Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy

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The objective of this study was to determine whether the use of intramuscular botulinum toxin A (BTX-A) increases upper limb function and skills in the context of a specific therapy programme in children with hemiparetic cerebral palsy. Twenty children (nine females, 11 males) aged 4 to 16 years who were thought likely to benefit from BTX-A treatment were included. After matched pairs were made, on the basis of Zancolli grade and age, randomization took place. All patients were given structured rehabilitation (physiotherapy and occupational therapy three times a week for 6 months), and half of the patients received intramuscular BTX-A. No placebo injections were given in the control group. Participants were assessed at baseline, at 2 and 6 weeks, and at 3, 6, and 9 months after injection. The Ashworth scale, active range of motion of arm joints, the Melbourne assessment of upper limb function, the Pediatric Evaluation of Disability Inventory, and the nine-hole peg test were used for outcome measurement. Observers were blinded for treatment allocation only for scoring the Melbourne test. The children in the treatment group showed a clinically relevant increase in active dorsal flexion, and tone reduction of the wrist. For the functional outcome measures, no statistically significant differences between the groups could be demonstrated. Intramuscular BTX-A added to an intensive therapy programme reduces impairment for at least 9 months; the effect on activity level is still uncertain.

See end of paper for list of abbreviations.

The beneficial effect of botulinum toxin A (BTX-A) injections (for pharmacology see Brin 1997) on children with spastic lower limb muscles has been quite well established (Cosgrove et al. 1994, Graham et al. 2000). However, with regard to arm–hand function in children with cerebral palsy (CP), a recent systematic review concluded that there is very little evidence to guide the choice of treatment (Boyd et al. 2001). Beside some uncontrolled studies (Wall et al. 1993, Hurvitz et al. 2003, Yang et al. 2003), only two small randomized studies of BTX-A in the treatment of arm function problems in children with CP have been published. In a randomized, double-blind placebo-controlled study describing the effects of BTX-A injections into the upper limb in 14 patients with CP, Corry et al. (1997) found a significant increase in active elbow and thumb extension, and a significantly reduced tone at wrist and elbow, at 12-week follow-up. The results on activity level of the International Classification of Functioning, Disability and Health (ICF; World Health Organization 2001) were inconclusive.

Fehlings et al. (2000) studied the additional effect of BTX-A injections in the arm muscles in 29 children with hemiplegic CP receiving occupational therapy in a randomized single-blind trial. They reported some improvement at activity level of the ICF, as measured with the Quality of Upper Extremity Skills Test (QUEST) and also in the self-care domain of the Pediatric Evaluation of Disability Inventory (PEDI).

Injections of BTX-A are proved to be effective at impairment level (tone, active range of motion [ROM]) for a period of 12 weeks (Corry et al. 1997). In the Fehlings et al. (2000) study, in which the children received limited occupational therapy once every 2 weeks, modest functional effects were found. Increasing the intensity of therapy might increase functional improvement at activity level (ICF; World Health Organization 2001). This hypothesis is corroborated by the theory of Huttenlocher (1990). Furthermore, it is known that BTX-A injections into the lower limb seem to be more effective than injections into the upper limb. This can be explained by the inevitable greater practice of the affected lower limb during walking when spasticity is reduced by BTX-A (Boyd et al. 2001).

The aim of the present study was to evaluate the additional effect of BTX-A injections on upper-limb function and skills in children with hemiparetic CP who were receiving an intensive rehabilitation programme.

Method

PARTICIPANTS

After approval of the Medical Ethical Committee of the Rehabilitation Foundation Limburg and the Academic Hospital Maastricht as well as the Dutch Medical Ethical Board and after informed assent, 20 patients (nine females, 11 males, aged 4 to 16y) with hemiparetic CP and a minimum developmental age of 3 years who were thought likely to receive functional benefit from BTX-A injections were included in the study.

The children were recruited from our paediatric rehabilitation centre or referred to us from neighbouring centres. Patients with obvious contractures (deficit of elbow extension, supination and wrist dorsal flexion of 30° or more) and severe impairment of hand function, unable to initiate voluntary movement (Zancolli III) were excluded (Zancolli and Zancolli 1987).

STUDY DESIGN

Ten pairs of patients were formed by matching as closely as possible for age and Zancolli grade (Fig. 1). One child of every pair was randomly allocated to either the BTX-A or the control group by choosing one opaque envelope of 10 (five BTX-A and five control), assigning the other child automatically to the other group. Sex was not considered relevant in the matching process.

INJECTION TECHNIQUE AND DOSAGE

The BTX-A injections were given under general anaesthesia in the daycare department of the Academic Hospital Maastricht. To determine which muscle to inject, each patient was given an individual clinical examination. Spastic hypertonia of a specific muscle disturbing strength and/or function in daily activities in relation to the Zancolli grade and House score were criteria for injecting that specific

Table I: Injected muscles and patient characteristics in BTX-A treatment group

Number	*Age (y)*	*Side of paresis*	*Zancolli grade at 0wk*	*House score at 0wk*	*Quantity of botulinum toxin A injected (U) per muscle*							*Body weight (kg)*	*U/kg body weight*
					M. add. poll.	*M. fl. poll br.*	*M. fl. carpi uln.*	*M. fl. carpi rad.*	*M. pron. teres*	*M. brachio-rad.*	*M. biceps*		
1	5	R	IIB	II	10	5	30	20	35			18.6	5.38
2	12	R	I	I	10		2×35				2×50	48.6	3.70
3	11	R	IIB	II	10	5	2×30	30	40	40		32.5	5.70
4	12	R	I	I	10		2×40	40	50			38.6	4.70
5	12	R	I	I	10		2×40		50			49.0	2.90
6	16	R	IIA	I	10		2×40	2×30	50	2×40		58.6	4.90
7	8	R	IIA	I	10		2×25	30	35			22.0	5.70
8	5	R	IIA	I	10		2×20		30		2×20	21.5	5.60
9	8	R	IIA	I	10		2×25		35		2×25	25.2	5.80
10	5	L	I	I	10							19.0	<1.00

House scores I: metacarpal adduction deformity; II: metacarpal adduction and flexion deformity; III: metacarpal adduction and hyperextension deformity with instability of the metacarpal joint; IV: metacarpal adduction and metacarpal and interphalangeal flexion deformity (House et al. 1981). M., musculus; fl., flexor; add. poll., adductor pollicis; poll. br, pollicis brevis; carpi vln, carpi vulneris; carpi rad., carpi radialis; pron. ters, prontor teres; brachiorad, brachioradialis; biceps, biceps brachil.

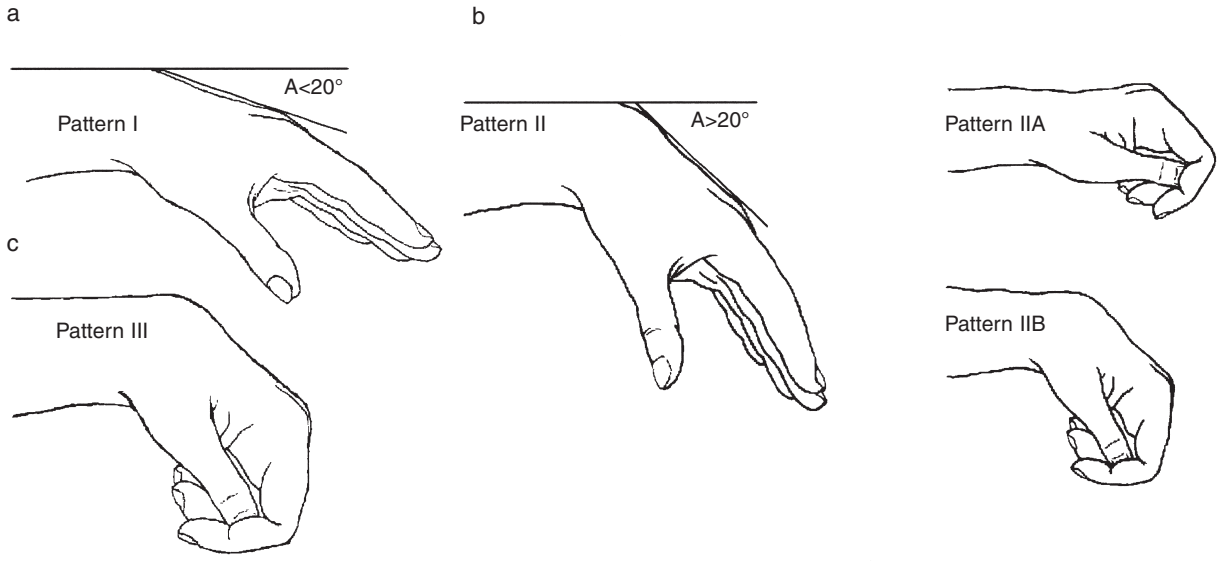

Figure 1: *Zancolli classification (Zancolli and Zancolli 1987). Diagram of grip and release pattern according to Zancolli. (a) Pattern I active finger extension with less than 20° (angle A) of wrist palmar flexion. (b) Pattern II active finger extension with more than 20° (angle A) of wrist palmar flexion; Zancolli IIA with wrist dorsal flexion possibility with fisted hand; Zancolli IIB no possibility of dorsal flexion of active wrist. (c) Pattern III: no active finger extension possible. (From Hoeksma et al. 1995; used with permission.)*

muscle (House et al. 1981). The target muscles were located with the help of electrical stimulation (O'Brien 1997). Botox from Allergan was used (dilution 5U per 0.1ml). The dosages were 2 to 3U/kg body weight above the elbow, 1 to 2U/kg in the forearm, limited to no more than 50U at any one site, with an overall maximum dose of 400U/kg body weight (Graham et al. 2000). In Table I an overview of the injected muscles and some patient characteristics are given. For ethical reasons regarding general anaesthesia without further necessary medical intervention, no placebo injections were given in the control group.

Table II: Characteristics and baseline scores in compared treatment groups

Characteristic	*Median score/degrees (min – max) or frequencies at baseline*	
	BTX-A (n=10)	*Control (n=10)*
Side paresis	9 R, 1 L	3 R, 7 L
Mean age in years (range)	9.4 (5–16)	9.7 (4–16)
Sex		
Male	5	4
Female	5	6
Zancolli		
I	4	5
IIA	4	1
IIB	2	4
House score		
I	8	6
II	2	3
III	–	1
Active dorsal flexion wrist	–18 (–51 to 45)	–6 (–55 to 55)
Active thumb abduction	26 (12 to 44)	21 (–10 to 37)
Active supination	6 (–62 to 50)	–24 (–70 to 50)
Ashworth wrist		
0	7	5
1	2	4
2	1	1
Ashworth elbow		
0	3	3
1	6	5
2	1	–
Melbourne assessment score (%)	69 (52 to 77)	61 (46 to 79)
PEDI self-care scale raw score	67 (54 to 73)	70 (47 to 73)

BTX-A, botulinum toxin A; L, left; PEDI, Pediatric Evaluation of Disability Inventory; R, right.

THERAPY PROGRAMME AND SPLINTING

The therapy programme for all the children consisted of 30 minutes of physiotherapy and 30 minutes of occupational therapy, by experienced child therapists, three times a week for a period of 6 months. A treatment protocol, describing time and degree of stretching, wearing of orthoses, time of strength and coordination training and task-specific training,

Table III: Frequencies of Ashworth scores for wrist and elbow

	Group	*Ash. score*	*Frequency*					
			0wk	*2wk*	*6wk*	*3mo*	*6mo*	*9mo*
Wrist	BTX-A	0	7	10	10	10	10	10
		1	2	0	0	0	0	0
		2	1	0	0	0	0	0
	Control	0	5	6	7	9	8	9
		1	4	2	2	1	2	1
		2	1	2	1	0	0	0
Elbow	BTX-A	0	3	7	5	7	6	8
		1	6	2	4	2	3	1
		2	1	1	1	1	1	1
	Control	0	3	4	6	5	6	6
		1	5	3	3	3	4	3
		2	2	3	1	2	0	1

BTX-A, botulinum toxin A; Ash. score, Ashworth score.

Table IV: Outcome measures at follow-up

Measure	*Group*	*Degrees/score: medians (min–max)*		*p value, 0wk to 2wk*	*Degrees/score: medians (min – max)*	*p, 0wk to 6wk*
		0wk	*2wk*		*6wk*	
Active dorsal flexion wrist	BTX-A	–17.5 (–51 to 45)	28 (–55 to 50)	0.092	33.5 (–30 to 55)	0.192
	Control	–6 (–55 to 55)	4.5 (–45 to 40)		9 (–34 to 40)	
Active thumb abduction	BTX-A	26 (12 to 44)	29 (17 to 50)	0.162	33 (12 to 38)	0.213
	Control	20.5 (–10 to 37)	24 (–10 to 43)		24.5 (0 to 36)	
Active supination	BTX-A	5.5 (–62 to 50)	10 (–85 to 50)	0.006	15 (–45 to 74)	0.113
	Control	–24 (–70 to 50)	–5.5 (–28 to 45)		12.5 (–50 to 55)	
PEDI raw score (maximum 73)	BTX-A	67 (54 to 73)	68 (54 to 73)	0.068	68 (59 to 73)	0.407
	Control	70 (47 to 73)	71 (51 to 73)		72 (46 to 73)	
PEDI <12y raw score (n=2×6)	BTX-A	65.5 (54 to 68)	65.5 (54 to 72)	0.127	66.5 (59 to 73)	0.436
	Control	66.5 (47 to 72)	66.5 (51 to 73)		68.5 (46 to 73)	
Melbourne score (%)	BTX-A	68.45 (51.6 to 77)	67.65 (58.2 to 78.7)	0.325	68.45 (55.7 to 77)	0.396
	Control	61.35 (45.9 to 78.7)	60.25 (44.3 to 78.7)		65.55 (48.4 to 81.1)	
Melbourne total ROM score	BTX-A	25 (21 to 35)	28 (20 to 36)	0.447	30 (21 to 35)	0.479
	Control	28 (13 to 33)	27 (17 to 31)		28 (15 to 38)	
Subjective judgement, child	BTX-A	1.5 (–1 to 3)	1 (–1 to 3)	0.484	2 (0 to 3)	0.5
	Control	2 (–3 to 3)	2 (–3 to 3)		1.5 (0 to 3)	
Subjective judgement, parents	BTX-A	–2 (–3 to 2)	–1 (–3 to 2)	0.171	0 (–1 to 2)	0.4
	Control	–1.5 (–3 to 0)	–1 (–2 to 0)		–0.5 (–2 to 2)	

Values of p are based on comparisons between treatment groups for change from baseline.
BTX-A, botulinum toxin A; PEDI, Pediatric Evaluation of Disability Inventory; ROM, range of motion.

was made for each level of hand function impairment (Zancolli grade). This was tailored to the individual patient, based on individual goal setting and clinical reasoning. Active ROM was treated by stretch techniques and passive ROM by the use of orthoses. All children wore a night splint with the elbow extended, the forearm neutral between pronation and supination, and the wrist in dorsal flexion with the thumb in abduction and the fingers in opposition. During the day only the children graded Zancolli IIB wore a cock-up splint almost all day; the children with less impairment needed a cock-up or a web-space splint only during specific activities. Strength and coordination were trained using specific activities and skills (more repeats, more weight bearing) according to individual goal setting for each patient. Skill training was performed in accordance with the theory of Fitts and Posner (1967).

FOLLOW-UP AND OUTCOME MEASURES

Outcome measures were collected at baseline, at 2 and 6 weeks, and at 3, 6, and 9 months after treatment. At 6 months the therapy programme ended.

At impairment level (ICF; World Health Organization 2001) outcome measures were active ROM of thumb abduction, wrist dorsal flexion, and supination, assessed in sitting position. For the wrist, the zero point was with the hand in the neutral position (straight in line with the forearm), and dorsal flexion was rated as positive degrees. For supination the neutral position was with the palm of the hand vertically oriented, and supination was rated positively. For the thumb, neutral (0°) was with the thumb against the palm, with abduction rated positively. The maximum deviation in degrees achieved voluntarily by the child was measured by a research physiotherapist who was not blinded to the child's treatment group, by using a clinical goniometer (UK patent 840.1841; MIE Medical Research Ltd.). Wrist and elbow tone were measured with the Ashworth score, taken in the supine position (Ashworth 1964).

At activity level (ICF; World Health Organization 2001) the Melbourne assessment of unilateral upper limb function developed by Randall in 1999 (Johnson et al. 1994, Randall et al. 2001) was used because it measures unilateral upper limb function in children with spasticity in the relevant age group, and can be scored from video recordings. It was performed and videotaped by experienced and trained occupational therapists. The videos of the Melbourne assessment were coded and scored in random order by a movement scientist who was unaware of the child's treatment group. The PEDI (Haley et al. 1992, Custers et al. 1997) was administered completely at baseline and at 6 months. During the other measurement sessions only the PEDI self-care scale was obtained. The nine-hole peg test (Mathrowitz et al. 1985) was administered to measure velocity. Finally, both the parents and the children themselves judged the functional use of their affected hand on a seven-point scale from very bad (–3) to moderate (0) to very good (+3).

At baseline and at 9 months after the start of treatment the Zancolli score (Zancolli and Zancolli, 1987) and the House score (House et al. 1981) for thumb position (Table I) were recorded.

STATISTICAL ANALYSIS

Data processing was performed with SPSS for Windows' version 11.0. For each outcome variable the change from the baseline value was calculated. The Mann–Whitney *U* test was used to assess the differences in these changes between the two groups. The level of significance was set at $p<0.05$, one-sided. Because of the small number of patients no statistical correction for baseline differences was performed.

Results

The children underwent the injections under general anaesthesia without any problems. No side effects or complaints

Table IV: continued

Degrees/score: medians (min – max) 3mo	*p, 0wk to 3mo*	*Degrees/score: medians (min – max) 6mo*	*p, 0wk to 6mo*	*Degrees/score: medians (min – max) 9mo*	*p, 0wk to 9mo*
40 (0 to 55)	0.225	45 (–20 to 60)	0.163	42.5 (–15 to 65)	0.12
17.5 (–30 to 60)		3 (–40 to 50)		17.5 (–60 to 40)	
36.5 (13 to 46)	0.145	31.5 (14 to 49)	0.298	30.5 (10 to 40)	0.298
26.5 (0 to 42)		28.5 (10 to 39)		25.5 (0 to 44)	
25 (–50 to 50)	0.061	17.5 (–30 to 80)	0.339	10 (–40 to 50)	0.011
–1.5 (–25 to 40)		7 (–60 to 40)		5 (–35 to 35)	
70 (62 to 73)	0.485	70 (62 to 73)	0.35	70 (62 to 73)	0.283
71.5 (52 to 73)		71.5 (58 to 73)		72 (57 to 73)	
68.5 (61 to 72)	0.404	68.5 (62 to 72)	0.436	69 (62 to 70)	0.373
69 (52 to 73)		67.5 (58 to 73)		66.5 (57 to 73)	
72.15 (49.3 to 82)	0.087	68.85 (55.7 to 82.8)	0.381	68.45 (49.2 to 82)	0.41
64.35 (47.6 to 76.2)		66.6 (49.2 to 77.9)		62.7 (47.5 to 85.2)	
29.5 (20 to 38)	0.198	29 (21 to 36)	0.187	28.5 (21 to 36)	0.312
26 (19 to 33)		28 (16 to 34)		24.5 (16 to 38)	
3 (0 to 3)	0.003	2 (1 to 3)	0.047	2 (0 to 3)	0.048
1.5 (–3 to 3)		2 (–3 to 3)		2 (–3 to 3)	
1 (–1 to 2)	0.131	0.5 (–2 to 2)	0.14	1 (–1 to 2)	0.279
0 (–3 to 3)		0 (–2 to 2)		0 (–2 to 3)	

about the treatment were reported. All participants completed the therapy and the measurement programme. Because of lack of cooperation from some of the younger children there were some missing values.

Baseline characteristics from both groups are shown in Table II. Apart from the side of paresis, active dorsal flexion and supination, there was no large difference between the groups. However, putting all baseline scores together, the condition of the patients in the control group was worse. Only active dorsal flexion of the wrist and the PEDI self-care score were better in the control group.

Median scores and frequencies of the outcome measures at the different follow-up times are shown in Tables III and IV. Wrist tone decreased in both study groups. In the BTX-A group there was maximal reduction already at 2 weeks after the injection, whereas the improvement in the control group was gradual. In both groups there was gradual improvement of elbow tone, at 2 weeks somewhat more in the treatment group. The improvement in active dorsal flexion of the wrist in the treatment group was larger than in the control group. This did not reach statistical significance for any follow-up period. Active thumb abduction showed modest changes in both treatment groups.

The statistically significant change in active supination at 2 weeks and at 9 months in favour of the control group can be explained by the very low baseline scores from three children with a Zancolli IIB score in this group. For reasons that are not clear, they achieved substantially better scores 2 weeks later. These results are, therefore, contradictory, despite eight patients receiving blockades in the pronator teres. Active supination in the BTX-A group steadily improved over the first 3 months and declined thereafter.

At activity level the Melbourne assessment was the primary outcome measure. The percentage score did not show much change from baseline in both groups. Some of the items of the Melbourne assessment are to do with fluency and target accuracy, which are not expected to be improved by BTX-A injections. We, therefore, also analyzed the sum of those items of the Melbourne test in which the posture of thumb/fingers, wrist and elbow/forearm are scored (Melbourne ROM score). With this item selection the BTX-A group showed some tendency towards improvement until the 6-week follow-up (although this was not a significant difference), whereas the control group did not.

With the PEDI self-care inventory neither the treatment nor the control group showed any substantial improvement. Because the children aged 12 years and above had a maximum score (ceiling effect) the analysis was also performed after excluding them. Among the younger children (six in each group) the change was indeed larger but was not statistically significant. At baseline both groups scored 10 points higher than in the Fehlings (2000) study, which leaves little opportunity for progression.

The children with a Zancolli IIB score and the youngest participant were unable to perform the nine-hole peg test. The remaining 11 children needed between 3.7 and 90 seconds. After 3 months the BTX-A-treated children were able to manipulate the nine pegs 11 seconds (SD 16) per peg faster. The control group children needed 2 seconds (SD 5) longer per peg. This difference is not statistically significant.

The BTX-A-treated children subjectively judged their hand function significantly better at 3, 6, and 9 months, whereas the children in the control group did not (Table IV). Nine children of the treatment group and six of the control group were satisfied and reached their goals. These varied from cutting with a knife, tying shoelaces, and carrying cups, to climbing, holding the bicycle handle, shaking hands, and hairdressing. However, the parents noted hardly any change.

Discussion

We evaluated the additional effect of BTX-A injections in the upper limb in children with hemiparetic CP receiving an intensive occupational and physical therapy programme on function and activities in a randomized trial. As could be expected from earlier research (Corry et al. 1997), this study showed a beneficial effect of BTX-A injections on wrist flexor tone. The effect was present as soon as 2 weeks after injection and remained for 9 months. In addition, dorsal flexion of the active wrist seems to be positively influenced by BTX-A injections for at least 9 months, although this effect did not reach statistical significance. The statistically significant negative effect of BTX-A treatment on supination that we found can be explained by the very low baseline scores of three patients in the control group.

At ICF activity level, no significant effect of BTX-A treatment was detected. The children in the BTX-A group were clearly more satisfied with their treatment result than those in the control group; however, the judgements of the parents of the children in both groups did not differ greatly. The velocity in the treatment group improved (not statistically significant), in contrast with that in the control group.

This was for the most part a non-blinded study. Only during the scoring of the Melbourne assessment from videos was the treatment modality concealed. Therapists were aware of the treatment group of the patients. However, it does not seem probable that there will have been any appreciable bias in favour of the BTX-A group because both groups received intensive therapy. The absence of blinding makes interpretation of the subjective judgement of the children difficult, especially because the parents did not notice any clear improvement.

The fact that this randomized study was small, and was based on an inhomogeneous study population, had a negative effect on the comparability of the two groups. It seems that the control group had a somewhat worse condition at baseline. Whether this biased the study towards a too large or a too small estimate of the treatment effect remains uncertain. Another negative effect of the small study size and non-homogeneous population is the negative influence on power to show existing effects. The same problem holds for the lack of sensitivity to change for the different effect measures. The Melbourne assessment, for example, might not be responsive enough because it contains many items relating to target accuracy and fluency, which are not expected to be influenced by BTX-A treatment. Indeed, we could show that the treatment effect was somewhat magnified when only ROM-related items were used.

All children received a relatively intense and prolonged course of rehabilitation therapy. This in itself might have led to some benefit in both groups of children, possibly reducing the extent of benefit to be detected. However, without therapy patients cannot avail themselves of potential benefit after BTX-A. So the effect of this course is uncertain.

Although some bias is likely because the study was not

placebo-controlled and was only partly blinded, we believe that the results are valid. They are consistent with other related research (Corry et al. 1997, Fehlings et al. 2000). They are internally consistent, with greater effects in measures that reflect most closely the effects of BTX-A.

At this stage the evidence specific to children with CP is insufficient to make any strong recommendations about the use of BTX-A in hypertonic arm muscles. For future studies, populations should preferably be larger and more homogeneous. In addition, it is necessary to develop outcome measures at ICF activity level that are more sensitive to change and to guarantee blinding where necessary without jeopardizing ethics.

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List of abbreviations

BTX-A	Botulinum toxin A
ICF	International Classification of Function
PEDI	Pediatric Evaluation of Disability Inventory, Disability and Health
ROM	Range of motion