

What is the effectiveness of Botulinum Toxin A in the reduction of upper limb spasticity in children with cerebral palsy?

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SUMMARY STATEMENT:

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REQUEST:

What is the effectiveness of Botulinum Toxin A in the reduction of upper limb spasticity in children with cerebral palsy?

REQUESTED BY:

Brian Hoare, Occupational Therapist, Occupational Therapy, Monash Medical Centre Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defined the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined NHMRC criteria (see Appendix).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomized controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodologic difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Some studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request:

Patients Children with cerebral palsy
Interventions Botulinum Toxin A
Comparisons All other
Outcomes Reduction of spasticity

Search terms:

The following search terms were used to scour electronic databases and websites:

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient-related	Muscle spasticity, spastic\$, cerebral palsy, hemiplegia
Intervention-related	Botulin toxin/s, botulinum toxin type a, botulin\$, botox, dysport

\$= truncation (any word starting with this)

Resources Searched

We searched the following databases and Internet websites:

Cochrane Library CD-ROM- Issue 3, 2000

Best evidence (OVID)- 1991 to September/October 2000

Medline (OVID)- 1966 to December Week 4 2000

CINAHL (OVID)- 1982 to October 2000

Journals @ Ovid Fulltext- 29 November, 2000

Current Contents (OVID)- 1993 Week 26 to 2000 Week 49

Pre-Medline (OVID)- 30 November, 2000

PE德罗- 1 December, 2000

Australian Medical Index- 1 December, 2000

National Guideline Clearinghouse- 1 December, 2000

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 1 December, 2000. Articles published in English were included.

RESULTS:

From our sources we identified 2 articles which we categorised as follows:

Table 2. Study designs of articles retrieved by search

Study Design	Number included
Systematic reviews or meta-analyses	0
Evidence-based clinical practice guidelines	0
Randomised controlled trials	2
Controlled trials, cohort or case-control analytic studies	excluded
Descriptive case series	excluded
Consensus reports, non-evidence-based clinical practice guidelines	excluded
Narrative reviews	excluded

Articles were excluded from further appraisal for the following reasons:

Table 3. Reasons for exclusion of articles retrieved by search

Reason for exclusion	Number
Unknown level of evidence	2
Unknown relevance	45
Level III studies	2
Level IV studies	7

The two randomised controlled trials were available for critical appraisal. We are reasonably confident these articles represent the most relevant findings published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are in the form of spreadsheets reproduced at the end of this report. Each spreadsheet contains the article citation, the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

1. National Health and Medical Research Council. A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines. Canberra: Commonwealth of Australia, 1999.

ARTICLES CRITICALLY APPRAISED

Level II evidence – Randomised Controlled Trials

Corry, I. S., A. P. Cosgrove, et al. (1997). "Botulinum toxin A in the hemiplegic upper limb: a double-blind trial [see comments]." Developmental Medicine & Child Neurology **39**(3): 185-93.

Fehlings, D., M. Rang, et al. (2000). "An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy [see comments]." Journal of Pediatrics **137**(3): 331-7.

ARTICLES NOT CRITICALLY APPRAISED

Level III evidence

Hurvitz, E. A., G. E. Conti, et al. (2000). "Motor control testing of upper limb function after botulinum toxin injection: A case study." Archives of Physical Medicine & Rehabilitation **81**(10): 1408-1415.

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Level IV evidence

Albright, A. L. (1995). "Spastic cerebral palsy - approaches to drug treatment." Cns Drugs **4**(1): 17-27.

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Gooch, J. L. and T. V. Sandell (1996). "Botulinum toxin for spasticity and athetosis in children with cerebral palsy." Archives of Physical Medicine & Rehabilitation **77**(5): 508-11.

Graham, H. K., K. R. Aoki, et al. (2000). "Recommendations for the use of botulinum toxin type A in the management of cerebral palsy." Gait & Posture **11**(1): 67-79.

Mall, V., F. Heinen, et al. (1997). "Treatment of cerebral palsy with botulinum toxin A: functional benefit and reduction of disability. Three case reports." Pediatric Rehabilitation **1**(4): 235-7.

Pavesi, G., R. Brianti, et al. (1998). "Botulinum toxin type A in the treatment of upper limb spasticity among patients with traumatic brain injury [letter]." Journal of Neurology, Neurosurgery & Psychiatry **64**(3): 419-20.

Simpson, D. M. (1997). "Clinical trials of botulinum toxin in the treatment of spasticity." Muscle & Nerve Supplement **6**: S169-75.

Unknown level of evidence

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Wall, S. A., L. A. Chait, et al. (1993). "Botulinum A chemodenervation: a new modality in cerebral palsied hands." British Journal of Plastic Surgery **46**(8): 703-6.

Unknown relevance

(1999). "THERAPY WITH THE DEADLY BOTULINUM TOXIN." American Journal of Nursing August **99**(8): 24RR.

Allen, M. C. (1998). "The Cerebral Palsies: Causes, consequences, and management. By Geoffrey Miller and Gary D. Clark. 368 pp. Boston, Butterworth-Heinemann, 1998. \$75. ISBN 0-7506-9964-7." New England Journal of Medicine November 12 **339**(20): 1484.

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APPENDIX

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Levels Of Evidence

As Defined By "A Guide To The Development, Implementation And Evaluation Of Clinical Practice Guidelines" (National Health & Medical Research Council, Canberra, 2000):

Level I		Evidence obtained from a systematic review or meta-analysis of all relevant randomised controlled trials.
Level II		Evidence obtained from at least one properly designed randomised controlled trials.
Level III	-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
	-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies or interrupted time series with a control group.
	-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.
Level IV		Evidence obtained from case series (either post-test or pre-test and post-test), opinions of respected authorities (narrative reviews), descriptive studies, reports of expert (i.e. consensus) committees, case studies.

<p>Evidence Summary Therapy</p> <p>Botulinum Toxin A for upper limb spasticity in children with cerebral palsy</p>	<p>Study 1</p> <p>Fehlings D, Rang M, Glazier J et al (2000) An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. <u>Journal of Pediatrics</u> 137:331-7</p>	<p>Study 2</p> <p>Corry IS, Cosgrove AP, Walsh EG et al (1997) Botulinum toxin A in the hemiplegic upper limb: a double blind trial. <u>Developmental Medicine & Child Neurology</u> 39(3): 185-93</p>
<p>STUDY DESIGN & NHMRC LEVELS OF EVIDENCE</p>	<p>Level II Randomised Controlled Trial</p>	<p>Level II Randomised Controlled Trial</p>
<p>DESCRIPTION: Subjects, Interventions, Comparisons, Outcomes, Inclusion & Exclusion Criteria</p>	<p>Patients: Children aged 2.5 to 10 years with diagnosis of hemiplegic cerebral palsy Intervention: Intramuscular injection of botulinum toxin A (BTA), dosage of 2 to 6 U/kg body weight, into at least 1 of 3 muscle groups. Comparison: No injection Outcomes: Quality of Upper Extremities Test (QUEST), self care section of the Pediatric Evaluation of Disability Inventory (PEDI), manual goniometric measurements of passive range of motion, modified sphygmomanometer measurements of grip strength, modified Ashworth score of spasticity. Incl & Excl Criteria: Included if moderate spasticity at the elbow, wrist or thumb with a modified Ashworth score $\geq 2^{13}$, full passive range, ability to initiate voluntary movement of the digits. Excluded if they were using a rigid splint.</p>	<p>Patients: Children with cerebral palsy who had a dynamic component to their contractures. Mean age 9 years. Twelve children had hemiplegia, and one had quadriplegia. Intervention: Intramuscular injection of botulinum toxin type A (BTA) into the upper limb Comparison: Injection of normal saline solution Outcomes: Range of movement and function; movement and tone of thumb, wrist and elbow; ability to open the hand for grasping and releasing a small object; ability to open, close and coordinate finger-thumb pinch; general improvement / deterioration score by parent. Incl & Excl Criteria: None stated</p>
<p>VALIDITY: Methodology, rigour, selection, opportunity for bias</p>	<p>Randomisation: Yes, using a uniform random number generator All patients accounted for: Yes Patients treated equally: Yes Similar groups: Yes for age, gender, side of hemiplegia, modified Ashworth score, QUEST baseline, PEDI baseline, grip strength. Potential for bias: The control group received more physiotherapy treatment sessions during the study than the control group. The patients/carers were not blinded to group allocation. Potentially small sample size.</p>	<p>Randomisation: Randomisation was restricted to ensure 7 patients in each group. Group allocations were placed in envelopes. All patients accounted for: Yes Patients treated equally: Yes, although BTA group were also able to receive general anaesthetic (only used on one patient). Different brands of BTA were used (BOTOX for 10 patients and Dysport for 4). Similar groups: Not stated Potential for bias: The groups may not have been similar at the start of the trial, the groups may not have been truly randomised. Potentially small sample size.</p>
<p>RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate</p>	<p>The BTA group scored statistically significantly better on QUEST than the control group ($F=4.69$, $df=1,83$; $p=0.039$). There were significant differences in QUEST scores between the groups at 1 month ($p=0.01$) but not at 3 ($p=0.13$) or 6 months ($p=0.14$). The BTA group scored statistically significantly better than the control group on the PEDI test ($F=4.68$, $df=1$; $p=0.04$). No significant differences between the treatment and control groups were found for grip strength, Ashworth score, or passive goniometry measurements.</p>	<p>After 2 weeks there were significant differences between the control and BTA groups for wrist resonance frequency ($p=0.02$), elbow extension (0.026), thumb extension ($p=0.036$), elbow tone ($p=0.01$), and wrist tone ($p=0.003$). After 12 weeks there were significant differences between the two groups for wrist resonance frequency ($p=0.045$), wrist tone (0.01) and grasp and release ($p=0.01$). Parents subjective rating showed a tendency for improvement to be detected and still appreciated at 12 weeks.</p>
<p>AUTHORS COMMENTS: Risk/benefit, limitations</p>	<p>"This study supports the effectiveness of BTA injections to improve upper extremity function of children with hemiplegia who have at least moderate spasticity."</p>	<p>"This double-blind study confirms the hypothesis that BTA has a detectable clinical effect after injection into the forearm muscles in spastic cerebral palsy."</p>

<p>Evidence Summary Therapy</p> <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>Botulinum Toxin A for upper limb spasticity in children with cerebral palsy</p> </div>	<p style="text-align: center;">Study 1 (cont...)</p> <p>Fehlings D, Rang M, Glazier J et al (2000) An evaluation of botulinum-A toxin injections to improve upper extremity function in children with hemiplegic cerebral palsy. <u>Journal of Pediatrics</u> 137:331-7</p>	<p style="text-align: center;">Study 2 (cont...)</p> <p>Corry IS, Cosgrove AP, Walsh EG et al (1997) Botulinum toxin A in the hemiplegic upper limb: a double blind trial. <u>Developmental Medicine & Child Neurology</u> 39(3): 185-93</p>
<p>REVIEWER'S COMMENTS: Risk/benefit, methodology, conclusions</p>	<p><u>Strengths</u></p> <ul style="list-style-type: none"> • Groups were similar at the commencement of the trial • Groups were randomised • Good follow up period and low drop out rate • More than one instrument used to assess outcomes • Investigator was blinded to group allocation when assessing outcomes <p><u>Weaknesses</u></p> <ul style="list-style-type: none"> • Subjects were not blinded to group allocation • Control group received more physiotherapy and did not receive injections • No sample size (power) calculations were performed. We are unsure if study had sufficient power to detect differences between groups 	<p><u>Strengths</u></p> <ul style="list-style-type: none"> • There was a hundred percent response rate and no drop out • The control group also received injections • Both patients/carers and investigators were blinded to group allocation • More than one outcome measure was used <p><u>Weaknesses</u></p> <ul style="list-style-type: none"> • Groups may not have been truly randomised • Groups may not have been similar at baseline • Small sample size, and no power calculation were reported. The study may not have had sufficient power to detect differences between groups