CONFERENCIA MAGISTRAL: "BOTULINUM TOXIN TREATMENT OF STRABISMUS"

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Introduction

The first thorough investigations of botulinum toxin were undertaken by Justinus Kerner and published in 1817-1822[1]. He made many original observations about causation, diagnosis, prognosis and treatment of botulinum toxin, and extracted the toxin from sausages. He demonstrated its effects in animals, correctly concluded that it paralyzed skeletal muscles and parasympathetic function, and proposed its use as a therapeutic agent in neurologic diseases such as chorea that are characterized by excessive motor movement. But it was a full 160 years after Kerner that the idea of therapy with botulinum toxin was implemented. We began in 1970-1971 with injection of various drugs into extraocular muscles as an alternative to surgical treatment for strabismus.[2] Among these was botulinum toxin.

Botulinum toxin molecules are long protein sequences (150,000 Daltons) with three domains (active portions of the molecule). The first domain binds to receptors found exclusively on nerve terminals; these are specific for clostridial toxin. Endocytosis then brings the toxin into the nerve terminal within vesicles. The second domain allows the toxin to enter the nerve cytoplasm from the vesicles. The third domain acts as an enzyme, each toxin type cutting a different and specific site on one of the three proteins required to attach vesicles to the nerve membrane for exocytosis of acetylcholine. This enzymatic part of the botulinum molecule is not transported by exoplasmic flow, but stays active at the nerve terminal for 1 to 3 months depending on age and on dose. With no transmitter, the muscle is denervated and undergoes denervation atrophy just as if the nerve were cut.

Initially, we thought that botulinum toxin treatment of comitant strabismus worked because the extraocular muscles (EOM) were permanently weakened by the induced denervation paralysis. Spencer and McNeer[3] showed changes in the outer (orbital) muscular layer of botulinum toxin-treated primate EOM, lasting for six months. But active contraction force returns fully to these muscles. We now believe that the muscles alter alignment of the eyes mostly by adapting their length to the new position of the eye by addition/deletion of sarcomeres. Botulinum toxin is just a way of getting the eye into a new position so that the muscles are stretched or shortened[4]. The tendency for this internal sarcomere reorganization varies from one individual to another. It also is dependent on the dose response, on creating a large angular change of alignment from the botulinum toxin injection paralysis, and on its persistence for at least one month. Therefore, it is not surprising that clinical responses to initial botulinum toxin injection are variable.

Indications and clinical results

Botulinum toxin injection in EOM is most efficient in non-restrictive strabismus. Scarring and paralysis restrict the inherent ability of the muscle to alter its length/tension characteristics.

In general, there is about a 30%-40% chance that one injection will correct the deviation to 10 prism diopters or less. See Table 1. Table 2 shows that smaller deviations are more frequently corrected to 10 prism diopters or less by one injection, but that the percentage correction of the deviation is around 60% in most categories. Esotropia and exotropia generally respond similarly and children and adults respond alike. Smaller deviations (horizontal or vertical) with minimal sensory changes have a superior prognosis. Large-angle deviations, more common in long-standing adult strabismus, often require repeated injections, resulting in a longer interval from the initiation of therapy to optimal correction. Despite this apparent disadvantage, many adults choose multiple botulinum toxin injections to avoid surgery.

A. Paralytic Strabismus

1. VI Nerve Paralysis

a. Acute cases of any age or origin are followed without treatment for 3-4 weeks. If healing begins within a month, it typically will be progressive and complete. Adults will be rehabilitated, and children seldom lose binocularity if alignment is restored in a month. After one month, if disabling diplopia persists and recovery is not progressing, or if a child remains esotropic in all gaze positions so that binocularity is threatened, then injecting the medial rectus (MR) on the affected side is appropriate. In a randomized trial in ambulatory adults with paresis of diabetic or vascular origin, there was little long-term difference in recovery between a botulinum toxin-treated (86%) and an untreated control group (80%)[5]. Thus, for these adults who have a generally good prognosis, the value of botulinum toxin treatment lies in earlier rehabilitation.

b. Delayed recovery. If recovery is delayed several months or takes place very slowly, MR contracture progresses and esotropia increases. Botulinum toxin injection of the MR in these non-acute cases allows the lateral rectus (LR) to recover against the treated MR of normal length, rather than against a strong and shortened MR. There is little risk of permanent overcorrection and the patient's alignment is improved, serving both functional and cosmetic goals while awaiting healing of the LR. The data from Metz and Mazow[6] indicate that there is a higher percentage of alignment in treated cases (Table 3).

c. Diagnosis. Persistent esotropia 6-12 months after onset may be due to limited LR recovery or to MR contracture in varying proportions. If there is abduction beyond the midline, good abduction saccades, or good LR force (30 gm or more), then a trial of MR botox injection to release of the MR contracture will often be fully curative. If LR force is between 10 gms and 30 gms, then recess-resect will be as effective as transposition. If LR force is under 10 gms, then transposition is indicated.

d. Permanent paralysis. Surgery by lateral transposition of the superior rectus (SR) and the inferior rectus (IR) together with botulinum toxin to the medial rectus (MR) gives the largest field of single binocular vision. The value of botulinum toxin here is primarily to preserve and lengthen the MR so that this muscle, now the only active horizontal mover, has a large range of contraction-relaxation. In contrast, surgical recession of an already short and contracted MR restores alignment but leads to further shortening and a further reduction in range of motion. Also important is that botulinum toxin leaves the anterior ciliary artery supply of the MR intact, obviating the threat of anterior segment ischemia. The ability of botulinum toxin to release MR contracture makes it appropriate to wait a full 6 months after the onset before undertaking transposition surgery. Botulinum toxin injection may be done a few weeks before surgery, or deferred until the time of surgery to allow accurate traction testing of the MR. Injection is then easily done under direct visualization. Where MR contracture is mild, injection is best deferred until postoperative alignment can be determined. It may be unnecessary and overcorrection could result. Injection even several months after surgery can correct undercorrected transposition cases, and should be considered before re-operating.

2. *III Nerve Paresis:* Saad and Lee[7] corrected 3 of 4 cases which had some residual MR function, and Metz and Mazow[6] similarly corrected a majority of their cases using botulinum toxin. Botulinum toxin is very useful in late aberrant III nerve regeneration, where small deviations interfere with primary-position alignment. The muscles seem to be especially sensitive; small doses should be used.

3. *IV Nerve Paresis:* Botulinum toxin injection is beneficial in unilateral IV nerve paresis. Lozano-Pratt[8] corrected 9/9 acute cases with 17-30 P.D. of vertical deviation, Buonsanti[9] corrected 9/15 (3 others partially improved), and we corrected 4 out of 6 patients. All series were followed over 12 months, and were injections of the overacting IO muscle. Garnham et al[10] found botulinum toxin injection of the yoke IR more useful in both acute and chronic IV paresis. I agree that this is correct for cases in which the vertical deviation is more pronounced in downgaze.

B. Adult Strabismus

1. *General:* Adults must be aware of the intended overcorrection and its cosmetic implications, as well as possible diplopia and spatial disorientation lasting 1-2 months. This will require patching in about a third of adult cases, mostly for the first week or two, followed by adaptation that allows its discontinuance. Some elderly persons are physically unstable, and many busy adults are unable to drive and work when monocular. Consider a trial of patching for a day or two before injecting adults without suppression or amblyopia.
   The strabismus is often complicated by cicatricial restrictions, excessive muscle recession, and poor fusion or amblyopia. Multiply operated strabismus patients unhappy with the surgical outcome are frequent candidates for botulinum toxin injection. The ease of injection and the frequently excellent outcome warrant a trial in most such cases. Because suppression and amblyopia are frequent, the effects of botulinum toxin-induced paralysis on the sensory status is often of no concern. In one exceptional report of 80 patients, 8 to 20 injections were given as chronic treatment. The intervals between recurrences gradually increased, and a number of patients became stable[11].

2. *Post-retinal detachment strabismus:* These patients have normal binocular vision in their favor. In most cases, the strabismic angle is modest. Scott[12] corrected 60% of cases with one injection; and Pettito and Buckley[13], 80%. Scarred extraocular muscles often require larger doses or a repeat injection. Injection of two muscles (e.g., the lateral rectus and inferior rectus simultaneously) is common.

3. *Thyroid ophthalmopathy:* Botulinum toxin is useful in acute or active cases to relieve diplopia.[14,15] Maintaining alignment to prevent or treat chronic cases is much less secure; surgery is avoided in about 25%-30% of cases. The medial rectus muscles are frequently affected in thyroid disease and the horizontal deviation is usually modest. Since multiple muscle surgery in thyroid eye disease carries a higher risk of ischemia, use of botulinum

toxin for the esotropia (ET) while operating on the vertical is very useful. Most late extraocular muscle restrictions are fibrotic. However, an occasional remarkable loosening of contracture shows that internal muscle shortening plays a role.

4. *Post-cataract strabismus:* Immediate diplopia after cataract surgery in previously fusing adults usually presents as hypotropia of the operated eye secondary to IR contracture following retrobulbar anesthesia. When prisms are inadequate and the patient wishes to avoid IR recession, botulinum toxin injection of the IR will correct over 60% of cases with a single injection. A second useful application is in long-standing unilateral cataract with exotropia and diplopia after cataract removal. Injection of the LR will restore alignment and subsequently maintain fusion in over half of these patients.

5. *Postoperative adjustment:* Avoiding multiple surgical procedures is an integral part of strabismus treatment. Botulinum toxin injections are an alternative to additional surgery for strabismus, particularly if the intended goal has not been achieved by recent surgery. Botulinum toxin may be used either early or late in the postoperative period [16] or in conjunction with surgery, especially if the planned surgical procedure (e.g., transpositions, additional surgery on rectus muscles) may compromise anterior-segment vascularity.

6. *Intrinsic muscle disorders:* Unexercised extraocular muscles and other tissues stiffen markedly in some persons but not in others. Strabismus in chronic myasthenia and progressive external ophthalmoplegia is surprisingly responsive to botulinum toxin when the eye is stiff on traction testing. The response is much less when the eye is readily moved.

7. *Nystagmus:* Acquired nystagmus with oscillopsia and reduced vision usually has a vertical or rotary component. A single retrobulbar injection creates ophthalmoplegia for 3-4 months to dampen such movements.[17] This has dramatically improved vision in several cases from 20/400 to 20/40. Because the induced ophthalmoplegia creates diplopia and marked spatial/balance problems, this works best for wheelchair-bound patients. Only one eye of an ambulatory patient should be injected in this manner. Vision can be improved by 2-3 lines by intramuscular injection of the horizontal recti in horizontal motor nystagmus (2.0 - 2.5 units per muscle) but the effect is transient.

C. Childhood Strabismus

1. *Infantile esotropia*

   Treatment of infantile esotropia by simultaneous bimedial botulinum toxin injection is quite successful. Table 4 shows the results of several independent series.[18,19,20,21] All these reports include 2 years or more of follow-up, and show high correction rates of 60-80% with multiple injections.

   The experience of these investigators suggests the following therapeutic program: 1) Simultaneous bimedial injection of 2.5 units of botulinum toxin per muscle. 2) Inject as early as age 3 months. The good results in the series of Campos et al. were all injected prior to 8 months. 3) Repeat simultaneous bimedial injection with recurrence of ET exceeding 15 prism diopters, increasing the dose to 3.0 units per eye unless ptosis is a limiting side-effect.

   The following comments are pertinent: 1) Large overcorrection to 20-40 prism diopters of exotropia, lasting 3-6 weeks, is usual and desirable. 2) Over one-third of infants presenting with esotropia and no refractive error when first seen will develop significant hyperopic/astigmatic refractive errors, and thus develop am accommodative component. Full-strength lens correction is essential. 3) All authors remark that the incidence of dissociated vertical deviation (DVD), "V," and "A" pattern strabismus appears to be lower following successful bimedial botulinum toxin treatment than with surgical correction, but no comparative data are available.

2. *Accommodative esotropia:* Bimedial rectus botulinum toxin injection has been useful for correcting a high AC/A ratio with residual ET at near.[22] Consecutive exotropia has not been seen.

3. *Acquired esotropia and the non-accommodative angle in accommodative esotropia:* Acquired esotropia here refers to strabismus developing after infancy that is neither paretic nor accommodative. Botulinum toxin will provide motor alignment, but the best responses are achieved if amblyopia can be improved or reversed prior to injection. Unilateral MR injection will often enhance or create hypertropia. Therefore, inject the hypotropic eye even if it is the fixing eye to help correct rather than worsen any vertical deviations.

4. *Intermittent exotropia:* As with surgery, full and lasting "correction" is less common in exotropia (see Table 1). An acceptable goal is a lesser exotropic angle with good control. In one investigation of intermittent exotropia,[23] 32 patients were treated by one or more simultaneous bilateral botulinum toxin lateral rectus injections and followed 3 years from the final injection. Sixty-eight percent developed a stable deviation of 10 prism diopters or less. Seven of the patients required surgery during the study period when injection failed to prevent recurrent

exotropic drift. The response between ages 3 and 5 years was better than in younger or older patients. With evidence of exotropia exceeding 10 prism diopters, injection should be repeated.

5. *Cerebral palsy:* Strabismus surgery for neurologically impaired infants and children is less predictable than in normals, has a high rate of overcorrection, and side effects of general anesthesia are more frequent. Botulinum toxin injection offers an alternative with an overcorrection rate of about 3%. Low-dose bimedial injections of 1.25-2.0 units are preferred with esotropia because the dose-response is less predictable. Exotropia responds normally and the usual beginning dose is 2.5 units. Reinjections are often necessary, increasing the dose as indicated (see Table 5). While overcorrection is possible in esotropia, it has not been seen in exotropia. Strabismus in older children with cerebral palsy is treated by unilateral injection to avoid past pointing and balance problems from the induced paralysis.

D. Injection Technique

Check the amplifier to assure that the batteries are working. A spare needle should be available in case the needle gets damaged or contaminated.

1. *Dosage:* Nearly all initial doses are 2.5 Units (see Table 5). Subsequent doses may be increased as much as 100% depending on the response to the earlier injection. Notice that dosage is not decreased for children, and may even be increased for those with large deviations.

2. *Anesthesia:* Use proparacaine (or tetracaine, cocaine, 4% lidocaine), a minimum of a drop a minute for 3 doses. A vasoconstrictor drop (e.g., epinephrine), given before instilling anesthetic drops, makes it easier to see and avoid the anterior ciliary vessels and enhances anesthesia. After the drops, a subconjunctival injection of 0.1-0.3 ml lidocaine over the muscle insertion does not diminish EMG activity and reduces discomfort in an eye with scar tissue.

3. *Sedation:* Diazepam or a similar oral drug, given an hour before the procedure, is helpful for the very apprehensive patient.

4. *Injection Technique:*
   a. Placement in the muscle is crucial. The neuromuscular junctions centered half-way back in the EOM, should be the target.[24] Injection outside the target muscle reduces the treatment effect and increases the likelihood of affecting adjacent muscles. Since the drug diffuses along needle tracks, a single accurate placement is most reliable. Steps that help in injecting horizontal muscles in an alert patient using an electromyogram amplifier are as follows:
   b. Prepare the syringe with the appropriate dose of botulinum toxin. You will often be in an awkward position to read the syringe marks, so fill with the exact volume desired and empty it completely into the EOM. If you have two muscles to inject (e.g., bimedials in children), fill a second syringe, or transfer the needle to the second syringe, again with the exact dose. Aspirate the volume of the proposed dose plus an additional 0.1-0.2 ml into the syringe. Attach the injection electrode firmly, and then inject the excess through the needle electrode to check for patency and any leak at the syringe/needle junction. and attach the monopolar needle electrode as described above. Note the position of the needle bevel so the orientation in the orbit can be determined.
   c. Attach a ground lead to the patient—at the forehead for the medial rectus, and laterally for the lateral rectus. Wipe this area beforehand with alcohol to ensure adhesion.
   d. Turn on the amplifier to half the volume and test the connections by touching the needle tip to the conjunctiva; it should make a loud "tick." If there is background static noise from the amplifier, turn off any fluorescent lights, check all connections, consider moving to a more electrically quiet area.
   e. Have the patient gaze at a target away from the field of action of the muscle. (For example, look temporally to inject the medial rectus.)
   f. Insert the needle electrode, its bevel facing the muscle, through the conjunctiva 8-10 mm from the limbus and, avoiding large vessels, push it 10 mm beyond the equator keeping to the orbit wall to avoid the globe. Slowly move the gaze target to the primary position to activate the target muscle.
   g. While listening to the EMG signals, advance the needle tip inward toward the muscle, following the direction of the loudest sound. When a crackling sharp EMG signal is heard, inject the fluid slowly. It is a good sign if the EMG sound diminishes with the injection, indicating that the solution pushed the nearby muscle fibers away from the tip. Leave the tip there for about 15-30 seconds until the pressure of the solution diminishes. Withdraw the needle slowly while the patient maintains primary gaze. Make a note of how reliable the EMG response and injection were, for future reference.

5. Special considerations in children

a. After age 6 years in an intelligent child, the technique can often be performed as in adults. We often attempt it in the office, knowing that a substantial number of cases will not be completed. For the successful ones we have saved time, anesthesia, and cost. Try this for unilateral cases, only.

b. For children aged 1-6 years and for those unable to cooperate, sedation is added under NPO conditions as for general anesthesia. 1) Intravenous (IV) ketamine, 0.5-1.0 mg/kg, will preserve EMG activity and keep the patient relatively quiet for 2-5 minutes. This is less than the usual anesthetic dose. The anesthesiologist should be informed that general anesthesia is not desired, but rather some degree of akinesia, amnesia, and light sedation. Remarkably little hallucination and postoperative effects are noted with IV ketamine. Topical anesthetic drops given before ketamine are essential. Intramuscular ketamine, 2-3 mg/kg, has a much longer duration of effect. The recovery period is also longer and hallucinations do occur. 2) Inhalational anesthesia is an acceptable alternative that does not require intravenous access. However, the EMG signal is much diminished. A small posterior conjunctival incision allows injection with the needle tip 10-15 mm posterior to the insertion under direct visualization. This is an excellent alternative when access to an efficient facility and anesthesia coverage are available. 3) Oral chloral hydrate is effective, but creates sedation for several hours.

c. From age 3 to 12 months, depending on the strength of the child, it is usually possible to anesthetize the eyes with drops and simply hold the baby down for the injection. Additional hands to hold the head are imperative. Avoid using a lid speculum. A bottle may sometimes keep the child at ease until the time of muscle penetration and injection. Parents need to be told that the procedure is mildly uncomfortable, just like immunization shots; that it is routinely performed under similar conditions in adults; and that it will spare the baby a general anesthetic. Crying should not be allowed to interrupt the procedure. However, if the head of a strong baby cannot be held still, terminate the procedure and plan to do the injections under sedation.

6. Injecting cyclovertical muscles:

Inferior rectus (IR). Inject via the lower lid in thyroid or other cases with restricted supraduction. Be sure to angle nasally 23° (straight back puts the needle into the lateral rectus!). If the inferior oblique (IO) is encountered, continue right through it—the IR should be behind it. Be sure to hold the needle in place 30 seconds after injecting to avoid back-flow of botulinum toxin into the IO.

Superior rectus (SR). Injection is just as effective as any other EOM, but because of the induced ptosis, the SR should be treated only when a hypertropia cannot otherwise be treated. The ipsilateral IO is usually injected simultaneously. Expect full ptosis for 2 months. Sometimes residual ptosis of 0.5 mm may persist!

Inferior oblique (IO). The IO is very close to the conjunctival surface infero-temporally when the eye is looking upward. Inject rather anteriorly to avoid the IR.

Superior oblique (SO). Injecting the SO muscle is not recommended. SO overaction and SO myokymia have been the indications, but ptosis occurs uniformly; there is a resulting SO palsy; and the basic condition recurs after a few months.

7. Technical Complications and Difficulties:

a. The target muscle cannot be found. An unusually positioned muscle may be found by carefully tilting and translating the whole needle and syringe. Try to avoid multiple needle thrusts that can cause hemorrhage, especially if made deep into the orbit.

b. The lateral rectus takes a course going downward from the insertion, below the horizontal in some patients. Recognizing this normal anatomical variant and repositioning the needle and syringe are usually effective.

c. Partial ptosis occurs in about 16% of adults and 25% of children. Complete ptosis is truly rare, and no case of amblyopia due to ptosis has been documented.

d. Vertical strabismus created by treatment of horizontal rectus muscles is much more common in medial than in lateral rectus injection. It persists for longer than six months in fewer than 1% of patients. The induced vertical deviation is usually a hypertropia after MR injection and hypotropia after LR injection. Take advantage of this phenomenon by injecting the MR of the hypotropic eye for esotropia, and the LR of the hypertropic eye for exotropia whenever possible. Vertical strabismus is much less common in children treated bilaterally; any vertical effect seems to balance out.

e. The rate of overcorrection at 6 months is 1.7%. Cases with muscles that respond strongly to botulinum toxin, resulting in overcorrection, are also easily reversed by injecting the antagonist. Smaller doses (1.0-2.0 Units) should be used.

f. Scleral perforation may be prevented by keeping the needle tangential to the globe until it is posterior to the equator and using the EMG signal to guide it. Highly myopic eyes, eyes where the injection is near a previous surgical site, and eyes with scleral buckles are particularly at risk.

g. Diplopia is the most common and annoying side-effect. The patient should appreciate that an overcorrection is necessary for a long-term beneficial effect. Adults may require patching, but may also be able to use a head turn to align the eyes. Patching is avoided in visually immature children except to prevent or treat amblyopia.

h. Since we usually treat the non-dominant eye, few patients develop spatial disorientation or past pointing because of the induced paralysis. Those who do are usually alternators or have part-time fusion. Patching the eye treats the problem, and adaptation usually occurs after a week.

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TABLE 1
Botox correction according to number of injections

	n	*Pre (PD)*	*Post (PD)*	*Correction to 10 PD or less*	*n*	*Correction*
Children ET	146	28	9	68%	101	38%
1 injection all patients	201	31	10	68%	178	68%
Children XT	66	26	12	54%	32	38%
1 injection all patients	95	26	13	50%	45	47%
Adults ET	225	28	9	69%	151	39%
1 injection all patients	384	30	11	68%	219	57%
Adults ET	139	28	11	61%	84	28%
1 injection all patients	293	31	12	61%	155	53%

Follow-up 6-83 months (average 20 months)

TABLE 2
Botox correction according to size of deviation

	Pre (PD)	*Percent correction of deviation*	*Final 10 PD or less*
Children ET	10-24	56%	78%
1 injection	25-39	63%	63%
all patients	40+	78%	65%
Children XT	10-24	59%	67%
1 injection	25-39	45%	25%
all patients	40+	55%	40%
Adults ET	10-24	62%	72%
1 injection	25-39		
all patients	40+	62%	35%
Adults ET	10-24	53%	67%
1 injection	25-39		
all patients	40+	64%	33%

Follow-up 6-83 months (average 20 months)

TABLE 3
Botulinum Toxin Correction of Non-Acute Sixth Nerve Paresis*

		% Recovered	
	Number	*Botulinum Toxin treated*	*Control*
Unilateral	34	70%	31%
Bilateral	11	90%	42%

*From Metz HS, Mazow M: Botulinum toxin treatment of acute sixth and third nerve palsy. Graefes Arch Clin Exp Ophthalmol 1988; 226: 141-144.

TABLE 4
Infantile Esotropia Treated by Botulinum Toxin (No Prior Surgery)

Authors	*N*	*Number of Injections*	*% Corrected to 10 pd or less*
McNeer et al	76	-	89
Scott et al	61	1.6	66
Gomez de Liano et al	107	1.6	73
Campos et al	50	1.0	76

See References 18 through 21.

TABLE 5
Botulinum Toxin Dosage for Initial Injections

	Units Botox
1. Horizontal strabismus	
a. Under 25 PD	2.0-3.0
b. Over 25 PD	2.5-5.0
c. Further refinements	
1. smaller doses for MR, larger for LR	
2. smaller doses for smaller squints, larger for larger squints	
3. smaller doses for small women (occasionally very sensitive)	
2. MR injection for lateral rectus palsy	
a. Early (1-3 months)	1.0-2.0
b. Later or in conjunction with transposition surgery	2.5
c. Later for partially or fully healed palsy but with MR contracture	2.5
3. Vertical muscles	
a. IR for comitant deviation	2.5
b. IR for thyroid	5.0
c. IO	2.5
d. SR (rare)	2.0
4. Children with infantile ET or XT (Bilateral injections)	2.5
5. Weak muscles - myasthenia, external ophthalmoplegia, aberrant regeneration, cerebral palsy	1.0-2.0
6. Retrobulbar injection for nystagmus	25.0