Current evidence for the use of botulinum toxin type A in the management of children with cerebral palsy: a systematic review
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Authors' objectives
To review systematically the current available evidence for botulinum toxin type A (BTX-A) in cerebral palsy management, compared with other options for the lower limb and general body involvement in children.

Searching
The following sources were searched in December 2000: MEDLINE from 1966; CINAHL (via OVID) from 1982; ClinPSYC from 1989; DARE, PEDro; EBM Reviews: Best Evidence from 1991; the Cochrane Database of Systematic Reviews (Issue 4, 2000); and the Cochrane Controlled Trials Register (CENTRAL/CCTR). The exploded terms used were 'cerebral palsy', 'Botulinum toxin A', 'lower limb', 'selective dorsal rhizotomy', 'intrathecal baclofen', 'surgery', 'physical therapy', 'casting', 'orthoses' and 'spasticity'. To be included, the articles had to be full publications in a peer-reviewed journal. Abstracts from meetings were handsearched for relevant studies. Authors of recent abstracts were contacted for further information, although unpublished data were excluded from the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), and prospective non-randomised studies with objective outcome measures, were eligible for inclusion.

Specific interventions included in the review
Comparisons of intramuscular BTX-A (irrespective of dose or muscle injected) versus placebo, control or comparison treatments were eligible for inclusion. The preparations used in the included studies were BOTOX, Dysport, or were unspecified. The dose and treatment regimens varied. The comparators were placebo (normal saline), casts or physiotherapy.

Participants included in the review
Children with cerebral palsy treated for movement disorders due to spasticity of the lower limbs were eligible for inclusion. The motor types and severity at baseline were tabulated for the included studies; these varied between the studies.

Outcomes assessed in the review
All reported outcomes were included. The outcomes were categorised according to ICIDH-2 (WHO International Classification of Impairments, Disabilities and Handicaps) categories, which included impairment measures, activity measures, participation, and contextual factors. Treatment-related adverse effects were also included if they were classified as major and minor. The outcome measures used in each of the included studies were tabulated; these varied between the studies.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The methodological quality of the studies was assessed using the PEDro scale. The following criteria were assessed: eligibility criteria specified; random allocation; concealed allocation; baseline prognostic similarity; blinding (participant, therapist, assessor); greater than 85% follow-up; intention to treat analysis; between-group statistical comparison for at least one outcome; and point estimates and measures of variability for at least one outcome. Each criterion was scored as present (1) or absent (0). The authors do not state how the papers were assessed for quality, or
how many of the reviewers performed the quality assessment.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted from the RCTs included: author, study design, patient numbers, age, motor types, severity at baseline, follow-up, drop-outs, loss to follow-up, intervention, outcome measures, complications/side-effects, and the main result. Additional data extracted from the non-randomised studies were the study aim, objective outcome, and the number of groups. Data required to assess methodological quality were also extracted from the RCTs.

**Methods of synthesis**

How were the studies combined?

A meta-analysis using a fixed-effect model was used to calculate the pooled weighted risk difference, along with 95% confidence intervals (CIs), for the noncontinuous outcomes reported in the RCTs. Summary tables of the non-randomised studies were constructed, and their findings were discussed separately.

How were differences between studies investigated?

A chi-squared statistical test for heterogeneity was used in the meta-analyses. The only means of evaluating differences between the non-randomised studies was to examine the tables.

**Results of the review**

Ten RCTs (n=407) and 7 prospective non-randomised studies (n=193) were included.

The methodological quality of the included RCTs was moderate to high (at least 7 points out of a possible 11); 9 trials had concealed allocation.

The pooled risk difference for BTX-A versus placebo was 0.25 (95% CI: 0.13, 0.37); this was based on 4 RCTs (n=204) that used the physicians rating scale as the primary outcome measure. The chi-squared test showed no statistically-significant heterogeneity (chi-squared 3.83, d.f.=3, P=0.28). Similarly, the pooled risk difference for BTX-A versus casting was 0.23 (95% CI: -0.06, 0.53); this was based on 2 RCTs (n=38) with no statistically-significant heterogeneity (chi-squared 0.24, d.f.=1, P=0.62). Pooling all 6 trials showed a risk difference of 0.24 (95% CI: 0.13, 0.36) and no statistically-significant heterogeneity. For this analysis, success was defined a priori as an increase of at least two points from the baseline composite physician rating scale score. The trials assessed the outcome at 6 to 16 weeks' follow-up.

**Authors’ conclusions**
The findings from the meta-analysis represent moderate treatment effects that are dose-dependent.

**CRD commentary**

This article reported a systematic review within a broader and less focused evidence summary. This abstract summarised only the results of the systematic review question. Readers interested in the categorisation of all identified papers (regardless of the inclusion criteria for the systematic review) according to the levels of evidence and the ICIDH-2 model, should read the original article.

The systematic review addressed a clear question in terms of the participants, intervention, comparators and study design, but not in terms of the outcome measures. A variety of appropriate sources were searched to identify trials. However, publication bias is a real possibility; publication in a peer-reviewed journal is not a guarantee of methodological quality, and is a questionable limitation to impose on a review in which the authors themselves critically appraise the primary studies. It is unclear whether or not language restrictions were imposed. Details of the
The results of the systematic review focused largely on the one outcome for which a meta-analysis of RCTs was possible. This involved dichotomising (as success or not; success being defined by the author) scores measured on a scale (Physicians Rating Scale). The limitations of this practice must be borne in mind when interpreting the reported risk differences. There appears to be considerable clinical heterogeneity between the RCTs, which also needs to be taken into account when interpreting the pooled results. Although non-randomised trials were specified in the selection criteria for inclusion, these studies were summarised in tables in the review, with no clear attempt at an overall descriptive evaluation of their findings.

The authors' conclusions appear to be based more on the broader levels of evidence hierarchy than the findings from the systematic review. The statement that treatment effects are dose-dependent is not conclusive from the evidence presented.

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

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

**Research:** The authors state that there are no long-term studies of outcome (including progression to surgery for ambulant patients and outcome of hip displacement in children with adductor spasticity) for BTX-A in children with cerebral palsy. Other areas that require more evidence include BTX-A management of apparent equinus or crouch, and the inter-relationship between BTX-A and orthoses, casting or surgery. Also, there is a need for the measurement of health-related quality of life and an economic evaluation. Future research must evaluate new indications, as well as traditional management options, to determine the optimal combinations of treatment for particular patient groups.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.