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Review

Botulinum Toxin in Poststroke Spasticity

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Poststroke hemiparesis, together with abnormal muscle tone, is a major cause of morbidity and disability. Although most hemiparetic patients are able to reach different ambulatory levels with rehabilitation efforts, upper and lower limb spasticity can impede activities of daily living, personal hygiene, ambulation and, in some cases, functional improvement. The goals of spasticity management include increasing mobility and range of motion, attaining better hygiene, improving splint wear and other functional activities. Conservative measures, such as positioning, stretching and exercise are essential in spasticity management, but alone often are inadequate to effectively control it. Oral antispastic medications often provide limited effects with short duration and frequent unwanted systemic side effects, such as weakness, sedation and dry mouth. Therefore, neuromuscular blockade by local injections have become the first choice for the treatment of focal spasticity, particularly in stroke patients. Botulinum toxin (BTX), being one of the most potent biological toxins, acts by blocking neuromuscular transmission via inhibiting acetylcholine release. Currently, focal spasticity is being treated successfully with BTX via injecting in the spastic muscles. Two antigenically distinct serotypes of BTX are available on the market as type A and B. Clinical studies of BTX used for spastic hemiplegic patients are reviewed in this article in two major categories, upper and lower limb applications. This review addresses efficacy in terms of outcome measures, such as muscle tone reduction and functional outcome, as well as safety issues. Application modifications of dose, dilutions, site of injections and combination therapies with BTX injections are also discussed.

Keywords: Botulinum toxin; Spasticity; Stroke

Spasticity is a well-known motor dysfunction arising from upper motor neuron lesions due to stroke, spinal cord injury, multiple sclerosis and traumatic brain injury. Clinically, it is diagnosed with the velocity-dependent resistance felt by passive examination of joint motion. In 1980, Lance[1] defined spasticity as "a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron syndrome." The pathophysiology of spasticity is not completely understood, but it is thought to be related to change in the balance of excitatory and inhibitory inputs to the motor neuron pool.

Poststroke hemiparesis, together with abnormal muscle tone, is a major cause of morbidity and disability. These patients often demonstrate recognizable antigravity postural patterns characterized by shoulder adduction, and elbow and wrist flexion in the upper limb, and hip adduction, knee extension and ankle plantar flexion in the lower limb. This "hemiplegic" posture, which is thought to result from increased motor neuron activity in antigravity muscles, significantly interferes with body image, balance and gait.[2] Although most hemiparetic patients are able to reach different ambulatory levels with rehabilitation efforts, upper and lower limb spasticity can impede activities of daily living, personal hygiene, ambulation and, in some cases, functional improvement. Paresis and increased muscle tone can also cause joint stiffness leading to contractures.

Despite the ease of diagnosis, effective spasticity management is often challenging for the clinician. The goals of spasticity management include increasing mobility and range of motion, attaining better hygiene, improving body image and functional level, and facilitating splint wear. In addition to standard conservative measures such as positioning, stretching and exercise, treatment options also include physical agents, oral antispastic drugs,

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neuromuscular blockade by local injections of phenol and botulinum toxin (BTX), and intrathecal baclofen. Oral antispastic medications often provide limited effects with short duration and frequently lead to side effects such as weakness, drowsiness, confusion, dizziness, sedation and dry mouth.[3,4] Neurolysis by phenol[5] and alcohol[6] injections reduce spasticity effectively in poststroke hemiparesis, but severe pain is considered to be a major limitation. Intrathecal baclofen, which can be administered by an implanted programmable pump, and used particularly in patients with intractable spinal spasticity, has been reported to be effective in a few studies in stroke patients.[7,8] Although intrathecal baclofen therapy is an invasive treatment method that requires an implantation procedure and can lead to adverse reactions such as headache, nausea, vomiting, excessive weakness and transient urinary retention, highly significant reduction of muscle tone and some subsequent functional gain can bring the procedure to a more favorable status to be considered for use in intractable spastic hemiplegic patients.[7,8] Surgical interventions like arthrodesis[9] and tendon release[10] can also be performed for severe spasticity, particularly in patients with contractures.

BTX, one of the most potent biologic toxins known to man,[11] acts by blocking neuromuscular transmission via inhibiting acetylcholine release. Since its introduction by Scott[12] to treat strabismus, it has been utilized in various neurologic and non-neurologic indications, such as dystonia, blepharospasm, tremor, hyperhydrosis and cosmetic applications. Focal spasticity, particularly resulting from cerebral disorders, is currently being treated successfully with BTX via injection in the spastic muscles, and BTX is now considered the pharmacological treatment of choice in focal spasticity.[13] There are seven serologically distinct toxin types named A, B, C, D, E, F and G. They all inhibit acetylcholine release into the synaptic cleft by binding one or more of the transport protein chains with high specificity.[14,15] These target proteins, on which the light chains of the toxin bind, vary among the different serotypes. Two antigenically distinct serotypes of BTX are available on the market as type A and B. BTX-A cleaves synaptosome-associated protein 25, whereas BTX-B cleaves vesicle-associated membrane protein. The specific site of action and the cleaved protein influence the duration of action of various BTX serotypes.[16] BTX-A has been shown to have a longer duration of effect in cervical dystonia compared with BTX-B.[17] The two serotypes differ from each other in their adverse effects. The anticholinergic unwanted effects such as dry mouth, dysphagia and voiding difficulties were found to be more common after BTX-B injections.[18,19]

Type A BTX formulations are available as Botox (Allergan, Inc., Irvine, CA) and Dysport (Ipsen Ltd., Berkshire, UK). Type B is available as Myobloc in the United States and NeuroBloc in Europe (Elan Pharmaceuticals, San Diego, CA).[20] Although no direct comparison of these products has been made, approximate equivalence obtained from clinical experience and general survey of the literature is reported as follows:[21]

1 unit of Botox ≈ 3-4 units of Dysport ≈ 40-75 units of Myobloc/Neurobloc

BTX doses are generally adjusted according to factors such as severity of spasticity, number of muscles involved, age, previous response to BTX therapy and adjunct therapy applications. Recommended BTX-A (Botox and Dysport) doses and dilutions for different muscle groups are well reviewed in the literature.[22,23] Antibody formation against BTX proteins (including neurotoxin and non-toxin components[24]) is one of the reasons for therapy failure. In order to overcome therapy failure, injecting increased BTX doses,[25] preventing short injection intervals and using different BTX serotypes[26,27] are suggested. The reports of antibody formation are mostly from patients with cervical dystonia. One study evaluating antibody levels in patients with poststroke spastic upper extremity has reported that repeated treatment cycles of BTX-A were not associated with detectable levels of antibody and this result was partly attributed to a shorter treatment duration compared with the results of cervical dystonia studies.[28]

Another drawback for BTX therapy is high cost and the transient nature of the toxin. Although pharmacoeconomic evaluations of the available spasticity treatment alternatives are limited, BTX has been found to be cost-effective in poststroke spasticity when compared with oral anti-spastic drugs.[29] Clinical studies of BTX used for spastic hemiplegic patients are reviewed in this article in two major categories, upper and lower limb applications. In addition to efficacy in terms of outcome measures such as muscle tone reduction and functional outcome, safety issues are addressed. Application modifications of dose, dilutions, site of injections and combination therapies with BTX injections are also discussed.

BTX for Upper Limb Spasticity

Functional recovery of the upper limb may be limited in stroke survivors. As arm and hand functions are crucial for many activities of daily living, rehabilitation efforts are focused on this aspect. Apart from loss of function due to paresis, spasticity may be a major contributing factor to disability. Therefore, even if there is no residual motor function in the upper limb muscles, management of spasticity should be strongly considered in an attempt to reduce disability in activities such as limb positioning, hygiene, dressing and walking.

Earlier case control studies suggest safe and effective use of BTX for upper limb spasticity.[30-33] Several spastic upper limb muscles of chronic hemiparetic patients were injected in these studies. Tone reduction assessed by the Ashworth or Modified Ashworth Scale[34] (0=normal muscle tone to 5=the effected part is rigid in flexion or extension) and improvement in functional outcome evaluated by the patients' global

Table 1. Placebo controlled trials of stroke related spastic upper limb treated with botulinum toxin (BTX).

Study (year)	No. of patients	Stroke duration (mean)	Injected muscles	Treatment groups compared to placebo	Result
Simpson[35] (1996)	39	37 months	BB, FCR, FCU	75 U Botox 150 U Botox 300 U Botox	• Significant decrease in Ashworth score with 300 U. • Improvement in global assessment scores with 75 and 300 U. • Significant improvement in grip strength with 75 U. • No difference between the groups concerning the adverse events.
Hesse[36] (1998)	24	7.45 months	BB, Brachialis, FCR, FCU, FDP, FDS	1,000 U Dysport+ES, 1,000 U Dysport, placebo+ES	• No significant difference between the study groups for Ashworth score and limb position.
Bakheit[37] (2000)	83	NA	BB, FCU, FCR, FDP, FDS	500 U Dysport 1,000 U Dysport 1,500 U Dysport	• Significant Ashworth score reduction and improvement of ROM in all active treatment groups. • No significant improvement in functional parameters.
Smith[38] (2000)	21 (2 patients with head injury)	36 months	Flexor muscles (names not given)	500 U Dysport 1,000 U Dysport 1,500 U Dysport	• Significant reduction in spasticity at the wrist and fingers associated with a greater range of passive motion at the wrist. • Dose dependent response in terms of magnitude. • Dose had little effect on response duration. • No change in the upper limb disability
Bhakta[39] (2000)	40	3.1 years	BB, Brachioradialis, FDS, FDP, FCU	1,000 U Dysport	• Significant reduction in finger and elbow flexor tone and improvement in wrist ROM. • Reduction in patient disability and burden.
Bakheit[40] (2001)	59	NA	BB, FDS, FDP FCR,FCU	1,000 U Dysport	• Significantly reduced Ashworth scores. • Passive ROM at the elbow significantly increased by week 16. • No significant functional improvement.
Brashea[41] (2002)	126	4.75 years	FCR, FCU, FDP, FDS in all subjects, 10 additionally FPL and 64 thumb muscles	200-240 U Botox	• Significant reduction in Ashworth score and improvement in four point Disability Assessment Scale (hygiene, dressing, limb position, pain). • No difference between the groups concerning the incidence of adverse events.
Brashear[42] (2004)	15	NA	BB, FCU, FCR, FDS, FDP	10,000 U BTX-B (MyoBloc)	• BTX-B did not decrease muscle tone in the elbow, wrist or finger flexors over 16-week period. • Dry mouth was common.
Childers[43] (2004)	91	25.8 months	BB, FCU, FCR, FDS, FDP	90 U Botox 180 U Botox 360 U Botox	• Dose dependent response in muscle tone reduction, but not in pain and global functional assessment measures.

Table 1 (continued). Placebo controlled trials of stroke related spastic upper limb treated with botulinum toxin (BTX).

Study (year)	No. of patients	Stroke duration (mean)	Injected muscles	Treatment groups compared to placebo	Result
Suputtitada[44] (2005)	50	8.4 months	BB, FCU, FCR, FDS, FDP	350 U Dysport 500 U Dysport 1,000 U Dysport	• All three doses of Dysport significantly reduced muscle tone and optimal dose for treatment of patients with residual voluntary movement in the upper limb is suggested to be 500 U.

BB, biceps brachii; FCU, flexor carpi ulnaris; FCR, flexor carpi radialis; FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis; FPL, flexor pollicis longus; ROM, range of motion; NA, not applicable; ES, electrical stimulation.

assessment scores were reported. However, global functional assessment scores such as Barthel, FIM and SF-36 have generally failed to show significant improvement after BTX injections. Placebo-controlled trials have also provided further evidence for safe and effective use of BTX in the management of upper limb spasticity (table 1).[35-44] As an extension to a 12-week double-blind study,[41] 111 patients were enrolled in a 42-week open label study.[45] In this study, repeated BTX injections for upper limb spasticity have resulted in significant and sustained improvement in both Disability Assessment and Ashworth Scores. These results were consistent with a study that suggested sustained antispastic effects of BTX after repeated injections for up to at least three treatment cycles.[46] Other uncontrolled trials with similar results have reported spasticity reduction in the hemiparetic upper limb without significant functional improvement in global assessment measures.[47-49] Interestingly, an exploratory meta-analysis, including two randomized, controlled trials, has revealed that reduction in spasticity was associated with significant improvement in arm function.[50]

Combined therapies were also studied in an attempt to enhance the effectiveness of BTX. In a randomized, double-blind, placebo-controlled study, Hesse et al[36] suggested that BTX could be more effective when combined with electrical stimulation. Moreover, Carda and Molteni[51] have demonstrated that muscle tone reduction was greater when adhesive taping was performed after BTX injections, compared to combined electrical stimulation and splinting after similar doses of BTX. In another attempt to increase the effectiveness of a given toxin dose, Francisco et al[52] have compared two different dilutions of BTX and found no difference between high and low concentration treatment groups. Contrasting results have been reported in another study, suggesting that higher concentrations of BTX-A provides greater spasticity reduction.[53]

BTX for Lower Limb Spasticity

As previously stated in the context of hemiplegic posture, the lower limb of a hemiplegic patient tends to be in the position with adducted hip, extended knee, plantar flexed and inverted ankle. Although some patients experience gait abnormalities related to stiff knee pattern, extended position of the knee is generally considered to be useful for ambulation in patients who do not have sufficient quadricep strength to lock their knees while standing or walking. However, ankle plantar flexion and inversion are major drawbacks for ambulation in spastic hemiplegic patients causing problems like impaired foot contact, dragging of toes, reduced stance duration and stride length. Most clinical trials concerning BTX use in stroke patients with lower limb spasticity are designed in order to find an answer to the question whether BTX effectively alleviates ankle plantar flexor spasticity and provides functional improvement. Compared to the extensively studied upper limb applications in placebo-controlled trials with relatively large sample sizes, lower limb studies are relatively insufficient. In one of the earliest studies of drop foot treatment in poststroke patients, Dengler et al[54] have reported improvement in 8 of 10 patients considering spasticity and facilitation of physiotherapy. Subsequently, Hesse et al[55] injected 400 U of BTX (Botox) to the spastic calf muscles of 12 patients and has been able to show statistically significant improvement in gait analysis parameters, including velocity, stride length and stance symmetry. In another study with a similar number of patients and injected muscles, Hesse et al[56] have investigated the effect of BTX on ankle muscle activity using dynamic electromyography. While correlation has been observed between muscle tone reduction and gait parameters, significant improvements have also been reported for walking speed, stride length and premature activity of soleus muscle after injection.

High cost and transient nature of effect are among the major drawbacks of BTX treatment. Hesse et al[57] have combined 2000 U of BTX (Dysport) with electrical stimulation of tibialis anterior and plantar flexor muscles in an attempt to enhance toxin effect. The combined treatment has been found to be superior with respect to the clinically assessed reduction of muscle tone, gait velocity, stride length, stance and swing symmetry.

Recently low dose (100 U Botox) BTX injections followed by short-term electrical stimulations were compared with high dose (400 U Botox) applications in poststroke spastic drop foot.[58] Improvement has been recorded in both groups, while this preliminary single-blind study was unable to find a difference in terms of effectiveness between the two treatment groups. Randomized controlled trials investigating safety and

Table 2. Randomized-controlled trials of stroke related spastic foot treated with botulinum toxin (BTX).

Study (year)	No. of patients	Stroke duration (mean)	Injected muscles	Treatment groups		Result
Burbaud[59] (1996)	23	23.5 months	Triceps surae, soleus, TP, FDL	1000 U Dysport	Placebo	• Significant improvement with BTX in Ashworth score, patient assessment and active dorsiflexion. • BTX was found less effective in patients with longer duration of spasticity.
Reiter[60] (1998)	18	23.6 months	GM, GL, TP, FHL, injected according to limb posture and EMG activity in the first group)	190-320 U	100 U TP only plus ankle taping for 3 weeks	• Average Ashworth score decreased by 1 point in each group but effect lasted shorter in the second group. • Significant ROM change in each group. Improvement in gait velocity and step length in each group.
Kirazli[60] (1998)	20	NA (<12 months)	Soleus, TP GL, GM	400 U Botox to targeted muscles	3 ml 5% phenol for tibial nerve block	• Significant decrease in Ashworth score in both groups. • Muscle tone reduction was significantly better at week 2 and 4, but not at week 8, and 12 with 400 U.
Johnson[62] (2004)	21	NA (<12 months)	GM, GL, TP	800 U Dysport combined with FES	Exercise only	• Significant improvement in walking speed and functional improvement in the treatment group.
Bayram[58] (2006)	12	36.6 months	GM, GL, TP, soleus	100 U Botox to TP with short term ES	400 U Botox to all target muscles	• Improvement in Ashworth, ROM, clonus, patient global assessment scores and time walking 10 meters in both groups. • No significant difference between the groups. • Effects lasted shorter in the first group.

GM, gastrocnemius medialis; GL, gastrocnemius lateralis; TP, tibialis posterior; FHL, flexor hallucis longus; FDL, flexor digitorum longus; ES, Electrical stimulation; FES, functional electrical stimulation; ROM, range of motion; NA, not applicable.

efficacy of BTX comparing other techniques and combination therapies with BTX are presented in table 2.[59-62] In general, the effect seems to have a shorter duration with lower doses. Longer spasticity duration is associated with poor outcome, and it is hard to demonstrate focal spasticity treatment efficacy by global functional assessment methods.

The above-mentioned studies are inadequate to provide strong evidence due to their relatively small sample sizes. However, a recent pooled data analysis of 9 double-blind, placebo-controlled studies, including 792 patients following stroke (482 upper, 310 lower limb) has revealed an acceptable safety profile for BTX.[63]

Conclusion

The results of the reviewed studies of BTX treatment in poststroke upper and lower limb spasticity suggest that BTX injections safely and effectively decrease muscle tone and increase range of motion. Although some functional improvements may be seen after BTX injections, global functional assessment methods do not consistently reflect these changes. In light of the previous results and current evidence, we believe that future studies with large sample size, carefully selected patients and appropriate clinical outcome measures will provide more insight for clinical utilization of BTX.

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