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Botulinum Toxin Type A Neuromuscular Blockade in the Treatment of Lower Extremity Spasticity in Cerebral Palsy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Summary: Increased gastrocnemius/soleus muscle tone in children with cerebral palsy may cause an equinus of the ankle. Botulinum toxin type A (BTX), a neuromuscular blocking agent, reduces muscle tone in various neuromuscular disorders. The safety and short-term efficacy of BTX injections were evaluated in a prospective, 3-month, double-blind, randomized clinical trial involving 114 children with cerebral palsy and dynamic equinus foot deformity. Outcome was determined by observational gait analysis, ankle range-of-motion measurements, and quantification of muscle denervation by nerve conduction. Patients in the BTX group demonstrated improved gait function and partial denervation of the injected muscle. No serious adverse events were reported. **Key Words:** Botulinum A toxin—Cerebral palsy—Lower extremity—Neuromuscular blockade—Pediatric—Spasticity.

Equinus foot position secondary to spasticity in young children with cerebral palsy interferes with function and, despite physical therapy and braces, may result in fixed contractures. Neuromuscular blockade produced by local injection or application of 45% alcohol or phenol has been used for >30 years to improve function, to aid in physical therapy or orthotic management, and to avoid or delay surgical interventions for abnormal positioning (5, 6,13). Complications from this approach, however, include skin slough, muscle fibrosis or scarring, permanent nerve damage, pain, and side effects related to general anesthesia, conscious sedation, or open surgical exposure of nerves (11).

Botulinum A toxin (BTX), when injected intramuscularly without anesthesia, has been demonstrated to be a practical neuromuscular blocking agent (3,4,8,15,19,20, 29). In pediatric cerebral palsy patients, BTX produces a variable degree of muscle denervation, provides a clinical reduction in functional muscle spasticity/tone, promotes better motor balance across joints, and improved ambulatory status and hand function (4,8,19,20,29). Injections appear to alter beneficially the natural history of patients with cerebral palsy and equinus foot deformity by delaying surgery (18). To date, large randomized, controlled studies evaluating the efficacy of BTX in children with cerebral palsy have not been completed.

To document adequately the efficacy and safety of neuromuscular blockade using intramuscular injections of BTX, a multicenter, placebo-controlled study was designed to evaluate BTX injections administered to ambulatory children with abnormal dynamic equinus foot deformity. The effects of neuromuscular blockade with BTX on the hypertonic gastrocnemius and on ankle function in children with cerebral palsy were evaluated.

METHODS

Study population

Ambulatory patients with cerebral palsy between the ages of 2 and 16 years were screened for enrollment in the study. All patients were either hemiplegic or diplegic; there were no quadriplegic patients. To be considered eligible for study participation, patients had to exhibit spasticity of one or both lower limbs characterized by an equinus positioning of the foot during the stance phase of gait. Informed consent was obtained from the prospective study participants' parents/guardians. Patient-exclusion criteria included (a) evidence of fixed contracture; (b) severe athetoid movements in the target leg(s); (c) a significant difference (>5 cm) between the length of the right and left legs; (d) obvious atrophy of the calf muscles of leg(s) to be treated in the study; (e) current need for surgery; (f) previous surgery of the foot, leg, and/or ankle; (g) previous injections of phenol or alcohol

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into the muscles to be injected in the study; or (h) current or previous therapeutic exposure to BTX.

Patients (n = 145) were enrolled and managed according to the study protocol. All patients were included in the evaluation of safety. Data from one center (n = 15) were excluded from the analysis of efficacy because regulations in that country prohibited the use of placebo in children; consequently, data from this center were not blinded. Data from 16 patients were excluded from efficacy evaluation because of failure to meet entry criteria. One hundred fourteen patients were evaluated for efficacy (Table 1).

Study medications

Patients were randomly assigned to receive injections of either BTX or placebo. The identity of the administered study medication was unknown to the investigator, the patient, or the guardian. Each vial of BTX contained 100 units of *Clostridium botulinum* toxin type A with human serum albumin and sodium chloride in a sterile, vacuum-dried form without preservatives (BOTOX Purified Neurotoxin Complex; Allergan, Inc.). Placebo, provided in identical and indistinguishable vials, contained human serum albumin and sodium chloride in a sterile, vacuum-dried form without preservatives (prepared by Allergan, Inc.). It was necessary for the placebo to include human serum albumin to be identical to the vehicle used for the BTX.

Dosing and injection procedure

All injections were prepared by reconstituting each vial with 1 ml of sterile saline to achieve a concentration of 10 units/0.1 ml in the BTX vials. An aliquot was drawn into a syringe based on the calculation of the dosage at 4 units/kg body weight and then brought up to a 4-ml volume for hemiplegic children and an 8-ml volume for diplegic children; 2 ml was then injected into the medial and lateral gastrocnemius of each involved leg. Because neither the safest nor the most effective dose for BTX treatment has yet to be determined, we were conservative and held the total dose constant at 4 units/kg body weight. In this way, although hemiplegic children received twice as much BTX per extremity as did diplegic children, they also had an increased chance of receiving an effective dose of BTX. In this protocol, anesthetic was not used before administering the injections. The maximal dose did not exceed 200 units at any injection.

Under sterile conditions, injections were performed by using 23- to 26-gauge needles and appropriately sized syringes. The muscle was palpated while being stretched passively, the needle was inserted through the fascia into the proximal one third of the muscle (approximate region of the motor end plates), and the drug was injected. Clinical experience demonstrated that the target muscle location was easily pinpointed without guidance. Electromyogram (EMG) needle guidance would have been, because of the large needles involved, more painful for the children. Pain on injection was reported as mild after either the toxin or placebo injections.

Procedures at each visit

Patients were seen at five scheduled visits: baseline and at 2, 4, 8, and 12 weeks after the first injection. At baseline, demographic data including age, sex, ethnic background, medical history, social history, and general physical examination were recorded. Dynamic gait pattern during walking and active and passive ankle dorsiflexion range of motion (ROM) also were evaluated. The first injection of study medication was administered. At each follow-up visit, the dynamic gait pattern and ankle ROM were evaluated, and any adverse events were recorded. All patients received a second injection of study medication (same medication as in the first injection for each patient) at week 4 unless medically contraindicated because of excessive weakness, gross muscle atrophy, or development of a fixed contracture of the injected muscles. Electrophysiologic measurements (EMG) of all injected muscles were performed at baseline (before injection), and at 4, 8, and 12 weeks.

Dynamic gait pattern during active walking

The dynamic gait pattern during active walking was evaluated by using a modification of the Physician Rating Scale (PRS) developed by Koman et al. (19,20) (Table 2). Evaluations of six functional aspects of the gait cycle were made while observing barefoot ambulation for a distance of ≥15 feet. The composite PRS score for each patient was determined by combining all of the component scores for that patient [gait pattern, hindfoot (ankle) position, hindfoot position, knee position, degree of crouch, and speed of gait]. The responder rate for the composite score was defined as the percentage of patients in each treatment group that exhibited an improvement from baseline in the composite PRS score of ≥2 points. The responder rate for each component of dynamic gait pattern in each treatment group was defined as the percentage of patients that exhibited any improvement from baseline in that particular component of the rating scale.

3-D motion analysis was not used because of the lack of testing facilities at most of the study sites. The PRS was created because of the unavailability of any other scales with appropriate specificity and intraobserver and interobserver reliability. Although the Ashworth spasticity scale was developed to measure spasticity, it is not

TABLE 1. *Demographics*[a]

	BTX	Placebo
Enrolled	56	58
Discontinued	3	3
Completed	53	55
Race		
White	46 (82%)	50 (86%)
Black	5 (9%)	3 (5%)
Hispanic	3 (5%)	3 (5%)
Other	2 (4%)	2 (3%)
Diagnosis		
Diplegia	41 (73%)	41 (71%)
Hemiplegia	15 (27%)	17 (29%)

[a] Of the subjects, 68 are boys and 46 are girls.

TABLE 2. *Physician Rating Scale (PRS)*

	Extremity	
	Left	Right
A. Gait pattern		
Toe–toe	0	0
Occasional heel–toe	1	1
Heel–toe	2	2
B. Hind foot position during foot strike		
Varus	0	0
Valgus	1	1
Occasionally neutral	2	2
Neutral	3	3
C. Knee position during gait (stance phase)		
Recurvatum >15°	0	0
Recurvatum 6–15°	1	1
Recurvatum 1–5°	2	2
Neutral or flexed	3	3
D. Hind foot (ankle) position during gait (stance phase) maximum foot/floor contact		
Equinus	0	0
Neutral	2	2
Calcaneus	0	0
E. Degree of crouch (hip, knee, ankle)		
Severe (>20°)	0	0
Moderate (5–20°)	1	1
Mild (<5°)	2	2
None	3	3
F. Speed of gait		
Only slow	0	0
Variable (slow–fast)	1	1

reliable for evaluating the ankle and has not been validated in children.

Passive ankle range of motion

Passive range of ankle motion with the knee flexed and extended was evaluated in a standardized fashion. The patient's knee was held flexed at 90°, and the foot was held in a supinated position to diminish subtalar motion and midfoot dorsiflexion. Maximal passive dorsiflexion was measured with a goniometer. The passive ankle ROM was obtained with the knee in full extension and with the foot held in a similar fashion.

Active ankle range of motion

ROM of the ankle was obtained from the flexor withdrawal reflex ("confusion response") to determine any change in ROM during treatment. The patient's knee was flexed 90° over a table edge. The patient was asked to flex the hip against the resistance of the examiner's hand, which was placed on the anterior portion of the midthigh (2). In a positive response, the ankle automatically dorsiflexes. Maximal active dorsiflexion was measured with a goniometer. This evaluation of active ROM may correlate with the available functional arc of motion and allow the detection of a fixed deformity and/or change in ROM.

Electrophysiologic measurements

An active surface electrode taped posteriorly over the greatest circumference of the gastrocnemius/soleus muscle complex referenced to the indifferent electrode over the proximal Achilles tendon was used to record the electrophysiologic response. Graded submaximal stimulation elicited the H-reflex by following standard procedures (16). By using the same stimulating and recording electrodes, supramaximal stimulation of the posterior tibial nerve in the popliteal fossa was used to generate an M (motor) response in the gastrocnemius/soleus complex. Standard nerve-conduction study filter settings (HFF, 10,000 Hz; LFF, 2 Hz) were used.

Adverse events

Reports of adverse events that occurred during the study period were solicited from patients and their parents or guardians and recorded at each visit.

Blood serum antibodies

Blood samples were collected at the beginning and end of the study. Serum was analyzed by the mouse protection assay for the presence of antibodies to BTX (14).

Statistical analysis

The prestudy estimate of power and sample size indicated that 98 evaluable patients (49 patients per treatment group) were required to detect a 30% difference between groups in success rate with 80% power, and a two-grade or more difference in mean change from baseline in composite score with 91% power. One hundred fourteen patients were included in the preferred analysis.

Baseline characteristics were compared between treatment groups by an analysis of variance (10) for age and by the χ^2 test (10) for sex and race (white vs. nonwhite). Treatment effects were assessed in mean change in composite score by using the Wilcoxon rank-sum test (10). Mean change in component scores and responder-rate differences between groups were compared by using the Cochran–Mantel–Haenszel test (21) adjusting for study site. Between-group differences in ROM variables were compared between groups by using the Wilcoxon rank-sum test and within groups by using the Wilcoxon signed-rank test (10). Between-group differences in electrophysiologic variables were compared with analysis of variance techniques, and within-group changes were assessed with a paired t test (10). Incidence of treatment-related adverse events was presented by treatment groups. All analyses were two-sided, and differences with a p value of ≤ 0.05 were considered statistically significant.

Poststudy power calculations were not necessary for the primary efficacy variable, dynamic gait pattern composite score, because there were statistically significant between-group differences in success rate at all follow-up visits and in mean composite score at all but one follow-up visit.

RESULTS

There were no differences between the two treatment groups in terms of age, sex, or ethnicity (Table 1). There were also no differences in the use of orthotics, walkers, casts, or previous surgery between the two groups. Groups were comparable in terms of diagnosis. The results did not vary from center to center.

Physician Rating Scale dynamic gait pattern

Groups were compared by using (a) the PRS composite score, and (b) individual components of the PRS.

Composite Physician Rating Scale score

The PRS composite score responder rate was significantly greater in the BTX group versus the placebo group at all follow-up visits ($p < 0.05$; Fig. 1A). For example, at week 8, 31 (61%) of 51 patients in the BTX group responded versus 14 (25%) of 55 in the placebo group. Improvement in the mean composite score was significantly greater in the BTX group than in the placebo group at every visit ($p < 0.05$; Fig. 1B). Results of a subgroup analysis of the PRS composite score for patients who received injections in one or both legs were consistent with results from the overall analysis.

Component scores

BTX-treated patients demonstrated significantly greater improvement in the component responder rate and the mean component score for gait pattern and ankle position at foot strike (Figs. 2A and B, and 3A and B). There were no significant between-group differences at any follow-up visit for the remaining four individual components of the PRS.

Range of motion

In the evaluation of active ankle dorsiflexion with the knee flexed, ROM was significantly greater in the BTX-treated group than in the placebo group at weeks 4 and 12 ($p < 0.05$). The mean increases from baseline in the BTX group were significant at all follow-up visits and ranged from 3 degrees at week 2 to 7 degrees at week 12. Within the placebo group, no significant changes from baseline were detected. There were no significant differences between the groups in passive ankle dorsiflexion.

Adverse events

The incidence of adverse events occurring during treatment was evaluated in 145 patients. Adverse events rated as probably, possibly, or remotely treatment related were reported in 12 (17%) of 72 BTX-treated patients and in three (4%) of 73 patients in the placebo group (Table 3). All adverse events were rated as mild to moderate; none was rated as severe. No patients exited the study because of an adverse event.

Electrophysiologic measurements

M-response

The amplitude of the M-response decreased significantly in the BTX group at all follow-up evaluations

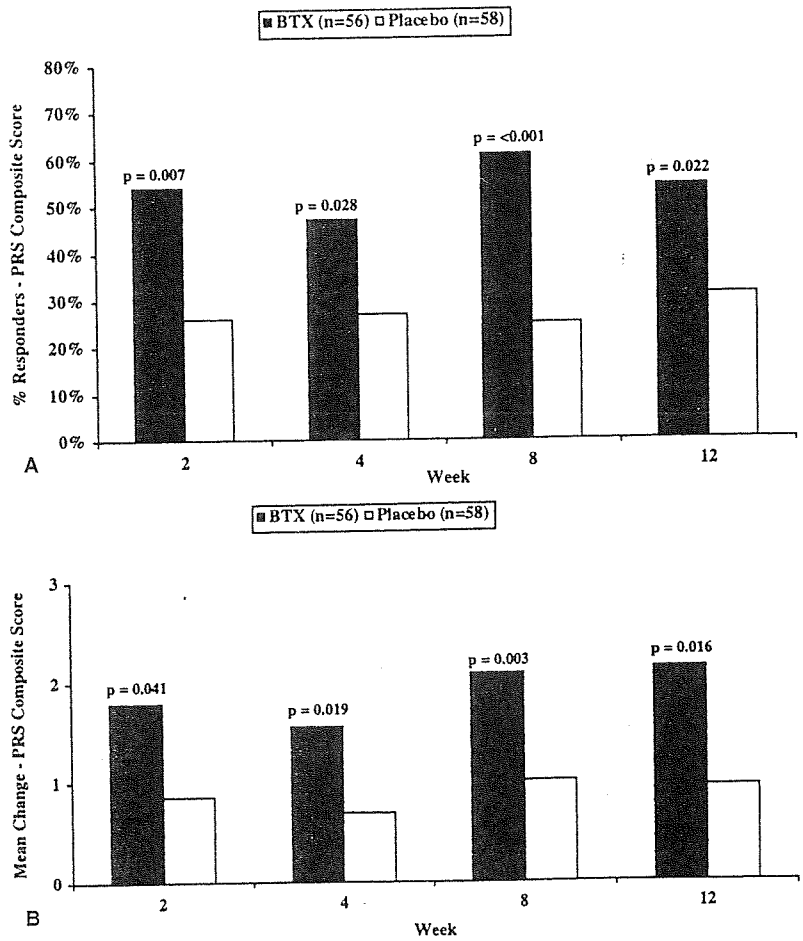

FIG. 1. A: Percentage of patients (responders) in the BTX ($n = 56$, solid columns) and placebo ($n = 58$, open columns) treatment groups that improved from baseline by >2 grades in the Physician Rating Scale composite score (range, 0–14). **B:** Mean change from baseline in the Physician Rating Scare composite score. Mean baseline scores were 6.16 for BTX and 6.77 for placebo.

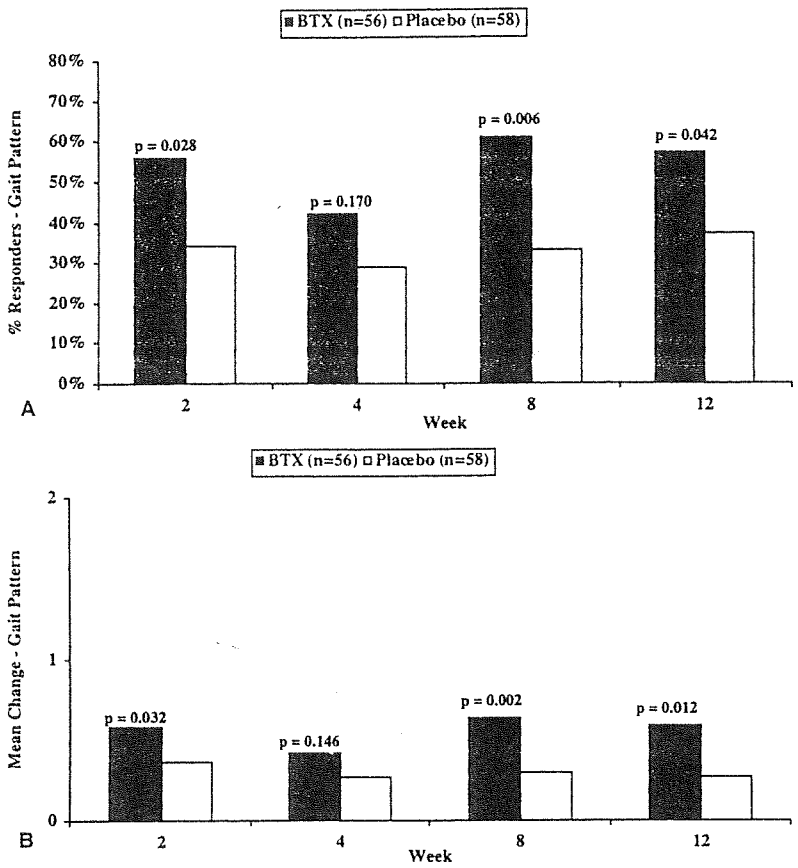

FIG. 2. A: Percentage of patients (responders) in the BTX (n = 56, solid columns) and placebo (n = 58, open columns) treatment groups that improved from baseline by >1 grade improvement in the Physician Rating Scale gait-pattern component score (range, 0–2). B: Mean change from baseline in the Physician Rating scale gait-pattern component score. Mean baseline scores were 0.10 for BTX and 0.19 for placebo.

(range, 1.97–2.28 mV; $p < 0.05$). The M-response of the BTX group was significantly different from placebo at week 4 ($p < 0.05$; Fig. 4).

H-reflex

There were no significant between-group or within-group differences in the mean H-reflex amplitude at baseline or at any follow-up visit.

Blood-serum antibodies

Antibodies to BTX were not detected in any of the patients' blood samples either at baseline or at the final study visit (week 12). Current recommendations suggest waiting 3 months between repeated toxin injections to reduce the possibility of antibody development.

DISCUSSION

This is the first large, well-controlled, randomized study to document that intramuscular injections of BTX lead to improvements in gait pattern. The improvements in gait pattern lasted a minimum of 8 weeks. Significant improvements were measured in the overall score of the PRS of Dynamic Gait Pattern and in the individual components of gait pattern and ankle position. This is consistent with the findings of previous preliminary investigations of the use of BTX in the treatment of spasticity in children with cerebral palsy (4,8,17,19,20,27).

Active ROM measures at the ankle showed significant increases after BTX treatment, whereas passive ROM did not change. It should be noted that the range used in gait and the passive range used on examination measure different things and are not necessarily correlated (7).

Patients injected with placebo also showed increased scores on the PRS, although the increases were significantly less than those seen after BTX injection. Such improvement in function was expected, even in the placebo group, as all patients continued their prestudy regimens of physical therapy, aided, in some cases, by orthotics.

The PRS was designed to measure changes in ambulation in patients with lower-limb spasticity, particularly pediatric patients, and consists of six separate gait-related components. In this study, the gait-pattern and ankle-position components showed the most significant changes after BTX injection. The other four components were not significantly changed after BTX injection. Changes in PRS scores were consistent across all of the investigation sites, and the statistical significance of the difference in PRS scores between toxin and placebo patients supports the use of the PRS as an outcome measure. This scale has also been used in other studies of patients with lower-limb spasticity, which showed similar changes in gait pattern in response to BTX treatment (7,9,20,30). Corry et al. (7) found good interinvestigator reliability in the assessment of the gait-pattern component, which they considered the component most likely to change with BTX-A treatment of spastic equinus.

There was no significant difference in the improve-

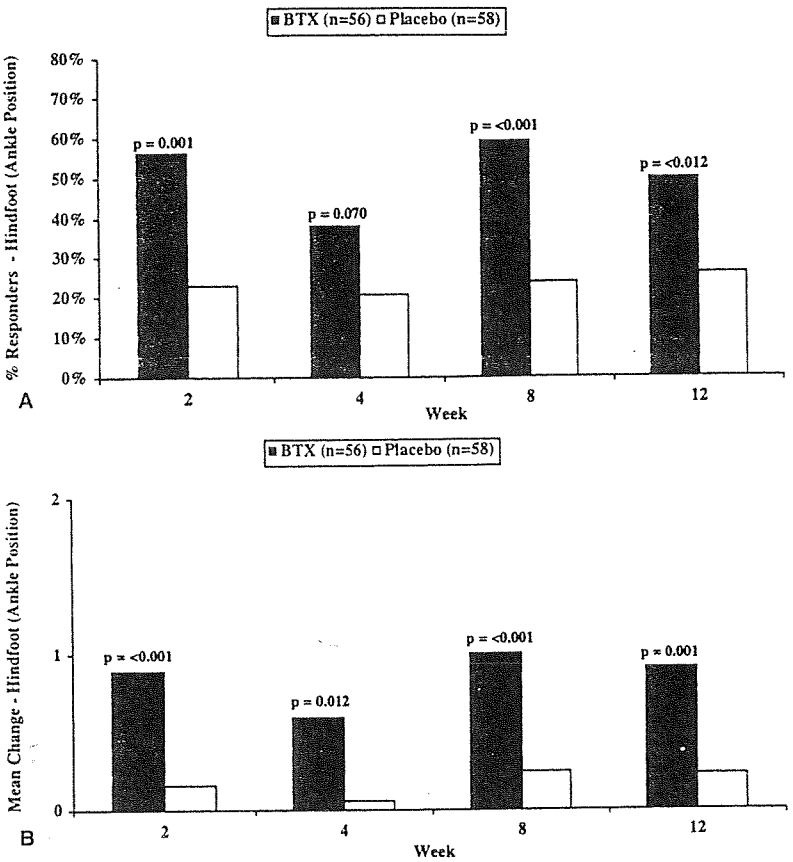

FIG. 3. A: Percentage of patients (responders) in the BTX (n = 56, solid columns) and placebo (n = 58, open columns) treatment groups that improved from baseline by >1 grade in the Physician Rating Scale hindfoot (ankle)-position component score (range, 0–2). B: Mean change from baseline in the Physician Rating Scale hindfoot (ankle)-position component score. Mean baseline scores were 0.24 for BTX and 0.60 for placebo.

ment seen in diplegic versus hemiplegic patients, even though the hemiplegic patients received twice the dose of BTX in the gastrocnemius muscle as did diplegic patients. This could mean that the smaller dose was sufficient to produce the measured increases in gait function. Alternatively, the extent of muscle relaxation may have been determined by the extent to which the BTX solution diffused across the muscle, because the same volume of fluid was given in each muscle.

This study found no correlation between the degree of gait improvement and patient age in patients without fixed contracture. It is possible that contractures and bony deformities, which are not affected by BTX, become more common as patients mature. The fact that, in this study, age is unrelated to the success of BTX treatment suggests that if patients are carefully chosen, BTX treatment can improve function even in older children.

Pain on injection was mild after either the toxin or placebo injections, and all of the patients agreed to a second injection. In our experience, topical anesthetics are not effective in diminishing the pain related to injection. This may be because the anesthetic does not affect the underlying, injected muscle.

No serious, severe, or irreversible adverse events were experienced by any of the patients treated with BTX, and the majority of adverse events were mild. The higher incidence of adverse events with BTX injection can be explained by the fact that the toxin does reduce muscle spasticity. This can lead to reports of muscle weakness, falling, fatigue, and unstable gait in individuals used to ambulating with spastic muscles. These findings are consistent with the published reports of BTX use in cerebral palsy and other neuromuscular disorders such as blepharospasm and cervical dystonia (1,3,8,15,19,20,28).

The decrease in the M-response after BTX injection into the gastrocnemius confirms the partial chemical denervation of the injected muscle (25). Recently it was suggested that therapeutic injections of BTX may exert additional beneficial effects through either direct central mechanisms or through alterations of muscle spindle afferent activity (12). The H-reflex, an electrically elicited

TABLE 3. *Adverse events related to study treatment*

Adverse effect	BTX (n = 72)	Placebo (n = 73)
Leg weakness	2 (3%)	0
Leg/calf pain	2 (3%)	0
Falling	2 (3%)	1 (1%)
Fatigue	1 (1%)	0
Unstable gait	1 (1%)	0
Malaise	1 (1%)	0
Ankle inversion injury	1 (1%)	0
Pain at injection site	1 (1%)	0
Lethargy	1 (1%)	0
Tingling sensation in back	1 (1%)	0
Foot callus	1 (1%)	0
Urinary incontinence	1 (1%)	0
Fever	0	1 (1%)
Knee pain	0	1 (1%)

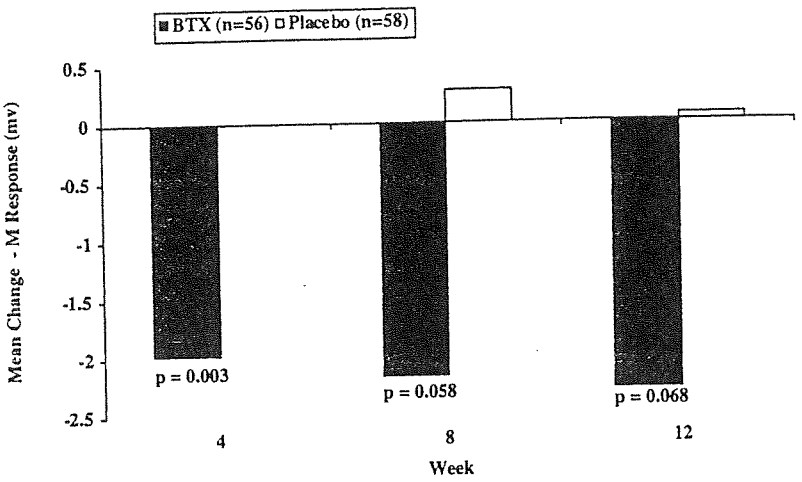

FIG. 4: Mean change from baseline in the M-response amplitude (mV) in the BTX (n = 56, solid columns) and placebo (n = 58, open columns) treatment groups measured at 4, 8, and 12 weeks after treatment. Mean baseline scores were 11.36 and 10.46 mV for BTX and placebo, respectively.

form of the muscle stretch reflex at the ankle, a well-standardized measure of central synaptic activity, did not change during this study. Thus evidence of significant central or "sensory" effects of the drug was not found. This observation supports the conclusion that BTX exerts therapeutic benefit by inducing paresis. The amplitude of the M-response is roughly proportional to the number of muscle fibers responding to a supramaximal nerve stimulation. Therefore any decrease in the amplitude of the M-response will be roughly proportional to the degree of muscle denervation produced by BTX injection (22,26). In our study, the M-response decreased by ~20%, suggesting that BTX injection produced a 20% partial denervation of the muscle.

Intermittent neuromuscular blockade with BTX allows the selective weakening of spastic muscles without the need for immobilization and may improve the patient's ability to strengthen weaker antagonist muscles. This chemically induced improvement in muscle balance appears to enhance the effects of physical therapy and orthotics. In the long term, BTX treatment may also delay the need for surgery. Theoretic advantages of delaying surgery in immature patients with excessive gastrocnemius/soleus spasticity include (a) a decrease in the incidence of recurrence of abnormal positioning and repeated surgery (23), (b) the maintenance of muscle fiber length (8,24), and (c) the facilitation of other therapy programs (7,19). In a series of 12 patients in whom tendoachilles surgery was recommended before BTX therapy, BTX delayed surgery an average of 21 months; three patients avoided surgery for >60 months (18). Treatment with BTX must be individualized because the value of repeated BTX injections depends on the patient's response to the injections. In the absence of procedures that can repair the causal central nervous system injury, a technique that selectively modulates increased muscle tone and spasticity in cerebral palsy patients is a valuable and heretofore unavailable modality.

The results of this study indicate that outpatient BTX injections into the gastrocnemius muscle in children with cerebral palsy provided a well-tolerated, nonsurgical modality for improving the equinus foot position in ~50–60% of patients, without significant morbidity or discomfort. Long-term consequences of intramuscular injections of BTX cannot be inferred from this study. Further evaluation is warranted and is necessary to evaluate the use of BTX as an adjunct to conventional therapies in pediatric cerebral palsy patients. Further studies will be required to evaluate the cost effectiveness and health-related quality of life associated with the use of this therapy.

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