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Botulinum Toxin for Spasticity in Children With Cerebral Palsy: A Comprehensive Evaluation

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Abstract

BACKGROUND—Spasticity is a prevalent disabling clinical symptom for children with cerebral palsy. Treatment of spasticity with botulinum toxin in children with cerebral palsy was first reported in 1993. Botulinum toxin provides a focal, controlled muscle weakness with reduction in spasticity. Interpretation of the literature is difficult due to the paucity of reliable measures of spasticity and challenges with measuring meaningful functional changes in children with disabilities.

OBJECTIVE—This study documents the effects of botulinum toxin-A (BTX-A) injections into the gastrocnemius muscles in children with spastic diplegia. Outcomes are evaluated across all five domains of the National Centers for Medical and Rehabilitation Research domains of medical rehabilitation.

METHODS—A randomized double masked placebo controlled design was applied to 33 children, with spastic diplegia with a mean age of 5.5 and Gross Motor Function Classification System Levels of I–III. Participants received either 12 units/kg BTX-A or placebo saline injections to bilateral gastrocnemius muscles. Outcomes were measured at baseline, 3, 8, 12, and 24 weeks after injection.

RESULTS—Significant decreases in the EMG representation of spasticity were documented at 3 weeks after BTX-A treatment. A significant decrease in viscoelastic aspects of spasticity was present at 8 weeks and subsequent increases in dorsiflexion range were documented at 12 weeks for the BTX-A group. Improvement was found in performance goals at 12 weeks and in maximum voluntary torque and gross motor function at 24 weeks for the BTX-A group. There were no significant differences between groups in satisfaction with performance goals, energy expenditure, Ashworth scores, or frequency of adverse effects.

CONCLUSIONS—The safety profile of 12 units/kg of BTX-A is excellent. Although physiologic and mechanical effects of treatment with BTX-A were documented with functional improvement at 6 months, family satisfaction with outcomes were no different. Communication is needed to ensure realistic expectations of treatment.

Keywords

cerebral palsy; botulinum toxin

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Since the first report on the use of botulinum toxin (BTX) to treat spasticity in children with cerebral palsy (CP) was published in 1993, there have been over 100 articles addressing the intervention. The present literature, including several meta-analyses, suggests that BTX provides focal, controlled muscle weakness and, by implication, reduction in spasticity.[1–8] The paucity of reliable measures of spasticity and the difficulty in measuring meaningful changes in function in children with disabilities makes interpretation difficult.

CP, a common chronic disabling condition of childhood, occurs in 1.5/1,000 to 3/1,000 live births with a similar prevalence rate into adolescence and adulthood.[9] Spasticity is a prevalent disabling clinical symptom seen in persons with CP. Spastic diplegia a very common form of CP, presents with a wide range of ambulatory outcomes and is most frequently accompanied by ankle joint spasticity. To justify an intervention, there must be a purpose for treating spasticity that is meaningful to patients and their caregivers. Goals of treatment may include simple aims such as reducing pain, increasing range of motion (ROM), prevention of secondary medical complications such as contractures or skin breakdown, or better tolerance of splinting and casting. Most patients and their families identify improved active function related to walking as the most important outcome. Not all patients identify the same functional goals nor do they attach the same priorities to those goals.

We comprehensively studied botulinum toxin type A (BTX-A) injections to gastrocnemius muscle in children with CP using fourteen outcome measures distributed among the five domains of science relevant to rehabilitation medicine as defined by the National Centers for Medical and Rehabilitation Research (NCMRR) of the National Institutes of Health.[10] These domains include pathophysiology, impairment, functional limitation/activity, disability/participation and societal limitation/contextual factors (see Tables 1 and 3). This approach afforded a 360 degree view of the intervention from the pathophysiologic to the societal level. For this project we have combined functional limitation with disability.

We proposed that BTX-A injection into plantar flexor muscles in children with spastic diplegia would produce a reduction of spasticity and a change in function which could be measured across all five domains. This project addressed the following clinical questions: (1) what is the natural history of the weakness associated with change in neuromuscular junction transmission after injection with BTX? (2) Does injection with BTX-A result in clinically relevant reductions in spasticity, measured by changes in torque and stiffness across the ankle joint, when compared to similar untreated patients? (3) What is the magnitude and durability of reduction of spasticity after treatment with BTX-A? (4) Does injection with BTX-A increase mechanical efficiency, as demonstrated by improvement in the Gross Motor Function Measure (GMFM), reduction of energy expenditure and improvement of gait? (5) What changes in motor function typically occur during the 6 months after injection with BTX-A? (6) Does injection with BTX-A result in a meaningful reduction in disability as described by the pediatric patient and his/her parents? (7) Does injection with BTX-A reduce societal limitation in the context of community, and school activities? and (8) are there serious adverse events or complications of injection with BTX-A during the first 6 months after the procedure?

Our primary hypothesis was that injection with BTX-A would reduce spasticity in plantar flexor muscles of children with spastic diplegia for 6 months' duration and that we could reliably measure that reduction in spasticity. We predicted that the pathophysiologic improvements and reductions in spasticity would return to baseline levels at 6 months. We also hypothesized that injections would improve functional ability and societal participation that although temporary, would be significant and meaningful.

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METHODS

Thirty-three children were randomized to either an experimental group (injection with 12 units/kg BTX-A) or a comparison group (sham injection of normal saline). Double-masked assessments were made at baselines 1 and 2 (7 days apart) and at 3, 8, 12, and 24 weeks post injection (see Table 1). Injections occurred at baseline number 2 after masked testing was completed. The timing of the first post intervention assessment at 3 weeks after injection was chosen based on previous published reports suggesting that the maximal effect of the neuromuscular blockade was obtained at 21 days.[11] The remaining time points were chosen to assess BTX-A effect duration and document its dissipation. At the end of 24 weeks, the randomization code was unmasked and patients in the sham injection group had the opportunity to cross over and have injection with BTX-A.

Study participants underwent conscious sedation with oral midazolam to improve tolerance of injections. Injections were performed solely by the principal investigator using EMG guidance at two injection sites in each of the medial and lateral heads of the gastrocnemius muscles. A total dosage of 12U/kg (never exceeding 400 units) was distributed among left and right gastrocnemius muscles. Assessments were performed in the same order on each assessment day following the schedule in Table 1. The active drug in this clinical trial was botulinum toxin Type A (brand name Botox, manufactured by Allergan Pharmaceuticals, Irvine, CA). Each 100 units of BTX-A was diluted with 1 ml of preservative free 0.9% Sodium Chloride for Injection. The placebo was 0.9% sodium chloride for injection, prepared to the same volume calculated for the active drug. Study drug was prepared using aseptic technique on the day of dosing. All doses were mixed within 4 hours of the time of the injection. The Investigational Drug Service at Children's Hospital and Regional Medical Center (CHRMC) performed the randomization and prepared all doses of study drug.

Participants were randomized into four strata based on age (3–7 years vs 8–12 years) and whether or not they were receiving oral baclofen. Preliminary power analysis was based on the primary outcome measures of spasticity and motor function [ie, spasticity measurement system (SMS) and Gross Motor Function Measure (GMFM)]. Based on the then current estimates of variance of primary outcome measures, with 18 subjects in each group, we predicted the ability to detect a 7.2 point change in total GMFM percent scores with a power of 0.9 at a two-tailed significance level of 0.05. The same sample size would yield a 15.3 point change in path length on the SMS with a power of 0.8 and will provide a two-tailed significance of 0.05. Based on our previous experience with measurement of GMFM and SMS, preliminary analysis of the statistical power of this study suggests that a minimum of 36 subjects would provide adequate power to be confident of our results. The investigators, study coordinators, physical therapists and participants were masked to treatment assignment. Only the staff of the Investigational Drug Service was unmasked. The Institutional Review Board at CHRMC granted approval for the study.

Study Participants

The multidisciplinary Spasticity Management Clinic team at CHRMC initially screened all potential participants. Participants were approached for enrollment if they presented with the clinical indications for gastrocnemius BTX-A treatment and fit the inclusion/exclusion criteria. Inclusion criteria were: (1) age 3–12 years, (2) diagnosis of spastic diplegia: defined as spastic motor impairment with more involvement of lower limbs than upper, fair to good trunk and head control, and little or no bulbar involvement, (3) community or indoor ambulation status,[12–14] (4) cooperative and tolerant to testing procedures during clinic screening, (5) No fixed musculoskeletal deformities greater than 15 degrees (ie, normal knee extension range of motion = 0 degrees, ankle dorsiflexion = + 15 degrees, (6) stable social environment, (7) ongoing physical therapy (PT) of a minimum of one 60-minute session per week, and (8)

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pharmacological treatment (baclofen) for spasticity was not a basis for exclusion. Participants were maintained on a stable, fixed dose 1 month prior to and throughout the 6-month study period. Orthotic type, wearing schedule, PT regimen and/or the clinical need for serial casting were documented but not controlled during the study period. All participants received direct physical therapy for a minimum of 1 hour per week during the study period. The therapy regimen was left to the discretion of the treating physical therapist.

A total of 106 children were screened between October 1997 and September 2001, of whom 60 were eligible and approached for participation in the trial. Final enrollment was 33 (55% enrollment rate). Informed consent was obtained from all participants and their guardians. Baseline demographics and outcome measures are presented in Table 2. Participants averaged 5.5 years in age (3.1–11.9) and mobility impairments fell into Gross Motor Function Classification System (GMFCS) levels I to III.[15,16] There were no significant differences between groups in the baseline measures, except for Walking Heart Rate ($p < 0.003$, Table 2). Seventeen participants were randomized to receive BTX-A and 16 received saline injections. Six children were taking oral baclofen and were equally distributed by treatment group. None of the participants had received BTX injections prior to participation.

Measurements

NCMRR domains of science were represented by 14 unique outcome measures. See Tables 1 and 4 for specific measures by domain. Primary outcome measures for the domains of impairment; and functional limitation/disability were total and elastic path length as a measure of spasticity (Spasticity Measurement System-SMS), and the Gross Motor Function Measure (GMFM-88 & GMFM-66). Secondary outcomes included: Quantitative Electromyographic Kinesiology (QEK) for the pathophysiology domain, Ashworth, deep tendon reflexes (DTR), clonus, ankle dorsiflexion passive range of motion (PROM) and maximum voluntary torque (Max Torque) of the gastrocnemius muscle for the impairment domain. The functional limitation/disability domains were also measured by energy cost index (ECI) and the performance portion of the Canadian Occupational Performance Measure (COPM). The satisfaction portion of the COPM and Goal Attainment Scaling (GAS) was administered to assess the societal limitation domain.

The QEK and SMS were collected by a study engineer and research assistant masked to group assignment in the research motion analysis laboratory at the University of Washington. Masked research physical therapists and nurses collected the remaining outcome measures in the pediatric clinical research center (CRC) at CHRMC. A masked research nurse conducted a structured adverse event interview at each research visit in person and by phone for the 8-week visit. Adverse events reported during those interviews were coded for date of onset and resolution, severity level, relationship to CP and/or treatment, effect on treatment, medical treatments administered and outcome.

Spasticity Measurement System (SMS)—An electromechanical method of eliciting and measuring spasticity was performed using automated measurement of ankle stiffness in response to passive ankle movements of various frequencies.[17,18] The participant was tested in the prone position and on the leg exhibiting the greatest motor impairment (greatest Ashworth score at screening visit) and with adequate ROM to perform the test. The foot was inserted into a foot binding aligned to the ankle joint and positioned at the subject's maximum dorsiflexion. The foot was passively rotated over 5 degrees at frequencies of 3 to 12 Hz via a custom designed computer-controlled actuator. Ankle torque and displacement signals were sampled at 2048 Hz via laptop computer (Apple PowerBook) running custom software written in LabVIEW (National Instruments) with an analog to digital card (National Instruments DAQCard 1200). Torque values were recorded in Newton-meters and the pathlength in

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Newton-meters per radian (N-m/rad). Data were collected over the course of thirty randomly applied 20-second trials (3 trials at each of 10 frequencies). Concomitant surface EMG measurements of tibialis anterior and gastrocnemius muscles, using a TECA TE4, provided visualization of the reflex responses and feedback to the examiner to ensure the subject was otherwise relaxed. Inertial and drag torques were computed and deducted from the total, resulting in computation of net passive resistance and spasticity induced elastic (ie, position dependent) and viscous (velocity dependent) ankle stiffness. Variation of ankle stiffness over the range of applied frequencies formed the basis for quantifying spasticity as a total path length and an elastic path length parameter. Larger path length values indicated greater variations in stiffness with frequency that, in turn, reflected an increased reflex mediated or spastic response.[19]

GMFM—The GMFM was employed to assess changes in gross motor skill and mobility.[20] The GMFM is a criterion reference tool designed to measure change in gross motor function over time, in children with motor impairment, and has been validated for sensitivity to change in children with CP. Only items from the standing and walk/run/jump dimensions were administered. Both the GMFM-88 and 66 scores were employed to take advantage of the improved scaling with the GMFM-66.[21] The masked research physical therapists achieved inter-rater reliability at greater than 80% point-by-point agreement[22] and maintained this for the study's duration by scoring of standard videotaped GMFM evaluations every 6 months. The two research physical therapists had a minimum of 8 years clinical experience each in the administration, use and scoring of the GMFM-88.

QEK and Max Torque—The QEK consisted of training the participants to maximally contract the gastrocnemius muscle group and then measuring the EMG-generated voltage amplitude and torque responses. The QEK evaluation was obtained in conjunction with the SMS evaluation. To perform this test, the SMS was used in a static (isometric) configuration with the foot positioned in relative plantar-flexion, ie, at the "low" end of the 5-degree movement range applied for the SMS measurement. The subject was provided with visual feedback of the torque response in order to encourage the maximal plantar-flexion effort. Data were collected over a 10-second period using the same hardware as described above for the SMS, but sampled at 500 Hz with EMG band-pass filtering over a range of 16 to 160 Hz. The peak plantar-flexing torque over the trial period was determined along with surface EMG signal parameters using custom software written in LabVIEW. A running average of the torque over a one second window was computed and the EMG signal in this averaging window, during which the torque was maximized, and was extracted. This represented the EMG activity, which occurred at the time of highest mean plantar-flexing torque. The extracted EMG signal was rectified and its mean value calculated and reported as the mean rectified voltage (MRV). MRV is a neurophysiologic representation of the total number of motor units available for muscular contraction. The change in MRV is proportional to the magnitude of the neuromuscular blockade. A brief trial period was carried out to train the participants in applying maximum plantar-flexing torque. With the aid of the visual torque feedback, family members and test personnel provided verbal encouragement to the subject to maximize the level of plantar-flexion torque generated. Three QEK determinations were obtained and the trial exhibiting the highest peak torque response was used as it reflected the most effective attempt.

Physical Examination Measures—Masked research physical therapists collected Modified Ashworth scores on the gastrocnemius muscle group,[23] passive dorsiflexion range of motion (PROM), DTRs and clonus of the ankle in a standardized manner. Inter-rater reliability of the research physical therapists was established for the Ashworth scale prior to the study. The research physical therapists had over 28 years combined pediatric clinical experience. The principal investigator (RH) trained the research therapists in the administration

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and scoring of ankle DTRs and clonus. DTR's were coded from 0 to 4 on an ordinal scale. Clonus was coded by beats palpated.

Energy Cost Index To evaluate the effect of treatment on energy expenditure, the ECI was measured by the research therapists and nurses.[24,25] Participants walked at a self-selected speed along an oblong 20-meter track for 5 minutes. The participant's average heart rate, and walking speed were recorded. ECI was calculated as the average number of heart beats per unit distance walked.

COPM and GAS Using a semi-structured interview recommended by the COPM guidelines, three performance outcomes (goals) were identified at baseline by the parent and child with the research physical therapist.[26,27] These included such goals as "decrease in falling on the playground at school or climb stairs without physical help." Serial measurements of the COPM performance and satisfaction scores were ranked by importance and then measured by report from the parent. The same three performance outcomes (goals) were then structured for goal attainment scaling in the GAS through semi-structured interview and by collaboration between the research physical therapist, parent and child.[28,29] The formula derived by Kiresuk and Sherman[30] was used to calculate standardized scores (*t* score), reflecting the composite change for the three a priori goals over the 6-month study period.

Adverse Events

Structured adverse event interviews were administered in-person by the research nurse at all visits except the 8-week visit, which was done by phone. All events reported during those interviews were coded for severity, and relationship to CP and BTX-A or saline injection.

Analysis

The data were entered into the SPSS for Windows (Version 10.05, ©SPSS Inc, 1989-1996) software format for analysis. Change scores were calculated from the average of the two baseline assessments to each follow-up assessments time point for the primary outcomes (Table 1). At each follow-up time point, the differences in change scores were compared between the BTX-A and placebo groups with the Wilcoxon Mann-Whitney-U nonparametric test for the primary outcome variables. Secondary outcome measures of Ashworth scale, clonus and DTR change scores at each follow-up time point, were also assessed by the same nonparametric statistic due to the lack of a normal distribution. Change score from baseline to each follow-up time point for QEK MRV, Max Torque, COPM performance and satisfaction; GAS, and ROM were compared between treatment groups by an unpaired *t* test. The frequency of adverse events by group was analyzed by chi-square. Baseline walking heart rate was found to be significantly different between treatment groups (Table 2) and was corrected for in the regression analysis of ECI change from baseline. Change score statistics (mean, standard deviation or median, range) for the appropriate tests for each outcome measure are displayed in Table 4.

RESULTS

Pathophysiology

The known neurophysiologic effect of BTX injections compared to placebo was confirmed at 3 weeks post injection by a significant decrease in QEK (MRV-uV, $p < 0.05$). This neurophysiological difference was no longer present by 8 weeks. By 24 weeks the BTX group QEK had surpassed the placebo group, although not significantly (Figure 1 and Table 4).

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Impairment

Significant decreases in SMS total ($p < .04$) and elastic path length ($p < .05$) changes from baseline were documented at 8-weeks post injection for the BTX group compared to the placebo group. A change in path length for the BTX group compared to the placebo from baseline was present at 12 weeks but did not reach significance (see Figures 2 and 3 and Table 4). No significant differences in change scores by group were found for Ashworth change scores at any follow-up time point (see Table 4). The changes in the clinical measures of Achilles DTR and clonus were significantly decreased in the BTX group at 3 weeks only (Table 4). Ankle dorsiflexion PROM with the knee extended significantly increased for the BTX group ($p < .05$) compared to the placebo group at 12 weeks with a mean difference of 4.2 degrees (Figure 4 and Table 4). QEK maximum torque changes from baseline were significantly greater for the BTX group at 24 weeks post injection ($p < .03$) (Figure 5 and Table 4).

Functional Activity/Disability

GMFM total scores approached a significant difference at 3 weeks with the BTX group scoring higher. Both groups improved their change from baseline scores over the study period with a significant median difference documented at 24 week ($p < .001$, Figure 9 and Table 4). GMFM-66 change from baseline scores for the BTX group was also significantly greater than the placebo group at 24 weeks (3.1 BTX vs 1.2 CTRL, $p < .03$, Figure 7 and Table 4). No significant differences between treatment group change scores were found at any follow-up time point for ECI (Table 4). COPM performance change scores from baseline were significantly greater for the BTX group at 12 weeks (1.7 BTX vs 1.2 placebo, $p < 0.04$). At 24 weeks the BTX group continued with higher change scores than the placebo group but did not reach significance (Figure 8 and Table 4). The significant changes from baseline documented for the BTX group suggest improved gait and related upright motor skills (ie, stair climbing, one leg balance, jumping).

Societal Participation

The COPM satisfaction change scores and GAS *t* scores increased from baseline to 12- and 24-week follow-up for both groups. No significant differences in change scores between groups were found at 12 or 24 weeks follow-up ($p > 0.12$ to 0.98) in Figures 9 and 10 and Table 4.

Adverse Events

A total of 56 adverse events potentially having any relationship to treatment (injection of BTX-A or saline) were reported during the 6-month study period for both treatment groups. The frequency of adverse events by treatment group (30 = BTX, 26 = placebo) was not significantly different between the groups ($p = 0.22$). Six of these events required ibuprofen for muscle soreness at injection site (three per treatment group) and three decreased their activity level for 24 hours post injection.

DISCUSSION

This is the first randomized controlled trial of BTX treatment to report outcomes globally across all domains of the NCMRR framework. We have attempted to address a question which has been characterized by Sheean[31] as the “Holy Grail” of BTX investigation which is: to document not only physiologic effect but functional benefit. We have also attempted to avoid the four most common barriers to good clinical research regarding BTX. These include: inappropriate outcome measures, inappropriate patient selection, inappropriate injection protocols and poor general study design.[31]

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We were gratified that our physiologic measure of motor strength reduction after treatment with BTX-A, the MRV measure of the QEK, differed significantly from the placebo group and mirrored the descriptions of BTX effect described in experimental animal studies. This finding, a significant reduction at 3 weeks, indicated that the neuromuscular junction transmission was genuinely altered and that the injection technique was valid and reliable.

Significant reduction in spasticity was documented. The most robust evidence was found in the change in mean total and elastic path lengths measured at 8 weeks using the SMS. This finding was supported by significant changes in the DTRs and clonus at the ankle joint. The increases in dorsiflexion ROM at 12 weeks may have been related to the changes in the viscoelastic properties of the muscle that followed the initial neuromuscular blockade and were maintained through more effective active use of the muscle in gait. Significant changes in the voluntary torque documented at 24 weeks may most likely be a direct response to the improved ROM. This apparent chain of improvements in different aspects of function is consistent with real physiologic change.

GMFM and gastrocnemius torque results show significant consistent changes in mechanical efficiency and motor function at 6 months after treatment. This was surprising and may represent the time required to adjust to the changes in motor strength, ROM, and the reduction of interfering spasticity. The later changes in motor function and strength support an argument for consistent therapy to maintain and maximize the effects of BTX-A treatment, to facilitate acquisition of new skills or improved efficiency and a longer period before re-injection with BTX. No significant change in energy expenditure using the ECI was found.

We measured a significant change in the experimental subjects' performance with the COPM after treatment compared to the placebo group but we were unable to demonstrate a meaningful difference in either the satisfaction scores of the COPM or the mean change in *t* scores via GAS. This result was intriguing.

The results of this project both parallel and contrast with other randomized control trials of BTX in ambulatory youth with CP. Sutherland and colleagues[32] documented improved ankle dorsiflexion and swing during walking with three dimensional gait analysis at 3 months post BTX injections. The improvement in GMFM-88 total and GMFM-66 scores found in this project at 6 months reflects global changes in walking skill and are in line with the gait analysis outcomes found by Sutherland. Using a clinical observational scale to quantify parameters of gait, Koman et al[33] also documented improved gait patterns at 12 weeks post injection with BTX in a mixed sample of youth with hemiplegia and diplegia CP. Komen and colleagues[33] also noted significant improvements in ankle range of motion which is consistent with data we report here in Table 4. In 2000, Ubhi and colleagues[34] reported significant improvements in GMFM walking skills at 3 months after BTX injections for ankle equinus in a group of children with hemiplegia (30%) and diplegia motor involvement. We did not find this improvement in gross motor skills in our study sample until 6 months after injection. The lack of significant improvement in the physiological cost index reported by Ubhi and coauthors is consistent with our findings for ECI. Their results contrast with the changes documented in ankle ROM (Table 4). These conflicting results may be a function of mixed study samples containing both youth with hemiplegia and diplegia as well as older children studied. None of these studies looked at outcomes at 6 months after injection.

Reddihough et al[35] did follow subjects for 6 months and documented no significant improvement in GMFM scores at 3 and 6 months after BTX injections in children with spastic diplegic CP. The age of their study population was similar to subjects in our project, but greater than 60% of their study sample were GMFCS levels III and IV suggesting they were treating subjects with lower walking skills levels than the subjects in our study sample of where 50%

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were GMFCS level II. Most recently Scholtes and colleagues[36] in the Netherlands also reported improved GMFM scores that were similar to our results at 6 months. They used multi-level BTX-A injections and provided comprehensive rehabilitation in 46 children across GMFCS levels I–IV.

CONCLUSIONS

It appears that the physiologic and mechanical effects of treatment with BTX-A are genuine and measurable in youth with spastic diplegia CP. However, these effects may not create enough change in the patients' function or the families' perception of function to register as a meaningful improvement in their societal participation. It is possible that these changes were too subtle to be recognized with conventional satisfaction measures. The failure to demonstrate a match between the measured effect and the perceived benefit of treatment is perhaps one of the most important findings of our study. Detailed information describing expected functional improvements after treatment, based on studies such as this one, must be communicated to families in useful, understandable terms to ensure that they enter into treatment with truly informed consent. Our study suggests that patients and families must have realistic expectations about BTX treatment before they enter into it or risk experiencing measurable effect without perceived benefit.

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Abbreviations

BTX
botulinum toxin

CP
cerebral palsy

BTX-A
botulinum toxin type A

NCMRR
National Center for Medical Rehabilitation Research

GMFCS
Gross Motor Function Classification System

SMS
spasticity measurement system

GMFM
Gross Motor Function Measure

QEK
quantitative electromyographic kinesiology

COPM
Canadian Occupational Performance Measure

GAS
Goal Attainment Scaling

MRV
mean rectified voltage

DTR
deep tendon reflexes

PROM
passive range of motion

ECI
energy cost index

CHRMC
Children’s Hospital and Regional Medical Center

PT

physical therapy

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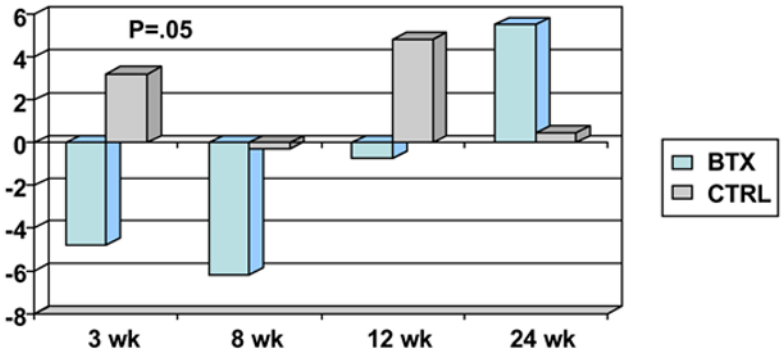

Figure 1.
QEK: Mean Rectified Voltage (μV) change from baseline by treatment group.

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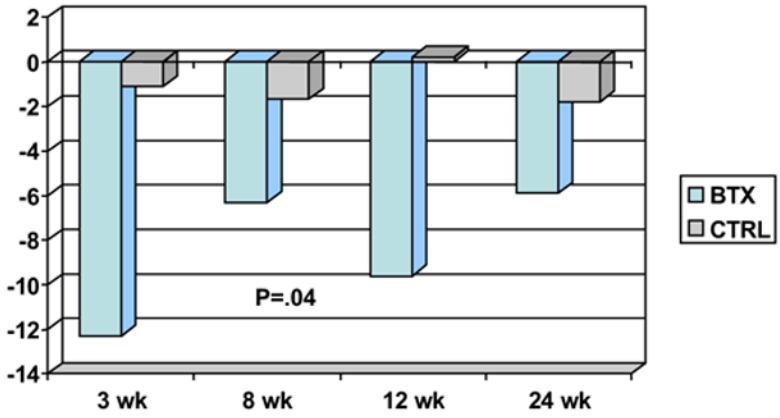

Figure 2.
Median SMS Total Pathlength (Nm/radian) change from baseline by treatment group.

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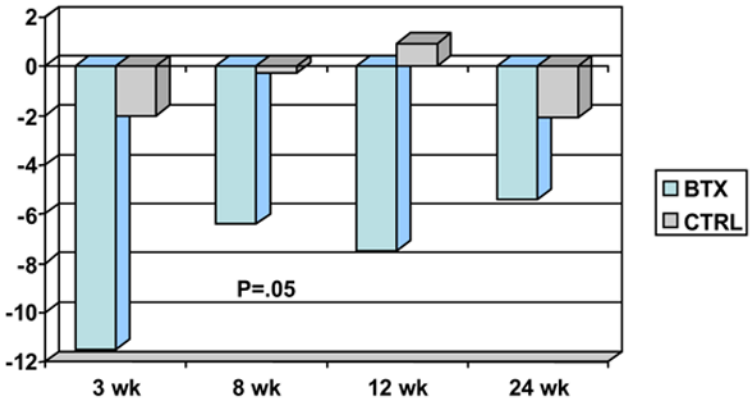

Figure 3.
Median SMS Elastic Pathlength (Nm/radian) change from baseline by treatment group.

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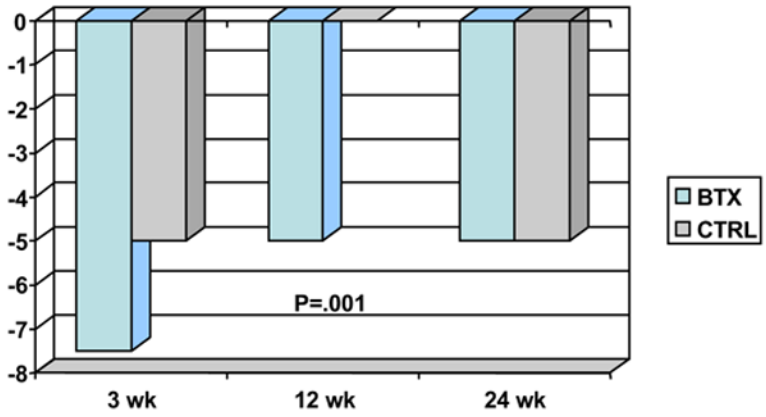

Figure 4.
Median Combined Left and Right Ankle ROM change from baseline by treatment group.

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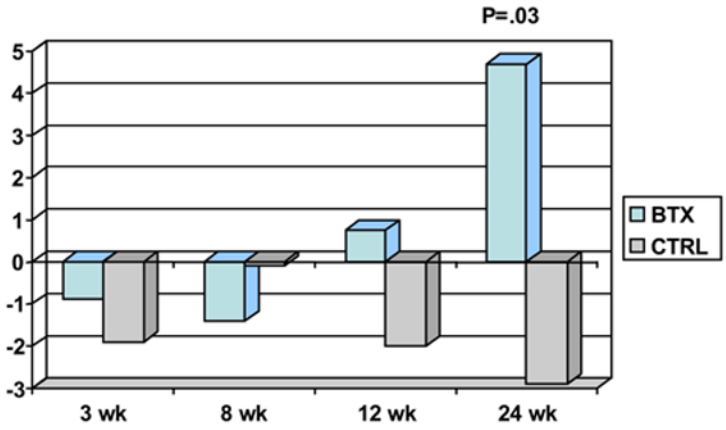

Figure 5.
Mean Max Torque (N-m) change from baseline by treatment group.

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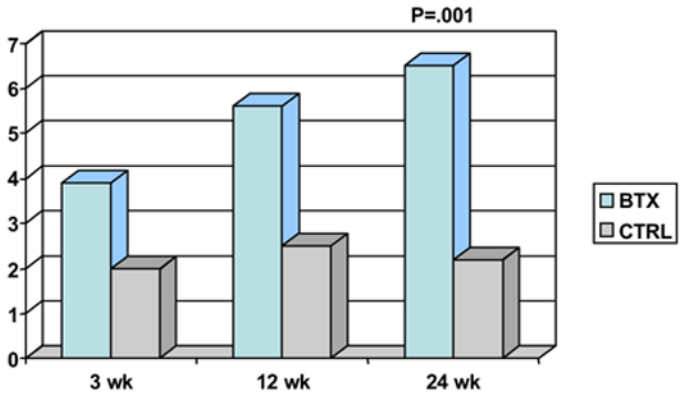

Figure 6.
Median GMFM-88 total scores change from baseline by treatment group.

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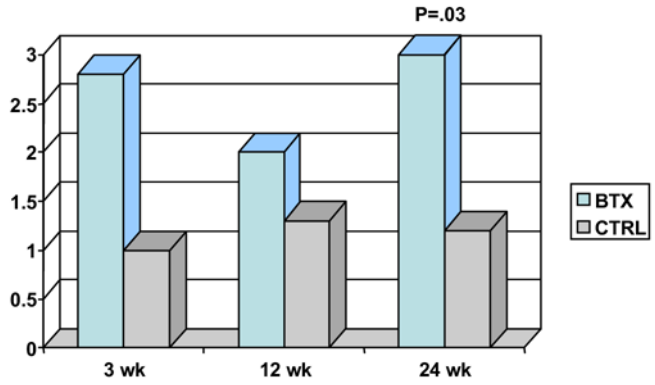

Figure 7.
Median GMFM-66 scores change from baseline by treatment group.

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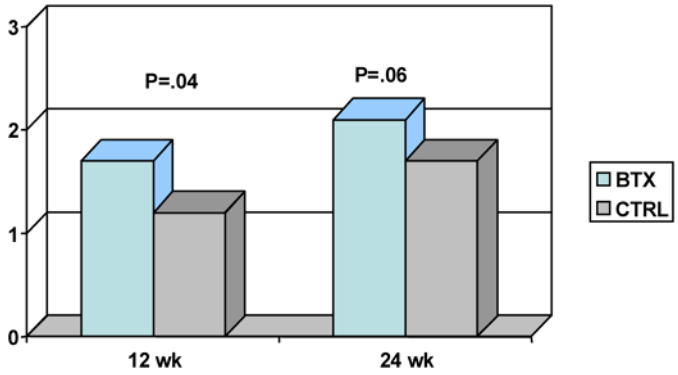

Figure 8.
Mean COPM performance scores change from baseline by treatment group.

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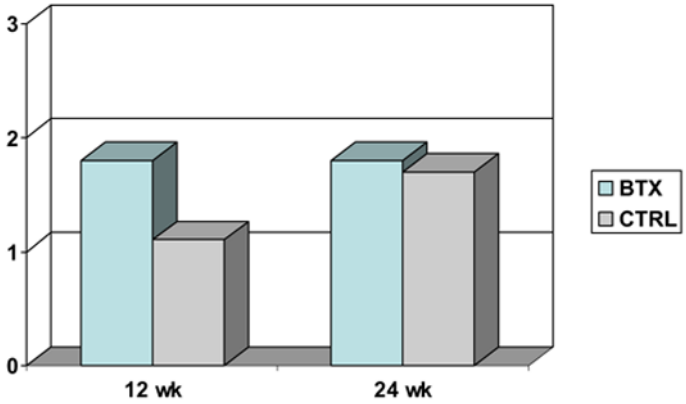

Figure 9.
Mean COPM satisfaction scores change from baseline by treatment group.

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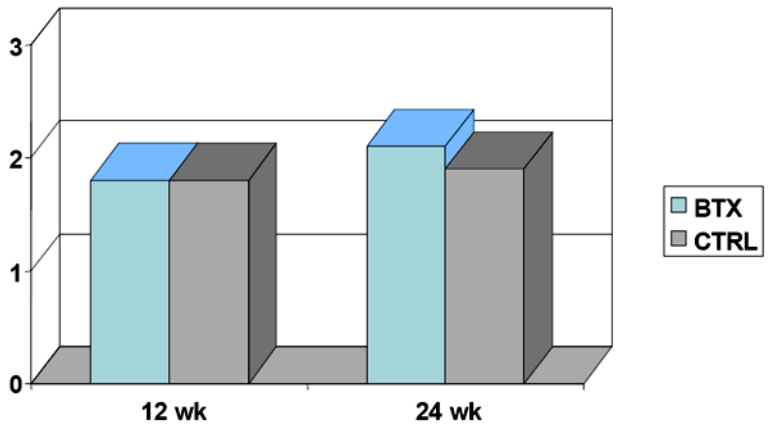

Figure 10.
Mean GAS standardized scores change from baseline by treatment group.

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Table 1

Assessment Timeline

Baseline 1	Baseline 2	3 Week	8 Week	12 Week	24 Week
SMS QEK Max Torque GMFM ECI PE COPM GAS	SMS QEK Max Torque GMFM BTX-A/Placebo Injection	SMS QEK Max Torque GMFM ECI PE COPM GAS AE Interview	SMS QEK Max Torque AE Interview	SMS QEK Max Torque GMFM ECI PE COPM GAS AE Interview	SMS QEK Max Torque GMFM ECI PE COPM GAS AE Interview

SMS-Spasticity Measurement System, QEK- Quantitative Electromyographic Kinesiology, GMFM-Gross Motor Function Measure (66 & 88)

Max Torque-Maximum Torque of the gastroc-soleus

ECI indicates Energy Cost Index; COPM-Canadian Occupational Performance Measure (Performance and Satisfaction Scale)

PE, Physical Exam measures (PROM, clonus, Ashworth scale, deep tendon reflexes[DTR]); AE Interview, Adverse events interviews.

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Table 2

Comparison of study sample baseline characteristics by groups.

	BTX-A *N* = 17	PLACEBO *N* = 16	Test	*p* Value
Gender (% Male)	70.59%	37.50%	†††	0.14
Age (SD)	5.38 (2.06)	5.55 (2.52)	†	0.83
Race n (% Caucasian)	7 (41.18%)	6 (37.50%)	†††	0.82
Baseline GMFCS Level (%)			†††	0.20
Level I	47%	25%		
Level II	41%	50%		
Level III	12%	25%		
QEK - Mean Rectified Voltage (μV)	19.57 (17.17)	22.20 (15.55)	†	0.36
SMS Total Path Length – Median N-m/radian (sd)	25.3 (76.2)	24.7 (81.9)	††	0.94
SMS Elastic Path Length - Median N-m/radian (sd)	21.5 (48.9)	21.5 (66.1)	††	0.69
L/R Ashworth – Median score	2.50	3.00	††	0.47
L/R DTR – Median score	3.00	3.00	††	0.82
L/R ROM – Median degrees	5.00	3.75	††	0.76
L/R Beats clonus - Median	5.50	5.50	†††	0.86
QEK Max Torque – Mean N-m	9.92 (10.63)	11.20 (9.06)	†	0.44
GMFM - 88 – Median Total % score	71.0 (82.5)	64.9 (87.9)	††	0.69
GMFM - 66 – Median % score	67.8 (43.4)	64.8 (43.1)	††	0.63
ECI -- Walking Heart Rate (WHR)– Mean	137.5 (14.7)	155.4 (17.6)	†	0.00
ECI - Walking Speed (WS) - Mean	37 (16.27)	35.87 (16.72)	†	0.85
ECI – Mean WHR / WS	4.94 (3.16)	6.41 (6.05)	††	0.40
COPM Performance - Mean	3.75 (1.27)	3.08 (1.08)	†	0.11
COPM Satisfaction - Mean	4.03 (1.59)	3.84 (1.39)	†	0.72
GAS - Mean	48.18 (.00)	48.18 (.00)	†	0.98

† two-tailed t-test;

†† Mann Whitney U;

††† Chi-square

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Table 3

Outcome Measures by NCMRR Domains of Science Relevant to Medical Rehabilitation

NCMRR Domains of Science	3 wks	8 wks	12 wks	24 wks
Pathophysiology				
Quantitative Electromyographic Kinesiology (QEK)	##	---	---	---
Impairment				
Spasticity Measurement System (SMS)**				
Total path length	---	##	#	---
SMS elastic path length**	---	##	#	---
Ashworth: Plantarflexors	---		---	---
Achilles Deep Tendon Reflexes	##		##	---
Ankle Clonus	##		---	---
Ankle Dorsiflexion passive range of motion (PROM)	---		##	---
Maximum Torque (gastroc)	---	---	---	##
Functional Limitation/Disability (Activity)				
Gross Motor Function Measure (GMFM-88)**	#		---	##
	---		---	##
Gross Motor Function Measure (GMFM-66)**	---	---	---	---
Energy Cost Index (ECI)			##	#
Canadian Occupational Performance Measure (COPM) Performance scale				
Societal Limitation (Participation)				
Canadian Occupational Performance Measure (COPM) Satisfaction scale			---	---
Goal Attainment Scaling (GAS			---	---

Significant $p < .05$

$p \geq .05–.10$

--- Not significant

** Primary Outcome Measure

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Table 4

Outcome Measure Change From Baseline by NCMRR Domains and Treatment Group at 3-, 8-, 12-, and 24-Week Assessments

NCMRR Domains:	3 wk			8 wk			12 wk			24 wk		
	BTX	**CTRL**	**p**	**BTX**	**CTRL**	**p**	**BTX**	**CTRL**	**p**	**BTX**	**CTRL**	**p**
Pathophysiology												
Mean QEK (μV)**	−4.8 (14.0)	3.2 (8.2)	.05	−6.2 (7.8)	−.27(7.4)	.28	−.74 (16.8)	4.8 (9.6)	.22	5.5 (19.0)	.45 (8.4)	.50
Impairment												
Median SMS Total (N-m/rad)*	−12.3 (69.0)	−1.1 (70.2)	.21	−6.3 (43.2)	−1.7 (72.4)	.04	−9.6 (40.4)	.21 (99.2)	.10	−5.9 (59.6)	−1.8 (85)	.82
Median SMS Elastic(Nm/rad)*	−11.5 (68.8)	−2.0 (59.3)	.30	−6.4 (29.8)	−.28 (69.2)	.05	−7.5 (30.9)	.92 (66.6)	.06	−5.4 (48.8)	−2.1 (65.2)	.55
Median L/R Ashworth*	−.5 (3)	0 (1.5)	.38				0 (1.5)	0 (1.5)	.71	0 (2)	0 (2)	.66
Median L/R DTR*	−1 (3)	0 (3.5)	.005				−.5 (2.5)	0 (3.5)	.02	0 (5.5)	0 (4.5)	.68
Median L/R Ankle ROM*	−7.5 (25)	−5.0 (27)	.76				−5.0 (27)	0 (17)	.001	−5.0 (35)	−5.0 (25)	.71
Median L/R Beats clonus*	−3 (15)	0 (15)	.001				−2 (28)	−.5 (26)	.40	−2 (18)	.5 (19)	.40
Mean Max Torque (N-m)**	−.88 (35.8)	−1.9 (8.6)	.77	−1.4 (2.3)	−.10 (16.9)	.94	.75 (3.5)	−2.0 (8.2)	.80	4.7 (14.0)	−2.9 (7.8)	.03
Functional Limitation/Disability												
Median GMFM-88 (%)*	3.9 (23.6)	2.0 (8.1)	.07				5.6 (23.2)	2.5 (17.1)	.70	6.5 (12.6)	2.2 (20.8)	.001
Median GMFM-66 (%)*	2.8 (13.3)	1.0 (13.8)	.14				2.0 (10.3)	1.3 (11.2)	.56	3.1 (11.2)	1.2 (11.3)	.03
Mean ECI (WHR/WS)*	−.15 (2.2)	−.38 (4.5)	.84				−.52 (1.1)	−.55 (3.6)	.98	−.56 (.89)	−.70 (4.7)	.98
Mean COPM Performance**							1.7 (1.4)	1.2 (1.7)	.04	2.1 (1.7)	1.7 (2.2)	.06
Societal Limitation												
Mean COPM Satisfaction**							1.8 (1.8)	1.1 (1.7)	.12	1.8 (2.2)	1.7 (1.8)	.60
Mean GAS**							1.8 (1.9)	1.8 (1.6)	.92	2.1 (1.6)	1.9 (1.7)	.80

* Wilcoxon Mann-Whitney U,

** unpaired t-test