BOTULINUM TOXIN TREATMENT OF SPASMODIC DYSPHONIA

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Dystonia is a chronic neurological disorder of central motor processing characterized by task-specific action-induced muscle spasms. It may be generalized or limited to one functional group of muscles. When it affects the larynx, it is usually focal, or isolated to that organ. In the vast majority of cases, laryngeal dystonia affects connected speech, although there are rare cases of breathing dystonia. Laryngeal dystonia, termed "spasmodic dysphonia" (SD) by otolaryngologists, typically begins in the mid-30s and is more common in women (63%).[1] Approximately 8 of 10 affected individuals have adductor SD, which causes inappropriate glottal closure, producing characteristic harshness, strain, and strangled breaks in connected speech. Abductor SD, in contrast, causes inappropriate glottal opening that produces hypophonia and breathy breaks. Because of compensatory maneuvers or mixed dystonic features, voice patterns encountered clinically may not always be typical or easy to discern. However, the classification of spasmodic dysphonia into abductor and adductor types is central to botulinum toxin (BTX)* treatment.

The diagnosis is based on a careful history and examination of the glottis during a variety of laryngeal tasks. Clues in the history include deterioration of voice quality under stress or on the telephone and improvement with sedatives, such as alcohol or benzodiazepines. Some patients find that certain tactile or proprioceptive maneuvers—so-called "sensory tricks," like chewing or supporting the head—can improve speech. The mechanism for this is not known. Singing or laughing will often result in greater fluency, probably by taking advantage of the task-specific nature of this disorder. The larynx is best examined with a flexible nasopharyngoscope. Insertion of a transoral laryngeal mirror or rigid rod-lens endoscope, combined with the necessary traction on the tongue, makes connected speech impossible and may mask the typical laryngeal features.

Occasionally, the diagnosis of SD can be challenging. There is no single pathognomonic feature of the history or examination. Essential voice tremor and muscle tension dysphonia, a functional disorder, both can cause voice breaks and form the most important entities of the differential diagnosis. The hyperadduction of muscle tension dysphonia generally is sustained and unlikely to be spasmodic, whereas the involuntary movement in essential tremor is rhythmic and often involves pharyngeal muscles and strap muscles. For further explication of the differential diagnosis of SD, the reader is referred to the superb presentation by Smith and Roy.[2]

TREATMENT ALTERNATIVES TO BTX

There is no specific antidystonia pharmacologic agent. Drugs are prescribed empirically, and unfortunately their utility is often limited by significant central nervous system side effects like sedation and memory loss. No drug has been found to replace, or even consistently complement, the effects of BTX.

Voice therapy is sometimes useful in an adjunctive role but does not yield marked improvement by itself.[3] Voice therapy can resolve muscle tension dysphonia, however, and may be helpful as a diagnostic maneuver. Psychotherapy may help patients manage the social stresses of this disorder, which can be considerable, and thereby minimize the deterioration of voice with stress. However, there is no convincing evidence that psychotherapy or psychological intervention can relieve the symptoms of spasmodic dysphonia.

Like other types of dystonia, adductor SD has been treated surgically. Recurrent nerve section,[4,5] recurrent nerve crush,[6] and recurrent nerve avulsion or resection[7,8] have all been performed to treat SD, often with encouraging short-term results. The underlying principle is the same as that of BTX treatment: denervation. Yet, when this is performed surgically, a disappointingly large number of patients have had recurrence of their symptoms after a period of time.[9-12] With respect to poor results from neurolysis, SD is similar to other types of dystonia, such as blepharospasm or torticollis. Reasoning that recurrence of symptoms is the result of reinnervation, for which there exists abundant electromyographic evidence, even after excision of a segment or recurrent nerve, Berke et al have proposed a selective distal denervation of the adductor branches of the recurrent nerve, with immediate reinner-

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*Unless otherwise indicated, botulinum toxin (BTX) refers to botulinum toxin type A (Botox; Allergan, Irvine, CA). Dosages discussed in this article also refer to Botox, and the reader should note that they are not equivalent to those for botulinum toxin type B (Myobloc; Elan Pharmaceuticals, Dublin, Ireland) or Dysport (Ipsen Ltd, Slough, UK), which is another preparation of botulinum toxin type A.

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vation using a nonlaryngeal nerve.[13] Convincing long-term data are not yet available regarding this procedure. Currently, we believe that surgery should be reserved for the rare patient who does not benefit or cannot tolerate BTX.

BTX TREATMENT OF SPASMODIC DYSPHONIA: RATIONALE

In his original description of recurrent nerve section, Dedo[4] proposed that the abnormality in SD was not solely a matter of abnormal neural signal to laryngeal muscles but also involved abnormal feedback from the larynx to the central nervous system. The well-known action-induced, task-specific nature of dystonia suggests that indeed, afferent feedback may play a role in the pathophysiology of SD. Furthermore, the phenomenon of the sensory trick suggests that the alteration of afferent signals may be useful alleviate symptoms. Over time, the sensory trick generally loses its effectiveness. The reason for this is not known, but it appears that the central nervous system tends to eventually overcome this change in input and return to sending inappropriate signals to involved muscles. This may explain why surgical interventions have been largely unable to control symptoms permanently in various dystonias. In the case of SD, although recurrent nerve procedures, anterior commissure release, and other surgical measures have all produced encouraging short-term results, long-term benefit has proven difficult to achieve.

The broad success of BTX as a treatment for focal dystonias, SD among them, may be the result of the specificity, repeatability, and reversibility of the chemodenervation. Nerve terminal recovery from poisoning is a continuous, multiphase process, beginning practically as soon as acetylcholine release is blocked.[14] The cycle of recovery and reinjection with BTX may make it impossible for the central nervous system to defeat the denervation, because it never reaches a stable plateau. That voice benefit from injection sometimes extends beyond that expected from the observed in vitro activity of BTX suggests that its clinical effect may be the result of more than simple acetylcholine blockade at the neuromuscular junction. Some authors have hypothesized that BTX may also affect neurotransmission in the afferent system. In fact, there is evidence that in dystonia, BTX transiently changes mapping of muscle representation areas in the motor cortex, and reorganizes inhibitory and excitatory intracortical pathways, probably through peripheral mechanisms.[15,16]

Although the treatment cycle of recovery and reinjection translates clinically into some fluctuation of voice quality, results are generally satisfactory, as seen in posttreatment voice function ratings by clinicians and, more importantly, by the patients themselves.[17-21] Today, the American Academy of Otolaryngology–Head and Neck Surgery endorses BTX as primary therapy for this disorder (Policy Statement: Botulinum Toxin. Reaffirmed March 1, 1999).

BTX TREATMENT OF SPASMODIC DYSPHONIA: INJECTION STRATEGY

Our injection treatment strategy for patients with SD has evolved as we have gained experience. The standard treatment for adductor SD at our center is bilateral electromyographic (EMG)-guided transcutaneous injections of the thyroarytenoid muscle, using equal amounts of BTX, based on our observation that the motor control disorder appears to be bilateral and symmetric in most patients. In patients with abductor SD, we inject both posterior cricoarytenoid muscles, although injections are not performed simultaneously for reasons of airway safety. Based on the response to initial treatment, we adjust dose and reassess the value of bilateral versus unilateral treatment. Rather than reinject after a predetermined interval, we instruct the patient to await the recurrence of symptoms. After a few cycles of treatment, the patient will often be able to anticipate the return of spasms before they become audible to others.

We use a standard dilution of 4 mL of preservative-free saline/100 U vial of BTX for the larynx, diluting the solution further in the syringe as needed for each patient. The effective dose is not proportional to body mass or dysphonia severity and varies considerably. Because injecting a large quantity of fluid into the vocal folds can cause dyspnea, we aim to limit the volume of each injection to 0.1 mL. For adductor spasmodic dysphonia, our initial dose is approximately 1 or 1.25 U per side, which represents a low average dose for our patient population. We may add a small dose a few weeks after the initial one if the voice does not become fluent. In the great majority of patients, dysphonia is well controlled for 3 months or more with injections of 0.625 U to 2.5 U to each side. For abductor SD, we initially inject one posterior cricoarytenoid muscle with 3.75 U of BTX and estimate the contralateral dose after evaluating vocal fold mobility 2 weeks later. A vocal fold that is completely unable to abduct requires that the other side be treated with a small dose, whereas a more mobile one permits a larger dose to be used. Asymmetric dosing is the rule in abductor SD. Fluctuations in disease severity in SD occasionally may require small adjustments in dose.

BTX treatment results in an initial period of marked muscle weakness lasting several days, followed by a months-long plateau of somewhat milder weakening that constitutes the principal therapeutic effect. The reason for this is not known but likely has to do with the two-stage mechanism of neural recovery from poisoning.[14] It is hypothesized that partially cleaved SNAP-25 is repaired early, allowing for partial recovery early. The completely cleaved SNAP-25, on the other hand, takes 3 or more months to undergo full repair or replacement. The breathy dysphonia that usually follows thyroarytenoid injection in adductor SD is a clinical manifestation of this pattern; the initial effect of the toxin causes some glottic insufficiency. Inasmuch as it is to an extent inevitable, it is not truly a complication, but efforts must be made to minimize it. In general, the two phases of BTX effect are proportional. In the case of adductor SD, for example, the duration of breathiness can usually be shortened by sacrificing the duration of the therapeutic effect. Naturally, patients want to minimize the frequency of injections, but each will have a different tolerance for a breathy voice. A person for whom voice is crucial, like a performer or a teacher, may opt for smaller doses at more frequent intervals.

Dyspnea is the equivalent early effect in abductor SD because the posterior cricoarytenoid is being weakened. Because this is potentially life-threatening, we treat only one side at a time, as detailed above. Even so, the potential for dyspnea imposes an important limitation in BTX treatment of abductor SD, and probably for this reason, results are less satisfactory than for adductor SD.[1] For this reason, approximately 30% of our patients take small doses of systemic therapy in addition to BTX. The combination of toxin and systemic therapy seems to offer better symptom control than either alone in these individuals.

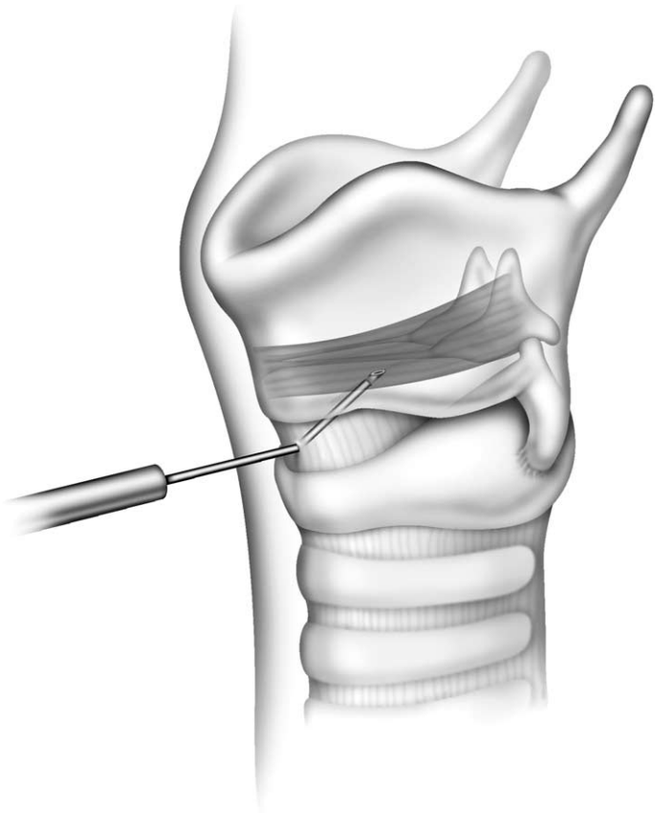

FIGURE 1. EMG-guided injection of the thyroarytenoid muscle for adductor spasmodic dysphonia.

A regimen of alternating unilateral injections is another means of controlling symptoms of glottic insufficiency, such as breathy dysphonia or dysphagia to liquids, in patients with adductor spasmodic dysphonia. In fact, at some centers, unilateral injection is the standard treatment, as it appears to provide essentially equivalent symptomatic relief with less adverse effects.[22-26] That unilateral treatment lessens symptoms from a motor disorder usually observed to be bilateral and symmetric again suggests that BTX has an effect on afferent neural systems.

BTX TREATMENT OF SPASMODIC DYSPHONIA: INJECTION TECHNIQUE

The small size and proximity of the laryngeal muscles to one another place a premium on accuracy in BTX injection. EMG guidance allows the clinician to locate deep, small muscles that are impossible to palpate and allows localization of the most electrically active areas of target muscles. EMG can help to minimize unwanted effects on neighboring muscles, as well as to maximize the benefit of each treatment by placing toxin close to its site of action at the motor end plates, allowing a smaller dose and volume to be used. We inject BTX though a 27-gauge insulated needle attached to an EMG, functioning like a monopolar electrode, in virtually all laryngeal application.

To treat the thyroarytenoid muscle, the patient is placed in a reclined position with the neck extended. A shoulder roll may be used. We find that local or intratracheal anesthesia is unnecessary in most cases and may interfere with the EMG signal.[27] It is helpful to bend the needle upwards some 30 to 45°, especially when injecting the female larynx, as the shorter anterior–posterior distance requires a more acute angle of entry under the inferior border of the thyroid cartilage (Fig 1). The needle is inserted through the skin at or just off of the midline at the level of the cricothyroid membrane and advanced superiorly and laterally toward the side of the target thyroarytenoid muscle. Often, the needle enters the air column in the laryngeal lumen after traversing the cricothyroid membrane, producing a characteristic "buzz" on EMG. This tells the injector that the needle lies medial to the vocal fold and must be directed more laterally. Crossing the endolaryngeal mucosa is irritating to the patient, however, and may provoke a cough or a swallow. By piercing the cricothyroid membrane a few millimeters to the side of the midline, the experienced injector may enter the thyroarytenoid muscle directly without first entering the airway, significantly decreasing patient discomfort. Once the needle is in an area that demonstrates crisp motor unit potentials, the patient is asked to phonate. Brisk recruitment and a full interference pattern in EMG confirms placement, and the BTX is injected. Experience will allow the clinician to identify the characteristic acoustic signature of the motor unit end plates, and make it unnecessary to refer to the visual signal.

The posterior cricoarytenoid muscle may be reached in two ways. Most commonly, the injector places his or her thumb at the posterior edge of the thyroid cartilage on the side to be injected and, using counterpressure from the other four fingers on the opposite thyroid lamina, rotates the entire larynx to expose its posterior aspect (Fig 2). The

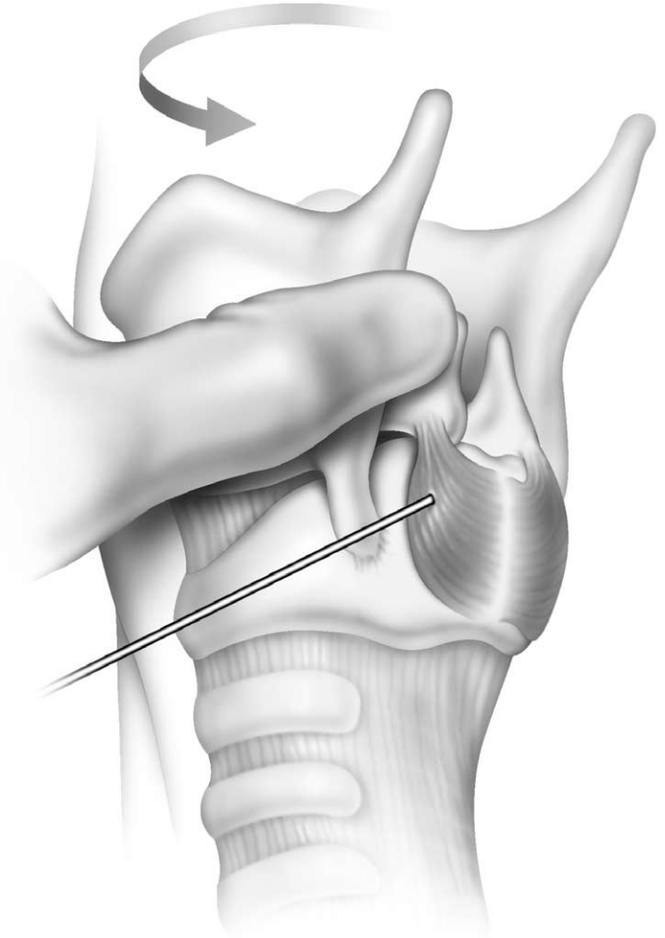

FIGURE 2. Retrocricoid EMG-guided injection of the posterior cricoarytenoid muscle for abductor spasmodic dysphonia.

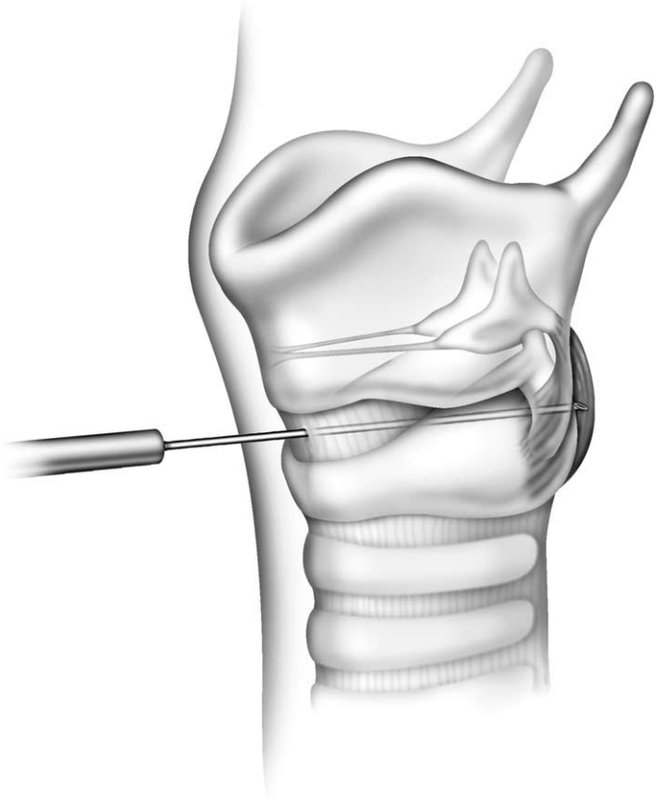

FIGURE 3. Transcricoid EMG-guided injection of the posterior cricoarytenoid muscle for abductor spasmodic dysphonia.

needle is inserted along the lower half of the posterior edge of the thyroid cartilage, traversing the inferior constrictor, and advanced until it stops against the cricoid. The needle is then pulled back slightly and the patient is asked to sniff to activate the posterior cricoarytenoid to check placement. Alternately, the needle may be inserted through the cricothyroid membrane in the midline, guided across the lumen of the subglottic space (again identified by the characteristic airway "buzz"), and through the posterior lamina of the cricoid cartilage to one side or the other of midline (Fig 3).[1,28,29] An intratracheal injection of plain lidocaine helps to prevent the coughing that can occur as the needle crosses the lumen of the larynx. Because the target muscle lies on the opposite side of the cricothyroid membrane, the local anesthetic does not affect the EMG interference pattern. Once through the cricoid cartilage, the first electrical signal encountered on the far side represents posterior cricoarytenoid muscle. Placement is confirmed by muscle activation during sniffing, and the BTX is injected. In our experience, this approach is most useful in the younger patients in whom the cartilage has not undergone extensive calcification. Even so, fragments of cartilage often plug the needle as it crosses the cricoid, and expelling them to begin injection may require considerable force on the plunger of the syringe.

Alternatives to EMG-guided injection include a variety of visually guided techniques. BTX may be administered transcutaneously, as described above, under flexible fiberoptic laryngoscopic observation.[30] It may be injected transorally via a curved needle under endoscopic or mirror control[31] or via the instrument channel of a flexible fiberoptic endoscope so equipped.[32] Probably only the last of these is suitable for reaching the posterior cricoarytenoid muscle. In any case, any method that allows the clinician to achieve chemodenervation reliably and repeatedly can be used to deliver the BTX. Subjecting the patient to a general anesthetic, as in the early days of the procedure, is no longer warranted.

CONCLUSION

Clinical features of dystonia vary between patients, as do functional requirements for voice; the physician must individualize the treatment of each patient. This includes selecting the muscles to be injected, adjusting doses, and varying the frequency of injections. There is often a balance between decreased spasms and loss of function, and the physician and the patient must arrive at an acceptable and flexible treatment plan together. Clinical experience and a detailed knowledge of anatomy and BTX pharmacology are invaluable in making these decisions.

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