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The place of the botulinum toxin in the management of multiple sclerosis

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Abstract

Multiple sclerosis (MS) is the most common disabling chronic disease of the central nervous system among young adults. These patients suffer from variety of symptoms that have a profound affect on their working ability, activities of daily living and general quality of life. Treatment of these symptoms is important in order to relief them and improve daily function and quality of life. Many of these symptoms are often resistant to treatment. Botulinum toxin A (BTX) is mainly used for spasticity and bladder dysfunction in MS. It is an effective treatment option for spasticity of the thigh adductor, pes equinus, striatal toe or adductor of the shoulder joint. BTX injections are effective in reducing incontinence episodes and urinary urgency, daytime frequency and nocturia, as well as sustained improvements in quality of life of MS patients with detrusor overreactivity. In addition, BTX is potentially effective in treating pain, trigeminal neuralgia, tremor, neuro-ophthalmologic complications, facial myokymia, gastroparesis, sialorrhea, and hyperhidrosis, however no studies have confirmed its efficacy in MS patients.

Key words: botulinum toxin, multiple sclerosis, symptoms, spasticity

Introduction

Multiple sclerosis (MS) is a chronic disease of the white matter of the central nervous system in which patients suffer from a variety of disabling symptoms that greatly affect their working ability, activities of daily living and quality of life. MS symptoms are usually undertreated due to the lack of awareness on the part of patients and physicians to the relevance of symptoms such as fatigue and pain or because many of the available drugs for the treatment of MS are off-label and therefore are not available to the patients. Moreover, evidence- or expert-based consensus treatment guidelines have been developed for only selected MS symptoms (1). Many of these symptoms, even when they are recognized, are resistant to treatment and show only partial response to medications. Botulinum toxin injections may present additional effective therapeutic options for various MS symptoms.

Botulinum toxin is produced by the bacterium *Clostridium botulinum*. It blocks presynaptic release of acetylcholine from nicotinic (neuromuscular junction) and muscarinic nerves. Therapeutic injections of botulinum toxin have been in use since the early 1980s. The toxin is available in two serotypes, type A (botulinum toxin-A) (BTX) and type B (botulinum toxin-B). There are two widely available formulations of BTX, Botox® and Dysport®. Importantly, these two formulations of BTX are not dose equivalent, largely for technical reasons. The main areas of BTX application in MS include spasticity and bladder dysfunction, but many other indications, such as pain management or neuro-ophthalmologic complications are potential indications as well. Many of these symptoms are not exclusively domain of the neurologist, so multidisciplinary approach between neurologist, urologist, ophthalmologist and physical therapist is of paramount inmportance.

This review will summarize current understanding on the application of BTX in symptomatic management of MS patients.

Spasticity

Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome. (2) Decisions of when to start treating spasticity rely on a number of factors, and the balance between negative and positive symptoms of upper motor neuron syndrome should influence the selection of an appropriate treatment. It should be emphasized that chronic spasticity reflects not only reflex resistance, but also resistance of rheologic (contractures, stiffness) origin. This also significantly influences treatment selection. Treatment decisions should always take into accounts the patient's overall clinical and social situation, the duration, severity and distribution of spasticity, the locus of injury and all the co-morbidities.(3) Urinary tract infections, urolithiasis, stool impaction, pressure sores, fractures, dislocations, ingrown toenails, and excessively restrictive clothing should always be ruled out before starting any treatment. It should also be borne in mind that optimal efficacy of any antispasticity treatment that is intended to relax a muscle requires physiotherapy to lengthen the muscle.

Before starting treatment for spasticity in MS, the expectations from the treatment should be discussed with the patient. Only in rare cases will active functional goals be achieved (this is especially relevant in overcoming the spasticity of MS relapse). The more realistic goals are pain relief, decrease in muscle spasm frequency, improvement in mobility or wheelchair propulsion, transfers, self-care, eating, and return to sexual activity and routine activities of daily living. This should be clearly explained to the patient to ensure that the expected outcome is realistic and acceptable.

Multiple sclerosis is a common cause of diffuse or regional muscle overactivity where the number of affected muscle groups may not be amenable to local treatments. In MS it is particularly difficult to assess the functional disability due to spasticty and the functional benefit due to treatment, so this is why it appears more appropriate to use therapeutic options with transitory effects like BTX. (4) The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. The rationale for treating features of the upper motor neurone syndrome must be better understood and sensitive, validated spasticity measures need to be developed. (5) Neverthless, there are some situations in which BTX treatment will be effective, specifically, leg adductor spasticity, spastic pes equinus and striatal toe. (6). Only about 7% of MS patients receive treatment of the upper extremity, mostly due to severe adductor spasticity of the shoulder joint (6). BTX usually can not help in enhancing the functional capacity of muscle weakness, but it can open a therapeutic window for other treatments for bedridden patients by lessening the amount of spasticity, and BTX will help in reducing the formation of decubital ulcers and the levels of pain.

The first study that showed efficacy of BTX in the treatment of spasticity was performed in 1990. Using a randomized crossover design, Snow and coworkers injected BTX 400 U (Botox®) into the thigh adductor muscles (adductor brevis 100 U, adductor longus 100 U, adductor magnus 200 U) to 10 non-ambulatory MS patients who had spastic contraction of the thigh adductor muscles that interfered with sitting, positioning, cleaning, and urethral catheterization. (7) The patients were followed for 6 weeks, and a crossover injection to the alternate therapy was performed at three months. The results showed a significant benefit of BTX versus placebo at 6 weeks in terms of reduction of the spasticity and hygiene scores, and there were no adverse events. A subsequent uncontrolled study on two patients with severe lower extremity spasticity showed an improvement in spasticity and in functional

status, but emphasized the possibility of reduction in muscle tone not only in injected muscles, but in non-injected muscles in the region as well. (8)

To further determine appropriate muscle selection in treatment of spasticity, Finsterer and coworkers used turn/amplitude analysis as an electromyographic (EMG) criterion, on 9 patients with severe spasticity (5 of them with MS). (9) Those authors used 40-240 MU of Dysport® and the patients achieved significant improvements in activities of daily living, pain, tone and range of motion. Hyman et al. then performed a placebo-controlled, dose-dependent study to assess the effect of three different doses of Dysport® (500, 1000, and 1500 U) in order to define a safe and effective dose for the treatment of hip adductor spasticity in patients with MS. (10) Altogether, 74 patients with disabling spasticity of the hip adductor muscles (Kurtzke EDS score >7), which caused moderate pain or difficulty in nursing care (hygiene score >2), were included. The results showed an improvement in distance between the knees for the 1500 U group, muscle tone reduction in all Dysport groups and improvement in hygiene scores in the 1000 U and 1500 U groups. Duration of benefit was significantly longer than placebo for all Dysport® groups ($p<0.05$). Importantly, all of these benefits were evident despite the extensive use of concomitant oral antispasticity medication and analgesics. The most frequent adverse events in the patients treated with Dysport were hypertonia (new or worsening spasticity) of injected and/or non-injected muscles (22%), weakness of non-injected muscles (14%), fatigue (7%), urinary tract infection (5%), headache (5%), micturition frequency (5%), back pain (5%), and diarrhea (5%). A risk-benefit assessment of that study suggested that the optimal starting dose for treating hip adductor spasticity in MS is 500–1000 U of Dysport® , divided between the two legs, with subsequent dose titration as required. One small, uncontrolled study showed that BTX is an efficient drug relieving pain in patients with spastic paraparesis, but only the use of high doses of BTX (bilaterally 400 U of Botox® or 2000 U of Dysport®) resulted in spasticity relief in lower

extremities and significantly increased the range of passive movements in articulations, which made care and rehabilitation easier. (11) Another study evaluated the effect of BTX (Botox®) on painful tonic spasms in MS patients. (12) The BTX was injected into the forearm finger flexor (80 units) and the flexor ulnaris carpi (80 units) for the upper limbs and on the gastrocnemius muscle (120 U) and the small flexor foot muscles (50 units) for the lower limbs. The pain intensity scores and the daily number of painful tonic spasms were significantly reduced in all 5 treated patients at days 8, 30 and 90. Only one study evaluated the safety of botulinum toxin type B in the treatment of lower-limb adductor spasticity in patients with MS. (13) Results of this study suggested that a starting dose of 30000 U of botulinum toxin type B could be safely utilized in the treatment of adductor spasticity in MS, but additional studies are needed to evaluate efficacy.

As noted above, optimal efficacy of antispasticity treatment requires concomitant physiotherapy to obtain the maximum benefit. The first randomized controlled trial that investigated the potential efficacy of BTX in combination with neurological rehabilitation to treat MS-related spasticity demonstrated the benefit of combination therapy consisting of BTX injection plus strengthening exercises. (14) That study however suffers from some limitations: the sample size was small and the functional outcome measures that are usually employed in clinical practice, such as the range of motion, spasm frequency scale and joint resting angles, were not applied.

In conclusion, BTX is an effective treatment option for spasticity in MS, mostly for treating adductor spasticity, pes equinus, striatal toe and adductor spasticity of the shoulder joint. The recommended doses are outlined in table 1. (15, 16) A maximum dose of 1500 units Dysport® (400 units Botox®) per treatment session and 250 U Dysport® (50 U Botox®) per injection site is recommended and for evaluation of treatment effects in hip adductor spasticity clinical examination with specific scales and measurements is recommended. (17)

There is, however, only one placebo-controlled, dose-dependent study of Dysport® for treating adductor spasticity in MS. Further studies for the other above-mentioned indications are needed to assess the safety, efficacy and cost-effectives of BTX treatment in MS. (18)

Table 1. Indications and dosage of BTX in the treatment of spasticity in MS. (15,16)

Indication	Muscles injected	Dosage (U) Botox®	Dosage (U) Dysport®
Adductor spasticity*	Adductor magnus Adductor longus Hamstrings (optional)	≥100/muscle/side	300/muscle/side
Pes equinus	Gastrocnemius – medial head Gastrocnemius – lateral head	100/muscle/side 100/muscle/side	150-400/muscle/side 150-400/muscle/side
Striatal toe	Extensor hallucis longus	20-50/muscle/side	100-150/muscle/side
Adductor spasticity of the shoulder joint	Pectoralis major Latissimus dorsi Teres muscle group Subscapularis	75/muscle/side 80/muscle/side 30/muscle/side 50/muscle/side	200-300/muscle/side 150-300/muscle/side 100/muscle/side 100-150/muscle/side

*Confirmed by a placebo-controlled, dose-dependent study

Bladder dysfunction

The synergy between the detrusor muscle and the external urethral sphincter is controlled by a specific area in the caudal brainstem, the pontine micturition center. Disruption of the pathways between this area and the caudal part of the spinal cord often results in detrusor-sphincter dyssynergia (DSD) (19). DSD has been defined as a detrusor contraction concurrent with an involuntary contraction of the urethral and/or periurethral striated muscle (20). DSD typically occurs in patients with a supra-sacral lesion (e.g., those with MS) and implies an

involuntary detrusor contraction accompanied by an involuntary contraction of the external sphincter, which prevents adequate voiding and which might lead to a low compliant and thick-walled bladder, elevated retrograde pressures in the ureter and pelvis, hydronephrosis, renal scarring and terminal kidney failure. Without adequate treatment, more than 50% of men with DSD will develop severe complications, while these complications are less common in women, perhaps due to lower detrusor pressures. (21) DSD is frequently encountered in MS and is one of the main urodynamic dysfunction in this disease. (22) The rationale for using BTX in the treatment of DSD was extrapolated from studies on patients with spinal cord injuries which showed that BTX decreases detrusor and urethral pressures and reduces post-voiding residual urine volume. (23) However, the first multicenter randomized, double blind, placebo-controlled study with BTX in MS patients who had chronic urinary retention and post-voiding residual urine volume between 100 and 500 ml showed negative results. (24) Those patients received a single transperineal injection of either BTX (100 U Botox®) or placebo in the sphincter: BTX significantly increased voiding volume (+54%, $p = 0.02$) and reduced pre-micturition (229%, $p = 0.02$) and maximal (221%, $p = 0.02$) detrusor pressures compared to placebo. Those authors concluded that a single injection of BTX (100 U Botox®) does not decrease post-voiding residual urine volume in MS patients with DSD.

On the other hand, given that partial spinal cord lesions are a hallmark of MS, the clinical picture is usually dominated by symptoms caused by detrusor overactivity (DO), namely, urinary urgency and urgency incontinence. In a one-center prospective study on 16 patients with 300 U of BTX (Botox®) into the bladder and into the external sphincter muscle authors have showed that BTX detrusor injections are very effective in the treatment of drug-resistant DO symptoms. (25) However build up of residual urine remains a problem of which patients must be informed. Another single-center, prospective, open-label study using

detrusor injections of 300 U of Botox® in patients with MS showed highly significant improvements in incontinence episodes and urinary urgency, daytime frequency and nocturia, and significant improvements in urodynamically demonstrated bladder function, as well as sustained improvements in all quality of life scores. The mean duration of effect was 9.7 months and similar results were seen with repeat treatments. (26) Ehren and coworkers performed a randomized, double blind, placebo-controlled study in patients with incontinence due to neurogenic DO (including MS patients) in order to evaluate the effect of a single injection of 500 U of BTX (Dysport®) on the use of oral rescue medication, bladder compliance, continence and quality of life. (27) The results of that study showed that it reduced the use of oral medication, high detrusor pressure and frequency of urinary leakage.

Other possible indication for BTX in managing urinary symptoms in MS is intradetrusor BTX injections for intractable catheter bypassing in patients with neurogenic DO. One small study showed that this is a very effective and safe treatment for this indication. (28)

In conclusion, there is still no evidence that BTX injections are effective in DSD in patients with MS. In MS patients with DO, however, BTX injections are effective in reducing incontinence episodes and urinary urgency, daytime frequency and nocturia, as well as in providing sustained improvements in quality of life parameters. The usual recommended Botox® doses are 200-300 U. Several questions still remain unanswered: what is the optimum dose? how many injection sites are required? what is the optimum frequency of treatment? It should be noted that all the trials that had been conducted thus far have been small in size and had a relatively short duration. Therefore, further studies are needed to determine the efficacy and tolerability of long-term application.

Pain

Pain is a common problem for patients with MS. Observational studies of patients attending neurology clinics have reported a prevalence of pain between 28.8-86% (29). Paroxysmal pain symptoms in MS patients are usually treated with antiepileptics, chronic neuropathic pain is treated with tricyclic antidepressants or antiepileptics, and musculoskeletal pain is treated with non-steroidal anti-inflammatory drugs and physiotherapy. There are several randomized controlled studies on the role of BTX in managing pain (30), but no studies have investigated the role of BTX in the management of pain specifically in patients with MS. Trigeminal neuralgia occurs in approximately 2% of patients with MS, either as a presenting symptom or during an MS relapse. (31)
The positive role of BTX in managing pain associated with spasticity is discussed in other sections.

Other indications

Tremor is the most frequent movement disorder in MS and is often very difficult to treat. Intention tremor is most frequently observed, but postural tremor also occurs. Very few studies have evaluated the effect of BTX on essential tremor. Rest, postural, and kinetic tremor were evaluated over a 16-week period in a placebo-controlled study using BTX 50 or 100 U (Botox®). There was significant improvement on the tremor severity rating scale at four weeks after injection, with 75% of the BTX-treated patients versus 27% of the placebo-treated patients ($p < 0.05$) having reported mild to moderate improvement. (32) There were similar results in another multicenter, double blind, controlled trial on 133 patients with

essential tremor. (33) Those patients were randomized to receive 50 or 100 U of BTX (Botox®) into wrist flexors and extensors, and they were followed for 4 months. The results of the study showed significant improvement in postural tremor, but only minimal improvement in kinetic tremor and functional assessments.

The effectiveness of BTX in head tremor was evaluated in only one study on 10 patients. In spite of the very small number of patients, the findings indicated that BTX may be useful for patients with essential head tremor who have failed to benefit from oral medications. (34)

Continuous facial myokymia is an infrequent clinical sign that almost always occurs in intrinsic brainstem lesions, particularly in MS. Treatment with BTX (Botox®) 2.5 U in the upper and lower eyelids, cheek and perioral muscles was shown to be an effective and safe approach for the treatment of this disorder in patients with MS, especially when the condition is uncomfortable and persistent. (35)

Internuclear ophthalmoplegia is another symptom very frequently seen in MS patients and one that is very difficult to manage if there is no recovery after corticosteroid treatment. In such instances, application of BTX can result in reduction of diplopia and occasional improvement of binocular function. These benefits are, however, limited by the need for repeated injections and they must be given by a very experienced physician. (36) Severe nystagmus is another MS symptom very difficult to manage. Three series reported somewhat beneficial results associated with BTX in patients with acquired nystagmus with oscillopsia, but with complications such as ptosis and diplopia being limiting factors. (37,38,39).

Tinnitus is another symptom in MS and it is potentially treatable with BTX. (40) One small, placebo-controlled study showed improvement in tinnitus handicap inventory scores and patient subjective results after a 50 U BTX (Botox®) injection equally divided and injected

subcutaneously into 3 sites around the ear, compared with placebo, suggesting a possible benefit of BTX in tinnitus management. (41)

Trigeminal neuralgia appears in 1% of patients with MS in whom it's progression is usually faster than in idiopathic trigeminal neuralgia (42). An open-label study has shown that BTX significantly reduces the duration and intensity of pain in cases of intractable trigeminal neuralgia, with the peak effect at day 20. BTX was also shown to reduce the use of preventive medication: the BTX dose depended on the reported pain surface (6.83 U for the ophthalmic branch, 6.45 U for the maxillary branch, and 9.11 for the mandibular branch. (43) A randomized controlled trial is needed to validate these results.

Gastroparesis is rarely seen in MS and is difficult to treat when it is present. (44) Two randomized controlled studies showed that, when compared with placebo, intrapyloric BTX injection did not successfully relieve subjective symptoms or improve objective measurements in patients with gastroparesis. Thus, at present, there is no evidence to recommend BTX injections for alleviation of gastroparesis. (45,46) BTX has already been successfully used for the management of chronic, refractory constipation in children and may be effective in MS patients as well, but further studies are needed to confirm this. (47)

Sialorrhea and hyperhidrosis are other potential indications for the use of BTX injections, but there are no studies on its application for MS with those symptoms. (15) As well other well known indications for BTX injections like hemifacial spasm or cervical dystonia which, although rarely, may be associated with MS, and in such instances should be treated with BTX.

Conclusion and discussion

Treatment of muscle spasm and DO by means of BTX injections can be recommended based on the results of prospective, placebo-controlled studies. It should be borne in mind, however, that those studies included small numbers of patients, and were of relatively short duration. Although it is potentially useful in the management of other symptoms in MS, BTX should be used with caution, and final validation of its effectiveness awaits more prospective, placebo-controlled studies. On the other hand, the safety of injected BTX is well established, but was not assessed in MS specifically. Fatigue, one of the potential side effects of BTX, especially if used in large doses, needed for spasticity treatment (48, 49) MS-related fatigue, if aggravated by BTX, can be a severe problem causing interference with home and vocational activities.

Another problem is that BTX is rather expensive treatment and evidence of the cost effectiveness of new treatments must be shown for them to be adopted and paid for by healthcare services. Similarly MS is very expensive disease. The total mean annual costs per patient in Europe is estimated at €18 000 for mild disease (Expanded Disability Status Scale (EDSS) <4.0), €36 500 for moderate disease (EDSS 4.0–6.5) and €62 000 for severe disease (EDSS >7.0). (50) Cost-effectiveness analysis in multiple sclerosis is, however, not straightforward because of the nature of the disease. MS in an advanced stage is associated with high costs and low quality of life and clinical benefits of BTX treatment, at least for spasticity, (51) outweigh the apparent high costs of this intervention, showing it to be a cost-effective treatment.

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