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Management of Spasticity in Cerebral Palsy with Botulinum-A Toxin: Report of a Preliminary, Randomized, Double-Blind Trial

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Summary: In order to evaluate further the efficacy of local intramuscular injections of botulinum-A toxin (BAT-A) in the management of dynamic equinus deformity associated with cerebral palsy, a randomized, double-blind, placebo-controlled study was undertaken. When evaluated using our Physician Rating Scale, 83% (five of six) of patients receiving toxin showed improvement, versus 33% (two of six) receiving placebo. There were no major complications. BAT-A injections appear to be safe and effective in children, and merit further prospective study. **Key Words:** Botulinum-A toxin—Cerebral palsy—Dynamic joint contracture—Spasticity.

The treatment alternatives for the foot and ankle deformities associated with spastic forms of cerebral palsy include neuropharmacologic agents, orthotic devices, physical therapy, and surgery (2,3, 13,25). An accepted treatment for small muscle spasms such as blepharospasm, strabismus, and spasmodic dysphonias, botulinum-A toxin (BAT-A), if effective in larger muscles as well, may allow delay or elimination of surgical intervention, diminish painful spasticity, and enhance orthotic techniques. In light of the results of an earlier open-labeled study (19), a small, double-blind, placebo-controlled study was designed to further assess the efficacy and safety of BAT-A in the management of symptomatic spasticity in pediatric cerebral palsy patients.

MATERIALS AND METHODS

Twelve ambulatory patients, 4–11 years old, were studied. Enrollment required a nonprogressive lesion resulting in spasticity (cerebral palsy), no other significant health problems, and equinovarus or equinovalgus foot deformities associated with dynamic (i.e., nonfixed) joint contracture unresponsive to physical therapy, orthotics (braces), or other nonoperative modalities, including neuropharmacologic agents. Four patients were considered hemiplegic; the remaining eight were considered diplegic. The goal of this trial was to determine the effects of two injections of BAT-A on the function of the lower leg over a 4- to 6-week treatment period.

Vials of toxin/placebo were prepared by Dr. Alan Scott (of the Smith–Kettlewell Eye Research Foundation). Informed consent was obtained from the patients' parents/guardians, and the study was approved by our Institutional Review Board. Six patients were randomly assigned to receive toxin, and six were assigned to receive matching placebo in a double-blind fashion. Vials of toxin/placebo were reconstituted with physiological saline. Intramuscular injections were made with a control syringe and a 23-gauge needle, and localized as described previously (19).

In hemiplegic patients, only the affected leg was assessed and injected. In diplegic patients, both legs were evaluated and injected. For the first injection, each patient received a toxin dosage (or saline placebo equivalent) of 1 U/kg body weight for each leg, i.e., hemiplegic patients received a total of 1 U/kg body weight, whereas diplegic patients received a total of 2 U/kg body weight. In equinovalgus extremities, injections were made into the medial and lateral gastrocnemius. In equinovarus extremities, the posterior tibialis muscle, as well as the medial and lateral gastrocnemius, was injected. Two weeks after the first injection, the patients were evaluated using our Physician Rating Scale (PRS) (Table 1).

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TABLE 1. *Physician Rating Scale (observational gait analysis determined for each leg injected)*

Dynamic function (range of motion)	No. of legs
1. Crouch	
Severe (>20° hip, knee, ankle)	0
Moderate (5–20° hip, knee, ankle)	1
Mild (<5° hip, knee, ankle)	2
None	3
2. Equinus Foot	
Constant (fixed contracture)	0
Constant (dynamic contracture)	1
Occasional heel contact	2
Heel-to-toe gait	3
3. Hind Foot	
Varus at foot strike	0
Valgus at foot strike	1
Occasionally neutral at foot strike	2
Neutral at foot strike	3
4. Knee	
Recurvatum >5°	0
Recurvatum 0–5°	1
Neutral (no recurvatum)	2
5. Speed of Gait	
Only slow	0
Variable (slow–fast)	1
6. Gait	
Toe–toe	0
Occasional heel–toe	1
Heel–toe	2
Total	

This evaluation was followed by the second injection given at double the initial dose/volume at the same injection sites. One patient received the same amount of toxin for the second injection because it was believed that significant clinical improvement had been reached and that a doubled dose might result in excessive weakness. The average active dose given was 50 U.

Lower-extremity function was assessed by observational gait analysis, physical therapy evaluation, Biodex evaluation, PRS, and a parent/guardian questionnaire. The physical therapy evaluation form was developed to assess global function both before and after injection (Table 2). The patients were evaluated by the physical therapists before gait was analyzed. Videotape recordings were made of all gait studies.

The Biodex isokinetic computerized dynamometer was used to measure muscle strength and endurance of both lower extremities. Parameters of peak torque and total work were determined during dorsiflexion and plantar flexion at both slow and fast speeds.

The PRS was used to evaluate ambulatory function (Table 1): a maximal score of 14 would indicate normal gait for that extremity.

The parent/guardian evaluation consisted of five questions concerning the child's progress during the study. The forms were seen only by the parent/guardian and the clinical nurse, and were identified only by the patient's medical record number.

No results of these evaluations were reviewed until all patients had completed the double-blind protocol. All evaluations were performed preinjection, at 2 weeks after initial injection, and at final evaluation.

RESULTS

Physical therapy evaluations

No consistent pattern in overall clinical performance was detected by summary score, thereby supporting the clinical observation of no adverse systemic effects associated with the injections. However, independent physical therapy evaluations of gait analysis films at the conclusion of the study suggested that BAT-A treatment improved gait as compared to placebo injections.

Biodex evaluations

When pre- and postinjection Biodex measurements were compared, no consistent differences between treatment groups were apparent. All the children had difficulty in complying with the rigorous demands of the Biodex evaluation, which suggested that this device might not be an appropriate evaluation tool in children with cerebral palsy.

Physician rating scale (PRS)

Comparison of the preinjection and the maximal posttreatment PRS scores showed the placebo group to have an average improvement of 2.3 following treatment (from 5.3 to 7.6) and the toxin group to have an average improvement of 3.1 (from 5.3 to 8.4). Two patients in the placebo group (33%) and five patients in the toxin group (83%) had an improved gait (Table 3). One patient receiving placebo had an apparent short-term improvement in the PRS; however, 3 weeks after termination of the study, clinical evaluation of this patient no longer showed improvement. This discrepancy is believed to be due to the patient's family providing exercise and stretching regimens that were excessive and abnormal when compared to those undertaken by the patient before enrolling in the study.

In the one patient receiving BAT-A who demonstrated marginal or no improvement, it was apparent that this patient had a significant degree of fixed contracture of the gastrocnemius/soleus complex, which could not be appreciated until the BAT-A injection had decreased some of the overlying spasticity.

Parent/guardian assessment

Before the double-blind code was broken, parents/guardians of four of the six children receiving toxin reported that their child's gait had improved during the trial. One who reported no improvement was the parent of the child who was found to have a fixed contracture and therefore could not improve. Parents/guardians of two of the six children receiving placebo reported that the child had improved during the trial. As stated previously, one

TABLE 2. *Physical therapy evaluation*

1. Supine to standing—upper extremity analysis (Circle one for left and one for right)	Upper extremity		Score
A. Stands up without using hands	R	L	4
B. Stands with one-hand contact on floor	R	L	3
C. Stands with two-hand contact on floor	R	L	2
D. Must pull up to stand	R	L	1
2. Supine to standing—lower extremity analysis			
A. Moves to standing through a straight plane			4
B. Moves to standing through ½ kneeling			3
C. Moves through "bear stance" legs not contacting[a]			2
D. Moves up to standing with one/both lower extremities internally rotating and adducting			1
3. Supine to sitting			
A. Sits up with neck and trunk flexion only			4
B. Sits up without trunk rotation and utilizing one arm to assist			3
C. Sits up with upper extremity assist and with knee(s) flexion			2
D. Rolls over to prone and moves to sitting			1
4. Sidesitting (Circle one for left and one for right)	Lower extremity		
A. Can assume by moving hips over lower extremities or lower extremities move around the body	R	L	4
B. Can assume by dropping over one leg	R	L	3
C. Can assume with assistance of upper extremities	R	L	2
D. Cannot assume sidesitting independently	R	L	1
5. Standing balance—*Right leg*			
A. Stand on leg 10 s			4
B. Stand on leg 5–10 s			3
C. Stand on leg 1–5 s			2
D. Attempts to stand on one leg and is unsteady[b]			1
6. Standing balance—*Left leg*			
A. Stand on leg 10 s			4
B. Stand on leg 5–10 s			3
C. Stand on leg 1–5 s			2
D. Attempts to stand on one leg and is unsteady			1
7. Sitting to standing (back of knees should not touch bench)			
A. Both heels remain flat on floor while standing			4
B. One heel remains flat on floor while standing			3
C. Both heels come off the floor			2
D. Gets up aided (using hand and/or back of knees touching bench)			1
		Total score = _____	

[a] Bear stance is identified as using hands and feet together at sometime during the transition.
[b] Unsteady—trunk moving over leg and only way to stop falling is to place opposite leg down, with or without excessive arm movements.

child reported as improved by the parent/guardian, physical therapy, and PRS evaluations had received unscheduled and excessive physical therapy during the trial, which resulted in short-term improvement, but this improvement was not maintained after a normal therapy routine was resumed.

Side effects

Intramuscular injection of BAT-A caused soreness of the injection site in three of the six patients.

TABLE 3. *Botulinum-A toxin double-blind trial: response to toxin and placebo*

Treatment	No. of patients with no improvement in gait pattern[a]	No. of patients with improved gait pattern[a]	Total no. of legs evaluated
Placebo	4 (67%)	2 (33%)	10
Toxin	1 (17%)	5 (83%)	8

[a] As assessed with Physician Rating Scale.

Injection of the placebo caused soreness of the injection site ($n = 3$), unsteadiness ($n = 2$), fatigue ($n = 1$), and headache ($n = 1$). These local side effects generally lasted 1–2 days; neither group had generalized or systemic complications.

DISCUSSION

Among the treatment alternatives for foot and ankle deformities associated with spastic forms of cerebral palsy, the oral neuropharmacologic agents, such as diazepam, often produce excessive sedation (9); intramuscular blocking agents, such as 45% alcohol and phenol, have short-term success, but require the use of general anesthesia for their administration (6,7,32), and, if improperly administered, may cause permanent muscle weakness, long-term denervation (6,7,32), and (with phenol) skin necrosis. Thus, surgical intervention was often the only viable treatment option for many patients with pro-

gressive deformity. BAT-A offers a potential alternative treatment modality for modifying muscle spasticity in the lower extremities of these patients.

BAT-A is a neurotoxin produced by the gram-positive bacterium *Clostridium botulinum* (21), and is the most potent known biological toxin (18,29). For clinical use, the unit dose of BAT-A is based on a mouse LD_{50} equivalent (28), the unit dose of toxin representing 0.4 ng of active toxin per unit. On the basis of data obtained in monkeys, the human LD_{50} for an adult male (70 kg) has been estimated at 2,000 ng, or 5,000 U (27,28). In the form the toxin supplied, preparation of a human LD_{50} for a 70-kg adult (5,000 U) would require 35.7 vials of toxin. As such, it would be difficult to administer an LD_{50} dose inadvertently. Intramuscular doses as high as 6 U/kg have been administered to human adults without systemic symptoms (A. B. Scott, personal communication, January 15, 1986). No data exist for pediatric doses.

BAT-A acts by interfering with presynaptic acetylcholine release at cholinergic nerve terminals (10,18,29) without destroying nerve endings, nerve terminals, or neuromuscular junctions. Thus, the toxin blocks neuromuscular control and functionally denervates the muscle (1). The inhibitory action of BAT-A is believed to involve three steps: (a) rapid binding of the toxin to the presynaptic nerve membrane; (b) internalization of the toxin across the presynaptic membrane; and (c) inhibition of acetylcholine release (23). The last does not involve either neurotransmitter synthesis or storage, but rather appears to disrupt the calcium ion-mediated release of acetylcholine (23). Three mechanisms have been hypothesized: the toxin may (a) inhibit calcium ion influx during nerve stimulation; (b) stimulate calcium ion efflux; or (c) act directly on the mechanism of acetylcholine release (23).

Muscle paralysis following botulinum exposure is dose-dependent and reversible over time (30). Muscle recovery occurs following sprouting of motor nerves and formation of new end-plates (12). Due to the rapid and high-affinity binding of the toxin to receptors at the neuromuscular junctions of the target muscle (11,14,23,27), little or no systemic absorption of toxin occurs.

Scott was the first investigator to use BAT-A clinically when he employed it in the nonoperative management of strabismus (26,27). BAT-A also has been used for the treatment of blepharospasm, hemifacial spasm, and spasmodic dysphonias (1,4,5,8,14–16,20,22,24,28). Prior to this report, its only reported clinical use in large skeletal muscles has been in the management of spasmodic torticollis (17,31,33–36).

The results of this probe study suggest a potential clinical efficacy of BAT-A in the treatment of lower-extremity spasticity in children with cerebral palsy. A multicenter, randomized, double-blinded study is currently underway employing more refined and more rigorous evaluations, including computerized gait analysis, as well as a more focal physical therapy rating scale to assess changes in knee and ankle range of motion. Electromyographic studies will follow the electrophysiology of the spastic muscles before and after BAT-A injection, and the PRS has been refined to further quantify the active and passive range of motion of the hindfoot.

BAT-A injections appear to be an important potential adjuvant to the available nonoperative management of spasticity in cerebral palsy. The benefit of a relatively painless, safe office procedure to aid in the treatment of lower-extremity spasticity would be significant. Although the use of BAT-A may not remove forever the prospect of surgical intervention, it may delay such treatment until the patient is older and at a lower risk for possible complications and recurrence of deformity.

CONCLUSIONS

This study provides further evidence that BAT-A is a potentially valuable nonoperative adjunctive technique in the management of dynamic deformities in pediatric patients with cerebral palsy. BAT-A injections are without significant local or systemic complications in this patient population. Clinical improvement is noted at a dose of 1–2 U/kg body weight/muscle group. The duration of improvement appears to be relatively constant (3–6 months), and is repeatable. From this study, it is clear that the benefits and advantages of BAT-A injections in spastic muscles of children with cerebral palsy merit additional prospective evaluation.

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