Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy (Review)

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ABSTRACT

Background
Children with cerebral palsy often have spasticity of the legs, a condition in which the legs are stiff because of involuntary muscle overactivity caused by the brain or spinal cord disorder. Spasticity causes poor coordination, spasms, abnormal posture and pain, and contributes greatly to the developmental deformities and disability of cerebral palsy. Conventional treatment with physiotherapy, splinting, oral medications and sometimes plaster casting and surgery may prove inadequate. Open label studies and some RCTs suggest that botulinum toxin injections into the spastic muscles can alleviate the spasticity and help some of these problems. Botulinum toxin blocks the release of acetylcholine from the neuromuscular junction and weakens the muscle. This and other effects may account for the apparent benefit in spasticity, but also highlight the importance of clarifying safety, especially in this group of growing children.

Objectives
To determine whether botulinum toxin (BtA) is an effective and safe treatment for lower limb spasticity in children with cerebral palsy. Functional outcomes are of particular interest.

Search strategy
Studies for inclusion in the review were identified using the Movement Disorders Review Group trials register, the Cochrane Controlled Trials Register, MEDLINE, pharmaceutical company databases, communication with other researchers in the field and reference lists of papers found using above search strategies.

Selection criteria
Studies were considered eligible for inclusion in the review if they evaluated the efficacy of BtA for the treatment of leg spasticity in children with cerebral palsy. They must have been randomised and include a concurrent control group receiving another intervention.

Data collection and analysis
A paper pro forma was used to collect data from the included studies using double extraction by two independent reviewers. Each trial was assessed for internal validity by each of the two reviewers.

Meta-analysis was not possible because results were presented in an incompatible form. A Peto odds ratio was calculated where this was appropriate, otherwise a descriptive summary of the results of the individual studies was compiled.

Main results
Three eligible studies were found each with small numbers of subjects. They were short term, used single injection sessions with follow-up of between 4 and 26 weeks.

One study (Koman), of twelve ambulant children, compared BtA with injection of a placebo and found non-significant improvements in gait in the BtA group compared to the placebo group.

Two studies (Corry, Flett) compared BtA with the use of casts. Each included 20 ambulant children and found improvements in gait, range of ankle movement and muscle tone in both the BtA and cast groups. However there were no significant differences between the
groups in either trial. One of these trials (Flett) also assessed motor function using the gross motor function measure (GMFM) (Russell, 1989) and found significant improvements in each group compared to baseline but no significant differences between the groups. The other trial (Corry) performed 3D gait analysis on those children able to co-operate. Maximal plantar flexion and maximal dorsiflexion during walking were both found to be significantly greater in the BtA group compared to the cast group. In all other dimensions there were no significant differences between the groups.

Authors’ conclusions
This systematic review has not revealed strong controlled evidence to support or refute the use of BtA for the treatment of leg spasticity in cerebral palsy.

Ongoing randomised controlled trials are likely to provide useful data on the short term effects of BtA for leg spasticity.

Future research should also assess the longer term use of BtA. Ideally studies should be pragmatic in their approach to dose and distribution of toxin to reflect practise. Outcome measures assessing function and disability would give the most useful information.

BACKGROUND
Cerebral palsy (CP) is a non-progressive neurological condition resulting from damage to the immature brain. It is relatively common with an incidence of 2:1000 live births (Nelson, 1995). CP is a heterogeneous condition, but 80 - 90% of cases will have spasticity, which usually affects at least one lower limb. This prevents normal movement, often hampering locomotion. It can also cause contractures and deformities as the child grows, due to the failure of the spastic muscles to grow as rapidly as neighbouring bone and soft tissue.

The treatment of spastic cerebral palsy includes physiotherapy, oral anti-spastic drugs, casts, splints and orthopaedic surgery. Use of botulinum toxin may potentiate the benefits or reduce or delay the need for these and is potentially less disruptive than some options.

Botulinum neurotoxin type A (BtA) is produced by the bacterium clostridium botulinum. It is one of seven distinct serological types of toxin known to be produced by this bacterium, and causes severe food poisoning when ingested (Hambleton, 1995). This paralytic illness is known as botulism. The symptoms of botulism include nausea and vomiting, blurred vision, diplopia, dysphagia, dysarthria, respiratory insufficiency and limb weakness (Stell, 1995).

BtA causes muscle weakness by neuromuscular blockade. The toxin consists of a heavy chain and a light chain connected by disulphide bridges. The heavy chain targets the toxin to cholinergic nerve terminals and, after being internalised, the light chain acts by preventing the release of acetyl choline. Affected neuromuscular junctions are inactivated causing a flaccid paralysis. Collateral sprouting results in the formation of new, temporary, neuromuscular junctions over a period of weeks or months before the original neuromuscular junctions recover (Hambleton, 1995).

Dr Vernon Brookes suggested in the 1950’s that BtA might be used to reduce activity in hyperactive muscles (Schantz, 1994). Following several years work Dr Alan B. Scott injected a patient with strabismus in 1977 and published the results of the first clinical trial of BtA for strabismus in 1980 (Scott, 1980). By 1982 Scott had treated patients for several other disorders of muscle function, including spasticity of the legs (Scott, 1994).

BtA is injected into selected muscles. At therapeutic doses it causes focal weakness, and although sophisticated neurophysiological techniques (single fibre electromyography) reveals distant spread of toxin, there is little or no clinically detectable generalised effect.

As with many therapies in paediatric rehabilitation, there is a risk of premature acceptance of the use of BtA in the treatment of CP. It has already been licensed for use for dynamic spastic equinus in CP in a number of countries. However, non-systematic reviews, such as those by Forrsberg & Tedroff, (1997) and Fehlings, (1998), show that most studies so far have been uncontrolled and short-term. They have generally tested small numbers of subjects, used multiple different end-points and surrogate measures.

The purpose of this systematic review is to provide information on:
- the current position concerning knowledge of the effects of BtA in CP.
- what trials are required to further that knowledge.
- which outcome measures are best, or whether new measures should be developed.
- which patients and muscle groups are worth treating, and with what dose.

We are aware that several studies are underway. A systematic review at this stage might encourage trialists to present results in a compatible form enabling future meta-analyses.

OBJECTIVES
To determine whether BtA is an effective and safe treatment for lower limb spasticity in children with cerebral palsy.
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies
A trial was considered eligible for inclusion in the review if it i) evaluated the efficacy of BtA ii) included concurrent control groups, receiving, for example, placebo injections, surgery, casts, physiotherapy iii) allocated patients through a randomisation procedure.

Types of participants
Eligible trials must have involved children (defined, for the purposes of this review, as individuals between the ages of 0 and 19 years old) with CP who had been treated for lower limb spasticity. Trials may be subdivided according to type of CP, distribution of spasticity, severity, dose of BtA, age at which BtA administered.

Types of intervention
Randomised controlled injection of BtA into lower limb muscles. Trials with different doses and muscles injected were included. Other interventions were permitted, (i.e. a study was still considered eligible for the review even if it did not exclude other interventions, such as physiotherapy, casts, etc.) provided that they were not systematically applied differently to the two groups.

Types of outcome measures
The most important outcome measures for this review were motor function measures including disability rating and gait analysis. (Gait analysis is often only of value as a secondary measure, as many children are unable to undergo full testing.) Sub-measures included spasticity, range of movement, quality of life, parental opinion and cost effectiveness.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Movement Disorders Group methods used in reviews.

Studies for inclusion in the review were identified using the following sources:
1. The Movement Disorders Review Group trials register. This includes trials from a search of EMBASE.
2. The Cochrane Controlled Trials Register.
4. Communication with other researchers in the field.
5. Pharmaceutical company databases and discussion with the companies.
6. Reference lists of papers found using above search strategies.

Keywords used for searching electronic databases were: botulinum toxin, cerebral palsy, spasticity, child, children, spastic, randomised controlled trial, and controlled clinical trial.

All languages were included.

METHODS OF THE REVIEW

a) Applying selection criteria
We assessed each trial that was identified for eligibility for inclusion in the review. Assessment was made independently by two reviewers who were aware of the origin of the report and its results. To be considered eligible for the review a trial had to be randomised and controlled. The study must have compared the use of BtA (treatment group) with another intervention (control group). Participation in the study must have been limited to those with CP who displayed leg spasticity. Finally the treatment group must have received BtA and the control group must not have received BtA.

b) Critical appraisal of eligible trials
Each trial was assessed for internal validity in order to prevent systematic errors (bias) in the review. Sources of bias looked for included:
- selection bias, including randomisation and chance differences in groups due to small sample size
- performance bias
- attrition bias
- detection bias
- selective reporting of results

Reports were then rated A, B or C as described in section 6.7.1 of the Cochrane Collaboration Handbook, version 4.0.

Any rating of ‘C’ would have required the reviewers to consider carefully whether that trial should be excluded from the review on the grounds of poor methodological quality or to include the trial but assess using subgroup or sensitivity analysis to determine its effect on the results of the review.

c) Data extraction
A paper pro forma was used to collect data from the included studies using double extraction by two independent reviewers. Study eligibility was cross-checked at this stage, using the excluded studies table. Results were compared and any differences resolved by discussion. Where necessary we attempted to contact the authors to clarify the data.

d) Analysis
Meta-analysis was not possible because results were presented in an incompatible form. Where appropriate a Peto odds ratio was calculated, together with 95% confidence intervals. (This was only appropriate where BtA was compared with placebo). Otherwise a descriptive summary of the results of the individual studies was compiled.
DESCRIPTION OF STUDIES

Types of studies
Three fully published randomised controlled trials that meet the criteria for inclusion in the review were found. Only abstracts of a further six RCT’s were available. Attempts to obtain further information have so far been unsuccessful. The information provided in four of the abstracts was judged insufficient to assess the quality of the studies, and they were therefore excluded from the review. The other two proved not to meet the inclusion criteria (see excluded studies table). The three trials included in the review compared BtA versus placebo (Koman), and BtA versus casts (Corry; Flett).

Participants
In all three included studies the participants were children with cerebral palsy and dynamic calf equinus. Their ages ranged from 2 to 11 years. There were more boys than girls in both the Corry - 13:7 - and the Flett - 11:7 - studies. Koman does not give this information. Severity of CP is not reported in any of the studies. However, they all include only children who are ambulatory, either with or without aids. Altogether 29 children had diplegia, 17 had hemiplegia, 3 had quadriplegia and one was classified as having triplegia.

Interventions
Intramuscular calf injections of BtA were given to the treatment group in each of the three studies. Two studies used plaster casts as the control intervention (Corry; Flett) while Koman gave placebo injections. All but two of the BtA injections were of Botox® , in the dose range 3 - 8 mu/kg. Corry used Dysport® at a dose of 15 mu/kg for the remaining two injections. The placebo injections were of normal saline. Injection techniques were broadly similar between the studies, with at least two sites injected in each calf and all targeting the medial and lateral heads of gastrocnemius. Koman also injected tibialis posterior if equinovarus deformity was present. Corry injected soleus in addition to gastrocnemius in all the children in the BtA group. Both studies using plaster casts as the control intervention applied light weight walking casts (below the knee) with the ankle in neutral, reapplying the casts after two weeks and leaving for a total of four weeks in the case of Flett and four to six weeks in the case of Corry . In addition to the study interventions Flett used night plasters on both groups for the eight weeks following the study intervention.

Outcomes
The outcome measures deemed a priori to be the most important to this review were those looking at disability and function. The three eligible studies all used a physician rating scale (PRS) for assessing gait, although each author had adapted it in a different way. Flett also used GMFM to evaluate motor function and a global scoring scale for video gait analysis. Corry used 3D gait analysis, but only on 12 of the 20 participants. The others were too small, too young or unable to co-operate with the procedure.

Other outcome measures used included those measuring impairment. Both Corry and Flett used an Ashworth scale for assessing muscle tone, and measured passive ranges of movement at the ankle. Koman attempted to measure muscle strength and endurance using the Biodex dynamometer, however the children all had difficulty in complying with its use.

METHODOLOGICAL QUALITY

The three included studies all used random allocation techniques in assigning participants to treatment groups. The allocation concealment was adequate in two trials. In one (Flett) it was pharmacy controlled, and in the other (Corry) cards, sealed in identical envelopes, were drawn and gave the instruction BtA or cast. The clinician selecting the patient for intervention was not involved in drawing the cards. (This issue was made clear by contacting the author). Allocation was unclear in the other trial as Koman makes no statement of allocation concealment in his paper.

Baseline differences between BtA and cast groups were assessed in terms of age and for the various outcome measures by Flett. No differences were found. Similarly, Corry assessed baseline differences between the groups for the outcome measures, but not for age. Again no differences were found. (Corry had considered stratifying or matching the randomisation but thought it would be too complicated and may have limited patient selection to such an extent that they would have had difficulty with numbers - personal communication). Koman did not compare the two groups at baseline.

One trial (Koman) was double-blind, with both participants and assessors blind to the intervention. One trial (Flett) was single-blind, with the outcome assessors blind to the intervention and the remaining trial (Corry) was single-blind for the PRS but otherwise there was no blinding.

Two studies had no drop-outs (Corry; Koman). The other study (Flett) had two children withdraw from the BtA group. Data from these children were not included in the analyses in his paper.

There does not appear to have been any other selective reporting in the trials reviewed.

RESULTS

BtA versus placebo
Disability measures: In the one trial that compared the use of BtA with a placebo in 12 children (Koman) 83% (5) of children who received the BtA and 33% (2) of children who received the placebo had an improved gait pattern (PRS) 4 - 6 weeks after the intervention. Statistical significance was not reported. The Peto odds ratio is 6.59 with a 95% confidence interval of 0.73 - 59.34 (ie. not statistically significant).
Parental opinion: This trial also reported parents’ perceptions of change in their child’s gait pattern. Sixty seven percent (4) of those whose child had received BtA felt that the child had improved and 33% (2) of those whose child had received placebo felt that the child had improved. Again statistical significance was not reported. The Peto odds ratio is 3.39 with a 95% confidence interval of 0.39 - 29.64 (i.e. not statistically significant).

Adverse effects: Mild adverse effects were reported in three of the children who received BtA. There were seven adverse events in the placebo group but is unclear how many children these affected. No other outcome measures deemed a priori to be clinically significant were reported in this trial.

BtA versus casts
Disability measures: The two trials that compared BtA with plaster casts (Corry; Flett) reported their results in different ways so that it was not possible to combine them statistically. Each reported statistically significant improvements in gait pattern (PRS) for both the BtA group and the cast group at 12 weeks (Corry) and 6 months (Flett) following intervention. However neither study was able to show a significant difference between the groups. One trial (Flett) used the GMFM to measure changes in standing function and dynamic function. Again there was a significant improvement following administration of BtA and of casts but no significant difference between the improvements of the two groups. The other trial (Corry) assessed 12 out of the 20 children using 3D gait analysis and found the improvement in maximal ankle dorsiflexion and plantar flexion at 12 weeks post intervention, to be significantly greater in the children who had received BtA compared to those who had worn casts. The other gait parameters did not show any significant differences between the groups.

Impairment measures: Muscle tone, rated on the Ashworth scale, improved significantly for both groups in one trial (Flett) however there was no significant difference between the groups. The other trial (Corry) found no significant change in muscle tone in either group.

Passive range of ankle dorsiflexion was significantly improved for each group in one trial (Flett) but only for the BtA group in the other trial (Corry). The difference between the groups was not significant in either trial.

Parental opinion: One trial (Flett) had questioned parents on their satisfaction with the treatment process (rather than their perception of how well that treatment had worked). All the reported comments from the BtA group were positive as were some from the cast group. The negative comments came from the cast group and included inconvenience while wearing casts and weakness of legs following their removal.

Economics: The two authors who had compared BtA with casts also compared the cost of each to administer, concluding that, once parental time and travel expenses had been taken into account, the two treatments were of similar cost.

Adverse effects: Calf pain in one child was the only reported adverse effect of BtA (Corry) for these two studies. The same study also reported 3 painful feet, 1 painful calf and 2 episodes of skin inflammation in the cast group. Flett did not report any adverse effects as such. However results of the parental questionnaire in this study, as reported above, revealed no adverse effects in the BtA group and 3 reports of weak legs following casts.

**Discussion**

**Findings of the Review**

The use of BtA in the treatment of lower limb spasticity in CP is becoming increasingly accepted as a viable alternative or addition to more traditional antispasticity therapy. This systematic review revealed that only three studies have been fully published so far that attempt to evaluate this in randomised controlled trials. There is only weak evidence from these studies to support widespread use of BtA.

The three studies included in this review are all short-term trials, using single courses of injections, injecting at single levels with different doses and preparations of BtA. Only one study (Koman) compared BtA to a placebo. Although the results of this study are promising they are not conclusive. The Peto odds ratio is 6.59 with the confidence intervals ranging from 0.73 to 59.34. This large range crosses the line of no effect and so, if the results of this trial were extrapolated to the population of children with cerebral palsy, the ‘real’ result may favour either BtA or placebo.

The trial was very small, only 12 subjects, and its allocation concealment was unclear, leaving it open to the risk of selection bias. The published report does not describe the subjects in any detail neither does it provide any analysis of differences between the groups. The report gives the diagnoses of the children but the number of legs evaluated (18) does not equate to the number of legs with potential to be treated (20 legs from 8 diplegics, 4 hemiplegics). This suggests that there were mismatches in the number of bilaterally and unilaterally affected children in each group. To overcome this, to some extent, the researchers appear to have only treated one leg in two of the diplegic children. In addition to the statistical error this produces, the legs of bilaterally affected children may be interdependent in their response to treatment. This may affect the outcome of treatment when only one leg is injected, compared to unilaterally affected children. These facts have great potential to bias the only outcome reported, i.e. the number of children with improved gait pattern, as measured by the PRS, which scores each leg individually.

Two studies (Corry; Flett) evaluated the efficacy of BtA by comparing its use to that of casts; despite the fact that these are also an unproven treatment. The results of these studies comparing BtA and casts were presented in such a way that meta-analysis was not possible. Each author had performed some statistical analysis and
CURRENT KNOWLEDGE REGARDING THE EFFICACY OF BOTULINUM TOXIN

Fully published, controlled evidence about the effectiveness of BtA for improving function in CP remains weak. There are no results published in sufficient detail, from properly designed randomised controlled trials that are large enough to prove clinical effectiveness. What evidence there is relates to single courses of injections with short term follow-up. CP is a life long condition so we need long term outcomes using measures of function, disability and handicap.

Cosgrove and Graham (1994) demonstrated that spasticity in the hereditary spastic mouse could be controlled allowing near normal longitudinal muscle growth. They have gone on to test the hypothesis that this muscle lengthening can be achieved in children with CP. The effect has been demonstrated in both gastrocnemius (Eames, 1996) and the hamstring muscles (Thompson, 1998). Although these studies do not provide evidence of a long term effect it is promising that muscle lengthening has been shown to occur. The challenge now is to maintain that lengthening through periods of rapid growth. In uncontrolled studies using repeated injections over at least a year (Sutherland, 1996; Koman, 1993; Koman, 1994) continuing improvements in gait have been demonstrated at up to 46 months of therapy. There has been a suggestion of a disease modifying effect in some younger children (Boyd, 1997).

The studies reviewed do not clarify which children, with what type of CP are best treated with BtA. Boyd and Graham (1997) offer advice, based on their experience, on which muscles to treat in the various types of CP. They advocate multilevel injections in some children. However all the studies reviewed targeted the same muscle group and used only one dose of toxin, which was similar in each. One trial uses Botox® for some injections and Dysport® for others. The Botox : Dysport conversion ratio used was 1 : ~2 - 2.5 which is potentially a rather low dose of Dysport®. The UK Botulinum Toxin and Cerebral Palsy Working Party recommend a ratio of 1 : 2.5 - 5 (Carr, 1998). The abstract of one randomised double-blind study comparing different doses of BtA reports that there were significantly better results from the high-dose group than the low-dose group (Wissel, 1996), but as this trial is not available for systematic review the results should be regarded with caution.

SAFETY

The review suggests that it is safe to use BtA in CP, at least in the short term. Only 4 events of calf pain were reported among the 26 children injected with BtA. This can be considered a mild adverse effect. There were more reported adverse effects among the control groups. Similar rates and types of adverse effects are reported in uncontrolled studies. A retrospective survey of adverse events during three months following BtA injection found that 22% of respondents had minor side effects and one (0.6%) had prolonged unwanted weakness (Gormley, 1997). However without a control group it is not possible to judge whether all of these were associ-
lated with BtA. The trials reviewed did not test the participants for the presence of antibodies to BtA and formation of these would seem unlikely after single injections. None were found in a study in which tests were carried out 12 weeks after injection (Koman, 1995).

OUTCOME MEASURES

Establishing strong evidence on the efficacy of any intervention relies on the outcome measures available. There is a shortage of good assessment tools for cerebral palsy (Boyce, 1991). The studies included in this review all used a PRS which does not have published data regarding reliability and validity. In fact each trial adapted the PRS to suit its own needs thereby reducing its reliability further. Corry did, however, test interrater reliability and the responsiveness of the measure to change. As participants in all the included trials were ambulatory the question was not whether injection of BtA enabled them to walk but whether it enabled them to walk better. The PRS is an attempt to measure this.

Computerised gait analysis, such as that used in one trial (Corry), measures parameters that determine the quality of the gait in a reproducible way (Kirkpatrick, 1994). However this is not an ideal outcome measure because young children may be too small or unable to co-operate with the procedure, and because it is expensive and not easily available.

One trial (Flett) used GMFM to assess functional progress following intervention. This is a well validated and reliable measure of the achievement of motor activities (Russell, 1989). It is not, however, designed to assess the quality of performance of those activities, which suggests that GMFM is unlikely to be very responsive when looking for change in a child who can already walk, especially change over a short period of time.

The Gross Motor Performance Measure (GMPM) has been developed for use alongside the GMFM. It looks at the quality of movement in 20 of the items and has been shown to be responsive to changes in that quality (Boyce, 1995). The combination of the GMFM and the GMPM has the potential to be a sensitive measure for changes following BtA administration.

A further outcome measure that has not, as yet, been used in any published studies of BtA is the Pediatric Evaluation of Disability Inventory (PEDI) (Nichols, 1996). This is a standardised assessment of functional abilities in children and is administered by questioning the parents or caregivers, so establishing how a child functions in everyday life. A similar tool is the Functional Independence Measure for Children (WeeFIM) (Sperle, 1997). Use of these measures would add a further dimension to the assessment of change following treatment with BtA.

Other outcome measures used in the reviewed studies quantify impairments which, while being indicative of a child’s condition, do not necessarily relate to their ability to function in the world. The Ashworth scale and its modified version are regarded as valid tools for measuring tone, but have not been tested for reliability in children with CP (Bohannon, 1987). Recent work, presented at the American Academy for CP and Developmental Medicine in 1998, adapted Tardieu’s method of spasticity measurement (Boyd, 1998) and found that it was sensitive to change following administration of BtA or placebo in a randomised, controlled, double-blind study. If either of these measures, or change in passive range of movements, could be found to correlate with and be predictive of change in motor function and performance they would be ideal measures, being quick and easy to administer. Unfortunately no such links have yet been established.

AUTHORS’ CONCLUSIONS

Implications for practice

Based on the currently available data this systematic review can provide no reliable conclusions. As the review did not find any evidence to support or refute the efficacy of BtA in improving function, it is recommended that all use of BtA for the treatment of leg spasticity in CP be as part of a clinical trial.

Implications for research

This systematic review has demonstrated the need for further research into the use of BtA for leg spasticity in children with cerebral palsy. It has also highlighted the need for good methodological quality and comprehensive reporting of results in a relevant format. This should include a full description and comparison of baseline characteristics of the children in each treatment group because i) the efficacy of BtA may vary with particular characteristics and ii) the trial subjects may not be representative of the wider population of children with CP, making it dangerous to generalise the trial or review conclusions. Suggested priorities for the design of future randomised, controlled trials include larger sample size; pragmatic treatment regimes; trial to extend for at least one year, ideally longer; multiple injection sessions and use of outcome measures relevant to function and disability rather than to impairment.

We also need to evaluate the place of BtA treatment in the overall management of children with spasticity from any cause. Does it minimise or delay the need for other interventions? Does it improve the effectiveness of other interventions? Is the overall strategy of using BtA better than the strategy of not using BtA? What are the economics of BtA use?

POTENTIAL CONFLICT OF INTEREST

The authors of this review are currently conducting a randomised controlled trial of the use of botulinum toxin for the treatment of lower limb spasticity in children with CP.
leg spasticity in children with cerebral palsy. Financial support for this trial is provided by Action Research and Ipsen Ltd.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Corry, 1998 [published and unpublished data]

Flett, 1999 [published data only]

Koman, 1994 [published data only]

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Koman, 1995

Richman, 1996

Wissel, 1996

Wyatt, 1998

Additional references

Bohannon, 1987

Boyce, 1991

Boyce, 1995

Boyd, 1997

Boyd, 1998

Bryman, 1994

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Cosgrove, 1994

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Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. 1286–1291.

Eames, 1996

Fehlings, 1998

Forrsberg, 1997

Gormley, 1997

Hambleton, 1995

Kirkpatrick, 1994

Koman, 1993

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Nelson, 1995

Nichols, 1996

Russell, 1989

Schantz, 1994

Scott, 1980

Scott, 1994

Sperle, 1997

Stell, 1995

Sutherland, 1996

Thompson, 1998
## Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corry, 1998</td>
<td>Randomised controlled, parallel group, trial with outcome assessor blinded for one outcome (PRS). Participants and person giving treatment were aware of treatment allocation. Randomisation was by means of instructions written on 20 cards sealed in identical envelopes, one of which was drawn for each child. Allocation concealment was adequate. 12 weeks follow-up. There were no drop-outs.</td>
<td>20 ambulant children with CP - 11 diplegia, 8 hemiplegia, 1 quadriplegia - and dynamic calf equinus. Severity of CP not given. Average age 4.6 years, age range 2 - 9 years. 13 boys and 7 girls.</td>
<td>Intramuscular injections of BtA (8 Botox, 2 Dysport) into calf muscles or stretching casts for 4 - 6 weeks. Doses of 6 - 8 mu/kg of Botox and 15mu/kg of Dysport. The total dose was split between the two legs for bilateral injections.</td>
<td>Physician rating scale, range of passive dorsiflexion, Ashworth scale, Vicon 3D gait analysis</td>
<td>Allocation concealment A – Adequate</td>
</tr>
<tr>
<td>Flett, 1999</td>
<td>Randomised controlled, parallel group trial with blinded outcome assessors. Participants and person giving treatment were aware of treatment allocation. Randomisation was pharmacy controlled. Allocation concealment was adequate. 6 months follow-up. 2 drop-outs from BtA group.</td>
<td>20 ambulant children with CP - 10 diplegia, 5 hemiplegia, 2 quadriplegia, 1 triplegia, (2 drop-outs not described) - leg spasticity and dynamic equinovarus or equinovalgus. Severity of CP not given. Average age 3.7 years (standard deviation 1.4 years). 11 boys and 7 girls (2 drop-outs not described).</td>
<td>Intramuscular injection of BtA (Botox) into calf muscles or plaster casts for 4 weeks. Doses of 4 - 8 mu/kg were used with a maximum of 20 mu/site. Both groups had night plasters for the 8 weeks following the study intervention.</td>
<td>Physician rating scale, global scoring scale for video gait analysis, modified Ashworth scale, goniometry, gross motor function measure (GMFM), parent questionnaire.</td>
<td>Allocation concealment A – Adequate</td>
</tr>
<tr>
<td>Koman, 1994</td>
<td>Double-blind randomised controlled trial, no statement of allocation concealment, parallel groups, 4 - 6 weeks follow-up, no drop-outs</td>
<td>12 children with spastic CP - 8 diplegic, 4 hemiplegic - and dynamic equinovarus or equinovalgus deformities. Severity of CP not given. Age range 4 - 11 years, average age and ratio of boys to girls not given.</td>
<td>Intramuscular injections of BtA (Botox) or placebo (saline) into medial and lateral heads of gastrocnemius. Tibialis posterior also injected if equinovarus deformity present. Initial dose of 1mu/kg/leg, 2 weeks later further injections of 2 mu/kg/leg</td>
<td>Physician rating scale, Biodex isokinetic computerised dynamometry, physiotherapy evaluations, parent/guardian assessment</td>
<td></td>
</tr>
</tbody>
</table>
**Characteristics of excluded studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baillieu, 1997</td>
<td>Main study outcome measure was post-operative pain. This is not included in this review</td>
</tr>
<tr>
<td>Chutorian, 1995</td>
<td>Published in abstract form only. So far, have been unable to obtain further information. Apparently the same study as Koman, 1995</td>
</tr>
<tr>
<td>Koman, 1995</td>
<td>Published in abstract form only. So far, have been unable to obtain further information. Apparently the same study as Chutorian, 1995</td>
</tr>
<tr>
<td>Richman, 1996</td>
<td>Published in abstract form only. So far, have been unable to obtain further information.</td>
</tr>
<tr>
<td>Wissel, 1996</td>
<td>Compared two doses of BtA but did not have a control group receiving another intervention.</td>
</tr>
<tr>
<td>Wyatt, 1998</td>
<td>Published in abstract form only. So far, have been unable to obtain further information.</td>
</tr>
</tbody>
</table>

**ANALYSES**

**Comparison 01. BtA versus placebo**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability measures</td>
<td></td>
<td></td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>Parental opinion</td>
<td></td>
<td></td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
</tr>
</tbody>
</table>

**Comparison 02. BtA versus casts**

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability measures</td>
<td></td>
<td>Other data</td>
<td></td>
<td>No numeric data</td>
</tr>
<tr>
<td>Impairment measures</td>
<td></td>
<td>Other data</td>
<td></td>
<td>No numeric data</td>
</tr>
</tbody>
</table>

**INDEX TERMS**

**Medical Subject Headings (MeSH)**

Botulinum Toxin Type A [*therapeutic use]; Cerebral Palsy [complications; *drug therapy]; Leg; Muscle Spasticity [*drug therapy; etiology]; Neuromuscular Agents [*therapeutic use]

MeSH check words

Child; Humans

**COVER SHEET**

**Title**
Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy

**Authors**
Ade-Hall RA, Moore AP

**Contribution of author(s)**
Information not supplied by author

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/

**Review first published**
/
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**Date of most recent SUBSTANTIVE amendment**  
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Information not supplied by author  

**Date new studies found but not yet included/excluded**  
Information not supplied by author  

**Date new studies found and included/excluded**  
Information not supplied by author  

**Date authors’ conclusions section amended**  
Information not supplied by author  

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**Editorial group code**  
HM-MOVEMENT  

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**Analysis 01.01. Comparison 01 BtA versus placebo, Outcome 01 Disability measures**  

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>Koman, 1994</td>
<td>5/6</td>
<td>2/6</td>
<td>6.59 [0.73, 59.34]</td>
<td>100.0</td>
<td>6.59 [0.73, 59.34]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 5 (Treatment), 2 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable  
Test for overall effect $z=1.68$ p=0.09
Analysis 01.05. Comparison 01 BtA versus placebo, Outcome 05 Parental opinion

Review: Botulinum toxin type A in the treatment of lower limb spasticity in cerebral palsy
Comparison: BtA versus placebo
Outcome: Parental opinion

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Koman, 1994</td>
<td>4/6</td>
<td>2/6</td>
<td></td>
<td>100.0</td>
<td>3.39 [0.39, 29.64]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6</td>
<td>6</td>
<td></td>
<td>100.0</td>
<td>3.39 [0.39, 29.64]</td>
</tr>
</tbody>
</table>

Total events: 4 (Treatment), 2 (Control)
Test for heterogeneity: not applicable
Test for overall effect z=1.11 p=0.3

Analysis 02.01. Comparison 02 BtA versus casts, Outcome 01 Disability measures

Disability measures

<table>
<thead>
<tr>
<th>Study</th>
<th>PRS</th>
<th>3D gait analysis</th>
<th>GMFM</th>
<th>Muscle tone</th>
<th>Passive ankle ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corry, 1998</td>
<td>BtA - significantly improved p=0.006 (Sign test)</td>
<td>Ankle at foot initial contact</td>
<td>No significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cast - significantly improved p=0.031 (Sign test)</td>
<td>Ankle range</td>
<td>No significant difference</td>
<td>Maximal dorsiﬂexion</td>
<td>p=0.04</td>
</tr>
<tr>
<td></td>
<td>No significant difference between groups (Mann-Whitney U test)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flett, 1999</td>
<td>BtA - significantly improved p=0.001 (MANOVA)</td>
<td>Standing dimension:</td>
<td>BtA - significantly improved p=0.01 (MANOVA)</td>
<td>Cast - significantly improved p=0.04 (MANOVA)</td>
<td>No significant difference between groups (ANOVA)</td>
</tr>
</tbody>
</table>
### Disability measures  
*Continued*

<table>
<thead>
<tr>
<th>Study</th>
<th>PRS</th>
<th>3D gait analysis</th>
<th>GMFM</th>
<th>Muscle tone</th>
<th>Passive ankle ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

#### Analysis 02.02.  Comparison 02 BtA versus casts, Outcome 02 Impairment measures

<table>
<thead>
<tr>
<th>Impairment measures</th>
<th>Study</th>
<th>PRS</th>
<th>3D gait analysis</th>
<th>GMFM</th>
<th>Muscle tone</th>
<th>Passive ankle ROM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Corry, 1998**
  - BtA group no significant improvement  
    - p=0.07 (Sign test)  
  - Cast group no significant improvement  
    - p=0.22 (Sign test)  

- **Flett, 1999**
  - BtA - significantly improved p<0.03  
    - (MANOVA)  
  - Cast - significantly improved p<0.001  
    - (MANOVA)  
  - No significant difference between groups (ANOVA)