

# LOCALIZED INJECTIONS OF BOTULINUM TOXIN FOR THE TREATMENT OF FOCAL LARYNGEAL DYSTONIA (SPASTIC DYSPHONIA)\*†§

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## ABSTRACT

Spastic dysphonia is a condition producing a strain-strangle phonation. We have previously classified most of these patients as having focal laryngeal dystonia, a disorder of central motor processing.

The initial success of recurrent nerve section in many of these patients has been followed by recurrence of symptoms in months to years. Bilateral involvement of the vocal cords with hyperfunction of the nonparalyzed vocal cord could explain these failures.

Injection of botulinum toxin (BOTOX) has been effective treatment for many focal dystonias. We have treated more than 100 patients with dystonia including five with laryngeal dystonia. All of the patients laryngeal had dramatic improvement after 48 to 72 hours; benefit lasted 3 to 9 months for each injection period. BOTOX injection can be performed on awake, ambulatory patients. Bilateral treatment and titration of dose can achieve the desired degree of weakness.

Spastic dysphonia is a condition first described by Traube (1871)<sup>1</sup> who thought this was a form of nervous hoarseness. Critchley (1939)<sup>2</sup> described the voice pattern as a condition in which the patient sounds as though he were "trying to talk whilst being choked." The pathophysiology of this condition remains elusive. Spastic dysphonia is now thought to take at least two forms: 1. the classical case of strain-strangle phonation punctuated by voicing arrests (adductor type), and 2. the patient who speaks in a whisper or weak, breathy voice especially at voicing onsets (abductor type). We have previously classified most patients with "spastic dysphonia" as a type of dystonia (laryngeal dystonia), that may present focally or in association with other dystonic movements.<sup>3</sup>

Dystonia is a neurological disorder of central motor processing characterized by abnormal, often action-induced, involuntary movements or uncontrolled spasms. Symptoms usually begin as focal dystonia involving a single region of the body. Spread to other body regions is commonly seen in childhood-onset dystonia, while the disorder tends to remain focal with adult-onset.<sup>4</sup> Examples of focal dystonia include blepharospasm (involuntary eyelid closure), oromandibular dystonia (involving the face, jaw, and tongue), torticollis (neck muscles), and writer's cramp (action induced involvement of hand and arm muscles).<sup>5</sup> The etiology of dystonia is usually idiopathic, but can be secondary to other disorders.<sup>6</sup>

Treatment of dystonia with medications usually results in an incomplete response and is frequently unsuccessful. Dedo<sup>7</sup> first performed recurrent laryngeal nerve section as treatment of patients with spastic dysphonia. Initial success of the treatment in many of these patients later proved temporary with a return of symptoms despite the continued paralysis of the vocal cord.<sup>8,9</sup> This experience is shared with nerve section of branches of the facial nerve for therapy of blepharospasm, and cervical rhizotomies for torticollis. Often these procedures result in only temporary relief and may have unacceptable complications.<sup>10</sup>

We have found that an effective alternative to nerve section is the use of local injections of botulinum toxin (BOTOX). BOTOX acts presynaptically at nerve terminals to prevent calcium-dependent release of acetylcholine.<sup>11</sup> When injected locally, the effect is that of chemical denervation. BOTOX has been used extensively and effectively for the treatment of blepharospasm.<sup>12,13</sup> Injections of BOTOX locally into the vocalis-thyroarytenoid muscle complex can be easily performed using electromyogram (EMG) localization of appropriate muscles.<sup>14</sup>

## METHODS AND MATERIALS

### Patients

We have already described our initial series of 96 patients with a variety of focal dystonias treated with local injection of BOTOX.<sup>14</sup> Approved by our Institutional Review Board, all patients gave written informed consent. Forty-six patients had idiopathic blepharospasm, and three had blepharospasm associated with progressive supranuclear palsy. Thirty patients with torticollis were treated. Four patients had oromandibular dystonia, 3 had limb dystonia, 1 had lingual dystonia, and 4 had hemifacial spasm. Most of the patients have failed numerous pharmacologic trials.

Five patients with laryngeal dystonia were treated with BOTOX. These patients were first evaluated with a standard history and physical examination including direct fiberoptic lar-

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laryngoscopy with video recording, a complete neurological exam, and a laryngeal EMG.

#### Toxin

Lyophilized botulinum A toxin (Oculinum) was obtained and stored frozen (-20°C) until reconstitution with sterile saline (without preservative) at the time of injection. The quantity of toxin is expressed in units, where 1 unit (U) represents the mouse LD-50. For the typical injection a dilution was performed to a final concentration of 2.5 U/0.1 ml.

#### Injection Technique

Injections were individualized for each patient. In general, doses were divided into 2.5 to 7.5 U (0.1 to 0.3 ml) aliquots. A tuberculin syringe was used for the injections, with a 25 gauge monopolar teflon-coated hollow EMG recording needle. All laryngeal injections were performed percutaneously, through the cricothyroid membrane and into the vocalis-thyroarytenoid complex, as previously described.<sup>2</sup> All injections were performed with EMG localization of the appropriate muscles. Initially, injections of only one vocal cord were performed, but with greater experience, we began treating both vocal cords simultaneously without complication.

#### Follow-up

The patients are asked to call within the first week after the injections. Typically, the effect of the toxin takes place within the first 48 to 72 hours. The patients' voices initially become very hoarse or breathy with some developing mild aspiration when drinking liquids. This effect is generally resolved within the first 3 days, and the voice becomes stronger, and very fluent.

### CASE REPORTS

#### Case 1

A 50-year-old salesman developed blepharospasm with associated involuntary contraction of the lower facial muscles. At age 54, he developed noisy breathing which progressed to chronic hoarseness. Examination at 63 years of age revealed a strained, tense, squeezed, occasionally hoarse voice with intermittent breaks and pauses. He stated that this type of voice has interfered with his functioning as a salesman. There was lower facial grimacing accompanying phonation. On indirect and fiberoptic laryngoscopy, no lesions were seen, and the vocal cords abducted and adducted normally. No tremor or other movement disorder was seen. Bilateral laryngeal EMG of the cricothyroid and vocalis muscles was normal. Using the hollow recording/injection electrode and EMG guidance, the patient underwent a series of BOTOX injections into the vocal cords. On September 11, 1984, the right vocalis was injected with 2.5 U (0.1 ml); there was no significant clinical improvement, and indirect examination was unchanged. September 25, 20 U BOTOX (0.4 ml) were injected into the left vocalis. Improvement was noted within 2 days; indirect laryngoscopy revealed paralysis of the left vocal cord. On October 30 there was fluency of speech without breaks or pauses. On November 27, the voice remained improved, but strain was returning; indirect laryngoscopy revealed cord function returning, but still weak. The right vocalis was injected with 18.75 U BOTOX in 0.3 ml. Benefit was noted within 2 days and lasted until January 10, 1985 when symptoms began to return. Indirect examination on January 22, 1985 revealed full cord function. EMG of the right vocalis revealed decreased numbers of action potentials and polyphasic with decreased amplitude, whereas the left vocalis was normal. Right and left vocal cords were each injected with 7.5 U BOTOX (in 0.3 ml). There was slight aspiration on the 1st and 2nd day postinjection. He had a breathy hypophonia on the 3rd and 4th postinjection day. Speech returned by the 5th postinjection day, and examination on February 5, 1985 revealed speech to be fluent, somewhat gravelly, and easily fatigued. Speech continued to improve, and he was fluent for 4 months. Fluency gradually deteriorated, and, on June 26, 1985, the right vocalis was again injected with 7.5 U BOTOX; improvement persisted for 8 months and gradually wore off. He did not deteriorate to his original level of disability, and on January 28, 1986, each cord was reinjected with 3.75 U of toxin. Benefit continues to date.

#### Case 2

A 40-year-old woman with dystonic adductor dysphonia and tremor. She has a paternal aunt and cousin with dystonia, and a maternal aunt with severe essential tremor and dystonia. In addition to dystonic adductor dysphonia, she has a mild left foot dystonia, and writer's cramp of the right arm. There is no tremor in the hand with dystonia. A spastic, tremulous voice with breaks and pauses was present during one choir rehearsal at age 15 and then resolved until age 18 when it permanently returned. Examination at age 40 revealed a moderately tremulous voice with occasional breaks and pauses; her voice appeared to catch at times. The pitch was high. She rated her level of vocal functioning at 25% of normal. Treatment with propranolol to 160 mg/day was without benefit. Trihexyphenidyl caused dizziness. Clonazepam up to 4.5 mg/day resulted in slight, transient benefit; higher doses had no effect. Tapering the last drug was complicated by insomnia, sensation of "speeding," and muscle spasms in the left (dystonic) leg; 8 months were required to gradually taper the drug without withdrawal symptoms.

On indirect and fiberoptic direct laryngoscopy, no lesions were observed, and the vocal cords abducted and adducted normally. Adductor spasm were noted on careful inspection during voicing onsets. In addition, there were abnormal rhythmical motions of the supraglottic and glottic structures on phonation suggestive of a tremor. Laryngeal EMG of the cricothyroid and vocalis muscles revealed no spontaneous activity with normal numbers, form, and amplitude of motor unit potentials on phonation. There were rhythmic bursts of activity at 10 Hz, characteristics of a tremor disorder.

Using the hollow recording/injection electrode and EMG guidance, the patient underwent a series of BOTOX injections into the vocal cords. On July 9, 1986, 7.5 U BOTOX was injected into the left vocalis muscle; there was no clinical effect. On July 23, the right vocalis was injected with 7.5 U. She felt hoarse after the injection; within 36 hours the hoarseness began to resolve into increased fluency. On July 26, she noted slight aspiration of fluids, and hypophonia; aspiration resolved by July 27. Repeat endoscopy (July 30) revealed that the vocal cords apposed each other with less strength, and the cords appeared more relaxed. The glottic tremor was present, albeit at a decreased amplitude. She noted a marked (80%) improvement from this series of injections; improvement persisted for 6 weeks, and then gradually began to wear off. A trial of 160 mg propranolol provided no additional benefit.

Reassessment on September 24, 1986 revealed her speech was back to baseline. She was injected with 3.75 U BOTOX into each vocalis muscle. Slight hoarseness developed the next day, and slight choking on fluids occurred on September 27. Nevertheless, enhanced fluency was evident by September 28; this was associated with slight hypophonia and difficulty with projection. In describing her marked improvement (86%), she wrote, "these injections have afforded me the most consistent relief I have experienced in perhaps 15 years or more."

Benefit began to diminish to about 50% in 8 weeks. However, examination on January 28, 1986 showed her speech to be fluent with occasional cracks, breaks, and quiver. The volume was normal. At that time, we injected 2.5 U BOTOX into the right and 3.75 U into the left vocalis muscle. The patient recalled the reaction: "By evening I noticed a substantial increase in fluency. I can feel that my cords are not locking as tightly as before the injections, but as yet I have no aspiration." By January 31, she noted hypophonia and slight choking on fluids; she experienced breathy aphonia February 1. By February 10, her voice began to gain strength and she was able to "phonate clearly" by February 11. "Some spasticity upon initiating speech" began on February 17, but while on vacation later that month, she "was almost totally free of any concern about my ability to speak."

Improvement persisted, but on May 13, 1986 examination revealed gravelly speech, but it was fluent with occasional glottic stops. Vocal tremor was heard on vowels; she rated her functioning at 50% of normal. The right vocalis was injected with 1.25 U BOTOX; there was no effect. The following week, we injected

TABLE I.  
Case Studies: Botulinum Toxin Injections.

Case	Age	Sex	Other Neurologic Involvement	Yrs. With Symptom	Vocal Cord Injected	Date	BOTOX Dose	Effect	Adverse Effects	Duration of Effect	
1	83	M	Blepharospasm facial spasms	13	R	9-11-84	2.5 U	(-)	None	—	
					R	9-25-84	20 U	(+)	V.C. paralysis	2 months	
					R	11-27-84	18.75 U	(+)	Sl. aspiration for 2 days	2 months	
					R + L	1-22-85	7.5 U	(+)	Breathy hypo- phonia—3 days	5 months	
					R	6-25-85	7.5 U	(+)	None	6 months	
					R + L	1-28-86	3.75 U	(+)	None	12 months	
2	40	F	Dystonia of R arm, L leg, hand tremor	15	L	7-9-85	7.5 U	(-)	None	—	
					R	7-23-85	7.5 U	(+)	Sl. aspiration,	2 months	
					L + R	9-24-85	3.75 U	(+)	hypophonia	3 months	
					L	1-28-86	2.5 U	}	3 days	—	4 months
					R	1-28-86	3.75 U				
					R	5-13-86	1.25 U	(-)	—	—	
					L	5-20-86	2.5 U	(+)	—	4 months	
					L + R	9-30-86	1.25 U	(-)	—	—	
					R	11-13-86	2.5 U	(+)	—	to present (6½ mo)	
					L	11-13-86	1.25 U	(+)	—	—	
3	37	M	Torticollis writer's cramp	15	R	9-23-85	7.5 U	(+)	—	3 months	
					L + R	1-7-86	5.0 U	(+)	—	2.5 months	
					L + R	10-21-86	5.0 U	(+)	—	5+ months	
4	24	F	Torticollis	12	L + R	2-10-87	2.5 U	(+)	—	2 months+	
5	64	F	Head tremor	3	L + R	2-24-87	2.5 U	(+)	Sl. aspiration for 24 hrs.	2 months	

2.5 U into the left vocalis; this was followed with further improvement which persisted for 3 months and then gradually wore off. A repeat injection of 1.25 U into each vocalis on September 30, 1986 had no effect. Injection of 1.25 U into the left and 2.5 U into the right vocalis on November 13 was met with marked improvement.

It should be noted that after the second series of injections, her speech disorder never returned to the original baseline level. Whereas she rated her pretreatment level of functioning at 25% of normal, her best post-BOTOX level of functioning was 90%, and worst level after the toxin began to wear off was 50%. She was able to return to school for a counseling degree in June, 1986.

#### Case 3

A 37-year-old man developed torticollis, writer's cramp, and left leg dystonia at age 19. Age 22, his voice became hoarse and constricted. Examination at age 30 revealed generalized dystonia, including marked speech involvement. There was marked constriction of voice, with marked difficulty in speaking during exhalation. The neck inflated during speech because of increased intrathoracic pressure.

On September 23, 1985, we injected 7.5 U BOTOX into the right vocal cord. There was a marked improvement in fluency which lasted for 6 weeks. On January 7, 1986, we injected 5.0 U BOTOX into each vocal cord. A marked benefit was experienced in 24 hours and continued for 2½ months. He was reinjected on October 21, 1986 with similar results.

#### Case 4

A 24-year-old woman with cranial dystonia. This right-handed Nigerian woman was well until age 12 when she developed shakiness and hoarseness of her voice. This was intermittent initially, and it occurred primarily under stress. At age 13, she developed involuntary head shaking with associated tonic deviation of the chin to the left and head tilt to the right. Since age 15, the shaking and pulling became persistent. Vocal symptoms progressed and stabilized by age 17. When seen at the Neurological Institute at age 20, she had vocal tremor with severe breaks and pauses and a strained, squeaky voice. Torticollis was present. Treated with trihexyphenidyl, clonazepam, diphenhydramine, diphenhydantoin, diazepam, carbamazepine, ethopropazine, tranquipromazine, tetrabenazine, and reserpine were either of no benefit, or resulted in side effects. Peripheral neck surgery resulted in only mild improvement in the torticollis.

Laryngeal EMG was normal. Fiberoptic laryngoscopy showed adductor spasms. On February 10, 1987, while on no medications, we injected 2.5 U BOTOX into each vocal cord. She developed a slight sensation of choking over the subsequent 3 days. This was associated with a marked improvement in her speech function.

#### Case 5

A 64-year-old woman presented with focal laryngeal dystonia. Her family history is remarkable for her mother having a head tremor beginning in her fifties; in her seventies her handwriting became illegible. Her maternal grandmother had a head tremor. No one in her family had speaking difficulties. The patient was well until age 52 when she was diagnosed as having carcinoma of the left vocal cord. This was removed surgically, and she then had cobalt radiation. There was no difficulty in speaking until age 61 when she had a sensation of feeling out of breath. Speech gradually became more difficult, and by age 62 was nearly aphonic. Previous treatment with speech therapy, alprazolam, benzotropine, ethopropazine, propranolol, trihexyphenidyl, and baclofen were of no benefit or had significant side effects. The speech revealed nearly complete aphonia with marked difficulty in enunciating either vowels or consonants. When phonating conversations her speech was extremely restricted. There was a suggestion of an underlying tremor. Laryngeal EMG revealed no signs of denervation, tremor, or myopathy. Fiberoptic laryngoscopy showed a normal exam except for tight adductor spasms on voicing onsets.

On February 24, 1987 we injected 2.5 U BOTOX into each vocal cord. Initially, she whispered for 24 hours; however, within 48 hours she had marked recovery of vocal function with a "tremendous range" and very little difficulty with pronunciation. She had slight difficulty with vowels and slight aspiration resulting in coughing and clearing her voice for about 3 days. Within a week, the voice lost its sluggishness. An examination 2 weeks after injection revealed no breaks or pauses. The pitch range was limited and volume was decreased but fluent and slightly gravelly. Prior to injections, she reported her vocal function at 8% of normal, and her postinjection status was 80% of normal.

## RESULTS

Five patients with laryngeal dystonia were treated consisting of two males and three females ranging in age from 24 to 64 with a mean age of 46. They all had

vocal symptoms for an average of 12 years. They were all failures on standard drug therapy. All the patients had focal dystonia of other muscles (Table I).

All of the patients had toxin effect within the first 24 to 72 hours, with a variable amount of breathy dysphonia and slight aspiration. This initial effect disappeared within 2 to 3 days, but the fluency of voice persisted for 3 to 6 months. All the laryngeal patients had benefit from the treatments. All of the patients felt that the effect of the toxin was preferable to the benefit derived from drug therapy. Almost all of the patients requested reinjection before their dysphonia returned to the original baseline laryngeal function. With time, patients had longer intervals between injections.

Since there were no previous studies as guidelines for laryngeal BOTOX injections, we initially only performed unilateral injections. The dose range was also very varied as we learned dose/response levels for the larynx. We now perform bilateral injections of the vocal cords with 1.25 to 3.75 U. We start with small doses and titrate each patient to achieve good responses.

#### DISCUSSION

Previous investigators have used local injections of BOTOX for the treatment of blepharospasm and torticollis.<sup>12,13</sup> We have extended this technique for the treatment of other focal dystonias.<sup>15</sup> We have found local injections of BOTOX valuable in relieving disabling dystonic spasms when limited to one muscle or a group of muscles.

In patients with focal laryngeal dystonia, most treatments including speech therapy, psychotherapy, and drug therapy have not significantly improved the speech of most of these patients. Recurrent laryngeal nerve section has had many late failures, which leaves a poor voice and a paralyzed vocal cord.<sup>9,9</sup> It appears that the return of symptoms in these patients is due to stressing the remaining functioning cord, thereby intensifying the dystonic symptoms.

In contrast to surgery, the use of BOTOX allows the treatment of both vocal cords.<sup>14</sup> The injections are performed on an ambulatory basis with little discomfort. The toxin is injected under EMG control for precise localization. Graded weakening can be achieved by using low doses initially, and then repeating injections to achieve the optimum weakness desired. After titrating these doses, one is able to determine the proper dose for future injections. If too much weakness is produced, the strength gradually returns with time. It is too soon to know how often injections will be necessary.

In contrast to systemic pharmacotherapy, with cognitive and sedative side effects, local injections of BOTOX were without clinically significant systemic

side effects. The long term effects of BOTOX on the larynx are not yet known. So far we have not found any disability produced by the toxin.

Others have reported a subclinical defect of neuromuscular transmission seen on single fiber EMG of limb muscles distal to the site of injection in patients treated with much larger doses for blepharospasm or torticollis.<sup>16,17</sup> We have also reported the production of antibodies to BOTOX-A in patients treated with much larger doses for torticollis.<sup>16</sup> These observations suggest spread into the bloodstream; there is a theoretical risk of developing additional immunologically mediated responses, such as anaphylaxis.

#### SUMMARY

"Spastic dysphonia" is a disease we have previously classified as a type of dystonia (laryngeal dystonia), that may present focally, or in association with other dystonic movements. We have treated these patients with BOTOX, also, used in the treatment of other focal dystonias.

We have used BOTOX to treat more than 100 patients with focal dystonias including five with focal laryngeal dystonia. BOTOX was injected directly into laryngeal muscles under EMG localization of the appropriate muscles. All of the patients had toxin effect within the first 24 to 72 hours, with a variable amount of breathy dysphonia and slight aspiration. This initial effect disappeared within 3 to 4 days, but the fluency of voice persisted for 3 to 6 months. All of the patients felt that the effect of the toxin was preferable to the benefit derived from drug therapy. Almost all of the patients requested reinjection before their dysphonia returned to the original baseline function.

Much work still remains in determining the exact mechanism of the toxin, the short- and long-term effects on muscle, the appropriate dose, and the correct frequency of injection. We feel, however, that BOTOX is an important new treatment option for patients with focal laryngeal dystonia.

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#### DISCUSSION

ROBERT MILLER, MD (New Orleans, LA): I recently moved from Baylor. As I mentioned in another meeting, we had treated two patients with severe spasmodic dysphonia with a botulinum toxin. We have stayed with the one cord injection rather than injecting both cords. We've not had any problems with aspiration. The results are equally dramatic.

I might also add that a number of these patients have numerous neurological problems related to their dystonias. We have found in some of the patients that we've injected botulinum toxin in that some of the other dystonias improve, and this is related to what

muscle physiologists refer to as resetting the motor system, so actually it may have more than just a local effect.

ABRAHAM EVIATAR, MD (Scarsdale, NY): I want to congratulate Dr. Blitzer on a beautiful study.

If we have to learn from the blepharospasm problem and the success that was obtained there with the same treatment, the results are dramatic in the beginning and they look very well. However, in the case of blepharospasm, after a number of years the method stops being helpful and the patient goes back to the exact problem that he had before treatments were initiated. So I hope that in a longer follow-up maybe we'll have better success in the larynx than we have in blepharospasm.

DR. GOLDSTEIN: Thank you. Are there any other comments or questions? Dr. Blitzer, do you want to make any closing comment?

What about its use in strabismus by the ophthalmologists?

ANDREW BLITZER, DDS, MD: I thank Dr. Müller for his comments. The reason we have gone to bilateral injection is that the doses that we currently use now to control the symptom is much less than the single dose in one cord. We can bilaterally weaken the cords without exaggerating the dystonic symptoms of the other cord. Therefore, since this is not affecting the posterior cricoarytenoid muscle, we're not afraid of any kind of inspiratory stridor, and the slight aspiration that we have encountered has not been more than people having to clear their throats for the first 24 to 48 hours. We are strongly opposed to the Baylor group and the NIH's protocol of single cord injection since a much greater dose of toxin is needed, and cord paralysis is the end point. This is no different than surgical recurrent nerve section.

Dr. Eviatar brought up blepharospasm. BOTOX is widely used for blepharospasm and strabismus, and is very effective. As opposed to the results he speaks of, in our group of 98 patients who were treated, about 60 of them had blepharospasm. To my knowledge, all of the patients are still having success with local injections. In two of the patients who have been injected for torticollis, where large amounts of the toxin had to be injected in many muscles, antibody developed over a number of years of injection. This creates two problems. One is that the toxin no longer has effect. Perhaps this is why Dr. Eviatar's patients had long-term failures. It may be related to large doses with antibody production, and the rendering of the toxin ineffective. The second problem is related to the possibility of the challenge to the immune system making the patients hyperimmune, producing anaphylaxis. This data again supports our premise of injecting the smallest dose possible as infrequently as possible.