

Title:

AACPDM systematic review of the effectiveness of therapy for children with cerebral palsy following botulinum toxin-A injections.

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Objective

The objective of the American Academy for Cerebral Palsy and Developmental Medicine (AAPDM) systematic review is to provide the biomedical research and clinical practice communities with the current state of evidence about various interventions for the management of developmental disabilities. AAPDM systematic reviews aggregate all that has been published about outcomes of an intervention for a medical condition, gauge the credibility (i.e., strength of the internal validity) of that evidence, and identify gaps in our scientific knowledge. The original version of these reports is published in The AAPDM Database of systematic reviews on the internet at www.aacpdm.org. The AAPDM reviews are not evidence-based "practice guidelines". As yet, the bodies of evidence in developmental disabilities are neither robust nor comprehensive enough to allow confident generalization to groups of people-at-large, a prerequisite for evidence-based practice guidelines. Absence of evidence of effectiveness in a systematic review should not be

construed as proof that a treatment is not effective; rather, it may reflect areas in which more meaningful research is needed.

Disclosure

Every effort has been made to assure that AACPDM systematic reviews are free from any real or perceived bias. The Academy's editorial review panel is a multidisciplinary group comprised of the current members of the AACPDM Treatment Outcomes Committee who serve three-year rotating terms. Potential conflicts of interest by authors and reviewers have been disclosed and are documented in The AACPDM database of systematic reviews. The Treatment Outcomes Committee is charged and overseen by the AACPDM Board of Directors with the task of developing systematic reviews and operates under an approved methodology of systematic review of the scientific literature and under approved procedures.¹ Final sanction for each report is granted by the Board.

Consensus Process

The review authors organize intervention outcomes in a predefined manner and answer predefined questions to describe the scientific evidence. Members of the editorial review panel give their input and resolve any differing opinions to reach agreement about statements made therein on behalf of the Academy. Nevertheless, the data in an AACPDM systematic review can be interpreted differently, depending on people's perspectives. Please consider the statements presented carefully.

Effects of therapy for children with CP following botulinum toxin-A injections

Cerebral palsy (CP) frequently produces motor disorders, including hypertonia.² Hypertonia is the increased passive resistance to stretch of a muscle group by external movement.³

Hypertonicity in children with cerebral palsy is often managed using medications to decrease spasticity, including botulinum toxin A (BTX-A). BTX-A is widely used⁴ and there have been a number of open-label and masked randomised controlled studies that confirm efficacy in the lower and upper limbs (e.g., Corry, Cosgrove, Walsh, et al.⁵; Flett, Stern, Waddy, et al.⁶). Research papers cite the need for such therapy management in conjunction with medical treatments for spasticity.⁷⁻¹¹ There is little evidence, however, regarding the value of adding therapy to pharmaceutical intervention.¹²

Whilst it has been suggested that the decrease in spasticity brought on by the medical interventions may potentiate the effect of therapy interventions to manage mechanical components of hypertonicity,^{7,13-15} there is little or no published evidence in support of this position. Current therapy practices for hypertonicity management following medical treatment of spasticity are based on clinical reasoning. This clinical reasoning is based on a developing literature base which supports these same interventions for children with CP who have not received medical intervention for spasticity. Physical and occupational therapy interventions used to address hypertonicity in conjunction with BTX-A include prolonged stretch, brief stretch (range of motion exercise), serial casting, splinting/orthotics, motor training, and strength training.¹⁶ Knowledge on the absolute and relative efficacy of BTX-A used in conjunction with such therapy techniques versus BTX-A alone is incomplete.^{15,17}

Method

INCLUSION CRITERIA

The intervention, *therapy*, includes occupational or physical therapy interventions such as prolonged stretch, brief stretch, range of motion exercises, serial casting, splinting/orthotics, motor training, and strengthening regimes.

This review includes only studies in which participants were children and youth (birth to 18 years) with cerebral palsy who had received BTX-A injections to either their upper or lower extremities. *Cerebral palsy* has traditionally been described as an evolving disorder of motor function secondary to a non-progressive pathology of the immature brain and is characterized by abnormalities of movement (i.e., spasticity, athetosis, chorea, dystonia, and ataxia)¹⁸.

Two-thirds of individuals with cerebral palsy have spasticity, either alone or in combination with the other movement abnormalities. The evidence table includes studies whose subjects were primarily individuals diagnosed with cerebral palsy with spasticity, alone or in combination with other types of abnormal movement. This review excludes studies of spasticity of spinal origin (e.g., multiple sclerosis or spinal cord injury) or of cerebral origin due primarily to other causes such as traumatic brain injury.

All participants in included studies received botulinum toxin A injections to muscle/s of their upper or lower extremities. This review excludes studies of the efficacy of injections of botulinum toxin A without therapy, and studies in which the effect of therapy following botulinum toxin A injections to muscle groups was evaluated for areas other than the upper or lower extremities (for example, the face).

LITERATURE SEARCH

The literature search was limited to published studies, full-text available in English and included the following electronic databases: MEDLINE (1956 through September 2003), CINAHL (1983 through September 2003), EMBASE (1980 to September 2003), Database of Reviews of Effectiveness (DARE), The Physiotherapy Evidence Database (PEDro^a), Science Citation Index, Australasian Medical Index, Best Evidence, Cochrane Database of Systematic Reviews^b (2nd quarter 2003), Science Citation Index (SCI), and Social Sciences Citation Index (SSCI). Reference lists in studies and review articles were also hand searched for citation tracking purposes. Unpublished, non-peer reviewed sources were excluded in line with AACPDPM review policy and procedures. The exploded MEDLINE terms used for searching were physical therapy, physical therapy techniques, occupational therapy, exercise movement techniques, exercise therapy, rehabilitation exercise, splints, casts, cerebral palsy, botulinum toxin, as well as types of studies (e.g. clinical trials). One author completed all searching.

Organization of evidence

AACDPM guidelines for classifying the outcomes were followed.¹ Each outcome measure was classified according to the component of ICF represented (Table 1). ICF is a classification that facilitates the measurement, management, and research of rehabilitation outcomes and minimizes the barriers between medical and social models of rehabilitation.¹⁹ The level of evidence of each study was determined (Table 2). Levels of evidence and other quality-rating schemes start with a hierarchy of research designs that range from the greatest

^a www.pedro.com.au

^b www.cochrane.org/

to least ability to reduce bias, and conclude with assessment of the soundness with which the research was carried out. Generally speaking, Level I studies produce the strongest and most definitive evidence. Level II studies produce tentative conclusions. Levels III and IV merely suggest causation. No conclusions regarding treatment efficacy can be drawn from Level V evidence.¹

Two reviewers independently read articles, completed a summary data form which documented level of evidence, conduct and summary information in line with AACPDMM methodology. If there was a discrepancy a third reviewer independently abstracted the data to reach consensus.

Summary of studies

Of the 229 papers retrieved during the search, 24 studies were identified that met the criteria for appraisal. Reasons for exclusion of 205 papers were: data contained children with diagnoses other than cerebral palsy or subjects were not children (n=46); intervention was not BTX-A with therapy (n=139); paper was second publication of same data (n=4); and paper was not in English language (n=16). Upon examination, nine of the 24 citations were research studies in which therapy techniques were used with children with CP who had received BTX-A injections to their upper or lower extremities. The remaining papers were Level V evidence, opinion or review papers without explicit appraisal. Table III summarizes the nine studies included in the review.

Eight citations investigated the effects of therapy on children who had received BTX-A to their lower limbs: one study used a randomized controlled design to investigate the effects of electrical stimulation after BTX-A,²⁰ three studies investigated the effect of casting post-BTX-A,²¹⁻²³ and four investigated the combined effect of physical therapy plus orthoses and/or casting.²⁴⁻²⁷ There was only one citation which investigated the effect of therapy on children who had received BTX-A to their upper limbs, this study investigated BTX-A plus occupational therapy (Friedman et al, 2000).²⁷ Only three studies used control groups, and only two of these allowed comparison of receiving BTX-A alone to BTX-A plus therapy.^{20,21} The remaining study using a control group design²² compared casting pre-BTX-A injection to casting post-BTX-A injection. The remaining five studies compared status before and after treatment with no control condition.²³⁻²⁷

Summary of results

Table V displays each of the outcomes that were investigated in the studies, the component of health which would be affected, the measure that was used to evaluate the outcome, the result of that measure and the inferential statistical data. Caution is advised concerning the correct interpretation of results that were not statistically significant since results may be *ns* because of lack of adequate power in the study. The power of a study is the probability that the study, given its design and sample size, can detect a true difference of a predetermined magnitude (effect size). In the absence of a power calculation in a study description, there is always the possibility that a true difference existed between the two conditions being compared, but that there was inadequate power to detect the difference. None of the included studies reported power calculations; thus their power is unknown and any *ns* results are more appropriately regarded as inconclusive, rather than negative or results of no difference.

Adverse effects and medical complications

None of the included studies reported adverse effects or medical complications for participants.

Analysis and discussion of the evidence

1. WHAT EVIDENCE EXISTS ABOUT THE EFFECTS OF THERAPY AT THE COMPONENTS OF BODY FUNCTION AND BODY STRUCTURE?

Spasticity

Only one study measured spastic signs, using the Ashworth Scale and deep tendon reflexes.²⁰

This level II study found no change in clinical measurements of spasticity or ankle

stiffness.²⁰ Findings from lower level studies appraised as part of this review were not consistent with this higher level study: six results indicated improvement in ratings of spasticity, however it must be noted that each study investigated different therapy interventions, and therefore data from one study would not be expected to be able to predict the effect that a different intervention might have on signs of spasticity. For instance, two lower level studies provide evidence that a combination of BTX-A injections and therapy, which included stretching exercises, effectively reduced spasticity (reductions of an average of 1.6 points on Ashworth Scale²⁴, and 2.7 points on Modified Ashworth scale (MAS)).²⁷

Range of movement

Range of movement is evaluated following provision of therapy to children with CP since improvements in range of movement are theoretically expected to carry over automatically to improvements in gait and functional participation activities. Three studies provided serial casting to children who have received lower limb BTX-A injections.^{21,22,26} Data from the two “moderate” quality level III studies showed that a short period of casting improves passive range of motion and ankle kinetics,²¹ and that it makes no difference if such casting is provided immediately prior to or following BTX-A injections.²² There is no high level evidence to suggest end-points for serial casting. Nor is there high level evidence investigating the outcome of other therapy interventions to increase range of movement of joints following BTX-A, despite their common use in clinical practice (for example, hand splinting).

Gait Parameters– ankle moment, ankle quotient

Whilst review articles frequently recommend the use of electrical stimulation to enhance sensory awareness and facilitate motor activity (e.g., Autii-Ramo⁸; Suputtitada²⁷; Leach²⁹; Hart³⁰), there is level II evidence that electrical stimulation for 30minutes, 6 times a day for 3 days post lower-limb BTX-A had no significant effect on gait parameters.²⁰ Analysis indicated no difference between participants who received electrical stimulation and those who did not; results were not statistically significant however, and group size may therefore have influenced the outcome since none of the included studies in this review reported power calculations.

Other aspects of impairment

There were no studies with Level III evidence or higher which measured the effect of therapy on strength. It is likely that this is reflective of the therapy provided in the included studies. There is lower level evidence (level IV- evidence based on case series without control group) which reported improved upper extremity function following the provision of agonist muscle strengthening programs given as part of occupational therapy after upper limb BTX-A injections²⁸

2. WHAT EVIDENCE IS THERE ABOUT THERAPY EFFECTS ON OTHER ICF COMPONENTS

No studies have investigated the effect of therapy provided following BTX-A injections to the upper or lower extremities on outcomes at the components of activity/participation or environment. Although all higher level studies reported the outcome of gait, the measures

used all evaluated gait parameters at the level of impairment or body function, not activity participation.^{20,21,22} A wide range of measures have been developed to measure aspects of disability of children, some developed to assess the impact of cerebral palsy (for example Gross Motor Function Measure³¹) and others designed to capture core dimensions across various conditions (for example the Pediatric Evaluation of Disability Inventory (PEDI)³²). In addition to measuring activity/participation the PEDI address the domain of the environment by including content related to modifying activities and participation.³³ Outcome measures which would provide evidence about the effects of therapy on ICF components other than body structure/function do exist, despite not being used in research reviewed for this systematic review.

Contextual factors

Clinical reasoning suggests that outcomes such as caregiver burden, financial cost, and improved cosmesis may have an indirect effect on the individual. However, the level IV study by Friedman et al²⁸ was the only instance where appearance and ease of managing the child's limb were assessed. No studies to date have measured the financial cost of providing therapy to children with CP who had received BTX-A. The limited, low level of evidence is able to provide only a suggestion, at best, that providing upper extremity therapy to children following BTX-A may improve appearance and make managing the upper extremity easier from a caregiver perspective.

3. WHAT EVIDENCE EXISTS FOR LINKAGES OF EFFECTS WITHIN AND BETWEEN ICF COMPONENTS ?

Highlighting results from all three appraised studies (level III evidence and above) appears to suggest that researchers believe that reduced impairment may be linked with improvement in activity outcomes, specifically that improved gait parameters are linked to improved gait.²¹ As discussed earlier, existing research has only evaluated gait at the level of impairment or body function, not activity participation^{20,21,22} which does not allow for evaluation of linkages between and across ICF dimensions.

4. WHAT KINDS AND MAGNITUDE OF COMPLICATIONS HAVE BEEN DOCUMENTED?

Complications and side effects have been documented elsewhere for botulinum toxin³⁴ as well as for some of the reviewed therapies, for example serial casting.^{35,36} Despite the risk of complications when using these interventions, no complications or adverse events were reported in the published studies reviewed. It is therefore not possible to discuss risks and complications from the published data that is summarized in Table V.

Summary and directions for future research

Credibility of results depends on methodologically robust research (see Table II). The levels of evidence indicate the extent to which the studies are more likely to inform than to mislead us. This body of evidence contains only one study of level II evidence about the non-significant effect of using electrical stimulation following BTX-A injections,²⁰ and one study that provide Level III evidence about reduction of spasticity and improved gait with serial

casting following BTX-A.²⁰ There is also Level III evidence about the equivalence of casting before or after BTX-A injections for the improvement of range of movement and gait.²² Otherwise, the research methodology of the overall body of evidence is weak for several reasons: only 236 participants were included across studies; none of the 9 included studies provided sample size calculation data to calculate the probability of chance findings; over 85% lacked a comparative control group and only one study (representing <5%) was a randomised controlled study; two-thirds of the research studies were capable of producing only Levels IV and V evidence; and over half of all retrieved papers which met the inclusion criteria of this review were excluded without appraisal for being Level V evidence

The main finding of this systematic review, therefore, is the paucity of evidence for the use of therapy following BTX-A injections in children with cerebral palsy. Further trials, utilising appropriate methods, are required before conclusions can be drawn about the effectiveness of individual therapy interventions following BTX-A injection. In considering the available evidence, therapy interventions do not have a high level or quality of evidence in support of their use following BTX-A. Since BTX-A is generally considered a concomitant treatment³⁷ it is of concern that the availability of evidence to support therapy given post-injection remains poor.

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Table I: ICF Components and Definitions

ICF Component	Definition
Body Function	Body functions are the physiological functions of body systems include psychological functions
Body Structure	Body Structures are anatomical parts of the body such as organs, limbs and their components
Activity	Activity is the execution of a task or action by an individual
Participation	Participation is involvement in a life situation
Context/Environmental Factors	Environmental factors make up the physical, social and attitudinal environment in which people live and conduct their lives

Table II: Levels of Evidence for Studies

Level	<i>Intervention (Group) studies</i>
I	Systematic Review of randomized controlled trials (RCTs) Large RCTs (with narrow confidence intervals) (n >100)
II	Smaller RCTs (with wider confidence intervals) (n <100) Systematic Reviews of cohort studies “Outcomes research” (very large ecologic studies)
III	Cohort studies(must have concurrent control group) Systematic Reviews of Case Control Studies
IV	Case series Cohort study without concurrent control group (e.g. with historical control group) Case-control study
V	Expert Opinion Case Study or report Bench research Expert opinion based on theory or physiologic research Common sense/anecdotes

Table III Summary of Studies: Interventions and Participants

Study	Level of evidence <i>Research design</i>	Therapy Intervention	Control Intervention	Population	Total n	Ages
<i>Lower Limb Studies</i>						
Molenaers et al [23]	V <i>Expert opinion based on retrospective chart audit</i>	Short-leg casting and/or orthotics	Not applicable	Children with spastic CP: diplegia (n=16) & hemiplegia (n=17)	33	Not reported
Molenaers et al [26]	IV <i>Case series</i>	Physiotherapy (three to five sessions per week)	Not applicable	Diplegic (n=8), hemiplegic (n=2), & quadriplegic (n=10) CP	20	Range 3 to 16 years.
Boyd et al [21]	III <i>Cohort study with concurrent control group (subgroup analysis of RCT)</i>	Serial casting plus physiotherapy following BTX-A	BTX-A plus physiotherapy without casting	Children with CP (hemiplegia and diplegia)	25	Mean age 5 years 7 months, (range 4 years 4 months to 9 years)
Hesse et al [25]	IV <i>Case series</i>	Physical therapy ^c	Not applicable	Diplegic (n=19) & hemiplegic (n=4) CP	23	Mean age 7 years (range 2 to 12 years).
Suputtitada, [27]	IV <i>Case series</i>	Orthoses Daily rehabilitation therapy (heating modalities, stretching, facilitation exercises)	Not applicable	Diplegic (n=6) and hemiplegia (n=4) CP	10	Mean age 34.8 month (range 2 to 5 years)
Desloovere et al [22]	III <i>Cohort study with concurrent control group^d</i>	Serial casting immediately after BTX-A injection	Serial casting immediately prior to BTX-A injections	Diplegic (n=22) & hemiplegic (n=12) CP	27	6 years 9 months (range 4.5 to 9.8 years)

^c No further details provided in the manuscript

^d Pseudorandomization reported (“alternate randomization”p77)

Study	Level of evidence Research design	Therapy Intervention	Control Intervention	Population	Total n	Ages
<i>Lower Limb Studies Continued...</i>						
Detrembleur et al [20]	II <i>Small randomised controlled trial</i>	Electrical stimulation for 30minutes, 6 times a day for 3 days post-BTX/A	BTX-A without Electrical Stimulation	Children with CP	12	Median age 5 years (range 4.75 to 6)
Paolicelli et al [24])	IV <i>Case series</i>	Physiotherapy (standing and walking exercises) Stretching Orthoses for 1 month	Not applicable	Diplegic & hemiplegic CP	54	Average 6.5 years, range 2 to 18 years
<i>Upper Limb Study</i>						
Friedman et al [28]	IV <i>Case series</i>	Occupational therapy including age-appropriate activities of daily living, fine motor coordination training and strengthening of agonist muscles	Not applicable	Hemiplegic (n=14), quadriplegic (n=17), & triplegic (n=1) CP	32	Mean age 6.8 years (median age 8).

Table IV Conduct of Study (Levels I, II, and III evidence only)

<i>Study</i>	<i>Level/Quality</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>	<i>6</i>	<i>7</i>
Boyd et al [21]	III-W (2/7)	√	√					
Desloovere et al [22]	III-M (5/7)	√	√	√	√			√
Detrembleur et al [20]	II-M (4/7)	√	√	√				√

Conduct of the study is judged as Strong ('yes' score of 6 or 7), Moderate (score 5 or 4), or Weak (score ≤ 3)

Legend: 1. Were inclusion and exclusion criteria of the study population well described and followed? 2. Was the intervention well described and was there adherence to the intervention assignment? (for 2-group designs, was the control exposure also well described?) 3. Were the measures used clearly described, valid and reliable for measuring the outcomes of interest? 4. Was the outcome assessor unaware of the intervention status of the participants (i.e. was there blind assessment)? 5. Did the authors conduct and report appropriate statistical evaluation including power calculations? 6. Were dropout/loss to follow-up reported and less than 20%? For 2-group designs, was dropout balanced? 7. Considering the potential within the study design, were appropriate methods for controlling confounding variables and limiting potential biases used?

Table V: Summary of studies: outcomes, measures, and results (Levels I, II, and III evidence only)

<i>Study</i>	<i>Outcome of interest</i>	<i>Measure</i>	<i>Components of Health</i>		
			<i>Body Structure/s Body Functions</i>	<i>Activities and Participation</i>	<i>Contextual Factors</i>
<i>Lower Limb Studies</i>					
Boyd et al [21]	Range of motion	Goniometry of ankle dorsiflexion	No statistical comparison between groups		
	Gait	Ankle power quotient	No statistical comparison between groups		
		Ankle moment quotient	No statistical comparison between groups		
Desloovere et al [22]	Gait	Time & Distance parameters	<i>ns</i>		
		Foot & Ankle parameters	<i>ns</i>		
		Knee Parameters	<i>ns</i>		
		Hip and Pelvis Parameters	<i>ns</i>		
	Muscle Activity	EMG	<i>ns</i>		
Detrembleur et al [20]	Range of motion	Goniometry of ankle dorsiflexion - knee extended	<i>ns</i>		
		Goniometry of ankle dorsiflexion - knee flexed	<i>ns</i>		
	Spasticity	Modified Ashworth Scale (ankle rated only)	<i>ns</i>		
		Deep Tendon Reflex Scale (ankle rated only)	<i>ns</i>		
	Gait	Physicians Rating Scale	<i>ns</i>		

Abbreviations:

ns Result not statistically significant

+ Result favored subjects who received BTX-A plus therapy intervention