Botulinum Toxin in the Treatment of Pediatric Upper Limb Spasticity

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Abstract

Botulinum neurotoxin (BoNT) is one of the mainstays in the treatment of pediatric spasticity and dystonia. When considering initiation of BoNT treatment for spasticity, treatment goals and responses to prior conservative measures such as passive range of motion exercises, splinting, and other medication trials should be reviewed. As a general rule, children should be engaged in therapy services around the time of the injections and have a robust home program in place. When managing spasticity in children with BoNT injections, the practitioner should be well versed in functional anatomy with specialized training in injection techniques. Localization techniques in addition to anatomical landmarks are recommended for improved efficacy and include limited electromyography, electrical stimulation, and/or ultrasound guidance. A follow-up visit for the purpose of reassessment during the peak effect of the drug is advised. It is known that BoNT is effective at reducing spasticity and improving range of motion, but it remains to be determined to what degree this translates into improved function, activity, and participation.

Keywords

- ▶ spasticity
- ▶ cerebral palsy
- ▶ botulinum toxin
- ▶ neurotoxin

Cerebral palsy is a form of static encephalopathy that results from an isolated event affecting the developing brain either prenatally, at the time of birth, or in the first few years of life. It is the most common motor disorder of childhood, and the predominant tonal abnormality observed in these children is spasticity.¹ Children who are older or teens may also have central nervous system events resulting in spasticity without carrying a diagnosis of cerebral palsy. Spasticity management is especially important in children when there is (1) an early onset of deficits, or (2) spasticity is severe. One of the main management goals is to limit the detrimental effects of unopposed hypertonicity during periods of growth with its negative consequences on the developing musculoskeletal system. Although the neurologic condition being treated may not change, the combined effects of spasticity, weakness, and impaired motor control may result in progressive deformities including shortened muscles, dysplastic joints, and bony rotational abnormalities not observed in adults with similar acquired tonal abnormalities. This is an additional complication on top of known architectural changes occurring within

muscles and impaired muscle joint relationships observed in any individual with spasticity.² In the very young child, a closed fist or flexed wrist and elbow may impede sensory exploration and normal weight bearing through the upper limb with learned neglect also as a consequence. Late intervention for severe spasticity or contracture may limit spontaneous use of the affected limb even if the distal segments are in a more desirable position.

Botulinum neurotoxin (BoNT) is one of the mainstays in the treatment of pediatric spasticity and dystonia. This unique medication was first proposed for the treatment of strabismus, a condition associated with abnormal muscular forces causing misalignment of the eyes.³ Since then, the applications for this group of neurotoxins has expanded to include many neurologic conditions with associated upper motor neuron syndromes including stroke, acquired brain injury due to trauma, and demyelinating disorders.

Since this drug was first implemented for clinical use, its mechanism of action and efficacy has been better elucidated. This specialized pharmacotherapy provides the advantage of

a treatment option for reducing excessive muscle contraction or overactivity focally in a reversible nature without permanent destruction of the neuromuscular junction. There are two serotypes used clinically, A and B, with onabotulinum toxin A (onaBoNT-A) being the most commonly used commercially available product in the United States. Although onaBoNT-A has had approval from the U.S. Food and Drug Administration (FDA) since 2010 for the treatment of upper limb spasticity in adults, it is not FDA approved at this time for similar use in children.

Clinical Evaluation

Over the years, consensus groups have strived to further define the subtypes of hypertonia associated with central nervous system conditions whether static or progressive in nature. This is of importance because successful responses to various medical and surgical treatments for hypertonia will be influenced in part by the proper recognition of the predominant tonal abnormality and whether its distribution is focal or generalized. Children with cerebral palsy may have many different neuroanatomical correlates resulting in coexisting subtypes of hypertonia, which can ultimately impact treatment selection outcomes. The Taskforce on Childhood Motor Disorders representing a multidisciplinary group of specialists have defined spasticity as “hypertonia in which one or both of the following signs are present: (1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or (2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle. Childhood dystonia is defined as “a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.”⁴

Indications and Timing

When considering initiation of BoNT treatment for spasticity, treatment goals and responses to prior conservative measures such as passive range of motion (ROM) exercises, splinting, and other medication trials should be reviewed. It is also important to know the developmental level of the child and his or her current level of function. The underlying etiology of spasticity and presence of other forms of hypertonia such as dystonia should be noted. Various measures are utilized for assessing tonal abnormalities in children such as the hypertonia assessment tool.⁵ Dystonia often proves more challenging to treat and can be influenced by emotional states and sensory triggers in the affected limb. As a general rule, children should be engaged in therapy services around the time of the injections and have a robust home program in place. Occupational therapy in conjunction with BoNT injections has been shown to improve outcomes following the procedure.⁶ Although the medication effect changes the pattern of excessive contraction in the muscles selected, the full benefit is not realized without adjuncts such as stretching and strengthening afterwards. Essentially, it is not the medi-

cation alone that results in a change toward goal attainment, but what is done afterwards that has the greatest impact. This is especially true for children who experience growth spurts, which can negatively impact the gains made following BoNT injections and shorten the duration of clinical effect.

In the pediatric population, BoNTs provide the advantage of targeted pharmacologic treatment where systemic medications may not be indicated, are ineffective, or have undesirable side effects or functional consequences. Many children with spasticity have oromotor incoordination and weakness, axial hypotonia with compromised trunk control, or may be receiving other medications with the potential for sedation or cognitive dulling. In severe generalized cases of spasticity, a combination of medications is employed to provide generalized tone reduction without side effects with focal injections prioritized in areas that are most impacting function, comfort, or care. Combination therapy or BoNT injections alone often provide an interim solution in spasticity reduction, especially in younger children who are not yet ready to undergo definitive surgical correction as well. This may be due to the child not being developmentally ready for postsurgical protocols designed at maximizing the surgical outcome or to allow for additional growth prior to surgery. In the context of surgical planning, injections are helpful to also simulate the effects of future surgery and allow the care team to observe whether ROM and strength, as well as function can improve even if this is transient. In contrast to this reassuring result supporting surgery, some children may demonstrate unmasking of dystonia, uncooperativeness, or inability to progress due to cognitive issues despite therapy interventions following BoNT injections, which could then dissuade a surgeon from proceeding with a permanent procedure at that time because it might have limited success or even be detrimental.⁷

Treatment

When managing spasticity in children with BoNT injections, the practitioner should be well versed in functional anatomy with specialized training in injection techniques. Weight-based guidelines for children exist such as those published in *We Move*.⁸ The initial dose is usually conservative for the amount of drug injected by weight per muscle group to avoid unmasking weakness. If the child is receiving injections simultaneously in the upper and lower limbs, the majority of the total dose is usually distributed in the leg(s) due to the larger muscle size. When needing to escalate dosing in the arm to achieve better results, one should consider injections of the arm(s) and leg(s) at separate visits.

Factors that influence the use and dosing of BoNT injections for spasticity reduction include the health status of the child, especially any pulmonary or hematologic comorbidity. There has been increased attention directed at identifying subgroups of patients at risk for complications and children who are considered more medically fragile—typically encountered in the Gross Motor Functional Classification System levels IV and V—do show an increased incidence of adverse events.⁹ In general, BoNT use is very safe when dosed

by weight, and there is adherence to the recommended interval of 3 months separation between injections. This ensures avoidance of toxicity and also antibody formation, which could result in a lack of efficacy with future drug administration. Children younger than age 2 also receive injections with onabotulinum toxin A routinely with the intent to prevent acquired musculoskeletal deformity by intervening early.

Frequently, injections are performed in an office setting with topical agents for pain relief and occasionally premedication for anxiolysis. The skin is prepped with alcohol and a clean, but not sterile technique is employed. Distraction techniques are imperative as well as having support staff from both nursing and the child's life. Children with significant anxiety or who are uncooperative to the point that safe and exact drug placement may be compromised are considered for sedation. This would be applicable to a child needing precise injections in the head, neck, and upper limb regions. This often entails general anesthesia and has the associated risks and expense, which some parents find undesirable. Sedation guidelines are in place at each institution ensuring that the personnel and space are adequately prepared for this type of support. The main goal for sedation is to provide amnesia and less movement to ameliorate anxiety and to ensure proper and safe placement of the drug, respectively.

Another risk associated with BoNT injections is local diffusion to adjacent muscles, which may produce an undesirable effect without frank toxicity. Thus, judicious dosing in the head and neck regions is advised given that many children have a pre-existing swallowing dysfunction. As with any injection, the risk of bleeding in a child on anticoagulant or antiplatelet therapy should be reviewed and included in the consent after a thorough discussion of the risks and benefits. Discomfort following the procedure is usually minimal and short lived.

Localization techniques in addition to anatomical landmarks are recommended for improved efficacy and include limited electromyography (EMG), electrical stimulation, and/or ultrasound guidance. Adjunctive techniques are viewed by many as accepted clinical practice^{10–12} and are not only used in isolation, but also in combination with other modalities. Teflon-coated needles attached to the drug-filled syringe aid in localization and are available from several manufacturers. The choice of which modality to use for localization is based on the muscle group being targeted, the child's cooperation level, and the experience and preference of the individual performing the injections. Electromyography gives immediate feedback both audibly and visually, regarding the position of the needle tip in relationship to the motor units after passing through the superficial soft tissues. For larger and superficial muscles, this modality is frequently employed; motor units will have a characteristic appearance and sound when in close proximity. Ideally, the drug is delivered to the motor endplate zone and/or sites where motor unit activity is robust.

For EMG, it should be noted that muscular contraction is necessary to observe a response and motor unit activation does not confirm exact needle location. In the forearm, many

muscles are overlapping and in the presence of spasticity a particular muscle may not be located in the typical place observed in normal healthy individuals. This is because muscular shortening and rotation may disrupt true anatomical position and alignment.¹³ In this situation, EMG cannot confirm with certainty the accuracy of needle placement within the targeted muscle. Electrical stimulation then would be desirable to selectively show confirmation of contraction of the desired muscle being injected. This also applies to injections in the smaller muscles of the hand. Ultrasound is being embraced as a technique for localization that adds even more precision; however, this modality requires significant time, expense, and staff support; its effect on functional outcomes remains to be determined.

Patterns of muscle overactivity can change over time, so ongoing customization of muscle selection in terms of which contribute to abnormal positioning and functioning should be analyzed and factored into decision making. Several muscles can contribute to motion at a particular joint, and differential dosing may be preferable for a particular child. An example is in the treatment of elbow flexor spasticity, where the biceps brachii, brachialis, and brachioradialis all contribute to the flexion deformity. Because the biceps brachii acts secondarily as a supinator, caution should be exercised when dosing higher in this muscle group for children lacking active supination or in those with severe forearm pronation spasticity. This is an example of secondary functions being compromised with intentional relaxation.

Techniques have been developed to impact drug diffusion and decrease systemic side effects, such as diluting the drug agent or limiting injection volumes at each site to 0.5 cc. A child with injections to the brachioradialis may have their effects spread to the wrist extensor group and compromise treatment of wrist flexor spasticity during the same session. This would be an example of where localization or dilution strategies help to prevent effects within adjacent muscles that could be counterproductive, even resulting in a loss of function. To avoid undesirable drug spread, especially in small muscular targets, a more concentrated preparation can be utilized. In a child receiving multiple injections to large muscle groups where the total dose may be limited by weight, a more dilute preparation may be favored to encourage a greater response.

Children at higher levels of functioning may be at higher risk for temporary loss of strength that could impact satisfaction with the injections. Precision and pre-procedure counseling become very important in these scenarios. A case in point would be a young child who uses involuntary finger flexion to grasp a swing suspended by rope who can no longer remain properly positioned when the hand is relaxed. Although most of the activities in that child's day will benefit from a relaxed hand, this one negative consequence may be quite bothersome to the patient or his or her parents.

Postinjection Care

A follow-up visit for the purpose of reassessment during the peak effect of the drug is advised in patients who have

undergone treatment for the first time. Particular attention should be paid to the dose response of the targeted muscle. Efforts should be made to direct additional therapeutic interventions including progressive splinting, neuromuscular electrical stimulation, and formal constraint protocols where needed. Excessive relaxation that is negatively impacting function should also be noted, as some children use their spasticity even if involuntary for functional benefit. The typical duration of effect is 3 to 6 months with the shortest interval between injections being 3 months. Determination of whether the injections will be repeated and at what intervals is an individualized decision made in conjunction with input from the parent and treating therapist.

Spasticity if mild may be ameliorated by BoNT injections for a prolonged period and with relatively small drug dosages; however, a patient with severe spasticity may show benefit for only a short period or to a very mild degree. It is in this circumstance where combination therapy should be considered. This may mean utilizing oral medications for spasticity, additional nerve blocks with phenol or alcohol, and in some cases intrathecal baclofen. Phenol requires very precise localization of the needle tip adjacent to the myelinated sheath of a nerve to achieve a successful block without side effects. For this reason, sedation is almost always required in addition to the use of electrical stimulation. A progressive disorder may show worsening of spasticity over time, which may necessitate higher dosing regimens or adjunctive interventions. It is also important to recognize when contractures are the main cause of restricted motion and abnormal positioning, as higher dosages of BoNT will not change these static deformities.

Research and Outcomes

There is an abundance of research supporting clinical effectiveness of BoNT in children with spasticity despite the lack of official labeling for this age group. The BoNTs share a similar mechanism of action, but it is important to note that they are not bioequivalent. They also have different side-effect profiles, with the B serotype showing greater sympathetic nervous system effects. After binding presynaptically at the neuromuscular junction, acetylcholine release is prevented, thus lessening the force of contraction in the targeted muscle. The duration of effect of 3 months relates to new synapse formation following terminal sprouting without degeneration of the nerve terminal. In the past, there have been concerns for antibody formation following repeated injections, especially at close intervals, but with refined purification of the BoNT proteins this has become far less common and less of a concern.¹⁴ Many factors can contribute to the lack of clinical efficacy, including inaccurate drug site delivery, inappropriate muscle selection and dosing, and the possibility of antibody formation.¹⁵

Additional research has focused on the safety and long-term anatomical changes with repeated injections as well as potential remote effects in children in particular. Toxicity can vary from mild anticholinergic effects such as dry mouth and constipation to the more severe picture of respiratory failure. Goldstein in

2006 published a retrospective review of 119 injections over a 2-year period. No systemic or serious adverse events were noted in children less than 45 kg receiving doses of onaBoNT-A in the range of 15 to 22 U/kg; however, one teen child at dosing of 23 U/kg did show mild systemic toxicity.¹⁶ Two other studies showed no significant adverse effects in children less than 2 years of age. In the first report, patients received a maximum total dose of 10 U/kg for the treatment of clubfoot. The second study stratified children by age and diagnosis, with dosages for non-obstetrical brachial plexus palsy patients ranging from 7.2 U/kg in those less than 1 year of age to 8.8 U/kg in those 12 to 24 months of age.^{17,18}

The impact on activity and participation following injections whether used in isolation or with other treatment modalities is yet to be determined. It is known that BoNT is effective at reducing spasticity and improving ROM, but as with any medical treatment the primary issue is whether this translates into improved function, activity, and participation. This is of particular interest to pediatric practitioners who want to customize treatments in a developing child who is at risk for growth-related complications. The tools we have to modify this course frequently outweigh the risks associated with no action, but to what degree a particular intervention is superior to others is still being determined. With a diverse patient population with differing clinical presentations, identifying who benefits most from various interventions at specific times of development is of utmost importance.

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