

Botulinum Toxin Type A and Post-stroke Spasticity of the Upper Limbs

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Abstract

Background: Stroke is a significant contributor to morbidity and mortality in the US and other developed nations. Stroke and its side effects are the primary cause of disability in the US and worldwide. Upper limb mobility factors are particularly detrimental to activities of daily living. Successful treatments to improve post-stroke spasticity are required. **Objective:** To assess the relevant medical literature related to the use of botulinum toxin type A and post-stroke spasticity of the upper limb. **Methods:** Literature review utilizing Medline with keywords of botulinum toxin, stroke, spasticity, and upper extremity since 2003. **Results:** Thirteen criteria-based articles investigated botulinum toxin type and post-stroke spasticity of the upper limbs. **Discussion:** Botulinum toxin type A is an effective agent in reducing post-stroke spasticity of the upper limbs.

Keywords

Upper motor neuron syndrome (UMNS), botox, spasticity, neurorehabilitation, botulinum toxin type A, stroke, upper extremity

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Stroke is the leading cause of disability in the US and is a major global health problem. It has been identified as one of the largest causes of lost productivity in late adulthood. The multiple life-altering complications that result from stroke—such as paresis, mood disorders, aphasia, cognitive deficits, dysarthria, dysphagia, and visual disturbances—may be confounded by the development of spasticity. Upper-limb spasticity can be particularly debilitating.

Spasticity is considered to be a positive sign of the upper motor neuron syndrome (UMNS) and, as such, is associated with exaggerated tendon jerks and repetitive stretch reflex discharges, or ‘clonus.’ Spasticity is a disorder of the sensorimotor system defined as an involuntary, velocity-dependent resistance to stretch, caused by a hyperexcitable stretch reflex. Spasticity is often a key component of a person’s experience of impaired mobility and activities of daily living, pain, skin breakdown, poor hygiene, insomnia, social isolation, and poor quality of life (QoL). These conditions also have a significant impact on care-giver burden. Treatment options for post-stroke spasticity include oral spasmolytics (e.g. baclofen, dantrolene, and diazepam) and may not be tolerated by patients due to their non-selective nature and systemic side effects such as sedation, dizziness, nausea, cognitive dysfunction, and general weakness. They may also yield limited functional benefit. Tolerance may lead to upward titration of the dose, increasing the likelihood of side effects. The use of botulinum toxin type A (BTX-A) has become a common treatment for post-stroke spasticity due to its favorable side effect profile, efficacy, and focal benefits. BTX-A acts by blocking presynaptic release of acetylcholine at the neuromuscular junction. It does this by action of the C-terminal

portion of the heavy chain of the molecule binding to the receptor on the motor nerve cell surface. It is then internalized by receptor-mediated endocytosis. When inside the cell, the light chain is released into the cytoplasm, where it cleaves SNAP-25. This prevents the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein from facilitating the release of acetylcholine into the synaptic cleft. As a result, muscle contraction does not occur or occurs to a lesser degree. It is also believed that BTX-A works similarly in sensory neurons, where it blocks the release of neuropeptide neurotransmitters and inhibits the sensitization of the pain nerve. The effects of BTX-A are reversible with re-innervation of the original nerve terminal occurring.

The US Food and Drug Administration (FDA) has recently reviewed safety information for all botulinum toxins, introducing a Risk Evaluation and Mitigation (REMS) Program for all available botulinum toxins. One of the goals of the REMS programs is to minimize the risks of medication errors related to the lack of interchangeability between botulinum toxins. To this end the FDA has assigned new and unique non-proprietary names (BOTOX® onabotulinumtoxinA, Dysport™ abobotulinumtoxinA, and Myobloc® rimabotulinumtoxinB). The studies reviewed herein used BOTOX and Dysport.

Objectives

This article focuses on post-stroke upper-extremity spasticity. A descriptive examination of the relevant literature was performed with the objectives of: examining the efficacy of BTX-A injection in post-stroke upper-extremity spasticity; investigating whether or not reduction of spasticity translates

into improvement in quality of life for patients and/or care-givers; and evaluating functional improvement in the upper extremities after injection. We have also considered the literature with regard to safety after the use of BTX-A for upper-extremity spasticity due to stroke.

Methods

The literature used for this article was obtained after conducting a Medline search for articles from 2003 to the present. The keywords used were: botulinum toxin, stroke, spasticity, and upper extremity. The material reviewed yielded 13 relevant articles including three meta-analyses, two randomized, double-blind, controlled trials, two case reports, five open-labeled prospective clinical trials, and one descriptive measurement study. Articles were excluded if they did not include study of the upper extremity or specific use of BTX-A. Articles were excluded if diagnoses other than stroke were included in the study. Only articles in English or previously translated into English were reviewed. This review was descriptive in nature.

Results Spasticity Scales

In the literature reviewed, the measurement scales used to grade spasticity are the Ashworth scale (AS) and Modified Ashworth scale (MAS) (see *Table 1*), and the Functional Independence Measure (FIM™) instrument.^{2-7,9,11-15} Of the reviewed studies, results showed statistical significance of improving spasticity in the muscles injected with BTX-A. This was evidenced by decreased MAS scores measured at the elbow, wrist, fingers, and shoulder.^{2-7,11-15} These findings were noted at multiple time periods after injection. The duration of the positive effect was seen to last for anywhere between 10 and 20 weeks, at which point re-injection was recommended. In one study, the improvement in MAS score and increase in range of motion was sustained until the 32nd week.² It has been suggested that there are larger improvements of spasticity in individuals who have retained some movement after stroke.¹²

Recurring Injections

Commonly, patients who need recurrent injections will receive them no more frequently than every three months, as it is thought that injecting more frequently than this may potentiate the development of antibodies to the toxin. This hypothesis has not yet been borne out in studies. In a study conducted by Bakheit et al.,⁵ they found no BTX-A antibodies detected from blood sample BTX-A antibody assays taken at baseline and on completion of the study, which was 12 weeks after the third treatment cycle of BTX-A.

Spasticity Reduction

The reduction of spasticity has been clearly defined in multiple studies. This change can translate into improvement in the QoL and/or functional improvement of patients. Upon review of the literature, there are both positive and negative findings with regard to this topic. One of the articles cited here is a meta-analysis reviewing 11 articles. In it, the Global Assessment Scale (GAS) was used as the objective measure for the perception of patient or care-givers of their QoL. A clinically significant improvement in GAS at four to six weeks after injecting BTX-A was found. Despite the fact that BTX-A injections reduced excessive muscle tone in the elbow, wrist, and fingers, with sustained benefit occurring when injections were repeated after 12 weeks, there was no observed

Table 1: Modified Ashworth Scale

0	No increase in muscle tone.
1	Slight increase in muscle tone manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion or extension.
1+	Slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout the remainder (less than half) of the range of motion.
2	More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved.
3	Considerable increase in muscle tone, passive movement difficult.
4	Affected part(s) rigid in flexion or extension.

improvement in the QoL as measured on the Short Form Health Survey (SF-36) in studied subjects.^{7,11} Other studies demonstrate BTX-A as effective and well tolerated in several placebo-controlled trials for the treatment of focal upper- and lower-limb spasticity, but it did not improve motor function.⁸ Overall consensus is lacking on the QoL issue, although on an individual basis there are reports of improvements. All but two^{7,11} of the studies reviewed showed functional improvement in the upper extremity after BTX-A injection. This improvement was observed using several outcome measures, including FIM, Wolf Motor Function Test (WMFT), Motor Activity Log (MAL), Box and Blocks Test (BBT), the upper-extremity subtest of the Fugl-Meyer Assessment of Motor Function (MF-UE), Barthel Index, Motor Assessment Scale, and the Nine Hole Peg Test (9HPT). This functional improvement was evidenced to a greater extent in those measures that specifically targeted the ability of the upper extremity versus those that measure global functioning.⁴ There is also evidence that greater functional improvements are likely achieved in patients who have undergone intervention with BTX-A paired with an aggressive therapy program such as constraint-induced movement therapy (CIMT).¹²

Botox Treatment for Spasticity

A statistical analysis was performed of data from nine double-blind, placebo-controlled studies that included 482 patients with upper-limb spasticity.¹⁰ These patients blindly received either BTX-A or placebo. Adverse events were reported by the patient or the monitoring clinician. Findings revealed that the majority of adverse events were rated as mild or moderate in severity and that nausea was the only event reported at a significantly higher rate in the BTX-A group than in the placebo group. Aside from this study, there have been reports of flu-like symptoms expressed by patients after injection. None of the studies reviewed reported serious adverse events found to be directly related to administration of BTX-A. A recent pilot study suggests that some degree of strength and active movement is necessary for the action of BTX-A on intrafusal fibres.¹

Summary

BTX-A is an efficacious treatment for upper-extremity spasticity after stroke. There exists an abundance of evidence from well-designed studies that exhibit the reduction of spasticity after BTX-A injection in the upper extremity. Although there continues to be a lack of consensus, the QoL for patients and care-givers is improved, likely given the fact that pain, hygiene, care-giver burden, and mobility are severely affected by spasticity. Functional improvements after injection have also been noted, mostly seen in measures that directly evaluate function in the extremity rather than global assessments of function. BTX-A has been found to be a safe

treatment causing reporting of mild to moderate side effects, if any at all. Treatment with BTX-A may also obviate the need for other spasticity management options described above that may be contraindicated or cause further problems in patients.

Discussion

There are numerous issues that make research for treatment of neurological rehabilitation patients difficult. Among them is the debate surrounding measurement tools. The AS and MAS remain the most commonly used clinical scales in the measurement of spasticity.⁹ Differences in training of examiners and the variability of spasticity with position, stress, temperature, illness, etc. make it very difficult to achieve standardized measurements. The variability of QoL results of these reviewed studies and others like them continue to drive the debate. QoL is a patient- and/or care-giver-specific issue. For example, patients have described perceived improvement in their physical appearance that may correlate with improved quality of life; however, it is extremely difficult to measure such a subjective point. For this reason, QoL measures will likely always be difficult to objectify. There exists great debate as to the actual functional improvements that can be achieved in patients with severe spasticity and differing degrees of paresis after BTX-A injections. Research has focused on using advanced techniques to improve injection accuracy such as electromyographic guidance (EMG) and electrical stimulation (ES) in patients who are unresponsive or sedated.¹⁷ Improvements seen in function in the above studies cannot be generalized to all stroke patients. More studies are needed with narrowly selected patient populations in order to provide further guidelines for treatment in specific patient populations. It should also be noted that upper-extremity function can be more important than lower-limb function for independent living and self-esteem.^{18,19} Additionally, there is no established standard approach to the administration of BTX-A. The dosing regimen, targeted muscle groups, and practice of administration vary with the clinical presentation of patients, as do the approach of the individual injecting the drug and goals of injections. The extent of denervation is determined largely by the dose and volume of the injection given.^{11,16} Studies are available that

demonstrate greater clinical improvement, fewer BTX-A-related side effects due to injection of the adequate dose of BTX-A to the accurate site of hyperactive muscles, and greater clinical improvement due to confirmation of hyperactivity of muscles with the use of EMG-guided injections.²⁰ Administration of BTX-A is often performed blindly and the procedure is not always well described in studies. These differences and others contribute to accounts of outcomes. This is compounded by the unresolved problem with measuring spasticity.²¹

There have been many advances over the years for the treatment of post-stroke spasticity. Of these, BTX-A is an accepted intervention. The improvement of measuring tools for spasticity, improved outcome measurement tools, and research regarding dosing and injection techniques are still required. Ideally, these measurement tools could take into account the goals of the patient or care-giver when evaluating functional improvement. Once this is done, it is possible to quantify improvements that have thus far been mostly qualitative in nature. ■



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