Botulinum Toxin A in the Treatment of Upper and Lower Limb Spasticity: A Systematic Review of Randomized Controlled Trials

This report and the French version entitled La toxine botulinique A pour traitement de la spasticité des membres supérieurs ou des membres inférieurs : étude méthodique des essais cliniques comparatifs et randomisés are available on CCOHTA’s web site.

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Botulinum Toxin A for Upper and Lower Limb Spasticity: A Systematic Review

Technology Name
Botulinum toxin A (BTX-A)

Disease or Condition
Spasticity is a symptom that can cause disability in affected patients. It is characterized by increased muscle tone. Because spasticity may interfere with voluntary movements, it can affect the activities of daily living. Spasticity is treated in an effort to decrease muscle tone, alleviate distressing symptoms, improve motor function or prevent contractures.

The Issue
BTX-A is approved in Canada to treat focal spasticity in patients with cerebral palsy or stroke. As the use of BTX-A increases, there is a need to review its relative benefit and harm. The objective of this assessment was to determine whether BTX-A is efficacious and safe when it is used to reduce focal spasticity in patients with upper and lower limb spasticity, compared with other interventions.

Methods and Results
The efficacy and safety of BTX-A for focal spasticity associated with any disorder was assessed through a systematic review of the literature. The relative benefit and harm of BTX-A in any disorder were determined by examining its demonstrated impact on muscle tone, range of motion, function and disability, pain, quality of life and adverse events.

A total of 33 RCTs are included in the review: 12 focused on patients with stroke, 15 on patients with cerebral palsy, two on patients with multiple sclerosis and four on patients with other disorders.

Implications for Decision Making
- **BTX-A has a demonstrated effect on muscle tone.** BTX-A reduced muscle tone in patients with stroke, cerebral palsy and multiple sclerosis.

- **With regard to the effect of BTX-A on range of motion, many studies report increased range of motion, improved gait and improved function.** Statistical significance is not always reached. The variability across studies may be due to the variety of disorders studied and their unique expression, and the differences in outcome measures and study design. Combining the results to improve clarity is sometimes impossible.

- **With regard to the relative harm of BTX-A, few adverse events are reported in most trials and are often transient.** Improved methods of reporting would allow for more robust conclusions about the relative safety of BTX-A.

- **With regard to the long-term effects of BTX-A, patient-specific and goal-focused outcomes are needed to further define clinically meaningful improvements in therapeutic outcomes.**

This summary is based on a comprehensive health technology assessment available from CCOHTA’s web site (www.ccohta.ca): Garces K, McCormick A, McGahan L, Skidmore B. Botulinum toxin A for upper and lower limb spasticity: a systematic review.
1 Introduction

Spasticity is a symptom associated with various conditions and characterized by excessive increase in muscle tone.\(^1,2\) In this hypertonic state, the affected muscles are contracted. This may cause stiffness and pain, and make movements awkward and unpredictable. Voluntary muscle control may be lost, making it difficult for those affected to perform the routine activities associated with daily living, such as walking, eating, dressing and maintaining personal hygiene.\(^3\) Spasticity is defined clinically as a resistance to passive stretching of the muscle that gives way suddenly as the passive stretch continues.\(^3\)

Spasticity is common in several conditions, including cerebral palsy, stroke and multiple sclerosis. It can be treated with pharmacologic or non-pharmacologic interventions or a combination of both. Treatment is aimed at decreasing muscle tone, relieving functional limitations, minimizing related uncomfortable symptoms, and preventing contracture (fixed shortening of the affected muscles).\(^2,3\)

Pharmacologic treatments can have non-selective or selective effects. Non-selective drugs produce systemic effects and can be used for treating generalized spasticity. These drugs, however, cause undesirable side effects, such as sedation and muscle weakness, which may limit their use. Local anesthetics and nerve-blocking agents act more selectively and can be injected locally. Local anesthetics temporarily block nerve conduction, while certain nerve-blocking agents chemically destroy nerves.\(^4\) Both are associated with undesirable side effects. Local anesthetics can be toxic to the cardiovascular and central nervous systems and nerve-blocking agents carry the risk of sensory impairment when used on the upper limbs.\(^4\)

Non-pharmacologic treatments provided by physical and occupational therapy may include stretching exercises to increase range of motion; splints, casts and orthoses to facilitate therapeutic stretching of the muscles; and electrical stimulation to activate muscles and enable patients to perform functional tasks. These types of therapy can be used with pharmacologic interventions to take advantage of the decreased muscle tone already achieved.

**Botulinum Toxin**

Botulinum toxin (BTX-A) is produced by the anaerobic bacterium *Clostridium botulinum*.\(^5\) It is used as a pharmacologic agent to decrease muscle tone by inhibiting the release of acetylcholine at the neuromuscular junction.\(^5\) BTX-A can be injected directly into affected muscles, resulting in a targeted, focal intervention. It is approved for therapeutic use in Canada for focal spasticity associated with cerebral palsy or stroke. BTX-A is commercially available as Dysport® (Ipsen) in Europe and as Botox® (Allergan) in North America and most other markets.\(^6,7\) The two formulations differ in potency. The appropriate dose is determined on an individual basis and is related to the characteristics of the muscle being injected. The pharmacologic effects of BTX-A injection normally last from two to four months.\(^6\) Like other treatments for spasticity, BTX-A has side effects and contraindications associated with its use. The most common local adverse effect is transient weakness in adjacent muscles. Systemic adverse events are rare, but include transient flu-like symptoms, excessive fatigue and anaphylaxis. Patients who are pregnant, breast-feeding or have significant nerve or muscle disease should avoid this treatment.\(^8\)
Botox® is approved in Canada as therapy for the following indications:  

- subjective symptoms and objective signs of cervical dystonia (spasmodic torticollis) in adults  
- blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients ≥12 years of age  
- strabismus in patients ≥12 years of age  
- dynamic equinus foot deformity due to spasticity in pediatric cerebral palsy patients ≥2 years of age  
- hyperhidrosis of the axilla  
- focal spasticity, including upper limb spasticity associated with stroke in adults.

As the use of Botox® increases and a growing number of people are exposed, there is a need to review its benefit and harm.

2 Objectives

The objective is to conduct a systematic review of the literature to determine if BTX-A is effective and safe compared with other therapies when it is used to reduce focal spasticity in patients with upper or lower limb spasticity.

3 Methods

Literature Review

A systematic review of the literature was conducted to identify studies involving the use of BTX-A in the treatment of upper and lower limb spasticity associated with any disease state. Research papers were obtained from several sources: core databases of published research; grey literature available from the web sites of health technology assessment and related agencies; clinical trial registries; and manual searches of bibliographies of selected papers. In addition, two manufacturers of BTX-A, Allergan and Ipsen, were invited to submit relevant product information. Searches included studies in any language. Most searches were performed in April 2002 and were updated throughout the project, with final updates occurring on April 29, 2004.

Inclusion Criteria

The literature review was conducted to report the relative benefit and harm of BTX-A compared with other interventions in the treatment of upper and lower limb spasticity associated with any disorder. To be included in the review, studies had to be randomized controlled trials (RCTs) that compared the use of commercially available preparations of BTX-A to any pharmacologic or non-pharmacologic intervention in patients experiencing spasticity in their upper or lower limbs. In addition, studies had to report at least one of the following outcome measures: muscle tone; passive range of motion (PROM); active range of motion (AROM); motion and gait analysis; function and disability assessed by physicians, patients or caregivers; pain; quality of life; or adverse events. Muscle tone was the primary outcome measurement of interest.
Data Abstraction
Two reviewers extracted information on study design, patient characteristics, outcome measures and adverse events, using a data abstraction form that was designed a priori. Missing data or patient information were requested from the primary author(s).

Assessment of Study Quality
The quality of each trial was evaluated by two independent reviewers using the Jadad scale and noting allocation concealment. This scale rates the quality of the trial by assigning points to aspects of trial design, including randomization, blinding and reporting of withdrawals. The highest possible score of five suggests that the study uses sound methods. Lower scores (≤2) are associated with exaggerated estimates of benefit. Researchers took this into account when performing further analyses and interpreting study results.

Statistical Methods
Where possible, study results were combined through meta-analyses with intention-to-treat data. Meta-analyses were performed when enough quantitative data were available and where trials were comparable in design and quality. Binary data are expressed as risk differences (RD) and continuous data are expressed as weighted mean differences (WMD). Point estimates are reported with their 95% confidence intervals (CI).

Measuring Outcomes
Various methods are used to quantify the outcomes reported in the trials reviewed. The Ashworth scale is a five-point rating scale for measuring muscle tone. Ratings from zero to four are assigned to increasing levels of muscle tone; the lower the score, the more relaxed the muscle. A modified version (MAS) and an expanded version (EAS) of the Ashworth scale exist. Different authors use different versions. Joint movement is measured with a goniometer,10 a device with arms that rotate around a central axis and measure the amount of movement in joints by degrees. PROM is measured when another person moves the patient’s limb. AROM is measured when the patient is in control of the joint movement. A patient’s gait or movement is often recorded on video and analyzed later. This is called video gait analysis (VGA) and is reported in many of the studies reviewed. Information on quality of life, functional improvement and pain are gathered using scales and questionnaires that are often specific to a trial. Using these scales, patients, caregivers and physicians are asked to rate their impressions of the effectiveness of treatment.

4 Results
A total of 33 unique RCTs reported in 37 citations (four duplicates) were identified for inclusion in this review. The studies reported on BTX-A in the treatment of upper or lower limb spasticity associated with stroke, cerebral palsy, multiple sclerosis and other conditions. The studies differed in the comparisons made, outcome measures reported and duration of follow-up. Variability in outcome measures prevented the pooling of results, except in two trials by Bakheit et al. that described BTX-A treatment in patients with stroke and upper limb spasticity.
Post-stroke Patients with Upper Limb Spasticity

Nine RCTs reported upper limb spasticity in stroke patients.\textsuperscript{11-19} Eight compared BTX-A to placebo; one compared BTX-A, with or without electrical stimulation, to placebo.\textsuperscript{14} Quality scores for the trials ranged from two to five points. Two trials adequately described how patients were allocated to interventions. While studies demonstrated a decrease in muscle tone, different outcome measures were reported across studies.\textsuperscript{11-19} There was evidence of increased PROM in four studies reporting this measure, but the increase was not always statistically significant.\textsuperscript{12,16} One of four trials reported a significant increase in AROM,\textsuperscript{16} but no quantitative data were presented to support the finding.

Pain was reported in five trials,\textsuperscript{11-15} but there was no common definition and no indication that the measures differed significantly between groups. Several studies reported that patients were able to function and perform daily activities better when treated with BTX-A.\textsuperscript{11-14,19} Reports by patients, caregivers and physicians on the effects of treatment were positive, but not always statistically significant. A multicentre study by Brashear et al.,\textsuperscript{19} used an investigator-rated disability assessment scale to assess functional ability on various tasks, dressing, limb position, and pain. When all areas of disability were evaluated, they found more improvement in patients treated with BTX-A than in patients receiving placebo. At 12 weeks, the Botox\textsuperscript{®} -treated group showed significant improvement; and significantly higher global assessment scores compared with those for placebo were reported by physicians, patients, and caregivers.

Adverse events were reported in all trials. In three trials,\textsuperscript{11-13} these events were reported in a manner appropriate for meta-analysis. No significant differences between groups were found when these three studies were combined and analyzed.

Post-stroke Patients with Lower Limb Spasticity

Three trials described in four publications reported on lower limb spasticity in stroke patients.\textsuperscript{20-23} All three trials used different comparisons. Quality scores for the trials ranged from two to five points.

Kirazli and On\textsuperscript{20} compared BTX-A to phenol and reported outcome measures for muscle tone, PROM, AROM and adverse events. Using the Ashworth scale to measure muscle tone at the ankle at two, four, eight and 12 weeks, they found that the mean decreases from baseline in the scores for ankle dorsiflexion and eversion were significantly greater for BTX-A recipients compared to phenol recipients at two and four weeks only. Improvements were noted in the BTX-A group for PROM and AROM, but significance levels were not reported for these measures. When reporting adverse events, the authors stated that 30\% of the phenol group experienced impairment in sensation (dysesthesia) for two to four weeks after injection. Two patients (20\%) experienced mild discomfort after receiving the BTX-A injection.

Johnson \textit{et al.}\textsuperscript{22} compared walking speed between a control group receiving physiotherapy alone and a treatment group receiving physiotherapy plus BTX-A. They found that the median walking speed was significantly higher in the treatment group.
Pittock et al.\textsuperscript{23} compared various doses of BTX-A with placebo. At four weeks, they found that treatment groups demonstrated statistically significant differences in muscle tone when compared to placebo. At eight and 12 weeks, only the 1,500 U group demonstrated a significant difference in muscle tone, when compared with placebo. The investigators also measured walking speed, step rate and step length, but did not find differences between groups. They did, however, find a significant difference in pain when measured at the knee, ankle or foot at eight weeks. Patients and investigators thought that the overall condition improved with BTX-A treatment compared to placebo, but these measures were not statistically significant.

**Patients with Cerebral Palsy and Upper Limb Spasticity**

Two trials involved patients with cerebral palsy and upper limb spasticity. Quality scores for the trials ranged from two to three and allocation concealment was unclear in both trials. Corry et al.\textsuperscript{24} compared BTX-A (Botox\textsuperscript{®} and Dysport\textsuperscript{®}, based on availability) to placebo. They found that treatment significantly improved muscle tone at the elbow at two weeks and in the wrist at two and 12 weeks. They also reported that patients in the treatment groups noted more improvement than did patients in the placebo group, but they did not indicate if the differences were significant.

Fehlings et al.\textsuperscript{25} compared a group receiving Botox\textsuperscript{®} plus occupational therapy to a group receiving occupational therapy only. Using the MAS to record muscle tone, they found that both groups showed a decline in spasticity throughout the study. The BTX-A group showed a greater rate of decline, but this was not statistically significant. The primary outcome measure in this study was the quality of upper extremity skills test (QUEST). QUEST is a standardized measure of upper extremity function. It revealed statistically significant improvement in the BTX-A group at one month. Significant improvements were also noted in the caregivers’ ratings of the children’s activities of daily living. No adverse events were reported during the study.

**Patients with Cerebral Palsy and Lower Limb Spasticity**

Thirteen trials with quality scores ranging from one to four points involved comparisons between BTX-A and other treatments for cerebral palsy and lower limb spasticity.\textsuperscript{26-41} Some trials used Botox\textsuperscript{®};\textsuperscript{27-29,31-34,38,41} others used Dysport.\textsuperscript{26,39,40} Comparisons were made primarily between BTX-A and placebo, but casting and physiotherapy were also used as comparators. The heterogeneity across studies regarding study design, comparators and outcome measures precludes the formation of an overall estimate of effect. Results are summarized according to outcome measure.

Muscle tone was assessed in three studies. Using the Ashworth scale, Corry et al.\textsuperscript{30} reported a significant decrease in calf muscle tone from baseline to two weeks in the BTX-A group. It was not indicated, however, whether the BTX-A group was significantly different from the placebo group. Reddihough et al.\textsuperscript{41} demonstrated a mean decrease in the MAS score at the left hip and calf at six months with BTX-A and physiotherapy, compared with physiotherapy. There were no significant differences in the MAS score between treatment with BTX-A and fixed plaster casting in the study by Flett et al.\textsuperscript{29}

Sutherland et al.\textsuperscript{31} measured PROM at the ankle joint with the knee flexed and found increased range in the BTX-A group, but decreased range in the placebo group. The authors did not report if
these differences were significant. Corry et al.\textsuperscript{30} also found differences in PROM scores at the ankle joint with the knee flexed and extended. The treatment and placebo groups were not significantly different with the knee extended. The authors reported that with the knee flexed, the treatment group demonstrated significant differences from baseline at weeks 2 and 12. Baker et al.\textsuperscript{35} found differences between groups at four weeks in the mean change from baseline PROM scores at the ankle joint when the knee was extended and flexed. Similarly, Reddihough et al.\textsuperscript{41} noted significant increases in the BTX-A group with the knee extended at three months and with the knee flexed at six months. Other studies measuring PROM did not find differences between groups.\textsuperscript{26,28,29}

Three trials reported that there were differences between BTX-A and placebo when measuring AROM. Sutherland et al.\textsuperscript{31} found that patients in the BTX-A group showed greater improvement in ankle dorsiflexion than patients in the placebo group. Koman et al.\textsuperscript{28} found that mean change from baseline was significantly greater in the BTX-A group than in the placebo group. Love et al.\textsuperscript{32} showed that dynamic muscle range improved in the BTX-A group compared with the placebo group at three and six months post-injection. Using a modified physician rating scale (PRS), Koman et al.\textsuperscript{28} found statistically significant improvements from baseline in the gait of patients receiving BTX-A compared with placebo. In an earlier study,\textsuperscript{33} 83% of patients in the BTX-A group had improved gait compared with 33% of patients in the placebo group, but the authors did not report the significance level. Corry et al.\textsuperscript{30} measured gait and found improvement in stance and plantar flexion at 12 weeks after injection or cast removal in the BTX-A group compared with the group with casts. Uhbi et al.\textsuperscript{26} used video gait analysis (VGA) and found a greater improvement in the BTX-A group compared with the placebo group at six and 12 weeks, but no difference at two weeks. The authors also used a clinician-rated Gross Motor Function Measure (GMFM) in which a change of \( \geq 6\% \) was considered to be clinically meaningful. They found clinically significant improvement in the BTX-A group compared with the placebo group at 12 weeks. Five additional studies\textsuperscript{29,34,35,40,41} reporting this measure did not demonstrate significant improvements from using BTX-A.

Reports from patients, parents and physicians were positive and generally indicated an increased improvement in function in the BTX-A treatment groups compared with placebo.\textsuperscript{33,35,40,41}

One trial, which was designed to look specifically at pain,\textsuperscript{27} reported a significant improvement with BTX-A treatment versus placebo after adductor release surgery at 24 hours and 48 hours. The study measured pain after adductor release surgery to treat or prevent hip dislocation in children with spastic cerebral palsy with or without pre-treatment with BTX-A.

Three trials reporting adverse events were combined and analyzed.\textsuperscript{26,33,35} The results showed that patients receiving BTX-A experienced significantly more adverse events than those receiving placebo. The adverse events noted were focal and temporary. Common adverse events were local pain and weakness.

**Patients with Multiple Sclerosis and Lower Limb Spasticity**

Two trials described in three publications\textsuperscript{42-44} compared BTX-A to placebo in patients with multiple sclerosis and lower limb spasticity that interfered with activities of daily living. The quality of the trials ranged from four to five and allocation concealment was unclear. One trial\textsuperscript{43} reported
significant reduction in spasticity at six weeks that was attributed to reduced muscle tone. The other trial found improvements in PROM in all treatment groups, but no significant differences in PROM, AROM, assessments of function or disability and adverse events were reported.

Patients with Upper and Lower Limb Spasticity in Various Disorders
Four trials involved patients with spasticity from a variety of diseases. The RCTs ranged in quality from two to four and allocation was adequately concealed in three of four trials. A crossover trial to evaluate BTX-A versus saline showed improvement in muscle tone in patients with spasticity. Another crossover trial investigating the effectiveness of Dysport for ankle plantar flexor and foot invertor spasticity showed that eight of 22 patients demonstrated decreased muscle tone and increased gait velocity change after Dysport, compared with placebo. A dose-response study showed that patients with upper limb spasticity associated with stroke or head injury had a significant decrease in muscle tone and an increase in PROM compared with placebo. In a parallel group trial investigating the effectiveness of BTX-A for managing focal hypertonia in adults, compared with placebo, BTX-A treatment produced significantly greater improvements in muscle tone and self-rated problem scores. A range of results were reported and no overall conclusions can be made because of the diverse patient population and treatment protocols.

5 Limitations
The ability of this review to meet its objectives is limited by the heterogeneity of the studies selected for review. Although all studies were RCTs, the authors used different outcomes; and different scales and measures to assess them. Studies were not comparable for many reasons, making it impossible to conduct a comprehensive meta-analysis of the relative efficacy and safety associated with the use of BTX-A to treat spasticity.

Most studies reported on physical functional outcome measures rather than functional, task-oriented outcomes. Few studies utilized goal-oriented meaningful outcome measures that allow patients, caregivers, and clinicians to assess whether treatment would help them with daily tasks and allow them to lead more independent lives.

6 Conclusion
BTX-A treatment demonstrates decreases in muscle tone across most trials and diseases. Increased range of motion, improved gait and improved function are shown in many studies, but statistical significance is not always reached. The variability in results across studies may be due to the variety of disorders studied; the unique expression of disease state in each clinical condition; and the differences in study designs and outcome measures used. Combining results to improve clarity is seldom possible. The adverse events reported in most studies are low in number and often temporary. The use of improved methods of reporting would allow more robust conclusions to be reached about the comparative safety of BTX-A. Long-term, patient-specific, goal-focused outcomes are needed to further define the clinically meaningful improvements in therapeutic outcomes.
7 References