ORIGINAL REPORT

Check for updates

INTRAMUSCULAR BOTULINUM TOXIN PRIOR TO COMPREHENSIVE REHABILITATION HAS NO ADDED VALUE FOR IMPROVING MOTOR IMPAIRMENTS, GAIT KINEMATICS AND GOAL ATTAINMENT IN WALKING CHILDREN WITH SPASTIC CEREBRAL PALSY

Fabienne SCHASFOORT, PhD[1,2], Robert PANGALILA, PhD, MD[2], Emiel SNEEKES, MSc[1], Coriene CATSMAN, PhD, MD[3], Jules BECHER, PhD, MD[4], Herwin HOREMANS, PhD[1], Henk STAM, FRCP, PhD, MD[1], Annet DALLMEIJER, PhD[4], Johannes BUSSMANN, PhD[1], on behalf of the SPACE BOP study group
From the ¹Department of Rehabilitation Medicine, Erasmus MC, University Medical Centre Rotterdam, ²Rijndam Rehabilitation, ³Department of Paediatric Neurology, Erasmus MC, University Medical Centre/Sophia Children's Hospital, Rotterdam, and ⁴Department of Rehabilitation Medicine, VU, University Medical Centre Amsterdam, Amsterdam, The Netherlands

Objective: Botulinum toxin (BoNT-A) is widely used in combined treatment for spastic cerebral palsy, but its added value preceding comprehensive rehabilitation for motor impairments, gait, and goal attainment has not been studied.
Design: A comparative multi-centre trial, in which two groups underwent comprehensive rehabilitation (i.e. high-intensive functional physiotherapy, and indicated casting/orthoses). One group received intramuscular BoNT-A prior to rehabilitation, and the other group did not receive BoNT-A.
Subjects/patients: Children with spastic cerebral palsy, Gross Motor Function Classification System (GMFCS) levels I–III, age range 4–12 years, indicated for BoNT-A treatment regarding mobility problems.
Methods: Sixty-five children participated (37 boys), mean age 7.3 years (standard deviation (SD) 2.3, range 4–12 years), equally distributed across GMFCS levels. Forty-one children received BoNT-A+ comprehensive rehabilitation and 24 received comprehensive rehabilitation only. Functional leg muscle strength, passive range of motion, angle of catch, cerebral palsy-related pain, walking speed, kinematic gait parameters, goal attainment, and proxy-reported general functioning were assessed at baseline, primary end-point (12 weeks) and 24-week follow-up. Statistical analyses were performed with linear mixed models.
Results: At the primary end-point there were no statistically significant differences in treatment effects between the groups, except for the angle-of-catch of the rectus femoris, which was in favour of comprehensive rehabilitation without BoNT-A (12° difference, 95% confidence interval (95% CI) 2:23, $p = 0.025$). Results at follow-up were similar.
Conclusion: At the group level, treating with BoNT-A prior to comprehensive rehabilitation did not add to the clinical effectiveness of rehabilitation. Thus, BoNT-A prescription and use should be critically reconsidered in this cerebral palsy age- and GMFCS-subgroup.

---

*This article has been handled and decided upon by Chief-Editor Kristian Borg

LAY ABSTRACT

For children with spastic cerebral palsy who are able to walk independently, botulinum toxin injections are often part of a combined treatment to improve their functioning. Although it is known from the scientific literature that such combinations are more effective than low-intensity standard care, the relative contribution of the costly botulinum toxin injections to the total treatment effect is unknown. The aim of this study was to determine the added value of providing botulinum toxin treatment prior to a period of comprehensive rehabilitation compared with comprehensive rehabilitation alone in a group of 65 children aged 4–12 years. The effect outcomes measured were: leg muscle strength, muscle length and spasticity of several leg muscles, CP-related pain, walking speed, several gait pattern parameters, the degree to which individual therapy goals were attained, and parent-reported general functioning. At the group level, no differences were found in effect between the group that received botulinum toxin injections and comprehensive rehabilitation, and the group that received comprehensive rehabilitation alone. This suggests that the widespread prescription and use of botulinum toxin for spastic cerebral palsy in this age- and severity-subgroup needs critical reconsideration.

Botulinum toxin (BoNT-A) has been widely used in the treatment of ambulatory children with spastic cerebral palsy (CP) since the 1990s (1, 2). BoNT-A injections in the leg muscles temporarily block the neuromuscular junctions and thereby provide (better) conditions to optimize and reinforce the effects of post-BoNT-A adjunctive interventions. However, there is a consensus that BoNT-A should never be a stand-alone intervention (3–8). Therefore, BoNT-A injections are

generally given as part of a combined, multimodal treatment package.

Although the body of evidence for such combined treatment packages including BoNT-A has increased since the first systematic review (3), the evidence is ambiguous (9) and even conflicting (10). Since it is difficult to perform controlled intervention studies in CP (5, 11), discussion about the content and contribution of both BoNT-A treatment and the adjunctive post-BoNT-A treatment modalities is ongoing (7, 11–24). However, previous controlled trials have shown that a more comprehensive treatment package including non-pharmacological interventions (such as functional and goal-directed physiotherapy, serial casting and/or ankle-foot orthoses (AFO)) following BoNT-A injections generally leads to better results than regular low-intensity "maintenance care" (e.g. 4, 11, 25–33).

An important characteristic of previous BoNT-A research is that the (adjunctive) non-pharmacological interventions are, in general, poorly described, with unknown content and of unknown quality (13, 16, 34–36). In 2006, Scholtes and colleagues noted that it was unclear to what degree positive effects of combined BoNT-A and comprehensive rehabilitation (CR) (compared with standard low-intensive care) could be attributed to BoNT-A injections or to characteristics of the other modalities applied in the ambulatory subgroup of children with CP (33). This "black box" issue has been reported frequently (11, 16, 34, 35, 37, 38). In recent years, there has also been increasing support for intensive individually tailored, functional and goal-directed physiotherapy-based interventions for spastic CP (in comparison with effectiveness of standard low-intensity care) (13, 39–51).

The added value of BoNT-A prior to CR (consisting of non-pharmacological modalities; physiotherapy, casting and orthosis) has not previously been explicitly studied, although there are a number of disadvantages to BoNT-A treatment (e.g. burden of treatment, toxin, use of anaesthetics, repeated treatments, expense). Therefore, we performed a clinical trial including economic evaluation named SPACE BOP (SPAstic cerebral palsy; Cost-Effectiveness of BOtulinum toxin and Physiotherapy). In this trial, the effectiveness and costs of BoNT-A plus CR were compared with the effectiveness and costs of CR alone in a group of ambulatory children with spastic CP in the age range 4–12 years. Both intervention groups received an equally high-intensity, best-available-evidence-based package of non-pharmacological interventions; physiotherapy, casting and orthosis. Improvement was found at the group level in both groups with regard to gross motor function, everyday physical activity levels and HRQoL, but there were no differences in effect between groups

(52). Because it is unclear whether (absent) improvements in a single category from the International Classification of Functioning Disability and Health/International Classification of Functioning Disability and Health-Children and Youth (ICF/ICF-CY) framework (53, 54) are related to (absent) improvements in other ICF categories (9, 55), the aim of this study was to determine the added value of BoNT-A preceding a period of CR for ambulatory children with spastic CP for a broad range of effect outcomes across ICF categories. This study evaluated CP-related pain, functional leg muscle strength, passive range of motion, angle of catch, walking speed and kinematic gait parameters, as well as proxy-reported general functioning and attainment of individual activity-related therapy goals.

METHODS

Study design, participants and enrolment

The study design, inclusion criteria and procedures have been described previously (52). This methods section provides only summary data.

A single-blind, partly-randomized, comparative multi-centre trial was performed, in which the effectiveness of BoNT-A plus a 12-week period of comprehensive rehabilitation CR (BoNT-A+CR) was compared with the effectiveness of a 12-week period of CR alone (only-CR). Two groups received CR, consisting of individually tailored, high-intensity, goal-directed physiotherapy (iPT), and, if necessary, serial casting and/or AFOs. One of the groups received BoNT-A injections prior to CR, and the other group did not receive any BoNT-A. Participants were randomized to 1 of 2 groups, except when objections to randomization were so strong that families refused to participate. These families were offered participation in the treatment group they preferred. Power calculations were performed for the primary outcome measure gross motor function. The total sample size of 65 children was considered sufficient for the effect outcomes presented here, especially since both legs were taken into account in the analysis of bilaterally measured outcomes (if spastic).

During regular spasticity-management team consultations in 2 Dutch university hospitals and 5 rehabilitation centres, experienced multidisciplinary teams of professionals assessed children for eligibility. The main inclusion criteria were: unilateral or bilateral spastic CP in the leg(s), classified at levels I–III of the Gross Motor Function Classification System (GMFCS), age range 4–12 years, with an indication for multi-level BoNT-A treatment for mobility problems.

Written informed consent was obtained for all participating children. The ethics committee of Erasmus MC approved the SPACE BOP study, and the trial was registered in the Dutch Trial Register (NTR TC1655).

Randomization and blinding

In case of randomized participation, children were centrally assigned to 1 of the 2 intervention groups and allocation was concealed until after baseline measurements. We attempted to mask the outcome assessors, the children's physiotherapists, and those administering casting and AFO to whether or not BoNT-A was injected. After anonymization and coding, data

analyses were performed by individuals not involved in the interventions or outcome assessments.

Procedures

To enable a fair comparison of both costs (see (52)) and effects between the 2 intervention groups, BoNT-A treatment plans were made for each child. The need for serial casting and prescription or (re)alignment of AFOs was also determined. In the group that received BoNT-A injections, these were administered under general anaesthesia by experienced clinicians in a paediatric hospital day-care setting. Clinicians adhered to recommendations about preparations, cautions, dose modifiers, localization techniques, and safety aspects, as described in the European Consensus 2009 (5). In all cases, preparations of botulinum toxin serotype A – Botox® (Allergan Inc., Eindhoven, The Netherlands) were used, and age- and weight-related maximum allowed doses were injected. Post-injection side-effects and/or adverse events were monitored. The CR period, during which all children had iPT, started one week after BoNT-A injections.

An iPT guideline was developed. based on best-available evidence in 2010 (46, 56). During a 12-week period, the children ideally had 3 45–60 min physiotherapy sessions each week, with at least 1 rest day between sessions. Sessions were individually scheduled at the children's special schools and/ or in private practices. Because of large heterogeneity that is inherent to CP, the content of each session was individually tailored within the framework of the guideline, and strongly relied on physiotherapists' clinical reasoning abilities. After a dynamic and playful warm-up, the main therapy components consisted of functional strength exercises and functional goal-directed activity-focused exercises. Progressive resistance exercises (PRE) were done to improve strength, based on current guidelines for typically developing children (46), and children with CP (i.e. intensity of 8–15 repetition maximum (RM)) (56). Functional goal-directed exercises were focused at the ICF activity/mobility categories, and were based on the families' request for help. Range of motion exercises were not included in therapy sessions except for some time to explain the "homework" (50). All involved therapists were specialized in paediatric physiotherapy. Information about therapy compliance and content of each session was obtained from the therapists' administrations and custom-made iPT diaries. After primary end-point measurements, the physiotherapy returned to the children's individual pre-study intensity.

In both intervention groups, 2–4 weeks of serial casting (i.e. weekly changed below-knee walking casts), starting about 1 week after the iPT period commenced, could be prescribed in cases in which passive ankle dorsiflexion with extended knee was less than 0°. The iPT sessions continued when children wore casts. If necessary, alignment of current or new AFOs was also arranged. Primary end-point measurements were performed when the 12-week iPT period had ended, and follow-up measurements were performed 12 weeks thereafter.

Outcome measures

Intensity of current CP-related pain was reported by the children using a paediatric visual analogue scale (VAS) with emoticon faces (5-point scale).

Functional leg muscle strength was measured with a Sit-to-Stand (STS) test (57), in which the child had to attain a standing position, without using the arms and with no assistance. The starting position is on a small bench, seated with feet flat on the floor and knees flexed at 90°. The maximum number of repeti-

tions in which the legs and hips were within 15° of the extended position within 30 s was counted. This STS test is valid and has been used before in effectiveness research (43, 49).

The guideline "standard physical examination of children with central motor paresis" (58) was used to determine the passive range of motion (passive ROM) and angle of catch (AoC). A Lafayette goniometer was used to measure the passive ROM (in absolute degrees) during slow passive stretch as an indicator of muscle length. This was done for 8 outcome measures: hip adduction, hip abduction in flexion, hip extension while prone, knee extension, the popliteal angle of the knee, knee flexion while prone, ankle dorsiflexion with knee flexed 90°, and ankle dorsiflexion with an extended knee, for both legs in case of bilateral CP.

As an indicator of spasticity, it was assessed whether there was a catch (i.e. a sudden increase in muscle tone, considerably blocking further movement) during fast passive stretch, for both legs separately in case of bilateral CP. The AoC were noted for fast passive stretches: hip abduction in flexion (AoC adductor muscles), the popliteal angle (AoC hamstring muscles), knee flexion while prone (AoC rectus femoris muscle), ankle dorsiflexion with knee in 90° flexion (AoC soleus muscle), and ankle dorsiflexion with extended knee (AoC gastrocnemii muscles). These 5 AoC outcome measures were expressed as the number of degrees short of a physiologically normal end of range for their corresponding passive ROM (i.e. the greater the deficit, the worse the spasticity). The number of degrees short was 0° if there was no catch present.

Walking speed and kinematic gait parameters were determined from 2-dimensional instrumented gait analysis, for both legs in case of bilateral spastic CP. This was done while walking barefoot and with footwear/AFO on a 10-m walkway, while children were instructed to walk at a comfortable walking speed. Two digital cameras were used to capture sagittal and dorsal views. Passive markers were attached to relevant bony markers, and the locations of the markers were digitalized and transformed. Walking speed and 2D kinematics were determined from the 2D space calibrated middle 3 m of the walk-way. Walking speed was calculated from the sagittal spatiotemporal information of the lateral malleolus.

From the sagittal position of the markers, 4 effect outcomes were determined: the inter-segmental joint angle of the ankle during mid-stance and during mid-swing, the knee angle during mid-stance and the maximum knee angle during the swing phase (i.e. absolute joint angle).

For each kinematic gait parameter, the deviation (in °) from a physiologically normal joint-angle-range (59) was also calculated. If the absolute angle was within a certain pre-defined bandwidth, it was considered as non-deviant. In our opinion, this better reflects improvements at the group level because a shift within a physiologically normal bandwidth range should not be considered as improvement. Moreover, it better adjusts for the different pathological walking types (60).

The satisfaction of primary caregivers regarding functioning of their child in general was assessed with a VAS with scores ranging from 0 (very dissatisfied) to 10 (very satisfied). Using a second VAS with the same scoring range from 0 to 10, the child's satisfaction with its own functioning was proxy-assessed.

Finally, goal attainment scaling (GAS) was used as an effect outcome. GAS is increasingly used in studies of BoNT-A treatment for CP (61–64), because its responsiveness is assumed to be better than that of more generic measures (7, 65–67). GAS measures the extent to which individual therapy goals are attained on a 6-point scale (–3 = deterioration; –2 = baseline score; –1 = improved but less than goal; 0 = goal attained; +1 = more

than goal attained; +2 = far more than goal attained). For each child, an individual "SMART" goal (i.e. specific, measurable, acceptable, relevant and time-related goals) in the ICF activity category was set before treatment started for the treatment period up to the primary end-point at 12 weeks. The GAS scales were set in dialogue between families and physiotherapist, based on the request for help as discussed in the spasticity management consultation, and were scored by the child's therapist at 12 and 24 weeks (with additional video check by an independent assessor not involved in any treatment modality).

Statistical analyses

First, baseline characteristics of participating children and the different treatment modalities they received in the 2 intervention groups were described and compared using conservative non-parametric tests. Subsequently, baseline comparability regarding the effect outcomes was checked in the same way.

The comparative effectiveness analyses compared treatment outcomes of BoNT-A+CR with the outcomes of only-CR to estimate differences in effect. For the randomized participants this was done according to the intention-to-treat (ITT) principle. Two separate analyses were performed to compare baseline scores with the scores at 12 weeks (primary end-point) and with scores at 24 weeks (follow-up), using linear mixed model analyses. We adjusted for the dependency of repeated observations in each subject with a random intercept, and also adjusted for the number of previous BoNT-A treatments, age and GMFCS level.

For the bilaterally measured outcome measures, in principle, both legs were included in the analyses for children with bilateral spastic CP (with an additional left/right adjustment). For muscle length, spasticity and gait, however, a leg was included in the mixed models analyses only when the child's BoNT-A treatment plan targeted muscles or muscle groups that were expected to have an effect on that particular effect outcome. For example, if a child's BoNT-A treatment plan targeted the gastrocnemius muscles, the leg was included only in the mixed models for the passive ROM effect outcomes knee extension, popliteal angle of the knee, knee flexion while prone, ankle dorsiflexion with knee flexed 90°, and ankle dorsiflexion with an extended knee, the effect outcome AoC for ankle dorsiflexion with extended knee, and all kinematic gait parameters. This grouping of "targeted muscle/effect outcome – combinations" was based on expert opinion injection schemes.

Finally, because our study was not fully randomized and we also allowed participation in the treatment group that was strongly preferred by families, we adjusted for the strength of the preference. All statistical analyses were carried out using IBM-SPSS statistics 21, and $p \leq 0.05$ was considered statistically significant, with no adjustment for multiple comparisons.

RESULTS

A total of 757 children were assessed for study eligibility between October 2009 and September 2013. Of these, 634 did not meet the inclusion criteria regarding their GMFCS level or age (see figure in Schasfoort et al. 2017 (52)). Of 123 families who were asked to participate, 65 had their child enrolled in our partly randomized study. For various reasons, 60% of the participants had such a strong preference for one of the two interventions that they had serious objections towards randomiza-

tion. Only 10 families (15%) were completely neutral towards receiving one or the other intervention.

There were 37 boys and 28 girls, with a mean age of 7 years and 4 months (standard deviation (SD) 2 years, 4 months, age range 4–12 years). Fourteen participants had unilateral spastic CP subtype and 51 had the bilateral subtype; and 19, 23 and 23 children were classified as GMFCS levels I, II and III, respectively. There were no drop-outs and few missing data (see right-hand columns in Tables III and IV).

After the baseline measurements, 41 children received BoNT-A+CR and 24 children started a 12-week period of CR alone. Except for a significantly higher number of previous BoNT-A treatments in the BoNT-A+CR group ($p = 0.002$), there were no significant differences between the 2 intervention groups regarding patient characteristics (Table I).

Children were evenly distributed over GMFCS levels between groups. For the children who received BoNT-A, the mean dose of intramuscular BoNT-A was 9 (SD 5), 17 (SD 5) and 17 (SD 4) units per kg bodyweight for GMFCS levels I, II and III, respectively. Except for the rectus femoris muscle ($p = 0.003$), there were no significant differences between the intervention groups regarding the particular muscles that were targeted in the children's prescribed BoNT-A treatment plans or the characteristics of the other treatment modalities (Table II).

Comparison of baseline scores for effect outcomes in the 2 intervention groups showed that the intervention groups were comparable, except for passive ROM for ankle dorsiflexion with an extended knee and the AoCs of the adductor and hamstring muscles (Tables III and IV).

Within both intervention groups, in general, changes over time for the different effect outcomes were in the same direction and of equal size between baseline and primary end-point (i.e. 12 weeks after the start of CR) (Table III). This was also the case for changes between baseline and follow-up (i.e. after 24 weeks; Table IV).

The comparative effectiveness analyses showed that there were no statistically significant differences in treatment effect between the 2 groups at primary end-point (Table III), except for the AoC of the m rectus femoris, which was a clinically relevant difference in effect in favour of the only-CR group (12° difference between groups, $p = 0.025$). At follow-up, the kinematic gait parameter maximum knee angle during the swing phase while walking barefoot was the only effect outcome that showed a statistically significant and clinically relevant difference in effect in favour of the BoNT-A+CR group (6° difference between groups in favour of BoNT-A+CR, $p = 0.034$). However, this difference in effect was not significant with gait parameters expressed as

Table I. Characteristics of the participants in the 2 intervention groups

Baseline characteristics of participants	BoNT-A+CR n = 41 children n = 75 spastic legs	CR-only n = 24 children n = 41 spastic legs	p-value
GMFCS level: I/II/III, %	29/32/39	29/42/29	0.656
CP type: unilateral/bilateral, %	17/83	29/71	0.258
Age, years and months, mean (SD)	7 y 6 m (2 y 5 m)	6 y 11 m (2 y 4 m)	0.324
Sex: boys/girls, %	54/46	62/38	0.486
Body weight (kg), mean (SD)	25.0 (9.4)	24.3 (9.6)	0.619
Length (m) mean (SD)	1.22 (0.14)	1.18 (0.15)	0.292
Growth between baseline and 12 weeks[a]	0.02 (0.02)	0.02 (0.01)	0.726
Growth between baseline and 24 weeks[a]	0.04 (0,03)	0.04 (0.02)	0.992
BMI, mean (SD)	16.3 (2.5)	16.7 (2.2)	0.345
Number of weeks of gestation, mean (SD)	33 (5)	34 (4)	0.554
Regular school/special school, %	49/51	46/54	0.818
Assistive devices, %			
Does not use assistive devices	2	4	
Uses orthopaedic shoes and/or AFO	39	42	0.888
Uses multiple devices, including (wheeled) walker, wheelchair	59	54	
Walking pattern type (Amsterdam Gait Classification[b]), %			
Barefoot, distribution across types 1–5	1/4/31/51/13	2/0/32/59/7	0.875
With footwear/AFO, distribution across types 1–5	4/13/19/60/4	3/5/13/72/8	0.082
Number of previous BoNT-A treatment 0/1/≥ 2, %	20/34/46	62/17/21	0.002*
Reported unpleasant experiences previous BoNT-A treatment, %	30	56	0.168

*p ≤ 0.05.
[a]Note that there were no differences in growth between the botulinum toxin (BoNT-A)+ comprehensive rehabilitation (CR) group and the CR-only group.
[b]Based on the Amsterdam Gait Classification (60), which distinguishes 5 different pathological gait types for spastic cerebral palsy (CP) due to muscle weakness and/or shortening and muscle activation problems (timing, hyperactivity). Spastic legs are classified according to the position of the knee (hyperflexion, normal or hyperextension) and foot contact (full contact or incomplete) during mid-stance during the gait cycle: type 1= knee position is normal but full foot contact (insufficient muscles causing problems in the swing phase), type 2= hyperextension knee plus full contact, type 3= hyperextension knee plus incomplete contact, type 4 = hyperflexion knee plus incomplete contact, type 5= hyperflexion knee plus full contact.
GMFCS: Gross Motor Function Classification System; SD: standard deviation; AFO: ankle-foot orthoses; BMI: body mass index.

Table II. Characteristics of different treatment components in the 2 intervention groups

Characteristics of individual treatment modalities	BoNT-A+CR n = 41 children n = 75 spastic legs	CR-only n = 24 children n = 41 spastic legs	p-value
Prescribed number of BoNT-A units/kg bodyweight, mean (SD)[a]	15 (6)	13 (6)	0.110
Legs in which particular hypertonic muscle was targeted, n (%)			
m psoas[a]	25 (33)	11 (27)	0.533
mm adductors[a]	20 (27)	6 (15)	0.167
m gracilis[a]	57 (76)	26 (63)	0.197
m semimembranosus[a]	59 (79)	29 (71)	0.340
m semitendinosus[a]	60 (80)	29 (71)	0.262
m rectus femoris[a]	21 (28)	2 (5)	0.003*
m gastrocnemius medialis[a]	52 (69)	22 (54)	0.109
m gastrocnemius lateralis[a]	36 (48)	19 (46)	0.998
m soleus[a]	11 (15)	4 (10)	0.569
m tibialis posterior[a]	8 (11)	6 (15)	0.560
other lower leg muscles[a]	7 (9)	1 (3)	0.257
Casting period prescribed for child (uni- or bi-lateral), %	59	33	0.072
Duration of casting period in weeks when prescribed, mean (SD)	3.0 (2.0)	3.0 (1.6)	0.782
Children with problem(s) with cast(s) during iPT period, %	29	38	0.663
New AFO(s) prescribed or realignment current AFO(s), %	34	29	0.677
Children with problem(s) with AFO(s) during iPT period, %	43	43	1.000
Sessions during the 12-week iPT period, mean (SD)[b]	31 (6)	31 (4)	0.989
Cost-declared PT min baseline – 12 weeks, mean (SD)[b]	1,668 (661)	1,536 (661)	0.903
Mean number of effective iPT min (i.e. spent with functional strength training & activity exercises according to iPT guideline), relative to cost-declared PT min between baseline - 12 weeks (%)[c]	1,290 (77)	1,196 (78)	
Number of weeks with minimum of 3 sessions during iPT period, mean (SD)[c]	8 (3)	8 (2)	
Sessions during the 12-week iPT period with a rest day following a session spent with functional strength training, mean (SD)[c]	23 (5)	23 (5)	
Cost-declared PT min between – 12 and 24 weeks, mean (SD)[b]	700 (393)	558 (236)	0.151

*p ≤ 0.05.
[a]Children in the "CR-only" treatment group did not receive botulinum toxin (BoNT-A), but treatment plans were made for all children to determine comparability of treatment groups as well as costs for an economic evaluation which was also part of our study, [b]based on PT business administrations of all 65 participants, [c]based on custom made iPT period therapy diaries of n = 64 participants as filled in by their PT.
CR: comprehensive rehabilitation; SD: standard deviation; AFO: ankle-foot orthoses; iPT; intensive physiotherapy; PT: physical therapy/therapist; min: minutes.

Table III. Linear mixed models analyses at primary end-point (12 weeks)

Linear mixed models analyses baseline – 12 week comparison	BoNT-A+CR base Mean (SD)	BoNT-A+CR 12 weeks Mean (SD)	Only-CR base Mean (SD)	Only-CR 12 weeks Mean (SD)	Estimated difference in effect[b]	95% CI	p-value	Number of observations[c] Baseline	12 weeks
Pain									
Current CP related pain intensity assessed by child (5-point emoticon faces VAS scale)	1.8 (1.1)	1.7 (1.0)	1.3 (0.6)	1.5 (0.9)	-0.28	[-0.89-0.33]	0.358	65	65
Muscle strength									
Functional muscle strength legs (maximum number of sit-to-stands in 30 s)[a]	12.9 (4.0)	14.6 (4.0)	13.0 (3.4)	13.7 (3.6)	-1.01	[-2.5-0.53]	0.194	65	65
Passive range of motion (absolute degrees as measured)									
Hip adduction[a]	15 (6)	14 (6)	14 (4)	14 (5)	1.0	[-2.3-4.3]	0.562	89	89
Hip abduction in flexion[a]	42 (9)	40 (8)	42 (10)	40 (10)	0.3	[-3.9-4.5]	0.879	89	88
Hip extension while prone[a]	18 (9)	16 (11)	13 (7)	14 (8)	3.0	[-3.7-9.7]	0.365	47	47
Knee extension[a]	-1 (12)	-1 (12)	-2 (8)	0 (7)	2.0	[-3.2-7.2]	0.452	84	84
Knee popliteal angle	51 (15)	54 (16)	53 (21)	53 (18)	3.9	[-1.3-9.1]	0.143	113	113
Knee flexion while prone[a]	153 (20)	145 (19)	136 (19)	119 (24)	-9.3	[-30.5-12.0]	0.383	47	47
Ankle dorsal flexion knee 90° flexion[a]	11 (9)	14 (8)	16 (13)	19 (15)	-0.2	[-5.5-5.2]	0.950	76	76
Ankle dorsal flexion knee extended[a] (*p=0.007)	5 (11)*	6 (9)	10 (11)*	9 (10)	-1.6	[-5.4-2.1]	0.395	113	113
Angle of catch (AoC, number of degrees short of physiologically normal end of range)									
Hip abduction in flexion (AoC mm adductors) (*p=0.002, physiological end range: 70°)	35 (19)*	37 (20)	50 (14)*	48 (18)	3.8	[-7.7-15.3]	0.509	92	90
Knee popliteal angle (AoC mm hamstrings) (**p=0.006, physiological end range: 0°)	38 (32)*	37 (31)	62 (22)*	52 (28)	9.6	[-2.6-21.8]	0.120	96	98
Knee flexion while prone (AoC m rectus femoris) (physiological end range: 160°)	15 (41)	21 (43)	12 (22)	6 (14)	12.3	[1.6-23.0]	0.025**	88	95
Ankle dorsal flexion knee 90 flexion (AoC m soleus) (physiological end range: 20°)	11 (18)	7 (13)	15 (19)	15 (19)	-5.6	[-17.9-6.7]	0.357	35	36
Ankle dorsal flexion knee extended (AoC mm gastrocnemii) (physiological end range: 20°)	33 (19)	26 (18)	29 (14)	31 (15)	-8.6	[-17.7-0.4]	0.062	113	112
Walking speed (m/s)									
Walking speed barefoot[a]	0.85 (0.3)	0.82 (0.3)	0.83 (0.3)	0.84 (0.3)	0.05	[-0.11-0.20]	0.540	64	63
Walking speed wearing (special) shoes and/or AFO(s)[a]	0.89 (0.3)	0.91 (0.3)	0.95 (0.3)	0.93 (0.3)	-0.04	[-0.19-0.11]	0.632	62	63
Gait (absolute degrees as measured)									
Ankle midstance – while walking barefoot[a]	-7 (12)	-1 (10)	-11 (11)	-5 (11)	-0.9	[-7.2-5.5]	0.783	76	74
Ankle midswing – while walking barefoot[a]	-19 (17)	-14 (16)	-23 (12)	-17 (13)	1.2	[-6.2-8.9]	0.752	76	73
Knee midstance – while walking barefoot	21 (20)	18 (17)	21 (17)	19 (14)	-0.3	[-5.6-5.0]	0.908	113	111
Knee maximum swing – while walking barefoot	16 (21)	12 (20)	14 (15)	13 (14)	-2.4	[-7.3-2.5]	0.327	113	110
Ankle midstance – while walking with footwear/AFO[a]	4 (5)	4 (5)	1 (7)	0 (7)	-0.7	[-3.9-2.5]	0.662	74	74
Ankle midswing – while walking with footwear/AFO[a]	-1 (7)	0 (7)	-5 (11)	-4 (8)	-0.9	[-4.2-2.4]	0.582	72	74
Knee midstance – while walking with footwear/AFO	19 (17)	18 (15)	19 (12)	14 (11)	3.7	[-0.7-8.1]	0.100	111	111
Knee maximum swing – while walking with footwear/AFO	9 (15)	11 (16)	14 (11)	10 (11)	1.1	[-3.6-5.8]	0.632	111	111
Gait (absolute number of degrees deviation from physiologically normal gait pattern joint-angle-range)									
Ankle midstance – barefoot (norm range: 2° plantar flexion – 10° dorsal flexion)	8 (9)	4 (5)	10 (9)	7 (7)	0.2	[-4.9-5.4]	0.924	76	74
Ankle midswing – barefoot (norm range: 5° plantar flexion – 5° dorsal flexion)	15 (15)	11 (14)	19 (12)	15 (12)	0.2	[-6.9-7.4]	0.948	76	73
Knee midstance – barefoot (norm range: 15° flexion – 0° flexion)	11 (16)	9 (12)	11 (10)	7 (9)	1.3	[-2.8-5.4]	0.536	113	111
Knee maximum swing – barefoot (norm range: 10° flexion – 5° hyperextension)	11 (17)	9 (15)	10 (9)	8 (10)	0.2	[-4.1-4.4]	0.943	113	110
Ankle midstance – footwear/AFO (norm range: 2° plantar flexion – 10° dorsal flexion)	1 (2)	0 (2)	2 (5)	2 (4)	-0.4	[-1.9-1.1]	0.617	74	74
Ankle midswing – footwear/AFO (norm range: 5° plantar flexion – 5° dorsal flexion)	1 (4)	1 (4)	4 (8)	3 (6)	1.1	[-0.6-2.8]	0.214	72	74
Knee midstance – footwear/AFO (norm range: 15° flexion – 0° flexion)	9 (13)	7 (11)	8 (7)	4 (6)	2.1	[-1.5-5.7]	0.247	111	111
Knee maximum swing – footwear/AFO (norm range: 10° flexion – 5° hyperextension)	9 (15)	7 (16)	7 (6)	5 (11)	0.2	[-3.6-4.0]	0.915	111	111
General functioning									
Satisfaction primary caregivers with general functioning child (0–10 point VAS score range)[a]	7.3 (1.6)	7.8 (1.2)	7.1 (1.1)	7.9 (1.0)	0.30	[-0.58-1.18]	0.494	65	65
Satisfaction child with own functioning (proxy-assessed 0–10-point VAS score range)[a]	7.3 (1.2)	7.6 (1.4)	7.7 (1.1)	8.1 (1.0)	0.07	[-0.85-0.98]	0.883	65	65

[a]Higher score indicates better functioning. *Presence of a significant difference between mean group scores at baseline with corresponding p-values (left-hand column).
[b]Negative estimated differences in effect are in favour of BoNT-A+CR treatment and positive estimated differences in effect are in favour of only-CR treatment (**p ≤0.05). Mixed models were adjusted for age, number of previous BoNT-A treatments, CP-severity GMFCS levels, strength of the preference, and relevant interactions. Bilaterally assessed outcome measures were additionally adjusted for left-right legs in the models.
[c]A total of 65 children participated, including 14 with unilateral CP type, hence the maximum is 116 observations for bilaterally measured outcome measures. CI: confidence interval; AFO: ankle-foot orthoses.

Table IV. Linear mixed models analyses at follow-up (24 weeks)

Linear mixed models analyses baseline – 24 week comparison	BoNT-A+CR Base Mean (SD)	BoNT-A+CR 24 weeks Mean (SD)	only-CR Base Mean (SD)	only-CR 24 weeks mean (SD)	Estimated difference in effect[b]	95% CI	p-value	Number of observations[c] Baseline	24 weeks
Pain									
Current CP-related pain intensity assessed by child (5-point smiley faces VAS)	1.8 (1.1)	1.6 (0.8)	1.3 (0.6)	1.5 (1.0)	-0.44	[-0.95–-0.07]	0.090	65	64
Muscle strength									
Functional muscle strength legs (maximum number of sit-to-stand in 30 s)[a]	12.9 (4.0)	14.6 (4.6)	13.1 (3.4)	14.1 (3.7)	-0.69	[-2.31–0.93]	0.397	65	65
Passive range of motion (absolute degrees as measured)									
Hip adduction[a]	15 (6)	14 (6)	14 (4)	14 (5)	0.1	[-3.2–3.5]	0.934	89	89
Hip abduction in flexion[a]	42 (9)	40 (9)	42 (10)	43 (10)	2.9	[-0.5–6.4]	0.097	89	88
Hip extension while prone[a]	19 (9)	17 (9)	13 (7)	13 (6)	2.3	[-4.7–9.3]	0.051	47	47
Knee extension[a]	-1 (12)	-2 (11)	-2 (8)	-2 (8)	1.3	[-2.8–5.5]	0.521	84	84
Knee popliteal angle	51 (15)	52 (15)	53 (21)	53 (20)	0.8	[-4.0–5.5]	0.748	113	113
Knee flexion while prone[a]	152 (20)	143 (20)	134 (19)	118 (18)	-6.4	[-25.3–12.4]	0.492	47	47
Ankle dorsal flexion knee 90° flexion[a]	11 (9)	14 (9)	16 (13)	15 (13)	-3.9	[-10.3–2.5]	0.232	76	76
Ankle dorsal flexion knee extended[a]*	5 (11)*	7 (9)	10 (11)*	9 (10)	-2.7	[-6.6–1.1]	0.164	113	113
Angle of catch (AoC, number of degrees shortage of physiologically normal end of range)									
Hip abduction in flexion (AoC mm adductors) (*, physiological end range: 70°)	35 (19)*	38 (20)	51 (14)*	52 (8)	1.3	[-8.8–11.5]	0.795	92	88
Knee popliteal angle (AoC mm hamstrings) (*, physiological end range: 0°)	38 (32)*	44 (32)	64 (22)*	58 (26)	12.0	[-5.4–29.4]	0.173	96	94
Knee flexion while prone (AoC m rectus femoris) (physiological end range: 160°)	15 (41)	21 (46)	13 (22)	18 (32)	0.9	[-15.6–17.3]	0.916	88	95
Ankle dorsal flexion knee 90 flexion (AoC m soleus) (physiological end range: 20°)	11 (18)	8 (14)	13 (19)	8 (16)	1.0	[-10.1–12.1]	0.857	35	38
Ankle dorsal flexion knee extended (AoC mm gastrocnemii) (physiological end range: 20°)	33 (19)	26 (19)	33 (14)	31 (13)	-4.9	[-11.4–1.6]	0.135	113	113
Walking speed (m/s)									
Walking speed barefoot[a]	0.85 (0.3)	0.93 (0.2)	0.83 (0.3)	0.90 (0.3)	-0.01	[-0.15–0.13]	0.887	64	65
Walking speed wearing (special) shoes and/or AFO(s)[a]	0.89 (0.3)	1.03 (0.3)	0.95 (0.3)	1.03 (0.3)	-0.05	[-0.20–0.10]	0.496	62	63
Gait (absolute degrees as measured)									
Ankle midstance – while walking barefoot[a]	-7 (12)	-5 (12)	-11 (11)	-10 (10)	-1.0	[-6.5–4.5]	0.726	76	75
Ankle midswing – while walking barefoot[a]	-19 (17)	-16 (18)	-23 (12)	-19 (10)	1.9	[-7.0–10.9]	0.667	76	70
Knee midstance – while walking barefoot	21 (20)	16 (18)	21 (17)	17 (14)	-0.4	[-6.3–5.5]	0.888	113	112
Knee maximum swing – while walking barefoot	16 (21)	10 (22)	15 (15)	14 (15)	-5.6	[-10.8–-0.4]	0.034**	113	112
Ankle midstance – while walking with footwear/AFO[a]	4 (5)	4 (8)	1 (7)	0 (6)	-0.7	[-5.9–4.6]	0.801	74	71
Ankle midswing – while walking with footwear/AFO[a]	-1 (7)	-1 (8)	-5 (11)	-6 (8)	-0.7	[-5.8–4.3]	0.770	72	68
Knee midstance – while walking with footwear/AFO	19 (17)	17 (18)	19 (12)	16 (13)	0.9	[-3.4–5.3]	0.669	111	108
Knee maximum swing – while walking with footwear/AFO	14 (18)	12 (19)	14 (11)	13 (13)	-1.1	[-5.2–3.0]	0.587	111	108
Gait (absolute number of degrees deviation from physiologically normal gait pattern joint-angle-range)									
Ankle midstance – barefoot (norm range: 2° plantar flexion – 10° dorsal flexion)	8 (9)	6 (9)	11 (9)	9 (9)	-0.4	[-5.0–4.2]	0.865	76	75
Ankle midswing – barefoot (norm range: 5° plantar flexion – 5° dorsal flexion)	15 (15)	13 (15)	19 (12)	15 (10)	2.5	[-4.7–9.7]	0.490	76	70
Knee midstance – barefoot (norm range: 15° flexion – 0° flexion)	11 (16)	8 (14)	11 (10)	8 (9)	-0.3	[-4.2–3.5]	0.864	113	112
Knee maximum swing – barefoot (norm range: 10° flexion – 5° hyperextension)	11 (17)	9 (16)	10 (9)	9 (11)	-1.4	[-5.7–2.8]	0.510	113	112
Ankle midstance – footwear/AFO (norm range: 2° plantar flexion – 10° dorsal flexion)[a]	1 (2)	1 (6)	2 (5)	2 (3)	0.1	[-3.4–3.5]	0.960	74	71
Ankle midswing – footwear/AFO (norm range: 5° plantar flexion – 5° dorsal flexion)	1 (4)	2 (6)	4 (8)	4 (6)	1.2	[-2.1–4.6]	0.466	72	68
Knee midstance – footwear/AFO (norm range: 15° flexion – 0° flexion)	9 (13)	8 (14)	8 (7)	6 (8)	0.6	[-2.8–4.0]	0.719	111	108
Knee maximum swing – footwear/AFO (norm range: 10° flexion – 5° hyperextension)	9 (15)	8 (15)	7 (6)	7 (9)	-0.3	[-3.7–3.1]	0.865	111	108
General functioning									
Satisfaction primary caregivers about general functioning child (10-point VAS score)[a]	7.3 (1.6)	7.6 (1.2)	7.1 (1.1)	7.9 (1.0)	0.46	[-0.50–1.43]	0.341	65	64
Satisfaction child about own functioning (proxy assessed10-point VAS score)[a]	7.3 (1.2)	7.5 (1.2)	7.7 (1.1)	8.0 (1.2)	0.11	[-0.73–0.96]	0.790	65	64

[a]Higher score indicates better functioning. *Presence of a significant difference between mean group scores at baseline (corresponding p-values are provided in Table III). Please note that the mean model estimated baseline scores may differ to some extent between Table III and IV.
[b]Negative estimated differences in effect are in favour of only-CR treatment and positive estimated differences in effect are in favour of BoNT-A+CR treatment (**$p \leq 0.05$). Mixed models were adjusted for age, number of previous BoNT-A treatments, CP-severity GMFCS levels, strength of the preference, and relevant interactions. Bilaterally assessed outcome measures were additionally adjusted for left-right legs in the models. [c] A total of 65 children participated, including 14 with unilateral CP type, hence the maximum is 116 observations for bilaterally measured outcome measures. CI: confidence interval; AFO: ankle-foot orthoses.
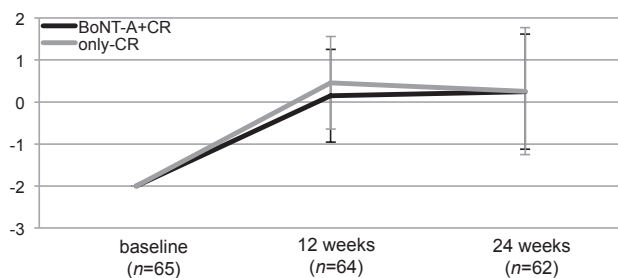
Fig. 1. Goal attainment scaling (GAS) for individual "SMART" goals at the ICF activity level, unadjusted mean scores at baseline, 12 and 24 weeks (SD). GAS scoring: –3 = deterioration; –2 = baseline score; –1 = improved but less than goal; 0 = goal attained; +1 = more than goal attained; +2 = far more than goal attained. SMART: specific, measurable, acceptable, relevant and time-related goals; BoNT-A: botulinum toxin; CR: comprehensive rehabilitation; SD: standard deviation.

the deviation in degrees from a physiologically normal gait range (1° difference between groups in favour of BoNT-A+CR, $p = 0.510$) (Table IV).

Goal attainment scaling showed similar patterns for both intervention groups (Fig. 1). There were no differences in effect between interventions at primary end-point (0.1 estimated difference in favour of only-CR, 95% CI –0.71–0.93, $p = 0.791$) or at follow-up (0.2 difference in favour of BoNT-A+CR, 95% CI –1.13–0.75, $p = 0.688$).

There were no serious side-effects and/or adverse events related to BoNT-A and/or CR, but the casting periods and/or alignment of AFOs was complicated in a number of cases in both groups, mainly due to pain or pressure complaints (Table I).

DISCUSSION

In the SPACE BOP study, the added value of BoNT-A treatment preceding a period of comprehensive rehabilitation (CR) was determined in an ambulatory group of 65 children with spastic CP in the age range 4–12 years, who were equally distributed across GMFCS levels I–III. Differences in treatment effects (and costs, as described previously (52)) were studied between a group of 41 children receiving BoNT-A+CR and a group of 24 children receiving only-CR. One full treatment cycle per child was followed, with a large number of outcome measures across ICF categories: pain, muscle strength and length, spasticity, walking speed, gait characteristics, proxy-reported overall functioning, individual goal attainment, gross motor function, everyday physical activity levels, and health-related quality of life.

For the effect outcomes, gross motor function, everyday physical activity levels and health-related quality of life, it was found previously that treatment regimes with and without BoNT-A were approximately equally effective (52). For the presently described effect outcomes pain, muscle strength and length, spasticity, walking speed, gait characteristics, proxy-reported overall fun-

ctioning and individual goal attainment, the findings at primary end-point in the BoNT-A+CR group were largely in accordance with previously reported findings (11, 32, 33, 68–71). However, similar results were found in the smaller intervention group that received only CR. Treatment regimes with and without BoNT-A appeared to be equally effective at the group level. Findings at 24-week follow-up also showed no difference in effectiveness between groups. Thus, at the group level, no evidence was found for the added value of BoNT-A injections when preceding CR for ambulatory children with spastic CP in the age range 4–12 years.

These results may appear to contradict previous findings, but this is not the case. When the literature is critically appraised, there are some indications that the relative contribution of factors other than BoNT-A to overall effectiveness of combined treatment packages may have been underestimated. For example, in the uncontrolled observational study by Molenaers et al. (14) in a very large group of children with CP ($n = 577$), all children received BoNT-A injections plus physiotherapy, plus additional casting and/or AFOs. Results showed that increased intensity of physiotherapy, post-injection casting and increased use of orthoses significantly contributed to better outcome (all $p \leq 0.005$), whereas the correlation between total BoNT-A dosage and goal attainment was not significant (14). In a randomized cross-over trial by Reddihough and colleagues, the physiotherapy period intensity during the more effective BoNT-A phase and the less-effective control phase differed (mean 28 vs 21 h) (69), indicating that intensity of PT may also be an important determinant of effectiveness. It has also been reported that larger parental satisfaction in the BoNT-A intervention group was not related to improvements (thereby suggesting a possible placebo effect), and that improvement lasted longer than the pharmacological effect (4). In the 2010 international consensus statement it was acknowledged that the effects of serial casting seemed to be at least as strong, and in some studies even stronger, than the effects of BoNT-A (6). In another uncontrolled small study by Yap et al., it was found that child, family, and treatment characteristics influence the degree of responsiveness to BoNT-A treatment (plus post-BoNT interventions), and that the contribution of contextual factors may be underappreciated (72).

In short, a stronger relative contribution of factors other than BoNT-A may equally well explain improvements, especially in view of the longer-term effectiveness. Assuming a positive effect of intensity of physiotherapy, this factor cannot counterbalance a possible positive effect of BoNT-A in our study: the mean intensity of physiotherapy was similar in the period until primary end-point, and remained/was higher

between primary end-point and follow-up in the group that received BoNT-A (700 min in this group vs 558 min in the only-CR group, Table II).

Since children have never been specifically excluded from regular standard care in the intervention groups in most, if not all, previous (randomized) controlled trials, conclusions regarding (especially long-term) BoNT-A effects have in fact been conclusions regarding the effects of BoNT-A *plus* (an)other co-intervention(s). This is especially the case in trials that focus on efficacy, safety and dosage of BoNT-A. However, efficacy and effectiveness research usually have different aims (73). The size of the contrast between intervention and comparator also differs, with generally larger contrasts in efficacy studies. Low-intensity "standard care" as comparative control intervention is, from a clinical effectiveness perspective, not the most logical choice, and may even be considered *a priori* inferior because they do not do justice to the current body of evidence for the non-pharmacological post-BoNT-A treatment packages for spastic CP. The comparative alternative intervention should be a full representative of best-available evidence for the non-pharmacological modalities that are applied in clinical practice to date.

As we pointed out earlier (52), up to now, research questions and designs have been based on the implicit assumption that BoNT-A is the most active component in combined treatment packages. However, given the consensus that BoNT-A should never be a stand-alone treatment and an interdisciplinary multi-modal team approach is required (5), it may, in our opinion, be likely that physiotherapy was intensified after BoNT-A treatment in the intervention groups. This cannot be checked, however, because the post-BoNT-A interventions and the interventions in the comparative intervention largely remained "black boxes" (35). It is difficult to weigh the current body of evidence, but based on our results, the assumption that BoNT-A creates better conditions to enhance the (long-term) effectiveness of adjunctive interventions may be questioned. It should be noted that, as long ago as 2000, Ade-Hall & Moore warned about premature acceptance of BoNT-A because of inconclusive evidence (3).

The current study does not question the working mechanism or efficacy of BoNT-A. This is related to the possibility of false indications for BoNT-A treatment, even though the medical specialists involved in the current study had ample experience with BoNT-A. Clinical assessment of responses to passive muscle stretch is complicated, as it is difficult to distinguish reliably between non-neural (tissue-related) and neural (central nervous system related) contributions to hyper-resistance (74). This clearly hampers the interpretation of findings because BoNT-A can only impact non-neural contributors to hyper-resistance, whereas pathophysio-logical responses to stretch can have multiple causes.

Further investigations are therefore clearly warranted, and the *p*-values presented in this paper should be interpreted with caution because of the disturbed randomization. In future research, instrumented/quantitative assessment of different components of hyper-resistance should be applied (74). At the same time, it is important to focus on opening the black box, by defining the content of treatment in both intervention and control groups, to enable us to better determine the best intervention for each patient (13, 75).

The main limitations of the current study were its pragmatically chosen partly-randomized design, the relatively small sample size, failed masking of outcome assessor (37%) or physiotherapist (69%), and the lack of a control group without intervention. These have been discussed extensively previously (52). The potential bias related to differences in BoNT-A treatment history between groups was not evident from the data. A strength of the current study is that, in contrast to most other studies, we included both legs in the comparative effectiveness analyses for children with bilateral spastic CP (instead of only the most involved leg). This better reflects the true effectiveness of interventions for the bilaterally measured outcome measures. We agree with Ade-Hall that it is important to reflect clinical practice as closely as possible (3), and therefore only included legs in the analyses for an effect outcome when a BoNT-A-targeted muscle was expected to have an effect on that particular effect outcome according to a scheme based on expert opinion. This is debatable, of course, but in our opinion is the most valid way to evaluate the effectiveness of multi-level BoNT-A treatment. Underdosing was highly unlikely because the medical specialists applied the maximum recommended BoNT-A doses per large muscle group in relation to the age of the child.

In conclusion, at the group level, giving BoNT-A injections prior to rehabilitation did not increase the effectiveness of multimodal comprehensive rehabilitation treatment for ambulatory 4–12-year-old children with spastic CP. Since this applies to a wide range of effect outcomes across different ICF categories, it is now relevant to critically reconsider the indications for and use of BoNT-A treatment in this specific CP subgroup.

ACKNOWLEDGEMENTS

REFERENCES

(complete referencelist availiable online)

1. Elkamil AI, Andersen GL, Skranes J, Lamvik T, Vik T. Botulinum neurotoxin treatment in children with cerebral palsy: a population-based study in Norway. Eur J Paediatr Neurol 2012; 16: 522–527.
2. Aisen ML, Kerkovich D, Mast J, Mulroy S, Wren TA, Kay RM, et al. Cerebral palsy: clinical care and neurological rehabilitation. Lancet Neurol 2011; 10: 844–852.
3. Ade-Hall RA, Moore AP. Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy. Cochrane Database Syst Rev 2000; CD001408.
5. Heinen F, Desloovere K, Schroeder AS, Berweck S, Borggraefe I, van Campenhout A, et al. The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy. Eur J Paediatr Neurol 2010; 14: 45–66.
6. Love SC, Novak I, Kentish M, Desloovere K, Heinen F, Molenaers G, et al. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. Eur J Neurol 2010; 17 Suppl 2: 9–37.
7. Strobl W, Theologis T, Brunner R, Kocer S, Viehweger E, Pascual-Pascual I, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. Toxins (Basel) 2015; 7: 1629–1648.
8. Pavone V, Testa G, Restivo DA, Cannavo L, Condorelli G, Portinaro NM, et al. Botulinum Toxin Treatment for Limb Spasticity in Childhood Cerebral Palsy. Front Pharmacol 2016; 7: 29.
9. Novak I, McIntyre S, Morgan C, Campbell L, Dark L, Morton N, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol 2013; 55: 885–910.
10. Sung KH, Chung CY, Lee KM, Lee YK, Lee SY, Lee J, et al. Conflict of interest in the assessment of botulinum toxin A injections in patients with cerebral palsy: a systematic review. J Pediatr Orthop 2013; 33: 494–500.
11. Ryll U, Bastiaenen C, De Bie R, Staal B. Effects of leg muscle botulinum toxin A injections on walking in children with spasticity-related cerebral palsy: a systematic review. Dev Med Child Neurol 2011; 53: 210–216.
13. Damiano DL. Meaningfulness of mean group results for determining the optimal motor rehabilitation program for an individual child with cerebral palsy. Dev Med Child Neurol 2014; 56: 1141–1146.
14. Molenaers G, Fagard K, Van Campenhout A, Desloovere K. Botulinum toxin A treatment of the lower extremities in children with cerebral palsy. J Child Orthop 2013; 7: 383–387.
15. Lannin N, Scheinberg A, Clark K. AACPDM systematic review of the effectiveness of therapy for children with cerebral palsy after botulinum toxin A injections. Dev Child Neurol 2006; 48: 533–539.
16. Koog YH, Min BI. Effects of botulinum toxin A on calf muscles in children with cerebral palsy: a systematic review. Clin Rehabil 2010; 24: 685–700.
19. Blackmore AM, Boettcher-Hunt E, Jordan M, Chan MD. A systematic review of the effects of casting on equinus in children with cerebral palsy: an evidence report of the AACPDM. Dev Med Child Neurol 2007; 49: 781–790.
23. Kahraman A, Seyhan K, Deger U, Kutluturk S, Mutlu A. Should botulinum toxin A injections be repeated in children with cerebral palsy? A systematic review. Dev Med Child Neurol 2016; 58: 910–917.
31. Delgado MR, Tilton A, Russman B, Benavides O, Bonikowski M, Carranza J, et al. AbobotulinumtoxinA for equinus foot deformity in cerebral palsy: a randomized controlled trial. Pediatrics 2016; 137: e20152830.
32. Dursun N, Gokbel T, Akarsu M, Dursun E. Randomized controlled trial on effectiveness of intermittent serial casting on spastic equinus foot in children with cerebral palsy after botulinum toxin-A treatment. Am J Phys Med Rehabil 2017; 96: 221–225.
33. Scholtes VA, Dallmeijer AJ, Knol DL, Speth LA, Maathuis CG, Jongerius PH, et al. 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: 1551–1558.
35. Sakzewski L, Reedman S, Hoffmann T. Do we really know what they were testing? Incomplete reporting of interventions in randomised trials of upper limb therapies in unilateral cerebral palsy. Res Dev Disabil 2016; 59: 417–427.
36. Reedman S, Boyd RN, Sakzewski L. The efficacy of interventions to increase physical activity participation of children with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol 2017; 59: 1011–1018.
37. Boyd RN, Dobson F, Parrott J, Love S, Oates J, Larson A, et al. The effect of botulinum toxin type A and a variable hip abduction orthosis on gross motor function: a randomized controlled trial. Eur J Neurol 2001; 8 Suppl 5: 109–119.
38. Bjornson K, Hays R, Graubert C, Price R, Won F, McLaughlin JF, et al. Botulinum toxin for spasticity in children with cerebral palsy: a comprehensive evaluation. Pediatrics 2007; 120: 49–58.
40. Verschuren O, Balemans AC. Update of the core set of exercise tests for children and adolescents with cerebral palsy. Pediatr Phys Ther 2015; 27: 187–189.
43. Verschuren O, Ketelaar M, Gorter JW, Helders PJ, Uiterwaal CS, Takken T. Exercise training program in children and adolescents with cerebral palsy: a randomized controlled trial. Arch Pediatr Adolesc Med 2007; 161: 1075–1081.
45. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy – do goals make a difference? Disabil Rehabil 2009; 31: 1808–1816.
47. Anttila H, Autti-Ramo I, Suoranta J, Makela M, Malmivaara A. Effectiveness of physical therapy interventions for children with cerebral palsy: a systematic review. BMC Pediatr 2008; 8: 14.
48. Mockford M, Caulton JM. Systematic review of progressive strength training in children and adolescents with cerebral palsy who are ambulatory. Pediatr Phys Ther 2008; 20: 318–333.
49. Scholtes VA, Becher JG, Comuth A, Dekkers H, Van Dijk L, Dallmeijer AJ. Effectiveness of functional progressive resistance exercise strength training on muscle strength and mobility in children with cerebral palsy: a randomized controlled trial. Dev Med Child Neurol 2010; 52: e107–e113.
50. Gorter JW, Becher J, Oosterom I, Pin T, Dyke P, Chan M, et al. To stretch or not to stretch in children with cerebral palsy. Dev Med Child Neurol 2007; 49: 797–800.
51. Moreau NG, Bodkin AW, Bjornson K, Hobbs A, Soileau M, Lahasky K. Effectiveness of rehabilitation interventions

to improve gait speed in children with cerebral palsy: systematic review and meta-analysis. Phys Ther 2016; 96: 1938–1954.

52. Schasfoort F, Dallmeijer A, Pangalila R, Catsman C, Stam H, Becher J, et al. Value of botulinum toxin injections preceding a comprehensive rehabilitation period for children with spastic cerebral palsy: a cost-effectiveness study. J Rehabil Med 2018; 50: 22–29.

54. Schiariti V, Masse LC. Identifying relevant areas of functioning in children and youth with Cerebral Palsy using the ICF-CY coding system: from whose perspective? Eur J Paediatr Neurol 2014; 18: 609–617.

56. Verschuren O, Ada L, Maltais DB, Gorter JW, Scianni A, Ketelaar M. Muscle strengthening in children and adolescents with spastic cerebral palsy: considerations for future resistance training protocols. Phys Ther 2011; 91: 1130–1139.

57. Verschuren O, Ketelaar M, Takken T, Van Brussel M, Helders PJ, Gorter JW. Reliability of hand-held dynamometry and functional strength tests for the lower extremity in children with Cerebral Palsy. Disabil Rehabil 2008; 30: 1358–1366.

58. Becher J. [Peadiatric rehabilitation medicine – manual standard physical examination in children with central motor paresis.] Amsterdam: Reed Business; 2011. (in Dutch).

59. Perry J, Burnfield J. Gait analysis: Normal and Pathological Function. (2010) 2nd edition. Thorofare, New Jersey: SLACK Inc.; 2010.

60. Becher J. Pediatric rehabilitation in children with cerebral palsy: general management, classification of motor disorders. J Prosthet Orthot 2002; 14: 143–149.

62. Lowing K, Thews K, Haglund-Akerlind Y, Gutierrez-Farewik EM. Effects of botulinum toxin-A and goal-directed physiotherapy in children with cerebral palsy GMFCS levels I & II. Phys Occup Ther Pediatr 2017; 37: 268–282.

63. Desloovere K, Schorkhuber V, Fagard K, Van Campenhout A, De Cat J, Pauwels P, et al. Botulinum toxin type A treatment in children with cerebral palsy: evaluation of treatment success or failure by means of goal attainment scaling. Eur J Paediatr Neurol 2012; 16: 229–236.

64. Tilton A, Russman B, Aydin R, Dincer U, Escobar RG, Kutlay S, et al. AbobotulinumtoxinA (Dysport®) improves function

according to goal attainment in children with dynamic equinus due to cerebral palsy. J Child Neurol 2017; 32: 482–487.

66. Steenbeek D, Gorter JW, Ketelaar M, Galama K, Lindeman E. Responsiveness of goal attainment scaling in comparison to two standardized measures in outcome evaluation of children with cerebral palsy. Clin Rehabil 2011; 25: 1128–1139.

67. Steenbeek D, Ketelaar M, Galama K, Gorter JW. Goal attainment scaling in paediatric rehabilitation: a critical review of the literature. Dev Med Child Neurol 2007; 49: 550–556.

68. Scholtes VA, Dallmeijer AJ, Knol DL, Speth LA, Maathuis CG, Jongerius PH, et al. Effect of multilevel botulinum toxin a and comprehensive rehabilitation on gait in cerebral palsy. Pediatr Neurol 2007; 36: 30–39.

69. Reddihough DS, King JA, Coleman GJ, Fosang A, McCoy AT, Thomason P, et al. Functional outcome of botulinum toxin A injections to the lower limbs in cerebral palsy. Dev Med Child Neurol 2002; 44: 820–827.

70. Desloovere K, Molenaers G, Jonkers I, De Cat J, De Borre L, Nijs J, et al. A randomized study of combined botulinum toxin type A and casting in the ambulant child with cerebral palsy using objective outcome measures. Eur J Neurol 2001; 8 Suppl 5: 75–87.

71. Read FA, Boyd RN, Barber LA. Longitudinal assessment of gait quality in children with bilateral cerebral palsy following repeated lower limb intramuscular Botulinum toxin-A injections. Res Dev Disabil 2017; 68: 35–41.

72. Yap R, Majnemer A, Benaroch T, Cantin MA. Determinants of responsiveness to botulinum toxin, casting, and bracing in the treatment of spastic equinus in children with cerebral palsy. Dev Med Child Neurol 2010; 52: 186–193.

74. van den Noort JC, Bar-On L, Aertbeliën E, Bonikowski M, Braendvik SM, Broström EW, et al. European consensus on the concepts and measurement of the pathophysiological neuromuscular responses to passive muscle stretch. Eur J Neurol 2017; 24: 981–e38.

75. Horn SD, DeJong G, Deutscher D. Practice-based evidence research in rehabilitation: an alternative to randomized controlled trials and traditional observational studies. Arch Phys Med Rehabil 2012; 93 (8 Suppl): S127–S137.