Botulinum toxin therapy
for cervical dystonia

Francis O. Walker, MD

*Department of Neurology, Wake Forest University School of Medicine,
Medical Center Boulevard, Winston-Salem, NC 27157-1078, USA*

Cervical dystonia, or torticollis, is perhaps the most common form of focal dystonia. The discovery that botulinum toxin was beneficial in the treatment of this disorder had a twofold impact. First, it silenced a small minority of physicians who believed that this disorder had a psychogenic basis despite convincing evidence to the contrary. Second, it alerted physicians to the broad potential of this novel therapeutic agent. The influence of botulinum toxin extended beyond therapeutics. It led to an enhanced understanding of the pathophysiology of the disorder, insight into how best to design clinical rating scales and an appreciation of the techniques used to administer the drug in other disorders. As such, cervical dystonia is a model disorder for tracing the effect of novel technology on a poorly understood disease.

Diagnosis

Features apparent by inspection

Cervical dystonia has distinctive features that make it easy to diagnose for clinicians who have experience with the disorder [1]. Misdiagnosis can occur, however—most commonly in children or in adults with fixed postural abnormalities of the neck [2,3]. One of the most distinctive features of true cervical dystonia is that the neck moves almost continually. Patients with neck pain, joint or bone abnormalities, fibrosis, or herniated disks all may present with postural abnormalities of the neck [1]. In these cases, the neck typically is held in a guarded posture, however, and attempts to "right" the posture may generate active resistance. In contrast, patients with cervical dystonia appear involved in a "tug of war" with their neck. As the neck

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E-mail address: fwalker@wfubmc.edu

tends to pull or deviate to an abnormal position, they tend to resist the movement initially, then succumb to it. In doing so, the patients adjust their posture to accommodate the movements. Occasionally, patients find a single "set" position, in which they can hold a stationary posture, but more commonly the neck continues to make adjustments, and they seem to adapt to this involuntary activity. Even in mild cases, this tendency of the head to shift slowly around is apparent. Only when the patient sleeps does the cycle break, allowing the head and neck to relax.

It is possible for patients with severe cervical dystonia, if untreated, to develop flexion contractures over years, but this complication now is seen rarely secondary to therapeutic innovations in the last 15 years. More commonly, patients with nondystonic fixed postures of the neck have structural problems that are readily identifiable by clinical examination or radiographic investigation. There are rare forms of torticollis in infants or children in which congenital fibrosis of the sternocleidomastoid leads to tethering of head rotation [1]. In these cases, the head and neck are freely mobile within the range of the fibrosed muscle but cannot be moved passively or actively beyond this. At rest, there is no ongoing muscle activation. Patients with a variety of ocular or labyrinthine conditions can develop compensatory posturing of the neck, but the origin of this posturing is usually self-evident [1]. The absence of ongoing or active muscle contraction when the eyes are closed or the dizziness is stabilized readily distinguishes these conditions from true cervical dystonia. Sometimes patients with tic disorders, such as Tourette's syndrome, can have recurrent jerking movements of the head and neck that resemble cervical dystonia; usually, however, these patients have other features of this disorder—migrating tics in other body areas and obsessive-compulsive personality traits that make this diagnosis self-evident [1].

Distinctive features on interview

In contrast to many disorders, demographic factors are of limited help in diagnosing cervical dystonia. The disorder can manifest at any age, but it is more common in women, and its onset is most often in the 30s and 40s [4,5]. Sudden onset or development of the disorder in childhood or adolescence should raise the index of suspicion for other disorders. Hepatolenticular degeneration (Wilson's disease) [1], structural brain or spinal cord lesions, or hereditary forms of torsion (generalized) dystonia should be considered.

As might be expected, most patients with cervical dystonia have a gradual onset and progression of symptoms. Sometimes patients can recall a self-limited period in the past when they had mild symptoms of the disorder that resolved without treatment [4,6]. Also, as expected, patients complain that the disorder is annoying and embarrassing.

Features that are not predicted by observation are most helpful in diagnosis. Despite the distinctly uncomfortable appearance of the disorder, pain is rarely the dominant or presenting complaint. Pain is present [4], but

it differs from that described by patients with acute or chronic neck pain or fibromyalgia. In contrast to herniated disks, arthritic pain, or neck strains, the discomfort in cervical dystonia rarely has a defined localization and never involves guarding. Point tenderness is absent. Patients with cervical dystonia do not hold their necks still or avoid particular postures and make no correlation of any particular head position with their discomfort [1–3]. It seems likely that the soreness, discomfort, and ache of cervical dystonia results from the relentless contraction of neck muscles, and it may be that one of the beneficial effects of botulinum toxin is that it induces a novel degree of muscle relaxation.

Most patients with cervical dystonia also have sensory tricks that paradoxically alleviate symptoms [1–3,7,10]. Most commonly, these tricks involve touching or holding the chin, but they can be related actions, such as leaning the head against the wall, bending forward, or lying down. Sometimes seemingly unrelated acts, such as yawning or shouting, seem to help. Patients sometimes are hesitant to volunteer the presence of these tricks. This hesitancy may be because the tricks do not make sense to the patient or because they are so accustomed to using them they no longer pay attention to them. Occasionally, patients deny using any such maneuvers—all the while resting their chin in their hands.

About 30% to 40% of patients describe a brief honeymoon effect of sleep [1,2]. When they first arise in the morning, they may be completely normal or much improved, only to have symptoms resume within minutes of assuming the upright posture. Patients often do not volunteer this information unless asked, perhaps because they do not see how this can be explained. Some describe it as a cruel trick of the disorder, giving them, almost daily, a false hope that the disorder will remit. Symptoms are almost always worse when the patient is tired or stressed.

In some patients, trauma may precede the development of cervical dystonia [4,5]. The etiologic significance of trauma is disputed, however. In the case of significant head trauma with loss of consciousness for more than 24 hours, the association seems likely, as it is in poststroke dystonia, a rare but well-documented syndrome [1,4]. With less severe forms of trauma, the relationship is less well established. Psychogenic dystonia may follow minor trauma, and special consideration of this uncommon disorder is appropriate in these cases [2,8].

It is well known that dystonia may have a heritable basis. A positive family history of dystonia or head tremor is common in affected patients [2,4,5,9,35]. The prior use of neuroleptics or metaclopramide sometimes is associated with dystonia, either acutely or as tardive dystonia [2,4,11]. Tardive dystonia often is accompanied by other more typical tardive movement disorders, such as orofacial dyskinesia and akathisia [2,4].

Phrasing questions regarding discomfort, symptom alleviation, and temporal fluctuations in an open-ended fashion is helpful when interviewing patients with suspected cervical dystonia. The incidence of psychogenic

cervical dystonia seems to be increasing as awareness of this disorder, the availability of information about cervical dystonia, and the popularity of botulinum toxin increase. Physicians who inadvertently alert psychogenic patients to the unusual symptoms of the disorder make it more difficult for others to diagnose these patients properly.

Crucial examination findings in cervical dystonia

As indicated previously, movement is a key finding in cervical dystonia. Another prominent finding is evidence of active muscle contraction in the form of muscle thickening and hypertrophy. An expanded neck size can occur, but this finding is less common now that patients are treated with botulinum toxin earlier in the course of their disease. Asymmetry of the sternocleidomastoid is often present in untreated patients. The beneficial effects of sensory tricks or lying down are often apparent on examination, as are changes in the dystonia with different postures or walking. Sometimes shoulder elevation, mild tremor, or dystonic movements in other parts of the body are observed.

A report suggested a slightly different way to look at the central nervous system mechanisms underlying cervical dystonia. Traditionally the motor homunculus is viewed as a map of simple body movements. In large part, this view is based on a limited set of experiments in humans involving single or brief electrical stimulation of motor cortex generating simple motor activation patterns. Using more prolonged stimulation of specific cortical sites in primates [12,13], investigators found that more complex movements emerge in primates. It seems that the cortex may code for the actual end posture of a given movement. In some movement disorders, such as cervical dystonia, a specific abnormal end posture may become preprogrammed at rest. If so, it might explain the observation that patients struggle with head position, resisting but never overcoming the tendency of their heads to assume an unnatural pose.

Cervical dystonia can manifest with almost limitless variations in head posture. The most common form is pure rotation to one side or another (torticollis), but forward flexion of the head (antecollis), backward flexion (retrocollis), or tilting is common. It is also common for movements to be composed of combinations of these positions [4]. Some patients, particularly those with more generalized dystonias, have fluctuating head postures that can assume different positions. Rarely, head thrusting, retraction, or lateral shifting occurs [8].

Other signs in cervical dystonia are less obvious. Persistent cocontraction of multiple neck muscles causes slowing of venous return and changes in vocal and facial expression compatible with straining and discomfort. This observation may explain why global physician rating scales seem to be more accurate than simple postural measures in detecting clinical improvement in therapeutic trials. The problem with protractor-based posture scores is that

they depend on the assumption that the degree of deviation of head position fully predicts clinical disability. Patients with neck casts or braces that require a positional change of the head readily adapt to their situation and suffer less than patients with dystonia who have similar degrees of posturing. The reason is that no extra muscle work is required if the head is braced in an anomalous position, whereas cervical dystonia requires ongoing muscle activation to induce an altered neck position.

The major problem with posture-based rating scales is that neck posture reflects only the difference of forces acting across the neck. Posture does not reflect the pathologic forces that are cancelled out by cocontraction of agonist and antagonist muscles. This cocontraction is an integral part of cervical dystonia. In rotational cervical dystonia, it is common for the ipsilateral sternocleidomastoid and contralateral splenius capitis to be much more active than their contralateral counterparts. This imbalance causes the head to rotate. The ipsilateral sternocleidomastoid and contralateral splenius capitis are antagonists, however, with respect to tilting and flexion of the head. As such, the degree of rotation of the head captures the differences of forces acting on neck rotators but fails to capture the forces of muscles acting on lateral and forward flexion. In a vector analysis, these forces cancel each other out, but from the patient's perspective, these forces are additive in that they involve real effort, work, fatigue, and discomfort [2]. Postural scales also fail to detect the force of contracting muscles in the neck acting to pull the head down on the cervical spine. Almost all cervical muscles are agonists with a force vector in this direction. After selective botulinum toxin injections, muscle weakness in the dominant sternocleidomastoid and splenius capitis results in some reduction in rotation of the head, but the reduction in forces downward and in lateral and forward flexion is not detected by postural analysis [2]. In contrast, a physician global rating scale can detect the postural improvement and reduction in strain as evidenced by facial expression, breathing patterns, voice, and other subtle clinical signs.

Electromyography findings in cervical dystonia

Although rarely needed as a diagnostic tool in cervical dystonia, electromyography (EMG) can help exclude the diagnosis in patients in whom it is in question and provides useful data for mapping out an injection dosing and distribution plan for patients who need botulinum toxin. At rest, minimal EMG activity is detectable in cervical muscles in patients without cervical dystonia [2,3]. The symmetry and balance of the human body require little muscular contraction to maintain an erect posture when it is achieved. An analogy is balancing a broom, upside down, in one's hand. Once in place, relatively little action of the hand is required to keep it in equilibrium. In patients with postural abnormalities of the head from causes other than cervical dystonia, it is rare to find much in the way of ongoing EMG activity. Typically, these patients find a posture that minimizes the

need for ongoing effort to accommodate their problem, be it a bony defor-
mity, a tethered or fibrotic sternocleidomastoid, or a dysfunctional joint.
Patients with psychogenic posturing of the head typically assume similar
low-effort positions because they rarely have activity on EMG [2]. In these
patients, it is advisable, however, to keep the volume of the EMG amplifier
low because some recognize that if they tighten their neck muscles volun-
tarily, it increases the sound output and interest of the examiner.

Patients with true cervical dystonia have active contraction of most
muscles that are agonists in the primary direction of movement and relative
relaxation in antagonist muscles. The extent of this contraction often does
not suppress appropriately with voluntary contraction of antagonistic
muscles [14]. Clinical correlation of EMG activity is required during exami-
nations. Symptoms often fluctuate in patients, and assessing EMG during
initiation and progression of the predominant movement is most in-
formative [14]. Rarely, insertion of the EMG needle acts as a sensory trick
causing significant alleviation of dystonic head movements. In these cases,
EMG activation must be interpreted in the context of ongoing head activity.
Patience may be required in some cases to observe the EMG patterns during
the dominant head movement. Patients should be encouraged not to fight
the head movements when undergoing needle examination to minimize
potentially confusing volitional activity of neck muscles.

Of particular interest is the erratic correlation of what is considered
a ''tight'' muscle by palpation and the presence of EMG activity. Muscles
can become taut either through contraction or by pulling, and in practice,
many muscles antagonistic to the primary direction of movement in cervical
dystonia are palpably tight without EMG activation. Palpation tends to bias
the examiner to the most superficial muscles, causing them to overlook
deeper, often substantially involved, muscles. The use of palpation alone for
identifying affected muscles in dystonia may be misleading [2].

Treatment

Oral medications

Two classes of therapeutic agents have established some track record of
success in managing patients with cervical dystonia. The first is anticholin-
ergic medications, such as trihexyphenidyl or benztropine [1,15,16]. In about
one third of patients, these agents are poorly tolerated because of typical
anticholinergic side effects of dry mouth, constipation, confusion, and
blurred vision and do not work in another third of patients. The remaining
one third of patients are willing to continue in their use, but in less than half
of these patients is a clear benefit discernible to physicians and family.
Nonetheless, a small group of patients have a sustained beneficial effect of
these medications, and as such they are reasonable therapeutic agents,
particularly in patients with mild symptoms that do not warrant botulinum

toxin injections or in patients who do not respond sufficiently to botulinum toxin. Benzodiazepines, particularly clonazepam, although associated with fewer side effects than anticholinergic medications, show a fairly similar efficacy profile [17]. Anecdotal reports suggest that the effects of these agents are more likely to occur in patients with myoclonic or jerky forms of dystonia. Indications for use of benzodiazepines are similar for that of anticholinergics. Rare patients with cervical dystonia can respond impressively to levodopa, and a 1-week trial of Sinemet is a reasonable consideration in any affected patient.

Many medications, ranging from anticonvulsants to antispasticity agents, have been reported to be successful in case reports or small case series [17]. The lack of consistency of these reports and rapidity with which patients discard these medications after using botulinum toxin suggest that their trial use should be restricted to patients who do not respond to other medications or who are comfortable trying low-yield interventions.

Surgical approaches

Several types of surgical procedures have been tried for the control of cervical dystonia, and most have met with limited success. Initial attempts to sever the sternocleidomastoid or to denervate it proved ineffective. This overly simplistic approach failed to take into account the fact that multiple muscles are active in cervical dystonia. Inexperienced neurosurgeons sometimes have denervated the wrong muscles because of lack of understanding of the kinesiology of cervical muscles.

More sophisticated surgical procedures followed, including selective denervation of multiple cervical muscles. This can be an extensive and disfiguring procedure, but it typically achieves a modicum of positive results [2,18,19]. With loss of substantial portions of neck musculature, neck posture becomes more influenced by the minor forces of smaller muscles that are not identified in the denervating process. As such, it is rare for these procedures to generate ideal results, and patients sometimes end up requiring botulinum toxin injections despite clinical benefit. The role of selective denervation procedures in cervical dystonia patients should be restricted to patients who have inadequate responses to oral medications and botulinum toxin. Because the success of botulinum toxin injection can vary significantly with the skill of the injector, a second physician with extensive experience with the technique should be involved before ruling out the success of botulinum toxin injections.

The latest surgical advance in the treatment of cervical dystonia is the use of deep brain stimulators (or ablation) of deep cerebral nuclei of the type commonly used in the treatment of Parkinson's disease [20,21]. Initial reports have indicated that this approach can be effective in patients with cervical dystonia. At this time, the ideal procedure to use has yet to be mastered, however. These procedures can be done unilaterally or bilaterally,

and at least three target nuclei can be considered. Although generally safe, the procedures can have serious complications, including infections, equipment failure, cerebral hemorrhage, stroke, and personality changes. Less disfiguring than selective denervation techniques, brain ablation or stimulation is still experimental in the treatment of dystonia. A small subset of patients with cervical dystonia, particularly patients with incipient generalized dystonia, eventually may prove to be candidates for this approach, but further clinical trials with long-term follow-up are needed to ascertain the indications, risks, and benefits of these novel procedures.

Botulinum toxin

At this time, there are several commercially available botulinum toxin products that vary in unit strength and dosing [22–26]. When ready for injection, each product is administered in a similar fashion when dosing and unit differences are taken into account. The author has accumulated most personal experience with the use of botulinum A toxin (Botox; Allergan, Irvine, California), so it is used as the primary example when discussing dosing. Appropriate dosage adjustments are essential if other forms of botulinum toxin are used.

Challenges in using botulinum toxin in cervical dystonia

The use of botulinum toxin in cervical dystonia is complicated by many factors [2,3,17,27,28]. First, the muscles involved in cervical dystonia overlap in multiple layers; as such, awareness of the depth of needle insertion is crucial because agonist and antagonist muscles may overly one another directly. Second, the muscles involved have complex kinesiology, such that injections for a given patient may involve anterior and posterior and right-sided and left-sided muscles. Third, posturing of the head makes it difficult to use a single set of landmarks based on the standard of normal posture for localizing affected muscles; patients often must be injected with the head in an unusual position. Fourth, cervical muscles are in close approximation to many vital vascular, oropharyngeal, respiratory, and neural structures. Inappropriate injections can lead to hemorrhage aspiration, focal weakness, or pneumothorax. Fifth, the nomenclature and location of muscles involved in cervical dystonia are unfamiliar to most physicians, even electromyographers. Sixth, the doses required to manage cervical dystonia are large and can lead to antibody formation and contribute to side effects. Seventh, patients routinely need to be injected while sitting up (movements are reduced in the supine position, and venous engorgement is minimized in this position), adding to the likelihood of problems with vasovagal reactions. Eighth, the depth of affected muscles may exceed the reach of small needles, requiring 35 mm or longer needles to reach desired targets. Ninth, cervical dystonia is a fairly rare disorder; only a limited number of clinicians in any given geographic area can accumulate

sufficient patients for optimal clinical and technical expertise. Tenth, few electromyographers have adequate clinical exposure to movement disorders to make them comfortable with managing atypical manifestations of cervical dystonia, and few movement disorders experts have sufficient experience with EMG to make them comfortable with this type of hands-on technology. Fellowship training that provides a combined experience in EMG and movement disorders is ideal.

For the interested physician, many courses, monographs, and hands-on workshops are available to help them develop competence in the elements of this technique. Most of the challenges concerning the injection of patients with cervical dystonia relate to simple principles of anatomy and kinesiology.

Choice of botulinum toxin agent

All commercially available versions of botulinum toxins are effective in the treatment of cervical dystonia. There may be variations in the duration of action and likelihood of antibody formation, but no convincing clinical data regarding these variations, if present, have been published. At this time, selection of agent should be based on experience with the drugs, cost, likelihood of side effects, responsiveness to the agent, and potential for antibody formation. It is worthwhile for physicians who use these agents to educate themselves on these issues so that they can make informed decisions on behalf of their patients.

Selection of starting dose

The typical starting dose for the treatment of cervical dystonia with Botox is 100 to 200 U [2,14,29]. When treated, clinical responsiveness is the best guide for increasing or decreasing the dose. Reports have indicated that some patients do well with reductions in overall dose over time, and anything that can reduce the overall toxin load and expense should be given serious consideration. For first-time injections, factors that favor the use of lower doses are smaller body size, female sex, need for injections of anterior cervical muscles (these injections are at greater risk for causing swallowing problems), milder forms of dystonia, experience of the injector, and risk aversiveness of the patient. Most investigators agree that doses greater than 300 U do not enhance the response in proportion to the higher dose, but it has been difficult to show convincing dose-response curves for botulinum toxin injections [2]. Anecdotal reports of high doses for cervical dystonia (>400 U) have been reported, but high doses should be used only with experienced injectors who have found lower doses to be inadequate [2].

Identifying muscles

The proper identification of muscles with EMG is challenging for reasons specified earlier. It is helpful to study the insertion and origin of cervical

muscles; their relationships to surrounding muscles; and relative locations with respect to easily identified landmarks, such as the mastoid process, occiput, posterior and transverse spinous processes, and surface landmarks. It is important to be able to visualize how these muscles change in depth, angle of orientation, and location with changes in head postures. Annotated skeletons, anatomy texts, gross anatomic cross-sections [30], and anatomy atlases all are helpful. Atlases based on true dissections are particularly helpful [31] because they best show significant nearby structures and are free of seductive oversimplification sometimes created by well-meaning illustrators.

When using EMG, it is helpful to understand the kinesiology of different muscles. The relative degree of activation of a muscle in a patient with cervical dystonia is often predictable with some degree of accuracy. The specific layer of muscle often can be surmised by the relative activation of different layers as they are traversed. When attempting to locate the oblique capitis inferioris in a patient who has significant ipsilateral rotation, a series of muscles are traversed if approached posteriorly. First, the needle enters a thin section of trapezius; as a contralateral rotator, this muscle is typically quiescent. The next muscle entered is splenius capitis, a thicker muscle that is a major ipsilateral rotator of the head; it typically has an active interference pattern. The next layer entered is semispinalis capitis, a thick muscle but a weak contralateral rotator that is typically quiescent. Next is encountered a modest fascial area without insertional activity. The final layer is the oblique capitis inferioris that is robustly active in rotation. In patients with large necks, injecting the oblique capitis inferioris may require complete insertion of a 37-mm-long needle, sometimes even with sufficient pressure to indent the skin [2,4,27].

Selection of muscles for injection

The choice of muscles for injection in cervical dystonia is based on several factors [2,3,14,27–29]. First, muscles normally involved in the primary movement of the head and neck should be given priority. The muscles that act most specifically in this direction should be given greater priority. The ipsilateral sternocleidomastoid should be given precedence over the ipsilateral trapezius in patients with rotation because the trapezius is a weaker rotator, but more equivalent precedence should be given in a patient with lateral flexion. In patients with retrocollis and rotation, the ipsilateral splenius capitis should be given more priority than the contralateral sternocleidomastoid because the splenius capitis retroflexes and rotates, whereas the sternocleidomastoid flexes and rotates. Conversely, in patients with antecollis and rotation, the contralateral sternocleidomastoid should be given preference over the splenius capitis. Second, muscles showing greater EMG activation during the primary movement should be given priority. If the splenius capitis shows more activation during the rotatory movement of a patient than sternocleidomastoid, it should be given a proportionately

higher dose. Third, in general, larger muscles should be given priority over smaller muscles. Sternocleidomastoid typically should be given more toxin than anterior scalene in antecollis. Fourth, muscles less likely to be associated with complications, including discomfort, should be given priority over muscles less likely to be involved. In laterocollis, splenius capitis is preferable to anterior scalene. Fifth, previously uninjected muscles should be given priority over injected muscles, if they are involved. The effects of botulinum toxin, particularly Botox, may last much longer than the traditional interinjection interval, so identifying and injecting previously uninjected significantly involved muscles may be additive in terms of overall response.

Several caveats are in order. EMG studies are conducted best with the patient seated; however, in some patients, cervical muscle activation varies with posture, and it is possible to adjust position sometimes while injecting. If not, reasonable adjustments need to be made in muscle selection. It is important to ensure that the patient is attempting to relax so that muscle contractions that are recorded are of dystonic and not volitional origin. Muscles active during typical clinically apparent dystonic movements are those most likely to contribute to symptoms. The inability of a muscle to relax during a volitional antagonist movement may provide additional support for selection for injection [14]. An issue related to muscle selection is that of muscle sampling. With EMG-guided recording and injection, the examiner gradually learns from experience the most commonly involved muscles in patients with different types of cervical dystonia, the variations in these muscles over time in the same patient, and the sometimes surprising variations in muscles affected in different patients with similar head postures. In rotational cervical dystonia patients, trapezius often is unaffected, whereas oblique capitis inferioris commonly is involved, but in some patients [32] this pattern is reversed or changes over time. In patients with shoulder elevation, levator scapulae tend to be much more active than trapezius. In some patients, large commonly injected muscles, such as sternocleidomastoid or splenius capitis, may be surprisingly quiet [2,4]. Muscle selection and sampling improve over time as the examiner gains experience and cumulative observation in multiple patients.

Selection of number of muscles to be injected

The ideal number of muscles to inject in cervical dystonia is not known. As a rule, less experienced and less successful injectors tend to sample and inject fewer muscles than clinicians with greater experience. If done quickly and with decisiveness, multiple EMG insertions are well tolerated in patients, particularly if they know this augments their response effect and duration. One helpful principle involves estimating the degree to which select muscles are robustly active. If four or five large muscles show pronounced EMG activation, the injections can be restricted to this subset. If these muscles show a low degree of activation and less than what might be

expected for similarly affected patients, it is often prudent to sample other deeper muscles, to see if there were other muscles that may be particularly active that would benefit from injection. Identifying and injecting these muscles, particularly in patients with multiple previous injections with declining responsiveness, sometimes can yield gratifying results. If no single muscle is found with a dominant EMG pattern, it may be helpful to inject more muscles with lower doses of botulinum toxin per muscle. Similarly, it can be helpful to inject muscles in different sites over time, to avoid the possibility of ''missing'' active areas not previously permeated by the toxin.

Selection of dose per muscle

Typical injection doses per muscle per torticollis type are standardized in Table 1. This should be used only as a rough guide, however, and the same principles for selecting muscles should be used to make adjustments in overall doses. The actual dose should vary after taking into account many factors. Larger or hypertrophic muscles in general should be given more toxin. Muscles whose primary actions are aligned most closely with the dystonic movement should be given more toxin. Muscles that show more activation by EMG should be given more toxin, as should muscles that are more superficial and more posterior (less likely to be painful or to have side effects, such as dysphagia). Muscles that have never been previously injected but that are significantly involved should be given more toxin than muscles that have been injected.

Selection of injection sites per muscle

Although there is some evidence in laboratory and animal models to suggest that identifying muscle end plates could enhance the effects of botulinum toxin, there is as of yet no study in humans that shows end plate identification enhances the effects of injections. Given the time, effort, and discomfort involved in identifying muscle end plates, seeking them out seems to offer little benefit. For most muscles, end plates are distributed randomly through their bulk, and as such it seems reasonable to spread the toxin out in any given muscle. Larger muscles may benefit from more spreading (injection sites) than smaller muscles. The author typically spreads more toxin throughout large muscles such as splenius capitis, sternocleidomastoid, and levator scapulae, using only a single needle insertion in smaller and more precariously located muscles. These include the scalene muscles that straddle the brachial plexus and the oblique capitis inferioris that is deep, hard to find, and located near the vertebral artery and superficial occipital nerve. Some experienced injectors report that as they sample previously injected muscles they can distinguish areas that are more active than other areas and that they prefer to inject in ''fresh'' areas when possible. Although the benefit of such an approach has not been documented by controlled studies, the logic is

Table 1
Average does, per muscle, in cervical dystonia

Common function of muscle	Muscle	Type of cervical dystonia and estimate of average botulinum toxin type A (Botox) dose* per muscle
		Retrocollis
Head extensors	Levator scapulae	20U(bilateral)
	Semispinalis capitis	30U(bilateral)
	Splenius capitis	20U(bilateral)
	Erector spinae	10U(bilateral)
	Rectus capitis posterior, major and minor	10U(bilateral)
	Trapezius	10U(bilateral)
		Antecollis
Head flexors	Sternocleidomastoid	50U(bilateral)
	Anterior scalenes	15U(bilateral)
	Platysma	10U(bilateral)
	Digastrics	5U(bilateral)
	Other suprahyoid[†] and infrahyoid muscles[†]	0
	Longus colli[†]	0
		Laterocollis
Common muscles that tilt the head (all ispislateral)	Sternocleidomastoid	40U(unilateral)
	Anterior scalene	20U(unilateral)
	Middle and posterior scalene	20U(unilateral)
	Levator scapulae	20U(unilateral)
	Splenius capitis/cervicis	40U(unilateral)
	Semispinalis capitis	20U(unilateral)
	Oblique capitis superioris	15U(unilateral)
	Intertransversarii	15U(unilateral)
	Trapezius	10U(unilateral)
		Torticollis
Common muscles that rotate the head	Contralateral	
	Sternocleidomastoid	70U(unilateral)
	Trapezius	20U(unilateral)
	Levator scapulae	15U(unilateral)
	Semispinalis	10U(unilateral)
	Ipsilateral	
	Splenius capitis	55U(unilateral)
	Oblique capitis inferioris	30U(unilateral)
		Shoulder elevation
Muscles that elevate the shoulder	Levator scapulae	35U
	Trapezius	15U

   * These are theoretical averages and are influenced by patient size, total dose of botulinum toxin (based on a standard 200 U botulinum toxin type A (Botox) dose per patient), degree of activation, types of movement, risks of side effects, responses to prior injections, and muscle hypertrophy. Note the variation in average dosing for different types of head movements.
   [†] Botulinum toxin injections pose significant risk for swallowing difficulties.

appealing, and the approach seems advisable if it can be done without undue stress to the patient.

Interval between injections

The effects of injections of Botox, from a patient perspective, typically last 3 to 6 months. The difference between 3 and 6 months is quite significant, however. The cost of two injections per year compared with four injections per year is measured in thousands of dollars, and coupled with the inconvenience of travel, multiple injections, and discomfort, this difference should be given due consideration. Evidence suggests that the frequency of injections is related to the likelihood of antibody formation. Steps that can increase interinjection interval can benefit patients, payers, and the long-term efficacy of the intervention. Patients should be given the opportunity to determine optimal dosing intervals, with prudent caution as to the costs and risks of making the intervals shorter and the potential for unneeded discomfort for making the intervals longer than needed. A flexible scheduling policy that can accommodate variations in patient requirements is optimal.

Electromyography-guided injections versus blind injections

Injections of botulinum toxin given without the use of EMG needle guidance are effective. There are many compelling reasons to use EMG guidance, however. The first is that EMG ensures that the needle is located in a muscle and in a muscle that is actively contracting in association with the disorder. Speelman and Brans [2] showed that even the most experienced of EMG injectors was frequently inaccurate in identifying needle placement in muscles of the neck. The error rate ranged from 15% in an easily palpated superficial cervical muscle, such as sternocleidomastoid, to greater than 50% in deeper muscles, such as levator scapulae and semispinalis capitis [22,26]. Comella and colleagues [26], in the only published study comparing experienced investigators using EMG versus palpation, showed that EMG was superior in terms of reducing side effects and obtaining clinical benefit. One simple, often overlooked problem with non–EMG-guided injections is that many injectors use needles too short to reach the muscles they are trying to inject (Figs. 1 and 2).

Most importantly, EMG provides ongoing information regarding anatomy and activation patterns of muscle to the injector not available from any other technique. The cumulative summation of information over time provides the injector with unique information regarding the recognition of patterns of activation, location of muscles, and other aspects of anatomy and kinesiology, information that enhances skill and speed. Particularly for newer injectors, who rarely have access to large numbers of patients with which to gather experience, familiarity and use of EMG seems to be warranted [2].

Fig. 1. Axial section through a cadaver human neck at approximately C2. Superimposed on this cross-section are three commonly used injection needles: a 10-mm-long needle, a 15-mm-long needle (typically used with tuberculin/insulin), and a 37-mm electromyography injection needle. The 10-mm needle barely can reach the most superficial trapezius, the tuberculin needle barely can reach the splenius capitis, and it takes the 37-mm needle to reach the oblique capitis inferioris. Patients with cervical dystonia may have muscle hypertrophy, so this cadaver measure may underestimate the depth needed to find target muscles.

Side effects of botulinum toxin in cervical dystonia

Botulinum toxin can cause a variety of side effects in cervical dystonia. The most common troublesome side effect, with a frequency approximating 10% to 12%, is dysphagia [17,23–26,28]. Dysphagia most likely results from local spread of botulinum toxin into swallowing muscles and is seen most commonly in patients receiving injections for antecollis, with an emphasis on anterior cervical muscles. Patients with antecollis are prone to dysphagia already, however, because neck flexion tends to make swallowing more

Fig. 2. Axial section through a cadaver human neck at approximately C7 shows the same three needles as in Fig. 1. At this point, the sternocleidomastoid is immediately adjacent to the skin and is accessible to all three needles; however, only the 37-mm injection needle can reach all three scalene muscles. Only with a perfect angle of insertion could the 15-mm tuberculin needle reach the anterior scalene.

difficult. Patients with less muscle bulk (eg, older women) seem to be at greater risk for dysphagia. For unclear reasons, sometimes patients experience dysphagia after one set of injections, having tolerated similar injections in the past without difficulty. Most commonly, dysphagia lasts a few weeks and is mild, but rare patients need support with a feeding tube. Use of EMG needle guidance, proper muscle selection, and sometimes dose reduction are needed to manage this side effect. Dry mouth, particularly with botulinum B toxin, can exacerbate a tendency toward dysphagia.

Excessive doses of botulinum toxin sometimes can cause patients to have difficulty maintaining an erect head posture. This side effect also typically is of short duration, on the order of several weeks, and can be managed with prudent use of a soft cervical collar. Dose reduction is advisable in patients who have had this type of problem.

Side effects from needle puncture, such as pneumothorax and hematoma, can occur but are rare. Injection of large nerve trunks, such as the brachial plexus, rarely can occur, and this can be associated with nerve injury. When injecting scalene muscles, it is important to ask the patient to alert you to any sensations of shooting pain or numbness associated with needle movement or injection. Nerves are robust structures and tolerate needle insertion alone usually without complication; however, bolus injection into a constricted perineural space can be injurious.

The large doses of botulinum toxin required to treat cervical dystonia expose the patient to the risk of antibody formation [33]. Typically, antibody formation manifests as a waning response to injections over time, followed by loss of all effect. Two factors seem to be associated with antibody formation that is under the control of the injector—total dose administered and the interval between doses [33]. The greater the dose and the shorter the interval, the more likely patients are to develop antibodies. Current studies are in progress to monitor the frequency of this occurring. The author, by policy, never injects patients more frequently than every 3 months and rarely uses greater than 300 U of Botox to treat patients. Further study is needed to determine optimal procedures for minimizing the risk of antibody formation.

Mechanism of action of botulinum toxin in cervical dystonia

The beneficial effects of botulinum toxin in cervical dystonia are indisputable, but the mechanism of action of the drug that results in this improvement is as yet unproven. The most likely primary mechanism of action is the reduction of muscle force during the dystonic muscle contractions. Injections of the drug into extensor digitorum brevis reduce the evoked motor response of the muscle and its mean rectified voltage during maximal voluntary effort by 60%, an effect that should improve symptoms [34]. Botulinum toxin interrupts the vicious cycle of untreated cervical dystonia: isometric muscle contraction and work resulting in muscle hypertrophy resulting in greater muscle contraction and work [2].

Despite the most obvious effect of botulinum toxin, there may be other mechanisms involved in its therapeutic effect than simply weakening muscle contraction. Some evidence suggests that the drug may interfere with muscle spindle activity and that this alteration in sensory feedback may help improve symptoms [7,10]. Other findings suggest that botulinum toxin may prevent the release of substances from nerve endings. Because it is known that pain fibers release a variety of chemical mediators, it is possible that botulinum toxin may be able to reduce the discomfort of cervical dystonia through a nonspecific antisecretory effect as well. Because of its structure, botulinum toxin is unable to effect any significant entry into the central nervous system. The closely related tetanus toxin is able to access the central nervous system, and this accounts for its profound central nervous system effects. Further study of specific mechanisms of botulinum toxin may shed light on ways to enhance its effects in cervical dystonia, and it is possible that manipulation of the drug itself or pairing it with other peripherally or centrally active drugs may enhance its effect. The discovery of new indications for the use of botulinum toxin should promote continued research and development of this remarkable compound.

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