Botulinum toxin-A (Botox) intradetrusor injections in children with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review


CRD summary
This review addressed the efficacy and safety of botulinum toxin type A (Botox) injections into the detrusor in children with neurogenic urinary incontinence. The authors concluded that Botox injections provided a clinically significant improvement with few side-effects. Insufficient details of the review methods and the low quality of the included studies mean that the reliability of these conclusions is uncertain.

Authors' objectives
To review the efficacy and safety of botulinum toxin type A (Botox) injections into the detrusor muscle in children with neurogenic detrusor overactivity and urinary incontinence or overactive bladder symptoms of neurogenic origin.

Searching
Searches were made in MEDLINE and EMBASE for English-language papers published in full between 1993 and March 2007. The search strategy was reported and reference lists of review articles published between 2005 and 2007 were checked by hand.

Study selection
Clinical studies evaluating the efficacy, safety, or both of Botox intradetrusor injections in children suffering from neurogenic detrusor overactivity or neurogenic overactive bladder symptoms were eligible for inclusion. Studies of urethral sphincter injection, patients with detrusor sphincter dyssynergia, or the alternative Botox brand Dysport were not eligible, nor were studies involving both Botox and Dysport, unless the results for each agent were presented separately. If a study was reported in more than one article, only the latest report with the highest number of patients or the longest follow-up was included.

The mean age of participants in the included studies was 6.9 to 13 years (range one to 20) and the most common disorder was myelomeningocele. All patients had neurogenic detrusor overactivity with urinary incontinence, neurogenic overactive bladder symptoms, or both, and these had not responded to antimuscarinic agents. The amount of Botox injected ranged from 5 to 12 units per kg with a maximum dose of 360 units. The most common regime was 30 injection sites (range 10 to 50) with 10 units per kg per mL (dilution range 10U/kg/20mL to 12U/kg/15mL). In all studies the injections were into the dome and base of the bladder, avoiding the trigone. Where stated, the intervention involved a rigid cystoscope under general anaesthesia. The duration of active treatment ranged from two to 52 weeks. The outcomes reported were bladder incontinence, maximum detrusor pressure, maximum cystometric capacity, reflex detrusor volume, and bladder compliance. At study entry, most patients used clean intermittent catheterisation for bladder emptying.

The authors did not state how the papers were selected for the review.

Assessment of study quality
The authors applied a level of evidence to each study, but they did not state the criteria and scale they used for these decisions and how many reviewers made the assessment.

Data extraction
Data on efficacy and side-effects were extracted. The mean absolute and percentage change between baseline and follow-up for each outcome was calculated.

Data extraction was performed by one reviewer and checked by a second. The authors did not state how discrepancies were resolved.
Methods of synthesis
Studies were combined in a narrative synthesis and grouped according to each outcome studied.

Results of the review
Six studies (108 participants) were included. All of them were open-label and they were all assigned an evidence level of three. Follow-up ranged from 12 weeks to 52 weeks after the final treatment.

Bladder incontinence (four studies): Rated on a scale from zero (no incontinence) to three, the absolute change from baseline score varied from -2.5 to -0.3 and the percentage change varied from -88% to -10%. Between 65% and 87% of patients became completely continent after Botox treatment.

Other measures: The absolute change in maximum detrusor pressure (six studies) varied from -56.1 to +2.2 cm H\(\text{2}\)O and the percentage change varied from -50 to +4%. The absolute change in maximum cystometric capacity (six studies) varied from 6.2 to 168.4 mL and the percentage change varied from 3 to 163%. The absolute change in reflex detrusor volume (four studies) varied from 11 to 226 mL and the percentage change varied from 15 to 314%. The absolute change in bladder compliance (five studies) varied from -1.7 to 35.1 mL/cm H\(\text{2}\)O and the percentage change varied from -11 to 222%.

The most frequent side-effects were procedure-related urinary tract infections, in 7 to 20% of patients. Muscle weakness was not reported in any study.

Authors’ conclusions
Botox injections into the detrusor provided a clinically significant improvement and seemed to be very well tolerated in children with neurogenic detrusor overactivity and incontinence or neurogenic overactive bladder symptoms that had not responded to antimuscarinics.

CRD commentary
The review addressed a clear research question and the participant and intervention inclusion criteria were well defined. The search was restricted to English-language studies and excluded unpublished data and studies published only in abstract form. It is possible that the results were affected by language and publication bias. Methods were used to minimise reviewer error and bias in the extraction of data, but it was not clear whether similar steps were taken in study selection.

The quality of the studies was assessed and levels of evidence assigned, but it is not clear how this was done. All of the studies were open label and it is unlikely that they were affected by bias, but they were small, ranging from 10 to 26 patients. The results appeared to vary over time within individual studies and the reasons for this were not clear. The authors acknowledged that the data on adverse events were poorly reported and their conclusions on the safety of Botox may therefore not be reliable.

Insufficient details of the review methods and low quality of the included studies mean that the reliability of the authors’ conclusions is uncertain.

Four of the authors were consultants for one or more of the following companies: Allergan, Medtronic, Ono Pharma, Bayer, Astellas, Pfizer, and Coloplast.

Implications of the review for practice and research
Practice: The authors stated that parents should be informed about the benefit-to-risk ratio of Botox intradetrusor injections in children before treatment.

Research: The authors stated that further studies should focus on the difference in benefit afforded by 10 compared with 30 injections; the duration of the effect; whether adjuvant antimuscarinic drugs have an impact on the efficacy or duration of the effect of Botox, with reporting of local and systemic adverse events; and the effect of re-injection, in randomised controlled trials. Studies should also assess the effect of repeated Botox injections on the risk of fibrosis and alteration in bladder compliance.
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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.