Effects of botulinum toxin type A on upper limb function in children with cerebral palsy: a systematic review
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CRD summary
This generally well-conducted review concluded that differences between studies, the use of unreliable methods of measuring outcomes and small sample sizes meant that there was insufficient evidence for the effect of botulinum toxin type A injections in the upper limbs of children with cerebral palsy. This conclusion appears appropriate.

Authors' objectives
To assess the effectiveness of botulinum toxin type A injections in the upper limbs of children with cerebral palsy in terms of body functions, structures and activities.

Searching
PubMed, EMBASE, CINAHL, PiCarta, PEDro and the Cochrane Controlled Trials Register were searched to September 2005; the keywords were reported. Articles written in English, French or German were eligible for inclusion. The reference lists of the included articles were screened for further relevant studies.

Study selection
Study designs of evaluations included in the review
Controlled trials and uncontrolled studies were eligible for inclusion.

Specific interventions included in the review
Studies that assessed botulinum toxin type A injections in the upper limbs were eligible for inclusion. In addition to botulinum toxin type A injections, some of the included studies also used occupational therapy, physiotherapy and orthosis. The controlled trials used saline injections, usual care, or physiotherapy and occupational therapy as their control intervention. The dosage of botulinum toxin type A varied within and between studies.

Participants included in the review
Studies of children with a clinical diagnosis of cerebral palsy were eligible for inclusion. The studies included participants aged from 1 to 19 years. The majority of the included participants had hemiplegic cerebral palsy. Other diagnoses were quadriplegic cerebral palsy, diplegic cerebral palsy, dyskinetic cerebral palsy, and stroke or cerebral palsy and asymmetric function of the upper limb.

Outcomes assessed in the review
Studies that assessed the level of body function (including spasticity and active or passive range of motion) and level of activity (according to the International Classification of Functioning, Disability and Health definitions) were eligible for inclusion. The review assessed outcomes in the short term (up to 3 months) and long term (more than 3 months). The included studies assessed spasticity and tone using the Ashworth Scale or a modification of this; the studies used a variety of measures to assess range of motion and activities. The outcomes in the included studies were assessed up to 9 months after treatment.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion in the review. Any disagreements were resolved through discussion.

Assessment of study quality
Randomised controlled trials (RCTs) were quality assessed according to the criteria developed for the Cochrane
Collaboration Back Review Group for Spinal Disorders. These criteria included method of randomisation, concealment of treatment allocation, similarity of groups at baseline, blinding, attrition, timing of outcome assessments and intention-to-treat analysis. The criteria were modified for the assessment of uncontrolled studies. RCTs were deemed high quality if six of 11 criteria for internal validity, three of six descriptive criteria and one of two statistical criteria were met. Uncontrolled studies were deemed to be of sufficient quality if four of seven criteria for internal validity, two of four descriptive criteria and one of two statistical criteria were met.

Two reviewers independently performed the quality assessment, with any disagreements resolved by discussion, or arbitration by a third reviewer if consensus was not achieved.

**Data extraction**
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The statistical significance of treatment effects was presented for each study.

**Methods of synthesis**
How were the studies combined?
The studies were grouped by outcome and timing of outcome assessment and combined in a narrative.

How were differences between studies investigated?
Differences between the studies were discussed.

**Results of the review**
Three RCTs (n=64) and 9 uncontrolled studies (n=107) were included in the review. The sample size ranged from 1 to 32.

The RCTs were of high quality and the uncontrolled studies were of sufficient quality.

Effects on spasticity and tone.

One RCT reported improved outcomes in the wrist and elbow at 2 weeks and 3 months in the intervention group. Four uncontrolled studies also reported improved outcomes in the wrist and elbow compared with the baseline measurement. The other 2 RCTs and 3 uncontrolled trials assessing this outcome reported no significant differences. Two RCTs and 5 uncontrolled studies measured long-term spasticity or tone; only one uncontrolled study reported a significant difference in comparison with the baseline measurement.

Effects on range of motion.

One RCT reported a significant increase in active range of motion in elbow extension and thumb extension at 2 weeks in the intervention group. One RCT reported a significant change in supination of the wrist after 2 weeks and 9 months in favour of the control group. None of the 5 uncontrolled studies reported any significant changes in short-term active range of motion or long-term active range of motion. One uncontrolled study found a significant increase in flexion of the wrist and the first carpo-metacarpal joint after 1 month.

One RCT and 5 uncontrolled studies found no significant short-term changes in passive range of motion. One RCT and 6 uncontrolled studies found no significant long-term changes in passive range of motion. One uncontrolled study reported a significant increase in wrist extension after 4 months.

Two uncontrolled studies measured range of motion with the web-space method. One reported a significant increase in the space between the thumb and index finger, but the length of follow-up was not reported. The other study reported no significant changes.

Effects on level of activity.
One RCT reported that the grasp and release score improved significantly in the intervention group compared with the control group after 3 months. One RCT reported a significant change in the Quality of Upper Extremity Skills Test score in the intervention group compared with the control group after 1 month; however no significant differences were found after 3 months. The same RCT also reported a significant improvement in the raw scores of the self-care domain of the Pediatric Evaluation of Disability Inventory (PEDI). Significant improvements in scores of the self-care domain of the PEDI were also reported in one uncontrolled study. However, one other RCT and two other uncontrolled studies that used the self-care domain of the PEDI found no significant differences.

One RCT and one uncontrolled study that used the Melbourne Assessment of unilateral upper limb function found no significant differences.

Five of the 9 uncontrolled studies that assessed the effects of botulinum toxin type A injections reported significant improvements in comparison with baseline measurements, whilst the other four found no significant improvements; a variety of outcome measures were used.

Two RCTs reported long-term measurements but found no significant differences between the intervention and control groups. Seven uncontrolled studies reported long-term measurements; two reported significant long-term improvements.

**Authors' conclusions**

Differences between studies, use of unreliable assessment instruments and small sample sizes meant that there was insufficient evidence for the effect of botulinum toxin type A injections in the upper limbs of children with cerebral palsy in terms of body functions or activities.

**CRD commentary**

The review question was clear in terms of the study designs, participants, interventions and outcomes of interest. A number of electronic databases were searched for relevant studies, and some attempts were made to reduce language bias. The authors made little attempt to identify unpublished studies and acknowledged that this raises the possibility of relevant studies having been missed. Two reviewers independently carried out the study selection and quality assessment procedures, thereby reducing the potential for errors and bias. The quality of the included studies was assessed using appropriate criteria, and the included studies were deemed to be of high or sufficient quality. The authors did not state how data were extracted from the included studies, therefore the potential for reviewer error or bias could not be assessed.

Adequate details of the included studies were presented. In view of the differences between studies in terms of the participants, interventions and outcome assessments used, the narrative synthesis was appropriate. The authors’ conclusion, that there was insufficient evidence of effectiveness of botulinum toxin type A, appears appropriate.

**Implications of the review for practice and research**

Practice: The authors did not state any implications for practice.

Research: The authors stated that well-designed controlled studies evaluating the impact of botulinum toxin type A injections in the upper limbs of children with cerebral palsy are required, and that the participants of such studies should be stratified by their probability of gaining dexterity. Studies should investigate whether children with some preservation of hand function might benefit more from botulinum toxin type A injections in terms of activities. Future studies should document the intensity and content of any exercise programmes applied alongside botulinum toxin type A injections, to control for cointerventions. The authors also stated that consensus on a core set of valid measurements at different levels of the International Classification of Functioning is needed.

**Bibliographic details**

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