ORIGINAL ARTICLE

The Combined Effect of Lower-Limb Multilevel Botulinum Toxin Type A and Comprehensive Rehabilitation on Mobility in Children With Cerebral Palsy: A Randomized Clinical Trial

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ABSTRACT. Scholtes VA, Dallmeijer AJ, Knol DL, Speth LA, Maathuis CG, Jongerius PH, Becher JG. The combined effect of lower-limb multilevel botulinum toxin type A and comprehensive rehabilitation on mobility in children with cerebral palsy: a randomized clinical trial. Arch Phys Med Rehabil 2006;87:1551-8.

Objective: To evaluate the combined effect on mobility of treatment with multilevel botulinum toxin type A (BTX-A) and comprehensive rehabilitation in children with cerebral palsy (CP).

Design: Randomized clinical trial using a multiple baseline design. The intervention group was treated 6 weeks after randomization. The control group was treated after a longer period of 18 to 30 weeks. Repeated measurements in both groups were continued throughout the process, before and up to 48 weeks after treatment.

Setting: Four departments of rehabilitation medicine in The Netherlands.

Participants: Forty-six children with spastic CP (mean age ± standard deviation, 8.0±2.1y).

Intervention: The intervention group (n=23) was treated with multilevel BTX-A and comprehensive rehabilitation. Control group subjects (n=23) continued with their usual physical therapy (PT) for 18 to 30 weeks, and then also received multilevel BTX-A and comprehensive rehabilitation.

Main Outcome Measures: The primary outcome measure was the Gross Motor Function Measure (GMFM-66); the secondary measures were problem score and energy cost.

Results: The treatment effect during the first 24 weeks of follow-up in the intervention group was compared with the effect of usual PT in the control group. Treatment with multilevel BTX-A and comprehensive rehabilitation provided a significantly greater improvement at 12 and 24 weeks in both the GMFM-66 (2.1 points, $P=.02$; and 3.5 points, $P<.01$, respectively) and problem score (1.8 and 1.7 points, $P<.001$, respectively) compared with usual PT. No difference was found in energy cost. Before-after analysis of the total group (n=46) showed a significant long-term improvement (48wk) on all outcome measures.

Conclusions: Treatment with multilevel BTX-A and comprehensive rehabilitation significantly improves mobility as measured by the GMFM-66 and problem score in children with CP.

Key Words: Botulinum toxin type A; Cerebral palsy; Clinical trials, randomized; Rehabilitation.

MOST CHILDREN WITH cerebral palsy (CP) have a deviating gait pattern. One of the typical patterns is characterized by flexion of the knee during midstance.[1] These children walk either with a crouch pattern[2] or with a jump knee pattern[2] without ever reaching full extension during the midstance. This is often caused by muscle imbalance resulting from a combination of spasticity of flexor muscles, weakness of extensor muscles, and/or coactivation of both flexor and extensor muscles, which may lead to fixed muscle contractures during development. The natural course of development in these children is a further deterioration in the flexion pattern,[3] which is generally accompanied by a deterioration in mobility.[4] Therefore, treatment at an early stage is indicated to improve knee extension in gait. A comprehensive rehabilitation approach is needed, aimed at both decreasing spasticity and improving muscle strength and length.

Since 1993,[5] injection with botulinum toxin type A (BTX-A) has been used for spasticity management in the lower-leg muscles of children with CP. BTX-A is injected into the muscle, where it produces a local, dose-dependent, and reversible paresis. To improve mobility in children who walk with a flexion pattern, multiple muscle groups should be treated in 1 session (multilevel BTX-A). To optimize the spasticity reduction induced by BTX-A injections, it has been suggested that the muscles should be actively and passively stretched after treatment, based on a comprehensive rehabilitation plan of serial casting and optimal orthotics.[6] Additionally, intensive physical therapy (PT) is indicated to improve muscle strength and length.[7] All these treatment options (casting, orthoses, intensive PT) can be summarized by the denominator of "comprehensive rehabilitation."

Although many randomized studies have evaluated the effect of a single-level BTX-A injection in the gastrocnemius muscle to improve equinus gait,[8-11] so far there have been only 3 randomized[12-14] and 2 nonrandomized[6,15] studies that exclusively evaluated the effect of multilevel BTX-A injections. Of these studies, only 1 used a control group that received the usual PT.[13] Moreover, evaluation of the primary outcome in these studies[6,12,15] was mostly at the level of impairment (range

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Table 1: Personal and Treatment Characteristics of All Participating Children and a Subgroup of Children Completing Energy Cost Measurements

Characteristics	Group		Energy Cost Subgroup	
	Intervention (n=23)	Control (n=23)	Intervention (n=11)	Control (n=10)
Sex (boys/girls)	16/7	16/7	6/5	7/3
Diagnosis (unilateral/bilateral)	3/20	1/22	1/10	0/10
GMFCS level (I/II/III/IV)	9/3/10/1	9/4/7/3	6/0/5/ND	3/3/4/ND
Mean age ± SD (y)	8.1±2.3	7.1±2.3	8.3±2.1	7.2±1.1
Range	4.2–11.5	4.5–11.0	4.5–10.1	5.7–10.6
Mean weight ± SD (kg)	26.76±7.63	25.59±8.27	27.00±1.87	24.33±9.88
Range	15.00–45.00	13.00–44.00	17.00–45.00	13.00–44.00
Mean dosage BTX-A ± SD (U)	442.83±132.84	460.00±101.23	471.36±92.74	449.00±98.06
Range	180–710	250–600	340–625	330–570
No. of limbs treated	42	40	20	18
Target muscle groups,* no. of limbs (hst+ps+gc/hst+ps/hst+gc/other)	8/18/9/7	10/14/13/7	4/7/6/3	5/2/9/2
Orthoses (insoles/AFO)	5/17	2/21	3/7	2/8
Casting (yes/no)	6/18	11/12	3/7	6/4

Abbreviations: AFO, ankle-foot orthosis; gc, gastrocnemius; GMFCS, Gross Motor Function Classification System; hst, hamstrings; ND, no data; ps, psoas; SD, standard deviation.
*Most frequently targeted muscles were hamstrings, gastrocnemius, and psoas in varying combinations. Other muscles injected were (alone or in combination) rectus femoris, soleus, adductors, and tibialis posterior.

of motion, spasticity, gait kinematics), while the main goal of multilevel BTX-A treatment is at the level of activity, in particular in the domain of mobility.[16] Improvement in mobility, in particular, is a more long-term treatment goal. Therefore, our purpose in this randomized study was to measure the effect on mobility of lower-extremity multilevel BTX-A treatment and comprehensive rehabilitation on children with CP who walk with flexed knees in midstance up to 1 year after treatment.

METHODS

Study Population

Between October 2001 and March 2003, 58 children from 4 Dutch departments of rehabilitation medicine were screened for participation in this trial. The screening included a standardized medical history and clinical examination, and frontal and sagittal plane gait video-recordings with surface electromyography.[17] Inclusion was based on the consensus of 4 participating pediatric physiatrists during a teleconsultation session in which the data collected were discussed via high quality audiovisual conferencing.[18] The inclusion and exclusion criteria are listed in appendix 1.

Forty-seven of the 58 children were found to be eligible and were enrolled. One child, however, withdrew after the first baseline assessment (at the parent's request) and was considered a drop-out. The remaining 46 children participated and were analyzed in the study (fig 1). Table 1 summarizes the patients' personal and treatment characteristics.

Study Design and Procedure

The children were randomly assigned to 1 of 2 groups: intervention and control (fig 1). An independent statistician (DLK) performed the randomization, using computer-generated random blocks of 4 (all permutations of AABB), stratified per center. The selection, randomization, and measurement procedures are shown in figure 1.

Intervention Group

Children in the intervention group (n=23) were treated with multilevel BTX-A injections and comprehensive rehabilitation. This group had 2 assessments during a 6-week baseline period and 4 follow-up measurements, at 6, 12, 24, and 48 weeks after treatment.

Control Group

Children in the control group (n=23) continued with their usual PT (low intensity, 1−2 sessions of 30−60min a week, some used orthoses) for a period of 18 to 30 weeks. They were assessed every 6 weeks. After this baseline period, the controls were also treated with multilevel BTX-A injections and comprehensive rehabilitation, with a follow-up at 6, 12, 24, and 48 weeks after treatment.

Multilevel BTX-A Injections and Comprehensive Rehabilitation

During the teleconsultation, a consent treatment plan was formulated for each child regardless of his/her group randomization; the plan included target muscle identification, calculation of injection dose, need for serial casting, and prescription of ankle-foot orthoses (AFOs). Possible target muscles were the psoas, mediolateral hamstrings, hip adductors, rectus femoris, gastrocnemius, soleus, and tibialis posterior. The principles of multilevel surgery were applied in the selection of target muscles, based on the result of gait analysis and clinical examination.[19] The injections were given with the subjects under general anesthesia, in at least 2 sites per muscle belly, to a maximum of 50U per site, with a dosage of 4 to 6U/kg of body weight of BTX-A (Botox) per muscle group. A maximum total dose was set at 25U/kg of body weight for children 5 years or younger, and 30U/kg of body weight for children 6 or more years old, with a maximum recommended dose of 600U. We used a dilution of 50U in 1mL of 0.9% NaCl solution. Injection sites were determined by palpation of the muscle belly, and needle placement was verified by either stretching or electric stimulation of the muscle.

Beginning 1 week after the multilevel BTX-A injections, each child was treated 3 to 5 times a week for 12 weeks by a physiotherapist, according to a standardized treatment protocol. Each session lasted 45 to 60 minutes, and the treatment consisted of stretching the flexor muscles, training to strengthen the extensor muscles, and functional mobility training.

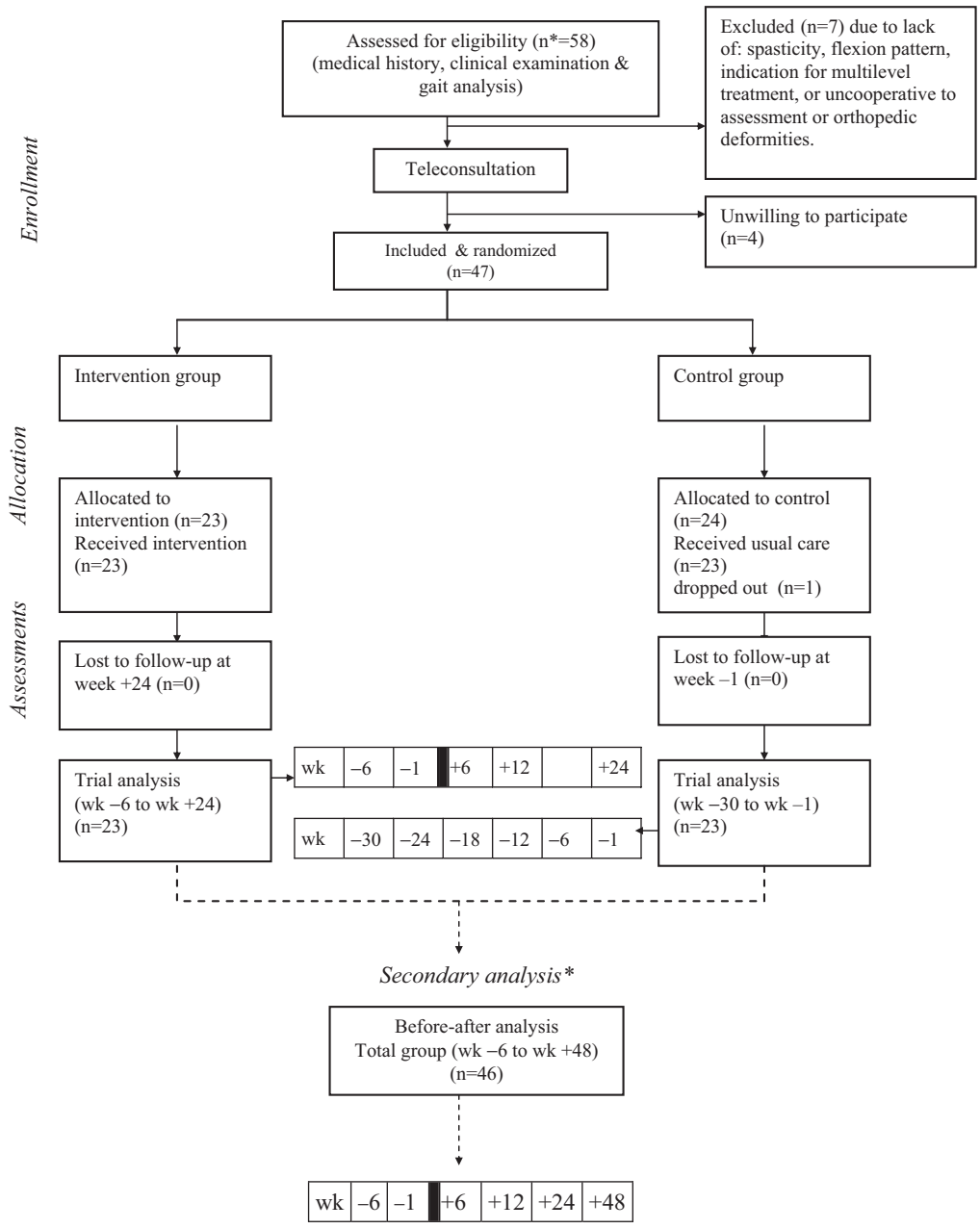

Fig 1. Schematic design of study and study assessments. The duration of baseline for children in the control group varied from 18 to 30 weeks. NOTE. Negative values for number of weeks before intervention; positive values for number of weeks after intervention. Thick black line in the intervention group analysis charts demarks multilevel BTX-A injections and comprehensive rehabilitation. *One child in the intervention group and 3 in the control group withdrew from the study after week 24 follow-up. They subsequently underwent myotenotomy of the gastrocnemius muscle, orthopedic surgery, or selective dorsal rhizotomy, on recommendation of the pediatric physiatrist (JGB).

If the passive ankle dorsiflexion with extended knee measured during screening was less than 0°, serial casting was initiated 1 to 3 weeks after the injection. Bilateral below-knee walking casts were applied and changed every week until 0° or more of dorsiflexion was achieved. Stiff insoles or AFOs were prescribed to support full knee-extension in terminal stance.

Outcome Measures

The primary outcome measure was the Gross Motor Function Measure (GMFM), a standardized observational instrument that requires a child to demonstrate various motor skills, as outlined in the GMFM administration and scoring guidelines. Consequently, it reports a child's actual ability level. In this study, we used the 66-item version of the GMFM (GMFM-66), an internationally recognized valid and reliable objective outcome measure, based on interval scaling.[20]

Our first secondary outcome measure was the gross energy cost of walking. Energy cost[21] (in $J \cdot kg^{-1} \cdot m^{-1}$) was determined by measuring oxygen uptake and carbon dioxide production with a portable gas analyzing system[a] during a 6-minute walk at a comfortable self-selected speed. Oxygen uptake was converted to joules and expressed relative to walking speed (in m/min) and body mass (in kilograms).[21] Mean steady-state values during the last 60 seconds were used for analysis. This test was performed in a subgroup (n=24) in 1 center only.

Another secondary outcome measure was a parent self-reported problem score, which recorded the 3 main problems related to lower-extremity mobility tasks experienced by their child. We used a semi-structured interview method and a standardized set of examples. Each problem was rated by the parent in terms of difficulty of performance on an 11-point scale (0 [no problem] to 10 [major problem]).

Table 2: Three Types of Results: Last Baseline Values for the Intervention Group (n=23) and Control Group (n=23); Trial Analysis of Estimated Mean Difference Between the 2 Groups in Change From Initial Baseline; and Before-After Analysis for Estimated Mean Long-Term Change From Baseline for the Total Group (n=46)

Outcome	Baseline Values*		Trial Analysis Estimated Mean Difference in Change†	P‡	Before-After Analysis Estimated Mean Long-Term Change	P‡
	Intervention Group	Control Group				
GMFM-66 (0–100)						
Baseline	67.91 ± 15.39	65.90 ± 11.37				
Week +6§			−0.77 (−3.07 to 1.52)	.50	−0.83 (−1.93 to 0.26)	.13
Week +12			2.07 (0.31 to 3.83)	.02	1.43 (0.69 to 2.17)	<.001
Week +24			3.48 (1.34 to 5.61)	.002	2.07 (0.96 to 3.18)	<.001
Week +48					2.26 (1.29 to 3.22)	<.001
Energy cost‖ ($J \cdot kg^{-1} \cdot m^{-1}$)						
Baseline	11.61 ± 6.57	10.77 ± 3.13				
Week +6			−0.88 (−2.75 to 0.99)	.35	0.26 (−0.46 to 0.98)	.46
Week +12			0.50 (−1.37 to 2.38)	.59	−0.07 (−1.40 to 1.26)	.91
Week +24			0.31 (−1.58 to 2.21)	.74	−0.90 (−1.59 to −0.20)	.01
Week +48					−1.78 (−2.64 to −0.92)	<.001
Problem score (0–10)						
Baseline	7.81 ± 1.66	8.25 ± 1.51				
Week +6			−0.70 (−1.44 to 0.04)	.07	−0.85 (−1.53 to −0.17)	.02
Week +12			−1.78 (−2.62 to −0.93)	<.001	−1.83 (−2.54 to −1.11)	<.001
Week +24			−1.65 (−2.81 to −0.48)	<.001	−1.90 (−2.54 to −1.27)	<.001
Week +48					−1.40 (−2.04 to −0.76)	<.001

NOTE. Values are mean ± SD or mean (95% CI). For GMFM-66 a positive value indicates improvement; for energy cost and problem score a negative value indicates improvement.
*Mean of –6 and –1 week for the GMFM-66 and energy cost, and –1 week for the problem score, respectively.
†Corrected for baseline differences.
‡*P* values with linear mixed-model analysis, models are adjusted for center.
§The positive values indicate the number of weeks after intervention.
‖Energy cost only presented for subgroup; in the before-after analysis 1 additional patient was left out of the analysis.

The GMFM-66 and energy costs were assessed during all baseline and follow-up measurements in both groups. At baseline, the problem score was assessed once in the intervention group and twice in the control group and at all follow-up visits. The children were assessed and treated in their own recruitment center. It was not possible to blind the observers for treatment group—the groups were transparent because of their different number of assessments. All observers were certified to administer the GMFM-66 and were fully trained to perform all the assessments. Moreover, to reduce testing bias in the subjective prediction of change in one of the outcome measures, the observers never reviewed any previous test values.

Based on the GMFM-66, this study had a power of 71% (47 subjects were initially enrolled) to detect a mean change of 1.6 points between the groups, with a 2.2-point standard deviation (SD) on GMFM-66 scores. This mean change of 1.6 points on the GMFM-66 could be considered a clinically meaningful change of motor function.[22]

Approval for the study was obtained from the Medical Ethics Committee of the VU University Medical Center in Amsterdam and full written informed consent was obtained from all parents and children 12 years of age or older before enrollment.

Statistical Analysis

Group characteristics were tested for differences with the Student *t* test (continuous data) or the chi-square test (dichotomous or ordinal data). We used 2 types of analysis to study the treatment effect. The strongest level of evidence was given by the trial analysis, in which the effect in the intervention group (−6wk before to 24wk after treatment) was compared with the usual PT effect in the control group (−30wk to −1wk before treatment). Additionally, using secondary before-after analysis, the long-term effect at 48 weeks after treatment was compared with before-treatment (−6 and −1wk) values. For these analyses, the full follow-up term of the total population (intervention group plus control group) was used. To identify characteristics of the children who might have responded differently to treatment, subgroup analysis were performed for the level of functioning classified with the Gross Motor Function Classification System (GMFCS)[23] and age (<7y, ≥7y), also in the total population.

All differences in effect were analyzed in a linear mixed-model analysis,[24,b] which estimated the treatment effect on the different outcome measures while adjusting for dependency of repeated observations in each subject. The factor "center" was considered in all statistical analyses. An independent statistician (DLK) and the principal investigator (VAS) performed all analyses. The level of statistical significance was set at *P* less than .05, which was adjusted in the subgroup analysis through Bonferroni adjustment. All *P* values were 2-sided.

RESULTS

The mean baseline period from the first baseline assessment until the time of treatment ± SD was 5.8±1.0 weeks in the intervention group (range, 4−8wk) and 23.6±6.8 weeks in the control group (range, 10−35wk). The groups did not differ with regard to personal characteristics (see table 1).

Each patient was treated with multilevel BTX-A in at least 1 limb. A mean dose of 18.01±4.74U/kg of body weight was injected, ranging from 5.63 to 27.14U/kg of body weight.

Trial Analysis

For all outcome measures the estimated mean difference between the 2 groups in change from initial baseline and the 95% confidence intervals (CIs) are shown in table 2 (see Trial Analysis).

A significant treatment effect on the GMFM-66 was found 12 and 24 weeks after treatment in the intervention group (fig 2A). On the energy cost test, 2 children with GMFCS level IV (control group) did not reach a steady state of oxygen uptake during walking. Another child was afraid of the mask, which made testing impossible (control group). These 3 were excluded from the analysis. Group characteristics of the remaining 21 children are presented in table 1. No significant treatment effect was found in energy cost (see fig 2B). On the problem score, the parents reported a total of 40 different problems involving balance (unaided standing, unaided walking, getting on or off a bicycle), falling or tripping, walking (walking longer distances, walking indoors or outdoors, walking with bare feet, climbing stairs, walking on uneven surfaces, walking in a supermarket), transfers (getting in or out of a car, rising from the ground unaided), running, and playing (jumping a rope, kicking a ball). A significant treatment effect on problem score was found in the intervention group 12 and 24 weeks after treatment (see fig 2C).

Before-After Analysis: Long-Term Effect

The last values assessed in both groups before treatment (mean of −6 and −1 week for the GMFM-66 and energy cost, −1 week for the problem score, respectively) were used as baseline values to compare the long-term effect (48 wk) for the total group (n=46). These are presented in table 2 (see Baseline Values). No significant differences were found. The results of these before-after analyses are also presented in table 2 (see Before-After Analysis), showing estimated mean changes from this baseline for the total group and 95% CIs at 48 weeks after treatment. Significant improvements were found in all outcome measures, GMFM-66, energy cost, and problem score, at 48 weeks after treatment.

Before-After Analysis: Subgroup Effect

Subgroup analysis showed that the energy cost in children with GMFCS level III was improved significantly more 48 weeks after treatment, compared with children with GMFCS levels I and II (see fig 3B).

For the other outcome measures, no significant differences in effects were found for different GMFCS levels (see figs 3A, 3C) or age subgroups (results not presented).

DISCUSSION

In this randomized clinical trial, we evaluated the effect of treatment with multilevel BTX-A and comprehensive rehabilitation on the mobility of children with CP who were walking with flexion of the knee in midstance.

In the trial analysis, we found that multilevel BTX-A given in combination with comprehensive rehabilitation significantly improved gross motor function. In addition, parents of the patients reported a significant improvement in the perceived difficulty of individually selected mobility tasks. We found no evidence, however, of a treatment effect on the energy cost of walking.

The improvement on the GMFM-66 (3.5 points) found at 24 weeks after treatment was a small, but significant, treatment effect. In the literature, the reported change over 1 year in children more than 5 years of age who received usual care was less than 1 point on the GMFM-66.[20] Recently, it was shown that a change score of 1.6 points is clinically meaningful, and a change score of 3.7 points discriminates moderate or no improvement from a great improvement.[22] Relative to these changes, we believe that our results indicate a clinically meaningful improvement in gross motor function. The secondary before-after analysis also indicates that long-term effects (>1y) on gross motor function can be expected, but this needs to be confirmed in a randomized controlled trial.

One other randomized study[13] also evaluated multilevel BTX-A with the GMFM and found no significant difference between the multilevel BTX-A group and the group continuing with regular (nonintensive) PT. This study had a crossover design that evaluated the effects over a period of 6 months. Because we showed that an effect 1 year after treatment can still be expected, a 6-month period might have been too short. Other randomized studies[8-11] failed to show any significant treatment effect of single level BTX-A injections without intensified PT on the GMFM in children walking with equinus. Our results might suggest that the combined effect of multilevel BTX-A treatment and comprehensive rehabilitation could be more effective in improving gross motor function than multilevel BTX-A alone. This is speculative, however, and can only be confirmed in a randomized trial that compares multilevel BTX-A alone to multilevel BTX-A and comprehensive rehabilitation.

Some authors[14,25] advise that multilevel BTX-A injections should only be given to children up to 7 years old. The results of our subgroup analysis, however, showed no difference in treatment effects between children of a minimum age of 7 and younger children.

Although the children in this study were selected on the basis of an energy-inefficient gait pattern of knee flexion,[26] we found no treatment effect on energy cost in the trial analysis. The small number of patients available for energy cost analysis might have influenced this. Nevertheless, the estimated mean changes at these different follow-ups were all less than 10%, which also does not seem clinically relevant. Secondary before-after analysis showed an improvement of more than 10% at 48 weeks, which was significant. Without the use of a control group, however, the study power of this analysis was 56%, which therefore limits the interpretation of these findings. In the long-term, children who used walking aids (GMFCS level III) improved significantly more than did children walking without aids (GMFCS levels I and II). As shown in figure 2B, this may be because children with GMFCS III, with a baseline energy cost twice as high as children with GMFCS level I, have more scope to improve. Children in the latter group seem to be nonresponsive to change in energy cost because their energy cost is already low, although it is higher than that of healthy children.

A significant treatment effect was seen on the problem score at 12 and 24 weeks. Compared with other reports, where the clinically relevant change was set at 10% of the total range of the scale,[9] our results indicate a clinically relevant change. Problems frequently mentioned by parents were (1) falling and tripping during walking, (2) limited duration of walking, and (3) problems with balance. Although the problem score is self-developed and not validated, it may reveal benefits associated with the parents' subjective experience of improvement in a child's mobility.

We also found a long-term improvement on the problem score at 48 weeks after treatment. All children continued with their usual PT after the period of intensive PT (12wk), with the same intensity as before the multilevel BTX-A injections; only 1 child was re-treated with a BTX-A injection and only in the rectus femoris muscle (at 30wk after treatment, without comprehensive rehabilitation), and none had serial casting again. Therefore, the long-term effects found in this study on all outcome measures might suggest that combined treatment of multilevel BTX-A and comprehensive rehabilitation can result in an overall long-term improvement in mobility, even 1 year after treatment. This should be confirmed in a randomized controlled study, however.

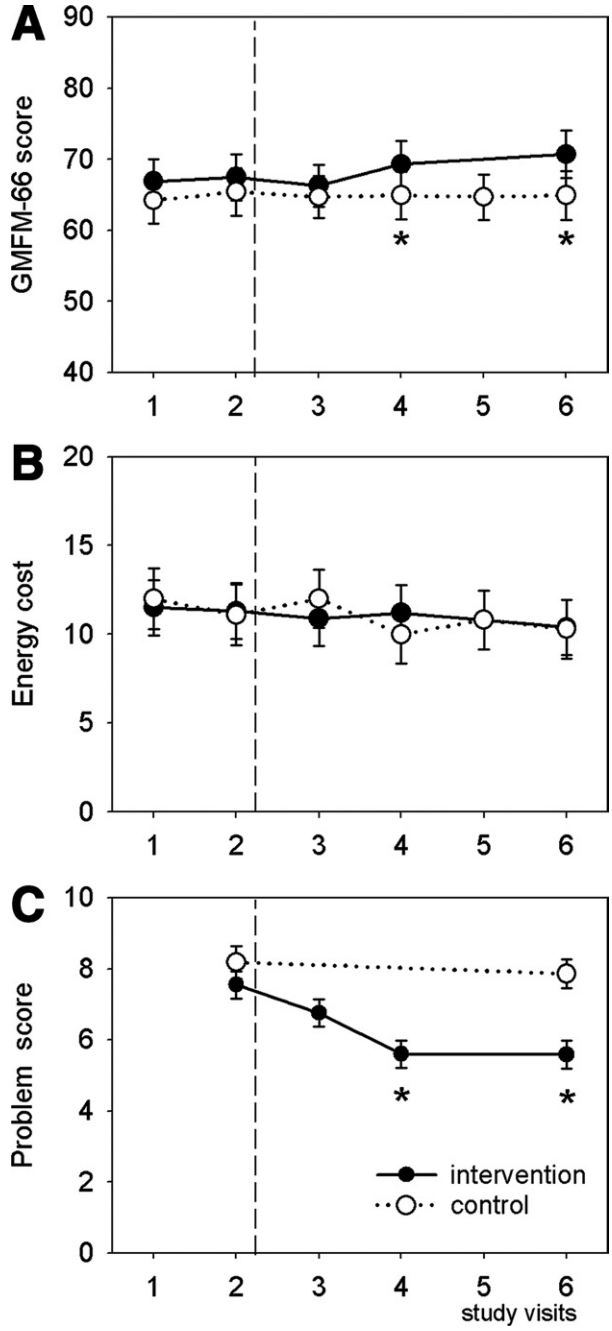

Fig 2. Estimated marginal means and standard errors of (A) GMFM-66, (B) energy cost (only presented for subgroup), and (C) problem scores on different study visits (6-wk intervals): trial analysis for intervention group (n=23) and control group (n=23). NOTE. Energy cost is in $J \cdot kg^{-1} \cdot m^{-1}$. Numbers on the *x* axis represent, for the intervention and control group, respectively: 1 (week −6, week −30); 2 (week −1, week −24); 3 (week +6, week −18); 4 (week +12, week −12); 5 (no assessment, week −6); and 6 (week +24, week −1). A dashed line demarks the multilevel BTX-A injections and comprehensive rehabilitation in the intervention group. *Significant difference in change between the intervention group and the control group, corrected for baseline differences ($P<.05$).

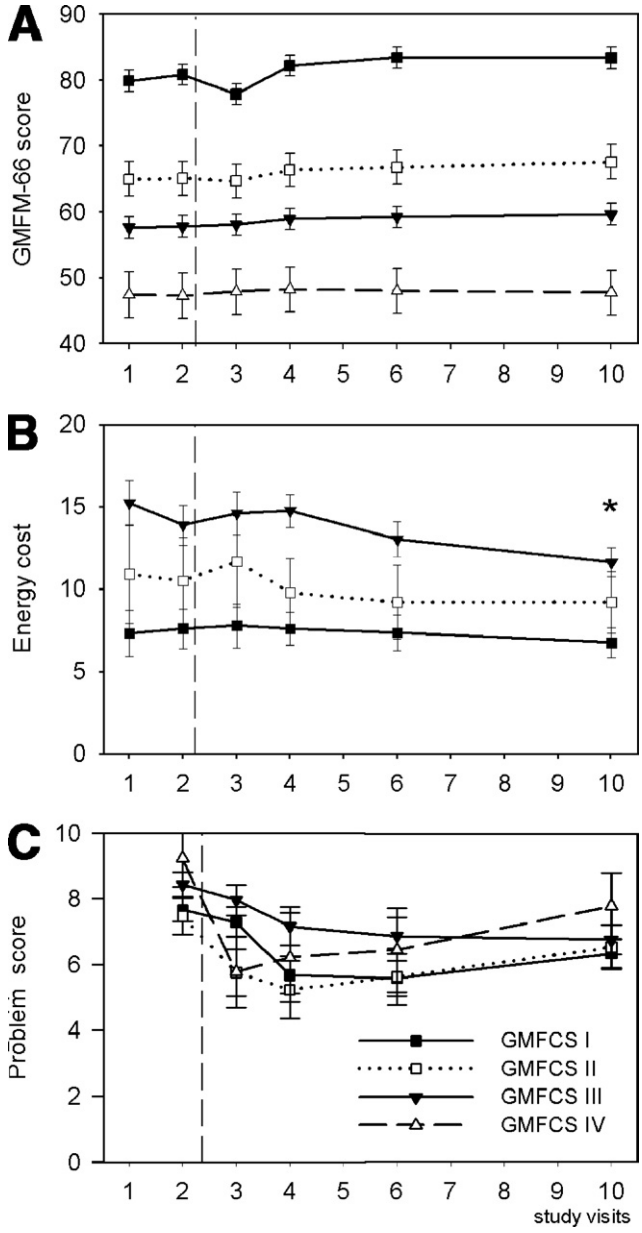

Fig 3. Estimated marginal means and standard errors of (A) GMFM-66, (B) energy cost (only presented for subgroup), and (C) problem scores on different study visits (6-wk intervals): before-after analysis in the total group (n=46) for subgroups based on GMFCS. NOTE. Energy cost is in $J \cdot kg^{-1} \cdot m^{-1}$. Numbers on the *x* axis represent: 1 (week −6); 2 (week −1); 3 (week +6); 4 (week +12); 5 (no assessment); 6 (week +24); 7 to 9 (no assessment); and 10 (week +48). A dashed line demarks multilevel BTX-A injections and comprehensive rehabilitation in the total group (n=46). *Significant difference in change between the GMFCS levels, corrected for baseline differences ($P<.05$).

Study Limitations

General shortcomings of this study were the use of multiple assessors (multicenter trial), the lack of assessor blinding, and the varying duration of baseline in the control group. To standardize the treatment and assessment methods, training sessions were organized before the study. All assessors also attended the GMFM course and passed its criterion test. A varying baseline for the control group was necessary because we had to strike a balance between what was scientifically desirable, practically obtainable, and clinically needed: if treatment was planned during the holidays, or a child complained of pain, the physician decided to schedule multilevel BTX-A treatment earlier. A period of 18 weeks was therefore set as a minimum in the control group. Using the linear mixed-model analysis, we adjusted for any missing visits during the study.[24] It is not clear whether the varying baseline influenced our results. Although all control children were scheduled to receive multilevel BTX-A treatment and comprehensive rehabilitation, we found stable baseline values for all outcome measures. If the baseline period had been 30 weeks for all children (including the ones who complained of pain), it would seem reasonable to expect stable values as well, or even slightly deteriorating baseline values rather than improved ones, leading to similar or even greater treatment effects.

We selected children with a flexion gait pattern for treatment. This pattern is caused by an imbalance of flexor and extensor muscle activity, which necessitated the application of a comprehensive treatment program. We chose the effect of the total program as the subject for this study, rather than the contribution of each component (multilevel BTX-A, intensive PT, serial casting and orthoses); therefore, we do not know, for example, how much of the effect is specifically contributable to the multilevel BTX-A injections alone, or to the intensive PT. Because the optimal combination of these factors is not known, the contribution of each of the components of the treatment program must be assessed in future research.

The main focus of this study was on the level of mobility, because this is the main and final goal of the BTX-A and rehabilitation treatment. Effect of the treatment on technical outcome measures was outside the scope of this study. We are currently preparing a second report that will discuss the effect of multilevel BTX-A and comprehensive rehabilitation on video-based gait analysis, range of motion as a measure of muscle length, and spasticity.

CONCLUSIONS

Combined treatment with multilevel BTX-A and comprehensive rehabilitation is an effective treatment modality that leads to clinically relevant improvements in gross motor function and self-reported mobility tasks in children who walk with flexion of the knees. We found no accompanying change in energy cost of walking.

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APPENDIX 1: INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria	Exclusion Criteria
Diagnosis of CP	BTX-A treatment in lower extremities within 16 weeks before inclusion
Spastic hemiplegia or diplegia (according to Hagberg[27])	Orthopedic surgery 24 weeks before inclusion
Age between 4 and 12y	Contraindication for BTX-A
Spasticity* in 2 or more lower-extremity muscle groups interfering with mobility	Contraindication for general anesthesia
GMFCS levels I to IV	Orthopedic deformities that have a bad influence on walking
Gait characterized by persistent flexion of the knee (≥10°) in mid-stance (barefoot or with AFOs/shoes)	(Sub)luxation of the hip with an MI >50°
Two or more muscle groups in 1 limb needing BTX-A injection	Hip endorotation contracture >15°
Ability to carry out instructions	Flexion contracture of knee >15°
Adequate knowledge of the Dutch language	Severe fixed contractures:
	Age <8y
	Ankle plantarflexion with knee extended >20°†
	Popliteal angle >90°
	Age ≥8y
	Ankle plantarflexion with knee extended >15°†
	Popliteal angle >80°
	Presence of ataxia or dyskinesia
	Other problems that have a negative influence on walking

Abbreviations: AFOs, ankle-foot orthoses, GMFCS, Gross Motor Function Classification System; MI, migration index.[28]
*Spasticity was defined during clinical examination as the occurrence of a "catch" (sudden increase in muscle tone) somewhere before the end of the range of motion in response to a fast passive stretch (in hamstrings, adductor, rectus femoris, gastrocnemius, and soleus muscles).
†From neutral.

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Suppliers

a. VmaxST, version 1.0; SensorMedics BV, PO Box 299, 3720 AG Bilthoven, The Netherlands.
b. Version 11.5; SPSS Inc, 233 S Wacker Dr, 11th Fl, Chicago, IL 60606.