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Abstract

The objective was to determine the effects of low-dose, high concentration, dual localized botulinum toxin A (BTX-A) injections on upper limb movement quality and function. Study design was an evaluator-blinded, randomized, controlled trial. Forty-two children (31 males, 11 females; range 2–8y, mean 4y [SD 1.6]) with hemiplegic cerebral palsy (Gross Motor Function Classification System level I) participated. All received occupational therapy. The treatment group (n=21) received one injection series (mean muscles injected 6 [SD 1.05]; total dose 82–220 units, mean 139 [SD 37.48]; dilution 100 units/0.5ml). Primary outcome of Quality of Upper Extremity Skills Test (QUEST) at 6 months was not significant (p=0.318). Secondary outcomes were average treatment effects at 1, 3, and 6 months, which favoured the treatment group: QUEST (p<0.001); Canadian Occupational Performance Measure (performance, p=0.002; satisfaction p=0.007); parent Goal Attainment Scaling (GAS; p=0.001), therapist GAS (p<0.001); Pediatric Evaluation of Disability Inventory (PEDI) functional skills (p=0.030); Ashworth (p<0.001). PEDI caregiver assistance was not significant (p=0.140). Therapy alone is effective, but at 1 and 3 months movement quality is better where BTX-A is also used. Moreover, function is better at 1, 3, and 6 months, suggesting BTX-A enhances therapy outcomes beyond the pharmacological effect. One- and 3-month Ashworth and QUEST scores suggest precise needle placement accuracy.

Keywords

dose, high, concentration, localized, botulinum, toxin, improves, upper, limb, movement, function, children, hemiplegic, cerebral, palsy, low

Disciplines

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Low-dose/high-concentration localized botulinum toxin A improves upper limb movement and function in children with hemiplegic cerebral palsy

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The objective was to determine the effects of low-dose, high-concentration, dual localized botulinum toxin A (BTX-A) injections on upper limb movement quality and function. Study design was an evaluator-blinded, randomized, controlled trial. Forty-two children (31 males, 11 females; range 2–8y, mean 4y [SD 1.6]) with hemiplegic cerebral palsy (Gross Motor Function Classification System level I) participated. All received occupational therapy. The treatment group ($n=21$) received one injection series (mean muscles injected 6 [SD 1.05]; total dose 82–220 units, mean 139 [SD 37.48]; dilution 100 units/0.5ml). Primary outcome of Quality of Upper Extremity Skills Test (QUEST) at 6 months was not significant ($p=0.318$). Secondary outcomes were average treatment effects at 1, 3, and 6 months, which favoured the treatment group: QUEST ($p<0.001$); Canadian Occupational Performance Measure (performance, $p=0.002$; satisfaction $p=0.007$); parent Goal Attainment Scaling (GAS; $p=0.001$), therapist GAS ($p<0.001$); Pediatric Evaluation of Disability Inventory (PEDI) functional skills ($p=0.030$); Ashworth ($p<0.001$). PEDI caregiver assistance was not significant ($p=0.140$). Therapy alone is effective, but at 1 and 3 months movement quality is better where BTX-A is also used. Moreover, function is better at 1, 3, and 6 months, suggesting BTX-A enhances therapy outcomes beyond the pharmacological effect. One- and 3-month Ashworth and QUEST scores suggest precise needle placement accuracy.

Children with cerebral palsy (CP) experience many daily challenges as a result of the upper motor neurone syndrome. Symptoms include the following: spasticity, weakness, loss of dexterity, poor motor control, and sensory impairment. Botulinum toxin A (BTX-A) reduces spasticity (Corry et al. 1997, Love et al. 2001, Delgado 2002, Boyd et al. 2003, Chin and Graham 2003, Yang et al. 2003, Hoare and Imms 2004) and is usually used with interventions such as physical and occupational therapy to help children attain functional goals. Reduction of spasticity in children with CP is clinically important because the following outcomes can occur: muscle length improvement leading to a slowing of contracture development rates (Corry et al. 1997); improved tolerance of splinting and casting interventions, which increase range and function (Delgado 2002); enhanced function (Russman et al. 1997, Love et al. 2001, Delgado 2002, Boyd et al. 2003); more opportunity for therapy interventions to be introduced (Russman et al. 1997); and reduction in pain (Delgado 2002). As recently as 2002 the use of BTX-A in the upper limb in CP was regarded as experimental (Wasiak et al. 2002); however, expert clinical opinion about its potential (Russman et al. 1997) is rapidly being complemented by positive findings of effect (Fehlings et al. 2000, Boyd and Hays 2001, Boyd et al. 2002, Wallen et al. 2004).

Accurate needle placement in BTX-A injection is important because this avoids severe side effects and helps to determine whether an observed lack of response to the drug is related to the region of injection. The use of localization techniques is known to improve needle placement accuracy (Chin et al. 2003). Manual localization techniques provide promising functional results (Corry et al. 1997, Fehlings et al. 2000). More recently, localization with the use of electrical stimulation has demonstrated good functional lower limb outcomes (Love et al. 2001) and sustained improvement in the upper limb (Boyd et al. 2003, Wallen et al. 2004). Ultrasound is an emerging localization technique (Westhoff et al. 2003), and electrical stimulation has been shown to be more accurate in needle placement than manual techniques (Chin et al. 2005). So far there have been no studies specifically examining BTX-A injected into upper limbs of children with CP with the use of both electromyography and stimulation. The use of electromyography should enable spastic muscles to be identified (O'Brien 2002) so that muscles with contracture can be excluded as injection sites. Enhanced accuracy in needle placement should also increase efficacy because lower total doses can be used in higher concentrations within muscles related to functional goals.

This study investigated whether or not there was a difference in clinical outcomes for young children with spastic hemiplegic CP receiving occupational therapy, if they received one session of low-dose, high-concentration BTX-A injected using dual-mode localization. The primary clinical outcome measure was quality of movement at 6 months. Secondary outcomes of interest were the weighted average of treatment effects at 1, 3, and 6 months in the following: (1) quality of upper limb movement (1 and 3 months, and percentage of participants with more than 20% improvement); (2) function; and (3) spasticity.

Methods

DESIGN

This study was a randomized, controlled, evaluator-blinded, prospective parallel-group trial based on Consolidated Standards of Reporting Trials (CONSORT) guidelines. Following

subject screening, informed consent was obtained from children's parents using Ethics Committee approved participant information sheets and consent forms. All outcome measures were administered at baseline and at 1, 3, and 6 months. The study was conducted through The Spastic Centre and the Sydney Children's Hospital and was approved by the Research Ethics Committees of South Eastern Sydney Area Health Service, the Spastic Centre, and the University of Western Sydney Macarthur, Australia. All analyses were determined prospectively with an intention-to-treat approach.

SAMPLE

To estimate sample size, an improvement of more than 20% in Quality of Upper Extremity Skills Test (QUEST) scores from baseline was used in power calculations. This degree of change was selected on the basis of a pre-study pilot and evidence of change likely from the control intervention alone (Hickey and Ziviani 1998). Twenty participants per group were estimated to

have at least 80% power to detect a 10-unit difference in QUEST score between groups (two-sided test at 0.05 significance), assuming that the SD of change in total QUEST score was 8.98 units. A convenience sample was used with participation invited through statewide recruitment advertisements and a mailout to all paediatricians.

The inclusion criteria were as follows: age 2 to 8 years; diagnosis of hemiplegic CP; presence of spasticity scoring at least 2 on the Ashworth Scale interfering with functional movement; at least 10° active range of movement in antagonistic muscle during use; volitional limb use observed by both parent and investigator when instructed to play bilaterally; access to occupational therapy after baseline assessment; and parental agreement to participate in a home programme.

The exclusion criteria were as follows: lower limb BTX-A in the past 6 months; upper limb BTX-A in the past 12 months; upper limb fixed contracture greater than 40°; lack of sensory response to light touch or pain in the affected limb; child refused or was unable on 100% of occasions to demonstrate volitional upper limb movement in response to parent or investigator instructions and parent confirmed that this was consistent with their upper limb use at home.

During 16 months of recruitment, 57 children were screened and 43 were enrolled. One child withdrew in the control group after 1 month because of travel difficulties. A total of 42 patients were analyzed at each follow-up: 21 in the treatment group and 21 in the control group; all were at GMFCS level I; age range 2 to 8 years (mean 4y [SD 1.6] for both groups); there were 31 males and 11 females.

Table I: Botulinum toxin A (BTX-A) exposure by muscle group

<i>Muscle group</i>	<i>Total number of units/kg/muscle group BTX-A-injected</i>
Elbow flexors	
<i>n</i>	4
Mean	3.5
SD	0.32
Range	3.1–3.9
Pronators	
<i>n</i>	18
Mean	3.3
SD	0.95
Range	1.1–4.3
Wrist flexors	
<i>n</i>	14
Mean	2.1
SD	0.75
Range	1.1–3.2
Wrist extensors	
<i>n</i>	1
Mean	1.0
SD	–
Range	1.0–1.0
Finger flexors	
<i>n</i>	12
Mean	2.2
SD	0.70
Range	1.0–3.2
Thumb adductor	
<i>n</i>	9
Mean	0.6
SD	0.15
Range	0.5–0.9
Thumb opponens	
<i>n</i>	20
Mean	0.7
SD	0.18
Range	0.5–1.1
Thumb flexors	
<i>n</i>	4
Mean	0.8
SD	0.31
Range	0.5–1.2

RANDOMIZATION

An independent officer used computer-generated random allocation sequences in numbered sealed envelopes to achieve randomization. Participants volunteered from rural and metropolitan locations. To plan for travel and accommodation, parents were informed of their group allocation before baseline measures. The study managed allocation awareness by requesting families not to tell raters their allocation and explaining why, by using standardized observational assessments in which performance could not reasonably be manipulated in the light of known allocation, and by conducting between-group baseline analyses.

INTERVENTION

Both groups received occupational therapy from the same occupational therapist, and the treatment group received intramuscular injections of BTX-A. The therapy provided was based on best available evidence including the use of individualized family goals (e.g. independent dressing or sports participation) with mutually agreed levels of attainment developed through two collaborative interviews. Individualized home programmes were developed with the family to implement in goal-relevant contexts of home or school/pre-school. Programmes drew on a suite of interventions offered by the therapist but driven by the family, including functional training, strengthening, splinting, casting, and motor learning (Copley and Kuipers 1999, Wilton 2003, Steultjens et al. 2004). Standard indicators were used to verify the need for and to prescribe splinting and casting (Copley and Kuipers 1999).

BTX-A intervention

Electromyography was used to exclude muscle contracture, to

assist in identifying the most spastic muscles and to identify muscle penetration to minimize trauma to other tissues. In all cases, electromyography guidelines (Perotto 1994) were used to assist in identifying injection sites. To refine the identification of the correct muscle point for injection, stimulation was used at threshold levels by observation of movement responses to stimulus. Injection muscle choice was based on the degree of spasticity (baseline Ashworth score of at least 2), estimated effect on functional abilities, and parental preference of likely arm posture if BTX-A was effective. The number of participants with affected muscles in treatment versus control were as follows: elbow flexor, 16:15; pronators, 20:21; wrist flexor, 17:16; wrist extensor, 1:2; finger flexor, 14:10; thumb adductor, 13:18; thumb opponens, 21:21; and thumb flexor, 6:4.

The total dose of BTX-A injected did not exceed 8 units/kg body weight, which is lower than the expert consensus maximum dose of 12 units/kg per session (Delgado 2002). A clinical estimate of likely muscle size was used to guide the appropriate dose calculation per muscle from the total of 8 units (Table I, range 0.5–2.0 units/kg/muscle). Dilution of 100 units of BTX-A was with 0.5ml of normal saline, which is more concentrated than usual. Volume of injection to muscle was determined by dose per individual muscle; number of muscles injected, mean 6 (SD 1.05); total dose 82 to 220 units, mean 139 (SD 37.48). Participants who received injections received nil by mouth and were admitted to a day-stay ward at the Sydney Children's Hospital. A eutectic mixture of local anaesthetics cream, chloral hydrate, pethidine, droperidol, and midazolam were used in various combinations to achieve adequate sedation and analgesia.

DATA COLLECTION AND INSTRUMENTS

Data were collected at baseline and at 1, 3, and 6 months. The baseline data were a therapy history survey and a physical examination (height, weight, pulse rate, and blood pressure). All other instruments were used on all four occasions.

Adverse events form

Safety was assessed by recording and reporting to the South Eastern Sydney Area Health Service Committee any adverse events (start and stop dates, relationship to the study medication, severity, frequency, action taken, and outcome).

Quality of Upper Extremity Skills Test (QUEST)

The primary outcome measure was two domains of the QUEST (dissociated movement and grasp) scored blind by one trained assessor from video footage of the QUEST (DeMatteo et al. 1992). Test authors report that the use of less than the total four domains is psychometrically sound. QUEST at 6 months was chosen because there was known sensitivity to capture change in CP, investigators were interested in whether BTX-A injection effect plus therapy outlasted known pharmacological effect timelines, there was a precedent for its use with young children (Fehlings et al. 2000), and psychometric properties were good (Hickey and Ziviani 1998). The total possible standard score across the two domains is 100.

Canadian Occupational Performance Measure (COPM)

Two trained, blinded occupational therapists administered and scored the COPM (Law et al. 1994), which had been adapted for use with children. COPM had been used to measure effectiveness of upper limb BTX-A intervention for children with CP (Boyd et al. 2003). Psychometric properties of the adapted instrument were generally good (Cusick et al. forthcoming). The total possible score was 20 (10 for performance and 10 for satisfaction).

Pediatric Evaluation of Disability Inventory (PEDI)

The PEDI (Haley et al. 1992) was scored from parental report interviews. The PEDI has robust psychometric properties (Feldman et al. 1990, Nichols and Case-Smith 1996) and has been used with children with spastic hemiplegic CP (Fehlings et al. 2000). The total possible score for self-care/ functional

Table II: Efficacy analysis

Measure	Baseline		1 mo		3 mo	
	Control score	BTX-A score	Control score	BTX-A score	Control score	BTX-A score
QUEST total	33.3 (2.6)	32.1 (2.4)	36.0 (2.7)	43.9 (3.3)	37.1 (2.6)	46.2 (3.5)
Family GAS	23.1 (0.6)	21.6 (0.9)	27.1 (1.4)	36.1 (2.8)	34.1 (2.0)	42.0 (2.2)
Therapist GAS	30.5 (1.8)	27.5 (1.3)	40.5 (2.6)	57.8 (3.0)	46.8 (2.7)	61.0 (3.8)
COPM performance	3.3 (0.3)	3.3 (0.3)	3.8 (0.3)	4.5 (0.2)	4.5 (0.3)	5.3 (0.3)
COPM satisfaction	3.5 (0.4)	3.8 (0.3)	4.1 (0.4)	5.1 (0.3)	4.7 (0.4)	5.8 (0.3)
PEDI functional skills	43.4 (3.1)	50.7 (3.0)	44.2 (2.9)	53.1 (2.5)	48.3 (2.4)	55.8 (2.5)
PEDI caregiver assistance	21.5 (2.7)	26.2 (2.3)	23.6 (2.4)	28.2 (1.8)	26.0 (2.0)	29.8 (1.7)
Ashworth						
Elbow flexors	2.3 (0.1)	2.2 (0.1)	2.3 (0.1)	1.4 (0.1)	2.1 (0.1)	1.4 (0.1)
Pronators	2.5 (0.1)	2.6 (0.1)	2.4 (0.1)	1.5 (0.1)	2.4 (0.1)	1.5 (0.1)
Wrist flexors	2.3 (0.1)	2.2 (0.1)	2.2 (0.1)	1.1 (0.1)	2.1 (0.1)	1.5 (0.1)
Wrist extensors	2.0 (0.0)	3.0 (0.0)	2.0 (0.0)	2.0 (0.0)	1.5 (0.5)	2.0 (0.0)
Finger flexors	2.2 (0.1)	2.4 (0.1)	2.2 (0.1)	1.4 (0.1)	2.2 (0.1)	1.6 (0.2)
Thumb adductor	2.2 (0.1)	2.2 (0.1)	2.2 (0.1)	1.1 (0.1)	2.2 (0.1)	1.6 (0.2)
Thumb opponens	2.1 (0.1)	2.2 (0.1)	2.1 (0.1)	1.0 (0.0)	2.1 (0.1)	1.4 (0.1)
Thumb flexors	2.0 (0.0)	2.3 (0.2)	2.0 (0.0)	1.2 (0.2)	1.8 (0.3)	2.0 (0.4)

^aTreatment effect is reported in terms of unit of measurement for each instrument. ^bThere were insufficient numbers for calculation. The *p* value given is that of repeat-measures analysis. Scores and effects are shown in brackets as mean. BTX-A, botulinum toxin A; QUEST, Quality of Upper Extremity Skills Test (DeMatteo et al. 1992); GAS, Goal Attainment Scaling (Kiresuk et al. 1994); COPM, Canadian Occupational Performance Measure (Law et al. 1994); PEDI, Pediatric Evaluation of Disability Inventory (Haley et al. 1992).

skills is 73, and for self-care caregiver assistance the maximum score is 40.

Goal Attainment Scaling (GAS)

Goal Attainment Scaling (Kiresuk et al. 1994) is recommended to identify clinically significant functional change after BTX-A injections (Russman et al. 1997) and has been used in other BTX-A upper limb trials (Boyd et al. 2003, Wallen et al. 2004). The family developed their own 'family GAS' of three to five goals before the administration of COPM. The goals and attainment levels were of their selection, design and priority, facilitated and later scored by two trained blinded occupational therapists. Another 'therapist GAS' was developed by an investigator; it identified functional tasks and levels of performance not covered elsewhere in other measures. Performance of 'therapy GAS' tasks was videoed and scored by a blind evaluator (dressing and toileting were not videoed because of child protection standards; parental report was used instead). There is no standardized total possible score; however, goal attainment across all goals is indicated by the 'T' score. A goal attainment T score of 50 (SD 10) equates to expected gains.

Ashworth Scale

The Ashworth Scale (Ashworth 1964) is sensitive to change from spasticity pharmacological management including BTX-A (Love et al. 2001). It was, therefore, used as a measure of the technical effect of the BTX-A. Reliability of the Ashworth Scale in elbow flexors is good (Bohannon and Smith 1987). Individual muscles are rated on a scale between 0 (normal) and 5 (most severe), with no total possible score.

Analysis of primary outcome measure

QUEST total score at 6 months was modelled by using linear regression; baseline QUEST score, age, and intervention assignment were covariates.

Table II: continued

		6 mo			
Control score	BTX-A score	Treatment effect ^a	95% CI	p	
39.6 (2.8)	40.7 (3.2)	7.7 (1.9)	4.0 to 11.5	<0.001	
40.1 (2.9)	46.8 (2.3)	7.5 (2.3)	2.9 to 12.1	0.001	
49.9 (2.7)	58.7 (3.4)	14 (3.5)	7.1 to 21.0	<0.001	
5.1 (0.4)	5.9 (0.3)	0.8 (0.3)	0.3 to 1.3	0.002	
5.4 (0.5)	6.2 (0.3)	0.8 (0.3)	0.2 to 1.4	0.007	
51.1 (2.6)	57.9 (2.2)	3.1 (1.4)	0.3 to 6.0	0.03	
26.7 (2.1)	32.0 (1.7)	1.9 (1.3)	-0.6 to 4.4	0.140	
2.0 (0.2)	1.9 (0.1)	-0.5 (0.1)	-0.7 to -0.4	<0.001	
2.4 (0.1)	2.2 (0.1)	-0.8 (0.1)	-1.0 to -0.6	<0.001	
2.3 (0.1)	1.9 (0.1)	-0.7 (0.1)	-0.9 to -0.5	<0.001	
1.5 (0.5)	2.0 (.)	0.3 (0.0)	0.3 to 0.3	^b	
2.2 (0.2)	2.1 (0.2)	-0.8 (0.1)	-0.9 to -0.6	<0.001	
2.1 (0.1)	2.0 (0.2)	-0.6 (0.1)	-0.8 to -0.4	<0.001	
2.1 (0.1)	2.1 (0.1)	-0.6 (0.1)	-0.8 to -0.5	<0.001	
1.3 (0.3)	2.2 (0.3)	-0.3 (0.1)	-0.4 to -0.1	0.001	

Analysis of secondary outcome measures

Secondary outcomes were changes in QUEST, Ashworth, family GAS, therapy GAS, COPM, and PEDI scores from baseline to 1, 3, and 6 months. Treatment effect sizes and standard errors were calculated with repeated-measures analyses (PROC GENMOD) adjusting for corresponding score baseline values, visit (as a categorical variable used because of the expectation of participant improvement over time) and age at baseline, and at 1, 3, and 6 months (with the exception of Ashworth scores). The estimated treatment effect was interpreted as the average treatment effect measured across the three post-baseline visits with a 95% confidence interval (CI). All tests were performed as two-tailed tests ($p \leq 0.01$). Another secondary outcome was the percentage of participants with at least 20% improvement in total QUEST scores over baseline at 1, 3, and 6 months. Two-sided Fisher's exact tests were used to assess significance.

Results

BETWEEN GROUP BASELINE ANALYSIS

There were no significant differences between groups in baseline QUEST, COPM, GAS (therapist or family), Ashworth measures, or self-reported history of involvement in therapy (physical or occupational; Table II). Baseline PEDI scores for caregiver assistance were significantly different, favouring intervention, which might possibly reflect their group allocation awareness, because BTX-A could reasonably be considered a 'high promise intervention' (Russman et al. 1997) and parent interviews might have permitted an expression of high hopes rather than a functional difference as other measures were not significantly different. During intervention, there was no difference in use of splinting (100% for each group) or contracture casting ($n=3$ in each group).

BETWEEN-GROUP OUTCOME ANALYSES

Table II summarizes study results in mean scores over time, and 6-month treatment effects and CIs for primary and secondary outcomes.

Safety

There were 31 adverse events reported by 15 participants and no between-group difference. No events were considered related to BTX-A by the South Eastern Sydney Area Health Service review panel.

QUEST

After adjusting for baseline score and age, differences in mean QUEST total scores between the treatment and control groups were significant at 1 month (9.7 points; 95% CI 5.5 to 13.8; $p < 0.001$) and 3 months (10.8 points; 95% CI 6.0 to 15.7; $p < 0.001$), but not at 6 months (2.7 points; SE 2.4; 95% CI -2.1 to 7.4; $p = 0.318$; Fig. 1). A significantly larger proportion of treatment group participants showed more than 20% change above baseline QUEST scores compared with the control group at 1 month (67 vs 19%; $p = 0.004$) and 3 months (71 vs 33%; $p = 0.03$), but not at 6 months (52 vs 48%; $p = 1.0$).

Children in the treatment group had better quality of upper limb movement sooner, even though all children improved with occupational therapy at higher levels than previously reported and all children sustained improvement at 6 months.

ASHWORTH

Greatest differences were seen at 1 and 3 months (Table II),

which suggests that the BTX-A was accurately localized.

FAMILY GAS

Table II illustrates that both the treatment and control groups increased average 'family' T scores over study duration. Results of the repeated-measures analysis showed a treatment effect size of 7.5 points (95% CI 2.9–12.1; $p=0.001$). This result shows the weighted average of treatment effects. It shows that all children made progress towards attaining goals developed by the family but the treatment group had consistently greater improvement that was sustained beyond the pharmacologically active period of BTX-A.

THERAPY GAS

Table II illustrates that both groups increased average 'therapist' T scores over the study duration. Results of repeated-measures analysis showed a treatment effect size of 14 points (95% CI 7.1–21.0; $p<0.001$). These results indicate that although all children made progress towards attaining goals developed by the therapist, the treatment group had the greatest improvement.

COPM

Both groups showed consistent improvement in performance and satisfaction scores (Table II). Results of repeated-measures analysis showed a treatment effect size for performance of 0.8 points (95% CI 0.3–1.3; $p=0.002$) and for satisfaction of 0.8 points (95% CI 0.2–1.4; $p=0.007$). These results indicate that although all children made consistent gains in function and their parents' level of satisfaction with their performance, the treatment group had consistently greater improvement.

PEDI

Both groups showed consistent improvement in functional skills and caregiver assistance (Table II). Results of the repeated-measures analysis showed a treatment effect size for functional skills of 3.1 points (95% CI 0.3–6.0; $p=0.03$) and for caregiver assistance of 1.9 points (95% CI -0.6–4.4; $p=0.140$). These results indicate that although all children made consistent gains in functional skills, the treatment group had greater improvement; they also show that although all children made gains in caregiver assistance scores, with scores being higher in the treatment group, they were not significantly different for the treatment group.

Discussion

BTX-A has already been shown to decrease spasticity in the hemiplegic upper limb and to enhance functional outcomes in children with spastic hemiplegic CP. This study complements previous study findings on BTX-A effects on upper limbs for children with CP. Our study was adequately powered, used measures directly targeting domains of interest, used blinded evaluation in most measures, and had therapy interventions that were consistently delivered and were based on best available evidence. The new finding is that although occupational therapy on its own is effective, clinical outcomes for children receiving occupational therapy are markedly enhanced by a single session of dual-mode localized BTX-A injection because it produces greater 1-month and 3-month gains in upper limb quality of movement, function, and spasticity, and greater 6-month gains in function. Children who receive BTX-A in addition to therapy, there-

fore, have greater clinical gain faster and this gain is sustained at 6 months. These short-term and long-term gains were made with lower doses and higher concentrations than previously reported, and with higher thresholds for clinical change required in QUEST scores (20% from baseline). Apart from this key result, findings related to administration technique, therapy programme, and injection candidate characteristics are worth comment.

The dual-mode localized administration technique seems to be an effective method for precise needle placement because low-dose, high-concentration injections had a marked clinical and 'technical' effect at 1 and 3 months. Because other non-invasive techniques such as manual or ultrasound localization are usually paired with a higher dose and lower concentrations, there may be merit in future research to compare invasive versus non-invasive localization techniques and different dose regimes. For now, it is clear that stimulation with electromyography provides enhanced precision in administration, offering the possibility of lower doses.

Therapy intervention was based on best available evidence and was delivered by one experienced therapist. This might explain the high level of improvement in quality of movement and function by all children in the study, including those who did not receive BTX-A injection. Improvement was greater than that previously reported in similar studies of younger children (Fehlings et al. 2000, Boyd et al. 2003, Wallen et al. 2004), and higher than the 4.5% change estimated to occur as a result of therapy intervention by QUEST test developers (DeMatteo et al. 1992). Although the effectiveness of therapy alone is a good result, the marked clinical benefit provided by BTX-A is important. It means that faster and greater functional gains can be made by children who have therapy if they receive BTX-A.

Injection candidate characteristics can also be considered in the light of this study. Exclusion and inclusion criteria were based on previous study findings (Corry et al. 1997, Fehlings et al. 2000) and they proved to be both practical and useful in sample selection because a uniform and positive

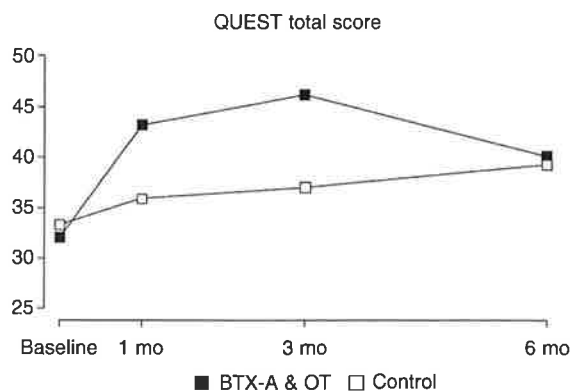


Figure 1: QUEST change over 6 months. QUEST, Quality of Upper Extremity Skills Test; BTX-A, botulinum toxin A; OT, occupational therapy.

response to BTX-A was demonstrated. These characteristics might, therefore, provide useful clinical guides for the selection of very young children with CP for BTX-A intervention, particularly when high efficacy is required, spasticity is not severe, therapy is received, and upper limb quality of movement and function are intervention goals.

LIMITATIONS AND RECOMMENDATIONS

Our study was limited by single evaluator blinding: both parent and child knew whether or not they were in the treatment group because placebo injections were not used. The study investigated only one injection administration technique. In practice the CP population of young children is quite diverse and the study inclusion and exclusion criteria were restrictive. This study used one injection, monitored for only 6 months, with occupational therapy intervention begun after baseline. The effect of repeat injections, previous occupational therapy, and longer-term outcomes of the single injection needs investigation.

Conclusion

Low-dose, high-concentration BTX-A injections localized with the use of both electromyography and stimulation seem clinically worthwhile for young children with CP, because they provide short-term quality of movement gains that are faster and greater than those generated by therapy alone, and better short-term and long-term functional gains are achieved.

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Competing interests

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