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Spasticity Associated with Cerebral Palsy in Children

Guidelines for the Use of Botulinum A Toxin

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Contents

Abstract 11
1. Cerebral Palsy (CP) 12
1.1 Definition and Incidence 12
1.2 Patterns of Involvement 12
1.3 Treatment Options in Spasticity 13
1.4 History of Botulinum A Toxin in CP 13
2. Botulinum Toxin Type A 13
2.1 Mechanism of Action/Pharmacokinetics 13
2.2 Neuromuscular Junctions 14
3. Toxin Preparation and Administration 14
3.1 Commercial Preparations of Botulinum A Toxin 14
3.2 Clinical Experience 14
3.3 Administration 15
4. Injection Techniques 16
4.1 Localization 16
4.2 Techniques 17
5. Pain on Injection/Management Methods 17
6. Safety Considerations 17
7. Indications for Toxin Injections 18
7.1 Availability 18
7.2 Randomized, Placebo-Controlled Trials 18
7.3 Equinus Deformity 18
7.3.1 Management 18
7.3.2 Physiologic Effects 19
7.3.3 Toxin as an Alternative to Casting 19
7.4 As an Adjunctive Intervention 19
7.5 Upper Extremity Indications 20
7.6 Impact on Health-Related Quality of Life 20
7.7 Indications for Use 20
8. Pre- and Post-Injection Assessment and Monitoring 20
8.1 Pre-Injection Assessment 20
8.2 Pre-Injection Goal Setting 20
8.3 Monitoring Treatment and Adverse Events 21
9. Conclusions 21

Abstract

Botulinum A toxin produces selective and reversible chemodenervation that can be employed to balance muscle forces across joints in children with cerebral palsy (CP). Currently, there are two commercially available botulinum A toxin formulations (BOTOX® and Dysport®[1]). The amount of botulinum A toxin required depends

1 The use of tradenames is for product identification purposes only and does not imply endorsement.

upon the number of muscles that are targeted, and the size of the patient. In order to achieve adequate chemodenervation with botulinum A toxin, the following conditions must be met: (i) a sufficient number of units of toxin must be injected in order to neutralize neuromuscular junction (NMJ) activity; (ii) an appropriate drug volume is required in order to optimize the delivery of the toxin to the NMJs; and (iii) localization of the injecting needle through the fascia of the target muscle is necessary. Localization of the injection may be facilitated by active electromyography, ultrasonography, palpation of the muscle belly, and/or use of anatomic landmarks.

Botulinum A toxin injections are indicated for use in pediatric patients with CP to: (i) improve motor function by balancing muscle forces across joints; (ii) improve health-related quality of life by decreasing spasticity and/or decreasing caregiver burden; (iii) decrease pain from spasticity; (iv) enhance self-esteem by diminishing inappropriate motor responses; and (v) provide a presurgical diagnostic tool.

Following intramuscular injections of botulinum A toxin, short-term benefits of reduced spasticity are observed in approximately 70–82% of children. The intermediate term (1–2 years) efficacy rate is approximately 50%. The most common deformity treated with toxin injections in pediatric patients with CP is equinus foot deformity. However, efficacy of toxin injections for the management of crouched gait, pelvic flexion contracture, cervical spasticity, seating difficulties, and upper extremity deformity also has been documented. In addition, toxin injections have been shown to manage painful muscle spasticity associated with surgery or application of casts and painful cervical spasticity with or without dystonia. Toxin injections can also be used as a diagnostic tool to determine the appropriateness of other interventions by observing the muscle response to the injection in order to gain additional information for the development of a treatment plan. Botulinum A toxin, when used in appropriate doses, is well tolerated.

In patients with cerebral palsy (CP), excessive spasticity (an exaggeration of the tonic stretch reflex) may interfere with function, produce pain, and impact negatively on the health-related quality of life of the patients and their caregiver(s). Injectable therapeutic agents that are utilized in the clinical management of muscle spasticity associated with CP include alcohol (ethanol) [45–100%], phenol (5–7%), and botulinum toxins (A and B). This article will review the pathophysiology of spasticity, the pharmacologic mechanism of action of botulinum A toxin, the techniques of toxin administration, the clinical use of the toxin to manage the manifestations of spasticity associated with CP, and the current indications for botulinum A toxin chemodenervation in CP.

1. Cerebral Palsy (CP)

1.1 Definition and Incidence

CP is defined as a nonprogressive injury to the brain before, at, or soon after birth, resulting in impairments of movement.[1,2] Peripheral manifestations of this injury include spasticity, movement disorders, weakness, and/or rigidity.[3] The anatomic distribution of disability depends upon the location of the CNS injury. The extent or magnitude of the classical signs associated with spasticity is secondary to the initial insult, the capacity for cortical or CNS reorganization, and/or the capacity for peripheral compensation.[4] Hyper-excitability of the stretch reflex in CP is secondary to injury to the CNS during its development.[4] Volitional activity occurs secondary to partial recovery through CNS repair and/or cortical reorganization. Incomplete recovery of the pyramidal and/or extrapyramidal spinal pathways decreases afferent and efferent pathways, affects α-motoneuron function, and results in weakness, spasticity, and/or movement disorders.[4]

The worldwide incidence of CP is unknown; however, it is a relatively common disorder with a prevalence of two cases per 1000 live births, although figures vary.[5,6] In the US, an estimated 500 000 children and adults have CP, and the annual cost to society to care for pediatric patients with CP is estimated at $US5 billion. Based on an inflation factor from the Bureau of Labor Statistics (CPI), $US5 billion in 1986 dollars translates to $US8.2 billion in 2002.[7]

1.2 Patterns of Involvement

The three most common patterns of CP are described by anatomic involvement. They are: (i) hemiplegia – involvement of the ipsilateral upper and lower extremity; (ii) diplegia – greater involvement of the lower extremities than the upper extremities; and (iii) quadriplegia – total body involvement (arms, legs, and trunk). The degree of muscle hypertonia varies from child to child. Movement disorders (dystonia, athetosis, chorea) may coexist with spasticity, muscle weakness is common, and peripheral sensibility is often impaired.

Although generalized spasticity may occur in patients with CP, specific patterns of spasticity are common, and differential

involvement between flexor and extensor muscles is frequently observed. In the upper extremity, typical deformities include internal rotation of the shoulder, elbow flexion, forearm pronation, wrist and finger flexion, and thumb-in-palm. In the lower extremity, hip flexion, hip adduction, knee flexion, and equinus foot deformity are most commonly observed (figure 1). Overall, excessive spasticity of the gastrocnemius producing equinus gait is the most prevalent functional abnormality in pediatric patients with CP.[8] Individual variability of the manifestations of the CNS injury characterizes pediatric patients with CP; excessive spasticity is often associated with other clinical problems. In the presence of muscle imbalance due to spasticity that prevents adequate joint range of motion, muscle fibers and/or tendons may shorten the joint capsule, or other joint structures may contract, and fixed contractions of joints may occur. Significant muscle imbalance over time may produce osseous deformity.[3]

Fig. 1. The most common patterns of spasticity in the upper and lower extremity, observed in pediatric patients with cerebral palsy, are: in the upper extremity – internal rotation of the shoulder, elbow flexion, forearm pronation, wrist and finger flexion, and thumb-in-palm; and in the lower extremity – hip flexion and adduction, knee flexion, ankle plantar flexion, hindfoot valgus, and forefoot pronation (reproduced from Koman,[9] with permission).

1.3 Treatment Options in Spasticity

The management of spasticity includes physical modalities, oral pharmacologic agents, peripheral injectable agents, intrathecal agents, and surgical intervention, including orthopedic procedures (table I).

1.4 History of Botulinum A Toxin in CP

Intramuscular botulinum toxin injections were initially utilized for managing strabismus by Alan Scott, MD at the Smith-Kettlewell Eye Institute of Visual Sciences, San Francisco, CA, US.[10-12] Early clinical trials demonstrated the tolerability of intramuscular toxin injections for the treatment of eye disorders and dystonia.[13-15] In 1988, Koman et al.[16] first utilized botulinum toxin A (Oculinum®) to balance joint forces in patients with dynamic extremity deformities secondary to spasticity from CP. Various studies published since 1993 have described the tolerability and efficacy of intramuscular injections of botulinum A toxin for the management of spasticity in patients with CP. Commercially produced botulinum A toxin (BOTOX®) became available in 1989. BOTOX® is approved by the US Food and Drug Administration (FDA) for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or seventh nerve disorders in patients 12 years of age and older. Since its introduction, BOTOX® has been labeled for use in both adults and children with CP in 49 countries, based upon its documented efficacy in the management of equinus foot deformity.[17] Dysport® is approved for use in the UK, the European Union, and many Commonwealth countries. Dysport® is indicated for the treatment of arm spasticity in stroke patients, dynamic equinus foot deformity in pediatric patients with CP, spasmodic torticollis, blepharospasm, and hemifacial spasm.

2. Botulinum Toxin Type A

2.1 Mechanism of Action/Pharmacokinetics

Botulinum A toxin is a parenteral agent that produces dose-related chemodenervation of agonist (target) muscles following intramuscular injection, without producing clinical effects on antagonist muscles. Following intramuscular injection of botulinum toxin, muscles are temporarily paralyzed, and therefore, muscle spasticity is decreased.[18]

Botulinum A toxin is one of seven antigenic toxin subtypes (A, B, C_1, D, E, F, and G) produced by the spore-forming obligate

Table I. Spasticity management

Physical modalities
Therapy (physical and/or occupational)
Orthotics
Other
Oral medications
Membrane uncoupling: dantrolene sodium
γ-Aminobutyric acid agonists: baclofen
α_2-Agonists: tizanidine
Enhancing spinal cord inhibition: benzodiazepines
Parenteral medications
Chemodenervation:
alcohol (ethanol) 45–100%
phenol 5–7%
botulinum toxins
GABA agonist intrathecal baclofen
Neurosurgical interventions
Rhizotomy
Peripheral neurectomy
Traditional orthopedic interventions
Tendon lengthening
Fractional recession of myotendinous units
Tendon transfer
Osteotomy
Joint fusion

GABA = γ-aminobutyric acid.

anaerobic bacteria *Clostridium botulinum*.[19] Botulinum type A is a 150kDa complex composed of a 100kDa 'heavy' chain and a 50kDa 'light' chain. The light chain is active, cleaves synaptosomal-associated protein of 25kDa (SNAP 25), a soluble N-ethylmaleimide-sensitive fusion protein receptor (SNARE) protein, and prevents the assembly of the fusion complex necessary for the release of acetylcholine (ACh) at the neuromuscular junction (NMJ), the critical step that is required to initiate a muscle response (figure 2).[20,21] The blockade of the release of ACh at the NMJ results in flaccid muscle paralysis. Following exposure to botulinum A toxin, functional NMJ activity ceases.[18,20] Nerve terminals exposed to botulinum A toxin have been noted to produce sprouts capable of neurotransmitter exocytosis that form a functional synapse.[22] In the ensuing 3–12 months, the original NMJ is reconstituted, the sprouts regress, and normal synaptic transmission via ACh resumes within the NMJ.[22] The extent of muscle paralysis is determined by the diffusion of toxin within the muscle, the binding affinity of toxin to SNAP 25, and the percentage of involved NMJs.[18]

2.2 Neuromuscular Junctions

Intramuscularly injected botulinum A toxin has an approximate 2–4cm diffusion radius, thus increasing the probability that the toxin is delivered to a large number of NMJs.[23,24] In contrast, alcohol (ethanol) and phenol exhibit limited diffusion. Other factors which affect the probability of delivery of toxin to the NMJs include the number of active toxin complexes injected, the volume in which those complexes are diluted, the location of the injecting needle in relationship to the NMJs, and the binding affinity of the toxin to specific NMJs. Theoretically, NMJs may vary in binding affinity based upon the muscle type. NMJs demonstrate different distribution patterns in specific muscles, become ineffective with age, vary in number per gram of muscle tissue in association with skeletal growth or atrophy, and remain relatively constant in absolute numbers in each muscle throughout life.[25-27]

3. Toxin Preparation and Administration

3.1 Commercial Preparations of Botulinum A Toxin

It is important to refer to the two commercially available A toxins (BOTOX® and Dysport®) by their tradenames because the potency of units for the two different preparations differs.[28] The calculation of the 'units' of the two preparations is based upon the dose that is lethal in 50% of animals for specific genetic mouse strains, and are therefore different, and are not interchangeable. One BOTOX® unit is equivalent to the amount of intraperitoneal injection of toxin that killed 50% of a group of 18–20 Swiss-Webster mice following intraperitoneal injection.[29] Both preparations require reconstitution of the lyophilized, frozen toxin with physiologic saline. In addition, both drugs have a limited shelf life, must be administered shortly after reconstitution, and are injected intramuscularly. There is peer-reviewed literature addressing both the clinical use of BOTOX® and Dysport®. Both toxin preparations have documented utility when used in the appropriate dosage. BOTOX® is injected intramuscularly in dilutions of 25–100 units/mL, while DYSPORT® is injected at a recommended dilution of 500 units/mL.[30]

3.2 Clinical Experience

The most common dilutions used for administering intramuscular injections of BOTOX® are 50 units per/ml and 100 units/ml. However, in a 114 patient multicenter study of pediatric patients with CP, the number of units for each injection were calculated based upon bodyweight, and then the units were diluted to a volume of 2ml for injection.[17] This particular study served as the basis for labeling of BOTOX® for CP in most countries. However, the dosages used represent drug delivery at a higher volume and lower concentration than was used in many of the other published studies.

Botulinum A toxin may be prepared as a 'standard concentration' or 'standard volume'. For standard concentration techniques, 20–100 units/ml of BOTOX® or 500 units/ml of Dysport® are selected arbitrarily by the physician; the volume varies based upon the number of units to be injected. For 'standard volume' techniques, the physician determines the number of units to be administered, and then the units are diluted to this 'standard volume' (e.g. 2–4cc). In this system, the concentration of the toxin varies. For both methods, the number of units is based upon the muscle to be injected, taking into account the size of the muscle and the patient's bodyweight. The optimal dilution required to produce maximal effects of botulinum toxin following intramuscular injection is not known because no systematic studies have been completed to address this question.

3.3 Administration

The maximum dose of botulinum A toxin is calculated based upon bodyweight of the patient. However, ideally the number of units should be based upon the number of NMJs in the muscle to be injected. The maximum dose administered at one injection session reported in the peer reviewed literature is 29 units/kg bodyweight of BOTOX®; this dose of toxin was divided among multiple muscles.[31] When only one or two muscles are injected, the recommended maximum single total dose is 10–12 BOTOX® units/kg bodyweight.[28,32] The dosage guidelines for Dysport® are not as well defined. For the upper extremity, in adults after stroke the package insert recommends 1000 units to be distributed among five muscles. For bilateral gastrocnemius/soleus injections in children with CP, the recommended total single dose is 30 units/kg bodyweight.[33,34]

For administering BOTOX® to pediatric patients with CP, the appropriate toxin dose of units is calculated empirically, based on 1–6 units/kg per bodyweight per muscle. This dosage was established arbitrarily by Koman in 1988, with a major variation being the number of units utilized per muscle, and the concentration of the toxin.[16,17,28,35] This dose has been shown to be well tolerated, while also demonstrating clinical efficacy. However, it is ex-

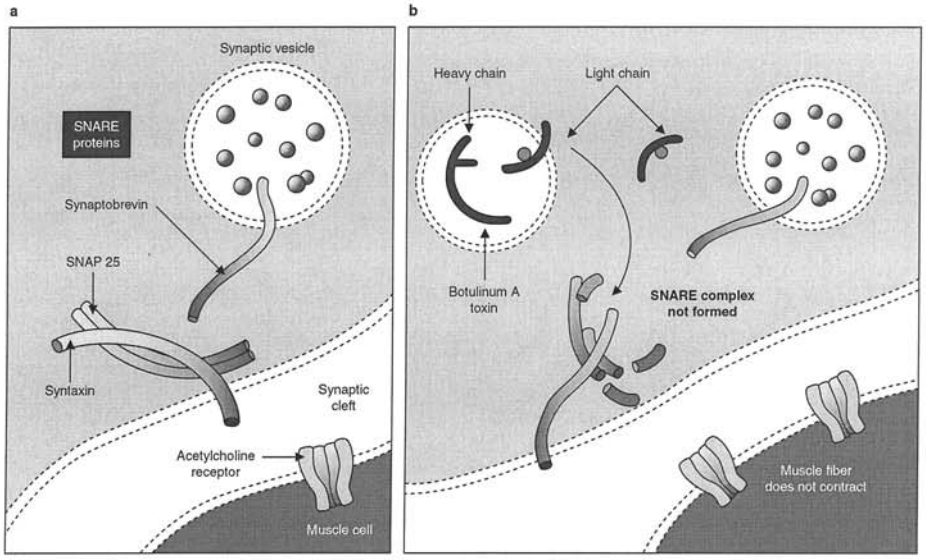

Fig. 2. Mechanism of action of botulinum A toxin. (**a**) In order for the muscle to contract, axonal control must be transmitted via the neuromuscular junction. Normally, a nerve impulse causes presynaptic vesicles to adhere to the cell membrane and acetylcholine is released. For this process to occur, SNARE proteins must be formed to facilitate vesicle contact with the cell membrane. (**b**) Botulinum A toxin blocks SNAP 25, one of three SNARE proteins, prevents fusion of the vesicle, blocks release of acetylcholine, and produces flaccid paralysis of the muscle.[21] **SNAP 25** = synaptosomal-associated protein of 25kDa; **SNARE** = soluble N-ethylmaleimide-sensitive fusion protein receptor (reproduced from Koman,[9] with permission).

tremely likely that the optimal dose should be based upon the number of NMJs per muscle and the mass of the muscle. When administering BOTOX®, multiple variables should be considered in establishing the optimal dose. These include: muscle mass, number of muscles to be injected, general health of the patient, target muscle strength, degree of joint deformity, and patient age. Table II provides a starting formula and may be adjusted based upon individual patient characteristics, with subsequent refinement of the toxin doses used for spasticity management based upon the outcomes experienced by individual patients. The wide range of doses used by various physicians reflects these considerations. Large total doses of botulinum A toxin (29 units/kg bodyweight) have been injected for the management of spasticity in pediatric patients.[31,36] However, the dilution of the toxin and patient characteristics impact the tolerability of the injected toxin dose and must be taken into account when evaluating the amount of toxin to be injected into each individual patient. There are no data published describing complications associated with doses in excess of 20 units/kg bodyweight, or following injections made with toxin dilutions containing <50 units/ml. Most clinic data report the use of botulinum A toxin injected at a concentration of 100 units/ml.

At this time, significant questions remain regarding the importance of various factors in relationship to the most effective administration regimen. These factors include NMJ distribution within the muscle, the volume of drug injected, and the concentration of toxin used. Furthermore, the relationship between the patient's age and toxin required for clinical efficacy is delineated incompletely. Theoretically, small children should require more toxin per bodyweight than adolescents or adults due to the increased density of NMJs in their muscles; however, no clinical reports in pediatric patients have been published that calculated toxin doses based on the number of NMJs. Currently, the number of units injected per muscle is based upon consensus recommendations[28,32] and the preference of specific authors. Based upon the peer-reviewed literature and consensus statements, the authors' dose recommendations for the treatment of specific deformities secondary to the commonly responsible muscles, using BOTOX®, are outlined in table II.

For administering Dysport® to patients with CP, the current recommendation for equinus foot deformity is 15 units/kg bodyweight per calf muscle (medial and lateral gastrocnemius).

The amount of text devoted to the discussion of Dysport® for the management of spasticity in children with cerebral palsy is proportional to the number of articles in the current literature describing the use of Dysport® in this disease. The current review references several articles describing the use of Dysport ® in pediatric cerebral palsy.[33,37-39]

Table II. Dosage guidelines

Clinical deformity	Frequently involved muscle(s)	BOTOX® (units/kg)[a,b]	Usual no. of injection sites
Upper extremity			
Shoulder internal rotation adduction	Subscapularis	1–4	2
	Pectoralis major	1–4	2
	Latissimus	1–4	2
Elbow flexion	Biceps	1–4	2
	Brachialis	1–4	2
Forearm pronation	Pronator teres	1–3	2
	Pronator quadratus	1–2	2
Wrist flexion	Flexor carpi radialis	1–4	2
	Flexor carpi ulnaris	1–4	2
Finger flexion	Flexor digitorum superficialis	1–2	2
	Flexor digitorum profundus	1–2	2
	Flexor pollicis longus	1–2	2
Thumb-in-palm	Adductor pollicis	1	2
	First dorsal interosseous	1	2
Lower extremity			
Scissoring	Adductor longus	1–4	2
	Adductor magnus	1–4	2
	Adductor brevis	1–4	2
	Gracilis	1–2	2
Hip subluxation	Iliacus	2–3	2
	Psoas major	2–4	3
Crouched Gait			
hip flexion	Iliacus	2–3	2
	Psoas major	2–4	2
knee flexion	Semimembranosis	1–3	2
	Semitendinosis	1–3	2
	Biceps femoris	1–3	2
	Rectus femoris	1–3	2
Equinus foot	Medial gastrocnemius	1–3	2
	Lateral gastrocnemius	1–3	2
Varus hindfoot	Posterior tibialis	1–4	2

a The units indicated in this table refer to botulinum A toxin purified neurotoxin (BOTOX®). Dysport® dosage is different. It is important to recognize that the muscle mass and number of neuromuscular junctions (NMJs) varies from muscle to muscle. Because the number of NMJs is relatively constant, very small children may require higher per kg bodyweight administration. The volume effects of toxin delivery are not defined.

b The number of units of Dysport® injected is left to the discretion of the treating physician. The ratio required to convert dosages of Dysport® to BOTOX® is postulated (see text), but not verified. For gastrocnemius ('calf') injections to manage pediatric cerebral palsy spasticity, the Dysport® package insert recommends a dosage of 15 units/kg bodyweight for each calf muscle.

4. Injection Techniques

4.1 Localization

Proper localization of the toxin injection in the desired muscle is crucial for maximizing the clinical effects of the toxin.

Fortunately, the delivery of botulinum A toxin to within 2–4cm of the NMJ is sufficient to ensure that the toxin reaches the target NMJs.[23,24] A study in the gastrocnemius muscle compared the delivery of botulinum A toxin to the 'mid-belly' of the muscle with toxin delivery to the proximal part of the muscle in a randomized, placebo-controlled trial.[40] There was no demonstrable effect on treatment outcome based upon the site that the toxin was injected.[40] These data and other reports support the importance of toxin diffusion for successful delivery of the toxin to the NMJs. Experience to date indicates that as long as the drug is delivered within the myofascial boundary of the target muscle, diffusion provides an opportunity for the toxin to attack the SNAP 25 protein within the NMJs, to produce denervation, and to result in partial flaccid muscle paralysis.[18]

4.2 Techniques

Localization of the muscle to be injected may be achieved by using anatomic landmarks, palpation with or without the muscle under stretch, ultrasound guidance, passive electromyography (EMG), and/or active EMG. The choice of localization technique depends upon the size and location of the muscle to be injected and the experience of the injector. In general, large, easily palpated muscles such as the gastrocnemius, biceps brachia, and hamstrings may be injected based upon anatomic landmarks and palpation with or without the muscle under stretch.[16,17,28] Deeper or smaller muscles (i.e. posterior tibialis, iliopsoas, flexor pollicis longus) require verification of needle placement using ultrasound or EMG prior to toxin injection.[41] Because inappropriate muscle activity may also be present in nontarget muscles, active EMG is more specific than passive EMG in localizing the injection site. Dynamic B-mode ultrasonagraphy alone, or combined with active EMG or passive range of motion of the target muscle, provides a simple, direct, accurate, and inexpensive technique for observing the target muscle.[41] The value of EMG or ultrasound guidance in enhancing the efficacy of injecting smaller amounts of toxin, or improving results when more concentrated aliquots of drug are administered, is a theoretical consideration.

5. Pain on Injection/Management Methods

Botulinum A toxin, when injected through a 25–27^{G} needle, produces a sensation described as both 'cool' and 'warm' during injection. This sensation does not persist beyond the injection, and normally no post-injection inflammatory reaction occurs.

There are no published studies that evaluate the pain associated with intramuscular toxin injections of botulinum A toxin. Practitioners perform injections using methods ranging from no intervention to general anesthesia. Options to diminish pain associated with the injection include: (i) nothing; (ii) topical anesthetics; (iii) topical thermal techniques; (iv) oral narcoleptics (conscious sedation); and (v) general anesthesia. All these procedures are efficacious and well tolerated;[32,37,39,42] however, some options (iv and v) are significantly more expensive, and are associated with morbidity.

The Wake Forest University experience, with over 7000 toxin injections, supports the use of minimal analgesia. For over 95% of our injections, patients received either no analgesia or topical cooling spray [e.g. dichlorodifluoromethane 15% plus trichloromonofluoromethane 85% spray (Fluori-Methane® Spray and Stretch)]. In a recent study of 50 children, pain assessments provided by family members and/or patients indicated that pain was 'minimal' 10 minutes after injection in 98% of the patients (unpublished observation). However, other practitioners have voiced concern over the emotional impact of the injections on the children and their parents. These practitioners prefer the use of sedation with narcoleptics or general anesthesia when administering toxin. Except in cooperative patients, EMG-guided injections require sedation or anesthesia. Multilevel injections, including injection of the psoas major, have been performed at Wake Forest University School of Medicine (unpublished observation); however, general anesthesia is appropriate for most children undergoing iliopsoas injections.[36]

Lidocaine (lignocaine)/prilocaine (2.5%/2.5%) cream (EMLA® cream) is reported to provide effective analgesia for the skin at the injection site; however, penetration of the analgesic beneath the skin is limited and is unlikely to prevent muscle discomfort during the injection. According to the package insert, the cream is applied to the area to be injected and is covered with an occlusive dressing. The dressing must be maintained in place over the injection site for 1 hour before the start of a routine procedure, or 2 hours before the start of a painful procedure, in order to provide optimal analgesia.

Oral midazolam, a short-acting benzodiazepine, may be utilized; however this drug requires the implementation of conscious sedation guidelines when doses ≥0.5 mg/kg bodyweight are used.

6. Safety Considerations

Contraindications to toxin injections are the presence of fixed contracture, allergy to the medication, excessive spasticity, neuromuscular diseases (e.g. myasthenia gravis), and the concurrent use of aminoglycoside antibacterials or other drugs that interfere with neuromuscular function.[43] Dysport® should not be used for: (i) individuals with known hypersensitivity to any com-

ponent of the formulation; (ii) in patients with generalized muscle activity disorders (e.g. myasthenia gravis); (iii) concurrently with aminoglycoside antibacterials or spectinomycin; or (iv) in female patients during pregnancy and lactation.[30] The same contraindications are observed for BOTOX®. Antibody formation in response to intramuscular toxin injections does occur and can interfere with drug efficacy. Because antibody formation is directly proportional to the antigen load delivered with the injection, and may be affected by prior sensitization of the patient to botulinum A toxin, injections should contain the lowest number of toxin units required to attain the desired clinical effect, and be spaced at the longest time interval that maintains a clinical response.[44-46]

Botulinum A toxin is well tolerated when used in doses of <15 units/kg bodyweight.[31] Multilevel lower extremity injections of the iliopsoas, adductors, gastrocnemius, and hamstrings are reported using doses of 29 units/kg bodyweight.[31,36] There are significant safety concerns when toxin dosages exceeding 12 units/kg bodyweight are injected in a single site or single motor group, based on anecdotal reports of untoward distant effects. Adverse events are dose-related. In a multicenter retrospective study of 758 patients who received 1594 treatments, adverse events were 5.1 times greater in patients (mean age 7.2 years) receiving over 1000 units of toxin (Dysport®) compared with children receiving <250 units.[33]

There are no reports of neuropraxia secondary to intraneural injection, a finding supported by basic research.[47] Botulinum A toxin has an excellent tolerability profile, as reported in a series of published reports[3,16,17,32,33,35,37-40,48-69] The most commonly reported adverse events include muscle soreness, transient but greater than desired muscle weakness, and pain. Other adverse events that have been described include: rash, difficulty swallowing, incontinence, instability during ambulation, leg or muscle cramps, stumbling, muscle atrophy, excessive weakness of injected muscles, and antibody formation.[17,33,59] No peri-injection deaths have been reported in the literature.

7. Indications for Toxin Injections

7.1 Availability

At the time of writing, botulinum A toxin (BOTOX®) is approved for use in CP in 49 countries. Although BOTOX® is not FDA-approved for use in pediatric patients with CP in the US, it is utilized for the management of dynamic deformity in children and adults with CP, with payment for its use by the majority of insurance carriers and Medicaid programs in most states. Dysport® is available and approved for the management of equinus gait in CP in the UK, many European countries, and some Commonwealth countries. Dysport® is not approved by the FDA for use in the US.

7.2 Randomized, Placebo-Controlled Trials

The clinical efficacy and tolerability of botulinum A toxin (both BOTOX® and Dysport®) has been demonstrated in five randomized, double-blind placebo trials.[17,39,48,50,63] A sixth trial performed in 1988 followed 12 patients for 4–6 weeks after botulinum A toxin injection.[35] A response to toxin occurred in 5 of 6 patients (83%), and a placebo effect was noted in 2 of 6 patients (33%). Although these results were not statistically significant, they demonstrated an effect of the injection in the majority of children receiving toxin.[35] The efficacy of toxin injections for reducing equinus foot deformity was demonstrated in three studies involving 178 patients;[17,39,63] for reducing specific upper extremity deformities,[50] and for reducing postoperative pain.[48] The tolerability of toxin injections was demonstrated in all six randomized, double-blind, placebo-controlled studies.

7.3 Equinus Deformity

7.3.1 Management

Approval for the use of botulinum A toxin (BOTOX®) for the management of spasticity associated with CP is based upon a multicenter trial that evaluated equinus foot deformity.[17] This seminal investigation employed a randomized, placebo-controlled clinical trial that evaluated 114 children with toe-walking secondary to spasticity related to CP. An additional 29 Canadian children were included in the safety analysis portion of the study. The dose of BOTOX® was 2 units/kg bodyweight, delivered in a volume of 2ml per muscle. A repeat injection was administered at 4 weeks. The patients randomized to the botulinum A toxin group demonstrated statistically significant improvement in gait that paralleled EMG evidence of selective denervation (M response). A response rate of approximately 70% was observed in patients who received toxin.[17] The gait of a subset of this cohort (n = 26) was evaluated using computerized gait analysis.[62] The kinematic and EMG gait data documented gait improvement, including increased dynamic ankle dorsiflexion, increased stride length, and increased antagonist activity in the anterior tibial muscle.

Ubhi et al.[39] evaluated 40 children (22 receiving toxin and 18 receiving placebo), and demonstrated clinically and statistically significant improvement in initial foot contact based on video gait analysis and gross motor function measures (i.e. the walking dimension at 6 and 12 weeks) after toxin injection. Dysport® was injected at a dose of 25 units/kg bodyweight in children with diplegia and 15 units/kg bodyweight in children with hemiplegia.[39] Passive ankle dorsiflexion was not affected;[39] how-

ever, we believe that the rigid study entry criteria meant that a statistically significant improvement in this measure was unlikely. In another prospective double-blind study of 20 children, Sutherland et al. evaluated the effects of toxin versus placebo on walking using computerized gait analysis. The study concluded that botulinum A toxin (BOTOX®) improved peak ankle dorsiflexion in the stance and swing phase of gait compared with placebo.[63]

An open-labeled follow-up study followed many of the patients in the multicenter protocol,[17] and additional children with equinus deformity, for a mean duration of botulinum A toxin exposure of 1.46 years (302 patient years).[59] BOTOX® at a dose of 4 units/kg bodyweight was utilized. In this open-labeled multicenter study, 207 children were enrolled in nine centers. Continued response to the toxin injections decreased over time from 58 to 41% of the patients. There were no serious adverse events. Patient complaints included pain at the injection site, leg cramps, stumbling, and calf atrophy. Antibodies were detected in 26% of children; however, only 6% (7/117) of the patients with detectable antibodies demonstrated no response to the injections. These two trials[17,59] used the original BOTOX® formulation which contained 25ng of protein per 100 units of toxin;[59] the formulation of BOTOX® that is currently available contains 5ng of protein per 100 units of toxin. Therefore, the protein load has been significantly decreased. In another open-labeled study using consistent data acquisition, 48 patients receiving BOTOX® for equinus gait were followed for an average of 3.4 years.[58] Twenty-five (52%) required heel cord surgery at an average age of 7 years during follow-up; 48% continued to respond to treatment with improved gait and a delay in 'the need for surgery'.

In support of the use of botulinum A toxin to affect the natural history of equinus gait, Garcia Ruiz et al. evaluated eight patients with isolated equinus gait at a mean follow-up of 33 months.[56] As judged by two blinded independent physicians who reviewed videotapes of the patients, all patients exhibited progressive improvement and none developed fixed contractures. Several additional prospective open-label, nonrandomized studies have demonstrated the efficacy of botulinum A toxin in the management of equinus deformity in patients with CP.[3,16,31-33,36-38,40,49,51,52,58,60,67-69]

These trials evaluating the efficacy of botulinum A toxin on the management of equinus deformity suggest: (i) a clinical response occurs in 50–70% of children; (ii) the length of time of clinical response is variable; (iii) adverse effects and complications are minor and resolve without sequelae; (iv) dosage and post-injection regimens vary widely; and (v) multilevel injections are frequently indicated thus, confounding data analysis.

7.3.2 Physiologic Effects

The physiologic effects of botulinum A toxin on the gastrocsoleus are addressed by Boyd et al.[49] in a prospective trial involving 25 children. Three-dimensional gait analysis was used to define two new measures of ankle kinetics: ankle movement quotient (AMQ), and ankle power quotient (APQ). Pre- and post-injection analysis of the gait studies demonstrated improvements in ankle biomechanics consistent with and supportive of 'biomechanical transformation of muscle (the gastrocnemius-soleus)'.[49] The findings described by Boyd et al.[49] are supported by a prospective study performed by Eames et al.[37] that evaluated 39 children who received isolated gastrocnemius toxin injections. Study data demonstrated a strong correlation between the dynamic component of the muscle spasticity noted before the injection and the magnitude of the post-injection response.

7.3.3 Toxin as an Alternative to Casting

Two randomized prospective studies evaluated the effects of botulinum A toxin compared with stretching casts in the treatment of equinus deformity.[51,54] Both studies evaluated children with incomplete passive ankle dorsiflexion or a degree of contracture for which one or more stretching casts were indicated clinically in order to restore range of motion and/or postpone calf surgery in younger children. In both studies, botulinum A toxin without casting demonstrated efficacy similar to casting alone, as assessed by clinical examination and video gait analysis.[51,54] Corry et al.[51] utilized a clinical examination in addition to three-dimensional gait analysis to demonstrate that botulinum A toxin injections improved ankle kinematics in both groups. However, this improvement was maintained in the botulinum A toxin group but relapsed in the 'cast only' group at 12 weeks.[51] Fewer adverse effects were observed in the botulinum A toxin group;[51] parents 'consistently favored botulinum toxin A and highlighted the inconvenience of serial casting'.[54] The average time to re-intervention was similar for both groups.[51]

There are no peer reviewed randomized trials evaluating short-term casting combined with botulinum A toxin, compared with botulinum A toxin alone or casting alone. This is unfortunate because many practitioners inject botulinum A toxin and then utilize one or more weeks of casting of the injected extremity. These practitioners report a synergistic response from the combination of toxin and casting that leads to improvements beyond the level that would be expected by either modality used alone.

7.4 As an Adjunctive Intervention

The importance of muscle strengthening and the efficacy of multi-modal interventions to manage equinus deformity was addressed in a prospective trial comparing botulinum A toxin (Dys-

port®) alone versus botulinum A toxin and functional electrical stimulation in 10 patients.[38] The combined treatment was statistically more effective in reducing muscle tone and improving gait velocity, stride length, stance, and swing-symmetry.[38] Another study demonstrated that a 'very' low dose (0.5–1.0 unit/kg bodyweight per muscle) of botulinum A toxin when combined with rehabilitation produced a long-lasting decrease in spasticity in addition to improvements in gait.[60]

7.5 Upper Extremity Indications

One prospective double-blind, placebo-controlled trial,[50] one prospective, randomized, single-blinded comparison of botulinum A toxin injections and occupational therapy versus occupational therapy alone,[53] and two prospective studies[55,65] support the use of botulinum A toxin in the upper extremity. The results of an open label trial have also been reported.[70]

Indications for upper extremity botulinum A toxin injections include: (i) thumb-in-palm; (ii) wrist flexion; (iii) forearm pronation; (iv) elbow flexion; and (v) shoulder internal rotation and/or adduction. Injections reliably decreased muscle power and spasticity, and patients demonstrated selective improvements in appearance, function, and caregiving; however, pre-injection response is not reliably predictable.[50,53,55] The total number of children evaluated is small (n = 102), the number of muscles evaluated is large (n = 6–7), and the length of follow-up is short.

7.6 Impact on Health-Related Quality of Life

The value of botulinum A toxin and its effects on improving the health-related quality of life of children and their caregivers is implied in most of the studies referenced. Adverse events such as excessive weakness, incontinence, and injection site pain clearly affect children and their families. Documented improvements in health-related quality of life associated with toxin injections include: (i) diminished pain from spasticity;[57] (ii) diminished postoperative pain with earlier hospital discharge;[48] (iii) decreased caregiver burden;[55,57,71] (iv) improvements in activities of daily living;[50,53,72] (v) avoidance of casts;[35,57] and (vi) improvements in self-esteem.[53] Barwood et al.[48] evaluated the impact of botulinum A toxin on postoperative pain associated with adductor tenotomies using a double-blind, placebo-controlled trial, and demonstrated diminished discomfort, decreased opioid use, and earlier hospital discharge in the patients who received toxin injections.

7.7 Indications for Use

The use of botulinum A toxin is supported for the following general indications in selected patients: (i) to improve function in patients with dynamic deformity; (ii) to improve health-related quality of life in children with excessive deformity and/or painful spasticity; and (iii) to potentiate or replace other treatment modalities. The specific use of botulinum A toxin injections has been reported or suggested for equinus gait, crouched gait, knee flexion deformity, scissoring, varus hindfoot, knee extension during swing phase, shoulder deformity, elbow flexion deformity, wrist flexion deformity, finger flexion deformity, thumb-in-palm, excessive pronation, painful spasticity, movement disorders (athetosis and dystonia), enhancement of neuromuscular electrical stimulation, facilitation and/or reduction of specific caregiver functions, decreased postoperative pain, alleviation of painful spasticity, and improvement in self-esteem due to decreasing reflex posturing.

8. Pre- and Post-Injection Assessment and Monitoring

8.1 Pre-Injection Assessment

Pediatric patients with CP followed at the Wake Forest University School of Medicine undergo a routine physical examination at each visit. Their degree of mobility is assessed, their functional abilities are evaluated using the Functional Independence Measure for Children (WeeFIM),[73] and their level of spasticity is evaluated using the Ashworth Spasticity scale. Their physical examination also includes an assessment of their spine, upper extremities, and lower extremities. Range of motion of the upper extremity (shoulder, elbow, forearm, wrist, and hand) and the lower extremity (hip, knee, and ankle) are recorded. Observational gait analysis is also performed in ambulatory patients. This physical examination is used to determine the degree of spasticity or the presence of any fixed contracture. Muscles that are noted to exhibit increased spasticity are identified and an injection plan is determined based on the number of muscles to be injected and the bodyweight of the child.

8.2 Pre-Injection Goal Setting

Botulinum A toxin treatment goals are discussed with the patients' parents/caregivers before injections are administered. The overall goals for upper extremity injections include reduced pain, improved function, improved self-esteem, improved ease of caregiving, and facilitation of hygiene. Specific goals for the upper extremity also are identified (table III).

Table III. Goals for treatment of the upper extremity with intramuscular botulinum A toxin injections, and the muscles injected most frequently to obtain these goals

Body area	Goals	Muscles injected
Shoulder	Increased abduction	Pectoralis major, latissimus dorsi
	Increased external rotation	Pectoralis major, subscapularis
	Increased internal rotation	Infraspinatus, teres minor
Elbow	Improved extension	Biceps, brachialis, brachioradialis
Forearm	Improved supination	Pronator teres
Wrist	Improved extension	Flexor carpi radialis, flexor carpi ulnaris
Hand	Improved finger extension	Flexor digitorium superficialis, flexor digitorium pollicis
Thumb	Increased abduction	First dorsal interosseous, adductor pollicis brevis

For the lower extremity, treatment goals may include improving gait, reducing equinus deformity, facilitating hygiene, improving seating ability, improving tolerance for orthotics, and/or reducing the need for orthotics.

8.3 Monitoring Treatment and Adverse Events

At each follow-up visit, patients are evaluated using the same physical examination used before the toxin injection. In addition, ambulatory patients may be followed using motion analysis performed before and after the injections. Parents/caregivers also complete health-related quality of life questionnaires in order to monitor the effects of the toxin injections from their perspective.

Parents/caregivers are instructed to call immediately if they notice any adverse events following their child's toxin injection. In addition, at each follow-up visit parents are asked to describe any adverse events they may have noted following their child's most recent injection. Although most patients do not report adverse events, the most commonly reported adverse event is soreness of the injected muscle.

9. Conclusions

Intramuscular injection of botulinum A toxin is well tolerated and efficacious if utilized to balance muscle forces across joints in the absence of fixed contractions. The two botulinum A toxin preparations that are currently available have different 'units', and therefore, the dose must be ascertained carefully. Localization of toxin to desired muscles is important and may be aided by electrodiagnostic methods or ultrasonography. Toxin effects are dose-related and multifactorial. Therefore, defining pre-injection goals and monitoring patients to document the continuing attainment of desired outcomes is an integral component of using repeated injections of botulinum A toxin. Botulinum A toxin is well-documented as a treatment option for patients with equinus deformity, is helpful in managing selected upper extremity deformities, and is a valuable adjunct in the global management of spasticity in selected patients with multilevel muscle spasticity. The drug may diminish pain related to spasticity or surgery, decrease caregiver burden, and enhance health-related quality of life.

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