Safety of botulinum toxin type A among children with spasticity secondary to cerebral palsy: a systematic review of randomized clinical trials

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CRD summary
The authors concluded that adverse events with botulinum toxin type A were more common among children with cerebral palsy than in people with other conditions, there was the potential for severe adverse events, and additional data were required. The review was well conducted, apart from a limited search, and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the safety of botulinum toxin type A in children with cerebral palsy.

Searching
MEDLINE was searched for articles published in English, French, Spanish or German, from January 1990 to February 2008. Search terms were reported and reference lists of reviews were screened.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if they compared adverse events associated with intramuscular injection of botulinum toxin type A (Botox, Dysport, or Xeomin) with placebo, rehabilitation, or both, in children (aged under 18 years) with spasticity secondary to cerebral palsy. Trials of botulinum toxin type B were excluded.

Most of the included trials evaluated Botox with doses ranging from 0.5 to 20 units per kg; other trials evaluated Dysport or both Botox and Dysport. In most of the trials the comparator was placebo, with or without rehabilitation; other comparators included electrical stimulation and casting. Participant ages ranged from 22 months to 16 years and most of them were treated for spasticity of the lower limb; some participants had spasticity of the upper limb.

Two reviewers independently selected trials and resolved disagreements by discussion.

Assessment of study quality
Two reviewers independently assessed validity according to Consolidated Standards of Reporting Trials (CONSORT) guidelines, with the extension for adverse events. A reference to CONSORT guidelines was given, but the individual quality items assessed and the maximum possible quality score were not reported.

Data extraction
Two reviewers independently extracted the incidence, intensity, and possible relationship of adverse events from botulinum toxin type A. The incidence of adverse events was estimated on a per-protocol basis from data presented in the original paper and used to calculate relative risks and 95% confidence intervals. Disagreements were resolved by discussion with a third reviewer.

Methods of synthesis
For each adverse event reported by more than one trial, pooled relative risks and 95% confidence intervals were calculated. Statistical heterogeneity was assessed using the I^2 statistic and fixed-effect or random-effects models were used, depending on the level of heterogeneity. Where there were zero events in one cell in any trial, 0.5 was added to all four cells. Sensitivity analysis was conducted, using two different continuity correction factors (0.5 and 0.1).

Results of the review
Twenty RCTs were included (n=882 children), with sample sizes ranging from 12 to 122. Six trials reported no adverse events; the remaining 14 reported 542 adverse events of 35 different types; the authors stated that the adverse events
were not clearly defined. Trials met between 12 and 19 of the quality items (average 16.3) and the duration of follow-up was between six weeks and three years.

Botulinum toxin type A was associated with a statistically significant increase, compared with control, in the following adverse events: respiratory tract infection (RR 15.82, 95% CI 3.86 to 64.83; four RCTs); bronchitis (RR 11.74, 95% CI 2.31 to 59.59; three RCTs); pharyngitis (RR 7.50, 95% CI 1.78 to 31.61; three RCTs); asthma (RR 6.40, 95% CI 1.20 to 34.00; three RCTs); muscle weakness (RR 5.60, 95% CI 1.44 to 21.84; three RCTs); urinary incontinence (RR 5.30, 95% CI 1.20 to 23.52; three RCTs); falls (RR 5.17, 95% CI 1.74 to 15.36; five RCTs); seizures (RR 4.24, 95% CI 1.85 to 9.71; five RCTs); fever (RR 2.77, 95% CI 1.04 to 7.34; three RCTs); unspecified pain (RR 2.44, 95% CI 1.39 to 4.27; 10 RCTs); vomiting (RR 3.99, 95% CI 1.39 to 11.48; six RCTs); and viral upper respiratory tract infection (RR 5.91, 95% CI 1.07 to 32.46; three RCTs). Data were also presented for another 12 adverse events that were reported only in single trials.

Sensitivity analysis, using the two correction factors, suggested that all the adverse events were underestimated because no cases were reported in the exposed groups, in some of the RCTs.

Authors’ conclusions
Botulinum toxin type A had a good safety profile during the first months of use. Adverse events were more common among children with cerebral palsy than in people with other conditions. There was the potential for severe adverse events with botulinum A, but the data were sparse and additional trials were needed to clarify the causal relationship.

CRD commentary
The review question was clearly stated and the inclusion criteria were appropriately defined. Limiting the search to one database plus references might have resulted in the omission of relevant trials and increased the possibility of publication bias. The inclusion of studies of non RCT design might have been useful for assessing rare adverse events that RCTs are underpowered to detect. Sufficient methods were used to minimise reviewer errors and bias during the review process. Trial validity was assessed, but only the aggregate scores were presented, without the range of possible scores and the quality criteria, which makes it difficult to judge the quality of the evidence. Appropriate methods were used to summarise the trials and the pooled data. Some limitations of the evidence were discussed, including the short duration of follow-up and the generalisability of the findings to less healthy and younger children.

Apart from the limited search, the review was well conducted and the authors’ conclusions are likely to be reliable.

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Implications of the review for practice and research

Practice: The authors stated that botulinum toxin type A use should be strictly monitored, using specific pharmaco-epidemiological surveillance systems.

Research: The authors stated that further research was required to examine the possible relationship between botulinum toxin type A, seizures, and death. There was a need to further analyse the data from national and international adverse drug reaction monitoring centres.

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Bibliographic details
Record Status
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.