ɔrs:

Suputtitada, MD

tion:

e Department of
tation Medicine, Faculty of
, Chulalongkorn University
Bangkok, Thailand.

s

ɔondence and requests for
nould be addressed to
uputtitada, MD, Department
ilitation Medicine, Jarern-
Building, Floor 1, Faculty of
ıe, Chulalongkorn University
al, Rama IV Road, Putumwan,
ɔok 10330, Thailand.

closures:

ɔported by an unrestricted grant
m Allergan, Inc.
ɛsented at the first ASEAN
habilitation Medicine Association
ngress, December 10–13, 1998,
iangmai, Thailand.
ɔo presented at the Second World
ngress of Neurological
habilitation, April 14–17, 1999,
ronto, Canada.

)94-9115/00/7904-0320/0
nerican Journal of Physical
edicine & Rehabilitation

Research Article

Managing Spasticity in Pediatric Cerebral Palsy Using a Very Low Dose of Botulinum Toxin Type A

Preliminary Report

ABSTRACT

Suputtitada A: Managing spasticity in pediatric cerebral palsy using a very low dose of botulinum toxin type A: preliminary report. *Am J Phys Med Rehabil* 2000;79:320–326.

Objective: To determine if very low doses of botulinum toxin type A (BTX-A) could reduce spasticity and improve gait in cerebral palsied children when combined with rehabilitation therapy.

Design: Ten trainable (IQ > 80), ambulatory, spastic diplegic or hemiplegic cerebral palsied children, with no fixed contractures in at least one limb, were selected for the study. Patients with a score of 3 on a modified Ashworth scale received 0.5 units of BTX-A/kg/muscle. Patients with an Ashworth score of 4 received 1.0 BTX-A/kg/muscle. After BTX-A injection, all patients received rehabilitation therapy and plastic ankle and foot orthoses for walking.

Results: Both groups exhibited improvement in Ashworth score and in gait within 72 hr of injection with botulinum toxin. Beneficial effects persisted for 10 to 12 mo in most patients, with three patients exhibiting benefits for at least 20 mo.

Conclusions: The results of the present study indicate that a very low dose of botulinum toxin type A combined with rehabilitation therapy resulted in a long-lasting decrease in spasticity and an improvement in gait in children with cerebral palsy.

Key Words: Botulinum Toxin Type A, Pediatric Cerebral Palsy, Rehabilitation Therapy, Spasticity, Gait

Spasticity is defined as an increased resistance to passive movement, secondary to hyperreflexia, after an upper motor neuron lesion. In children with cerebral palsy, it can interfere with mobility, self-care, positioning, and longitudinal muscle growth, and can contribute to the development of fixed myostatic contractures. Current treatments include systemic medications, electrical stimulation, heating modalities with passive range of motion exercises, orthotics, phenol nerve blockade, tendon-lengthening procedures, rhizotomies, and neurectomies. None of the more conservative of these treatments is particularly successful at increasing range of motion or decreasing spasticity, and the more aggressive treatments are associated with considerable risk in a pediatric patient population. However, several studies have suggested that intramuscular injections of botulinum toxin type A can be both safe and effective in relieving spasticity in pediatric cerebral palsy patients.[1–9]

In the treatment of cerebral palsy, studies have demonstrated that botulinum toxin type A can (1) diminish painful paravertebral spasticity,[1] (2) facilitate positioning and hygiene,[1] (3) improve ambulation,[1–7] (4) improve upper limb function,[9] and (5) be a useful diagnostic aid in determining the efficacy of surgery.[1] It is also possible that botulinum toxin type A treatment may be an effective alternative to serial casting,[8] may facilitate or replace bracing, or may augment the effects of physical therapy and potentially delay or obviate the need for surgery. Of particular relevance to ambulatory pediatric cerebral palsy patients is that botulinum toxin type A seems to improve dynamic foot deformity.[4,7,8] Moreover, botulinum toxin type A injections can be easily administered in the physician's office, without the need for anesthesia,[1–4] and it is not associated with any of the risks inherent in surgical interventions or systemic medications.

In previous studies of botulinum toxin type A as a treatment for cerebral palsy, the minimum dose that appeared to be required for focal muscle weakness was 1 to 2 units of toxin per kilogram of body weight per major muscle group injected.[1–8] However, for the sake of safety as well as cost considerations, it is always desirable to use the minimum effective dose of any therapeutic agent. Therefore, in the present study, I investigated the ability of very low doses of botulinum toxin type A (0.5–1.0 Unit/kg of body weight/muscle) combined with rehabilitation therapy to effectively reduce spasticity and improve gait in children with cerebral palsy.

TABLE 1
Modified Ashworth scale

Description	Score
No increase in muscle tone	0
Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the affected part is moved in flexion or extension	1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion	1+
More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved	2
Considerable increase in muscle tone, passive movement is difficult	3
Affected part is rigid in flexion or extension	4

MATERIALS AND METHODS

Study subjects

Ten ambulatory, spastic diplegic or hemiplegic cerebral palsy patients (16 treated legs total) with scissoring, crouch, equinovarus, or equinus gait were selected. A total of 16 legs were treated. All patients had received at least 6 mo of rehabilitation therapy before the start of the study.

Patients of either sex were included in the study if they were between 2 and 5 yr of age, were medically stable (e.g., no uncontrolled systemic disease), were ambulatory with or without assistive devices, had an IQ of 80 or greater (were trainable), and had a hip adductor, knee flexor, or ankle plantar flexor tone of grade 2 or higher on the Ashworth scale (Table 1).

Patients were excluded from the study if they had fixed contracture of the limb to be studied, previous phenol block or surgery for spasticity in the limb to be studied, profound atrophy of the muscles to be injected, previous botulinum toxin therapy, instability of the knee such that treatment of the gastrocnemius muscle with botulinum toxin type A could further destabilize the knee, known sensitivity to any components of the study medication, active infection at the injection sites or systemic infection, or were currently being treated with aminoglycoside antibiotics or other agents that may interfere with neuromuscular transmission.

Study Medication

Botulinum toxin type A (BOTOX, 100 Unit vial; Allergan, Inc., Irvine, CA) was reconstituted for injection with 50 Unit/ml of 0.9% sterile unpreserved saline.

Study design

In this open-label, uncontrolled study, patients were assigned to one

of two treatment groups on the basis of their score on a modified Ashworth scale (Table 1). Patients with an Ashworth score of 3 (group 1) received 0.5 Unit/kg of body weight/injected muscle, and patients with an Ashworth score of 4 (group 2) received 1.0 Unit/kg of body weight/injected muscle.

All patients received bilateral intramuscular injections at one site in the medial head and one site in the lateral head of the gastrocnemius muscles of the leg or legs to be treated. Patients who presented with varus position and spasticity of the tibialis posterior muscles were also given injections into the tibialis posterior muscles of each leg. Patients with scissoring gait and spasticity of the hip adductor were given injections in the hip adductor muscles (adductor magnus) of each leg. If the patients presented with crouch gait and spasticity of knee flexors, the knee flexor muscles (semimembranosus) of each leg were also injected.

A 27-gauge Teflon-coated combination electromyographic electrode/injection needle (BOTOX Injection Needle; Allergan) was used to both locate the optimum injection site within each muscle and inject the toxin. The choice of injection site was also guided by anatomic knowledge of the location of the motor end plate for each muscle (for which standard guidelines have been established).[10]

After botulinum toxin type A injection, all patients received rehabilitation therapy and plastic ankle and foot orthoses for walking. Heating modalities, stretching exercises, and therapeutic facilitation exercises were prescribed for all patients everyday.

Outcome measures

The effects of treatment were assessed by (1) an observational gait assessment by using video recording and a physician's rating scale (PRS; Table 2), (2) passive and active muscle tone and degree of spasticity as measured on the modified Ashworth scale, and (3) the parental or caregiver evaluation of overall response. The PRS was used to assess the presence of crouch and equinus foot, hind foot position, knee curvature, and speed of gait and gait dynamics. Passive range of motion in hip abduction, knee extension, and ankle dorsiflexion were measured with a plastic manual goniometer. All patients were examined while in the supine position by using standard anatomic landmarks.

All patients were evaluated at baseline, postinjection days 1 through 7, and weeks 2, 5, and 8. Patients were then evaluated every 2 mo until spasticity returned to the levels observed before botulinum toxin type A injection.

The author participated in all measurements. For most patients, a third-year resident in the clinic also took Ashworth and PRS measurements, and the results determined by the two observers were the same. However, no formal interobserver reliability testing was performed.

TABLE 2
Physician rating scale for gait analysis (determined for each limb injected)

Dynamic Function (Range of Motion)	Score
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-to-toe	0
Occasional heel-to-toe	1
Heel-to-toe	2

RESULTS

Patient population

The mean age (±SD) of the subjects at the time of study entry was 34.8 ± 9.0 mo, with a minimum age of 26 mo and a maximum age of 53 mo. Four patients exhibited spastic hemiplegia (40%) and six patients exhibited spastic diplegia (60%). The mean IQ score was 89 ± 4.83, with a minimum of 82 and a maximum of 97. All patients were fitted with plastic ankle foot orthoses. The type most commonly used covered both the medial and lateral malleolus and controlled both plantarflexion and mediolateral deviations.

Efficacy findings

Botulinum toxin type A combined with rehabilitation therapy effectively reduced spasticity in both study groups (Tables 3 and 4). The effects of the injections were not evident immediately in all patients, but the parents or guardians noted significantly decreased spasticity during range-of-motion exercises in the first 24 to 72 hr after injection. Improvements in both Ashworth scores and PRS were apparent in both groups by 2 and 4 wk after injection, respectively. Table 5 shows the mean modified Ashworth score, for all patients combined, for the different muscles at baseline, and at 2 wk after injection. In general, the peak improvement in Ashworth score occurred at 2 wk, and then remained constant at the time intervals measured (each 2 mo) until returning to baseline. At

TABLE 3

Treatment and outcome summary for group 1 (0.5 U/kg/muscle)

Patient	Sex	Age (mo)	BW (kg)	Type of CP	IQ	Muscles Injected	Dose (Unit)	Modified Ashworth Scale		PRS		Duration of Effect (mo)
								Baseline	2 Wk	Baseline	4 Wk	
1	M	26	12	Spastic diplegia	97	R. gastrocnemius		3	1	9	13	20
						Medial head	6					
						Lateral head	6					
						L. gastrocnemius		3	1			
						Medial head	6					
						Lateral head	6					
						Total	24					
2	M	28	14	Spastic diplegia	85	R. gastrocnemius		3	1	8	13	12
						Medial head	7					
						Lateral head	7					
						L. gastrocnemius		3	1			
						Medial head	7					
						Lateral head	7					
						R. hip adductor	7	3	1			
						L. hip adductor	7	3	1			
						Total	42					
3	M	38	18	Spastic hemiplegia	95	R. gastrocnemius		3	1.5	7	14	12
						Medial head	9					
						Lateral head	9					
						Total	18					
4	M	27	13	Spastic diplegia	82	R. gastrocnemius		3	1	7	13	20
						Medial head	6.5					
						Lateral head	6.5					
						L. gastrocnemius		3	1			
						Medial head	6.5					
						Lateral head	6.5					
						Total	26					
5	M	53	20	Spastic diplegia	90	R. gastrocnemius		3	2	7	13	10
						Medial head	10					
						Lateral head	10					
						L. gastrocnemius		3	2			
						Medial head	10					
						Lateral head	10					
						R. hip adductor	10	3	1.5			
						L. hip adductor	10	3	1.5			
						Total	60					

BW, body weight; CP, cerebral palsy; PRS, physician's rating scale.

baseline, the mean PRS score was 7.4 ± 2.83 (range, 5–9). Four weeks after treatment with botulinum toxin type A, the mean PRS score was 13.2 ± 0.92 (range, 11–14). In general, the peak improvement in PRS score occurred at 4 wk after injection. As was seen for the Ashworth score, the PRS score then remained constant at the time intervals measured until it returned to baseline.

There were also considerable improvements in gait after treatment. After botulinum toxin injections into the calf muscles, there was a gradual reduction in dynamic equinus. During the swing phase, there was an increase in ankle dorsiflexor activity; this active movement mediated by the ankle dorsiflexors improved ground clearance and placed the foot in a better position for heel strike in anticipation of ground contact. The duration of the beneficial effects of botulinum treatment (defined as time to return to baseline Ashworth score) was 10 to 12 mo in most patients, with three patients exhibiting benefits for at least 20 mo.

Safety findings

The only adverse events observed in this study were discomfort during

TABLE 4

Treatment and outcome summary for group 2 (1.0 U/kg/muscle)

Patient	Sex	Age (mo)	BW (kg)	Type of CP	IQ	Muscles Injected	Dose (Unit)	Modified Ashworth Scale		PRS		Duration of Effect (mo)
								Base-line	2 Wk	Base-line	4 Wk	
6	F	26	15	Spastic hemiplegia	89	R. gastrocnemius		4	1	5	14	12
						Medial head	15					
						Lateral head	15					
						L. tibialis posterior	15					
						Total	45					
7	F	40	20	Spastic diplegia	92	R. gastrocnemius		4	1.5	5	11	11
						Medial head	20					
						Lateral head	20					
						L. gastrocnemius		4	1.5			
						Medial head	20					
						Lateral head	20					
						R. hamstrings	20	4	2			
						L. hamstrings	20	4	2			
						R. hip adductors	20	4	2			
						L. hip adductors	20	4	2			
						Total	160					
8	F	25	12	Spastic diplegia	90	R. gastrocnemius		4	1.5	9	13	20
						Medial head	12					
						Lateral head	12					
						L. gastrocnemius		4	1			
						Medial head	12					
						Lateral head	12					
						Total	48					
9	F	39	20	Spastic hemiplegia	84	R. gastrocnemius		4	1.5	5	14	12
						Medial head	20					
						Lateral head	20					
						R. tibialis posterior	20					
						Total	60					
10	M	34	16	Spastic hemiplegia	86	R. gastrocnemius		4	1	5	14	12
						Medial head	16					
						Lateral head	16					
						R. tibialis posterior	16					
						Total	48					

BW, body weight; CP, cerebral palsy; PRS, physician's rating scale.

injection and crying during injection. No other adverse events were recorded.

DISCUSSION

The results of the present study indicate that very low doses of botulinum toxin type A, which in previous studies had no therapeutic effect, reduced spasticity in cerebral palsy patients when combined with rehabilitation therapy. It is unlikely that the effects seen are the result of the rehabilitation therapy alone, because there were no significant improvements in Ashworth or PRS scores in any of these children during the 6 mo of rehabilitation therapy before injection. Although two different doses were used in this study (0.5 and 1.0 Unit/kg), the small number of patients enrolled and the open-label design prohibit any conclusions about the relative merits of the two doses.

After botulinum toxin injections into the calf muscles, there was a gradual reduction in dynamic equinus during the first 72 hr. During swing, there was an increase in ankle dorsiflexion; this active movement mediated by the ankle dorsiflexors allows ground clearance and places the foot ready for heel strike in anticipation of ground contact. Two possible explanations for this improvement are that weakening of the spastic plantar flexors increased the ability of the dorsiflexors to overcome the equinus or that with the ankle in a lesser degree of equinus at the start of the swing phase, the dorsiflexors are

TABLE 5

Muscle tone as measured by the modified Ashworth scale (mean scores for all patients in both treatment groups)

	Baseline (mean ± SD)	2 Wk (mean ± SD)
Rt. lower extremities		
Ankle dorsiflexion	2.8 ± 1.55	1.05 ± 0.64
Knee extension	1.1 ± 1.10	0.90 ± 0.57
Hip abduction	1.5 ± 1.35	0.96 ± 0.54
Lt. lower extremities		
Ankle dorsiflexion	2.7 ± 1.49	1.00 ± 0.62
Knee extension	0.9 ± 1.20	0.70 ± 0.67
Hip abduction	1.3 ± 1.50	0.75 ± 0.72

placed with greater mechanical advantage with a longer lever arm.

In an earlier randomized, multicenter clinical study, the short-term use of botulinum toxin type A was associated with a 70% response rate, including clinical improvements in gait and ankle range of motion.[2] This previous study also demonstrated that the functional improvement observed was directly related to a partial functional denervation and resultant weakening of the treated muscles.[2] Gait analysis before and after botulinum toxin type A injections demonstrated statistically significant improvement compared to vehicle.

In the present study, patients whose knees were excessively flexed throughout the gait cycle at baseline exhibited more complete extension of the knee during gait after botulinum toxin injection of the hamstring muscles. This increased the patients' stride length and allowed the heel to be more readily presented at foot contact. Cosgrove et al.[4] suggested that hamstring injection in any patient who extended the knee to within 15 degrees of neutral in gait, even if there was a reduced popliteal angle, requires careful consideration, because there is a risk of recurvatum with botulinum toxin injections. This risk increases in the presence of calf contractures. However, in the present study, there were no occurrences of recurvatum in any patients.

One possible reason that the very low dose of botulinum toxin type A used in the present study effectively reduced spasticity is that the subjects were very young children (2–5 yr old). Experimental work in animals suggests that spasticity interferes with longitudinal muscle growth, which results in the conversion of dynamic contractures to fixed permanent contractures.[11] Cosgrove et al.[4] have reported that the response of calf muscles to injection of botulinum toxin type A was limited in older children. This may be the result of an increased incidence of fixed myostatic contractures in older children. It is possible that in young children, selective injection of botulinum toxin type A may allow sufficient time to regain muscle length before the muscle tone returns,[5] thus reducing the conversion to fixed contractures.

The clinical improvement observed in the present study persisted for 10 to 12 mo. In addition, there were patients who had some return of spasticity after 12 mo but who were nonetheless able to maintain a satisfactory gait pattern for much longer. It is possible, although unlikely, that this is a direct effect of the toxin injection. However, it is also possible that long-term physiological changes occurred in the treated muscles and their antagonists that allowed the beneficial effects of treatment with botulinum toxin type A to persist after the direct effects of the toxin on the injected muscle or muscles had worn off. It is possible that the weakening of the treated muscles allowed the antagonistic muscles to become stronger and better capable of countering the effects of any spasticity that began to return as normal neuromuscular transmission was restored in the treated muscles. Strengthening of the antagonists after surgical lengthening of the calf and hamstring has been reported previously.[12] It is also possible that relaxation of the spastic muscles may have facilitated longitudinal growth, which has previously been reported in developing children,[4] and that this resulted in a decrease in spasticity. Moreover, it is also possible that the rehabilitation therapy that these children received (heating modalities, stretching exercises, therapeutic facilitation exercises, and plastic ankle and foot orthoses) may have helped promote the relaxation of spastic muscles, which, together with strengthening of the antagonist muscles, may have promoted long-term reductions in spasticity.[5,13]

In summary, this study demonstrates that very low doses of botulinum toxin type A (0.5–1 Unit/kg of body weight/muscle) combined with rehabilitation therapy decreased spasticity and improved gait in cerebral palsied children. The long-term effects of this combination of treatments suggest that the initial effects were likely the result of a direct botulinum toxin–mediated blockade of neurotransmission, but that the sustained effects resulted from long-lasting compensatory mechanisms that developed as a result of the combination with rehabilitative therapy. However, more studies are warranted to further investigate the long-term physiologic changes that occur in the spastic muscles of very young pediatric cerebral palsy patients who receive this combination of treatments and, also, how this may affect the overall clinical features of their disease.

ACKNOWLEDGEMENTS

We thank Dr. David Simpson at Mount Sinai Hospital in New York

City for graciously reviewing and helping to edit the manuscript.

REFERENCES

1. Koman LA, Mooney JF III, Smith BP, et al: Management of cerebral palsy with botulinum-A toxin: preliminary investigation. *J Pediatr Orthop* 1993;13:489–95

2. Koman LA, Ferrari E, Mubarak S, et al: Botulinum toxin type A (BTA) in the treatment of lower-limb spasticity associated with cerebral palsy. *Dev Med Child Neurol* 1995;37:19–20

3. Koman LA, Mooney JF III, Smith BP, et al: Management of spasticity in cerebral palsy with botulinum A toxin: report of a preliminary, randomized, double-blind trial. *J Pediatr Orthop* 1994;14: 299–303

4. Cosgrove AP, Corry IS, Graham HK: Botulinum toxin in the management of the lower limb in cerebral palsy. *Dev Med Child Neurol* 1994;36:386–96

5. Calderon-Gonzalez R, Calderon-Sepulveda RF, Rincon-Reyes M, et al: Botulinum toxin A in management of cerebral palsy. *Pediatr Neurol* 1994; 10:284–8

6. Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG: Injection of botulinum A toxin into the gastrocnemius muscle of patients with cerebral palsy: a 3-D motion analysis study. *Dev Med Child Neurol* 1995;37:17–8

7 Koman LA, Mooney JF, Smith BP, Goodman A, Mulvaney T: Management of spasticity in cerebral palsy with botulinum A toxin: report of a preliminary, randomized, double-blind trial. *J Pediatr Orthop* 1994;14:299–303

8. Corry IS, Cosgrove AP, Duffy CM, et al: Botulinum toxin A as an alternative to serial casting in the conservative management of equinus in cerebral palsy. *Dev Med Child Neurol* 1995;37:20–1

9. Wall SA, Chail LA, Temlett JA, et al: Botulinum A toxin chemodenervation: a new modality in cerebral palsied hands. *Br J Plast Surg* 1993;46:703–6

10. Delagi EF, Perotto A: *Anatomic Guide for the Electromyographer,* ed. 2. Springfield, Charles C. Thomas, 1980

11. Ziv I, Blackbum N, Rang M, Koreska J: Muscle growth in normal and spastic mice. *Dev Med Child Neurol* 1984;26: 94–9

12. Reimer J: Functional changes in the antagonists after lengthening of the agonists in cerebral palsy. *Clin Orthop* 1990; 253:30–7

13. Tardieu G, Tardieu C: Cerebral palsy: mechanical evaluation and conservative correction of limb joint contractures. *Clin Orthop* 1987;219:63–9