital esotropia initially had favorable responses to this treatment, but that 66% subsequently required surgical procedures for unacceptable deviations.[7]

By performing surgery for congenital esotropia just a single time, the eyes of more than 80% of afflicted infants can be made cosmetically straight.[7,24] It is a greater technical challenge to inject the toxin into the extraocular muscles of children,[84] and the complications of ptosis and hypertropia are amblyogenic factors at this age (however, there are no reports of amblyopia from this treatment). Parents who do not want a surgical procedure performed on their children also tend not to want them to receive repeated injections. Therefore, it remains problematic whether to use botulinum toxin injections as the treatment of first choice for children with esotropia.

Fig. 3. This patient has optic atrophy in the left eye (visual acuity: 20/200). Ten units of botulinum toxin were injected into the left lateral rectus. *Left:* Primary gaze before botulinum toxin injection. *Right:* Primary gaze one month after the injection.

Large vs. small deviation: This treatment is less suitable for initial large angle deviations (especially more than 40 prism diopters), because too many injections would be needed.[1,86,120,129,132] Carruthers et al reported, in adult patients without fusion, that the patients with an initial deviation of 20 prism diopters or less tended to respond better than those with one of greater than 20 prism diopters.[16] Nevertheless, the patients with sensory deviation may accept repeated injections if told that surgery will often only keep the eye straight temporarily.

Long-term vs. short-term efficacy: To determine the longterm efficacy of botulinum treatment in children, Magoon compared shortterm results (range: 6–24 months) and longterm results (range: 2–5.5 years) for 62 children younger than 14 years. The longterm results show that 50 esotropes had mean deviations of 35 prism diopters before and 5 prism diopters after injections, and 12 exotropes had 30 and 5 prism diopters, respectively. These results are similar to the shortterm observation.[85] In older patients (more than 12 years old) with strabismus, substantial correction was observed more than six months after the most recent injection and, in some cases, over twelve months after a single injection.[80]

Local vs. general anesthesia in children: Regarding the anesthesia for infants and children, Magoon noted that children less than one year of age or older than six years of age could receive injections after topical drop anesthesia, but that low-dose ketamine sedation was usually necessary for children one to six years of age.[81] He noted that infants given a bottle frequently were quiet throughout the procedure.[84] Ketamine is considered a suitable anesthesia for botulinum toxin injection, because it preserves the electromyographic response of muscles during the procedure. Other sedative agents, such

as nitrous oxide, fluothane, and barbiturates, reduce or eliminate the electromyographic activity, which makes it difficult for surgeons to orient the position of the needle electrode properly.[130] The side effects of ketamine are emesis, nausea, and hallucinations. The incidence of emesis and nausea is 7%, and this figure can be reduced by preadministration of glycopyrrolate or atropine.[122,129]

b. Nonrestrictive Strabismus: Vertical

Because the levator muscle is sensitive to the toxin, injections in the superior rectus muscles cause a prolonged period of ptosis.[86,97] Therefore, vertical deviations are usually treated by injections into the inferior rectus muscles. Magoon and Dakoske reported 76% of pretreatment vertical deviations in sixteen patients were corrected by the injection of the inferior rectus or inferior oblique muscle.[79] On the other hand, McNeer treated the nondominant eye of five patients with disassociated vertical deviation (DVD) by injecting the toxin into the superior rectus muscle, and mean deviation was reduced from 20 prism diopters to 5 prism diopters.[93] To treat five patients with postoperative residual and overcorrective vertical deviations, he injected botulinum toxin into the superior rectus, inferior rectus, or inferior oblique muscle, and three patients achieved orthophoria.[92]

c. Restrictive Strabismus Caused by Dysthyroid Myopathy

Surgical correction for patients with the acute phase of dysthyroid myopathy is contraindicated because of the severe inflammatory reaction and unpredictable postoperative results.[25] In this phase, orbital radiation therapy, systemic corticosteroid, or immunosuppressive drug administration is needed. Botulinum toxin injection may be a suitable treatment for ocular misalignment in this phase, and good results have been reported by some investigators.[25,133] Botulinum toxin treatment may reduce the number of muscles requiring surgery and effectively decrease diplopia so that residual diplopia can be corrected by prisms. This may provide relief for the patients, who have to bear with the diplopia until the inflammatory phase becomes inactive, even if strabismus surgery is eventually needed.

Restrictive myopathy in the chronic stage is usually considered nonresponsive to botulinum toxin injection because of fibrotic changes. Dunn et al[25] stated that restrictive myopathy is caused by several factors, which include muscle shortening due to inflammatory spasm, reduction in the number of sarcomeres, and secondary muscle fibrosis. While the fibrotic changes are irreversible, the other components can recover. Therefore, these authors believed that the response of the restrictive myopathy to botulinum toxin depended on several factors.[25]

Injection of muscles in thyroid disease usually requires a larger amount of toxin than that used for comitant strabismus because of muscle enlargement and contracture.[25,129] Dunn et al reported that initial injections of 5 units provided the best response. In their series (eight patients), this treatment reduced the mean ocular deviation from 19.5 to 2.25 prism diopters (mean follow-up: 9.8 months).[25] Magoon and Dakoske reported that an average of 62% of the pretreatment deviation in nine patients was corrected by botulinum toxin injections in Graves' disease.[79] However, Scott treated 27 patients with vertical strabismus by injections into the inferior rectus and 16 patients required surgical corrections.[129] He noted that the operative rate for cases of strabismus in thyroid disease previously treated by botulinum toxin injection was almost as high as the rate for cases not treated by botulinum toxin.[121]

We treated three patients with dysthyroid myopathy. These patients had a poor response to the botulinum toxin injections. They had a mean reduction in deviation of 24%. One patient had six injections, but achieved only 33% reduction in his deviation. It is suspected that irreversible fibrotic change had already occurred in these patients.

2. Paralytic Strabismus

It is generally agreed that botulinum toxin injection may be effective in sixth nerve palsy.[7,43,44,57,86,115,116,128,135,146] Contracture of the antagonist muscle can be avoided by botulinum toxin injection into the medial rectus muscle,[115,128] and fusion may be obtained without a marked head turn.[57] Even if the palsy is permanent and transposition surgery becomes necessary, botulinum toxin injection of the medial rectus may improve the surgical result by reducing the contracture of the adductor muscle. Often the surgeon can completely avoid the recession of the medial rectus muscle.[57,86,109,115,116] Armenia and Sigal noted that botulinum toxin injection can be used as a diagnostic measure to determine whether the palsy is completely paralytic or paretic.[4] Metz and Mazow reported that 71% of patients with acute sixth nerve palsy had lateral rectus recovery following botulinum toxin injection, whereas only 31% of the control group not treated with botulinum toxin injection recovered.[96] However, the therapeutic value of botulinum toxin injection in promoting sixth nerve reinnervation needs to be studied more because spontaneous recovery frequently occurs. Generally, a sixth nerve palsy due to a vascular lesion, such as

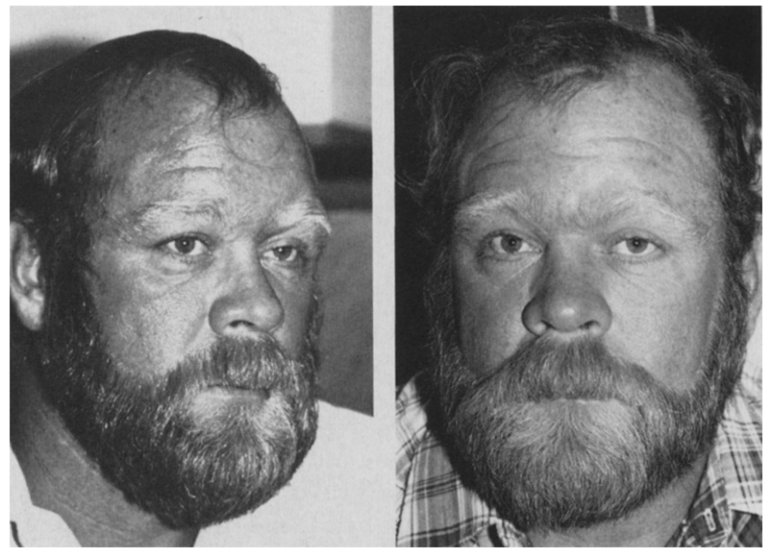

Fig. 4. Patient with a chronic left sixth nerve palsy. Before the injection, he had a left head turn in order to fuse (left). After 1.25 units of botulinum toxin were injected into the left medial rectus, he could fuse without head turn (right). This result has lasted more than eleven months.

diabetes mellitus, hypertension, or atherosclerosis, tends to recover spontaneously and would not require a botulinum toxin injection.[101,110] Since there has been no definitive study to date addressing this issue, it has been suggested that a randomized, double-masked study is necessary to determine conclusively the effectiveness of this therapy.[7,96]

In cases of chronic total sixth nerve palsy, it is difficult to control the ocular misalignment by botulinum toxin injections alone.[115] Shortening and stiffness (contracture) in the medial rectus may be caused by a decrease in the number of sarcomeres in the muscle fibers. This can be partially relieved by botulinum toxin injection, but the effect of the injection may not be seen as soon as in the treatment of nonparalytic, nonrestrictive strabismus.[47,115,146] This is different from the fibrotic changes seen in thyroid ophthalmopathy, which are considered irreversible.

Some authors recommend intraoperative botulinum toxin injections to weaken the contracture of the medial rectus in transposition procedures.[4,54,96,109] Fitzsimon et al[36] and Rosenbaum et al[109] treated patients with a combination of botulinum toxin denervation of the medial rectus and lateral transposition of the vertical recti. They demonstrated that satisfactory results were achieved without medial rectus recession. In transposition surgery, patients over 20 years old have a greater risk of anterior segment ischemia.[35] Botulinum toxin injection can be used for "chemical recession" of the medial rectus muscle, while simultaneously reducing the risk of anterior segment ischemia. However, Keech et al recently reported that anterior segment ischemia with an atonic iris sphincter occurred after a transposition procedure in an elderly patient despite the use of botulinum toxin injection.[71]

Depending on the etiology, third nerve palsies have a variable prognosis for spontaneous recovery. Metz and Mazow also reported that botulinum toxin injection into the lateral rectus muscle might enhance medial rectus recovery; however, the function of the superior and inferior rectus muscles, which were not injected, recovered poorly.[96]

We treated seven patients with strabismus caused by nerve palsies (sixth nerve palsy, n = 6; third nerve palsy, n = 1). Two patients had bilateral sixth nerve palsies. The patients with sixth nerve palsies responded to botulinum toxin treatment with a

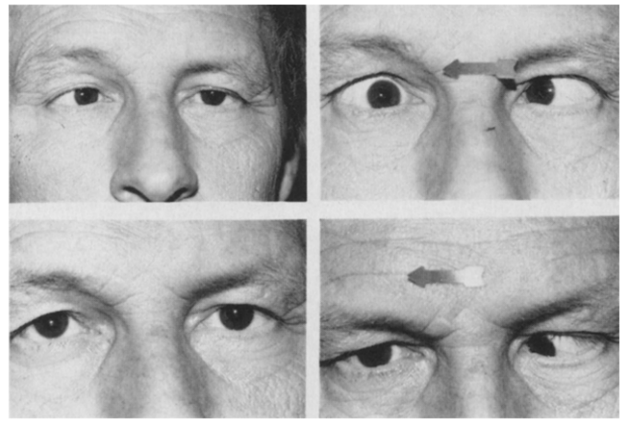

Fig. 5. Patient had right sixth nerve palsy after a motor vehicle accident. Five units of botulinum toxin were injected into the right medial rectus. Primary gaze (top left) and right (top right) before the botulinum toxin injection. Primary gaze (bottom left) and right gaze (bottom right) one month after the botulinum toxin injection.

48% mean reduction in their deviations. Of four chronic cases, only one developed fusion and had his head turn eliminated after injection (Fig. 4). Two patients did not develop fusion, but were satisfied with their psychosocial appearance (Fig. 5). The patient with the third nerve palsy had a 50% reduction of his deviation after four lateral rectus injections. Our patients with bilateral sixth nerve palsies did not have successful results. In general, bilateral sixth nerve palsies have a poorer prognosis for recovery than unilateral ones.[96]

3. Strabismus Following Retinal Detachment Surgery

In cases of diplopia after retinal detachment surgery, strabismus surgery is not always safe because of the risk of redetachment and the reopening of scleral drainage sites. Scott used botulinum toxin (1.5–7.5 units) in treating twenty patients with postoperative diplopia after retinal detachment surgery. Twelve patients had regained fusion in primary gaze after treatment (mean: 24 months), and three had partial elimination of diplopia.[131] In Petitto's report, 72% of patients (n = 18) achieved deviations of ten prism diopters or less.[106]

C. SIDE EFFECTS AND COMPLICATIONS (TABLE 2)

The most common side effects of botulinum toxin injection are ptosis and hyperdeviation. In Scott's 1988 data, ptosis was found in 16% of adults and 25% of children after injection of horizontal muscles.[129] The levator is considered extremely sensitive to even a small amount of botulinum toxin, and it is not uncommon that ptosis occurs after injection into the inferior rectus.[79] Some authors noted that ptosis occurred at higher rates in patients who had medial rectus injections than in those who had lateral and inferior rectus injections.[86,119] In addition, the incidence of ptosis increased when previously operated recti muscles were injected.[13] However, Burns et al reported that no difference was found in the incidence of ptosis between patients who had injections in the medial rectus muscles and patients who had them in the lateral rectus muscles.[13] Stavis noted the ptosis was significantly reduced when patients sat up immediately after injections and remained in an upright position for that evening.[140] In the case of persistent, minor ptosis, phenylephrine eye drops will stimulate Müller's muscle and produce a temporary lid elevation.[76]

Vertical deviation was found in 17% of patients, with 2% having vertical strabismus of two or more prism diopters for six months or more.[129] This side effect most commonly occurs in patients who have had injections into their medial rectus muscles.[135]

Fig. 6. Five units of botulinum toxin were injected into the left medial rectus. Marked ptosis was seen at the clinic one week after injection and lasted for two months. It took three months for the ptosis to completely disappear.

To protect the adjacent muscles from diffusion of botulinum toxin, Scott injected antitoxin into them. This was most effective if done within five hours, but not immediately, following botulinum toxin injection.[119]

Five cases of pupillary dilatation were reported. Two had Adie's pupils, probably caused by the injury of the ciliary ganglion, and one had a decreased accommodation.[129] Botulinum toxin injection in strabismus treatment may affect the ciliary ganglion or the sphincter muscle of the iris. Retrobulbar hemorrhage occurred in sixteen cases (0.2%); one required a decompression procedure.[1,129]

Scleral perforation occurred in nine out of 8300 injections (0.11%);[129] eight of the patients did not have visual loss or a retinal detachment. In one case, vitreous hemorrhage induced visual loss for several months.[129,132] In cases where there has been previous strabismus surgery, scar tissue and relocation of muscles makes accuracy of the needle position difficult to achieve. No toxic effects were reported after intravitreal injections. Wienkers et al injected botulinum toxin into the vitreous cavity of rabbit eyes. No significant changes were noted over a two-month period in the external examination, intraocular pressure, ophthalmoscopy, electroretinogram, or light microscopy.[147] Visual evoked potentials were also unchanged.[55]

In our series of 59 injections, there were nine occurrences (15%) of ptosis (Fig. 6). Three injections (5%) caused significant vertical deviations (more than 10 prism diopters), and two other ones (3.4%) caused bothersome diplopia. None had reduction of accommodation. All patients were dilated after injections, but none had evidence of perforation. As a result of the injection, one patient had a severe hemorrhage, which was believed to be subconjunctival, but may have been retrobulbar (Fig.

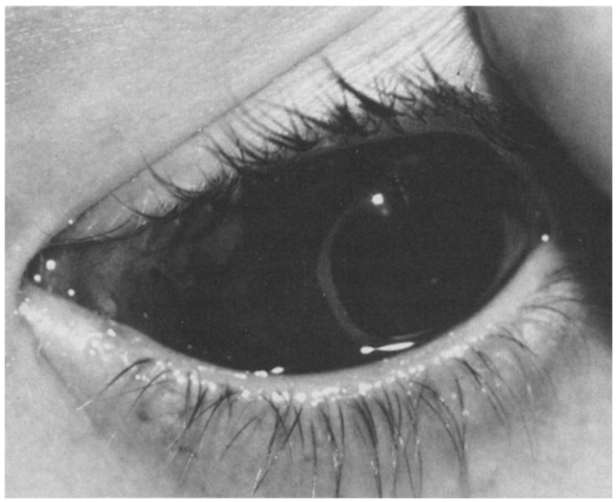

Fig. 7. Severe subconjunctival or possible retrobulbar hemorrhage occurred after injection into the medial rectus. The patient started moving during procedure.

7). This occurred in a 12-year-old child who became uncooperative during the procedure. Because of this, we have avoided using topical anesthesia in children and prefer ketamine. Of the nine patients who had previous strabismus surgery, two developed ptosis and one developed a hyperdeviation.

We did not find a tendency for medial rectus injections to cause ptosis more frequently than lateral rectus injections, nor did we find that patients who had undergone prior strabismus surgeries had a higher incidence of ptosis.

IV. Botulinum Toxin in Treatment of Facial Spasm

A. TYPE OF FACIAL SPASM

1. Essential Blepharospasm

Essential blepharospasm (Fig. 8) is an involuntary and repetitive eyelid closure caused by spasmodic contraction of the orbicularis oculi muscles. It is usually bilateral (88%)[87] and is often progressive.[62] About half of the patients with blepharospasm have other involuntary movements.[62] Symptoms in most patients become stable in three to five years.[123] Patients may become functionally blind[14,28,89,137,142] and sometimes require psychiatric treatment for depression.[68,148]

Dyskinesias of the lower face, mouth, jaw, neck, and soft palate may occur. These dyskinesias often present as lip pursing, chewing, jaw opening, dysarthria, and dysphonia.[10,60] The combination of blepharospasm and lower facial dystonia is termed Meige's syndrome (Fig. 9).[94]

About two-thirds of these patients are female,[26,68,87,127,148] and about two-thirds are 60 years

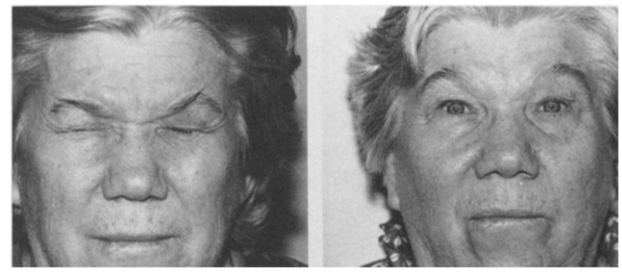

Fig. 8. Left: Essential blepharospasm patient prior to injection of 60 units of botulinum toxin around both eyes. *Right:* After the injection she had relief that lasted sixteen weeks.

of age or older.[26,127] About one-third of the patients have at least one first- or second-degree relative with a movement disorder, such as blepharospasm, Meige's syndrome, essential tremor, or Parkinsonism.[61,87]

The etiology of blepharospasm remains unclear. Previously, the cause was believed to be a psychiatric disorder;[18] however, it is now considered to be the result of an organic dysfunction of the rostral brain stem.[59,60,70,87]

Pharmacological therapy such as trihexyphenidyl, diazepam, clonazepam, tetrabenazine, levodopa, and benzhexol has been prescribed in the past. However, responses to these medications are

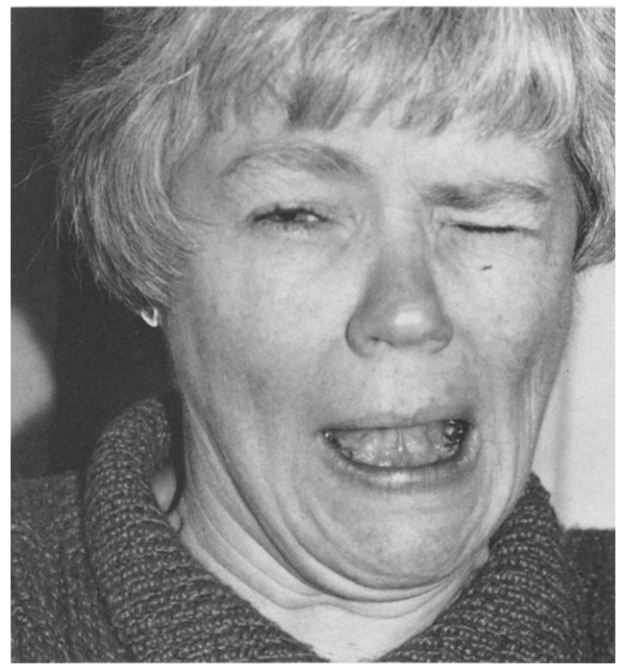

Fig. 9. Patient with Meige's syndrome demonstrates blepharospasm and lower facial dystonia.

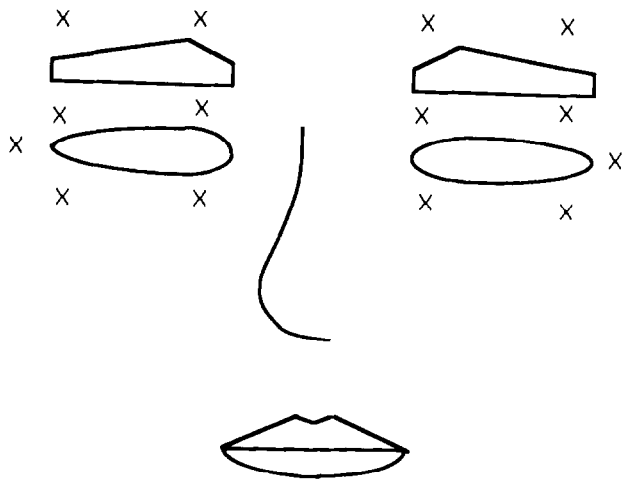

Fig. 10. Sites of botulinum toxin injections in blepharospasm patients. 2.5–10 units of botulinum toxin are injected at each spot. Sites and doses may vary depending on the severity of the condition and the previous response to treatment.

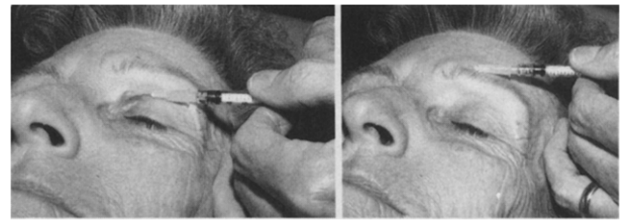

Fig. 11. Left: Botulinum toxin is injected subcutaneously into the upper eyelid for blepharospasm. The central eyelid is avoided because of the hypersensitivity of the levator muscle. *Right:* Botulinum toxin is injected into the eyebrow region.

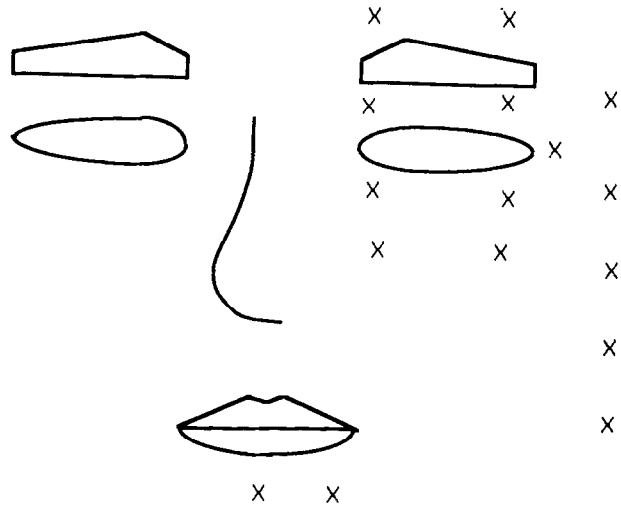

Fig. 12. Sites of botulinum toxin injections in hemifacial spasm patient. 2.5–10 units of botulinum toxin are injected at each spot. Sites and doses may vary depending on the severity of the condition and prior response to treatment.

inconsistent.[60]

Two different surgical procedures are used as therapy: one is myectomy of the orbicularis muscle and adjacent eyebrow muscles, and the other is neurectomy of selected facial nerves. Numbness of the forehead and swelling of the eyelid (lymphedema) may result from myectomy.[68,148] Neurectomy may produce brow droop, lagophthalmos, corneal exposure, and ectropion.[14,87] More than 50% of patients have recurrent spasms.[14,87] McCord et al reported that secondary operations were needed 4.5 times more often with selective facial nerve avulsion than with muscle stripping.[90]

Other treatments include psychotherapy, hypnosis, acupuncture, thermolysis of the facial nerve, and biofeedback. The efficacy of these treatments is variable.[142]

Botulinum toxin injections were first used for treating essential blepharospasm in 1983.[39,65] Although the denervation of the muscles was temporary and periodic reinjections were required, more than 90% of patients experienced significant improvement.[10,20,26,28,29,33,40,88,89,137] Botulinum toxin injections have been found to be beneficial in double-blind studies of patients with blepharospasm and Meige's syndrome.[20,34,63,65] Botulinum toxin injection has become the treatment of first choice for blepharospasm. The full effect of the toxin occurs within a few days, and the relief from spasm lasts about three months.[127] The reported duration of the effects ranges from ten to sixteen weeks.[20,26,32,33,88,89] Most patients tolerate transient local side effects, and when spasm recurs they prefer reinjection of the toxin to the alternative treatments.

We have performed 238 botulinum toxin injections on 49 patients with essential blepharospasm (14 men, 35 women; mean age at onset: 55.9 years, ranging from 33 to 76 years) and four patients with Meige's syndrome (three men, one woman; mean age at onset: 65.8 years). We classified the spasm intensity using a scale as follows: 0—none; 1—increased blinking caused by external stimuli; 2—mild, noticeable fluttering, not incapacitating; 3—moderate, very noticeable spasm, mildly incapacitating; 4—severely incapacitating (unable to drive, read, etc.). The sites for the injections for blepharospasm patients are shown in Fig. 10. Eyebrow and eyelid injections are usually performed (Fig. 11). Meige's syndrome required injections in the lower face. Injection sites for patients with hemifacial spasm are shown in Fig. 12.

Forty-nine (92%) of the patients with blepharospasm and Meige's syndrome had significant improvement (Fig. 8). Forty-one of these patients have required subsequent injections. Eight continue to have relief from symptoms one to two months later, although they will likely need further injections. Two patients decided to have surgery and underwent myectomy, and two (one with essential blepharospasm and one with Meige's syndrome) did not return for a follow-up visit after the injection.

It is difficult to judge the effectiveness of the toxin objectively, because the spasms spontaneously vary in their frequency and force. Patients may even complain about them despite objective weakness of the orbicularis muscles. Other patients are satisfied despite residual spasm.[40,136] Engstron et al postulated that underlying psychiatric factors influenced a patient's response.[33] When the closure forces are reduced to between 10% and 20% of the initial level, patients usually are asymptomatic (posterior vector force of a lid is measured by a force transducer which is connected to a contact lens).[39,42] Patients become symptomatic again when the closure force returns to between 40% and 50% of the initial level.[42,123,127] The duration of the subjective relief from spasm is considered more important in judging the effectiveness of this procedure than is any objective criterion.

Some authors report that the spasm-free interval and intensity of paralysis are correlated with the dose of botulinum toxin.[40,114,132] In contrast, Dutton et al reported that there was no clear relationship.[26] Scott reported that, if the duration of the spasm-free interval did not last three months, the dose could be increased about 50% with each subsequent injection until side effects occur.[127] However, higher doses of toxin greatly increase side effects, such as ptosis and diplopia, with only small increases in the duration of the spasm-free interval. The reason may be that the range of specific and nonspecific protein binding of toxin within whole muscle is low, and residual toxin may easily diffuse into adjacent muscles.[20,40] Therefore, large increments in the dose of toxin are not recommended.

Some authors have shown that the duration of the spasm-free interval was constant after repeated injections.[20,26,88] On the other hand, Engston et al found that the duration of the spasm-free interval increased following each of the first three injections. They postulated that this was due to negative feedback from the previous injection (i.e., the patient's fear of repeat injections) and/or to the secondary atrophy of injected muscles.[33] In our series, the durations of the spasm-free interval (mean ± SD) in the same patients (n = 19) who had four consecutive injections were 14.1 ± 6.5, 17.0 ± 6.7, 19.7 ± 9.1, 18.4 ± 7.8 weeks in order of injections. The spasm-free interval following the first injection was shorter than those following subsequent injections. Perhaps this was due in part to the muscle becoming atrophic and in part to the dosage of the first injection being smaller than subsequent injections to avoid complications at the outset.

TABLE 3

Duration of Botulinum Toxin Effect Between Groups of Patients with and without Prior Surgery

	Previous operation (−)	Previous operation (+)	F-test
Essential Blepharospasm*			
Number of patients	34	4**	
Number of injections	N = 152	N = 22	
Duration of effectiveness (weeks)	15.9 ± 8.7	23.1 ± 13.3	P < 0.01
Hemifacial spasm			
Number of patients	22	7***	
Number of injections	N = 76	N = 20	
Duration of effectiveness (weeks)	18.2 ± 11.3	21.9 ± 9.9	N.S.

*Not including Meige's syndrome. **3 myectomies, 1 neurectomy. ***All had Jannetta procedures.

Some authors report that prior surgery, such as myectomy and neurectomy, prolongs the duration of the spasm-free interval,[30,137] whereas others report that these procedures have no influence.[26,33,105,142] Four of our patients with essential blepharospasm had previous surgery (three myectomies, one neurectomy). The mean durations of symptomatic relief after 152 injections in 34 patients without previous surgery was 15.9 weeks. After 22 injections in our four patients with previous surgery, the mean period of relief was 23.1 weeks (Table 3). Thus, in our small series, patients who had previously undergone surgery had longer responses than patients who had not.

Engstron et al reported that patients with mild spasm had a longer response time than those with severe spasm,[33] whereas Elston found no such relationship.[32] In our series, for patients without prior surgery, twelve with mild spasm (intensity 1–2) had relief for 15.7 weeks on average, while twenty-one patients with severe spasm (intensity 3–4) were relieved for 16.4 weeks. These durations are almost the same. However, our doses and sites of injections are adjusted depending on the degree of spasm. Therefore, the similarity of the responses might re-

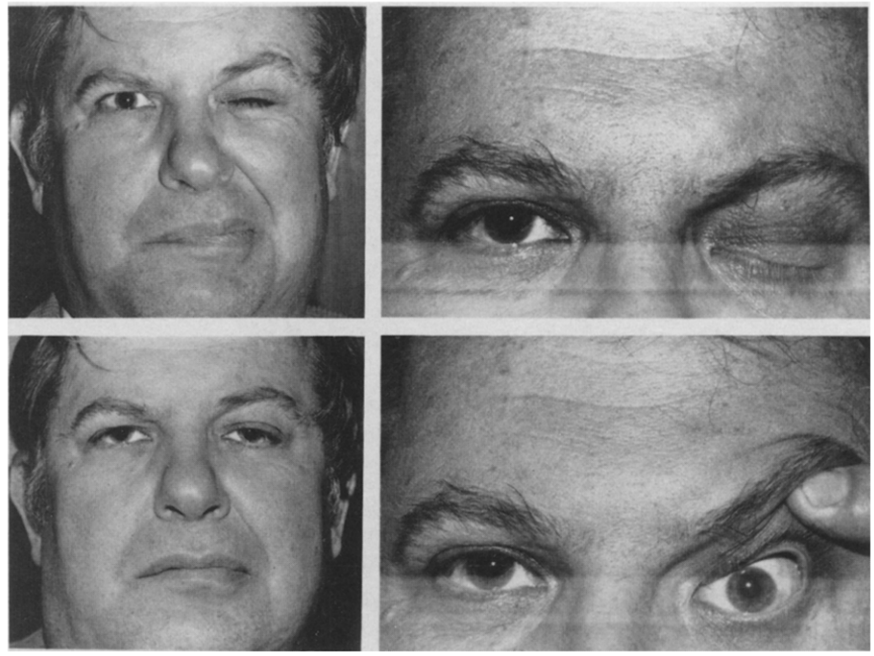

Fig. 13. Upper and bottom left: Hemifacial spasm patient before injection, with spasm and without spasm, respectively. He had 75 units of botulinum toxin injected to the left side of the face: upper eyelid (10 units), brow (10 units), lateral canthus (5 units), lateral face (20 units), and cheek (30 units). One week after the injection, the patient had complete ptosis (top right) and hypodeviation in the same eye (bottom right). It took about four weeks for ptosis to disappear. The patient also had diplopia which resolved before the ptosis disappeared completely.

flect these adjustments.

Patients might require increased doses of the toxin to achieve an effect identical to that of the initial injection if there were systemic antibody production.[39,105,114] However, no detectable antibody has been found in sera from patients with blepharospasm who have had consecutive injections.[9,48,49] This is consistent with the finding in some longterm follow-up studies that the spasm-free interval was constant after consecutive treatments.[26,32,88] In our series, eight patients had more than six consecutive injections. The duration of spasm-free intervals after the later injection were similar to the earlier ones. One patient had 25 injections with a consistent response in effectiveness of ten to twelve weeks. Failures occurred sporadically with patients who had responded well to earlier and/or later injections. There were fifteen instances which required reinjections of the toxin within four weeks after the original injections.

Meige's syndrome may be more difficult to control than blepharospasm. The spasm-free interval has been reported to be shorter than that for blepharospasm.[26,33,63,114] However, in our series, the mean duration of symptomatic relief after 22 injections in patients with Meige's syndrome was 18.7 weeks, which was similar to the response in blepharospasm.

2. Hemifacial Spasm

Hemifacial spasm (Fig. 13) is characterized by unilateral, periodic, tonic contractions of facial muscles. It usually begins in the orbicularis oculi muscle and gradually spreads to involve the rest of the facial muscles. Spasms occur while patients are asleep as well as awake.[40,100] Hemifacial spasm usually begins in middle age and is more common in females than males.[22,49] Familial occurrences have been reported.[17,38]

Hemifacial spasm is usually the result of mechanical-vascular compression of the seventh cranial nerve root in the cerebellopontine angle. Vascular compression was found in over 90% of patients at the time of operation.[77] The vessels most often responsible are the anterior inferior cerebellar artery (34%), the posterior inferior cerebellar artery (18%), and the internal auditory artery (7%).[22] Less than 1% of the cases are caused by posterior fossa tumors,[138] the most common tumors being epidermoids and cholesteatomas of the cerebellopontine angle.[22,75] The compression damages and irritates the facial nerve. Thus, the orbicularis oculi muscle on the affected side is often weaker, despite the spasms, than its counterpart on the normal side.[39,137] The "ectopic/ephaptic excitation"[103] and "kindling effect"[99] theories explain the electrophysiological mechanism of hemifacial spasm. A nerve damaged (demyelinated) by mechanical irritation has an abnormally low threshold that permits ectopic excitation. Ephaptic transmission is a "cross-talk" effect. A polarity change in one neuron will produce a mass effect by activating many damaged axons at ectopic sites. Kindling effects are caused by a hyperexcitability of the facial nucleus due to anti-

dromic stimulation from an ephaptic trigger zone.[99,103]

Many treatments have been tried, such as carbamazepine, clonazepam, orphenadrine, nerve blocks, botulinum injection, myectomy, selective facial nerve neurectomy, and neurosurgical microvascular decompression.[22,58] Of these treatments, microvascular decompression (Jannetta procedure)[66,67] is the most successful, and 88% of the patients are reportedly cured after the operation with a recurrence rate of less than 10%.[22,58,67,77] However, there are complications, such as hearing loss (8–13%), permanent facial paresis, otitis media, meningitis, intracranial hemorrhage, epilepsy, and death.[49,51,58,67,77]

Although neurosurgical decompression may be the definitive form of treatment, botulinum toxin injections are quite effective in controlling the hemifacial spasm, especially when the spasm has recurred after a surgical procedure. The duration of the effectiveness of botulinum toxin is reported to be about four months, with an average range between twelve and seventeen weeks.[31,49,112,127] This duration is longer by about one month than that for blepharospasm. Scott reported that some patients experienced prolonged remissions of hemifacial spasm.[127,132] Some authors reported that injection of the periocular muscles alone led to significant relief of lower facial spasms.[1,31,49,112]

In our clinic, 129 injections of botulinum toxin were performed on 35 patients with hemifacial spasm (15 men, 20 women; mean age at onset: 52.2 years, ranging from 22 to 73). Thirty-four patients (97%) had significant improvement after injection. The durations of the spasm-free interval (mean ± SD) in the same patients (n = 10) who had four consecutive injections were 12.2 ± 5.5, 18.0 ± 9.6, 22.0 ± 12.5, 20.2 ± 8.0 weeks in order of the injections. The influence of a prior Jannetta procedure is shown in Table 3. This difference was not statistically significant. With regard to the relationship between the pretreatment spasm intensity and the posttreatment spasm-free interval, eight patients with mild spasms and fourteen with severe spasms, all of whom had no prior surgery, responded similarly, i.e., 18.9 and 18.1 weeks, respectively.

B. SIDE EFFECTS AND COMPLICATIONS

Local side effects, such as ptosis, corneal exposure, diplopia, lower facial weakness, and epiphora, occur with this procedure (Table 4), but these are transient.

1. Essential Blepharospasm

The rate of complication is 21–27%.[20,26,127] Ptosis (7–11%) and corneal exposure (5–12%) are common.[10,26,88,127] Ptosis is due to the diffusion of the toxin from the upper eyelid injections to the levator muscle. As the levator muscle is extremely sensitive to botulinum toxin, the central upper eyelid should be avoided.[57,83,114] In addition, injection of a total dose of more than 25 units of toxin per eye significantly increases the incidence of ptosis.[14,26] Frueh and Musch reported that only eyebrow injections could cause ptosis.[40] A patient's risk of having at least one experience of ptosis increases with the number of treatments. About half of the patients who had more than four treatments experienced ptosis at least once.[26,30]

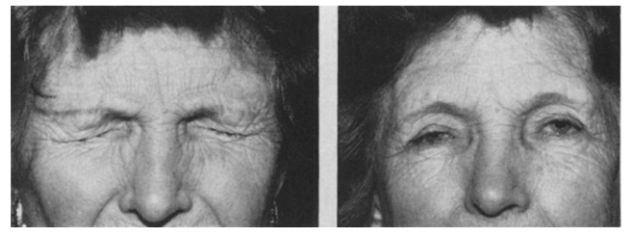

Fig. 14. Left: Patient with severe blepharospasm before the botulinum toxin injection. She had 30 units injected around each eye: lateral canthus (5 units), upper eyelid (10 units), and brow (15 units). *Right:* After the injection, the patient had relief from spasm for fifteen weeks, but moderate ptosis occured in both eyes and lasted for three or four weeks.

Corneal exposure, with resultant dry eye, is due to the infrequency of blinking and incomplete eyelid closure (lagophthalmos) caused by the paralysis of the orbicularis oculi muscle. This side effect usually causes superficial punctate keratopathy and lasts one or two weeks. Symptoms are relieved by the use of topical lubricants and conscious, forced blinking.[39] There are no reports of corneal ulceration or loss of vision from corneal exposure in patients treated with botulinum toxin.[127] However, as will be discussed below, there have been reports of corneal ulcerations in patients treated for hemifacial spasm.

In our cases, we tried to avoid injecting the toxin into the central upper lid, but we still had a very high incidence of ptosis. For the most part, these effects were mild to moderate. Ptosis was observed by us or reported by the patients in 99 (42%) in our series of 235 injections (Fig. 14). With an increasing number of injections, the risk of experiencing ptosis increases. Besides the ptosis, there were two occurrences of diplopia, three of lower facial weakness, six of superficial punctate keratopathy, and one of ecchymosis.

For all facial spasm patients, the difference in the

mean spot dose injected into the upper eyelid between the group which had ptosis (mean dose: 8.8 units) and the group which did not (mean dose: 7.7 units) was statistically signifiant [Scheffe F-test, $F = 7.37$, $P < 0.01$]. Although it is apparent that ptosis is associated with an increased dose of injected toxin in the upper eyelid, individual differences in sensitivity to the toxin also affect the incidence of this side effect.

Patients with corneal exposure and dry eyes developed superficial punctate keratopathy and blurred vision. Many of the patients receiving botulinum toxin injections, especially those with blepharospasm, were older and their tear function may have been already reduced. Therefore, it may be advisable to recommend artificial tears to these patients after injections.

Diplopia resulting from weakness of the extraocular muscles, including the inferior oblique, superior rectus, and lateral rectus muscle, has been reported as a complication.[26,28,32,83,127] The incidence is very low (less than 1%).[26,127] It is thought that paralysis of the superior rectus occurs commonly after lid injection of toxin; however, diplopia does not become apparent because of ptosis and, after treatment of essential blepharospasm, because of bilateral superior rectus paresis.[127] It is controversial whether or not the lower lid should be injected. Frueh et al noted that diplopia is most commonly caused by paresis of the inferior oblique muscle, which is quite vulnerable during injection of the lower eyelid. They reported that patients who received no lower lid injections had relief of spasm for the same intervals as patients who received them.[40,41] On the other hand, Scott reported that paralysis of the lower eyelid was important in relieving blepharospasm and that the difference in results was statistically significant.[127]

Several deaths unrelated to the injection have been reported.[10,76] It is postulated that, in some, the cause of death might have been cardiovascular stress from the increased physical activity following the relief of the disability due to blepharospasm.[10] Clinically, systemic effects of the toxin have not been reported; however, abnormal neuromuscular transmission in arm muscles was observed in testing with single-fiber EMG after periocular injection of 12.5 units of toxin.[111] It has also been shown that the injection of a single high dose (more than 280 units) in patients with torticollis slightly reduced the neuromuscular transmission in the biceps branchii, which is distant from the site of injection.[74,104]

Several authors have noted that lower facial weakness is more common as a side effect for Meige's syndrome patients than for blepharospasm patients.[26,40,76,112] Therefore, it has been recommended that the injection of the retractor muscles at the corners of the mouth be avoided with these patients to prevent difficulties with articulation and salivation.[127]

TABLE 4

Complications of Botulinum Toxin Treatment of Facial Spasm

1. Ptosis
2. Lagophthalmos (with resultant dry eye, blurred vision, keratitis, photophobia, and corneal ulceration)
3. Entropion
4. Ectropion
5. Epiphora
6. Diplopia
7. Ecchymosis
8. Lower facial weakness

2. Hemifacial Spasm

The side effects are almost the same as those experienced by blepharospasm patients; however, diplopia and lower facial weakness are more common. Scott reported a higher incidence of diplopia following treatment of hemifacial spasm (5%) than blepharospasm.[123] It is thought that the paralysis of the unilateral superior rectus muscle becomes symptomatic in hemifacial spasm.[127]

In our series, there were 39 occurrences of ptosis (30%), 22 of lower facial weakness (17%), 15 of diplopia (12%), 10 of superficial punctate keratopathy (8%), and one of epiphora. Epiphora may be caused by the dysfunction of lacriminal ducts or corneal punctuation. We found it difficult to detect which extraocular muscles caused diplopia. There was a statistically significant difference in the mean total dose to the uper lid region between those with diplopia (8.5 units) and those without diplopia (6.3 units) [Scheffe F-test, $F = 5.78$, $P < 0.02$]. In addition, ptosis was present in 67% of the patients who had diplopia (Fig. 13). Therefore, we believe that diffusion of the toxin into the superior rectus muscle is the cause of diplopia in many of these cases.

Paresis of the buccolabial muscles caused lower facial weakness, and patients occasionally complained that they bit their buccal mucosa when chewing. Paresis of the zygomaticofacial muscles caused temporary loss of the nasolabial fold and drooping and incomplete closure of the mouth.[39]

Clinically, it seemed that the dose to the cheek region correlated with the degree of lower facial weakness; however, this could not be confirmed by statistical analysis. The difference was significant, however, when the mean total dose to the lower eyelid, cheek, and side face region was compared for the group that developed lower facial weakness

(47.2 units) as opposed to the group which did not (36.9 units) [Scheffe F-test, $F = 5.01$, $P < 0.03$]. Therefore, the total of the doses of toxin seems to be the important factor in this complication.

Recently, two corneal ulcerations were reported after botulinum toxin treatment for hemifacial spasm (personal communication from Dr. Scott). One of these patients eventually had a corneal perforation which required grafting. Patients with hemifacial spasm frequently have muscle weakness on the affected side from seventh nerve compression in the cerebellopontine angle. Physicians must be aware that the added paresis from botulinum toxin injection may be greater than anticipated.

V. Other Disorders for Which Botulinum Toxin Has Been Used

A. LOWER LID ENTROPION

Spastic entropion may be caused by laxity of the lid septum and canthal tendons, accompanied by the upward movement of preseptal and pretarsal parts of the orbicularis muscle.[19] It is not curable by botulinum toxin injection; however, injection into the lower orbicularis muscles will provide temporary relief.[14,15,19,76,83,127] This approach is suitable if the patient is a poor surgical candidate or refuses surgery. In our study, one patient with spastic entropion received botulinum toxin injection. The efficacy was short-lived, and surgery was required.

B. MYOKYMIA

Eyelid myokymia (eyelid twitching) can be seen in either the lower or upper eyelid of otherwise healthy patients and is a self-limited, benign process.[108] It is necessary to differentiate this benign myokymia from facial myokymia, which is usually unilateral, characterized by continuous undulating and involuntary movements of the facial muscles, and caused by tumors of the brain stem or multiple sclerosis.[22,87,108] Botulinum toxin has been used for 47 persistent eyelid myokymia patients.[123,127] We have successfully treated the lid of a patient with facial myokymia who also had multiple sclerosis. Botulinum toxin, 20–25 units, was injected into the lower lid and cheek and the effects lasted 12–13 weeks.

C. ABERRANT REGENERATION OF THE SEVENTH CRANIAL NERVE

Aberrant regeneration of the seventh cranial nerve occurs after facial nerve trauma or Bell's palsy and causes anomalous facial movements. Botulinum toxin injections were effective in controlling the anomalous facial movements, when given in a manner similar to that for hemifacial spasm.[10,11,29,107]

D. LID RETRACTION

Botulinum toxin injection of the lavator muscle frequently causes superior rectus paralysis and symptomatic diplopia. The amount of ptosis is difficult to predict. Botulinum toxin treatment is not recommended for thyroid eyelid disease.[133]

E. CORNEAL DISEASE

Tarsorraphies have been used to treat corneal exposure and indolent corneal ulcer. Some authors have produced a pharmacologic tarsorraphy by inducing ptosis with botulinum toxin injections into the levator muscle.[73,83] The advantages of this procedure are that it is easier to examine the patient and instill topical medications than with other forms of tarsorrhaphy, and the lid margins remain undamaged. Kirkness et al reported that 90% of indolent ulcers healed after injection of the toxin into the levator muscle. Transient weakness of the superior rectus muscle was reported in 68% of patients. Three of twenty-five patients had diplopia, and one needed prisms for six weeks. Usually, recovery of the superior rectus muscle (mean: six weeks) occurred before recovery of the lid (mean: 8.5 weeks).[73]

F. NYSTAGMUS

Helveston et al[53] used botulinum toxin to control the symptoms of two patients whose acquired nystagmus produced oscillopsia and decreased visual acuity. These patients had vertical, horizontal, and rotary components to the nystagmus, and it was judged necessary to reduce the actions of all of the extraocular muscles. Injection of the toxin (25 units) into the retrobulbar space unilaterally improved visual acuity from 20/200 to 20/60 and from 20/80 to 20/30, respectively, and reduced the symptoms of oscillopsia. No complications except minimal blepharoptosis were produced. The effects were transient, however, lasting from five to thirteen weeks.

G. SPASMODIC TORTICOLLIS

Spasmodic torticollis is a disorder of unknown etiology characterized by abnormal posture of the head due to overactivity of the neck muscles. The benefits of medication and surgery are limited. Jankovic and Schwartz reported that 71% of patients treated by botulinum toxin injection had subjective improvement, and the duration of effectiveness was 11.2 weeks on average (total mean dose: 224 units).[64] In a masked, placebo-controlled trial, patients treated by botulinum toxin (18–36%) showed

a statistically significant improvement compared with controls (0–3%).[45,50,143] Neck weakness, fatigue, malaise, antibody formation, brachial plexus neuropathy, and dysphagia are side effects.[2,45,64,144,145] Dysphagia may be due to the diffusion of the toxin into the muscles of deglutition.[2,45,64] Tsui et al reported antibody to botulinum toxin was found in four (12.5%) of thirty-two patients.[145] Glanzman et al reported that brachial plexus neuropathy occurred after the injection into the strenocleidomastoid (45 units) and trapezius (75 units). Systemic effects and branchial plexus neuropathy may be related to immune-mediated reaction or the spread of the toxin within the body.[46,141]

H. ADDUCTOR SPASTIC (SPASMODIC) DYSPHONIA

Adductor spastic dysphonia is a disorder in which there is excessive vocal cord closure during speech.[78] It is characterized by intermittent phonation, vocal straining, vocal hoarseness, and difficulty in initiation of phonation.[66,78] Resection of the recurrent laryngeal nerve is the most common therapy; however, three-year follow-up examinations showed a high percentage of failures (64%).[5] Botulinum toxin injections into the thyroarytenoid muscles have been effective in producing temporary relief from symptoms.[3,12,78,98] Ludlow et al reported that the side effects of dysphonia and aspiration could be avoided by unilateral injections.[78]

VI. Future Research

Recently, doxorubicin was used to treat blepharospasm patients with encouraging results.[68,148] Doxorubicin (Adriamycin®) is a cytotoxic anthyracycline used to treat disseminated neoplasms, and it also has a chemomyotoxic and chemodenervation effect. Doxorubicin opens Ca^{2+} channels in terminal cisternae and activates Ca^{2+} release from sarcoplasmic reticulum. This mechanism alters intracellular calcium homeostasis and injures a muscle.[149] Animal experiments have shown that the toxin damages muscle fibers relatively selectively. Muscle mass is lost, and this effect is greatest close to the site of injection.[91] In the treatment of facial spasm, doxorubicin produces fibrosis of muscles and a more permanent weakness than botulinum toxin.[6,91]

VII. Summary

Many clinical studies, including our own, have shown that the injection of botulinum toxin is beneficial for patients with blepharospasm and hemifacial spasm. In strabismus, extraocular surgery produces a more stable and often a more predictable result than botulinum toxin injections. However, injection of toxin may have a role in the treatment of neuroparalytic deviations and subacute dysthyroid myopathy of the extraocular muscles. Botulinum toxin injections are particularly useful in treating small deviations and sensory deviations. Botulinum toxin can also be useful in longstanding strabismus in adults by identifying cases in which intractable diplopia might occur after surgical correction. Because botulinum toxin can be injected with safety and low morbidity, it has achieved FDA approval. It is now commercially available to the practicing ophthalmologist.

Chemodenervation therapy with this agent has been applied to other neuromuscular disorders, such as spasmodic torticollis and adductor spastic dysphonia, with favorable results. Thus, we can expect further applications for botulinum toxin therapy in fields other than ophthalmology.

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