Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Botulinum Toxin A for Spasticity and Associated Pain Following Damage to the Central Nervous System: Clinical and Cost Effectiveness and Guidelines for Use

Date: 28 May 2008

Context and policy issues:

Spasticity is a widespread disabling form of muscle overactivity affecting patients with central nervous system (CNS) damage as a result of stroke, cerebral palsy, traumatic head injury, or multiple sclerosis.[1] Spasticity leads to interference with voluntary muscle movements and pain, negatively impacting health-related quality of life.[1] Usually, non-pharmacologic interventions such as physical and occupational therapy are used in combination with pharmacologic interventions or surgery to manage spasticity. Oral medications such as dantrolene, baclofen, tizanidine, benzodiazepines, cannabinoids, and gabapentin are commonly used for generalized spasticity due to their non-selective effects.[2] However, systemic side effects such as sedation, confusion, dizziness, and generalized weakness increase the risk for injurious falls.[1] Periodic liver function tests are also recommended with baclofen, tizaidine, and dantrolene due to potential adverse effects on the liver.[3] Phenol or alcohol injections can also be used to reduce spasticity, but severe pain is considered a major limitation to their use.[1]

In 2001, Health Canada approved botulinum toxin A (BTX-A) as an alternative treatment option for the management of spasticity.[4] BTX-A inhibits the release of acetylcholine at the neuromuscular junction, resulting in muscle relaxation.[2] The aim of therapy with BTX-A is to reduce muscle tone, contractural deformity, relieve disabling pain, and improve function.[5,6] When initiated early, BTX-A may prevent complications of spasticity such as fixed contractures.[7] BTX-A is commercially available in North America under the brand name Botox® (Allergan) and in Europe under the brand name Dysport® (Ipsen).[4] These two formulations differ in potency and are not interchangeable. Approved indications for BTX-A in Canada include the treatment of dynamic equinus foot deformity due to spasticity in pediatric patients two years of age or older with cerebral palsy, and for the management of focal spasticity including the treatment of upper limb spasticity associated with stroke in adults.[8]

BTX-A is administered by injection in a clinic or hospital setting.[4] Dose is adjusted according to factors such as severity of spasticity, number of muscles involved, age, previous response to botulinum therapy, and adjunctive therapy.[9] The pharmacologic effect of BTX-A injection usually lasts 2 to 4 months.[5,6] Injections may be repeated every three to eight months to maintain the effect, sometimes delaying or obviating the need for surgery.[5,6] Higher doses or more frequent administration may result in neutralizing antibody formation and loss of efficacy.[8] In general, adverse events occur within the first week following injection, and are predictable, local, and transient.[8] Localized pain, tenderness, and bruising may occur at the injection site.[8] Weakness of adjacent muscles may occur as a result of spread of the toxin. Systemic adverse events are rare and include fever, flu-like symptoms, and anaphylaxis.[8]

A 2005 systematic review completed by Canadian Agency for Drugs and Technologies in Health (CADTH) found that while there is evidence that BTX-A decreases muscle tone for upper and lower limb spasticity, statistical significance was not always reached for increased range of motion, improved gait, or improved function relative to other interventions or placebo.[4] Due to its high cost, further evidence for the long term safety and efficacy of BTX-A for upper and lower limb spasticity is necessary to help guide formulary decisions. This report will discuss literature published since the CADTH systematic review to determine if any new evidence exists as to the clinical and cost effectiveness of BTX-A relative to other therapies for the treatment of spasticity and associated pain following damage to the CNS. Current guidelines for the use of BTX-A for this indication will also be discussed.

Research questions:

1. What is the clinical effectiveness of botulinum toxin A for the management of spasticity and associated pain following damage to the central nervous system?

2. What is the cost effectiveness of botulinum toxin A for the management of spasticity and associated pain following damage to the central nervous system?

3. What are the guidelines for use of botulinum toxin A in clinical practice for the management of spasticity and associated pain following damage to the central nervous system?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and May 2008 for economic studies, and between April 2004 and May 2008 for systematic reviews/health technology assessments, clinical trials, observational studies and guidelines. The results are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/health technology assessments, clinical trials, observational studies, guidelines and economic studies. This search was supplemented by hand searching the bibliographies of selected papers.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by economic evaluations, randomized controlled trials, observational studies and evidence-based guidelines.

Summary of findings:

Health Technology Assessments

No health technology assessments were identified.

Systematic Reviews and Meta-Analyses

Post-Stroke Spasticity

Two systematic reviews were identified for the use of BTX-A in post-stroke spasticity.[3,10]

A 2008 systematic review pooled data from nine placebo-controlled double-blind randomized controlled trials (RCTs) to evaluate the safety and efficacy of either Botox® or Dysport® preparations for upper and lower limb spasticity (Table 1).[10] Results showed clinically significant improvement between baseline and 4-6 weeks in the Modified Ashworth Scale (MAS) and Global Assessment Scale (GAS) spasticity scores with BTX-A treatment. There was no significant difference between placebo and BTX-A for the frequency of adverse events. Although the studies reviewed showed statistically significant reductions in muscle tone, an overall effect on functional disability was not fully observed.

A 2006 systematic review pooled data from 9 placebo-controlled double-blind RCTs to examine the safety of BTX-A in post-stroke spasticity (Table 1).[3] Results did not show a significant difference in total adverse events between the BTX-A group compared with those receiving placebo. The most frequently reported adverse events (5-10% frequency) were respiratory infection, seizures, incoordination, and injection site pain, none of which occurred at a significantly higher rate in the BTX-A group (all $p > 0.05$). The majority of adverse events were rated as mild or moderate in severity. Only nausea was reported at a significantly higher rate in the BTX-A group (2.2% versus 0% with placebo; $p=0.011$). In contrast, injection site pain, chest pain, and allergic reaction were reported significantly more frequently in the placebo group (all $p<0.05$).

Table 1: Systematic reviews for BTX-A in post-stroke spasticity

STUDY	DESIGN	MAJOR RESULTS	CONCLUSIONS
Rosales *et al*., 2008[10]	**Inclusion criteria:** Patients with hemiplegic stroke and moderate to severe muscle spasticity of the upper or lower extremities **Exclusion criteria:** Patients previously treated with BTX-A, phenol or alcohol, or those with fixed contractures, or profound muscle atrophy **Included studies:** 9 double-blind placebo-controlled RCTs (n=464) **Intervention:** BTX-A Dysport® 500-1500 U/IM injection or Botox® 200-360 U/ IM injection vs. Placebo **Follow-up:** 4-6 weeks after treatment	**Change in MAS score after 4-6 weeks** WMD= 0.87 95% CI: 0.52-1.22 Z= 4.89, p<0.0001 **Improvement in MAS score of one or more points after 4-6 weeks** OR= 4.5 95% CI: 2.79-7.25 Z = 6.7, p<0.00001 **Improvement in GAS score after 4-6 weeks** OR= 5.85 95% CI: 3.12-10.95 Z= 5.52, p<0.00001 **Total Adverse Events** OR= 0.84 95% CI: 0.55-1.28 Z= 0.82, p=0.41	BTX-A is superior to placebo for improving muscle tone in upper and lower limb spasticity following stroke and is well tolerated. **Limitations:** Significant heterogeneity in trials due to different BTX-A preparations, injection techniques, muscle groups being injected in the upper and lower limbs. Poor inter-rater reliability for the MAS score. Lack of comparison to other treatment modalities. Long-term outcomes not assessed.
Turkel et al., 2006[3]	**Inclusion criteria:** Patients with upper or lower spasticity post-stroke **Exclusion criteria:** Patients previously treated with surgery, BTX-A, intrathecal baclofen, phenol or alcohol, or those with neuromuscular disease, fixed contractures, or profound muscle atrophy **Included studies:** 9 double-blind placebo-controlled RCTs (n=792) **Intervention:** BTX-A Botox® mean dose 231 U (range, 59-400U) 1-3 treatments vs. Placebo **Follow-up:** Mean 17.8 weeks (range, 0.1-44.7 weeks) after treatment	**Total adverse events** BTX-A: 65.9% Placebo: 63.2% p=0.475	BTX-A has an acceptable safety profile for patients with focal spasticity following stroke. **Limitations:** Only a third of patients received more than 1 injection with BTX-A. Lack of comparison to other treatment modalities. Long-term adverse effects not reported.

RCT= Randomized controlled trial, MAS=Modified Ashworth Scale, GAS= Global Assessment Scale, WMD= Weighted Mean Difference, OR=Odds Ratio

Cerebral Palsy

Four systematic reviews on the treatment of upper limb[11,12] and lower limb[13,14] spasticity with BTX-A in cerebral palsy were identified.

Results from two systematic reviews[11,12] indicate that there is a absence of good quality evidence to support or refute the clinical use of BTX-A for spastic upper limb management in children with cerebral palsy (Table 2). Considerable variation in doses, dilution volume, method of administration, selection of target muscles, characteristics of subjects, and assessment scales make it difficult to compare the results of the included studies.

Two systematic reviews[13,14] assessed the use of BTX-A for lower limb spastic equinus in patients with cerebral palsy (Table 2). A 2006 systematic review pooled results from 6 placebo-controlled double-blind RCTs and reported statistically significant gait improvement with BTX-A treatment relative to placebo with minor and self limited adverse effects.[14] A 2007 systematic review examined the effect of casting (the application of fiberglass and/or plaster to the lower limb to immobilize the ankle) either alone or in combination with BTX-A.[13] Results showed that there is no consistent evidence that combining these two treatment modalities is superior to either intervention alone or that the order of treatment affects functional outcome.

The lack of specific functional outcome measures for children with spasticity and of reliable spasticity measures makes interpretation of current research literature difficult. There is still limited information about the long-term efficacy and safety of BTX-A with regard to growth and maturity in children with cerebral palsy. Long-term effects of repeated BTX-A injections such as prevention of fixed contractures, surgical intervention, and long-term improvement in gait and function require further analysis.

Table 2: Systematic reviews for BTX-A in children with cerebral palsy

STUDY	DESIGN	OVERALL CONCLUSIONS
Reeuwijk *et al.*, 2006[11]	**Inclusion criteria:** Children with upper limb spasticity from cerebral palsy **Included studies:** 3 RCTs (n=64) 9 Prospective uncontrolled studies (specific study design not described) (n= 107) **Intervention:** BTX-A vs. placebo or physical/occupational therapy (3RCTs) BTX-A with physical or occupational therapy (Prospective uncontrolled studies) **Follow-up:** Range 19 days-229 days	There is insufficient evidence for the use of BTX-A to reduce spasticity and improve range of motion and upper limb function in children with cerebral palsy. **Limitations:** Significant heterogeneity in treatment goals, localization and severity of spasticity, invalid assessment instruments. Insufficient statistical power to demonstrate true treatment effects. Long-term safety and efficacy not reported.

STUDY	DESIGN	OVERALL CONCLUSIONS
Park *et al*., 2006[12]	**Inclusion criteria:** Children with upper limb spasticity from cerebral palsy **Included studies:** 4 RCTs 8 Case Series 4 Descriptive Case Reports (n= not reported) **Intervention:** BTX-A Dysport® <500 units/session or 29 units/kg body weight or Botox® <400 units/session or 12 units/ kg body weight (Other Interventions not described) **Follow-up:** (not reported)	Due to limited high quality evidence and inconsistent results among studies, there is insufficient information to support or refute the usefulness of BTX-A injection for the management of upper limb spasticty in children with cerebral palsy. **Limitations:** Significant heterogeneity in treatment goals, localization and severity of spasticity, invalid assessment instruments and insufficient statistical power to demonstrate true treatment effects. Long-term safety and efficacy not reported.
Cardoso et al., 2006[14]	**Inclusion criteria:** Children with spastic equinus foot from cerebral palsy **Included studies:** 6 double-blind placebo-controlled RCTs (n= not reported) **Intervention:** BTX-A vs Placebo **Follow-up:** (not reported)	Treatment of patients with spastic equinus foot in cerebral palsy with BTX-A resulted in statistically significant gait improvement tested using the Physician Rating Scale and Video Gait Analysis (Peto OR= 3.99; 95% CI: 2.20-7.22). Adverse effects were more frequently observed after the use of BTX-A (Peto OR= 2.62; 95% CI: 1.47-4.67) but were mild and self limited. **Limitations:** Major outcomes were represented by medical evaluation and video gait analysis, both of which are subjective. Lack of objective standardized outcomes with long-term follow-up.

STUDY	DESIGN	OVERALL CONCLUSIONS
Blackmore *et al*., 2007[13]	**Inclusion criteria:** Children with spastic equinus foot from cerebral palsy **Included studies:** Casting only (1 RCT, 10 case series, 1 single subject study) Casting vs. BTX-A (3 RCTs) Casting plus BTX-A vs casting (2 RCTs, 1 cohort study) BTX-A plus casting vs BTX-A (2 RCTs) Casting then BTX-A vs BTX-A then casting(1 RCT) (n= not reported) **Follow-up:** Maximum 12 months	There is no strong and consistent evidence that combining casting and BTX-A is superior to either intervention alone or that either casting or BTX-A is superior to the other immediately after treatment. There is no evidence that the order of treatment affects outcome. **Limitations:** Small sample sizes, lack of power calculations, poor methodological quality of studies, lack of long-term follow-ups for safety and efficacy

RCT= Randomized controlled trial, MAS=Modified Ashworth Scale, OR=Odds Ratio

Randomized Controlled Trials

There were eight RCTs identified that were not included in the previously discussed systematic reviews.[15-22]

Post-Stroke Spasticity

Two double-blind RCTs assessed the utility of BTX-A for hemiplegic shoulder pain in stroke patients.[15,16] Yelnik *et al.* compared a single injection of BTX-A with placebo in twenty patients after ischaemic stroke or heamorrhagic stroke.[15] Results showed a significant improvement in pain at week 4 with BTX-A versus placebo (p=0.025). A significant improvement was also noted for lateral rotation (p=0.018) and finger flexors (p=0.025) at week 4 for the BTX-A group compared with placebo. There were no treatment-related adverse events in the BTX-A group. In the placebo group, one patient experienced severe injection site pain. Lim *et al*. compared the efficacy of a single intramuscular injection of BTX-A with a single intraarticular injection of triamcinolone acetonide in 29 hemiplegic stroke patients with shoulder pain.[16] At 12 weeks after treatment, there were significant improvements in pain (p=0.051) and shoulder range of motion (p=0.059) in the BTX-A group versus the triamcinolone acetonide group. However, no significant differences were noted for other outcomes including the MAS and physician global rating. No adverse events were observed in either group. These trials suggest that that intramuscular injections of BTX-A may be superior to placebo and intraarticular steroids for the management of shoulder pain in spastic hemiplegic patients although larger long-term trials are needed to confirm these findings.

Cerebral Palsy

Hawamdeh *et al.* conducted a single-blind RCT to determine the long-term effects of multi-injections of BTX-A on muscle tone and functional abilities in children with calf spasticity.[17] Forty patients were randomized to receive 3 successive doses of BTX-A to the calf muscle at intervals of 3 to 4 months with physical therapy or physical therapy alone. Muscle tone and ankle range of motion showed statistically significant improvements following BTX-A injection at

3 months (p< 0.0001, p=0.04, respectively) and at 18 months (p=0.0005, p=0.007, respectively) after the last injection compared with the control group. Gross motor function only showed significant improvement at 18 months (p=0.02). These findings suggest that intramuscular injections of BTX-A may be beneficial as an adjunct to conventional physical therapy to reduce muscle stiffness, improve motor function, and improve range of motion for up to 18 months after 3 successive sessions. Adverse effects were not reported in this trial.

Results from three small RCTs indicate that BTX-A in combination with occupational therapy in children with upper limb spasticity from cerebral palsy is more effective than occupational therapy alone for the attainment of functional goals.[18-20] No differences in treatment-related adverse events were observed in these trials.

One placebo-controlled double-blind RCT evaluated the effects of BTX-A in 61 children with adductor spasticity.[21] Four weeks after treatment, results showed that BTX-A was significantly better for a reduction in adductor muscle tone and for functional outcomes compared to placebo. The most frequently observed adverse events were muscular weakness, dysphagia and increased frequency of passing urine (numbers in each group and statistical analysis not reported).

A placebo-controlled RCT (n=33) in children with spastic diplegia showed no difference in the family's satisfaction with the child's function, despite documentation of improvement in spasticity and function in the BTX-A treated group after 24 weeks using a variety of objective measures.[22] There were no significant differences between groups for frequency of adverse effects. These observations suggest that treatment benefits may be subtle and that providers should communicate realistic expectations to the family prior to initiating treatment with BTX-A.

Interpretation of these studies is difficult because of the absence of reliable measures of spasticity and challenges with measuring meaningful functional changes in children with disabilities. The long term safety and efficacy of BTX-A in this population requires further study.

Observational Studies

Two observational studies evaluating long-term safety and efficacy of repeated injections of BTX-A for post-stroke spasticity were retrieved in the search.[23,24]

Gordon *et al.* reported the long term safety and efficacy of patients with upper limb spasticity post-stroke (n=110) who received a maximum of three injections of 200 to 240 U of Botox® during a open-label study over 42 weeks.[23] Significant and sustained improvements were observed for the Disability Assessment and Ashworth scores. The most frequently reported treatment-related adverse events were muscle weakness (5.5%) and injection-site pain (3.6%) which did not increase in frequency or severity as treatment progressed. One patient discontinued the study due to severe muscle weakness and increased incoordination which later resolved. Only one patient developed neutralizing antibodies and did not respond to treatment with BTX-A. The authors concluded that repeated treatments of BTX-A over 42 weeks significantly improved function and tone in post-stroke upper limb spasticity.

Similar results were also observed in a prospective open label trial of 41 patients with upper limb muscle spasticity post-stroke.[24] A dose of 1000 U of Dysport® was injected at baseline and repeated every 12, 16, or 20 weeks as clinically indicated. Each patient received a total of three treatment cycles and efficacy was assessed using MAS. Improvements were observed in all outcome measures. Mild to moderately severe treatment related adverse events were reported in 24% of cases. The most frequently reported treatment-related adverse events were

pain at the injection site (24%), fatigue (14%) and dysphagia (2%). There were no serious adverse events. No neutralizing antibodies were detected in any of the patients. The authors concluded that the effect of BTX-A can be maintained with repeated treatment cycles with duration of effect between 12 and 20 weeks and without the development of neutralizing antibodies at the given dose.

These trials are limited by small sample size and by a study design that does not control for confounding factors or selection bias. Further long term RCTs are necessary to confirm these findings in various subgroups of patients with upper and lower limb spasticity.

Economic Evaluations

Two cost-effectiveness studies[25,26] and one costing study[27] were identified in the literature search.

Ward *et al.* used a decision tree model to compare the cost-effectiveness and treatment outcomes of oral therapy (using benzhexol, baclofen, or tizanidine) with BTX-A in post-stroke patients with flexed wrist/clenched fist spasticity in the United Kingdom.[25] All patients also received physiotherapy. Effectiveness data were collected from an expert panel experienced in the treatment of post-stroke spasticity. Cost effectiveness was calculated based on the number of successfully treated months per year and the cost of providing treatment (including cost of drug, professional time, surgery, orthotics, and hospitalization due to spasticity). Successfully treated months were defined as months in which patients received sufficient benefit to warrant continuation of therapy. Results showed that 35% of patients receiving oral therapy showed an improvement in pre-treatment functional targets compared with 73% and 68% of patients treated with BTX-A as first- or second-line therapy, respectively. The cost per successfully-treated month was £942 for BTX-A as first-line therapy, £1387 for BTX-A as second-line therapy, and £1697 for oral therapy alone. A sensitivity analysis demonstrated the robustness of these results. The authors concluded that BTX-A is a cost-effective and clinically efficacious treatment for post-stroke spasticity. A limitation to this study is that estimates of effectiveness were based on expert opinion which may be subject to bias and uncertainty. A systematic review of the literature would have provided more robust estimates.

Ruiz *et al.* conducted a retrospective survey to evaluate the cost-effectiveness of BTX-A for the management of cerebral palsy in children in a German tertiary care hospital.[26] Overall, 214 patients were recruited with 107 in the BTX-A group and 107 in the non-BTX-A treated group. Data on healthcare resource use and clinical outcomes over 12 months were collected from the date patients received their first injection and from the date controls were first admitted into hospital. BTX-A use led to an 85% reduction in the number of children requiring surgery relative to control patients ($p<0.0001$). In addition, there was a 60% reduction in hospitalization bed days ($p<0.0001$). However, there were no statistically significant differences between the groups in terms of ambulatory rating, manual disability, or brace wear tolerance at 12 months. The total costs during the first year of treatment were Euro 16,700 per child treated in the BTX-A group and Euro 33,800 for the control group. The length of hospital stay and the cost of orthotics and mobility aids collectively accounted for 88% of the cost of treating patients in both groups. The authors concluded that BTX-A led to a significant reduction in the requirement for surgery and health care resources during the first year following treatment, without any loss of clinical improvement. However, it is unknown how BTX-A affected the need for surgery and associated outcomes in subsequent years. This study is limited by its retrospective design that does not control for confounding variables and selection bias. The study period of 12 months was inadequate to account for long-term effects of BTX-A treatment.

Dickson *et al*. compared cerebral palsy patients treated with BTX-A versus those not treated with BTX-A to assess the total cost of care in the United States.[27] The cost of services was derived from the paid claims of Medicaid recipients from 1995 to 2001. A total of 406 patients (58 in the BTX-A group and 348 in the non-BTX-A group) were used in the analysis. The mean two year cost of treatment for BTX-A users was US$44,761 versus US$41,553 for non-BTX-A users. The authors concluded that over the 24 months studied, treatment with BTX-A did not significantly add to the total cost of care. This study is limited by the small number of patients used in the analysis.

Guidelines and Recommendations

Five guidelines discussing the role of BTX-A in adults and children with various conditions with spasticity were identified in the literature search.[28-32]

New guidelines released in 2008 from the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology review the use of BTX-A in adult spasticity and childhood spasticity resulting from cerebral palsy.[28] A systematic review retrieved 14 RCTs in adult spasticity and 6 RCTs for spastic equinus and adductor spasticity in pediatric cerebral palsy. On the basis of evidence from these studies, they concluded that BTX-A should be offered as an option for the treatment of spasticity in adults and should be considered to improve active function. However, there is insufficient evidence to recommend an optimum technique for muscle localization at the time of injection. For cerebral palsy, the guidelines recommend that BTX-A injections into the calf muscles should be offered as a treatment option for equinus vasus deformity in children. BTX-A should be considered for adductor spasticity and for postoperative pain control in children undergoing adductor-lengthening surgery. BTX-A should also be considered as a treatment option in children with upper extremity spasticity. The guidelines note that no optimal dosage based on age or body weight has been established. Given the high degree of intra- and inter-patient variability, doses must be established for each BTX-A preparation on an individual basis.

A 2006 consensus statement from the Neurotoxin Spasticity Consensus Group presents a treatment algorithm for the management of adult spasticity with BTX-A.[29] In this algorithm, BTX-A appears as an adjunctive treatment along with other interventions including oral medications, physical or occupational therapies, phenol injections, surgery and intrathecal baclofen. Based on a systematic review of the literature, therapy with BTX-A was recommended if the spasticity is focal (Level 1b; based on evidence from RCTs).

Guidelines developed from a 2006 European consensus table on BTX-A for children with cerebral palsy state that the use of BTX-A in combination with other treatment modalities (including functional therapy, orthoses, casting, splinting, surgical interventions, intrathecal baclofen, or other pharmacotherapy) has the potential to achieve functional benefits for children with cerebral palsy.[30] Information on safe dosage ranges based on preparation are discussed and the ranges are presented in Table 3. The guidelines note that local weakening beyond the therapy goal, distal local adverse effects (e.g. bladder dysfunction), and generalized weakness can occur when preparation specific and dilution guidelines are not respected. Dosing specific to different age groups is not discussed in these guidelines.

Table 3: Dosing recommendations for different preparations of BTX-A in children with cerebral palsy

Preparation	Dosing Recommendations
Botox®	Safe range (U/kgbw): 6-25 Total dose (U): 400-600
Dysport®	Safe range (U/kgbw): 15-25 Total dose (U): 900

U=Units, kgbw=kilogram body weight

Guidelines for the use of BTX-A in multiple sclerosis were published in 2004 from the National Collaborating Centre for Chronic Conditions in the UK.[31] The guidelines were based on a non-systematic review of the literature and a rating scheme was used to rank the strength of the recommendations. Intramuscular BTX-A is not recommended for routine use for spasticity and spasms but may be considered for relatively localized hypertonia or spasticity not responding to other treatments (rating B; based on evidence from non-randomized or quasi-experimental studies or extrapolated from systematic reviews, meta-analyses, or RCTs). The guidelines recommend baclofen or gabapentin as first-line pharmacological therapy for this indication (rating A; based on evidence from systematic reviews, meta-analyses, or RCTs). For contractures at the joints, local BTX-A injections are recommended in combination with other treatment modalities including serial plaster casts and surgery (rating D; based on evidence from committee reports or opinions and/or clinical experience, or extrapolated from available studies).

Guidelines published in 2006 by the New Zealand Guidelines Group discuss the use of BTX-A in traumatic brain injury.[32] A systematic review of available literature was used to develop these guidelines and a rating scheme was used to rank the strength of the recommendations. The guidelines state that carefully monitored therapy with BTX-A for the treatment of focal spasticity in children or adults with traumatic brain injury may be considered (rating C; based on internal expert opinion)

Limitations

There is an absence of well designed RCTs evaluating the long-term safety and effectiveness of BTX-A injections for upper or lower limb spasticity in children and adults. Future trials will need to address methodologic challenges of study design including enrollment criteria for more homogenous etiologies and degrees of severity and use outcome measures adequate to demonstrate active motor function. There is a need for consensus on a core set of valid measurements suitable to evaluate clinically meaningful long-term outcomes of BTX-A injection.[33] Only a few economic evaluations were identified but none were based on a systematic review of the literature or prospective RCTs for estimates of efficacy. Indirect societal costs or effects on quality of life were not addressed in any of these evaluations. Furthermore, none of these studies were conducted in Canada, limiting generalization to the Canadian health care system. Several guidelines recommended BTX-A as a treatment option for different indications but more research is needed to help guide long-term therapy, optimal dosing in children and adults, choice of muscles for injection and injection technique (i.e. whether the use of electromyographic guidance, ultrasonography, and electrical stimulation are needed to optimize treatment technique), as well as the utility of combination with other treatment options for spasticity.

Conclusions and implications for decision or policy making:

In summary, there is an absence of trials comparing BTX-A with other treatment modalities including oral antispasticity medications and phenol injections. There is good quality evidence that BTX-A is safe and effective relative to placebo for the treatment of post-stroke adult spasticity in the upper and lower limb. Open label observational trials suggest that these benefits continue to occur after repeated injections. However, it is not clear that these improvements are sustained long-term, nor is there strong evidence that there is an improvement in function or quality of life. There is some evidence that BTX-A is effective for the treatment of spastic equinus in children with cerebral palsy. However, there is insufficient evidence to support or refute the benefit of combining casting with BTX-A injection in these patients. There is insufficient evidence to support the use of BTX-A for cerebral palsy patients with upper extremity spasticity. There is limited evidence from economic evaluations that BTX-A may be cost-effective in the management of spasticity relative to other treatment options. Few trials included improvement in pain as an outcome measure but there is evidence that BTX-A may be useful for hemiplegic shoulder pain in stroke patients. No new evidence was identified for other disorders associated with spasticity.

Although generally safe, the US Food and Drug Administration issued a warning in early 2008 about reports of life-threatening systemic toxicity from local BTX injections when used for a variety of indications.[34] The warning was based on reports of severe difficulty swallowing or breathing in several patients and occurred mostly in children with cerebral palsy receiving local injections for limb spasticity. The FDA has launched an ongoing review of the issue and in the interim recommends that providers considering botulinum toxin products be alert for potential systemic effects occurring up to several weeks after treatment.

At this time, important questions remain regarding the long term safety and efficacy of BTX-A for different populations with upper and lower limb spasticity. Until further evidence is available, clinical experience and institution-specific cost considerations will be required to help guide coverage decisions.

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