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REVIEW

Patient considerations in the treatment of cervical dystonia: focus on botulinum toxin type A

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Abstract: Cervical dystonia is the most common form of focal dystonia characterized by involuntary muscle contractions causing abnormal movements and posturing of the head and neck and is associated with significant pain. Botulinum toxin is considered first-line therapy in the treatment of pain and abnormal head posturing associated with cervical dystonia. There are currently three botulinum toxin type A neurotoxins and one botulinum type B neurotoxin commercially available and US Food and Drug Administration (FDA) labeled for the treatment of cervical dystonia. This review will focus on the efficacy, safety, and therapeutic use of botulinum type A neurotoxins in the treatment of cervical dystonia. We conclude with a discussion of factors influencing toxin selection including therapeutic effect, duration of effect, side effect profile, cost, and physician preference.

Keywords: spasmodic torticollis, neurotoxin, pain, onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA

Introduction

Dystonia is classified as a movement disorder characterized by sustained or intermittent, involuntary muscle contractions causing twisting, repetitive movements, or abnormal postures.[1–3] Dystonia can be focal (affect a specific area of the body), segmental (spread to two or more adjacent body regions), multifocal (involving two or more noncontiguous body regions), or generalized (involving a majority of the body). The multiple etiologies of dystonia include inherited (or genetic in origin), acquired (or due to a known cause), and idiopathic (or unknown cause).[3] Focal dystonia is the most common form of dystonia and can involve any body part including the neck (cervical dystonia [CD]), limbs (limb dystonia), hands (focal hand dystonia), eyes (blepharospasm), mouth (oromandibular dystonia), or trunk (camptocormia).[2]

CD

CD, also known as spasmodic torticollis, is the most common form of focal dystonia resulting from involuntary contractions of muscles in the neck and shoulders. The prevalence of CD in the United States is estimated to be around 400 per 100,000,[4] and it is estimated that approximately 89 per million people worldwide are living with CD.[5] CD is slightly more common in females, with a male-to-female ratio of 1 to 1.2.[6] CD can occur in patients of all ages; however, the peak age of onset is around 41.8 years.[6] Most cases of CD are idiopathic and there is a family history in about 12% of cases.[7] CD can also be secondary to trauma or musculoskeletal, spinal cord, intracranial, ocular, and vestibular disorders.[8]

CD is characterized by abnormal posturing of the head and neck in the form of tilting, flexion, or extension movements of the head combined with elevation or anterior

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placement of the shoulders.[9] CD may present as a sustained posture, spasm, jerks, or tremor. CD is classified into four types according to the dominant head position or movement. Simple rotary torticollis (abnormal rotation of the head in the horizontal plane) is the most common type.[10] Other complex patterns include laterocollis (tilt in a coronal plane toward one shoulder), retrocollis (head pulls back with the neck hyperextended), and anterocollis (head pulls forward with neck flexion).[10]

Based on a review of 300 patients with CD, the most common muscles involved include the sternocleidomastoid (78%), trapezius (67%), splenius capitis (57%), scalenus (8%), and platysma (6%).[7] Although simple rotary torticollis, the most common dystonic posture in CD, typically involves the sternocleidomastoid, splenius capitis, and the obliquus capitis muscles, there may also be involvement of the levator scapulae muscles.[11] In one study of polymyographic recordings in patients with CD, a dystonic pattern was seen in the ipsilateral levator scapulae in up to 30% of patients with simple rotary torticollis.[12]

Patients with CD characteristically have a variety of sensory tricks, also referred to as geste antagoniste, that serve to alleviate the dystonic posture or help to correct the abnormal movement by touching the lower face, chin, or neck with the hand ipsilateral to the abnormal posture.[13] In a study of 154 patients with CD, 89.6% reported the use of sensory tricks and 83% of those patients noted partial or marked improvement with the use of these alleviating maneuvers.[13]

Common pitfalls in diagnosis

Underdiagnosis of CD is a significant problem as there is no standard diagnostic test for CD and the recognition of CD in the medical community is poor. In a review of 300 patients with CD, the average number of physicians consulted for neck symptoms prior to their first visit to a movement disorder specialist was 6.8.[7] Misdiagnosis was encountered in 87 patients (29%) and, of those patients, 37% were diagnosed with arthritis or other vertebral abnormality, 24% were thought to have a psychiatric cause, 9% were diagnosed with Parkinson's disease, 9% with temporal mandibular joint syndrome, and 21% were classified as having other miscellaneous conditions.[7] Although CD is the most common form of dystonia, it can take up to 44 months and visits to multiple medical providers before proper diagnosis and treatment is received. In one study, a total of 108 patients saw a mean of 3.5 providers over a mean period of 44 months from symptom onset to diagnosis.[14]

In a study evaluating the pattern of muscle involvement in CD determined by clinical evaluation versus the use of polymyographic electromyography (pEMG), it was found that, without the use of EMG mapping, 41% of dystonic muscles would not be identified and 25% of inactive muscles would be recognized as dystonic.[15] This study found that the sensitivity of clinical examination was 59% and the specificity was 75%.[15] The authors concluded that physical examination alone is not sufficient in detecting the muscles involved in CD and the use of pEMG guidance can improve proper muscle selection that can aid in the treatment of CD.[15]

In a systematic review of muscle selection for the treatment of CD with botulinum toxin (BoNT), the authors concluded that pEMG reveals a different pattern of muscle involvement compared to clinical evaluations in CD patients and recommend the use of pEMG to help improve the treatment response to BoNT.[11] This review also identifies two prospective studies using positron emission tomography (PET)/computed tomography (CT) imaging as a method of selecting dystonic muscles and CT or ultrasound guidance for the injection of deep cervical muscles adjacent to important structures.[11] Both studies achieved a positive response rate and concluded PET/CT imaging and image-guided injections with CT or ultrasound were superior to the use of physical examination or pEMG.[11] However, neither study used a control group in which muscles were selected without PET/CT imaging in order to provide a comparison. Therefore, further studies are needed to evaluate the value of these newer imaging techniques in the identification of dystonic muscles in patients with CD and effect on treatment response to BoNT.

Complications of CD

Neck or shoulder pain is present in up to 70% of patients.[10] Pain is usually described as diffuse and can be intermittent or continuous. CD can affect a patient's ability to work and can be severely disabling. Psychiatric comorbidity as well as a higher incidence of anxiety and depression is commonly identified in patients with CD compared to normal controls.[16,17] The health-related quality of life has also been demonstrated to be significantly lower in patients with CD compared to the general population.[16] Although spontaneous remissions of CD have been reported, in the majority of cases, CD is a lifelong disorder that waxes and wanes in severity and in some cases may progress to segmental or generalized dystonia.[9]

Treatments for CD

Intramuscular injections of BoNT into involved dystonic muscles is effective in alleviating symptoms of CD and is considered first-line treatment. Several studies have confirmed the long-term efficacy and safety of BoNT use for dystonia.[18,19] Potential side effects of BoNT use include

muscle weakness, dysphagia, local bruising, dry mouth, and flu-like symptoms.

Oral medications may be used as adjunctive therapy to BoNT injection for symptomatic relief and include anticholinergic agents, baclofen, muscle relaxants, and benzodiazepines. However, these medications are often of limited benefit due to systemic side effects. Surgical treatments for dystonia refractory to medications and BoNT therapies include deep brain stimulation (DBS) and selective peripheral denervation. DBS with electrodes placed in the globus pallidus interna has been effective in the treatment of generalized dystonia; however, there have been inconsistent results with the use of DBS for CD.[20] Potential side effects of globus pallidus interna stimulation include speech abnormalities, paresthesias, and incoordination.[20] Several case series report the effectiveness of selective peripheral denervation surgery in patients with BoNT-resistant CD.[21–23] Side effects reported included dysphagia and reinnervation leading to recurrence of symptoms.[23]

In a review of the effectiveness of physiotherapy alone or added on to BoNT injections for CD, there is evidence to suggest that a multimodal physiotherapy program in addition to BoNT therapy may improve head position, decrease pain levels, and improve functioning in everyday activities for the short term.[24,25] A multimodal physiotherapy program can consist of active exercises, stretching, massage, relaxation, active and passive mobilization of the cervical spine, EMG biofeedback, or electrical stimulation of antagonist muscles.[24] Further high-quality studies are needed to confirm the effectiveness of physiotherapy and the type of physiotherapy program most beneficial in the treatment of CD.

The character, severity, and response to treatment in patients with CD can be assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) or the Tsui scale. The TWSTRS (range, 0 to 85) is composed of three subscales that grade severity of CD (range, 0 to 35), disability (range, 0 to 30), and pain (range, 0 to 20).[8] The Tsui scale (range, 0 to 25) grades the severity of postural deviance and highlights the presence or absence of head tremor in addition to evaluation of the movement as continuous or intermittent.[8] The TWSTRS is considered a recommended scale for the assessment of CD based on a review by the Movement Disorder Society Task Force on Rating Scales.[26]

BoNT

The most potent neurotoxin known is released by the bacterium *Clostridium botulinum* and is responsible for causing botulism. There are seven different serotypes of *C. botulinum* (A–G), but only the serotypes A, B, and E cause human botulism via colonization of the lower gastrointestinal tract after ingestion of contaminated food. Botulism can present as muscle weakness, paralysis, dysarthria, dysphagia, constipation, and urinary retention. Death can occur in up to 10%–25% of cases.[27]

The earliest historical records of botulism date back to the 18th century, to Justinus Kerner, a German physician, poet, and philosopher who published detailed and accurate descriptions of symptoms of botulism from 1817–1822, which he attributed to "sausage poisoning." Although he did not define the causative agent, he was credited with recognizing the potential therapeutic use of "sausage poison" to block hyperexcitability of the motor and autonomic nervous system.[27,28] In 1897, Emile Pierre van Ermengem described the pathogen *C. botulinum* after discovering the pathogen was a bacterium and isolating the anaerobic microorganism in food and human tissue.[28]

BoNT inhibits the release of acetylcholine (ACh) at the neuromuscular junction, thereby blocking neuromuscular conduction and muscle contraction. The normal release of ACh at the neuromuscular junction occurs through the formation of the synaptic fusion complex of ACh vesicles bound to the presynaptic membrane by soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins. SNARE proteins form a trans complex of three proteins including syntaxin 1, synaptosomal-associated protein 25 (SNAP-25), and synaptobrevin which mediate the docking and exocytosis of ACh vesicles at the presynaptic nerve terminal. The mechanism of action of the various serotypes of BoNT are similar in that all cleave the SNARE proteins; however, BoNT A, C, and E cleave SNAP-25 and BoNT B, D, F, and G cleave synaptobrevin.[29]

Formulations of BoNT

The US Food and Drug Administration (FDA) approved BoNT type A and B for the treatment of CD in 2000. There are currently four neurotoxin products approved for therapeutic use in CD in the US (Table 1). The type A formulations include: onabotulinumtoxinA (Botox; Allergan, Inc., Irvine, CA, USA), abobotulinumtoxinA (Dysport; Ipsen Ltd, Slough, UK), and incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Greensboro, NC, USA). The one available BoNT type B is rimabotulinumtoxinB (Myobloc; Solstice Neurosciences, LLC, a subsidiary of US WorldMeds, LLC, Louisville, KY, USA). Each neurotoxin product has it own unique characteristics based on molecular weight, complexing proteins, onset of action, and diffusing properties. Therefore, it is important to note that these agents are not therapeutically interchangeable.[2] These differences among

Table 1 Types of botulinum toxin

Nonproprietary name	Type	Molecular weight	SNARE target	Company name	Trade name
OnabotulinumtoxinA	A	900 kDa	SNAP-25	Allergan, Inc., Irvine, CA, USA	Botox
AbobotulinumtoxinA	A	500–900 kDa	SNAP-25	Ipsen Ltd, Slough, UK	Dysport
IncobotulinumtoxinA	A	150 kDa	SNAP-25	Merz Pharmaceuticals, Greensboro, NC, USA	Xeomin
RimabotulinumtoxinB	B	700 kDa	Synaptobrevin	Solstice Neurosciences, LLC, a subsidiary of US WorldMeds, LLC, Louisville, KY, USA	Myobloc

Abbreviations: SNAP, synaptosomal-associated protein 25; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor.

the various neurotoxins may also contribute to the clinical differences observed in the prevalence rates of adverse side effects between the various formulations of BoNT. The most common side effects reported in BoNT treatment for CD include dysphagia, neck muscle weakness, hoarseness, and dry mouth.[19]

BoNT is considered the most effective treatment for CD. Based on the results of eight double-blind, randomized controlled clinical trials meeting the criteria for Class I studies, the efficacy and safety of BoNT type A and B for treatment of CD has been established.[30,31] These studies provided level A evidence supporting all four types of BoNT for the treatment of CD.[30,31] However, the dosing equivalency between the four brands of neurotoxin have not been well established and there is a need for more controlled randomized comparative trials.

In this review, we will discuss the use of BoNT type A therapy for CD. The injection technique, preparation, and dosage of each type of BoNT will not be described as this is beyond the scope of this publication.

OnabotulinumtoxinA efficacy

In one of the initial clinical trials evaluating the effectiveness of BoNT for the treatment of CD, the use of onabotulinumtoxinA for CD produced both subjective and objective improvements, including significant pain relief.[32] No serious adverse events were noted and side effects were minimal.[32]

Various clinical trials have since confirmed the efficacy of onabotulinumtoxinA for the treatment of CD.[33–36] In a double-blind, placebo-controlled trial of BoNT for the treatment of CD, onabotulinumtoxinA produced significant improvement in the severity of torticollis, disability, pain, and degree of head turning at rest. No serious side effects were reported. During the double-blind phase, 61% of treated patients improved and 74% of patients improved during a following open-label phase at a higher dose of onabotulinumtoxinA.[33]

In a systematic review of 36 randomized controlled trials, comprising 1,425 subjects who received treatment with onabotulinumtoxinA for a variety of conditions, mild-to-moderate adverse events were reported at a rate of approximately 25% in the onabotulinumtoxinA-treated group compared to 15% in the control group. Focal weakness was the most common adverse event reported in the onabotulinumtoxinA-treated group, and no serious severe adverse events were reported.[2,37]

The original onabotulinumtoxinA formulation had a slightly higher neurotoxin complex protein load than the current onabotulinumtoxinA; however, both are produced by the same strain of *C. botulinum* and have the same formulation. In a systematic review of the various formulations of BoNT type A, the dysphagia rate was significantly lower with the current onabotulinumtoxinA formulation compared with the original formulation, at 3.4% versus 7.1%, respectively.[38] Thus, several clinical trials have established the safety as well as effectiveness of onabotulinumtoxinA for improving head posture and pain in the treatment of CD.

AbobotulinumtoxinA efficacy

Several clinical studies provide evidence for the efficacy of abobotulinumtoxinA treatment in CD based on results showing significant improvement in disease severity scores.[6,39–42] In a randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of abobotulinumtoxinA for the treatment of CD, abobotulinumtoxinA produced a significant decrease in mean TWSTRS total scores compared with placebo at week 4 (primary efficacy endpoint) with significant improvements sustained to week 12.[39] Significant improvements were also seen in TWSTRS subscales, visual analog scale for pain, and subject's/investigator's visual analog scale symptom assessments compared to placebo.[39] Improvements were also seen during the open-label treatment in mean TWSTRS total and subscale scores at week 4 post-treatment in all treatment cycles.[39] Treatment-related adverse events were mild and similar between abobotulinumtoxinA and placebo groups, at 47% versus 44%, respectively.[39] The most common adverse event with abobotulinumtoxinA was dysphagia that did not appear to be dose- or treatment cycle-related.[39] This study provided evidence in support of the safety, tolerability, and efficacy of abobotulinumtoxinA for the treatment of CD.

IncobotulinumtoxinA efficacy

IncobotulinumtoxinA differs from the other formulations of BoNT type A in that it does not have accessory proteins. It has not been established at this time if the absence of accessory proteins confers any unique properties to the therapeutic use of BoNT. IncobotulinumtoxinA has been shown to be noninferior to onabotulinumtoxinA in the treatment of CD, with no difference seen between the two formulations in safety, efficacy, onset of action, and duration of effect.[2,43]

In a prospective, double-blind, placebo-controlled trial of 233 patients with CD who were randomized to receive either 120 units or 240 units of incobotulinumtoxinA or placebo, active treatment with either dose of incobotulinumtoxinA resulted in a significant improvement in total TWSTRS score after 4 weeks compared to placebo.[44] Adverse events occurred at a frequency of 41.9% in the placebo group, 56.4% in the 120-unit group, and 55.6% in the 240-unit group.[44] The most frequently reported adverse events in the incobotulinumtoxinA groups were dysphagia, neck pain, and muscle weakness which were usually mild.[44] Therefore, incobotulinumtoxinA has been shown to be noninferior, safe, and effective in the treatment of CD compared to onabotulinumtoxinA.

Side effect profile

Dysphagia is the most common treatment-related side effect seen with BoNT type A treatment for CD. In a systematic review of the various preparations of BoNT in the treatment of CD, a significantly higher rate of dysphagia and positive dose-related effect was reported with abobotulinumtoxinA compared with the current formulation of onabotulinumtoxinA or rimabotulinumtoxinB.[38] Dry mouth was reported more frequently in the studies of rimabotulinumtoxinB compared to the formulations of BoNT type A; however, a dose-related effect was not seen with rimabotulinumtoxinB.[38]

This finding was also seen in a randomized, double-blind study comparing BoNT type A and B for the treatment of CD that found a prevalence of dry mouth in 80% of patients treated with rimabotulinumtoxinB versus 41% treated with onabotulinumtoxinA.[45] Flu-like symptoms have been reported in 1.7%–20% of patients treated with BoNT type A and in 5%–55% of patients treated with BoNT type B.[46] It is possible that the increased frequency of flu-like symptoms seen in BoNT type B could be due to the higher antigenicity seen with BoNT type B compared to type A, although this theory has not been proven. Although previously thought that immunogenicity was a major factor of nonresponsiveness to BoNT treatment, more often a lack of response may be due to other factors including inadequate dosing or incorrect muscle selection.[19] Given the evidence of increased rates of dysphagia with higher doses of abobotulinumtoxinA compared to onabotulinumtoxinA, more head-to-head trials with all three formulations of BoNT type A are needed to further establish tolerability and side effect profiles, as these differences may have safety implications.

Duration of effect

There is no consensus on duration of effect of the various BoNT neurotoxins in the treatment of CD. The injection interval of BoNT for the treatment of CD is typically 3–4 months in most clinical practices.[47] Due to the temporary effect of BoNT and the need for regular administration of BoNT to maintain clinical benefit, a longer duration of effect would decrease the frequency of repeat injections which would benefit patients by decreasing co-pay costs and the overall health care system by reducing health care cost utilization.[47] Although higher doses of BoNT are generally considered to provide longer duration of clinical benefit, there is no consistent data to confirm the dose–response relationship and the duration of effect of BoNT.[47]

In a comparative study of BoNT preparations for the treatment of CD, a significant difference in overall duration of effect was seen between the various groups with a mean duration of 104.3 days for the current formulation of onabotulinumtoxinA, 75.7 days for abobotulinumtoxinA, and 91.2 days for rimabotulinumtoxinB.[38] However, the duration of effect was not defined in many of the studies, and those in which it was used differing definitions, while some studies did not report this variable, thus the authors suggest caution with interpreting these results.[38]

In a study of incobotulinumtoxinA for the treatment of CD comparing two treatment doses of 120 units and 240 units versus placebo, both doses showed improvement versus placebo, but the trial was not designed to show improved efficacy or duration of effect with the higher dose.[44] In another study, examining the efficacy and safety of abobotulinumtoxinA at doses of 250, 500, and 1,000 units, there were improved benefits seen with both the 500- and 1,000-unit doses compared to the 250-unit dose and placebo.[40] The mean duration of effect seemed to be longer and greater in the 1,000-unit group, although significantly more adverse events were noted.[40] The measure of duration of effect was determined indirectly and the differences observed were not statistically significant.

In a systematic review of studies reporting the duration of effect of onabotulinumtoxinA in the treatment of CD,

among the 18 studies that were analyzed, the mean duration of effect was 13.2 to 13.5 weeks in the patients treated with onabotulinumtoxinA.[47] Higher doses of onabotulinumtoxinA were associated with a longer duration of effect with doses greater than 180 units at 15.3 weeks compared to doses less than 180 units at 12.5 weeks.[47] However, the results of this study are limited due to the non-standardization of the definition of duration of effect between the various studies included in the meta-analysis.[47]

Cost-effectiveness

Data on health-related quality of life, treatment costs, and labor participation of patients with focal dystonia are limited and there are no current studies analyzing the cost–benefit ratio of BoNT use for CD in the US. Further studies are needed to determine the cost-effectiveness of BoNT therapy for CD in the US.[48]

BoNT selection

BoNT neurotoxin products differ in molecular uniformity, weight, and size of their toxin complexes, resulting in the uniqueness of each formulation of BoNT type A. These differences potentially affect their diffusion properties, adverse event profiles, therapeutic effect, and dosing.

When selecting the type of BoNT to use in the treatment of CD, the side effect profile, duration of effect, and cost of each toxin may likely play a role. These factors may also have implications for health management and reimbursement organizations in making decisions about cost-effectiveness and the economic comparability of the various toxins. Physician preferences based on an individual's experience with a particular type of BoNT may also play a role in toxin selection. In our clinical experience, third-party reimbursement and cost to the patient is one of the most important considerations when selecting a BoNT. Cost can be a limiting step to access to treatment for patients with CD.

Conclusion

BoNT is considered the treatment of choice for CD. There are three BoNT type A formulations that are currently approved and each has its own unique pharmacologic properties that may confer different side effect profiles, duration of therapeutic effects, and dosing recommendations. Challenging issues in the management of CD include underdiagnosis due to poor recognition of CD, no standardized method of diagnosis, and proper selection of muscle injection sites. Future studies are needed to establish dosing equivalency, duration of effect, and cost comparisons among the various formulations of BoNT type A. Accessibility to BoNT treatment is essential to CD patients when the diagnosis is made, since most patients have been dealing with symptoms for over 3 years before being diagnosed. Treatments and choice of toxin are individualized to the particular patient. It is important for the practitioner to understand the different properties of each BoNT, and often patient preference is determined by using the particular agent correctly and minimizing side effects.

Disclosure

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