


Botulinum Toxin in Pediatric Neurology: Switching Lanes From Death to Life

Global Pediatric Health
January-December 2015: 1-9
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DOI: 10.1177/2333794X15590149
gph.sagepub.com


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Abstract

Botulinum neurotoxins are natural molecules produced by anaerobic spore-forming bacteria called *Clostridium botulinum*. The toxin has a peculiar mechanism of action by preventing the release of acetylcholine from the presynaptic membrane. Consequently, it has been used in the treatment of various neurological conditions related to muscle hyperactivity and/or spasticity. Also, it has an impact on the autonomic nervous system by acting on smooth muscle, leading to its use in the management of pain syndromes. The use of botulinum toxin in children separate from adults has received very little attention in the literature. This review presents the current data on the use of botulinum neurotoxin to treat various neurological disorders in children.

Keywords

botulinum toxin, children, neurological uses

Introduction

Several anaerobic bacteria of the genus *Clostridium* produce botulinum neurotoxins that cause botulism.^{1,2} The ingestion (or injection) of botulinum toxin (BoNT) can produce symptoms of a serious nature including loss of strength and diffuse muscle weakness, double and/or blurred vision, drooping eyelids, dysphonia, dysarthria, dysphagia, urinary incontinence, and dyspnea resulting from paralysis of the respiratory muscles.³ The latter can lead to death.⁴ The clinical disease entity of botulism had been well described since the early 19th century. However, the bacterium *C botulinum* was identified, as its causal source, by van Ermengem in 1895.⁵ By the 1920s, BoNT-A was isolated in a purified form as a stable acid precipitate by Sommer at the University of California, San Francisco.⁶

Mechanism of Action

There are 7 immunologically distinct serotypes of botulinum neurotoxins designated A through G. All toxins produced by clostridial bacteria are high-molecular-weight protein complexes. Although each toxin is antigenically distinct, they have similar molecular weights and structures. All the toxins consist of a light and heavy chain linked by a disulfide bond. The light chain is a protease that binds to synaptobrevin at the neuromuscular junction, inhibiting vesicles from anchoring to the

cell membrane, thus preventing acetylcholine release. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction, interferes with nerve impulse transmission, and results in flaccid paralysis of treated muscles.⁷⁻¹¹

Botulinum Toxin Formulations

Currently, there are 3 commonly used formulations of botulinum toxin A: onabotulinum toxin A (Botox or Vistabel; Allergan, Irvine, CA), incobotulinum toxin A (Xeomin or Bocouture; Merz Pharmaceuticals, Frankfurt, Germany), and abobotulinum toxin A (Dysport [Medicis, Scottsdale, AZ] or Azzalure [Ipsen, Paris, France]). Each formulation is purported to have unique benefits; however, it is unclear if these differences are clinically significant.¹²

Safety and Adverse Effects

Local reactions to BoNT at administration site commonly include pain, edema, erythema, ecchymosis,

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headache, and short-term hyperesthesia. In addition, local reactions can occur following migration of the toxin into adjacent muscles. Systemic adverse reactions following BoNT administration primarily comprise nausea, fatigue, malaise, flu-like symptoms, and rash. Specific systemic adverse events may be associated with toxin migration into particular muscles, for example, treatment of cervical dystonia is often associated with dry mouth.¹³ In general, adverse effects of BoNT use are minimal and uncommon especially when it does not exceed the recommended dose. Also, side effects are relatively mild, transient, and resolve within couple of weeks.¹⁴

Contraindications

The clear contraindications to the use of BoNT include known allergy to the drug, presence of inflammation or infection at the site of proposed injection, during pregnancy and breastfeeding, patients with some neuromuscular disorders such as myasthenia gravis, muscular dystrophy, and so on. Anatomic abnormalities like obesity or deformity can make the injections difficult or impossible. The patients who are on calcium channel blockers or those who suffer from coagulopathy (including therapeutic anticoagulation) are also not appropriate candidates to receive BoNT injections. BoNT injections should be avoided in patients taking aminoglycoside antibiotics, because aminoglycosides may interfere with neuromuscular transmission and potentiate the effect of BoNT therapy.¹⁵

Although BoNT has not yet been approved for use in children, it is used in a variety of clinical conditions due to its safe, predictable, and reversible effects on the motor system. The aim of this review is to ascertain the role of BoNTs in treatment of different neurological disorders in the pediatric age-group either consolidated or as rare indications.

Clinical Applications of Botulinum Toxin in Pediatric Neurology

As botulinum neurotoxin acts at the neuromuscular junction, blocking acetylcholine release with subsequent reversible alteration of muscle tone and functional denervation of the targeted muscle, it is used extensively in disorders of muscle overactivity, such as spasticity, facial movement disorders, as well as limb and neck dystonias. Also, BoNT injections have been involved in the treatment of painful syndromes such as headache and low back pain with some success.¹⁶

Spasticity

Spasticity is defined clinically as an involuntary motor disorder characterized by hypertonic muscle tone with increased excitability of the muscle stretch reflex and increased tendon reflexes.¹⁷

Cerebral palsy (CP) is a group of permanent disorders of movement and posture development, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. It is the most common cause of spasticity and physical disability in children. However, spasticity can occur with other genetic and metabolic diseases that cause dysfunction or damage to the developing central nervous system (CNS).^{18,19} Spasticity commonly leads to muscle contractures and eventual bony deformities, which may result in decreased functional ability as a child's development progresses.^{20,21}

In 1993, Koman et al reported the successful use of BoNT-A in children with CP for the first time.²² In 1998, BoNT-A became licensed for use in children over the age of 2 years for management of dynamic equinus foot deformity in ambulant children with CP. This remains the only Food and Drug Administration (FDA)-approved indication; however, many studies have supported the efficacy of BoNT-A^{23,24} as the first-line treatment for focal or multifocal spasticity. The BoNT treatment modality is usually carried out as an adjunct to other rehabilitative strategies, which are based on individualized, multidisciplinary programs that are targeted to achieve patient goals.²⁵ The toxin is optimally combined with common conservative treatment options (physiotherapy, orthotic management, casting, and even oral medication). The fundamentals of this integrated approach are proper muscle selection, an appropriate dosage of BoNT-A, an accurate injection technique, and trade-off between reduction of spastic hypertonia and preservation of residual motor function. In this integrated approach, the interdisciplinary team with a variety of medical professionals should be involved.²⁶

Patient Selection. Spasticity is not always harmful as patients with a combination of muscle weakness and hypertonic muscles may rely on the increased tone to maintain their posture and to aid standing or walking.²⁷ So it is important to select the correct group of children for treatment. BoNT is predominately used for children with CP; however, it is also indicated in other conditions associated with spasticity. Children should be considered for injections when spasticity is focal or segmental in either upper and/or lower limbs and if it interferes with active or passive functioning.^{28,29} It can be also used to

improve function for children with CP who are ambulant with relatively few and minor complications.²⁹

There is limited evidence for using BoNT-A in children with CP who are nonambulant to reduce pain and improve ease of care.³⁰

Timing of Use. Spasticity limits movement that leads to contractures and deformities as the child grows. This is why targeting the correct children for BoNT treatment early is crucial. The toxin can be used in all ages, but research suggests a better response in children less than 8 years of age³¹ to prevent soft tissue shortening, which results from the combined effect of spasticity and limb immobility.³²

Muscle Selection. Botulinum toxin injections should be fine-tuned for each patient individually following an extended standardized clinical examination; observation of movement, which is thought to be the decisive factor in BoNT treatment; and evaluation of posture, gait, and/or other motions. This allows the specific description of the pattern of motion at each joint and identification of the muscles that cause the pathological pattern, according to which the treatment can be modified. Spasticity in the upper and lower limbs can be assessed with many different methods such as the Modified Tardieu Scale and passive resistance of the muscle with the Modified Ashworth Scale. The Gross Motor Function Classification System and Manual Ability Classification System are usually used for assessment of motor skills.²⁶

Dose of Botulinum Toxin. Dosing guidelines for BoNT-A as Botox, for adults and children, have been developed by consensus.^{33,34} In children, maximum dosing should take into consideration the child's weight, muscle bulk, and degree of spasticity.³⁵ Pediatric doses of BoNT-A in the treatment of children with spastic CP ranged from 12 to 16 U/kg and from 15 to 25U/Kg of body weight for Botox and Dysport, respectively.²⁸ Higher BoNT-A doses of 15 to 22 U/kg and of 20 to 30 U/kg have also been used without serious adverse events for Botox³⁶ and Dysport,³⁷ respectively. Maximum doses of BoNT-A should not exceed 300 U Botox and 900 U Dysport per injection session.²⁸ BoNT is taken up by the neuromuscular junction within 12 hours. The effects of injection are seen at 3 to 6 days and the peak at 6 weeks.³⁸ The lowest effective dose with an injection interval of at least 3 months or more should be used to minimize the risk of antibody development, and a nonlinear dose-response relationship should be expected.³⁹

Dystonias

Dystonia is characterized by involuntary, sustained, and patterned contractions of opposing muscles, causing twisting movements and abnormal postures.⁴⁰

Botulinum toxin has become the treatment of choice for most patients with focal or segmental dystonia such as blepharospasm, cervical dystonia, laryngeal dystonia, oromandibular dystonia, and limb dystonia.⁴¹ The safety and efficacy of BoNTs to treat focal dystonia have been documented in several open-label and controlled studies.⁴¹⁻⁴³ In most cases, BoNT injections are given intramuscularly, often under electromyography guidance, and need to be repeated every 3 to 6 months.⁴⁴

Blepharospasm. Blepharospasm is a focal dystonia characterized by recurrent involuntary contraction of the orbicularis oculi muscles leading to frequent blinking or forceful eyelid closure.⁴⁵ In 1989, BoNT-A received FDA approval for use in the treatment of essential blepharospasm.⁴⁶ Several studies support BoNT-A as the treatment of choice for blepharospasm, with 90% of the patients benefiting from the injection of the toxin when compared to placebo.⁴⁵⁻⁴⁷ Other studies have shown that the treatment with BoNT also improves quality of life in those patients.⁴⁸⁻⁵⁰ BoNT is administered subcutaneously, medially, and laterally into the junction between the preseptal and orbital parts of the upper and lower orbicularis oculi muscles of the eyes.⁵¹ Common side effects are transient and relatively short-lived. They include dry eye, ptosis, lagophthalmos, and diplopia.^{47,52}

Cervical Dystonia (Spasmodic Torticollis). Botulinum toxin has been considered the treatment of choice in patients with cervical dystonia.^{53,54} Meta-analysis of several double-blind, placebo-controlled trials have demonstrated that over 70% of the patients who received BoNT-A have beneficial effects on multiple domains, such as dystonia severity and pain relief, versus placebo. Its effect normally lasts around 12 weeks.^{26,55} On December 21, 2000, BoNT-A received FDA approval for the treatment of cervical dystonia. In addition to Botox, the other 2 forms of BoNT-A products, Dysport and Xeomin, and BoNT-B (Myobloc or NeuroBloc) are also approved by the FDA to treat cervical dystonia. Although there are no significant differences in terms of their efficacy in cervical dystonia treatment, BoNT-B generally shows higher immunogenicity in those patients. The greater benefit of BoNT-B treatment is for BoNT-A-resistant patients.⁵⁶⁻⁵⁹

Focal Hand Dystonia (Writer's Cramp). Injection of BoNT has been found to provide relief for writer's cramp,⁶⁰ particularly in those with pronation/flexion pattern.⁶¹ A number of studies have shown improvement in 80% of patients following at least one injection series, with efficacy evident at 1 week and lasting up to 12 weeks.⁴⁷ Pain is generally improved more than motor function. However, the relief is only symptomatic and it does not

reverse the associated dysfunction of primary motor and premotor cortex. It was also found that the writing speed improves both subjectively and objectively.^{60,62} About 36% of patients continued to have relief when followed-up for a mean period of 12 months and about 51% were still on BoNT treatment. Side effects include hand weakness, mostly mild and transient, and localized pain at the injection site.^{61,63}

Spasmodic Dysphonia (SD). It is characterized by task-specific, action-induced spasm of the vocal cords that can occur independently or as part of other syndromes or disorders including tardive dyskinesia.⁴⁷ Approximately 80% of affected individuals have adductor spasmodic dysphonia, causing inappropriate glottal closure. Conversely, abductor spasmodic dysphonia results in a weak, breathy voice.^{64,65} Over the past 2 decades, injection of BoNT-A has become the preeminent approach for treatment of adductor SD,⁶⁶ which can be improved for as long as 15 weeks after treatment.⁴⁷ Long-term effects of BoNT-A were retrospectively evaluated in 55 patients, showing a decrease in the dose, with increase in treatment intervals and effect duration over the years.⁶⁷ The reported experience with BoNT-B is still limited. Adler and colleagues reported a good effect in 8 of 10 patients, lasting up to 8 weeks.⁶⁸ In contrast to adductor SD, reports on abductor SD are limited, showing less impressive and variable results.⁶⁹⁻⁷¹ A number of different injection methods can be used for SD, including with laryngoscopic and/or electromyography guidance, transorally, transnasally, and point touch method. The latter is better tolerated but may have higher failure rates.⁴⁷ Some studies have reported side effects including mild breathiness and choking.⁷²

Oromandibular Dystonia. Oromandibular dystonia (OMD) refers to involuntary spasms of masticatory, facial, and lingual muscles leading to repetitive or sustained jaw opening, closure, deviation, or any combination of these movements.⁷³ Although most of the data of BoNT for the management of OMD comes from open studies, they have been sufficiently compelling to dictate BoNT as the treatment of choice, particularly in patients with jaw-closing OMD.⁴⁷

Hemifacial Spasm

Hemifacial spasm is neuromuscular disorder characterized by frequent, involuntary facial muscle contraction due to neurovascular compression at the root exit zone of the facial nerve.⁷⁴ It generally affects middle-aged and elderly people, and its occurrence in children is extremely rare.⁷⁵ However, some studies reported young-onset hemifacial

spasm.⁷⁶⁻⁷⁸ BoNT-A was approved by the FDA to treat hemifacial spasm in 1989. It is seen that about 95% of patients had moderate to marked improvement.⁷⁹

Postperipheral Facial Nerve Synkinesis

Synkinetic movements comprise abnormal involuntary contractions of one or more facial muscle groups that follow the desired contraction of another facial muscle group. They are frequently encountered in patients with long-standing facial paralysis.⁸⁰ The most common therapeutic modality is BoNT-A injections for selective chemodeneration of the affected muscle groups.⁸¹ It is seen that a single injection is highly effective in reducing the synkinetic movements for 3 to 9 months.^{82,83}

Tremors

Tremors are involuntary, rhythmic movements, usually affecting hands, but also can affect head, legs, and voice. The most common cause is benign essential tremors. Almost all types of tremors have been reported to benefit from BoNT injections, with greater success (50% to 60% improvement) for essential tremors of the hand.^{84,85} However, the data available are limited; the reported benefits were usually modest and the side effects, such as hand weakness, hoarseness, and swallowing difficulties, were, in some studies, too frequent. Thus, BoNT therapy for treating essential tremor should be considered only in medically refractory cases.²⁴

Tourette's Syndrome (TS)

It is a chronic neurodevelopment disorder characterized by tics (repetitive, involuntary movements) and vocalizations. These symptoms can have a significant impact on patients' daily functioning across many domains.⁸⁶ It was found that BoNT reduced frequency and severity of tics in patients with TS, with improvement in urge and/or premonitory symptoms preceding tics.⁴⁷

Botulinum Toxin and Pain

BoNT as a mediator of pain relief is a subject of considerable speculation.^{87,88} The known effect of BoNT at the neuromuscular junction has considerable implications in treating pain of muscular origin.^{87,89} Several studies suggest that other pathways may also play a role in the analgesic effects of BoNT.⁴⁵

Analgesic Effect Secondary to Muscle Relaxation. Many chemicals, including bradykinin, serotonin, potassium, prostaglandin E2, and several neuropeptides such as

substance P, glutamate, and calcitonin gene-related peptide (CGRP) can sensitize muscle nociceptors. Because activation of these nociceptors may be related to the degree of contraction of a muscle, BoNT may ameliorate pain simply by reducing the extent of muscle spasm or contraction.⁹⁰ Also, BoNT may decrease pain due to muscular spasm, by decreasing distortion of structures attached within the muscles and also by decreasing the compression of nerves as they pass within the muscle.⁹¹

Analgesic Effect Secondary to Inhibition of Peripheral Sensitization. BoNT may have a direct effect on noncholinergic neurons and reducing peripheral sensitization. It inhibits the release of the nociceptive or inflammatory neuropeptides substance P^{92,93} and CGRP, directly or indirectly, by inhibiting the release of glutamate, which in turn stimulates the release of substance P (peripherally and centrally) and CGRP.⁸⁹

Analgesic Effect Secondary to Inhibition of Central Sensitization. Some studies suggest that BoNT-A is transported by axons to the CNS after intramuscular injection.⁹¹ Many neurotransmitters are released by mechanisms that are dependent on the SNARE proteins, which are the target of BoNTs. Therefore, BoNT blocks the release of more neurotransmitters that are involved in pain transmission or modulation within the CNS tract.⁸⁹ Changes in the central sensory system “neuroplasticity” secondary to pain stimuli could also be affected by BoNT.⁹³

Analgesic Effect Through Alteration of Autonomic Function. Blood flow is clearly related to inflammation and ischemic pain and is probably involved in the sensitization of nociceptors. Autonomic neurons alter regional blood flow by controlling the smooth muscle walls of small arterioles. BoNT may block some of the autonomic vascular control functions and at the same time may alter the release of a variety of nonacetylcholine agents that also affect blood flow. Also, autonomic function mediated by the release of acetylcholine is associated with both emotional behavior and stress through complex CNS circuitry. BoNT-A may alter the global perception of pain and or the patient’s overall response to pain through this linkage.⁸⁹⁻⁹³ In a double-blinded, placebo controlled trial, Barwood et al reported profound antinociceptive activity of BoNT-A injection when administered prior to orthopedic surgery in children with CP. Children treated with BoNT-A had a reduced need for narcotic analgesics and had better outcomes than the placebo group.⁹⁴

Headache

Headache is a common problem affecting children and adolescents with significant impact on their lives. It may

result in school absence, decreased activities, and poor academic achievement. Headaches may be a primary disorder, such as migraine, tension type, or cluster, or they may be secondary to a systemic illness or primary CNS disorder.^{95,96} The most frequent types of recurrent headache in childhood and adolescents are migraine and tension-type headache, respectively. BoNT injections were first proposed as headache treatment when it was observed that patients with chronic headaches receiving cosmetic botulinum injections experienced headache improvement. This promoted several case series supporting its benefit. In October 2010, the FDA approved BoNT-A for prophylactic treatment of chronic migraine based on 2 clinical trials conducted in Europe and the United States.⁹⁷

Several strategies of injection (fixed or “follow the pain”) using a wide range of doses have been suggested for different forms of headache without conclusive results.²⁴ One controlled trial has shown the efficacy of the BoNT therapy in headache.⁹⁸ In this study, which was designed for the prophylactic treatment of chronic migraine, patients received 155 units of BoNT-A every 12 weeks administered to 31 injection sites across 7 specific head and neck muscle areas using a fixed-site, fixed-dose injection paradigm.⁹⁹ Furthermore, up to 40 optional units could be administered using a “follow-the-pain” strategy with injection at sites of maximum pain or tenderness.²⁴ The results showed a significant improvement over placebo treatment in multiple headache symptom dimensions after 24 weeks of follow-up, such as headache frequency, episodes, severity per day, and as well as total cumulative hours of headache.⁹⁸ Furthermore, patients treated with BoNT used significantly less triptans and had a reduction of headache-related disability. Adverse effects, including muscular weakness, ptosis, muscle tightness, and local pain, were usually transient, mild to moderate, and occurred in fewer than 10% of patients.^{24,98} In summary, the authors concluded that BoNT-A is an effective and safe prophylactic treatment for patients who have chronic migraine.²⁴ Finally, the same cohort was followed an additional 32 weeks in an open-label phase. The results showed permanent long-term benefits after repeated injections of BoNT.⁹⁸

Pediatric data are still limited to 3 retrospective studies and one retrospective case series with long-term follow-up showing promising effects and a good tolerability profile in several patients suffering chronic primary headache.¹⁰⁰

Trigeminal Neuralgia

Botox is found to be effective in the treatment of majority of patients with drug-refractory trigeminal neuralgia

with reduction or even disappearance of the pain. It is also effective in combination with pharmacotherapy, or to considering more invasive therapies such as surgery or gamma knife radiosurgery.²⁴

Conclusion

Botulinum toxin are valuable agents in multiple therapeutic strategies of pediatric neurological disorders. They are used as single agents or as an adjunct to other rehabilitative procedures. Although they demonstrated minimal side effects, better outcome, and improved quality of life, many applications are still off-labeled. Further studies are required as many issues are still unclear, such as lack of standardized rating tools for many clinical indications in pediatric field, assessment of long-term safety and efficacy of BoNT injection especially on growth and maturity of children. Also, comparative head-to-head trials are required to establish whether one serotype or brand of BoNT is more effective than another, and to determine the dosing equivalency and relative antigenicity between different serotypes.

Author Contributions

EM contributed to design, drafting and revision of the manuscript. EA contributed to design and critically revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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