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# Treatment of focal dystonias with botulinum neurotoxin

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## Abstract

This is a review on the use of injections of botulinum toxin for the treatment of focal dystonias. Disorders covered include cranial dystonia, cervical dystonia, spasmodic dysphonia, and focal hand dystonia. Considered are clinical aspects, alternative treatment strategies and principles of use of botulinum toxin injections.

### Keywords

Botulinum toxin; Focal dystonia; Cranial dystonia; Cervical dystonia; Spasmodic dysphonia; Focal hand dystonia

There is a long history of treating the focal dystonias with botulinum neurotoxin (BoNT) and the treatment is now relatively standard in most clinics. Currently, there are four brands of BoNT available in many countries, including three brands of BoNT-A (Botox®, Dysport®, and Xeomin®) and one brand of BoNT-B (Myobloc®/Neurobloc®). All brands could well be used for any indication discussed here, although experience differs in the different situations. Generally, we report on the most common experience.

## 1. Cranial dystonia

Under the term cranial dystonias a set of focal dystonias is comprised which can occur separately or as it is often the case in combination. The following syndromes are included: blepharospasm without levator inhibition, blepharospasm with levator inhibition, orofacial dystonia, lingual dystonia, oromandibular dystonia (jaw-closing type, jaw-opening type, jaw-deviation type), Meige syndrome (blepharospasm plus pharyngeal, jaw and lingual dystonia), and Brueghel syndrome (blepharospasm plus oromandibular dystonia of the jaw-opening type and cervical dystonia). Levator inhibition is often called apraxia of eyelid

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opening, and the terms Meige syndrome and Brueghel syndrome are not used by some experts.

The etiology and differential diagnosis of cranial dystonia are similar to those of other focal or segmental dystonias. BoNT-A therapy is now an established treatment for patients with cranial dystonias, especially in patients suffering from blepharospasm and oromandibular dystonia of the jaw-closing type. BoNT-A therapy is used to decrease the intensity and frequency of abnormal spasms or continuous dystonic activity as well as to decrease the intensity of secondary pain syndromes.

### 1.1. Blepharospasm

In patients suffering from pure blepharospasm the disease is characterized by intermittent or persistent, involuntary, usually bilateral eye closure produced by phasic and/or tonic contractions of the orbicularis oculi muscles. Blepharospasm is a common form of cranial dystonia, the prevalence of blepharospasm is estimated to be 5 per 100,000 (Nutt et al., 1988). Blepharospasm typically begins insidiously in the 5th to 7th decade of life and it is more common in women. Disease progression is generally slow and although it usually remains focal, sometimes over years the dystonic features may spread to nearby facial muscles or to oromandibular, lingual and cervical muscles. Often early symptoms such as photophobia and ocular discomfort are reported. In the first years of the disease often intermittent muscle contractions dominate, later the contractions are more and more tonic and severe leading even to functional blindness in some patients. Blepharospasm often worsens in bright light, and when the patients are tired, it can be less pronounced when the patient is speaking or singing rather than listening.

When using BoNT-A, therapy normally starts with small doses, since the appearance of side effects such as severe ptosis will influence the compliance of the patient in regard to future therapy sessions. The average starting dose per eye amounts to 20/20/60 units (Botox®/Xeomin®/Dysport®). The dose per eye is divided into 4 portions which are injected into the orbital portion of the orbicularis oculi around the eye. In patients with levator inhibition smaller doses of BoNT-A (10/10/40; Botox®/Xeomin®/Dysport®) into the pretarsal, or preseptal and orbital region of the orbicularis oculi muscles are injected.

### 1.2. Oromandibular dystonia

This type of dystonia mainly involves the masticatory muscles, but often lower facial, and tongue muscles are additionally involved. On the basis of the clinical picture, patients can be classified as having jaw-closing, jaw-opening, or jaw-deviation dystonia. The majority of patients with jaw-deviation also have jaw-opening. Best therapeutic results by application of BoNT-A can be observed in patients with jaw-closing and jaw-deviation. In these types of oromandibular dystonia injections into both masseters and temporalis muscles are performed. For the masseters, doses of 25/25/100 units (Botox®/Xeomin®/Dysport®) are normally used, for the temporalis muscles doses of 20/20/80 (Botox®/Xeomin®/Dysport®) lead to a sufficient decrease of dystonic hyperactivity. If the effect is not satisfying, in addition the internal pterygoid at doses of 15/15/60 (Botox®/Xeomin®/Dysport®) can be tried.

The therapy of patients with jaw-opening is much more challenging, the most important muscle to be treated in this situation is the external pterygoid. However, the digastricus and also the base-of-tongue muscles can play a role. The external (lateral) pterygoid is treated with doses of 15/15/60 units (Botox®/Xeomin®/Dysport®), and for the digastricus doses of 10/10/40 units (Botox®/Xeomin®/Dysport®) are normally used.

In jaw-deviation often combined with protrusion, the contralateral external pterygoid muscle is the most important muscle in the majority of patients, when jaw-protrusion is dominating both external pterygoid muscles is often involved. In the majority of patients the therapeutic effect of BoNT-A is not leading to a satisfying result, in this situation especially the application of deep brain stimulation of the globus pallidus internus on both sites has to be considered.

The pterygoid muscle injections have to be performed with EMG guidance as the muscles are not easy to palpate. The use of EMG is also often helpful for other jaw muscles (digastricus, masseter, temporalis) to improve the precision and accuracy of botulinum toxin injection. During EMG recordings patients are asked to voluntarily open and close their mouth and jaw, to deviate their jaw to the right and the left, or to open the mouth forcefully to identify the various muscles to be injected in more detail.

### 1.3. Orofacial and lingual dystonia

In orofacial dystonia mainly muscles are involved which are supplied by the 7th nerve. Orofacial dystonia occurring mainly in Meige syndrome in conjunction with blepharospasm has to be considered individually. Injections are performed under EMG guidance, mainly the zygomaticus major and minor, the orbicularis oris and the buccinators are treated on both sides. Doses applied on an average amount to 5/5/20 units (Botox®/Xeomin®/Dysport®) on each side.

In lingual dystonia especially in patients with severe tongue protrusion, results are often disappointing. Injections of 10/10/40 units (Botox®/Xeomin®/Dysport®) into the intrinsic tongue muscles can be used. In this difficult circumstance, deep brain stimulation of the globus pallidus internus might be considered.

## 2. Cervical dystonia

Cervical dystonia (CD), also known as spasmodic torticollis, is a focal dystonia arising from involuntary activation of muscles in the neck and shoulders causing turning, tilting, flexion or extension movements of the head, sometimes combined with elevation or anterior shifting of the shoulders. Pain is present in approximately 60% of patients, and can be the most disabling feature. Cervical dystonia is a frequent dystonia, with a crude prevalence of approximately 20–200 per million (Defazio et al., 2004). Although transient remission of symptoms may occur, typically CD is a life-long disorder that waxes and wanes in severity.

Oral medications may be of limited benefit for CD and include anticholinergic agents, baclofen, and benzodiazepines. However, side effects are common. In most CD patients, BoNT treatment is the most effective approach to CD.

BoNT-A was first evaluated for CD in a single blind study of 12 CD patients (Tsui et al., 1985) using a maximum dose of 200 units of BoNT-A as Oculinum (Smith-Kettlewell, San Francisco, CA). This study showed improvement in head posture and pain in 92% of the patients, with the only adverse event being transient neck weakness in 3 patients. Subsequently, there have been approximately 80 studies that have evaluated BoNT in cervical dystonia. Of these, 8 prospective, double-blind, randomized controlled clinical trials meet the criteria for classification as class I evidence (Simpson et al., 2008). These studies have shown the efficacy of BoNT-A and BoNT-B for head posture and pain in both previously untreated CD patients and those who have been effectively treated with BoNT in the past. The most frequent adverse events in these studies included dysphagia and neck weakness. These studies provided level A evidence that BoNT injections are an effective treatment for CD, and are probably more effective than trihexyphenidyl (Simpson et al., 2008).

Although BoNT is well established as a treatment for CD, there are several issues pertaining to its use that have not been adequately addressed. One of the main issues is dealing with the four brands of BoNT, the three brands of BoNT-A (Botox®, Dysport®, and Xeomin®) and one brand of BoNT-B (Myobloc®/Neurobloc®). Attempts to establish a dose equivalency among these brands for the treatment of CD has been complicated by the lack of consistent results. There are two studies that directly compared one brand of BoNT-A (Botox®) to another (Dysport®) (Odergren et al., 1998 and Ranoux et al., 2002). One blinded, parallel arm study comparing dose ratio of 1 unit Botox® to 3 units Dysport® in 73 CD patients showed equivalent improvement in the Tsui cervical dystonia scale, and similar occurrence of adverse effects in the two groups (Odergren et al., 1998). However, a subsequent three period crossover study evaluating dose ratios of Botox® to Dysport® of 1:4 and 1:3 found greater improvement in the Tsui scale with Dysport®, a longer duration of action and increased occurrence of side effects. In contrast to the first study, the authors of this study concluded that the dose equivalency of Botox® to Dysport® was less than 1:3 (Ranoux et al., 2002).

Direct comparisons of Botox® to Myobloc®/Neurobloc® have been evaluated in two studies, one study at a dose ratio of 1 unit Botox® to 40 units Myobloc®/Neurobloc® and another using a ratio of 1:66.6 (Comella et al., 2005 and Pappert and Germanson, 2008). Both studies showed equivalent improvement in the Toronto Western Spasmodic Torticollis scale (TWSTRS) at week 4. In the 1:40 unit ratio study, the Botox® treated group had a modestly longer duration of benefit (approximately 2 weeks) and fewer occurrences of dysphagia and dry mouth than the Myobloc®/Neurobloc® group (Comella et al., 2005). In the 1:66.6 study, there was no difference in either treatment arm for duration or adverse events (Pappert and Germanson, 2008).

Only one study compared Botox® to Xeomin®. This study used a parallel arm design and reported that Xeomin® was not inferior to Botox® for efficacy or side effects using a 1:1 dose ratio. No additional studies have been done, but are needed to confirm this finding (Benecke et al., 2005).

These comparative trials taken together indicate that simple dose ratios are not applicable among the different brands of BoNT. In the light of differences in the mechanism of action between serotypes, and differences in composition and manufacturing processes among the brands, it is not surprising that each BoNT brand is distinct. Furthermore, the complexity of CD and the limitations of the outcome scales used may preclude straightforward translations of dosing from one brand to another.

## 3. Spasmodic dysphonia

Spasmodic dysphonia is a laryngeal dystonia which is most often focal, but may be present in cranial or more generalized dystonia. It most often affects connected speech. Two main types have been identified: an adductor type in which there is an irregular hyperadduction of the vocal folds during speaking producing a “strain-strangled” voice; and an abductor form in which there is irregular and inappropriate abductor spasms during speaking producing breathy breaks or whispering. There are also cases of compensatory or pseudoabductor patients who whisper as a compensatory strategy for the tight adductor spasms they experience. Some experts believe that all of the patients are a mixed adductor/abductor with a predominance of one form. We have seen several patients who are truly mixed and have both adductor and abductor spasms. We also have seen several patients in whom their primary form changes with time (for example, switching from adductor to abductor).

In addition we have identified a “Singer's laryngeal dystonia” in which the vocal abnormalities occur during singing. We also described a rare form of laryngeal dystonia in which there are adductor spasms during respiration. The paradoxical motion creates stridulous noises during inspiration, but usually does not produce hypoxia. Other laryngeal activities are normal.

The most recent review of our series of laryngeal dystonia (1984–2007) includes 1300 patients. Of this group, 82% had the adductor type, 17% the abductor type, 13 patients had adductor breathing dystonia, and 5 had Singer's dystonia. Females predominated as 63% of the total group. There was a positive family history of dystonia in 12% of the group. Most of the group maintained a focal distribution (82.4%, 12.3% progressed to another cranial site (most blepharospasm), and 5.3% progressed to extracranial sites).

For many years, the only treatment options for these patients were speech therapy and psychotherapy. Both had overall poor results. In 1976, Dedo (1976) published a study first using a test dose of a local anesthetic agent to cause a motor blockade of the recurrent laryngeal nerve, followed by a nerve section in those patients with a positive result. Others followed with nerve crush and nerve avulsion or resection. All of these procedure had initial good results, with many long-term failures. Berke et al. (1999) more recently proposed a selective denervation of the adductor branches of the recurrent nerve bilaterally with immediate reinnervation using the ansa cervicalis nerve. Convincing long-term data is not yet available for this procedure, and this surgery should be reserved for the rare patient who does not benefit from BoNT therapy.

Long-term relief of the laryngeal symptoms with systemic agents was similarly of limited value in this group of patients. Based on the significant symptom response of blepharospasm

to intermittent injections of BoNT, we gave the first laryngeal injection of this agent for spasmodic dysphonia in April 1984 (Blitzer et al., 1988). Our initial injection strategy was to inject one thyroarytenoid muscle in an adductor SD patient with a small amount of toxin. We finally achieved a good response at 3 units. Since this injection, and many thousands of injection sessions later we have several different injection strategies which are dependant on patient response (Blitzer et al., 1998). Most of the patients receive bilateral thyroarytenoid muscle injections given via a hollow-bore 27-gauge Teflon coated EMG needle with EMG control. All of our data is based in injections of Botox®. Our average dose is 0.9 unit/0.1 ml per vocal fold. A number of patients cannot tolerate the bilateral injections or prefer unilateral injections, and they receive unilateral injections averaging 1.5 unit/0.1 ml. The duration of benefit of these unilateral injections appears to be less than bilateral. In some patients, they cannot tolerate adequate doses that relieve the symptom without extended breathiness, and at lower doses do not have symptom relief. In these patients, we stagger the injections (2 weeks apart) to allow for the transient recovery of one side before weakening the other. This most often gives satisfactory results. In still another group, in whom no downtime is tolerable, we have given more frequent “mini” dose bilateral injections at very low doses (a few at 0.05 unit/0.1 ml). We have also been able to treat successfully patients who had previous recurrent laryngeal nerve sections who had return of symptoms. They receive unilateral doses usually to the functional vocal fold (Sulica et al., 2003). Some of the effect of the toxin injections may be related not only to blockade of efferent signal, but also an effect on the afferent feedback loop.

The results in the entire adductor group reveal the average onset of action to be 2.4 days; the average peak effect is 9 days; the average duration of benefit is 15.1 weeks; and the average benefit was 91.2% of normal function as rated by the patient. The side effects of the adductor injections were 25% with mild, transient breathy voice; 10% with mild, transient cough on drinking fluids; and less than 1% with local pain, bruising or itch.

In the adductor breathing dystonias, we treated 12 patients with an average dose range of 0.6–3.75 units given bilaterally. The average improvement was 55% over many injection sessions. The mean duration of benefit was 14 weeks. In the Singer's laryngeal dystonia, small doses were given since treatment causes decreased loudness, vibrato and truncated pitch. This group cannot tolerate many of the changes and still be able to sing professionally, making their treatment extremely difficult.

The strategy for the abductor group is to treat one posterior cricoarytenoid muscle (PCA), which is the only abductor of the vocal folds. The consequence of too much abductor weakness is inability to abduct the vocal folds during inspiration causing stridor and dyspnea. Therefore we begin with 3.75 unit/0.15 ml in the PCA that appears on laryngoscopy to have greater spasms on speaking. The patients are seen again at 2 weeks, and if their voice still has breathy breaks, another laryngoscopy is performed to evaluate the airway. A dose is then chosen for the contralateral PCA ranging from 0.6 to 2.5 unit/0.1 ml and given under EMG control. Twenty percent of our group only need one PCA injected. Ten of the patients also had cricothyroid muscles injected as suggested by Ludlow and colleagues (Cyrus et al., 2001), and 12 had unilateral thyroplasty surgery with implants as well as BoNT therapy.

The results of the abductor group show the average best voice at 70.3% of normal as rated by patients. The limitation is stopping further therapy if the patient has any airway symptom or has a very narrow airway on exam. The average onset was 4.1 days; average peak effect was 10 days; and the average duration 10.5 weeks. The side effects of the abductor injections were 2% of the patients with mild exertional wheezing and 6% with mild transient dysphagia to solids.

In conclusion, a 24-year experience in 1300 patients has shown that BoNT can safely be used to treat the symptoms of the many forms of laryngeal dystonia. It takes many different treatment schemes and dosing patterns to fit the many varieties of patient presentations, but significant improvement in function can be achieved in almost all of them.

## 4. Focal hand dystonia

Of focal limb dystonias, the upper extremity is affected more commonly than the lower extremity, and most experience with BoNT is in the upper extremity. Upper extremity dystonia usually begins in the hand and is often task specific. This means that only one task is affected, while others are normal. At times, when the disorder gets worse the task specificity is lost, and the dystonia can affect other tasks and even become spontaneous. The task specificity is actually only clinically apparent; with careful assessment a more pervasive, if mild, motor control disorder can be demonstrated. Since the task affected appears to derive from repetitive activities in an occupation, the term occupational cramp is used. These include musician's cramp and, most commonly, writer's cramp.

BoNT is currently the treatment of choice and will be detailed below. Oral medications such as anticholinergic drugs can have some effect, but only in a limited number of patients. Brain surgery with either lesions or deep brain stimulation of the Vo nucleus of the thalamus might well be effective, but has not often been undertaken for this indication (Taira and Hori, 2003). There are a number of experimental treatments that have been described in recent years. Limb immobilization by a plastic splint for 4–5 weeks followed by retraining has been advocated, but further studies do not seem to be as positive as the initial report (Priori et al., 2001). Sensory training by learning braille reading and practicing for 30–60 min per day for up to 1 year, also has salutary effects (Zeuner et al., 2002 and Zeuner and Hallett, 2003). Motor training by practicing writing with each finger independently can be helpful (Zeuner et al., 2005). Low frequency transcranial magnetic stimulation has also been reported to improve writing performance (Murase et al., 2005 and Siebner et al., 1999).

For focal dystonias, injection of BoNT into the muscles responsible for the abnormal postures can be very effective and is often considered the first choice. There has been one Class I double-blind, randomized, placebo-controlled trial that used Dysport® (Kruisdijk et al., 2007). In this investigation, 40 patients received either BoNT-A or placebo injections in two sessions. The primary outcome measure was the patients' choice to continue with the treatment at 3 months, but patients were followed for one year. Fourteen of 20 patients receiving BoNT-A reported a beneficial effect and chose to continue treatment compared with 6 of 19 patients in the placebo group. These subjective results were supported by several clinical scales. There have been three double-blind trials considered Class II

demonstrating efficacy all with Botox® (Cole et al., 1995, Tsui et al., 1993 and Yoshimura et al., 1992). There has also been a specific study showing utility for musician's cramps (Cole et al., 1991). Patients can continue to respond to injections for many years (Karp et al., 1994 and Marion et al., 2003).

The first step in the treatment of focal hand dystonia is to identify the muscles that show the most severe spasms. It is these muscles that should be targeted with the drug. The muscles may well be obvious from clinical inspection, but it is important to separate out the dystonic movement from any compensatory movement. One useful trick is to let the dystonic hand relax and do the task with the contralateral hand. Mirror dystonia might well appear in the dystonic hand (Marion et al., 2003). If the situation is still not clear, it would be appropriate to employ multichannel EMG recordings. In some circumstances, it is possible to use surface electrodes or needle electrodes. In other circumstances such as in the forearm, it is necessary to use fine wire electrodes. The fine wires allow the patient to move freely and to perform the task that provokes the dystonia while at the same time permitting isolation of individual muscles. Needle electrodes would be too painful and surface electrodes are often not sufficiently selective.

BoNT is injected focally into the selected muscles. The dose of BoNT is based on the size of the muscle affected, the intensity of the spasm, and the number of muscles affected. Injections are given about every 3 months.

EMG guidance in doing these injections is likely to be helpful in many circumstances. BoNT does diffuse in the tissues for at least several centimeters. Some authorities suggest just making the injection based on knowledge of the anatomy. Certainly, with deep muscles or small, closely packed muscles, it would seem that EMG guidance would help assure that the medication was delivered to the correct target and that nearby muscles would not be weakened unnecessarily. EMG identification of specific muscles for injection does appear to increase the likelihood of therapeutic success (Molloy et al., 2002).

There are several techniques for EMG guidance. They all employ a 27-gauge hollow needle coated with Teflon except for the tip and hub. The hub is connected to the active input of an amplifier with an alligator clip. The reference electrode can be a surface electrode. Once the site is identified, the toxin is injected through the same needle. There are 4 methods for verifying the correct location of the needle:

1. Asking the patient to voluntarily, selectively activate the muscle and looking for the EMG interference pattern. This seems straightforward, but has some difficulties since it is not always easy to activate a muscle selectively. Moreover, patients with dystonia seem to have a particular difficulty with selective activation.
2. Passive movement of the joint on which the muscle acts. The passive movement stretches and relaxes the muscle which should cause the needle to move back and forth. This is an excellent technique for superficial muscles and gives very precise localization. (The syringe must be disconnected from the needle for this maneuver since the weight of the syringe makes the movements difficult to assess.)

3. Stimulating through the needle. With low currents this will cause a small localized muscle twitch that should identify where the tip of the needle is located.
4. Use of ultrasound. This is a relatively new technique for this purpose, but makes it possible to visualize the muscle and even see the BoNT being injected.

Knowledge of anatomy that is sufficient for routine electromyography is not always enough for injections. For example, if the problem affects only the middle finger, it is not adequate to find the flexor digitorum superficialis (FDS); the injection should be into the fasicle of that muscle specific for the third finger.

The toxin has its effect only at the endplate, and in quantitative studies it has been demonstrated that the toxin is more effective if delivered at the endplate. It would be useful, therefore, to identify and inject into the endplate zone, but given the large size of the endplate zone and the diffusion of the toxin, all authorities have been content with injections into the mid-belly of the muscle.

Having patients exercise the muscles right after injection will increase the efficacy, at least in terms of weakness, since the toxin is taken up more avidly when a muscle is active (Chen et al., 1999). Improved efficacy in symptom reduction has not been demonstrated however.

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