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Botulinum Toxin A Therapy in Early Post-stroke Spasticity: Providing a Wider Treatment Avenue

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Abstract

The use of Botulinum toxin type A (BoNT) to address spasticity has been established over the years, and recently considered first line treatment in chronic post stroke patients. With its promising results, BoNT is now being combined with early neurorehabilitation to treat post-stroke spasticity in order to address the various neuromuscular and biomechanical impairments, contracture prevention, dystonia, associated reactions and pain. The beneficial effects of BoNT as an adjunct to early stroke rehabilitation, in contrast to customary physical therapy alone, is the case in point of this review, so as to suggest another complementary treatment avenue in rehabilitation care.

Keywords: Botulinum toxin; Rehabilitation; Post-stroke; Spasticity; Early care

Introduction

One of the most evident and disabling sequel of stroke is spasticity, in which more than two thirds of stroke survivors who initially experience post-stroke spasticity (PSS) have residual deficits [1-3]. It is believed that spasticity (i.e., involuntary activation of muscles that is intermittently or continuously seen) [4] consequently causes development of secondary complications such as pain and contractures, and henceforth, impaired functional recovery. It is worth note-taking that the phenomenon of spasticity usually precedes the development of the aforementioned secondary complications [5-7]. It is estimated that around 30% of stroke survivors are affected by significant spasticity [8] and 50% who present to hospital with stroke develop at least one severe contracture [9].

Spastic paresis is a complex condition that may be associated with soft tissue contracture, pain and limitations of day-to-day activities, which therefore, substantially impacts on patients' and caregivers' quality of life [10]. The management of spasticity usually involves interdisciplinary subspecialties [11]. However, rehabilitation approaches are generally varied and are aimed primarily at preventing secondary complications and minimizing aggravating factors instead of focusing on the abnormal muscle activity itself [11]. In current practice, treatment of spasticity is delayed until complications are established. It is possible that once initiation of spasticity management is postponed, musculoskeletal impairments may progress to a degree that they already are almost impossible to eradicate [12].

An upper motor neuron (UMN) lesion produces a state of imbalance between the supra-spinal inhibitory and excitatory inputs, disinhibiting the spinal reflexes. These include proprioceptive (stretch) and nociceptive (flexor withdrawal and extensor) reflexes. Changes in muscle tone is believed to be caused by disruption in the balance from reticulo-spinal and other subcortical descending pathways to the motor and interneuronal circuitry of the spinal cord, and the lack of an intact corticospinal system. Alterations in the descending tonic or phasic excitatory and inhibitory inputs to the spinal motor system and the disturbance in the segmental excitatory-inhibitory control may be observed [13]. Following brain and/or spinal cord injury, the input from higher levels (sensori-motor cortex) may be reduced or completely lost, resulting in insufficient regulation of muscle (stretch reflex) activity. The clinical appearance is a non-physiological flexion or extension of affected limbs. Furthermore, reduced activity in the agonist contributes to shortening and over-activity in a usually less-paretic antagonist

muscle. As a result, torque imbalance occurs around joints, which leads to the well-known limb deformities.

Based on meta-analysis derived from well-conducted, randomized controlled clinical trials [14], botulinum toxin type A (BoNT) proved to be safe and efficacious in treating upper and lower limb spasticity. In fact, BoNT has been thought to be a first line treatment in focal/multifocal spasticity in the post-stroke rehabilitation setting [15].

It is now understood that the overall involvement of antagonist resistance, whether of a reflex nature or not, is the critical factor in movement impairment in spastic paresis [16,17]. Hence, the understanding of the pathophysiology of spasticity and its consequences, if recognized, could result in better goal setting and possibly more favorable patient outcomes.

Our aim here is to show how, incorporating BoNT injection in early neurorehabilitation, provide a wider avenue of available treatment options in improving muscle tone and functional ability of the paretic limb in patients suffering from PSS. The focus problem areas in this present work will be on areas of spasticity-related co-contraction, dystonia, associated reactions, local biomechanical changes, contracture and pain. The case in point, being to perhaps shift a frame of mind from what happens of spasticity, left not adequately addressed, lest the "myth" (Figure 1) of not being able to do anything more, remains.

Post-Stroke Spasticity

Definition

The term 'spasticity' has been inconsistently defined [18]. Measures used to assess spasticity usually do not correspond to the defined clinical features of spasticity. Exaggeration of stretch reflexes leading to velocity-dependent increase in passive resistance to stretch of muscle or muscle groups is the fundamental feature of spasticity [19]. In the 1980s, focus was placed on spinal reflexes, as spasticity was described

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Figure 1: The "myth" regarding post-stroke spasticity.
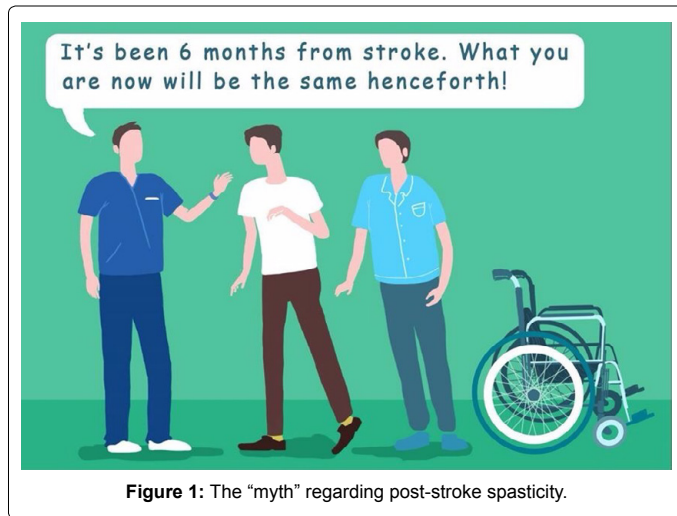
as "a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the UMN syndrome" [20]. In the SPASM consortium in 2005 (European Thematic Network to Develop Standardized Measures of Spasticity), the positive symptoms were combined and spasticity was described as "disordered sensorimotor control, resulting from an upper motor neuron (UMN) lesion, presenting as intermittent or sustained involuntary activation of muscle" [13].

Epidemiology and burden of disease

Reported prevalence of PSS ranges from 4% to 27% during the first 6 weeks after stroke [21-23]. The rate has been reported to be 19% at 3 months, 21.7% to 42.6% at 4 and 6 months, [21-24] and 17% to 38% at 12 months [25,26] post-stroke. In addition to the increased muscle tone of PSS, indirect effects, such as limitations of activities and participation due to physical impairments, have significant impacts on a patient's daily functioning (e.g., personal hygiene, housework, and work place activities) and quality of life [27].

Spasticity and its associated impairments

Spastic co-contraction: Spastic co-contraction refers to inappropriate antagonist recruitment triggered by the volitional command on an agonist in the absence of stretch. Spastic co-contraction primarily results from an abnormal pattern of supra-spinal drive, which can be aggravated by abnormal peripheral reflex reactions, particularly to the degree of stretch tonically imposed on the overactive muscle [16,28]. Although some co-contraction (i.e., simultaneous activity in both agonist and antagonist muscles) is common during normal human movement [29], in the scenario of spastic paresis, it is present to an excessive degree.

Spastic co-contraction directly impedes voluntary movement and hence, may be one of the most disabling types of muscle over activity. As muscle over activity predominates in some muscles in spastic paresis, producing agonist–antagonist imbalance [30,31], intramuscular injection of BoNT has been proposed to restore balance around joints by focally reducing muscle over-activity [14]. In a study by Vinti et al. [32], it has been found that in spastic hemiparesis, stretch may facilitate agonist recruitment and spastic co-contraction. On the other hand, in the non-injected antagonist, co-contraction may be reduced by enhanced reciprocal inhibition from a more relaxed, and therefore

stretched, agonist or through decreased recurrent inhibition from the injected muscle [32].

Spastic dystonia: Spastic dystonia is defined as a stretch-sensitive tonic muscle contraction in the absence of phasic stretch of the affected muscles and in the absence of voluntary command to adjacent muscles [32]. Simply put, spastic dystonia implies a relative inability to rest muscle that is responsive to the amount and duration of the tonic stretch enforced on the muscle. It alters resting posture and thus contributes to deformity and impairment in passive function (i.e. tasks involving the paretic limb as a passive object such as washing hand or donning sleeve) [33].

Spastic dystonia is highly responsive to the amount and duration of tonic stretch imposed on the dystonic muscle [30]. Along with soft tissue contracture, spastic dystonia is an important factor in increased resistance to passive movement and deformity. In most cases, tonic stretch maintained for at least several seconds inhibits spastic dystonia and improves the ability to rest the muscle. Muscle lengthening should raise the recruitment threshold of the stretch receptors in the muscles affected and thus reduce the severity of these potentially disabling forms of over-activity (in particular spastic dystonia) [32].

Spastic-associated reactions

Associated reactions are abnormal postural reactions commonly observed in the affected side of hemiplegic patients and most easily seen in the upper limb [34]. Recent studies have demonstrated that associated reactions in the upper limb are purposeless and do not contribute posturally to the realization of voluntary movement [35]. Functionally, they are considered to be the product of effort [36,37] and a reflection of underlying postural instability [38]. Their clinical impact is vast. They have been implicated in preventing the return of selective movement in the hemiparetic limb, increasing the probability of contracture formation and interfering with function [39-41].

Consequently, clinicians have targeted associated reactions in various management strategies and have viewed their improvement as a measure of patient progression [42].

Local biomechanical changes and contractures

In patients with UMN syndrome, spasticity is held responsible for the velocity-dependence of muscle hypertonia. However, it must be reiterated that in patients with UMN syndrome, muscle hypertonia is a complex phenomenon, and that spasticity is just one aspect. Studies conducted on animals show that immobilization of muscles at short lengths reduces number of serial sarcomeres [43] and increased the proportion of connective tissue present in the muscle [44]. These changes that emerge very early during stages of immobilization augment muscle resistance to passive movements and increase the resting discharge of muscle spindles and hence, their sensitivity to stretch [45-47]. It is possible that in patients with UMN syndrome, muscle contracture is formed by similar adaptations. In this subset of patients, muscle contracture contributes significantly to hypertonia [48-50]. Thus, in early PSS of less than three months, an opportunity is there to treat prior to occurrence of local biomechanical changes [51] and perhaps even contracture [52].

Spasticity-related pain

Pain can directly induce spasticity [53]. It has been shown that in healthy subjects, lengthening of a contracted muscle can cause interference of some muscle fibers with the release of nociceptive substances [54]. When a spastic muscle is stretched, the same process

is expected to happen. In addition, all the positive and negative features of UMN syndrome, in combination with soft tissue changes, disturb distribution of body weight thus inducing unwarranted stress on joint structures and causing pain [55].

Disturbances in sensory inputs also play a role, including the case of post-stroke central neuropathic pain from parietal, thalamic, and brainstem lesions. All of these factors lead to perceived pain by patients with UMN syndrome. The relationship between pain and spasticity is made stronger by the fact that pain increase spasticity, creating a spasticity-pain-disability cycle [56].

Current Rehabilitation Practices

Over the last decades, several non-pharmacologic strategies have been used to address spasticity, including muscle stretching, muscle strengthening, physical modalities, and pain management [57]. These procedures may have neurophysiological and biomechanical effects on the spastic movement disorder. It has been validated in a meta-analysis addressing physical regimens, and how these would influence in the management of upper and lower limb PSS [58]. In the case of early PSS, Table 1 summarizes physical modalities that have been performed (Table 1).

Use of BoNT in early spasticity

In the post-stroke rehabilitation setting, BoNT represents a first-line treatment for focal spasticity. Many studies and meta-analyses demonstrated its safety and efficacy in decreasing spastic hypertonia and pain, improving arm posture and basic upper limb activities such as hand hygiene and facilitation of dressing [59-65].

Botulinum toxin A: Grade A recommendation has been given by the 2016 Guidelines Development Subcommittee of the American Academy of Neurology on the use of BoNT for the treatment of adult spasticity [66]. An earlier meta-analysis of 16 clinical studies with BoNT indicated that it decreases muscle tone and increases range of motion safely and effectively [67]. BoNT exhibits dual peripheral effects through chemodenervation of cholinergic transmission in both extrafusal and intrafusal muscle fibres [68]. BoNT-induced changes in muscle spindle proprioceptor inputs through denervation of the intrafusal muscle fibers are particularly essential in modulating loss of presynaptic inhibition in dystonia, and this phenomenon of afferent effects also may be true in the case of spasticity [68]. BoNT injections into the shorter of the two co-contracting muscles around the joint will augment stretching activities. There is also some evidence for modulation of sensori-motor loops at the spinal and supra-spinal level, as assessed by neurophysiological and functional MRI technologies (i.e. before and after BoNT treatment) [69].

Interestingly, there are looming good data that BoNT, as applied in person-centered goal-attainment scaling process, may have a better impact in the individuals with PSS [70].

A minimum of 24 to 72 h requires BoNT to take effect. The peak effect occurs at about 10 days, and clinical improvements usually last for up to 12 weeks [71]. It must be recognized that though BoNT use is limited in multifocal and generalized spasticity, and treatment effects are only temporary [72,73] it does open a therapeutic window for a combined neurorehabilitative approach. The reversibility of BoNT effects may lead to repeated treatment in chronic spasticity, but perhaps may modify the course of spasticity in early post-stroke intervention [74].

Optimally, the best time to administer BoNT may be when spasticity becomes evident and bothersome to the patient, resulting in impairment of functions both actively and passively, disability and associated reactions, or when it induces pain [74]. It was shown by the Upper Limb International Spasticity Study (ULIS)-II that 80% of patients with post-stroke upper limb spasticity treated with BoNT in a real-life clinical setting achieved their treatment goals, that is, pain reduction and return to various functions [75]. Early (less than 3 months after stroke) single-dose BoNT treatment of spasticity has been investigated in three upper limb studies [76-78], aimed at reducing muscle tone, contracture prevention and improving function. With the objectives of hypertonia reduction and improving ambulation, the advantage of early BoNT therapy for lower limb PSS and non-progressive brain lesions, have likewise been demonstrated [79-81]. A summary data on the specific effects of early BoNT intervention in PSS of upper and lower limbs is presented in Table 2. Undoubted effects on hypertonia can be derived with early use of BoNT for upper and lower limb PSS. While the jury is not yet there in regard to early use of BoNT in PSS to improve active function, clinical trials may have to be designed to include longer (i.e., >6months) observation periods for outcomes, as the nervous system adapts to the new changes in the evolution of spasticity.

Rehabilitation Management	Examples of Modalities	Goals
Muscle Stretching [60]	Passive stretching Active stretching Prolonged positioning Isotonic stretching Isokinetic stretching *Often in combination with other interventions such as orthoses, casting, surgery and spasticity-reducing modalities* [61]	To improve the visco-elastic properties of the muscle-tendon unit, and to reduce the risk of muscle-tendon injury
Muscle Strengthening [58,62]	Muscle training Biofeedback Electrical Stimulation	To generate increased level of muscle force under specific sets of testing conditions to improve muscle strength
Physical Modalities [60]	Shock wave therapy Ultrasound therapy Cryotherapy Thermotherapy Vibration Electrical stimulation	To increase local metabolism, circulation, extensibility of connective tissue and tissue regeneration
Constraint-induced Movement Therapy (CIMT) [63]	Forced use and the massed practice of the paretic arm by restricting the unaffected arm. The unaffected arm and hand are prevented from moving with a glove and a special arm rest.	To improve reaching, grasping, and manipulating objects using the paretic arm and improve bi-manual tasks in many aspects of activities of daily living such as eating, bathing, dressing, and toileting

Table 1: Rehabilitation procedures in the management of early post-stroke spasticity.

Therapeutic Goals	YES		NO	
	Upper Limbs	*Lower Limbs*	*Upper Limbs*	*Lower Limbs*
Reduce hypertonicity	-Cousins et al. [77] -Hesse et al. [78] -Rosales et al. [79]	-Verplancke et al. [80] -Fietzek et al. [81] -Tao et al. [82]		
Reduce pain	-Hesse et al. [78] -Rosales et al. [79]			
Improve disability	-Hesse et al. [78]		-Rosales et al. [79]	
Improve functionality (Motor control)	-Cousins et al. [77] -Hesse et al. [78]	-Tao et al. [82]	-Hesse et al. [78] -Rosales et al. [79]	
Prevent contracture	-Hesse et al. [78]	-Verplancke et al. [80]		
Sustained effect up to 6 months (Reduction of hypertonicity)	-Rosales et al. [79]			

Table 2: Summary of the Use of Early BoNT (type A) in Spasticity (<3 months from Ictus).

Early use of BoNT may also extend the time window for motor re-learning with physiotherapy by decreasing overactive extrafusal muscle fibers and reducing muscle spindle sensitivity through chemodenervation of intrafusal muscle fibres [51]. In effect, the early BoNT intervention paradigm may potentially modify the natural progress of spasticity, prevent spasticity/dystonia-related complications or even delay re-injection [74].

Combination of BoNT and Neurorehabilitation

Upper limb rehabilitation

rTMS/OT, and BoNT: Low-frequency repetitive transcranial magnetic stimulation (rTMS) combined with intensive occupational therapy (OT) have been reported to improve the motor function of the paretic upper limb after stroke [82-84]. This combination was based on the premise that that neural activation is facilitated with concomitant application of the two interventions. At present, the combination of rTMS/OT is safely used in several institutions as a therapeutic tool not only for treatment in non-spastic but also for treatment in spastic upper limb hemiparesis [85,86]. However, the effect of rTMS/OT seems to be affected by the severity of the motor functional impairment of the affected upper limb, and this is largely related to the presence or absence of spasticity. Based on these effects, it could be hypothesized that local injection of BoNT into the spastic muscles before the application of rTMS/OT, may potentially enhance the treatment outcome especially in patients with spasticity and post-stroke upper limb hemiparesis.

In a study by Yamada and cohorts [87], eighty patients with PSS were randomized into either the BoNT plus rTMS/OT group versus the rTMS/OT only group. A total dose of 240 units BoNT was injected into the spastic muscles before rTMS/OT. It was shown that both groups showed significant improvements in terms of spasticity and motor function. However, the addition of BoNT led to better improvement as assessed by the Fugl-Meyer Assessment score and Modified Ashworth Scale of finger flexor muscles (p<0.05). It was concluded that the triple-element protocol consisting of BoNT, rTMS and intensive OT, is a promising therapeutic program for spastic upper limb hemiparesis following stroke.

Lower limb rehabilitation

Ambulatory rehabilitation and BoNT: The benefits of high intensity ambulatory rehabilitation programs over the customary care following BoNT have been examined by Demetrios et al. [88] for PSS among Australian adults. Following BoNT injections for PSS, participants were divided into 1) high intensity ambulatory programs (greater than or equal to three times weekly of one-hour sessions for a total of approximately ten weeks) or 2) customary care programs (less than or equal to two times weekly of one-hour sessions). Assessor-blinded outcomes were completed at baseline (0), 6, 12, and 24 weeks. It was found that both groups had significant improvement in goal attainment and participant satisfaction until 24 weeks; no overall between-groups differences were significantly seen. However, there was a statistical trend (p=0.052) for participants to achieve more upper limb goals in the high intensity therapy group. The authors therefore forwarded that there was a trend for high intensity therapy to be related to greater upper limb goal attainment even if patient-centered outcomes after BoNT injections for PSS were not influenced by the intensity of ambulatory rehabilitation strategies [88]. A further research is required to evaluate such effect and determine which elements of therapy programs enhance post-BoNT outcomes. Interestingly for the lower limb spasticity, a Chinese cohort receiving functional electrical stimulation combined with conventional rehabilitation program (as against the conventional rehabilitation program alone) improved mobility and activities of daily living in early PSS [89]. The latter phenomenon opens a divide on whether BoNT (in combination with rehabilitation) [79-81] may still impact on improved care for this group of patients with lower limb PSS (Table 2).

Conclusion and Recommendations

In today's milieu, where PSS and its residual deficits remain to be one of the most incapacitating conditions, comprehensive rehabilitation is of utmost importance. BoNT therapy, in combination with stroke neurorehabilitation programs, when instituted in the early stages (3 months post-ictus), aims to provide a wider avenue of available therapeutic interventions to improving muscle tone, dystonia, associated reactions, contracture prevention and pain among patients suffering from PSS.

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