Botulinum Toxin as an Adjunct to Serial Casting Treatment in Children with Cerebral Palsy

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Background: Although botulinum toxin A is frequently used to augment serial casting in the treatment of soft-tissue contractures in children with cerebral palsy, its effectiveness for this purpose has not been evaluated. The purpose of the present study was to determine whether botulinum toxin A injection increases the efficacy of serial casting.

Methods: A prospective, randomized trial was undertaken to compare serial casting only with serial casting combined with botulinum toxin A (Botox) injection for the treatment of ankle equinus contractures in twenty-three children with cerebral palsy. Range-of-motion testing, spasticity assessment, and computerized gait analysis were performed as long as twelve months after treatment.

Results: There was no difference between the groups with regard to the duration of casting required to correct the equinus contracture. Both groups maintained a significant improvement in passive ankle dorsiflexion throughout the follow-up period, although the group managed with casting and Botox had a significant loss of dorsiflexion when the values at six, nine, and twelve months were compared with the value at three months. Peak dorsiflexion during the stance and swing phases was significantly improved in both groups at three months but only in the group managed with casting alone at twelve months. Plantar flexor spasticity was significantly decreased at three months in both groups, but it was significantly decreased at six, nine, and twelve months only in the group managed with casting alone. Spasticity was significantly greater in the group managed with casting and Botox than it was in the group managed with casting only at six, nine, and twelve months.

Conclusions: The present study demonstrates the efficacy of serial casting in the treatment of equinus contractures in children with cerebral palsy who are able to walk. Contrary to our hypothesis, the addition of botulinum toxin A to a serial casting regimen led to earlier recurrence of spasticity, contracture, and equinus during gait. The results of the present study suggest that botulinum toxin combined with serial casting for the treatment of fixed contractures will lead to a recurrence of plantar flexor spasticity and equinus contracture by six months in this patient population. While previous research has indicated that the injection of botulinum toxin A is superior to casting for the treatment of dynamic equinus, the present study suggests that serial casting alone is preferable for the treatment of fixed equinus contractures in children with cerebral palsy.

Level of Evidence: Therapeutic study, Level I-1a (randomized controlled trial [significant difference]). See Instructions to Authors for a complete description of levels of evidence.

Botulinum toxin A has been used for the treatment of spasticity in children with cerebral palsy since 1990. When injected intramuscularly, botulinum toxin A effectively denervates a muscle by inhibiting the release of acetylcholine at the neuromuscular junction[1]. It decreases a spastic muscle's ability to generate forceful contractions, thus decreasing the strength of the spastic response and allowing the muscle to function in a more lengthened position[2]. The clinical effect of botulinum toxin A lasts for three to six months.

Since botulinum toxin A works to decrease the force of muscle contraction or spasticity, it is commonly used to treat dynamic abnormalities rather than fixed contractures in children with cerebral palsy[3-5]. Botulinum toxin A is also commonly used in conjunction with serial casting for the treatment of fixed contractures, although the efficacy of these combined treatments has not been documented in the literature. Anecdotal evidence suggests that the addition of botulinum toxin A to a serial casting regimen appears to enhance the speed of resolution of contracture and may delay the recurrence of contracture. Although there have been a few reports in the literature in which casting was compared with the injection of botulinum toxin A for the treatment of dynamic equinus[6,7], we are aware of

no studies that have examined the impact of botulinum toxin A on serial casting for the treatment of fixed equinus contractures.

Serial casting involves immobilization of a muscle in a lengthened position for a prolonged period of time, thereby gradually increasing the extensibility of the muscle and surrounding soft-tissue structures. The mechanism by which this process occurs has been theorized to be an increase in both the length and the number of sarcomeres in the target muscle[8].

Children with cerebral palsy often have a combination of fixed contracture and spasticity in the triceps surae[9]. Spasticity can make it difficult for some children to tolerate immobilization in serial casts. By combining the injection of botulinum toxin A for the reduction of spasticity with serial casting for the treatment of an underlying contracture, it may be possible to decrease the length of time that a child must be treated with immobilization in a cast. Additionally, the range of motion and the amount of functional improvement that are achieved may be greater and may be maintained for a longer period of time than is the case with serial casting alone.

The main objective of the present study was to determine whether better outcomes are achieved when botulinum toxin A is added to the casting regimen in the management of children with cerebral palsy who have plantar flexion or equinus contractures as well as dynamic spasticity. We hypothesized that patients who received botulinum toxin A injections in combination with serial casting would have significantly faster resolution of contracture, greater reduction of equinus during gait, greater reduction of spasticity, greater improvement in gross motor function, and longer maintenance of these benefits when compared with patients who received casting alone.

Materials and Methods

A prospective, randomized trial was performed to compare serial casting alone with serial casting combined with injections of botulinum toxin A for the treatment of ankle equinus contractures in children with cerebral palsy. Institutional review board approval was obtained prior to initiation of the study.

Subjects

Twenty-three children with cerebral palsy participated in the study. The study group included twelve boys and eleven girls with a mean age of 7.1 ± 3.0 years (range, 4.3 to 13.8 years). Nine subjects had hemiplegia, thirteen had diplegia, and one had quadriplegia. All subjects were able to walk, although four subjects used a walker and one used forearm crutches. Children were recruited from the Orthopaedic Clinic at the authors' institution as well as from state-funded physical and occupational therapy clinics for children with orthopaedic and neurological conditions (California Children's Services Medical Treatment Units). The criteria for eligibility for inclusion in the study were (1) a diagnosis of cerebral palsy with associated spastic diplegia, hemiplegia, or quadriplegia, (2) an age of four years or more, (3) a plantar flexion or equinus contracture associated with a decreased range of passive dorsiflexion of ≤0° with the knee extended, (4) an ability to walk independently with or without assistive devices (i.e., walker, crutches, or cane), and (5) no history of orthopaedic surgery or selective dorsal rhizotomy in the preceding twelve months. Children with so-called mixed cerebral palsy, ataxia, or athetosis were excluded from participation.

Procedures

Informed consent was obtained from the parents or guardians of all subjects prior to enrollment. All children underwent initial assessments that were conducted by two experienced physical therapists (S.A.R. and A.F.-B.). These assessments included measurement of range of motion and spasticity (S.A.R.); administration of dimensions C (crawling and kneeling), D (standing), and E (walking, running, and jumping) of the Gross Motor Function Measure[10,11] (A.F.-B. and S.A.R.); and a complete computerized gait analysis (S.A.R.). Gait analysis included measurement of three-dimensional bilateral joint kinematics with use of a seven-camera VICON motion capture system and data processing with use of VICON Clinical Manager software (Oxford, England). After initial assessment, children were randomly assigned (with use of a random-number generator) to one of two treatment groups: one group was to be managed with serial casting for equinus contracture following the injection of Botox (Allergan, Irvine, California), and the other group was to be managed with serial casting only. All investigators, except for the study coordinator (S.A.R.) and the physician performing the Botox injections (R.M.K.), were blinded with regard to the subjects' group assignments.

In the group that was managed with casting combined with Botox, Botox injections were given by a single physician who was one of the principal investigators (R.M.K.). Botox was injected into the affected gastrocnemius muscle or muscles of all of the subjects in this group. Botox was also injected bilaterally into the soleus in one subject and into the medial hamstrings in two others. A dosage of 8 units per kilogram of body weight was used (with a maximum dose of 400 units per subject), with the toxin divided between the various injection sites. Botox injection was followed by serial casting for equinus contracture, which was initiated one to three weeks after the injection. In the group that was managed with casting only, serial casting was started immediately after the initial assessment. Subjects in both groups who had tight hamstrings and a potential to crouch were supplied with knee immobilizers for nighttime use.

Serial casting for equinus contracture was performed by a physical therapist and a physical therapy aide who were experienced with the technique. The same therapist and aide performed the casting for all children. Short-leg fiberglass walking casts were applied and changed every two weeks until ≥5° of dorsiflexion was reached with the knee extended. Casts were applied with the ankle in neutral supination-pronation and in maximum passive dorsiflexion. Casts were lined with stockinette and Webril, and polycushion was applied over osseous prominences. Support for the longitudinal arch was incorporated into the cast, and an extension was added for support under the toes. When necessary, posting was added under the hindfoot (when the ankle was plantar flexed) or the forefoot (when the ankle was dorsiflexed) to allow the patient to walk

without hyperextension or excessive flexion of the knee. The children used cast shoes during walking. Children with hemiplegia were managed with casting on the affected side only, whereas those with diplegia and quadriplegia were managed with bilateral casting (except in the case of one child with asymmetric diplegia, who was managed with unilateral casting because of a unilateral contracture). Once casting was complete, the subjects were given new bivalved fiberglass splints, positioned in maximum passive dorsiflexion, for nighttime use. The subjects were provided with ankle-foot orthoses for daytime wear upon completion of serial casting. The type of ankle-foot orthosis was determined by the treating physician and physical therapist and therefore varied among the subjects. All orthoses were fabricated by the same certified orthotist.

Passive dorsiflexion was measured in degrees and was recorded by the same physical therapist at the time of each cast change with use of a standard goniometer. Plantar flexor spasticity was also recorded by the same therapist at the time of each cast change and was rated with use of the modified Ashworth scale[12]. According to this system, a muscle's resistance to passive stretch is rated on a scale of 0 to 4, with 0 indicating no spasticity and 4 indicating rigidity in flexion or extension. An additional grade of 5 was added to the scale to indicate a fixed contracture that prohibited the assessment of underlying spasticity.

Reassessments were conducted at three, six, nine, and twelve months after the start of treatment. These assessments included repeat range-of-motion and spasticity measurements, with all measurements being made by the same investigator (S.A.R.). Administration of dimensions C, D, and E of the Gross Motor Function Measure was also conducted at these time-points. The Gross Motor Function Measure tests were conducted by two physical therapists (S.A.R. and A.F.-B.) who were experienced with the use of this system. Computerized gait analysis was repeated at the three and twelve-month time-points.

Subjects who were receiving physical therapy continued their regular regimen throughout the course of the study. The treating physical therapists completed a treatment log for each subject in order to document the total number of hours of therapy and the activities performed at each session. Parent-reported compliance with brace wear also was recorded for each child.

Statistical Methods

The demographic characteristics and baseline measures in the two groups were compared with use of the nonparametric Mann-Whitney rank-sum test and Fisher's exact test. As the two groups had similar proportions of subjects with unilateral and bilateral involvement, the statistical analyses were performed with each casted limb being considered as a unit.

The outcome measures included the duration of casting required for contracture resolution; differences in passive dorsiflexion, spasticity, and peak dorsiflexion during the stance and swing phases for each limb; and Gross Motor Function Measure scores. The Mann-Whitney rank-sum test was used to compare these outcome measures between the two groups. We also studied the change in these outcome measures over time. The nonparametric Wilcoxon and Friedman tests for matched data were used to test for significance within each group. The level of significance was set at $p < 0.05$.

Results

The groups did not differ in terms of age, gender, walking ability, type of cerebral palsy, or amount of physical therapy received (Table I). Three children (including one in the casting-plus-Botox group and two in the casting-only group) had un-

TABLE I Demographic Data

	Casting + Botox (N = 11 Subjects)	Casting Only (N = 12 Subjects)	P Value
Age* *(yr)*	6.9 ± 2.8	7.3 ± 3.3	0.9020
Gender *(no. of subjects)*			1.0000
Male	6	6	
Female	5	6	
Walking ability *(no. of subjects)*			1.0000
Aided	2	3	
Independent	9	9	
Type of cerebral palsy *(no. of subjects)*			0.6802
Hemiplegia	5	4	
Diplegia	6	7	
Quadriplegia	0	1	
Physical therapy			
Number of days per year*	28.4 ± 36.6	22.1 ± 27.6	0.7742
Total number of hours*	19.5 ± 28.6	16.7 ± 21.3	0.9714

*The data are given as the mean and the standard deviation.

TABLE II Baseline Measures

Outcome Measure	Casting + Botox* (N = 16 Limbs)	Casting Only* (N = 20 Limbs)	P Value
Passive dorsiflexion *(deg)*	–6.4 ± 8.3	–3.7 ± 8.7	0.2642
Peak dorsiflexion *(deg)*			
Stance	–2.4 ± 11.2	–9.7 ± 17.5	0.2791
Swing	–12.3 ± 11.1	–16.9 ± 15.1	0.4078
Plantar flexor spasticity *(Ashworth grade)*	2.6 ± 1.2	2.6 ± 1.1	0.8544
GMFM (C, D, E)† *(Percent score)*	75.8 ± 20.1	66.4 ± 23.1	0.0686

*The data are given as the mean and the standard deviation. †GMFM (C, D, E) = Gross Motor Function Measure (dimensions C, D, and E).

dergone previous multiple-level orthopaedic surgical procedures that had included bilateral gastrocnemius recession. In all three cases, the previous procedures had been performed at least four years (4.0, 4.6, and 6.4 years, respectively) before enrollment in the present study. These subjects were included in the statistical analyses because the number of these subjects was small and because of the length of time since the procedures had been performed. None of the children in the present study had undergone previous selective dorsal rhizotomy.

The groups did not differ with respect to any of the baseline measures (Table II). There were no complications related to either the serial casting or the Botox injections. Five of eleven subjects in the casting-plus-Botox group and five of twelve in the casting-only group received physical therapy during the course of the study. Two subjects in each group showed poor compliance or noncompliance with orthotic wear after casting. The data on these subjects were included in all statistical analyses. All other subjects were fully compliant. One subject in each group withdrew from the study after the six-month assessment and underwent surgical lengthening of the triceps surae. An additional subject from the casting-only group withdrew from the study after six months and underwent bilateral lengthening of the Achilles tendon at the recommendation of her physician, although no recurrent contracture had been detected at the time of the six-month assessment.

The duration of casting did not differ between the two groups ($p = 0.76$). The mean duration of casting was 6.0 ± 3.1 weeks in the casting-plus-Botox group and 5.5 ± 1.5 weeks in the casting-only group. The duration of casting also was similar when the equinus contractures were defined as mild (≤10°) and severe (>10°); specifically, the mean duration of casting for subjects with mild contractures was 5.2 ± 2.7 weeks in the casting-plus-Botox group and 5.5 ± 1.7 weeks in the casting-only group, and the mean duration of casting for subjects with severe contractures was 6.4 ± 3.4 weeks in the casting-plus-Botox group and 5.5 ± 1.4 weeks in the casting-only group.

With the numbers available, there were no significant differences between the two groups with regard to the magnitude of improvement in any of the outcome measures during the casting period. At the three-month evaluation, both groups had significant improvement in passive and dynamic dorsiflexion as well as decreased spasticity (Table III).

Both groups maintained a significant increase in passive dorsiflexion when the values at six, nine, and twelve months were compared with the baseline value. However, the casting-plus-Botox group had a significant decrease in passive dorsiflexion when the values at six, nine, and twelve months were compared with the value at three months. Post hoc analysis indicated that the change occurred between the three and six-month time-points. There were no significant differences between the groups with regard to passive dorsiflexion at any time-point (Fig. 1).

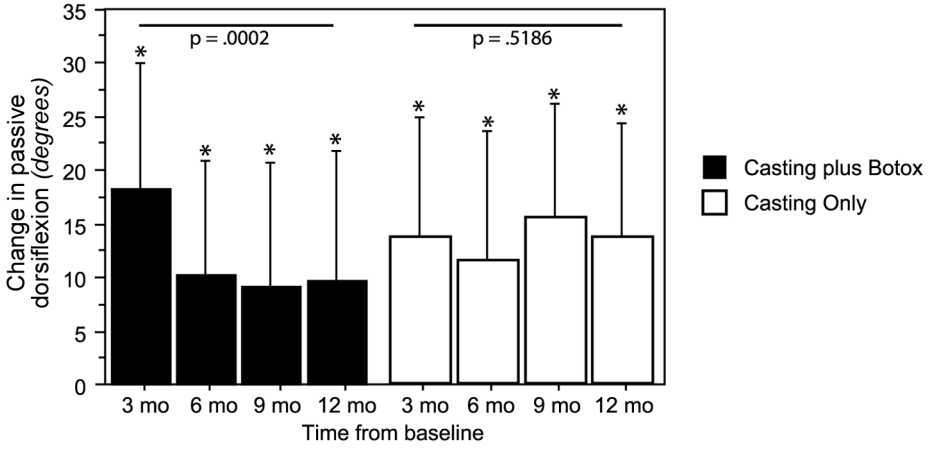

Fig. 1
Illustration depicting the improvement in passive dorsiflexion from baseline. An asterisk (*) indicates a significant change from baseline. The p values pertain to the changes over time between three and twelve months. Post hoc analysis indicated that there was a significant change between three and six months in the casting-plus-Botox group. There was no significant difference between the groups at any time-point.

TABLE III Change from Baseline at Three Months After Treatment

Outcome Measure	Casting + Botox (N = 16 Limbs)		Casting Only (N = 20 Limbs)		
	Change at Three Months*	P Value†	Change at Three Months*	P Value†	P Value‡
Passive dorsiflexion *(deg)*	18.4 ± 11.7	0.0021	13.9 ± 11.8	0.0005	0.3206
Peak dorsiflexion *(deg)*					
Stance	13.9 ± 9.4	0.0029	16.9 ± 15.2	0.0004	0.8763
Swing	12.5 ± 9.3	0.0022	15.1 ± 11.8	0.0003	0.6971
Plantar flexor spasticity *(Ashworth grade)*	–0.9 ± 1.0	0.0122	–1.1 ± 1.2	0.0031	0.7061
GMFM (C, D, E)§ *(Percent score)*	2.5 ± 7.5	0.2853	–1.3 ± 5.1	0.8105	0.2702

*The data are given as the mean and the standard deviation. †The p values pertain to the change from baseline. ‡The p values pertain to the difference between the groups. §GMFM (C, D, E) = Gross Motor Function Measure (dimensions C, D, and E).

Peak dorsiflexion during the stance and swing phases decreased significantly between three and twelve months in the casting-plus-Botox group. The casting-only group maintained improved dorsiflexion during the stance and swing phases at twelve months. With the numbers available, the differences between the groups at twelve months were not significant (Figs. 2 and 3).

The significant reduction in plantar flexor spasticity at three months was lost over time in the casting-plus-Botox group. Post hoc analysis suggested that the change occurred between the three and six-month time-points, although the difference was not significant because of the small sample size. The significant reduction in spasticity from baseline was maintained in the casting-only group at six, nine, and twelve

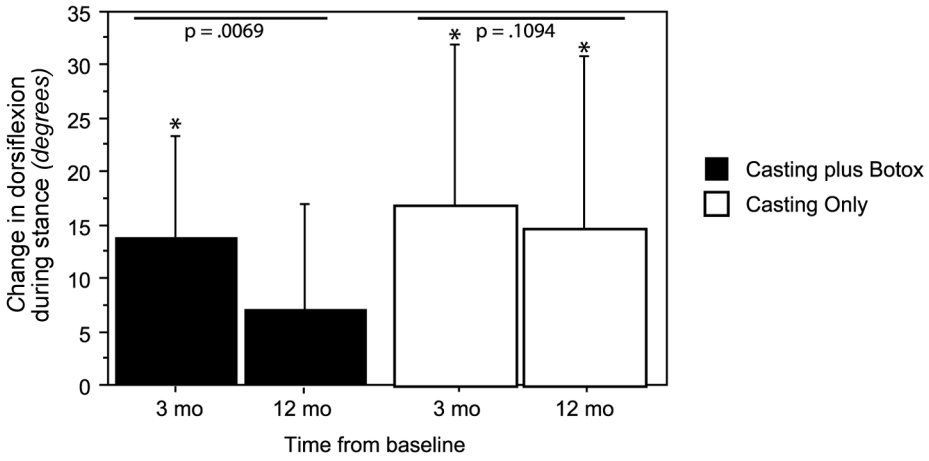

Fig. 2
Illustration depicting the improvement in peak dorsiflexion during the stance phase of gait from baseline. An asterisk (*) indicates a significant change from baseline. The p values pertain to the changes over time between three and twelve months. There was no significant difference between the groups at any time-point.

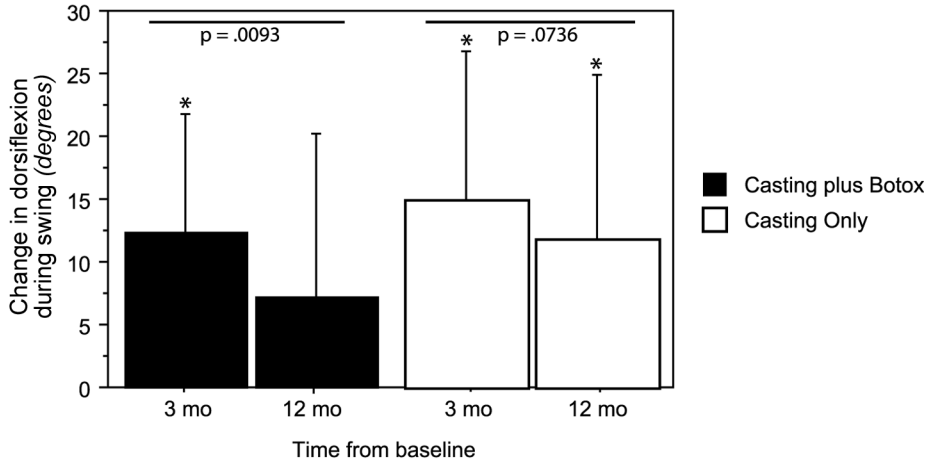

Fig. 3
Illustration depicting the improvement in peak dorsiflexion during the swing phase of gait from baseline. An asterisk (*) indicates a significant change from baseline. The p values pertain to the changes over time between three and twelve months. There was no significant difference between the groups at any time-point.

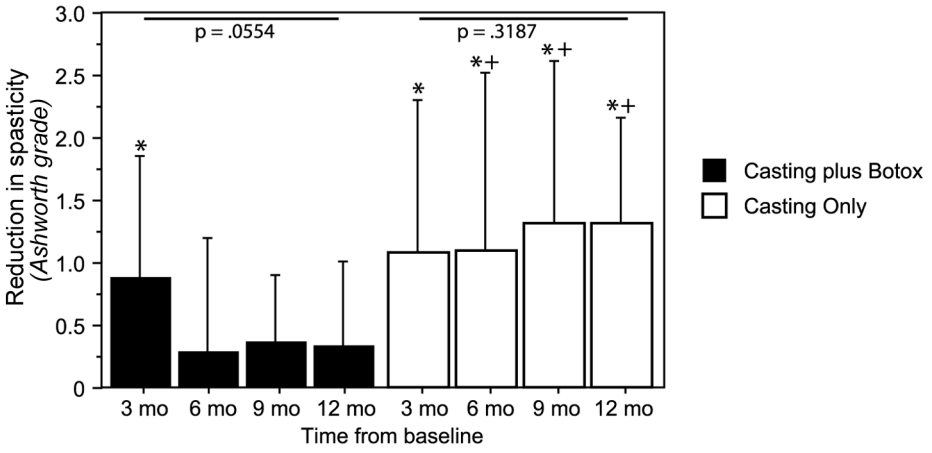

Fig. 4

Illustration depicting the reduction in spasticity from baseline. An asterisk (*) indicates a significant change from baseline, and a plus sign (+) indicates a significant difference between the groups ($p < 0.03$). The p values pertain to the changes over time between three and twelve months.

months. Plantar flexor spasticity was significantly greater in the casting-plus-Botox group than in the casting-only group at six, nine, and twelve months (Fig. 4).

The Gross Motor Function Measure scores did not change significantly in either group during the first three months (Table III), but they did increase significantly after the first three months, such that the change from baseline was significant starting at the six-month time-point in both groups (Fig. 5). With the numbers available, the amount of change did not differ significantly between the two groups.

Discussion

Although botulinum toxin A is widely used to augment serial casting in the treatment of fixed contractures in children with cerebral palsy, the present study is the first to evaluate its effectiveness when used for this purpose. The addition of botulinum toxin A did not decrease the duration of serial casting in the present study. It also had no effect on contracture correction, improvement in dorsiflexion during gait, or decrease in plantar flexor spasticity immediately after treatment. Both groups experienced significant short-term improvements, regardless of the degree of contracture that had been present before treatment. Because casts were changed and measurements were taken at two-week intervals, it is possible that one group may have experienced an earlier resolution of contracture during the last two-week interval that we were unable to detect. However, even if such a difference existed, it would not have reduced the total number of cast changes needed.

Contrary to our hypothesis, the addition of botulinum toxin A to a serial casting regimen appeared to lead to earlier recurrence of spasticity, contracture, and equinus during gait in the present study. The casting-only group experienced a significant benefit in the form of improved passive and dynamic dorsiflexion and decreased plantar flexor spasticity, which lasted for a longer period of time than was the case in the casting-plus-Botox group. The difference in response between the two groups was not related to age, the amount of physical therapy received, or compliance with bracing. Despite the earlier recurrence of equinus in the casting-plus-Botox group, both groups showed significant improvement in gross motor function that was maintained over the twelve-month period.

Our findings differ from those of previous studies that demonstrated improved, longer-lasting results in association with injections of botulinum toxin A than in association with serial casting alone[6,7]. However, those studies examined shorter-term effects (twelve and twenty-four weeks, respectively) than did the present study. The discrepancy between the results of the current study and those of previous reports cannot be ex-

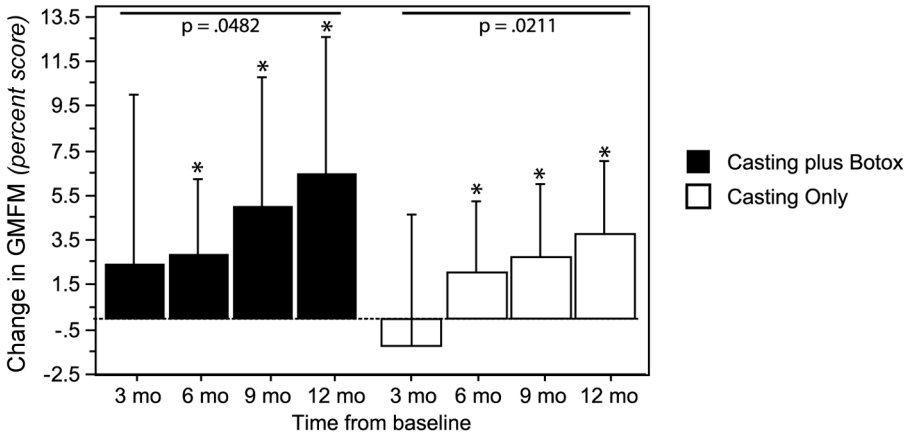

Fig. 5

Illustration depicting the change in the Gross Motor Function Measure score from baseline. An asterisk (*) indicates a significant change from baseline. The p values pertain to the changes over time between three and twelve months. There was no significant difference between the groups at any time-point.

plained by differences in the dosage of Botox. The dosage used in the current study (8 U/kg) was equal to or greater than those used in the studies by Flett et al.[7] and Corry et al.[6] (4 to 8 U/kg and 6 to 8 U/kg, respectively). The response to botulinum toxin A is thought to be dosage-dependent[13,14], and the response therefore would have been expected to be greater and of longer duration in the current study. However, previous studies regarding botulinum toxin A and serial casting excluded patients with fixed contractures, with serial casting being used only for spasticity reduction[3,4]. There may have been differences in architecture or structure between muscles with and without contracture that accounted for the different responses observed.

In the current study, equinus contracture partially recurred and spasticity and dynamic equinus returned almost to baseline levels between three and twelve months in the casting-plus-Botox group whereas all variables were improved at all time-points in the casting-only group. This finding suggests that serial casting was effective for reducing the fixed portion of the equinus for all subjects, whereas recurrent spasticity led to earlier recurrence of dynamic and static equinus in the casting-plus-Botox group.

Return of muscle function after the injection of botulinum toxin A occurs through extensive sprouting from nerve terminals. Axonal sprouting peaks at approximately eight weeks after the injection of botulinum toxin A[15]. At that time, function in the original terminals returns whereas function in the sprouts declines, with the full process being completed by about twelve weeks after the injection. There is evidence from animal studies that polyneuronal innervation (contact of a given muscle fiber with axon terminals from several motor neurons, similar to that seen during prenatal development) occurs in response to nerve injury[14,16]. A process of synapse elimination follows in which axons decrease their connections over time until each endplate is eventually innervated by a single axon. It is unclear how long polyneuronal innervation persists, with one study showing that it was present for as long as two years in frogs[14]. It has been suggested that the rate of synapse elimination may be dependent on use or disuse of the connections[17]. Therefore, immobilization of a muscle recovering from denervation (as during serial casting) may delay synapse elimination and prolong polyneuronal innervation. There has been extensive research related to neuronal recovery after physical injury[14,16-19] but very little research related to recovery from chemical denervation as occurs after the injection of botulinum toxin A. Serial casting for the treatment of fixed contractures is known to result in an increase in the number of sarcomeres in series for a given muscle[20]. The effect of changes in muscle architecture caused by serial casting combined with changes in the structure, organization, and function of the recovering neuromuscular junction after the injection of botulinum toxin A have not been studied. These factors may have been related to the earlier recurrence of spasticity as well as static and dynamic equinus in the casting-plus-Botox group in the current study. Additional study is needed to elucidate these mechanisms.

The current study included patients in whom the plantar flexor spasticity was mild to moderate, with an average grade of 2.3 on the modified Ashworth scale (which included a grade of 5 for fixed contractures). Casts were applied with great attention to positioning and with adequate padding and were monitored closely by the physical therapist. Therefore, all subjects tolerated serial casting well, without skin irritation or breakdown. Patients with more severe spasticity or dystonia, however, may not tolerate serial casting because of skin problems. Despite the findings of the current study, such patients may benefit from botulinum toxin A injections combined with serial casting to maximize tolerance of the casting procedure itself. This benefit may outweigh the risk of early recurrence of spasticity in these cases.

The small sample size was a limitation of this study. However, the data were sufficient to show some important differences between and within the groups over time. Even when significance was not reached, a trend of loss of improvement was seen for all measures of static and dynamic equinus and plantar flexor spasticity in the casting-plus-Botox group. Another limitation was the lack of establishment of reliability for the range of motion, spasticity, and Gross Motor Function Measure assessments. We did not perform formal reliability testing, but all range-of-motion and spasticity measurements were performed with use of a consistent technique by the same physical therapist, who had more than fifteen years of experience. The Gross Motor Function Measure tests were performed by two experienced physical therapists (S.A.R. and A.F.-B.) with use of standardized procedures for testing and scoring[11].

In summary, the use of botulinum toxin A to facilitate serial casting in the treatment of fixed equinus contractures may hasten a recurrence of contracture, spasticity, and equinus during gait. The mechanism behind these findings is unclear. The effects of the higher doses of Botox currently favored by many practitioners on recurrent equinus are also unknown. There is a great need for further research into the response to botulinum toxin A injection at the level of the neuromuscular junction. The use of botulinum toxin A with serial casting for the treatment of fixed contractures may be more appropriate for patients with severe spasticity or mixed hypertonia who do not tolerate casting well, in whom such treatment may minimize skin problems. Previous research has indicated that the injection of botulinum toxin A is superior to casting for the treatment of dynamic equinus. However, the results of the current study suggest that serial casting alone is preferable for the treatment of fixed equinus contractures in patients with cerebral palsy. ■

NOTE: The authors thank Los Angeles County California Children's Services for providing valuable assistance with this project. They also thank Cheré Dryden, MA, PT, and Clement Chan for their services with serial casting and Linda Chan, PhD, for assistance with the statistical analyses.

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In support of their research or preparation of this manuscript, one or more of the authors received grants or outside funding from Allergan, Incorporated (Irvine, California). None of the authors received payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or nonprofit organization with which the authors are affiliated or associated.

References

1. **Aoki KR, Guyer B.** Botulinum toxin type A and other botulinum toxin serotypes: a comparative review of biochemical and pharmacological actions. *Eur J Neurol.* 2001;8 Suppl 5:21-9.
2. **Cosgrove AP, Graham HK.** Botulinum toxin A prevents the development of contractures in the hereditary spastic mouse. *Dev Med Child Neurol.* 1994; 36:379-85.
3. **Sutherland DH, Kaufman KR, Wyatt MP, Chambers HG.** Injection of botulinum A toxin into the gastrocnemius muscle of patients with cerebral palsy: a 3-dimensional motion analysis study. *Gait Posture.* 1996;4:269-79.
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. **Koman LA, Mooney JF 3rd, 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.
6. **Corry IS, Cosgrove AP, Duffy CM, McNeill S, Taylor TC, Graham HK.** Botulinum toxin A compared with stretching casts in the treatment of spastic equinus: a randomised prospective trial. *J Pediatr Orthop.* 1998;18:304-11.
7. **Flett PJ, Stern LM, Waddy H, Connell TM, Seeger JD, Gibson SK.** Botulinum toxin A versus fixed cast stretching for dynamic calf tightness in cerebral palsy. *J Paediatr Child Health.* 1999;35:71-7.
8. **Gajdosik RL.** Passive extensibility of skeletal muscle: review of the literature with clinical implications. *Clin Biomech (Bristol, Avon).* 2001;16:87-101.
9. **Graham HK.** Botulinum toxin type A management of spasticity in the context of orthopaedic surgery for children with spastic cerebral palsy. *Eur J Neurol.* 2001;8 Suppl 5:30-9.
10. **Russell DJ, Rosenbaum PL, Cadman DT, Gowland C, Hardy S, Jarvis S.** The gross motor function measure: a means to evaluate the effects of physical therapy. *Dev Med Child Neurol.* 1989;31:341-52.
11. **Russell DJ, Rosenbaum PL, Avery LM, Lane M.** *Gross motor function measure (GMFM-66 and GMFM-88) user's manual.* 3rd ed. London: Mac Keith; 2002. p ix, 234.
12. **Bohannon RW, Smith MB.** Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther.* 1987;67:206-7.
13. **Eames NW, Baker R, Hill N, Graham K, Taylor T, Cosgrove A.** The effect of botulinum toxin A on gastrocnemius length: magnitude and duration of response. *Dev Med Child Neurol.* 1999;41:226-32.
14. **Werle MJ, Herrera AA.** Elevated levels of polyneuronal innervation persist for as long as two years in reinnervated frog neuromuscular junctions. *J Neurobiol.* 1991;22:97-103.
15. **de Paiva A, Meunier FA, Molgo J, Aoki KR, Dolly JO.** Functional repair of motor endplates after botulinum neurotoxin type A poisoning: biphasic switch of synaptic activity between nerve sprouts and their parent terminals. *Proc Natl Acad Sci USA.* 1999;96:3200-5.
16. **Barry JA, Ribchester RR.** Persistent polyneuronal innervation in partially denervated rat muscle after reinnervation and recovery from prolonged nerve conduction block. *J Neurosci.* 1995;15:6327-39.
17. **Costanzo EM, Barry JA, Ribchester RR.** Competition at silent synapses in reinnervated skeletal muscle. *Nat Neurosci.* 2000;3:694-700.
18. **Ijkema-Paassen J, Meek MF, Gramsbergen A.** Reinnervation of muscles after transection of the sciatic nerve in adult rats. *Muscle Nerve.* 2002;25:891-7.
19. **Waldeck RF, Murphy EH, Pinter MJ.** Properties of motor units after self-reinnervation of the cat superior oblique muscle. *J Neurophysiol.* 1995; 74:2309-18.
20. **O'Dwyer NJ, Neilson PD, Nash J.** Mechanisms of muscle growth related to muscle contracture in cerebral palsy. *Dev Med Child Neurol.* 1989; 31:543-7.