CHAPTER 25

Chemodenervation of Extraocular Muscles—Botulinum Toxin

The idea of substituting surgery with less invasive methods has been one of the dreams of strabismologists. Despite the success achieved with surgery in the treatment of strabismus, there are some disadvantages. In most instances the operation is performed on normal muscles and there are the risks of tissue scarring and infection or the unknown effects of changing the dynamics of muscle function by shortening the muscle or changing its insertion. Various attempts have been made over the years to change extraocular muscle activity by means other than surgery. Alcohol or anesthetic substances have been injected intramuscularly[52] but these experiments were not pursued or published since it soon became apparent that the effect of injected anesthetics fades out too rapidly to be effective. In the early 1970s Alan B. Scott of San Francisco began experimenting with chemodenervation of the extraocular muscles in an attempt to find a viable alternative to surgery. He established, first in animal experiments and then in clinical trials, that injection with botulinum toxin type A (Botox, Allergan) is the most effective method to paralyze a muscle temporarily. He also showed that the dreaded systemic side effects of this powerful neurotoxin can be ignored provided a highly diluted solution is used. This was the beginning of pharmacologic treatment of strabismus in our time.[51, 58] Among numerous contributors to this rapidly developing field, the names of A. B. Scott, McNeer, Magoon, Lee and Elston, Campos and coworkers, and Lennerstrand and coworkers have become connected with increasing the scope of applications of Botox and with the collection of clinical data on its effectiveness in various forms of strabismus.

Mechanisms of Action

Botox treatment for strabismus is based on the property of this toxin, a competitor of acetylcholinesterase at the neuromuscular junction, to cause a flaccid paralysis of the injected muscle. This effect is temporary, because reinnervation takes place within 40 to 60 days and the injected muscle regains its contractile power. Spencer and McNeer[60] showed histologic changes in injected medial rectus muscles of adult rhesus monkeys. These changes were most apparent in the orbital, singly innervated muscle fibers, which in the acute stage exhibited denervation-like hypertrophy with dispersion of the central mitochondria toward the periphery of the fibers. There was also obliteration of the capillary network as a secondary response to disuse. Neuromuscular junctions were still present on all fibers, although evidence of sprouting was apparent. In the long term (42 to 56 days) the muscle fibers appeared normal and the vasculature had recovered. In another study it was shown that

Botox produces a gradient of denervation in a given muscle, which is dose-dependent.[6] Even repeated injections of Botox do not appear to cause irreversible muscle atrophy or other degenerative changes.[5] Finally, injection of Botox has been shown to induce temporary changes in the diameter of myofibers in the orbital layer of the superior rectus muscles of rabbits: the diameter was first reduced and eventually increased at 5 weeks after injection, compared to that in the control eyes. In contrast, no change in the diameter of muscle fibers was found in the intermediate layer zone.[44]

The effect of Botox in *paralytic strabismus* is easily understood. In this condition the strabismus is caused by overaction of the unopposed antagonist of a paralyzed muscle and is reversed by creating a temporary paralysis of that muscle. This avoids contracture of the chemodenervated muscle until such time that the function of the paralyzed muscle returns. In the interim this treatment may provide the patient with a useful zone of single binocular vision and avoid a compensatory and, in the case of a complete paralysis, often excessively abnormal and uncomfortable head posture. Acheson and coworkers[2] showed a dissociated effect of Botox in patients treated for a chronic lateral rectus muscle deficit. They found that the ocular realignment caused by Botox can persist after saccadic function has been restored. They interpret this finding with the hypothesis that Botox may have a more profound and long-lasting effect on the orbital singly innervated fibers. These fibers are active tonically at rest to hold gaze, whereas there is a relative sparing of the additional motor units recruited during fast eye movements.

The effect of Botox in *comitant strabismus* is less clearly understood. Even though repeated injections are required in most patients there are conditions, such as essential infantile esotropia, in which the ocular realignment may persist even after the effect of chemodernervation has worn off. It has been suggested that the temporary paralysis induced by Botox favors activation of its antagonist.[52] As an example, the unopposed lateral rectus muscle of a patient with esotropia becomes tight by creating a temporary paralysis of the medial rectus muscle. After the effect of Botox has worn off, a balance would be reached between the action of the excessively innervated medial rectus and the tightened lateral rectus and the effect of the injection may become permanent.[32, 52] This hypothesis has, to our knowledge, not been verified.

Injection Technique

The original approach developed by A. B. Scott consisted of injecting an extraocular muscle under electromyographic (EMG) control. This is tolerated in adults, but requires sedation with ketamine hydrochloride (Ketalar) in children because muscle activity has to be preserved for EMG recording.[51, 57] Injections must often be repeated more than once. In infants this necessitates repetition of sedation and usage of an operating facility, which causes both ethical and economical problems. Moreover, many pediatric anesthesiologists dislike the use of ketamine hydrochloride in children because of its side effects.

In adults, an electrode is placed on the forehead of the patient and an eye speculum is inserted after use of a local anesthetic. The conjunctival site of the needle perforation is further anesthetized by application of a cotton swab soaked with 4% carbocaine. A specially designed needle electrode connected to a regular syringe containing Botox as well as to the EMG apparatus is used for the injection. Only the tip of the needle is not insulated. The needle is inserted transconjunctivally into the muscle (Fig. 25–1*A*), close to its insertion, and then moved forward tangentially. The patient is then asked to move the eye in the direction of action of the muscle to be injected (Fig. 25–1*B*). If the needle has been placed correctly an EMG signal appears on the monitor and an auditory response is obtained as well. At this point Botox is injected into the muscle. The whole procedure takes 1 to 2 minutes for an experienced person.

When Botox is used in children the above approach is not possible. A. B. Scott injected the substance under EMG control and sedation as stated above. McNeer and coworkers[39–41] use inhalation anesthesia (nitrous oxide and ethrane) and obtain recordings from the injected muscle within the first few minutes of insufflation. Campos and coworkers,[11, 48, 50] when injecting Botox in patients younger than 5 to 6 years old, prefer halothane (Fluothane) or sevoflurane insufflation anesthesia. The conjunctiva is opened, the muscle is engaged on a muscle hook, and Botox is injected into the muscle under direct visualization and without the aid of EMG. This ensures adequate penetration and distribution of the substance in the muscle. It also reduces the spread of Botox to adjacent extraocular muscles and prevents blepharoptosis. Botox is diluted in 4 mL of a 0.9% solution of

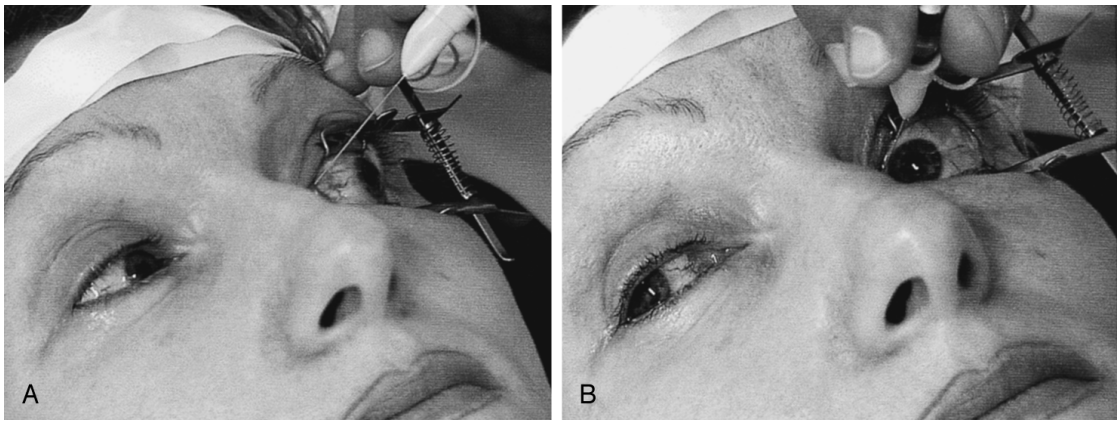

FIGURE 25–1. *A,* A needle electrode is inserted transconjunctivally into the medial rectus muscle. *B,* While the patient adducts the eye the ophthalmologist listens for the auditory response of the amplifier to confirm correct placement of the needle prior to injection.

NaCl so that 0.1 mL equals 2.5 units. Most authors have employed 1.5 to 2.5 units per muscle in children, but Campos and coworkers inject 3 units into each muscle.

Indications

Botox in Infantile Esotropia

In the past, Botox was injected into only one medial rectus muscle. The result was a paralytic exotropia, which made alternating fixation impossible and created the risk of developing amblyopia in the injected eye. An analysis of the literature of this approach reveals conflicting results.[4, 16, 32, 38, 54] The patient groups injected were quite heterogeneous and the age of the patients at injection time varied over a wide range. Moreover, attempts to correlate the dosage of Botox injection with the effect obtained produced variable results.

Considering that the effect of muscle surgery is fairly predictable in most patients with essential infantile esotropia, the variable outcomes after Botox and, in particular, the frequent need for repeated injections did not generate enough enthusiasm among most pediatric ophthalmologists to employ chemodenervation as a primary therapy in this condition. Its usefulness as a secondary therapy after surgical overcorrection or undercorrection has been suggested but long-term follow-up studies establishing the value of this therapy are still lacking.[10–12, 39, 62]

More recently, surgeons have injected both medial rectus muscles at the same session, and the results have become more encouraging than after single-muscle injection.[4, 20, 27, 40, 41, 45, 46] However, the data are still difficult to compare because different types of strabismus were included in many of the studies. Patients with essential infantile esotropia of 30Δ to 40Δ were considered together with others who had an esotropia of 20Δ and the patients' ages at the time of treatment varied over a wide range.[41, 45] Some patients were injected at an age of less than 12 months and others between the ages of 12 and 24 months.[38, 40, 41, 45]

In 1989 Campos and coworkers began injecting both medial rectus muscles in patients with essential infantile esotropia and alternating fixation between 5 and 8 months of age and obtained stable correction of the strabismus in 53 (88%) of 60 cases after an average follow-up of 10 years.[9, 11, 13, 48, 50] Other authors replicated this approach and followed essentially the same scheme of treatment.[15, 20, 31, 61] The stability of results obtained with only one injection could be due to several factors: First, Botox injection was performed presumably before a contracture of the medial rectus muscles could develop and before the establishment of sensorimotor sequelae of strabismus (anomalous disjunctive movements).[8] Both of these factors are capable of decreasing or nullifying the effect of surgery. The fact that recurrences or undercorrections or both, are common in patients treated after the age of 8 months, even after injection of both medial rectus muscles, seems to be in favor of this possibility. Second, Botox injection under direct visualization under anesthesia allows for more accurate control of the injection site and for more Botox reaching the muscle, thus causing a greater effect.

Campos and coworkers evaluated visual acuity and the binocular sensory functions in 21 of their 60 patients and found normal visual acuity in each eye. However, stereopsis as tested with the TNO test was not present in a single instance. In essence, normal binocularity was never achieved, but anomalous binocular vision or subnormal binocular vision was always present. This result is comparable to that after surgery in terms of ocular alignment and binocular functions[43] (see Chapter 16).

In conclusion, Botox offers some advantages and some disadvantages when compared to surgery in the treatment of infantile esotropia.[23] Its limitations are related to the difficulties involved in gaining access to patients with infantile esotropia that early in life, to the frequent need of repeated injections unless treatment is begun prior to the age of 8 months, and to lack of precision in the dose-response relationship. Many studies published during the last 5 years, especially those in which bilateral injections were used, are encouraging. However, until the stability of alignment after one injection reported by Campos and coworkers can be confirmed by additional studies employing the same strict criteria, the use of Botox in infantile esotropia cannot be unequivocally advocated at this time.

Botox in Other Forms of Comitant Strabismus

Attempts have been made to employ Botox in adult *exotropia.*[25] Repeated injections are obviously necessary. We are convinced that surgery is preferable, yet in selected cases this option may be offered to the patient.

Botox has been employed in *normosensorial late-onset esotropia.* Campos and coworkers obtained favorable results with one injection in both medial rectus muscles, shortly after the onset of this condition.[9, 48, 50] These results have been confirmed.[15]

The use of Botox has also been suggested as a preoperative diagnostic tool in adult patients by simulating a surgical result and predicting the postoperative diplopia.[30, 63] We feel that prismatic correction of the preoperative angle of strabismus or of a local anesthetic injected into a muscle can be used with the same purpose without inducing long-term effects, which may require a delay of surgery.

Botox is useful in *sensory exotropia* following a traumatic cataract and monolateral aphakia, provided that useful visual acuity is achieved.[3, 21, 49] After successful cataract surgery and lens implantation the fusional amplitudes of such patients are insufficient to overcome the exodeviation and diplopia is present. However, after injection of Botox into the lateral rectus muscle the sensory exotropia may disappear and the patient regains sufficient fusional amplitudes to control whatever exodeviation remains after recovery of lateral rectus muscle function.

Botox in Paralytic Strabismus

A logical expansion of Botox indications has been its use in muscle deficits due to lesions to the corresponding nerve or its fibers, that is, in recently acquired paralyses of neurologic origin. Injection of Botox into the medial rectus of patients with *sixth cranial nerve paralysis* is used by many clinicians, if the deficit is of recent origin.[12, 16, 17, 19, 26, 35, 56] The iatrogenic paralysis induced with Botox counterbalances the original paralysis of the antagonist muscle. The recovery periods of the original paralysis and the iatrogenic paralysis are approximately matched and 80% of the patients do not require surgery. It is well known that the majority of acquired sixth nerve paralyses recover spontaneously but a contracture of the antagonist muscle may remain and cause a permanent esotropia with diplopia. Botox appears to prevent this contracture.[56] This view has been challenged by Lee and coworkers.[33] They found equal recovery rates in patients with unilateral abducens palsy, whether treated or not treated with Botox, and concluded that there is no evidence that Botox prevents the contracture of the medial rectus muscle. Be this as it may, Botox injection improves the quality of life for the patient during the recovery period by providing a useful field of binocular single vision in or near the primary position. For this reason we feel that its use is still warranted in suitable patients. Caution is advised, however, not to increase the field of diplopia with Botox in patients with incomplete abducens paralysis who are able to maintain single binocular vision with a moderate head turn.

Botox may also be useful in patients with *multiple sclerosis,* who may recover spontaneously from a sixth nerve paralysis or paresis but suffer from diplopia during the active phase of the disease.

An interesting application is the injection of

Botox into the medial rectus of patients who have to undergo a *transposition procedure* for a complete abducens paralysis.[18] Botox injection 15 to 20 days before surgery eliminates the need of combining the transposition procedure with a recession of the hyperactive antagonistic medial rectus muscle, even in the presence of contracture, revealed by positive forced ductions. This approach is of particular interest in elderly patients, who are at risk of developing anterior segment ischemia after multiple muscle procedures. We have used it for the last 10 years but in one case the iatrogenic medial rectus muscle paralysis persisted for 1 year, with troublesome exotropia and diplopia.

Botox has also been suggested to temporarily weaken the ipsilateral inferior oblique muscle in *acquired fourth nerve paralysis.*[26, 35] We have found it impossible to inject the inferior oblique muscles under EMG control and a closed sky technique without spreading Botox to the adjacent inferior rectus muscle, although others have been successful in doing this.[36] At this time it remains doubtful that this application of Botox will gain a firm place in the management of trochlear paralysis.

Botox in Endocrine Ophthalmopathy and Other Ocular Motility Disturbances

There are some other, ancillary indications for Botox deserving mention. Botox works well if injected into tight muscles in *endocrine myopathy* in the florid stage, that is, when the muscles become imbibed with mucopolysaccharides.[37, 53] It is of no use in this condition once the fibrosis stage is reached.

Botox has also been used to treat strabismus after surgery for *retinal detachment* when vision in the eye operated on is low and corrective muscle surgery appears risky.[34, 55] Botox injections have to be repeated periodically in this condition. Considering the altered anatomy of these globes after extensive surgery the risk of perforation with repeated injections is probably higher than with surgery and we do not advocate this treatment.

The use of Botox in *Duane's syndrome,* proposed by White and Lee,[64] seems not warranted because of the temporary effect of Botox on a fibrotic muscle.

Botox in Nystagmus

Botox has been used successfully in acquired nystagmus with *oscillopsia.* Retrobulbar injections or injections in the horizontal rectus muscles have been proposed.[14, 22, 35, 47] The treatment has to be repeated periodically and only one eye can be injected at a time, as there is a risk of losing binocular vision after injection. Some but not all patients benefit from this treatment. No rational indications for Botox exist in congenital nystagmus, in spite of some reports in the literature to the contrary.

Other Ophthalmologic Indications

One of the most effective applications of Botox is the injection of both upper and lower lids in patients with *essential blepharospasm.* Although the injection must be repeated every 3 to 6 months the overall patient satisfaction and the extent of rehabilitation in this debilitating condition is impressive and gratifying.

Botox is also effective in spastic entropion, where it has to be used chronically. The injection of Botox in the *levator palpebrae superioris* has been suggested for inducing a long-lasting ptosis in patients with corneal pathologic conditions who otherwise require prolonged use of a bandage. Yet a persisting hypotropia following this procedure has been described.[24]

Neurologists use Botox for movement disorders, such as oculofacial spasms and spastic torticollis.[12] Other indications include spastic dysphonia, esophageal spasm, bladder sphincter spasm, spastic paralysis, hyperhidrosis, and the removal of facial wrinkles.

Alternatives to Botox for Chemodenervation

Botox is probably not the ideal substance for chemodenervation.[1] As a biological substance its action cannot be precisely predicted since its toxicity varies in different lots. Moreover, repeated injections may induce immunoreactions, which can decrease the efficacy of treatment.[29, 59] This problem is more relevant to movement disorders than to strabismus. Still, when using repeated injections in infantile esotropia, as suggested by various authors, one has to consider this alternative.

Ideally, synthetic substances interfering with

muscle function are preferable. Breinin and coworkers have experimented with the calcium channel blocker cadmium and diltiazem.[7, 28] Since this approach seems to be quite rational, it is unfortunate that these studies have not been continued. Antibiotics such as doxorubicin, used against immunoreactions, have also been suggested as an alternative to Botox.[42] Doxorubicin induces a localized necrosis and causes a destruction of the injected muscle with some skin reaction. Perhaps one day its use may be considered for movement disorders in which Botox treatment is chronic, whereas one single injection could solve the problem permanently. Whether this approach, if properly modified, could also be applied to some strabismus forms remains to be seen.

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