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High dose botulinum toxin A for the treatment of lower extremity hypertonicity in children with cerebral palsy

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Abstract

The aim of this study was to determine the safety profile of high dose (15–25 units/kg) of botulinum toxin A (BTX-A) in children with cerebral palsy (CP) and increased lower extremity muscle tone. We performed a retrospective review of 929 patient encounters at the Movement Disorders Center at Washington University. A total of 261 patients (105 females; 156 males) were treated during these visits, ages 6 months to 21 years (mean 8y 4mo [SD 4y 8mo]). Ambulatory ability at the time of BTX-A injection was independent ambulation (36.4%, *n*=95), ambulation with a walker (27.6%, *n*=72), and non-ambulatory (31.8%, *n*=83). A few patients (4.2%, *n*=11) were able to ambulate with a cane or crutch at the time of injection. Participants were characterized according to BTX-A dose, CP etiology, motor involvement pattern, muscles injected, ambulatory ability, and use of oral tone medications. Follow-up records were searched for reported adverse events (AEs), with a mean time to AE assessment of 6.5 weeks (SD 3.38). The AE occurrence was determined for doses of 0 to 4.9 units/kg, 5 to 9.9 units/kg, 10 to 14.9 units/kg, 15 to 19.9 units/kg, and 20 to 25 units/kg. The overall AE occurrence was 4.2%. Standard doses of BTX-A had side-effect occurrences of 3.9% for 5 to 10 units/kg and 7.6% for 10 to 15 units/kg. Among higher doses (15–20 units/kg and 20–25 units/kg) the AE occurrence was 3.5% and 8.6% respectively. No patient developed botulism. AEs were randomly distributed across dosing groups, CP etiologies, clinical phenotypes, ambulatory status, and treatment duration. All doses were associated with a significant increase in passive range of motion using the Tardieu scale. We conclude that higher dose BTX-A is safe in children with a spectrum of CP phenotypes and are well tolerated over time.

Cerebral palsy (CP) is a common neurological condition causing cognitive and motor disability in a large percentage of children born preterm.[1] The positive (increased tendon jerks and clonus) and negative (limitation of range of motion, joint deformity, and

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contracture) symptoms of spasticity found in CP are theorized to occur via chronic hyperactivity of the spinal reflex. Botulinum toxin A (BTX-A) is a potent neurotoxin produced by the bacterium clostridium botulinum that causes reversible chemodenervation by irreversibly binding to the acetylcholine receptor at the neuromuscular junction. Botulinum toxin presumably relieves the symptoms of spasticity by disrupting the hyperactive spinal reflex at the level of the neuromuscular junction.

Despite numerous studies demonstrating efficacy and safety of botulinum neurotoxin A in children, many patients have unmet tone needs and it is unclear if higher doses of BTX-A can be safely used. The efficacy of BTX-A injection for children with CP and excessive lower extremity tone has been demonstrated in several placebo-controlled studies with joint range of motion as the primary outcome measure.[2–4] However, gait analysis performed on ambulatory children who received BTX-A injections in the lower extremities demonstrated no significant improvement.[5] These discrepancies may reflect uncertainty with respect to dose, dilution, or injection technique for the treatment of increased motor tone in children.[6–8]

The majority of previous studies of children with lower extremity botulinum treatment for spasticity have used a maximum dose of 10 units/kg Botox or 30 units/kg Dysport (the preparation of BTX-A commercially available in Europe). A conversion ratio of 1 unit Botox: 4 units Dysport has been suggested based on head to head efficacy trials.[8] Two recent studies have reported the experience with higher dose toxin in children. Heinen et al. reported 495 multilevel treatment sessions with a cumulative mean dose of 16.6 units BTX/kg bodyweight (9.9–23.9) in patients with spastic diplegia, with a mean adverse event (AE) rate of 8.8% (5–22.2%).[9] Goldstein reported a retrospective study of 94 children and 14 adults who received a mean injection dose of 19.1 units/kg and 15.2 units/kg botulinum respectively to the upper and/or lower extremities.[10] AEs after a single injection were reported in three patients, one of whom contracted generalized botulism.

In addition to using lower doses of BTX, previous investigations have included only patients with mild to moderate spasticity. Patients with dystonic CP, mixed spastic-dystonic CP, those also taking oral tone reducing medications (such as baclofen, levodopa, or benzodiazepines), and those who are severely affected have largely been excluded from published studies.

To address uncertainties in the literature regarding higher dose BTX-A in children, we performed a large retrospective chart review of children injected at our center to determine the safety of high dose BTX-A in children with lower extremity hypertonicity due to CP.

Method

PARTICIPANTS

This retrospective chart review was approved by the Washington University School of Medicine Human Studies Committee. Our study included 261 patients who underwent 929 injection visits to the Pediatric Botulinum Toxin Clinic at the Washington University Movement Disorders Center (MDC) in St Louis between January 1 1999 and May 6 2006. Children were eligible for lower extremity BTX-A injections if they demonstrated dynamic joint contracture due to increased muscle tone in the lower extremities.[11,12] The majority of patients were referred from St Louis Children's Hospital Cerebral Palsy Center (CPC) by a Washington University pediatric neurologist who specializes in CP. All patients were injected with BTX-A in a pattern determined by the treating physician and had a postinjection physiotherapy plan. Patients who underwent repeat injection were treated according to the clinical need and potentially had the location, dose of toxin, or postinjection

physiotherapy plan adjusted. We defined an AE as any new symptom/complaint or a worsening of chronic symptoms/complaints that occurred after botulinum injection, excluding the effects of the injection itself such as immediate injection pain, soreness, or bruising. Face to face assessment for AEs took place via open-ended questioning 4 to 6 weeks postinjection at the CPC by the same physician for all patients, at subsequent physical therapy sessions by a physical therapist experienced with CP, and at the MDC by the same physician for all patients if repeat injections were received. No anesthesia or sedation was used for any injections.

DATA COLLECTION AND STUDY DESIGN

We searched the database of the MDC at Washington University which contains the office visit information for all adults and children seen in our MDC for injection information using the following search criteria: ICD 9 code=343.9 (spasticity due to perinatal injury) AND age <25 AND keyword='botulinum'. A second search included the search terms keyword='cerebral palsy' OR 'diplegia' OR 'quadriplegia' OR 'hemiplegia' AND age <25. The output from both searches was combined and these patients had an initial chart review. Patients were excluded if they had an evaluation for BTX-A injections but did not receive injections, did not receive any BTX-A injections in their lower extremities, or no follow-up information was available. Eight patients were excluded because they were lost to follow-up, i.e. they did not return for any physical therapist, MDC, or CPC appointments. The total number of patient encounters excluded was 40, the majority of which were excluded because the patient received only upper extremity BTX-A injections.

For each of the selected 261 participants, the MDC database patient chart was reviewed and the following information extracted for each visit: the anatomical location of each injection, the amount of BTX-A injected per site, pre-injection range of motion measurements (when available), visit date, sex, and date of birth. One muscle group was injected in 837 patient visits, two muscle groups in 86 patient visits, and three muscle groups in six patient visits. We then reviewed each patient's CPC chart for the following information we felt could influence the occurrence of AEs: etiology of CP (as determined by the referring pediatric neurologist after diagnostic evaluation), pattern of motor involvement (diplegia, hemiplegia, or quadriplegia), characterization of motor hypertonicity (spastic CP, dystonic CP, or mixed CP), ambulatory ability (independently ambulatory, ambulant with cane/crutch, ambulant with walker, or non-ambulatory), and use of tone-reducing medications (levodopa, benzodiazepines, and/or baclofen).

Assessment for AEs took place on at least two occasions after each BTX-A injection, first at the CPC by the referring pediatric neurologist 4 to 6 weeks postinjection and again at the MDC by the movement disorders neurologist 4 to 6 months after injection (during evaluation for repeat injection). AEs were occasionally reported via telephone to the MDC, or to other Washington University physicians. Follow-up records, including phone call records (when available) at both centers, were reviewed for AEs and postinjection modified Tardieu scale measurements.[13] Each patient's general outpatient chart (which contains hospitalization information and notes from outpatient visits to other physicians at Washington University) was also reviewed for possible AEs. Injection maps and follow-up records were complete for all reported patients.

Pre- and post-Tardieu range of motion measurements were available for 442 muscle group injections. For clinical response, as measured by the change in Tardieu range of motion, each limb was considered independently since dose/kg/limb could be different. This resulted in a doubling of the outcome observations for change in range of motion.

Patients were selected for longitudinal safety analysis if they received greater than six sets of BTX-A injections (range 6–16 sets of injections) over at least 24 months (range 24–60mo). Forty-eight patients met these criteria for a total of 423 patient visits. The injection history for these patients showed whether they received high (15–25 units/kg) or low (1–14.9 units/kg) doses of BTX-A over time. Long-term safety analysis was performed for the low dose group and for the high dose group.

DATA ANALYSIS

All statistical analyses were performed with SPSS version 13.0. For the purpose of this study, patients were grouped by motor group: hamstrings, adductors, and gastrocnemius/soleus complex. In addition, doses administered were grouped as follows: 0 to 4.9 units/kg, 5 to 9.9 units/kg, 10 to 14.9 units/kg, 15 to 19.9 units/kg, and 20 to 25 units/kg. AE rates were calculated for each motor group by dose, and compared across dosing groups, CP subtypes, CP etiologies, ambulatory abilities, and medication use. The frequency of AEs was compared with a χ^2 test using the crosstabs function in SPSS. Mean changes in range of motion were compared using a two-tailed *t*-test. All means are reported as standard deviation (SD). Results were considered clinically significant if $p<0.05$.

Results

PATIENT DEMOGRAPHICS

Complete data were available on 261 patients (105 females, 156 males) who completed 929 injection visits. Age ranged from 6 months to 21 years with a mean of 8 years 4 months (SD 4y 8mo). The most common etiology of CP was perinatal brain injury (79.7%, *n*=207), which included complications of prematurity, complicated labor, or delivery. Children with other ‘secondary’ causes of CP were also included in this study (Table I). Lower limb function, as evidenced by ambulatory ability at the time of BTX-A injection, was nearly evenly divided between independent ambulation (36.39%, *n*=95), ambulation with a walker (27.59%, *n*=72), and non-ambulatory (31.8%, *n*=83). A few patients (4.2%, *n*=11) were able to ambulate with a cane or crutch at the time of injection. Medications for the treatment of increased tone were used in 79 (30.23%) patients. Baclofen was administered most often (14.17%, *n*=37), followed by levodopa (8.8%, *n*=23), then benzodiazepines (1.9%, *n*=5). Benzodiazepines were most often prescribed for the treatment of coexisting epilepsy. Fourteen (5.3%) patients were taking a combination of tone reducing medications at the time of botulinum injection. One hundred and eighty-two (69.7%) were not taking additional treatment for increased motor tone.

ADVERSE EVENTS

AEs of any type were reported overall in 39 of 929 (4.2%) of injections. Of these, 10 occurred in the 15 to 19.9 units/kg, and 5 occurred in the 20 to 25 units/kg dose group (Table III). The remaining 24 AEs were reported in patients receiving 5 to 14.9 units/kg. There were no AEs reported among those that received fewer than 5 units/kg. The most frequently reported AE was motor weakness or fatigue. There was no increased frequency of motor weakness or fatigue in low dose (0–14.9 units/kg, *n*=4.9%) versus high dose (15–25 units/kg, *n*=4.6%). Motor AEs were generally not severe enough to limit function. Transient (<48h) injection site soreness/pain, redness, or bruising was reported after eight visits. There was no report of persistent muscle pain or soreness or change in bowel or bladder continence. Both instances of increased dryness of pulmonary secretions occurred in a patient dependent on a ventilator and required no additional treatment. One instance of lower respiratory tract infection occurred in a patient with tracheotomy who had a precedent upper respiratory tract infection and had a history of frequent lower respiratory tract

infections. Another patient with a diagnosis of epilepsy had a seizure approximately 24 hours after injections. There was no case of botulism.

There was no significant difference in overall AE rates or subcategories of AEs between dosing groups based on dose, CP etiology, motor pattern of involvement, hypertonicity subtype, ambulatory status, or medication use. Although there was no reported AE in the 0 to 4.9 units/kg dosing group, the difference between this group and the other groups combined was not statistically significant. The injection dose did not explain the distribution of injection site side-effects.

A longitudinal safety analysis of 48 patients who received between 6 and 16 sets of injections over 24 to 60 months was performed. Twenty-nine patients received 15 to 25 units/kg for a total of 251 visits (high dose); the remaining 19 received less than 15 units/kg over 172 visits (standard dose). Seven patients in each group experienced AEs, and the AE occurrence over patient visits was 4.38% for the high dose group and 5.2% for the low dose group. There was no statistically significant difference of AE occurrence between high and low doses of botulinum when given over prolonged periods of time.

High doses of BTX-A are given in our center either initially for severe dynamic contracture or as the result of a titration. Further analysis of the 29 patients who received high doses of BTX-A for at least 24 months revealed no difference in the AE occurrence when a high dose was begun and continued versus when that dose was achieved through titration (2% vs 2.4%). There was no statistically significant difference in the occurrence of any AE, particularly regional weakness, generalized weakness, or fatigue between these two groups, suggesting that high doses of BTX-A were well tolerated for the duration of treatment.

RANGE OF MOTION OUTCOME

Range of motion outcome was available for three muscle groups: hamstrings, adductors, and gastrocnemius/soleus complex. The mean change in range of motion as measured by the Tardieu scale was 9.6° (hamstrings), 7.4° (adductors), 0.8° (gastrocnemius), and 1.2° (soleus). These differences were all significant (Table II). Although the mean changes in the gastrocnemius/soleus complex were small, the range of response was substantial. There was no clear relationship between dose of BTX-A and change in range of motion.

Discussion

The role of BTX-A in the treatment of excessive lower extremity tone in children with CP has recently been questioned due to reports of inferiority to serial casting[14,15] and earlier recurrence of contracture.[16] This is in contrast to studies which demonstrate the efficacy and safety of BTX-A, and support its use in the pediatric population.[17] Our retrospective analysis of open label use of BTX-A investigated the safety of higher dose BTX-A injections in commonly encountered clinical scenarios in children with CP. Previously published studies have used relatively low doses of BTX-A for concern of causing serious systemic AEs, and it is possible that this has led to inadequate treatment in recent studies. This study suggests that doses of BTX-A between 15 and 25 units/kg can be administered to the hypertonic lower limbs of children with CP regardless of etiology, clinical phenotype, severity, functional ability, or medication use with an AE rate that is comparable with lower doses.[18] An advantage to our study is that the study participants represent a variety of CP phenotypes seen in clinical practice, enabling us to infer safety across a broad spectrum of neurological involvement. Contrary to a recent study, we report safety data beyond a single injection, up to 5 consecutive years of receiving higher doses without increase in AE. Given the very careful manner in which AEs are assessed in our center, we believe that the absence of severe AEs is likely due to technical differences in injection technique.

As with other studies, we found that patients treated with BTX-A experienced improved range of motion as measured via the Tardieu scale. The lack of a dose-response relationship is likely due to the fact that BTX-A was administrated in an open label, non-randomized fashion. It is also likely that there is a ceiling event with improved range of motion and that children injected undergo repeat injection prior to complete wearing off, therefore not demonstrating marked changes in range of motion during subsequent visits. Interestingly, parent and patient satisfaction was greatest among those who received heel cord injections, which had the least absolute change in range of motion. Hamstring range of motion measurements had the greatest absolute change, but parent perception did not reflect this. Rather, parents reported little functional benefit most often after hamstring injections in spite of the significant gains in hamstring range of motion simultaneously observed by the treating physician and physical therapist. This highlights the difficulties of previous studies in demonstrating clinical benefit, especially with injection into larger muscle groups, since those studies incorporated endpoints such as Tardieu scale, passive range of motion, and 3D gait analysis, which may be more relevant to the treating physician than to the patient. It is possible that higher doses of BTX-A in these muscles may result in greater functional benefits but refining our endpoints to clinically meaningful patient outcomes is still essential.

Another benefit of our study population is the opportunity to study AEs as related to subpopulations of disease and treatment. It has been suggested that dystonic muscles are more sensitive to BTX-A and, theoretically, these patients may be at higher risk for developing AEs related to muscle weakness.[19] This was not found to be true in our analysis. Furthermore, the interaction between tone reducing medications and BTX-A has not been well studied. Patients with dystonia or those taking tone reducing medications did not have more AEs in any dosing group, and appear to be appropriate candidates for BTX-A injection as well.

Finally, our data show no evidence of incremental toxicity after up to 5 years after injection. Animal studies of the short-term events of botulinum on growing muscle tissue have suggested that BTX-A injected muscle causes myofibril atrophy and decreased relative muscle growth.[20] This decrease in muscle growth was attenuated by postinjection exercise and, curiously, associated with up-regulation of Myo D, a protein expressed in hypertrophied muscled in response to increased load bearing. No human studies have investigated the short- or long-term physiological or pathological effects of botulinum on developing hypertonic muscles. Therefore, further studies of childhood exposure, AEs, benefit, and muscle physiological changes are needed, especially given the long duration of therapy for most children.

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List of abbreviations

AE	Adverse event
BTX-A	Botulinum toxin A
CPC	Cerebral Palsy Center
MDC	Movement Disorders Center

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Table I

Etiology of cerebral palsy

Cerebral palsy etiology	Number of occurrences (%)	Description (n)
Perinatal brain injury	207 (79.7)	Brain injury due to perinatal asphyxia or associated with prematurity
Traumatic brain injury	13 (4.9)	Accidental and non-accidental
Vascular/hypoxic event	10 (3.8)	Embolic stroke (2)
		Arterial stroke of unknown etiology (2)
		Sagittal sinus thrombosis (1)
		Global hypoxia/anoxia during cardiac arrest (1)
		AVM rupture (2)
		Stroke associated with CNS vasculitis (1)
		Factor V Leiden deficiency (1)
Postinfectious	11(4.2)	Encephalitis NOS (2)
		Congenital viral meningitis (CMV, HIV, HSV) (6)
		Bacterial meningitis (2)
		Malarial cerebritis (1)
Structural abnormality	8 (3.1)	Amniotic banding with cerebrocraniofacial abnormalities (1)
		Congenital spinal cord malformation (2)
		Brain tumor (1)
		Encephalocele (2)
		Dandy Walker malformation (2)
Inherited disorder	7 (2.7)	Mitochondrial encephalopathy (3)
		Leukodystrophy (2)
		Chromosome translocation (1)
		Genetic syndrome of unknown type (1)
Movement disorder	3 (1.2)	Huntington disease (1)
		Generalized dystonia (1)
		Olivopontocerebellar atrophy (1)
Metabolic disorder	2 (0.8)	Hartnups (1)
		Pyruvate dehydrogenase deficiency (1)

AVM, arterial venous malformation; NOS, not otherwise specified; CMV, cytomegalovirus; HSV, herpes simplex virus.

Table II

Change in range of motion with botulinum toxin A injections

Muscle group	Dose/muscle/kg Mean (SD)	Preinjection ROM Mean degrees (SD)	Postinjection ROM Mean degrees (SD)	p value
Hamstrings (*n*=288)	8.1 (5.3)	−44.5 (11.3)	−34.9 (12.7)	<0.001
Adductors (*n*=47)	7.7 (1.8)	31.3 (16.2)	38.7 (18.5)	<0.001
Gastrocnemius (*n*=60)	4.5 (2.0)	7.7 (10.1)	8.5 (8.0)	0.02
Soleus (*n*=47)	4.8 (2.2)	11.7 (9.3)	12.9 (9.3)	0.001

ROM, range of motion.

Table III

Adverse events for all doses of botulinum toxin A administered in 929 patient visits

Botulinum toxin A dose injected units/kg of bodyweight	**0–4.9 U/kg**	**5–9.9 U/kg**	**10.1–14.9 U/kg**	**15–19.9 U/kg**	**20–25 U/kg**	**Total**
	n=87	**n=233**	**n=263**	**n=288**	**n=58**	
Adverse events *n* (%)	0 (0)	9 (3.9)	15 (5.7)	10 (3.5)	5 (8.6)	39 (4.2)
95% CI	0–4.2	2–7.2	3.5–9.19	1.9–6.3	3.7–18.6	3.1–5.7
Muscle weakness or fatigability	0	7	9	5	5	26
Flu-like symptoms – fever, malaise, generalized fatigue	0	0	3	2	0	5
Increased dryness of pulmonary secretions	0	2	0	0	0	2
Seizure	0	0	0	1	0	1
Respiratory tract infection	0	0	0	1	0	1
Other (diarrhea, irritability)	0	0	3	1	0	4
Injection site events – bruising, tenderness, swelling	0	0	5	1	2	8

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