



Botulinum toxin-A for treating detrusor overactivity

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Abstract

Background: The purpose of this review is to examine the evidence regarding the use of botulinum toxin-A (BTX-A) in the treatment of detrusor overactivity that is refractory to anticholinergic treatment.

Clinical Question: What is the safety and efficacy of botulinum toxin-A treatment of detrusor overactivity refractory to anticholinergic treatment?

Methods: We searched The Cochrane Library, including The Cochrane Database of Systematic Reviews, DARE, CENTRAL and HTA in October 2007. We also searched OVID Medline and Embase. We included systematic reviews or controlled trials published in English.

Studies were selected and appraised by one reviewer using inclusion, exclusion and appraisal criteria established a priori.

Results: A recent (2007) Cochrane systematic review was found that examined botulinum toxin injections for adults with overactive bladder syndrome. A search of recent publications identified a single trial that had been published subsequent to the date of the literature search for the review.

The authors of the Cochrane review identified 8 published randomised or quasi-randomised controlled trials that involved a relatively small number of patients. The limited evidence from this small number of trials suggests that BTX-A improves the symptoms of overactive bladder syndrome and therefore shows promise as a treatment of detrusor overactivity. There is insufficient data available to determine the most effective dose and there are no published studies of the long-term effects of this treatment

The results of the recent randomised controlled trial found that BTX-A at a dose of 200 U was safe and effective for idiopathic detrusor activity and that the beneficial effects persisted for at least 24 weeks.

Conclusions: There is some limited evidence available from controlled trials regarding the efficacy and safety of botulinum toxin-A for detrusor overactivity. The findings from the small number of controlled trials published to date have demonstrated beneficial effects. There is a need for additional controlled trial data to confirm these findings. Similarly the preliminary evidence in relation to safety is promising but additional evidence is needed in order to more fully determine the safety of this treatment including any long term effects.

Background

Botulinum toxin is a potent neurotoxin. It is derived from the bacterium *Clostridium botulinum*. The serotype A product of botulinum toxin (BTX-A) has been used in a number of clinical areas since the 1980s. Botulinum toxin is known to block the release of acetylcholine and will temporarily paralyse any muscle into which it is injected. One area of potential application of BTX-A is the treatment of voiding dysfunction and in particular the problems associated with detrusor overactivity including urinary urgency, frequency and/or urinary urge incontinence. The symptoms of detrusor overactivity are usually referred to as overactive bladder syndrome. The conventional methods of treatment for this condition have included lifestyle modification, bladder retraining, the use of anticholinergic medication and intermittent self catheterisation. Intradetrusor injections of botulinum toxin have emerged as a second line option to treat patients with detrusor overactivity refractory to anticholinergics.

The purpose of this review is to examine the evidence regarding the use of botulinum toxin A in the treatment of detrusor overactivity that is refractory to anticholinergic treatment. This evidence review is provided in reference to the request by Southern Health urology specialists for BTX-A to be available for use for specified urological indications.

Clinical Question

What is the safety and efficacy of botulinum toxin-A treatment of detrusor overactivity refractory to anticholinergic treatment?

Methods

Study Selection Criteria

Patient	Patients with detrusor overactivity refractory to anticholinergic treatment				
Intervention	Treatment with serotype A product of botulinum toxin (BTX-A)				
Comparison	Placebo				
Outcomes	Any				
Study Type	Systematic review or controlled trial	Publication Date	Any	Language	English

Search Strategy

Evidence Source	Date of Search or Issue searched
Cochrane library	10 th October 2007
Medline (Ovid)	17 th October 2007
Embase	17 th October 2007

Search

1	detrusor.mp or exp Urinary Tract/ or bladder.mp
2	exp Botulinum Toxins/ or exp Botulinum Toxin Type A/ or botul\$.mp
3	1 and 2 This search was undertaken in Medline and adapted for use in other databases

Data Collection & Analysis

Studies were selected and appraised by one reviewer in consultation with colleagues using study selection and appraisal criteria established a priori.

The literature search identified one evidence-based guideline, two recent systematic reviews, and a small number of controlled trials. The guideline commissioned by NICE addressed the management of urinary incontinence in women and was published in 2006¹. A systematic review was undertaken to inform the development of the guideline. This review did not identify any controlled trials. Based on the evidence from case series only, the guideline recommends the use of BTX-A for treatment of detrusor overactivity only in cases in which the patients have not responded to conservative treatments and the only remaining alternatives are major surgical interventions with high morbidity. The two systematic reviews identified in the literature search were both published in 2007.^{2,3} Both of these systematic reviews have similar conclusions regarding Botulinum toxin for treatment of detrusor overactivity. The Cochrane review by Duthie et al² was selected as most appropriate for appraisal in this evidence review as the results were based on eight controlled trials as opposed to three trials covered in the other review. The Cochrane review included research published up to November 2005. A search of the Cochrane library, Embase and Medline were undertaken in order to identify any systematic reviews or controlled trials published after this date. One additional RCT was identified.⁴

Results

The Cochrane review² examined the evidence regarding the efficacy of botulinum toxin injections for adults with overactive bladder syndrome. Most of the evidence regarding the use of botulinum toxin for detrusor overactivity has been presented in the research literature as either case reports or case series. The authors identified 8 published randomised or quasi-randomised controlled trials. The trials involved a relatively small number of patients ranging from 14 to 59 participants. The limited evidence from this small number of trials suggests that botulinum toxin can improve the symptoms of overactive bladder syndrome. There is insufficient data available to determine the most effective dose and there are no published studies of the long-term effects of this treatment. Only one study has compared the effectiveness of the botulinum injection with alternative treatments. This study observed superior outcomes for botulinum toxin over intravesical resiniferatoxin.

The RCT⁴ examined the efficacy and safety of botulinum toxin-A for treating idiopathic detrusor overactivity in a single centre, randomised double-blind placebo controlled trial. Significant increases in maximum cystometric capacity (the primary endpoint) were observed at 4 and 12 weeks in patients treated with BTX-A compared to placebo. An extension was added for follow up in the botulinum toxin-A group for a further 24 weeks. Treatment with BTX-A reduced frequency and urge incontinence episodes at 4 and 12 weeks and reduced urgency at 4 weeks, compared to the placebo. In patients receiving BTX-A post-void residual increased at 4 weeks but became insignificant at 12 weeks. Significant improvements in quality of life were observed following BTX-A in comparison to the placebo group. The results of the extension study demonstrated that the beneficial effects of BTX-A observed in the study persist for at least 24 weeks. It should be noted that the authors reported a relationship with the company that produces the Botulinum Toxin medication.

A summary of the study characteristics and results and a critical appraisal of the study quality for both the Cochrane review and RCT is presented at the end of this report. Both of the publications included in this review were found to be of high quality.

Discussion

There is limited evidence available from controlled trials regarding the efficacy and safety of BTX-A treatment for detrusor overactivity refractory to anticholinergic. The evidence that is available from the initial controlled trials suggests that the treatment may be effective and safe although further research is needed to confirm these findings. In particular there is a need for additional evidence in order to determine the optimal dose or dose range and to more fully examine the safety of the treatment including any long term effects.

Conclusions

Botulinum toxin-A shows promise as a therapy for detrusor overactivity refractory to anticholinergics. The findings of the initial controlled trials suggest that the treatment is effective and safe however additional evidence is needed to confirm this. The optimal dose has not yet been demonstrated.

References

1. National Institute for Health and Clinical Excellence (NICE). The Management of Urinary Incontinence in Women (2006). www.nice.org.uk/CG040.
2. Duthie J, Wilson DI, Herbison GP, Wilson D. Botulinum toxin injections for adults with overactive bladder syndrome. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005493. DOI: 10.1002/14651858.CD005493.pub2
3. MacDonald, R, Fink, HA, Huckabay, C, Monga, T and Wilt, TJ (2007) Botulinum toxin for treatment of urinary incontinence due to detrusor overactivity: A systematic review of effectiveness and adverse effects. Spinal Cord, Vol 45 (8), 535-541
4. Sahai, A, Khan, M, Dasgupta, P. (2007) Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: Results from a single centre, randomised, double-blind, placebo controlled trial. The Journal of Urology, Vol 177, 2231-2236

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Table 1. Appraisal of Systematic Review**Study:** Botulinum toxin injections for adults with overactive bladder syndrome (Cochrane Systematic Review) Duthie et al 2007**Study Characteristics**

Patients	Adults with neurogenic or idiopathic overactive bladder
Intervention	Intravesical botulinum toxin injection
Comparisons	No intervention, other interventions – lifestyle modification, bladder retraining, pharmacological treatments, surgery, bladder instillation techniques, neuromodulation.
Outcomes	Incontinence episodes, bladder capacity, maximum detrusor pressure, quality of life.
Inclusion Criteria	RCT or quasi-randomised controlled trials, adults, intravesical injection of botulinum toxin versus placebo or alternative treatment.
Exclusion Criteria	Other studies

Study Validity

Focused research question	Yes	Includes a description of a clear and focused of research question and the specific hypotheses addressed in the systematic review
Specified inclusion/ exclusion criteria	Yes	Includes a detailed description of the inclusion and exclusion criteria for studies to be included in the review
Explicit and comprehensive search strategy	Yes	Describes search strings used in the search and the methods used in the search strategy which involved a search of the Cochrane Central Register of Controlled Trials (CENTRAL) the Cochrane Incontinence Group's Trials Register, hand searching of journals and conference proceedings.
Validity of included trials appraised	Yes	The review authors assessed the methodological quality of the identified trials using the Cochrane Incontinence Review Groups quality assessment tool. Any disagreements were decided in a discussion with a third person.
Homogeneity between studies assessed	Yes	Synthesis of results across studies was not possible due to the small number of studies identified and included in the review and the different designs and outcome measures used.
Summary of main results presented	Yes	Includes a description of the results of the studies and tables summarising the methods and results of each study
Strengths and limitations of included studies discussed	Yes	Includes a discussion of the quality and scope of the studies.

Results

Eight studies met the inclusion criteria. Results varied across studies. Injection of Botulinum A was found to produce superior outcomes to placebo in relation to incontinence episodes, bladder capacity, maximum dose detrusor pressure and quality of life. There is insufficient data available to determine the most effective dose. Only one study has compared the effectiveness of the botulinum injection with alternative treatments. This study observed superior outcomes for bolulinum toxin over intravesical resiniferatoxin.

Author's Conclusions

Intravesical botulinum toxin shows promise as a therapy for overactive bladder symptoms, but as yet there is limited evidence to demonstrate the efficacy and safety of this therapy. The optimal dose has not yet been demonstrated.

Our comments

A high quality review. The initial findings from controlled trials suggest that intravesical botulinum toxin shows promise as a therapy for overactive bladder symptoms. Further research is required to substantiate the efficacy and safety of this therapy and to compare the effectiveness of this approach with alternative therapies. There are no published studies examining the long-term effects of the intervention.

Table 2 Appraisal of Randomised Controlled Trial

Study: Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: Results from a single centre, randomised, double-blind, placebo controlled trial Sahai et al, 2007

Study Characteristics

Study	Study Type	N (total)	Setting	Patients	Intervention	Comparison	Outcomes
Sahai et al (2007)	RCT	34	Single centre trial in London, UK. May 2004 to Feb 2006.	Male and female patients with symptoms overactive bladder for at least 6 months & urodynamically proved idiopathic detrusor overactivity refractory to anticholinergics.	Intradetrusor injections of 200 U botulinum toxin-A BTX-A (n=16). The injection technique involved 20 injections of 10 U/ml per injection site into the bladder wall.	Intradetrusor injections of placebo (n=18).	Primary outcome - change in maximum cystometric capacity. Secondary outcome measures - changes in overactive bladder symptoms, post-void residual, maximum detrusor pressure during filling cystometry & reflux detrusor volume and quality of life. Followup at 4, 12 and 24 weeks.

Study Validity

Specified inclusion/ exclusion criteria	Yes	Clear objective criteria in relation to symptoms of overactive bladder/idiopathic detrusor overactivity. The criteria in relation to previous treatment with anticholinergics are less clear.
Adequate method of randomisation	Yes	Randomisation code was generated by independent statistician
Concealment of allocation	Yes	Randomisation code was sent to pharmacist
Groups similar at baseline	Yes	Baseline characteristics were similar except for urgency which was more severe in the BTX-A group.
Blinding - patients/ investigators/ assessors	Yes	BTX-A and placebo preparations were identical in appearance. Patients, investigators and others involved in conducting the study remained blinded to treatment assignment for the duration of the study to the point of the 12 week follow up. At this point the study was unblinded and an extension to the study was added which involved further follow-up in the botulinum toxin-A group for a further 24 weeks.
Duration of follow-up	Yes	The follow-up periods were 4 and 12 weeks. An extension was added for follow up in the botulinum toxin-A group for a further 24 weeks.
Proportion lost to follow up	Yes	Not stated clearly but appears to be low as missing values were reported to be less than 2%.
Objective & independent assessment of outcomes	Yes	Included objective measures of maximum cystometric capacity, maximum detrusor pressure during filling cystometry and quality of life. Self-reported overactive bladder symptoms were recorded by patients in a diary with some potential for subjectivity.
Inclusion of all subjects in analysis		Two patients in the BTX-A group were excluded from the analysis because they did not meet the inclusion criteria (no evidence of detrusor overactivity).
Other comments:		One potential limitation of the study is the concomitant use of anticholinergics. All patients had taken part in a trial of anticholinergic treatment prior to the trial – this treatment had been unsuccessful due to poor efficacy or tolerability. Patients taking anticholinergics despite a history of poor treatment efficacy were asked to continue unless they believed it unnecessary. Those not taking anticholinergics were advised not to restart. The authors of the study declared a “financial interest or other relationship” with Allergan Inc which produces Botulinum Toxin medication.

Results

Significant increases in maximum cystometric capacity (the primary endpoint) were observed at 4 and 12 weeks in patients treated with BTX-A compared to placebo. Treatment with BTX-A reduced frequency and urge incontinence episodes at 4 and 12 weeks and reduced urgency at 4 weeks, compared to the placebo. In patients receiving BTX-A post-void residual increased at 4 weeks but became insignificant at 12 weeks. Significant improvements in quality of life were observed following BTX-A in comparison to the placebo group. The results of the extension study suggest that the beneficial effects of BTX-A observed in the study persist for at least 24 weeks.

Author's Conclusions

The authors concluded that Botulinum toxin-A at 200 U is safe and effective for treating patients with idiopathic detrusor overactivity refractory to anticholinergics and that the beneficial effects persist for at least 24 weeks.

Our comments

A recently published high quality randomised control trial which contributes to the growing body of evidence from controlled trials that indicates that botulinum toxin-A is safe and effective for treating patients with detrusor overactivity refractory to anticholinergics.
