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ARTICLE

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## ABSTRACT

OBJECTIVES. The purpose of this work was to assess the effect of botulinum toxin A and occupational therapy compared with occupational therapy alone on body structure, activities participation, and self-perception in a sample of children (aged 3–16 years) with hemiplegic cerebral palsy recruited from a statewide register.

PATIENTS AND METHODS. Participants of this single-blind, randomized, controlled trial identified from a population-based cerebral palsy register received either an individually prescribed and localized injection of botulinum toxin A with 4 sessions of occupational therapy over 4 weeks (intervention) or occupational therapy alone (control). Outcomes were assessed from 2 domains of the World Health Organization International Classification of Functioning, Disability, and Health: body structure (Modified Ashworth Scale and Tardieu Scale) and activities participation (Assessment of Motor and Process Skills, Goal Attainment Scale, Pediatric Evaluation of Disability Inventory, and Pediatric Quality of Life Inventory). Self-perception was also measured.

RESULTS. All of the participants (intervention: $n = 21$; control: $n = 22$) provided data at baseline and 3 and 6 months. Mean age was 8.6 years; 23 were boys and 20 were girls. At 3 months, children allocated to receive the intervention performed significantly better in terms of body structure and activities participation. They reported improvements in self-perception for the global self-worth domain. At 6 months, the differences between the intervention and control groups persisted for the measures of body structure but not for activities participation or self-perception.

CONCLUSION. Botulinum toxin A injection combined with a low-intensity occupational therapy program achieves significant improvements in body structure, activity participation, and self-perception.

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**Key Words**
botulinum toxin A, cerebral palsy, hemiplegia, child preschool, child, adolescent, disability evaluations, self-concept, randomized, controlled trial, upper extremity

**Abbreviations**
CP— cerebral palsy
BTX-A— botulinum toxin A
GAS—Goal Attainment Scaling
MAS—Modified Ashworth Scale
AMPS—Assessment of Motor and Process Skills
ADL—activities of daily living
PEDI—Pediatric Evaluation of Disability Inventory
PedsQL—Pediatric Quality of Life Inventory
SAE—serious adverse event
CI— confidence interval

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CEREBRAL PALSY (CP) is defined as a nonprogressive lesion of the immature brain[1] resulting in disorders of movement and postures.[2] It is the most common physical disability in childhood,[3] with an incidence of 2 to 2.5 per 1000 live births.[3,4] In ~80% to 90% of children with CP, the motor deficit is spasticity.[4,5] In hemiplegic CP, almost all children achieve independent walking,[6] but many have significant difficulty in every day functional activities because of involvement of the upper limb[7] with more severe limitation in bimanual fine motor activity[8] and reduced motor ability with increasing age.[9] The effect of CP on self-esteem and body image is unclear, but there is evidence of reduced self-concept for adolescent girls with CP.[10] Reduced self-worth may be an issue among all children with CP; however, the magnitude of the deficit and the effectiveness of treatment programs are unknown.

Botulinum toxin A (BTX-A) injection into the upper limb of children with CP has been studied in several nonrandomized trials[11–16] with varying degrees of improvement in spasticity, cosmesis, and nonvalidated participation level outcome measures. In randomized trials involving children with hemiplegic CP, BTX-A injection into the upper limb has been shown to reduce muscle tone,[17–19] improve joint range of motion,[17,19,20] and improve some aspects of function.[18,19,21] Both Fehlings et al[21] and Lowe et al[19] demonstrated an improvement on the Quality of Upper Extremity Skills Test. However this measure, which is tested under verbal instruction, illustrates what the child can do and not what they actually do in real-life situations. Lowe et al[19] also used Goal Attainment Scaling (GAS) to demonstrate that function could improve, indicating a benefit favoring the intervention group. In both of these trials, therapy for the control group was undertaken, and the control group improved on the outcome measures from baseline, but there was no evaluation of the amount or type of therapy given. Two other studies investigating the effects of BTX-A injection in the upper limb quantified the amount of occupational therapy given.[18,20] In 1 study,[18] a modest dose of therapy (weekly therapy for 6 weeks) resulted in both intervention and control groups showing functional improvement from baseline. In the other study,[20] intensive therapy (30 minutes of therapy 3 times per week for 6 months) resulted in no changes from baseline for the primary outcome measure in both control and intervention groups, so the effect of therapy remains unclear.

Sufficient evidence to support routine treatment has been lacking.[22,23] There is a need to include reliable and valid outcomes that measure children's abilities to carry out necessary activities of daily living and meet specified goals[22] at different levels of functioning to evaluate the impact of treatment.[23]

The purpose of this trial was to assess the effect of an individually prescribed and localized injection of BTX-A and occupational therapy compared with occupational therapy alone on body structure, activities participation, and self-perception in a sample of children with hemiplegic CP.

## METHODS

### Setting and Participants

Children were recruited (June 2004 to September 2005) from the South Australian Cerebral Palsy Register,[24] which contains details of all of the children with CP (confirmed after physical examination) living in metropolitan, rural, and remote areas of South Australia. The study was approved by the research and ethics committees of the Women's and Children's Hospital and the Flinders Medical Centre, South Australia.

Children were eligible to participate if they met the following criteria: diagnosis of hemiplegic CP, aged 3 to 16 years, passive joint range of motion within defined limits (elbow extension to neutral, wrist extension to 30° past neutral with fingers extended, supination of the forearm of 30° past neutral, and thumb extension to neutral), ability to initiate movement of the fingers, and a Modified Ashworth Scale (MAS) spasticity score[25] of ≥2 on 4 at the elbow or wrist. Children were ineligible if they had received an injection of botulinum toxin in the upper limb ≤1 year before the study and in the lower limb ≤6 months before the study. Informed consent was obtained from parents (and children cognitively able to consent).

### Random Assignment

Random assignment occurred in blocks of 10. The random assignment schedule and envelopes (concealed, opaque, and foil lined) were prepared by an independent statistician using a computer-generated table of random numbers. The Pharmacy Department at the Repatriation General Hospital maintained the envelopes. The research assistant telephoned the Pharmacy Department to obtain the assignment group, organize the referral for occupational therapy, and, if applicable, referred to the pediatric rehabilitation specialist for scheduling of injection. Allocation was recorded in a logbook locked in a filing cabinet and was not revealed to the research occupational therapists at any time.

### Intervention Group

Children allocated to the intervention group received individually prescribed and localized injections of BTX-A into the affected upper limb and weekly occupational therapy for 4 weeks. Children were admitted to the day patient ward at the Women's and Children's Hospital or the Flinders Medical Centre for injection of the BTX-A under general anesthesia. A muscle stimulator[26] assisted with localization of the muscles injected, because this technique has been shown to greatly improve the accu-

racy of needle placement.[27] The muscle stimulator (electrical low frequency stimulator model ELF-001 from Gorman ProMed Pty, Ltd, Melbourne, Australia) is designed to deliver constant current pulses adjustable from 0 to 20 mA intensity with a fixed 0.3-millisecond duration at a rate of 3 pulses per second.

The maximal dose of BTX-A per muscle according to Russman et al[28] was followed; however, all of the muscles across the upper limb were injected if tone was affected (tone [MAS] = 0: the muscle was not injected; 1–1+/4: half the maximal dose was injected; 2–3/4: the maximal dose was injected). Total injected dose did not exceed 12 U/kg of body weight, to a maximum dose of 300 U of Botox (Allergan, Australia Pty Ltd). The dilution of botulinum toxin used was 100 U of Botox per milliliter of normal saline. Postinjection the children were allowed to leave the hospital once they were medically stable. Weekly 1-hour standardized occupational therapy sessions under the supervision of a pediatric occupational therapist were performed over 4 weeks. The focus of each therapy session was on upper-extremity weight bearing, ball skills, fine motor strengthening (through the use of resistive putty-based activities), and bilateral functional activities (which included activities assisting finger agility and dexterity). Before outcome assessment, participants were instructed to avoid revealing treatment allocation to the research staff.

### Control Group

The control group received the standardized occupational therapy program. No placebo injections were performed in the control group because of the requirement for general anesthesia.

### Data Collection and Instruments

Measures of body structure included a neurologic assessment, the MAS,[25] and the Tardieu Scale.[29] All of the measures were performed at baseline, 3 months, and 6 months by a pediatric rehabilitation specialist. Participants also reported whether they felt they were the same, worse, or better since the intervention with respect to function and cosmesis. All of the assessments performed by the pediatric rehabilitation specialist were unblinded. This occurred because, at the time of the study, there was only 1 rehabilitation specialist trained to inject botulinum toxin into the upper limb of children using the technique described, and this was also the only specialist available for data collection. Because the principle outcome measures were functional measures and assessments were blinded, the investigators felt that it was acceptable to proceed with the trial with this limitation.

Data for IQ was taken from the Cerebral Palsy Register and was completed for 41 participants (95%). Testing used a number of standardized tests for 28 participants (65%). Where a standardized test was not used, the assessor was asked to rate the level of intellectual function, and this occurred for 15 children (35%).

The primary outcome measures of activity participation were the Assessment of Motor and Process Skills (AMPS) and the GAS. Both measures were undertaken at baseline, 3 months, and 6 months by a trained assessor blind to treatment allocation.

The AMPS is a reliable and valid tool to measure instrumental (complex or domestic) activities of daily living (ADL).[30,31] In using the AMPS measure, key skills and actions that facilitate or hinder performance in ADL at the level of expected achievement are identified.[30] The assessment is undertaken in the person's usual environment[32] and is consistent with the person-environment-occupational approach of the revised International Classification of Functioning, Disability, and Health.[30] A more detailed account of the specific protocol used in this study is provided elsewhere.[9]

The GAS[33] is a sensitive measure used to assess individual goals after treatment[34] and is recommended for children undergoing BTX-A injection.[28] Desired outcomes are ranked from −2 (much less than expected outcome) to +2 (much greater than expected outcome). The scores are converted to a T score with 50 (SD: 10) as the expected or average outcome score.[35]

The Self-Perception Profile for Children[36] and the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children[37] are valid and reliable[37–39] measures used to evaluate children's self-perception. The Self-Perception Profile for Children is a 36-item scale for children ≥8 years of age and was designed to evaluate domain-specific judgments of children's perceived competence in the domains of scholastic competence, social acceptance, athletic competence, physical appearance, and behavioral competence, as well as a global perception of self-worth. The Scale of Perceived Competence and Social Acceptance for Young Children was designed for young children up to age 7 years. Twenty-four items evaluating self-perception are shown in picture form representing 2 ends of a continuum, and the child decides which they are most like. The scoring allows evaluation in 4 domains: cognitive competence, physical competence, peer acceptance, and maternal acceptance.[37]

Other measures assessed at baseline, 3 months, and 6 months by a blind assessor included the Self-Care Domain of the Pediatric Evaluation of Disability Inventory (PEDI)[40] and the Pediatric Quality of Life Inventory (PedsQL 4.0).[41] The PEDI was scored from parent interviews. The PedsQL was administered to all of the parents and children >4 years of age. Pain was reported at baseline and at the 3- and 6-month follow-up using a visual analog scale.

Serious adverse events (SAEs; an event that was life threatening, fatal, or resulted in hospitalization or permanent disability) were reported by participants and

their families at all of the follow-up assessments. They also reported any other event or complication that they felt was related to the procedure or to their involvement in the trial.

### Sample Size

Published AMPS data for children 3 to 12 years old were used to calculate the sample size required to observe an improvement of 0.5 on the AMPS logit scale.[30] The AMPS data report a mean of 1.63 and an SD of 0.58. We estimated that the number of children required to detect a significant difference between the 2 groups was 36 (18 per group; assuming power 80%, $\alpha = .05$ and a 1-sided test). To account for attrition, we increased the sample size by 20% to 44 (22 per group).

### Statistical Analysis

Analyses were on an intention-to-treat basis using SPSS 11.5 (SPSS Inc, Chicago, IL). Means and medians (95% confidence intervals [CIs]) were calculated according to data distribution. Comparisons between groups for categorical variables were made using the $\chi^2$ or Fisher's exact test. For group comparisons of continuous variables, the independent sample *t* test or the Mann-Whitney *U* test was used. A significance level of .05 was used throughout.

## RESULTS

### Study Population

Of the 143 children with hemiplegic CP (aged 3–16 years) identified from the South Australian Cerebral Palsy Register, 108 (76%) were assessed, and 51 (47%) were eligible to participate. Forty-three (84% of eligible children) consented and were randomly assigned (Fig 1). Twenty-two were randomly assigned to the control group and 21 to the intervention group. Follow-up data were obtained for all of the participants at 3 and 6 months.

### Baseline Comparisons

The demographic, functional, and quality-of-life characteristics of the study groups were similar at baseline (Table 1). The mean (95% CI) age was 8.6 (7.4–9.8) years. The majority of participants were boys ($n = 23$), had hemiplegia of the right side ($n = 25$), were left-hand dominant ($n = 25$), and were not receiving occupational therapy at the time of the study ($n = 27$). Twenty-one participants (49%) reported pain: 13 mild to moderate and 8 severe. The self-concept domain of athletic competence was significantly different at baseline, favoring the control group.

### Dose of BTX-A and Occupational Therapy

The mean (SD) units of Botox per kilogram of body weight injected per child was 8.0 U/kg (2.2) with a

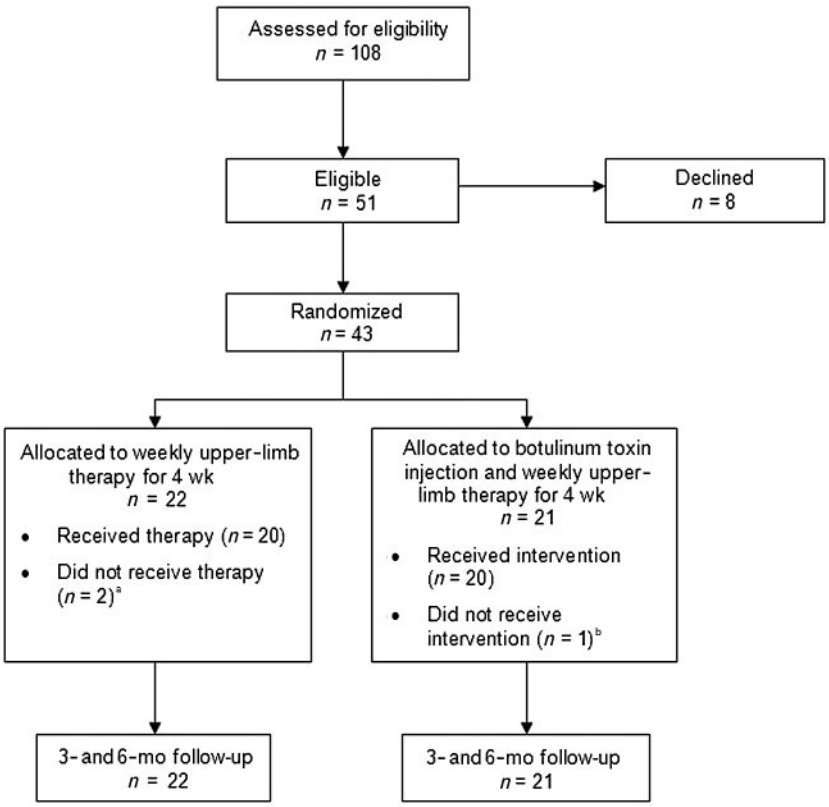


FIGURE 1
Flow of participants through each stage of the randomized, controlled trial. [a] After enrollment, 2 children did not undertake therapy, but intention-to-treat follow-up was completed. [b] After enrollment, the family refused intervention, but intention-to-treat follow-up was completed.

TABLE 1 **Baseline Characteristics of the Study Participants**

| Characteristics | Control ($n = 22$) | Intervention ($n = 21$) | $P$ |
|---|---|---|---|
| Demographic | | | |
| Age, mean (95% CI), y | 8.7 (7.0 to 10.4) | 8.4 (6.5 to 10.2) | .772[a] |
| Gender, male/female, *n* | 12/10 | 11/10 | .887[b] |
| Side of hemiplegia, right/left, *n* | 11/11 | 14/7 | .268[b] |
| Dominant hand, right/left, *n* | 11/11 | 7/14 | .385[b] |
| IQ, *n* | | | |
| Above average, >110 | 2 | 5 | .545[b] |
| Average, 90–109 | 10 | 9 | |
| Below average, 70–89 | 5 | 2 | |
| Cognitive impairment, <70 | 3 | 4 | |
| Body structure | | | |
| Tardieu[a] | | | |
| R2-R1, mean degrees (95% CI) | | | |
| Elbow | 68.8 (53.1 to 84.7) | 75.7 (61.7 to 89.7) | .503 |
| Wrist | 120.7 (93.7 to 147.7) | 95.9 (60.3 to 131.6) | .256 |
| MAS[c] | | | |
| Elbow, median (95% CI) | 2 (1+ to 2) | 2 (1+ to 2) | .725 |
| Wrist, median (95% CI) | 2 (2 to 2) | 2 (1+ to 2) | .201 |
| Activity participation | | | |
| PEDI, mean (95% CI)[a] | 55.2 (49.5 to 61.0) | 54.1 (46.8 to 61.4) | .801 |
| PEDsQL, mean (95% CI)[a] | | | |
| Parent | 54.7 (48.1 to 61.4) | 55.6 (47.1 to 64.1) | .982 |
| Child | 66.5 (59.3 to 73.7) | 71.9 (62.2 to 81.7) | .334 |
| AMPS[a] | | | |
| Motor, mean (95% CI) | 0.18 (−0.12 to 0.49) | 0.08 (−0.36 to 0.52) | .684 |
| Process, mean (95% CI) | 0.16 (0.22 to 0.53) | −0.20 (−0.75 to −0.36) | .276 |
| Self-concept[c,d] | | | |
| Median (95% CI) | | | |
| Athletic competence | 3.2 (2.7 to 3.5) | 2.6 (1.0 to 3.2) | .050 |
| Global self worth | 3.3 (3.0 to 3.7) | 3.5 (2.8 to 4.0) | .616 |

[a] Data are from an independent Student's *t* test.
[b] Data are from a Pearson $\chi^2$ test.
[c] Data are from a Mann-Whitney *U* test.
[d] Data include only older children ≥8 years old ($n = 22$).

minimum dose of 5.0 U/kg and maximum dose of 11.6 U/kg. The dose of occupational therapy received by each participant was equivalent, with no significant differences between the 2 groups for number of sessions (mean, 95% CI: control: 3.41, 3.39–3.43; intervention: 3.81, 3.80–3.82; $P = .240$), time (minutes) spent in therapy per session (mean, 95% CI: control: 50.22, 49.99–50.45; intervention: 51.38, 51.29–51.47; $P = .81$), or time (minutes) for activities within the sessions, which included weight bearing, ball skills, fine motor strengthening, and bilateral functional activities.

### Activity Participation Measures

At 3 months, children receiving the botulinum toxin injection achieved greater improvements in the GAS and global self-worth than children receiving occupational therapy alone but were worse off for athletic competence (Table 2). At 6 months, none of these differences persisted. Both groups improved their motor and process skill ability of the AMPS from baseline (Fig 2); however, the differences between the groups were not significant. Similarly, there were no significant differences between the groups in the PEDI or PedsQL.

### Body Structure Measures

At 3 and 6 months, elbow and wrist tone were significantly improved in the intervention group compared with the control group. Similarly, elbow and wrist spasticity improved significantly in the children who received the intervention at 3 and 6 months compared with the control group.

Subjective evaluation of the effects of treatment on function and cosmesis (esthetics) at 3 and 6 months revealed significant differences at both times for function, favoring the intervention participants. For cosmetic appearance more children in the intervention group improved at 3 months compared with the control group (14 of 21 vs 1 of 22; $P < .000$), but this significant difference did not persist at 6 months (4 of 21 intervention versus 1 of 22 control; $P = .185$)

At 3 months, fewer children reported pain ($n = 2$, intervention group; $n = 2$, control group) than at baseline. Both groups had 1 participant with mild-to-moderate pain and 1 each with severe-to-overwhelming pain related to falls affecting the upper limb, which resolved spontaneously. At 6 months, 2 children reported mild-to-moderate pain, 1 in each of the study groups.

TABLE 2 **Outcome of the Study Participants**

| Characteristic | Control ($n = 22$) | Intervention ($n = 21$) | *P* |
|---|---|---|---|
| AMPS[a] | | | |
| Motor, mean (95% CI) | | | |
| 3 mo | 0.72 (0.44 to 0.99) | 0.50 (0.14 to 0.86) | .326 |
| 6 mo | 0.83 (0.62 to 1.03) | 0.68 (0.25 to 1.12) | .518 |
| Process, mean (95% CI) | | | |
| 3 mo | 0.51 (0.18 to 0.84) | 0.37 (0.00 to 0.74) | .563 |
| 6 mo | 0.70 (0.41 to 0.99) | 0.52 (0.11 to 0.93) | .465 |
| GAS, mean (95% CI)[a] | | | |
| 3 mo | 31.6 (27.1 to 36.0) | 44.6 (38.2 to 50.9) | .001 |
| 6 mo | 39.2 (32.5 to 46.0) | 43.1 (34.9 to 51.2) | .453 |
| Self-concept[b,c] | | | |
| Global self worth | | | |
| 3 mo | 3.0 (3.0 to 3.5) | 3.7 (3.3 to 4.0) | .030 |
| 6 mo | 3.3 (3.0 to 3.8) | 3.8 (3.0 to 4.0) | .149 |
| Athletic competence | | | |
| 3 mo | 3.0 (2.7 to 3.7) | 2.5 (2.2 to 2.8) | .016 |
| 6 mo | 3.2 (2.7 to 3.5) | 3.2 (2.2 to 3.7) | .474 |
| PEDI, mean (95% CI)[a] | | | |
| 3 mo | 59.7 (54.4 to 65.0) | 54.8 (48.6 to 61.0) | .214 |
| 6 mo | 59.6 (54.5 to 64.7) | 58.8 (52.5 to 65.1) | .842 |
| PEDsQL, mean (95% CI)[a] | | | |
| 3 mo | | | |
| Total score, parent | 60.3 (52.9 to 67.6) | 56.4 (45.7 to 67.0) | .976 |
| Total score, child | 67.8 (59.0 to 76.6) | 64.8 (56.7 to 73.0) | .800 |
| 6 mo | | | |
| Total score, parent | 60.0 (52.6 to 67.4) | 60.6 (52.1 to 69.1) | .998 |
| Total score, child | 72.2 (64.0 to 80.4) | 73.5 (62.5 to 84.6) | .535 |
| Tardieu, mean degrees (95% CI)[a] | | | |
| 3 mo R2-R1 | | | |
| Elbow | 99.7 (61.7 to 137.7) | 9.0 (−9.83 to 27.8) | .000 |
| Wrist | 122.6 (95.6 to 149.7) | 15.0 (−6.8 to 36.8) | .000 |
| 6 mo R2-R1 | | | |
| Elbow | 66.4 (58.0 to 74.8) | 39.5 (22.6 to 56.4) | .006 |
| Wrist | 142.8 (115.3 to 170.3) | 31.0 (1.4 to 60.6) | .000 |
| MAS scores, median (95% CI)[a] | | | |
| 3 mo | | | |
| Elbow | 2 (1 to 2) | 1 (1 to 1) | .000 |
| Wrist | 2 (1+ to 2) | 1 (0 to 1) | .000 |
| 6 mo | | | |
| Elbow | 2 (1+ to 2) | 1+ (1 to 1+) | .001 |
| Wrist | 2 (1+ to 2) | 1+ (1 to 1+) | .000 |
| Reported functional effects[d] | | | |
| 3 mo | | | |
| Worse | 2 | 1 | .000 |
| No change | 15 | 1 | |
| Better | 3 | 19 | |
| 6 mo | | | |
| Worse | 1 | 0 | .001 |
| No change | 14 | 3 | |
| Better | 6 | 18 | |

[a] Data are from an independent Student's *t* test.
[b] All other domains showed no significant differences.
[c] Data are from a Mann-Whitney *U* test.
[d] Data are from a Pearson $\chi^2$ test.

## Safety

There were 29 adverse events reported by 20 participants over 6 months. Five SAEs were reported by control participants (2 hospital admissions for seizures in 1 child with epilepsy and 3 hospital admissions for medical reasons in another). There were no minor adverse events reported by the control group. There were 23 adverse events that occurred in the intervention group, 1 of which was an SAE in a child with epilepsy (admission to hospital after a seizure). The most frequently reported adverse events during the study were feeling unwell after the anesthetic (vomiting and cough) in 4 children

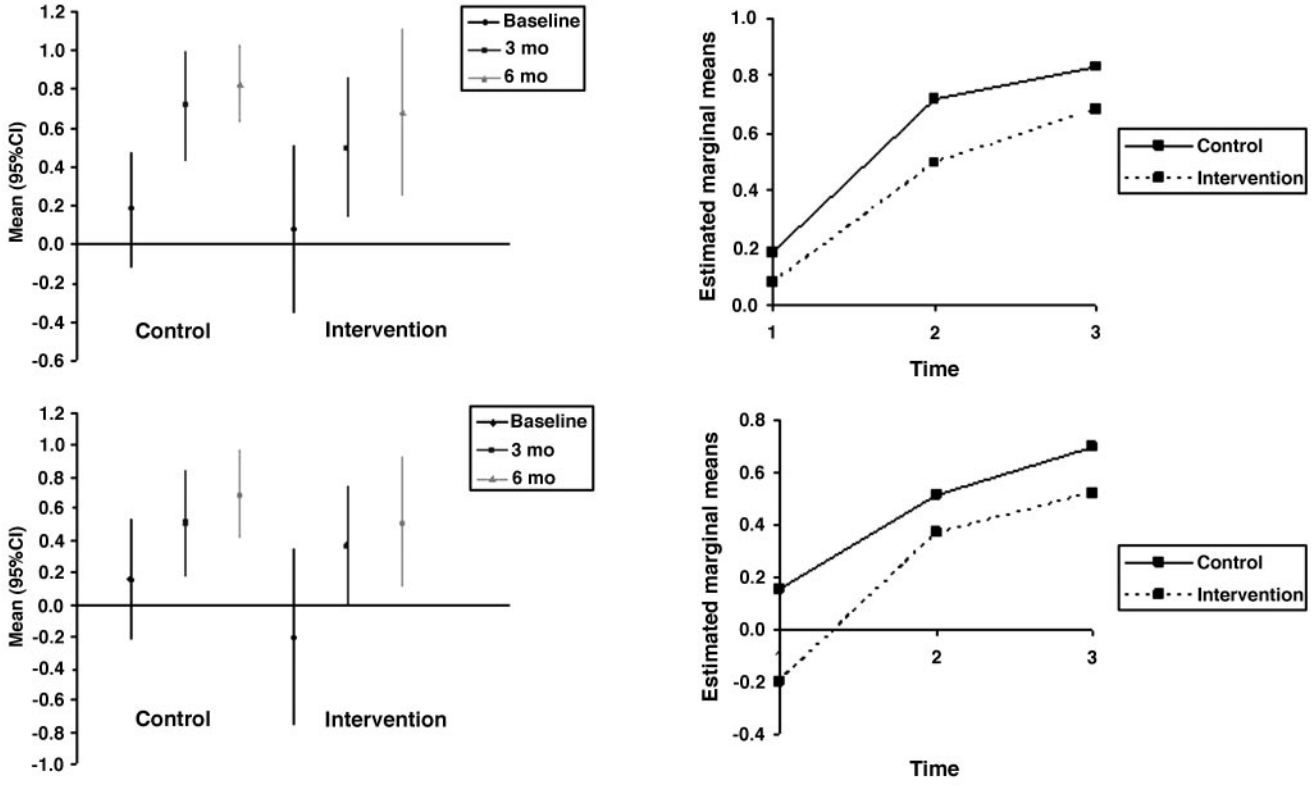


FIGURE 2
Estimated marginal means and 95% CIs for ADL motor scores (top) and ADL process scores (bottom) for treatment versus control groups at baseline, 3 months, and 6 months are shown.

and excessive weakness in the injected limb in 5 children, which was prolonged in 2 of the 5. Headache was reported by 2 participants. Flu-like symptoms were experienced by 1 child for 1 day. A fainting episode experienced by 1 child occurred on a hot day, and he recovered with rest and fluids. He had experienced these episodes in the past. One adolescent participant experienced anxiety, and 1 experienced depression, but each had similar episodes in the past, and both recovered without specific intervention. One child experience alopecia and had skin scrapings, which confirmed fungal infection, and this was treated. The family of 1 child with fatigue felt that this was related to activities at the end of the school term.

## DISCUSSION

This single-blind, randomized, controlled clinical trial provides modest support for the use of upper-limb BTX-A injection and therapy in children with hemiplegic CP. When compared with the control group, we found a statistically significant improvement in body structure at 3 and 6 months, as well as statistically significant improvements in activity participation level function on the GAS and global self-worth at 3 months.

The group that received therapy and botulinum toxin experienced an increase in self-worth, whereas the therapy alone group experienced a decrease in this outcome measure. It is possible that the decrease in self-worth in the therapy-alone group resulted from an increased focus on achieving functional outcomes, whereas there was in fact no real shift in spasticity or tone.

The improvements in self-worth are important given the critical role that self-esteem has in development.[42] Children with hemiplegia are more likely to function in mainstream school environments alongside their typically developing peers when compared with other CP types,[43] and improvements in self-worth are likely to influence their socialization, peer relations, and other areas of functioning. The use of BTX-A has been noted to enhance self-esteem by diminishing inappropriate motor responses[44]; however, these were not evaluated in our study. A systematic review of studies that have evaluated self-concept in groups of children with CP[10] concluded that adolescent girls with CP have a lower self-esteem than girls without disability, but there was insufficient evidence to conclude that children with CP in general have lower self-esteem than their nonaffected peers. Our study has shown that self-esteem can be positively influenced and should be measured in future studies evaluating interventions in children with CP.

In light of the findings in improved self-worth, it is interesting that there were no reported changes in quality of life. However, quality of life may depend on multiple factors not influenced by the intervention or may

reflect a response shift with children's internal standards and values changing over time.[45,46]

Although we found a significant difference in athletic competence at 3 months, favoring the control group, this did not persist to 6 months when both groups improved. Athletic competence in the control group was significantly better at baseline, which may explain the significant difference at 3 months and is possibly a result of type 1 error. Alternatively, the tone-reducing effects of the BTX-A may have altered the child's perceived ability to perform at his or her usual level of athletic competence. This potential effect requires additional investigation to clarify the preinjection counseling of children and their families. For example, in the context of competitive sporting activities, children and their families may elect to alter the timing of injections to minimize the impact of these changes.

The improvement in the GAS outcome measure for the intervention group at 3 months was statistically significant but not at 6 months because of the control group improving between 3 and 6 months. Children in the intervention group reached their desired goals sooner than the control group and then stabilized, a finding that is consistent with previous work.[19] The ability for the intervention to allow the child to realize their stated goals more quickly may have widespread positive effects in relation to their sense of achievement and self-perception and is supported by our finding that global self-worth was also significantly better for the intervention group at this time point. Although results of the PEDI did not improve for the intervention group at 3 months, they did for the control group despite not achieving their stated goals as measured by the GAS. This finding is interesting and difficult to explain, but there were no statistically significant differences in the PEDI at either time point.

Our results support the findings of previous studies on the effect of BTX-A on tone and spasticity.[14,17,19] The duration of the effect was well beyond the published therapeutic effect of the botulinum toxin, being 12 to 16 weeks of clinically useful relaxation.[4] The prolonged duration of effect may relate to the assessment for tone and spasticity being unblinded at 3 and 6 months or that we injected muscles that may not routinely be injected (tone $<2$ on a MAS), although this method was not adopted by previous investigators, who also reported a prolonged effect.[14,19] There may have been an augmenting effect provided by the occupational therapy. Although there is general agreement that the physical modalities must continue after injection of BTX-A to maximize the treatment episode,[47,48] the combined effects of BTX-A injection and therapy remain unclear and warrant additional investigation.[49] We quantified the amount of therapy received by all of the participants, but comparison to a true control group (ie, those who received no therapy) was not undertaken.

In general, the injection procedure was well tolerated. The 2 participants who had hospital admissions for prolonged seizures (1 intervention and 1 control) had a history of epileptic seizures before inclusion in the study. One subject in the control group had 3 admissions to hospital for unrelated medical reasons, but this child recovered fully on each occasion. The children experiencing the fainting, fatigue, anxiety, and depression had these problems in the past. The child with the alopecia recovered fully. The remaining adverse events were relatively minor and self-limited and are consistent with the known adverse events occurring with general anesthetic[50] and BTX-A injection.[28,51] Weakness experienced by 2 participants was prolonged. Excessive weakness has been reported previously.[14,17] Prolonged atrophy experienced in masseteric hypertrophy after injection of BTX-A $\leq$12 months is known to occur,[52] but how this relates to the duration of effect of injection in other muscles is unclear. The individualized injection plans used in this clinical trial resulted in the treatment of muscles affected by a lesser degree of spasticity (MAS 1–1+), which may also be a factor.

A high incidence of pain was reported at the initial assessment. Previous studies have reported a similar incidence of pain in children with CP.[53–55] Regardless of where the pain originated, it improved over time for both the treatment and control groups. This is an important finding, and additional evaluation of pain and its treatment in this population of children is required.

Limitations of this study include the inability to give placebo, the single-blinded nature of follow-up, and the lack of true control subjects who received no therapy. Children and their families knew their assignment group. This may have led to unintentional disclosure, which may have influenced the results. These methodologic problems in pediatric research are difficult to overcome.[56] Moreover, it is argued that drug trials should test medication against standard therapy and not placebo alone.[57] Children in this trial were a subgroup of children with hemiplegic CP and, in general, when considering the inclusion criteria for the trial, could be considered less severely affected.

## CONCLUSIONS

Botulinum toxin injected into the affected upper limb of children with hemiplegic CP and a low-intensity program of occupational therapy achieves significant improvements in body structure, activity participation, and self-perception. This study adds to previous studies investigating the effects of injection of botulinum toxin in the upper limb of children with CP but is unique given the findings related to improvement in self-worth. Given the relatively short-term improvements over the control group, which were sustained to 6 months at a greater (but not statistically significant) value for self-worth, clinicians can better inform children and their families

about the potential benefits weighed against the inconvenience and cost of providing this treatment. Furthermore, the potential for repeated injections to sustain the significant improvements found at 3 months warrants additional investigation.


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# Upper-Limb Botulinum Toxin A Injection and Occupational Therapy in Children With Hemiplegic Cerebral Palsy Identified From a Population Register: A Single-Blind, Randomized, Controlled Trial

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