Botulinum Toxin for the Treatment of Movement Disorders

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Abstract After botulinum toxin was initially used to treat strabismus in the 1970s, others started using it to treat movement disorders including blepharospasm, hemifacial spasm, cervical dystonia, spasmodic dysphonia, and oromandibular dystonia. It was discovered that botulinum toxin can be an effective treatment for focal movement disorders with limited side effects. Over the past three decades, various formulations of botulinum toxin have been developed and the therapeutic use of these toxins has expanded in movement disorders and beyond. We review the history and mechanism of action of botulinum toxin, as well as describe different formulations available and their potential therapeutic uses in movement disorders.

Keywords Botulinum toxin · Movement disorders · Dystonia · Blepharospasm · Hemifacial spasm · Cervical dystonia · Spasmodic dysphonia · Oromandibular dystonia · Tremor · Focal limb dystonia · Tics · Sialorrhea

Introduction

Botulinum toxin is one of the most potent poisons known to humans. The naturally produced toxin is responsible for botulism, an acute illness characterized by neuromuscular weakness and other anticholinergic symptoms. The first reports of botulism date back to the 18th century, and were linked to the consumption of improperly preserved sausage [1]. In fact, the term botulism stems from the Latin word botulus meaning sausage [1]. The anaerobic bacterium Clostridium botulinum, which produces botulinum toxin, was subsequently identified by the microbiologist Emile Pierre Marie van Ermengem in the 1890s [1]. With further research during World War I and World War II, botulinum toxin was developed as a possible mode of biologic warfare [1]. In 1946 Edward Shantz, PhD, isolated the toxin in a crystal form and in 1949, ASV Burgen discovered that botulinum toxin blocks neuromuscular transmission. In 1972 Shantz developed a method of isolation and purification that led to therapeutic trials. The therapeutic use of botulinum toxin in humans was first tested by ophthalmologist Alan B. Scott in 1977 for the treatment of strabismus [2]. During the early 1980s, Scott and others began using botulinum toxin as treatment for movement disorders including blepharospasm, hemifacial spasm, and cervical dystonia [3–5]. In 1989, the US Food and Drug Administration (FDA) approved botulinum toxin A for the treatment of strabismus, blepharospasm, and hemifacial spasm. Since then, other formulations of different types of botulinum toxin have been developed for commercial use and are used to treat various movement disorders. In this review, we refer to the different types of botulinum toxin by their trade names, which are commonplace in the medical literature.

Structure and Mechanism of Action

Botulinum toxin is an exotoxin produced by the anaerobic bacteria Clostridium botulinum. Clostridium botulinum synthesizes seven serotypes of toxin: A-G. Clostridium butyricum produces type E, and Clostridium baratii produces type F. Active botulinum toxin is a di-chain polypeptide composed of a heavy chain (100 kDa) and a light chain (50 kDa)

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linked by a disulfide bond [6]. The toxin forms a complex associated with nontoxic proteins (hemagglutinins and non-hemagglutinins) [6]; initially thought to prevent protein degradation, the role of these nontoxic proteins is unclear [7]. Botulinum toxin binds with high affinity to peripheral cholinergic nerve terminals of the neuromuscular junction as well as parasympathetic and sympathetic ganglionic and postganglionic terminals [6]. Botulinum toxin binds to an acceptor protein via the C-terminal of the heavy chain on the presynaptic membrane of the acetylcholine nerve terminal and is internalized through endocytosis [8]. The N-terminal of the heavy chain forms a pore in the endocytic membrane to release the light chain into the cytosol. The light chain is a zinc protease that cleaves soluble N-ethylmaleimide-sensitive factor attachment receptor proteins (SNARE proteins) [8]. SNARE proteins are docking proteins for acetylcholine vesicles that allow for calcium-mediated release of acetylcholine into the synaptic cleft [8]. Serotypes A and E cleave SNARE protein SNAP 25 located on the inner membrane, and serotypes B, D, F, and G target synaptobrevin located on the vesicular membrane [8]. Type C cleaves both SNAP 25 and synaptobrevin [8]. With the blockade of acetylcholine release at cholinergic synapses, temporary synapses are formed in a process called axonal sprouting [9–11]. An in vivo imaging study, involving mice treated with botulinum toxin, demonstrated that recovery from muscle paralysis was associated with newly formed sprouts capable of neurotransmission. Eventually synaptic activity resumes in the original nerve terminals, with subsequent sprout regression [12].

The effect of botulinum toxin on nerve and muscle has been studied via electromyography (EMG) and ultrasound [13]. One such study demonstrated a decline in compound muscle action potential (CMAP) amplitude within 48 h of botulinum toxin injection with maximal decline at day 21 [13]. Muscle thickness, as evaluated by ultrasound, demonstrated approximately 40 % decrease in muscle volume at day 42 [13]. In addition to local effects, botulinum toxin may also have distant subclinical effects on noninjected muscles [14–17]. A double-blind study involving 42 cervical dystonia patients treated with Botox evaluated limb muscles with single-fiber EMG pre- and post-injection [15]. Two weeks post-injection, mean jitter in the toxin group was significantly higher than placebo, indicating distant alteration of neuromuscular transmission [15]. Several studies suggest that botulinum toxin may inhibit muscle spindles, leading to decreased sensory input and decreased muscle contraction [18–20]. Botulinum toxin may also alter spinal cord, brainstem, and central pathways leading to cortical reorganization and plasticity [21]. These central effects may be secondary to modulation of sensory input to the central nervous system. Furthermore, although botulinum toxin has not been shown to penetrate the blood–brain barrier in humans, animal studies have demonstrated retrograde axonal transport and penetration of the central nervous system at supratherapeutic doses [22, 23].

Botulinum Toxin Formulations

The commercially available formulations of botulinum toxin worldwide include five type A formulations and one type B formulation (Table 1). The type A formulations include Botox (Allergan Inc., California, USA), Dysport (Ipsen Ltd., Slough, UK), Xeomin (Merz Pharmaceuticals, North Carolina, USA), Hengli (Lanzhou Biologic Products, Lanzhou, China) and Meditoxin (Medy-Tox, Ochang, South Korea). The type B formulation is known as Myobloc (US WorldMeds, Kentucky, USA). In 2009 the US FDA began using generic names for botulinum toxin drugs: onabotulinumtoxinA (Botox), abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), and rimabotulinumtoxinB (Myobloc). Type A formulations are available in a crystallized form that needs to be dissolved in normal saline, while Myobloc is available in solution. Most formulations need to be stored in a cool environment except for Xeomin, which is stable at room temperature. The unit of measure for botulinum toxin is the mouse unit, which is equivalent to the amount of botulinum toxin that kills 50 % of a mouse colony by intraperitoneal injection [24].

The various formulations of botulinum toxin have been compared. Since there is no universally accepted method of determining equivalent doses of Botox, Dysport, and Myobloc, studies comparing toxins are difficult to interpret. A systematic review of four randomized controlled trials comparing Botox and Dysport for various movement disorders (blepharospasm, hemifacial spasm, cervical dystonia) found a trend for Dysport to have greater efficacy and longer duration of action but increased frequency of side effects, particularly dysphagia [25]. Botulinum toxin B may have a tendency for greater autonomic side effects (dry mouth, accommodation difficulties, constipation) than type A toxin [26–28]. Xeomin is a unique formulation of botulinum toxin A, which is free from complexing proteins and has less inactive toxin; long-term studies evaluating the immunogenicity of Xeomin in humans have yet to be reported.

Therapeutic Failure and Immunoresistance

Although botulinum toxin can be very effective for many patients, some do not have an adequate clinical response. Some patients have primary therapeutic failure at the initiation of treatment, while others have secondary failure after initial successful treatment. Primary nonresponse to botulinum toxin may be seen in difficult-to-treat conditions such as anterocollis, or in misdiagnoses such as

Table 1 Commercially available formulations of botulinum toxin

	Serotype	Generic	US FDA-approved movement disorders indications	Other names
Botox	A	OnabotulinumtoxinA	Blepharospasm, cervical dystonia	Oculinum
Dysport	A	AbobotulinumtoxinA	Cervical dystonia	————
Xeomin	A	IncobotulinumtoxinA	Blepharospasm, cervical dystonia	NT201
Myobloc	B	RimabotulinumtoxinB	Cervical dystonia	Neurobloc
Hengli	A	Not available in US	Not available in US	Redux, Prosigne, CBTX-A
Meditoxin	A	Not available in US	Not available in US	Neuronox

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ptosis in myasthenia gravis mistaken for blepharospasm. Injection of inappropriate muscles or inadequate dosing can also contribute to primary or secondary therapeutic failure. Furthermore, a proportion of patients with classic, uncomplicated blepharospasm or torticollis may be primary nonresponders. In torticollis, different muscles may become involved over time and can lead to secondary therapeutic failure if not identified and injected.

Neutralizing antibodies to botulinum toxin may be seen in some nonresponders [29, 30]. Multiple factors contribute to the formation of antibodies including dose per treatment, frequency of injections, and total duration of treatment. One study reported neutralizing antibodies in 24 (4.3 %) of 559 cervical dystonia patients treated with Botox [29]. This value may be an underestimate since not all patients were screened for antibodies [29]. Risk factors for resistance to Botox were assessed in 76 cervical dystonia patients [29]. Eight (10 %) were resistant to botulinum toxin as determined by antibodies or lack of sternocleidomastoid (SCM) atrophy [29]. Compared to control subjects, resistant patients had greater frequency of injections, "booster" injections 2 to 3 weeks after injection and a larger dose of Botox per injection [29]. Another study tested for antibodies in 86 patients treated with Botox for cervical dystonia or oromandibular dystonia [30]. Sixty subjects were tested based on inadequate clinical response, four per patient request, and twenty-two were randomly selected [30]. Twenty (23 %) patients had antibodies; these nonresponders had earlier age of symptom onset, higher mean dose of Botox per injection, and higher cumulative dose of Botox over time compared to responders [30]. A study assessing antibodies in 100 cervical dystonia patients treated with Myobloc found antibodies in 31 (34 %) who did not have antibodies at baseline [31]. In this study, the formation of antibodies was associated with total cumulative dose of Myobloc [31].

Studies have investigated ways to overcome therapeutic failure [32–34]. One study examined whether a higher dose of botulinum toxin would overcome secondary therapeutic failure in eight patients with cervical dystonia and neutralizing antibodies [32]. High doses of Dysport did not improve clinical response in subjects with complete therapeutic failure

[32]; however, in one patient with partial therapeutic failure and low antibody titers, original benefit was obtained without side effects by quadrupling the dose of botulinum toxin [32]. Since antibodies are specific for toxin serotype, patients with therapeutic failure may respond when treated with another serotype [33]. One study evaluated the response to botulinum toxin F in 15 cervical dystonia patients resistant to Botox as indicated by neutralizing antibodies and lack of muscle atrophy [33]. In this study, 10 out of 15 patients had subjective improvement, and 11 out of 13 patients had muscle atrophy with the different toxin serotype [33]. In contrast, another study evaluated the clinical improvement with Myobloc in 10 patients who experienced therapeutic failure and developed type A antibodies [34]. Although all patients had improvement after the first dose, 6 out of 10 patients developed therapeutic failure after the second or third dose, and 5 patients tested positive for antibodies to serotype B [34]. Thus, switching serotypes can be tried in nonresponsive patients but may not be successful.

In 1997 a new batch of Botox was prepared which contains 5 ng of neurotoxin per 100 units compared to the original batch, which contained 25 ng of neurotoxin per 100 units. One study compared the frequency of antibody formation in 42 patients treated with the original Botox only versus 119 subjects treated with the current batch of Botox (all with inadequate response) [35]. Four (9.5 %) subjects treated with original toxin and none of the subjects treated with current toxin developed antibodies [35]. Xeomin, which is free of complexing proteins, may be less immunogenic than other formulations of botulinum toxin. In fact, a double-blind, placebo-controlled study evaluating Xeomin for the treatment of 148 patients with spasticity did not detect neutralizing antibodies after 20 weeks [36]. A further open-label extension of this study did not detect antibodies in 145 patients followed for an additional 69 weeks [37].

There are a few different tests to detect neutralizing antibodies, including the mouse bioassay, the mouse diaphragm assay, and an immunoprecipitation assay [38]. The mouse bioassay is an animal-based test that detects serum antibodies based on the survival of a mouse population [38].

This test only provides semiquantitative results and takes several days [38]. In contrast, the mouse diaphragm assay detects serum antibodies based on decrease of mouse hemidiaphragm force [39]. This test produces quantitative results in a few hours [39]. When the mouse diaphragm assay was compared to the mouse bioassay, the former was more sensitive [40]. The immunoprecipitation assay is not animal-based and detects antibodies based on radioactive labeling [41]. It also produces quantitative results in a few hours [41]. When the immunoprecipitation assay and mouse diaphragm assay were compared, there were concordant results in 82 % of samples tested [42]. The mouse diaphragm assay was more sensitive but mainly for detecting antibodies in subjects with low titers and partial nonresponse [42].

There are several patient-based tests to measure therapeutic failure that may correlate with the presence of antibodies. The simplest test to evaluate for therapeutic failure is to inject a test dose into the unilateral corrugator or frontalis and look for asymmetry in frowning or eyebrow elevation [43]. One study evaluated the sensitivity and sensitivity of eyebrow and forehead injections compared to clinical nonresponse in patients treated with Botox [43]. The sensitivity was 79 % versus 100 % and specificity was 90 % versus 83 % for eyebrow and forehead injections, respectively [43]. Another test is the extensor digitorum brevis test that involves measuring the CMAP of the peroneal nerve before and after injection of the extensor digitorum brevis [44]. One study utilized this test in 16 subjects with cervical dystonia who were secondary nonresponders to Dysport [44]. CMAP was significantly reduced 4 weeks after injection compared to baseline in all subjects who tested positive for antibodies [44]. Another patient-based test to evaluate for therapeutic failure is the SCM test [45]. This test involves EMG measurement of maximal voluntary contraction (M-EMG) of the SCM after injection of toxin [45]. The SCM test was evaluated in 17 cervical dystonia patients with secondary therapeutic failure [45]. The test was abnormal in all six patients who tested positive for antibodies, and normal in 10 out of 11 patients without antibodies [45]. The one patient with an abnormal test later developed antibodies [45]. Some have used injection of the SCM to examine lack of atrophy as an indicator of nonresponse as well. When assessing a nonresponder to botulinum toxin, re-evaluating the muscles involved and appropriate dosing are the initial steps. Confirming a patient's report of subjective nonresponse by examination 4 weeks after injection can provide useful information. A simple clinical test to look for immunoresistance such as the eyebrow elevation test mentioned above can be performed. As antibody assays are not readily available in clinical practice, testing for neutralizing antibodies is not routinely done at our center.

Treatment Indications in Movement Disorders

There are several movement disorders treated with botulinum toxin, some with US FDA approval and other off-label uses. We review a selection of the multiple studies evaluating botulinum toxin for the treatment of movement disorders (Table 2) [46••].

Blepharospasm

Blepharospasm was one of the first movement disorders to be treated with botulinum toxin. Two of the earliest studies were double-blind, placebo-controlled trials [47, 48]. One double-blind, placebo-controlled study evaluated Botox in nine subjects with blepharospasm [47]. After 14 injection series, all Botox patients significantly improved compared to baseline on the severity rating score, self-assessment score, and videotape evaluation [47]. In comparison, there was no significant benefit with placebo [47]. A multicenter, double-blind, placebo-controlled study assessed several doses of Dysport compared to placebo in 120 subjects with blepharospasm [49]. There was a statistically significant, dose-related improvement in spasm and functional disability compared to placebo [49]. Studies comparing formulations of botulinum toxin for the treatment of blepharospasm have also been conducted [50–52]. A randomized, double-blind study compared Botox and Dysport in 212 patients with blepharospasm [50]. The duration of benefit was similar in both groups but the rate of side effects was greater in the Dysport group, particularly ptosis [50]. The authors speculate that the higher incidence of side effects with Dysport was related to higher drug diffusability [50]. In contrast, a single-blind study comparing Dysport and Botox in 42 patients with blepharospasm demonstrated similar efficacy, mean duration of benefit, and side effect rate, with ptosis being the most common [51]. Xeomin was also compared with Botox in 300 patients with blepharospasm in a randomized, double-blind study [52]. Based on clinical ratings, Xeomin was noninferior to Botox [52]. Meditoxin was compared with Botox in 60 patients with blepharospasm in a double-blind study [53]. There was a significant reduction in spasm severity with both toxins, with no significant difference between groups [53]. There was also no significant difference in the rate of side effects [53]. A double-blind study compared Prosigne versus Botox in 21 patients with blepharospasm [54]. There was no significant difference between groups with regard to clinical benefit, duration of effect, or incidence of side effects [54]. Treating blepharospasm with botulinum toxin involves the injection of the orbicularis oculi surrounding the eyes (Fig. 1). The most common side effect is ptosis, which may be minimized by avoiding midline of the upper lid. Blepharospasm with apraxia of eyelid opening is more difficult to treat and may

Table 2 Botulinum toxin use in movement disorders

Condition	References of select studies	US FDA-approved indication	Main side effects
Blepharospasm	[46••, 47–53]	√	Ptosis
Hemifacial spasm	[50, 53–55]	√	Ptosis, facial weakness
Cervical dystonia	[56–64]	√	Dysphagia
Spasmodic dysphonia	[65–70]	X	Dysphagia, breathiness
Oromandibular dystonia	[71–73]	X	Dysphagia
Focal limb dystonia	[74–83]	X	Excess weakness
Tremor	[84–90]	X	Excess weakness
Tics	[91–95]	X	Excess weakness
Sialorrhea	[96–100]	X	Dry mouth, dysphagia

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require relatively larger doses. Treating blepharospasm may significantly improve a person's quality of life, allowing them to resume many activities of daily living.

Hemifacial Spasm

Hemifacial spasm is a cranial movement disorder that has been successfully treated with botulinum toxin. Muscles of the upper and lower face may be involved and injections are given accordingly (Fig. 1). Botulinum toxin has been shown to be an effective treatment for hemifacial spasm in several studies [51, 55, 56]. One particular placebo-controlled study evaluated Botox in 11 patients with hemifacial spasm [55]. There was subjective improvement after 23 (79 %) Botox injection sessions compared to 1 (11 %) with placebo injections [55]. Blinded clinical assessment demonstrated improvement after 84 % of Botox injections compared to 38 % of placebo injections [55]. Side effects (most commonly facial weakness) occurred in 97 % of those with Botox injections [55]; however, weakness was mild and was outweighed by

Fig. 1 Possible injection sites for blepharospasm and hemifacial spasm. *Black Circle* = blepharospasm. *Black Star* = hemifacial spasm. Number of injections and location will vary based on clinical examination

benefit [55]. Another study evaluated Botox in 101 patients with hemifacial spasm (93 open-label, 8 double-blind) [56]. Based on clinical evaluation, all patients in the open-label phase and 6 patients in the double-blind portion improved after the first injection [56]. Side effects were seen in 63.4 % of patients, with the two most common being dry eyes (19.8 %) and facial weakness (19.8 %) [56]. Dysport was compared to Botox in a single-blind study involving 49 subjects with hemifacial spasm and 42 subjects with blepharospasm [51]. The duration of effect and the percentage of patients requiring booster injections were similar in both groups [51]. Furthermore, the rate of side effects was similar in both groups (Dysport 50 %, Botox 47 %), with facial weakness and ptosis being the most common side effects in hemifacial spasm and blepharospasm, respectively [51]. A prospective, double-blind study comparing Prosigne and Botox in 36 subjects with hemifacial spasm found no significant difference in mean duration of benefit, efficacy based on clinical rating scale, and frequency of adverse effects [54]. As several muscles of the face may be involved in hemifacial spasm, selecting the most active muscles for injection is most helpful. Balancing therapeutic effect with the side effect of excess facial weakness is key. It should be noted that the dose per injection in hemifacial spasm is generally lower than that required by blepharospasm.

Cervical Dystonia

Treatment of cervical dystonia with botulinum toxin has been shown to be effective for improving abnormal postures of the neck and reducing associated pain. Depending on the abnormal movement (rotation, tilt, flexion, extension) a different combination of muscles may be involved and selected for injection (Fig. 2). There have been several studies evaluating different formulations of botulinum toxin for cervical dystonia [57–67]. One study compared Botox with placebo in 55 patients with cervical dystonia in a double-blind fashion as well as an open-label extension [57]. Compared to placebo, Botox significantly improved the severity of torticollis, degree

of head turn, pain, and disability [57]. A double-blind, placebo-controlled study evaluated Dysport in 116 subjects with cervical dystonia [62]. Subjects treated with 500 units of Dysport had significant clinical improvement compared to placebo at week 4 [62]. The rate of side effects was similar in both groups, with dysphagia (9 %) being the most common and only seen with Dysport [62]. Another study compared Dysport with trihexyphenidyl in 66 patients with cervical dystonia in a double-blind, randomized fashion [59]. Clinical improvement at 12 weeks was significantly greater with Dysport [59]. There was a greater frequency of side effects with trihexyphenidyl, the most common being dry mouth, forgetfulness, and fatigue [59]. Another study evaluated the efficacy of varying doses of Neurobloc compared to placebo in 109 patients with cervical dystonia in a double-blind fashion [58]. Subjects were treated with one of two doses of Neurobloc (5000 or 10,000 units) or placebo [58]. Both doses of Neurobloc had significant clinical improvement compared to placebo [58]. Drug-related adverse events were most common in the 10,000-unit group, mainly dry mouth and dysphagia. [58]. A similar study was completed in type A resistant patients with similar results [61]. A double-blind, placebo-controlled trial of Xeomin for 233 subjects with torticollis showed significant clinical improvement with Xeomin compared to placebo at week 4 [64]. The most common side effects were mild dysphagia, neck weakness, and neck pain [64]. A double-blind study compared Botox versus Dysport in 73 patients

with cervical dystonia [64]. Subjected were treated with a ratio of Dysport versus Botox of 3:1 [65]. The improvement in clinical rating score was similar at 2 weeks post treatment and the duration of benefit was similar in both groups [65]. Furthermore, the frequency of side effects was similar in both groups [65]. A multicenter, double-blind study compared Botox with Myobloc in 139 subjects with cervical dystonia and followed them for 20 weeks [66]. At 4 weeks post-injection, the improvement in clinical rating scores was not significantly different between groups [66]. Of those who demonstrated improvement, duration of benefit was slightly longer in the Botox versus Myobloc group (14 vs 12.1 weeks) [66]. Dysphagia and dry mouth were more frequent in the Myobloc (48 % and 80 %) compared to the Botox group (19 % and 41 %) [66]. Another randomized, double-blind noninferiority trial compared Botox with Myobloc in 111 cervical dystonia patients [67]. At 4 weeks post-injection, Myobloc was not inferior to Botox based on clinical evaluation [67]. There was no significant difference in the median duration of effect, nor in the incidence of dysphagia or injection site pain [67]. Mild, but not moderate or severe, dry mouth was more frequent with Myobloc than Botox [67].

Spasmodic Dysphonia

Spasmodic dysphonia refers to dystonia of the larynx. Adductor spasmodic dysphonia is characterized by a strangulated

Fig. 2 *Black Triangle* Possible injection sites for torticollis. Number of injections and location will vary based on clinical examination
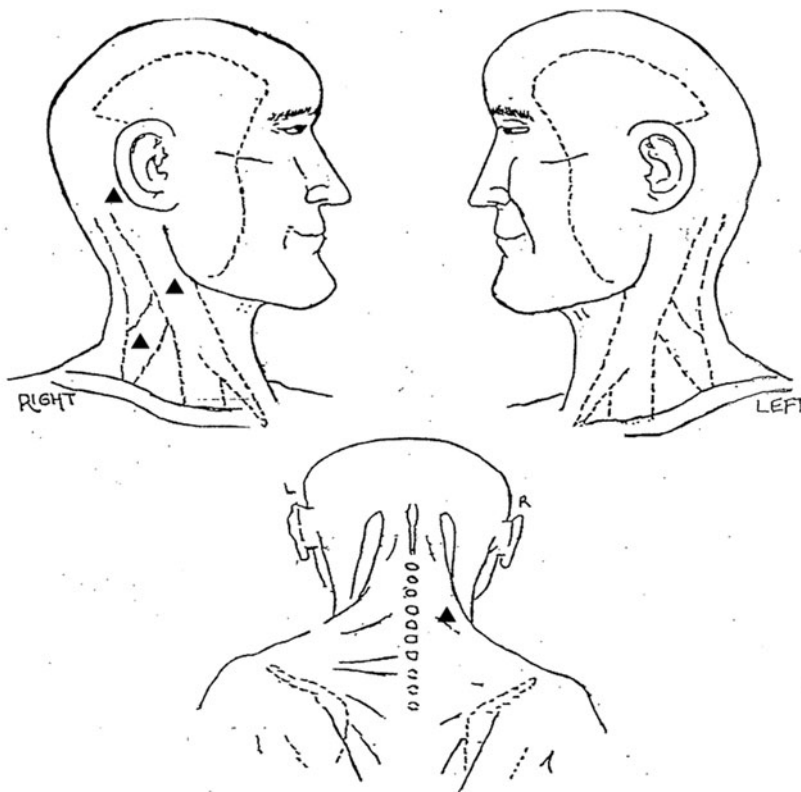
voice; abductor dysphonia by a breathy voice quality. Abductor spasmodic dysphonia is less common than adductor and less successfully treated. For adductor spasmodic dysphonia, the thyroarytenoid muscles are commonly injected; the posterior cricoarytenoid is commonly injected for abductor spasmodic dysphonia. Several studies, including double-blind, placebo-controlled trials, have demonstrated the efficacy of botulinum toxin for spasmodic dysphonia [68–70]. A double-blind study compared Botox versus placebo in 13 subjects with adductor spasmodic dysphonia [70]. Compared to baseline, at 4 days post-injection, there was significant improvement with Botox based on patient report, clinical evaluation, and objective voice analysis [70]. In the Botox group, two subjects had breathiness of voice and one had mild bleeding as a side effect [70]. One subject in the placebo group had vocal cord edema [70]. An open-label study evaluated the safety and efficacy of Myobloc in 13 subjects with adductor spasmodic dysphonia [71]. Subjects were injected with 1 of 3 doses of Myobloc: 50, 100, or 200 units [71]. At 8 weeks post-injection, a greater proportion of subjects receiving Myobloc 200 units showed improvement based on patient rating and blinded video assessment [71]. Side effects included breathiness (4 patients) and vocal cord discomfort (3 patients) [71]. An open-label study evaluated Botox in 18 subjects with abductor spasmodic dysphonia using an asymmetric dose escalation protocol [72]. Fourteen out of 18 subjects had subjective improvement in dysphonia [72]. A review of 901 patients with spasmodic dysphonia treated with Botox for over 12 years reported an average improvement of 55 % of normal function in adductor spasmodic dysphonia patients, and an average of 37.3 % improvement in abductor spasmodic dysphonia [72]. Side effects were mild coughing with fluids (35 %) and breathiness (21 %) in adductor spasmodic dysphonia patients, and exertional stridor (3 %) and dysphagia (6 %) in abductor spasmodic dysphonia patients [72].

Oromandibular Dystonia

Oromandibular dystonia includes dystonia of the jaw (opening, closing, lateral deviation), lips, and tongue (mostly protrusion). Treatment of oromandibular dystonia with botulinum toxin can improve speech and chewing. There are few studies evaluating this approach for oromandibular dystonia [74–76]. An open-label study evaluated Botox for the treatment of oromandibular dystonia in 62 subjects with jaw/mouth opening, closing, or deviation [75]. Injected muscles included masseters, submental, temporalis, and pterygoids. Over 73 % of subjects had a favorable response based on a global rating scale [75]. Side effects occurred in 37 % of injections, most commonly dysphagia [75]. Another study reported long-term follow-up in 162 subjects treated with Botox for oromandibular dystonia (>1/2 with jaw-closing dystonia) with mean follow-up of 4.4±3.8 years [76]. On a scale of 0–4

(4 = complete resolution) the mean clinical effect of Botox was 3.1±1.0, with the best response in jaw-closing dystonia [76]. Adverse effects, including dysphagia and dysarthria, were seen in 11.1 % of all injections [76]. There is also some open-label experience with genioglossus injection of low-dose Botox for lingual protrusion dystonia that demonstrates efficacy [77]. Nine subjects with lingual protrusion dystonia were injected with Botox into the genioglossus muscle (mean dose 13.3.units per side) [77]. A moderate to marked improvement in lingual protrusion was achieved in five patients [77]. Out of 89 injections, severe dysphagia requiring a temporary feeding tube occurred once after one set of injections into the genioglossus and lateral pterygoid [77].

Focal Limb Dystonia

Focal limb dystonia such as writer's cramp and musician's dystonia can be treated effectively with botulinum toxin, avoiding systemic side effects of oral medications. Several studies, including double-blind trials, have reported the benefit of botulinum toxin for focal limb dystonia [78–83]. One double-blind study compared Dysport with placebo in 40 patients with writer's cramp [78]. There was a greater improvement on most clinical rating scales in the Dysport group, and a significantly higher proportion of patients treated with Dysport decided to continue treatment [78]. The most common side effect was mild, transient hand weakness [78]. The largest retrospective study, with the longest follow-up of focal hand dystonia, described 20 subjects treated with botulinum toxin for ≥10 years [83]. Nearly all subjects were treated with Botox (one injection was Myobloc) and all with EMG guidance [83]. Based on patient rating scales after injections, 11/20 subjects reported mild benefit and 9/20 subjects had mild weakness [83]. There was a trend for greater benefit in women and in subjects with shorter intervals between injections [83]. No subjects developed toxin immunity during follow-up [83]. A retrospective study evaluated botulinum toxin treatment in 88 musicians with hand or embouchure dystonia [84]. After the injection of Dysport with EMG guidance, 69 % of musicians had subjective improvement in their performance, with 43 % reporting an obvious improvement in performance (ie, advancement of orchestra position) [84]. Botulinum toxin can also be helpful for patients with Parkinson disease and painful focal dystonia. An open-label study evaluated Botox in 32 subjects with Parkinson disease and painful dystonia during the "off" period [85]. All patients reported an improvement in pain within 10 days, and 21 subjects had complete resolution of pain for 4 months [85]. Furthermore, there was also a significant decrease in disability due to dystonia [85].

Botulinum toxin injections may be guided by tools to help localize muscles; this may be particularly useful in the

limbs that have numerous target muscles of varying depths. Studies have evaluated the utility of using EMG guidance and electrical stimulation for the localization of muscles prior to injection [86, 87]. One study looked at the accuracy of botulinum toxin injections based on palpation and surface landmarks in 14 patients with focal hand dystonia [87]. When the location of the needle was verified with EMG, only 37 % (14/38) of injections were in the intended muscle or fascicle [87]. Forty percent of injections (18/38) were in another muscle or fascicle, and 16 % (6/38) were completely outside of muscle [87]. One study compared targeting of muscles by EMG guidance versus electrical stimulation in 12 patients with focal hand dystonia [86]. Four out of eight subjects injected with EMG guidance had weakness of the target muscle and three out of four subjects injected with the aid of electrical stimulation had target muscle weakness [86]. This small study suggests that EMG and electrical stimulation may have similar accuracy for localizing target muscles [86]. Electrical stimulation may be advantageous in patients who are unable to isolate a specific muscle for voluntary contraction [86]. When electrical stimulation activates motor axons in addition to muscle fibers, leading to contraction of several muscles, EMG may be preferable for muscle localization [86].

Tremor

Botulinum toxin may be helpful for medication-resistant tremors of varied etiology. As tremor may involve many parts of the body, selection of one area with the most prominent tremor is most beneficial. Two randomized, placebo-controlled trials assessed the efficacy of botulinum toxin for tremor [88, 89]. One study included 25 subjects with essential tremor and injected the flexor and extensor muscles of the dominant hand with Botox [88]. Four weeks post-injection there was significant clinical benefit with Botox compared to placebo [88]. At weeks 4 to 8, a ≥30 % reduction in mean postural tremor amplitude measured by accelerometry was seen in a greater proportion of Botox subjects [88]. Transient finger weakness was present in all patients, although not disabling [88]. Another double-blind trial compared Botox with placebo in 133 essential tremor subjects [89]. Flexor and extensor arm muscles were injected with Botox 50 units, 100 units, or placebo and followed for 4 months [86]. There was significant clinical improvement in postural tremor with both doses compared to placebo at weeks 6, 12, and 16 [89]. Meanwhile, kinetic tremor only had significant clinical improvement with Botox at week 6 [89]. Mild subjective improvement was only reported at week 6 compared to none with placebo [89]. There were mixed results for motor function and disability scores [89].

Open-label studies have also demonstrated benefit of botulinum toxin A for voice tremor [90, 91]. One study showed significant benefit with three doses (1.25, 2.5, and 3.75 units) of bilateral vocal cord injections in 13 subjects with voice tremor [91]. There was significant improvement in tremor severity as evaluated by blinded raters as well as decreased functional disability [91]. Voice breathiness and dysphagia were the most common side effects [91].

Studies evaluating botulinum toxin for head tremor have produced mixed results [92, 93]. A double-blind, placebo-controlled, crossover study evaluated botulinum toxin in 10 subjects with essential head tremor [93]. While there was clinical and subjective improvement that favored toxin-treated patients, these differences were not significant [93]. Objective measures by accelerometry were also not statistically different between groups [93]. This study may have been limited by a small sample size [93]. An open-label study evaluated the efficacy of Dysport in 14 subjects with essential head tremor and 29 subjects with dystonic head tremor [92]. Two to three weeks post-injection, there was significant clinical improvement in both groups and a significant decrease in tremor amplitude as measured by accelerometry [92]. Furthermore, all patients with essential head tremor and 26 patients with dystonic head tremor had significant subjective improvement and less pain [92]. Another cranial tremor that may benefit from botulinum toxin is jaw tremor as reported in three patients with Parkinson disease [94]. After EMG demonstration of muscle activity in the masseter and digastric muscles, Dysport (average 53 units) was injected into bilateral masseters [94]. There was subjective and clinical improvement documented by video assessment 4 to 9 weeks after injection without side effects [94].

Tics

Tics may also benefit from botulinum toxin injections [96–99]. When medications are ineffective or cause intolerable side effects, botulinum toxin may be used to treat the most bothersome focal tics. There is one double-blind, placebo-controlled, crossover trial evaluating Botox in 18 subjects with simple motor tics [96]. The median relative change in treated tics per minute was significantly greater with Botox as was the average change in urge scores [96]. An open-label study evaluated Botox for the treatment of phonic tics in 30 subjects [97]. After an injection of 2.5 units of Botox in both vocal cords, 28 (94 %) subjects noted an improvement and 15 (50 %) had resolution [97]. The only side effect was hypophonia in 24 (80 %) subjects, and this side effect lasted 10± 3 days [97]. There are also reports of botulinum toxin injections of the vocal cords improving coprolalia with a decrease in premonitory urge [98, 99]. Thus, botulinum toxin may improve motor and phonic tics; treating simple motor tics (ie, eye blinking, head turning) that are most troublesome for the patient may provide the most benefit.

Sialorrhea

Botulinum toxin can effectively treat sialorrhea (drooling) in patients with Parkinson disease, avoiding systemic side effects of oral medications. Double-blind, placebo-controlled trials have demonstrated the efficacy of both botulinum toxin A and botulinum toxin B for sialorrhea compared to placebo [99–103]. Side effects included dry mouth and mild dysphagia. A double-blind, placebo-controlled, crossover study compared Dysport with Neurobloc in 27 patients with sialorrhea [104]. Fifteen patients had amyotrophic lateral sclerosis (ALS) and 12 had Parkinson disease; only 14 subjects completed the study [104]. The total dose was Dysport 250 units or Neurobloc 2500 units injected into bilateral submandibular and parotid glands with ultrasound guidance [104]. Subjective and objective measures of sialorrhea were similar in both groups as was duration of benefit; however, time to onset of benefit was shorter with Neurobloc [104]. There was no significant difference in side effects between groups [104]. At our center, botulinum toxin type B is generally used to treat sialorrhea since type B produces greater autonomic side effects compared to A. This can be used for Parkinson disease, atypical parkinsonism, and as show in one of the above discussed studies, ALS.

Conclusions

Key benefits of botulinum toxin injection in movement disorders include its localized effect with similarly localized, reversible side effects. Therapeutic failure may be an issue for some patients, especially those with anterocollis, tremor, and abductor spasmodic dysphonia. Failure may be due to incorrect diagnosis, incorrect location of injections, incorrect doses, and side effects overshadowing response. Secondary resistance to botulinum toxin may be decreased by using the smallest effective dose and the longest inter-injection interval possible. Switching to another serotype may also be successful in patients with therapeutic failure with one type of toxin. Botulinum toxin is an effective treatment for several movement disorders. While many conditions are not approved indications, botulinum toxin may be considered in patients with disabling symptoms, unresponsive to other conventional therapies.

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