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Review

Adjuvant treatments associated with botulinum toxin injection for managing spasticity: An overview of the literature

Alessandro Picelli [a,b,*], Andrea Santamato [c], Elena Chemello [a], Nicoletta Cinone [c], Carlo Cisari [d], Marialuisa Gandolfi [a,b], Maurizio Ranieri [c], Nicola Smania [a,b], Alessio Baricich [d]

[a] Neuromotor and Cognitive Rehabilitation Research Center, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy
[b] Neurorehabilitation Unit, Department of Neurosciences, Hospital Trust of Verona, Verona, Italy
[c] Physical Medicine & Rehabilitation Section, 'OORR' Hospital, University of Foggia, Foggia, Italy
[d] Health Sciences Department, Università del Piemonte Orientale, Novara, Italy

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ABSTRACT

Background and objective: A wide range of adjunct therapies after botulinum toxin administration have been proposed. The aim of the present paper is to provide an overview of major writings dealing with adjuvant (non-pharmacological) treatments associated with botulinum toxin for managing spasticity in order to provide some up-to-date information about the usefulness of the most commonly used procedures.
Methods: The literature in PubMed was searched with the MeSH terms botulinum toxins, muscle spasticity, physical therapy modalities, and rehabilitation. The results were limited to studies focusing on adjuvant treatments associated with botulinum toxin for managing spasticity. We excluded papers on the use of non-drug treatments for spasticity not associated with botulinum toxin serotype A (BoNT-A) injection. Relevant literature known to the authors along with this complementary search represented the basis for this overview of the literature.
Results: Adhesive taping and casting effectively improved the botulinum toxin effect in patients with upper- and lower-limb spasticity. There is level 1 evidence that casting is better than taping for outcomes including spasticity, range of motion and gait. However, consensus about their most appropriate timing, duration, target and material is lacking. In terms of physical modalities combined with botulinum toxin injection, we found level 1 evidence that extracorporeal shock wave therapy is better than electrical stimulation for some post-injection outcomes including spasticity and pain. Furthermore, electrical stimulation of injected muscles might be useful to boost the toxin effect. However, the best stimulation protocol has not been defined. In addition, we found level 2b evidence that whole-body vibration therapy might reduce spasticity with cerebral palsy.
Conclusion: Future research in this field should focus on investigating the most appropriate post-injection treatment protocol for each goal to achieve.

1. Introduction

Spasticity is a common consequence of upper motor-neuron disorders including stroke, acquired brain injury, spinal cord injury, multiple sclerosis, and cerebral palsy [1]. It has been defined as a state of increased muscle tone with exaggerated reflexes characterized by a velocity-dependent increase in resistance to passive movement [2].

Botulinum toxin type A (BoNT-A) has been found effective and safe for treating focal spasticity [3]. The major causes for the loss of BoNT-A response in patients with focal spasticity are an inadequate goal for treatment, inaccurate selection and identification of the correct muscle for injection, insufficient drug dosages, inadequate injection technique, development of changes in the muscle, and formation of neutralizing antibodies [4].

A multidisciplinary team should manage spasticity, considering BoNT-A administration as part of an integrated rehabilitation

* Corresponding author. Neuromotor and Cognitive Rehabilitation Research Center, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, P.le L.A. Scuro, 10, 37134 Verona, Italy.
E-mail address: alessandro.picelli@univr.it (A. Picelli).

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treatment program [5,6]. A wide range of adjunct therapies after BoNT-A injection have been proposed [5–9]. The aim of the present paper is to provide an overview of major writings dealing with adjuvant (non-pharmacological) treatments associated with BoNT-A injection for managing spasticity in order to provide some up-to-date information about the usefulness of the most commonly used procedures.

2. Methods

The literature in PubMed was searched with the MeSH terms botulinum toxins, muscle spasticity, physical therapy modalities, and rehabilitation. The results were limited to studies focusing on adjuvant treatments associated with BoNT-A for managing spasticity. We excluded papers about the use of non-drug treatments for spasticity not associated with BoNT-A injection. Relevant literature known to the authors along with this complementary search represented the basis for this literature overview [5–8].

3. Results

Several studies reported on adjuvant treatments associated with BoNT-A for managing spasticity. Results from studies identified for this literature overview are described.

3.1. Muscle stretching

Muscle stretching includes several procedures that can be applied by moving the joint through its range of motion (ROM) manually or with different devices [10]. The goal of stretching procedures in managing spasticity is to maintain or increase joint mobility by normalizing muscle tone, improving soft tissue extensibility, and reducing contracture [8]. Stretching was hypothesized to increase the extensibility of soft tissues by a mechanism that involves viscous deformation and structural adaptations of muscle and other soft tissues such as tendon, connective, vascular, dermal and neural tissues [1,6,8].

Muscle stretching can be obtained by means of several procedures, including passive stretching, active stretching, prolonged positioning, isotonic stretching, and isokinetic stretching [8]. Some different features of stretching have been defined: intensity (amount of tension applied), velocity (speed of elongation), repetitions (number per session), duration (time of elongation per repetition), dose (total time of elongation), and frequency (periodicity of the stretch) [8,11].

There is high-quality evidence that stretching does not have clinically important effects on joint mobility in people (with or without neurological conditions) if performed for less than 7 months [10]. Furthermore, from a clinical practice point of view, some adverse events of stretching procedures have been reported, including skin breakdown, bruising, blisters and pain [8,12]. Well-designed studies are needed to better assess the effects of stretching associated with BoNT-A treatment in patients with spasticity.

3.2. Taping

Adhesive taping techniques are used for managing spasticity to obtain a progressive stretch of hypertonic muscles by applying strips of adhesive tape in order to reach the maximal elongation [8].

For the upper limb, a case–control study of 65 adults with stroke found greater reduction of muscle hypertonia with adhesive taping (in place for 6 days and checked daily) than electrical stimulation (ES) of the injected muscles plus splinting in stroke patients with wrist and finger flexor spasticity treated with BoNT-A [13]. For the taping protocol, the authors suggested that after the first application (requiring about 45 min), taping should be checked daily to maintain the strips firmly pulled and tensioned (checking requires about 10 min) [13]. More recently, a randomized controlled trial (RCT) of 70 stroke patients (PEDro score 8/10) compared adhesive taping to daily manual muscle stretching combined with BoNT-A in stroke patients with wrist and finger flexor spasticity [14]. Spasticity and disability was decreased more with taping (10 days of application with daily check) (assessed by the Disability Assessment Scale) than daily sessions of muscle manual stretching plus passive articular mobilization of wrist and fingers and splinting [14].

For the lower limb, an RCT of 18 stroke outpatients (PEDro score 5/10) found that ankle-foot taping combined with low-dose BoNT-A injection into the tibialis posterior muscle was as effective as the usual BoNT-A injection scheme (several muscles and higher doses) for treating spastic equinovarus foot in patients with stroke [15]. An RCT of 23 stroke patients (PEDro score 6/10) compared taping (maintained for 5 days and checked daily), ES (5 Hz, rectangular biphasic balanced current stimulation of the injected muscles for 5 days, 30 min twice a day) and stretching (30 min stretching of the calf muscles twice a day for 7 days) after BoNT-A injection at the medial and lateral gastrocnemius muscles in patients with stroke [16]. Taping and ES groups performed better on Modified Ashworth scale (MAS) and motor action potential (MAP) was reduced at 3-month follow-up [16].

An RCT of 20 stroke patients (PEDro score 7/10) compared kinesiotaping versus sham taping as adjuvant treatment associated with BoNT-A injection for managing spastic equinus due to stroke, reporting no clear benefit of kinesiotaping [17]. From a technical point of view, kinesiotaping differs from usual adhesive taping. Indeed, the kinesiotaping was applied following 4 steps:

- (supine) strip placed from the midfoot and attached just below the fibular head over the tibialis anterior muscle;
- (prone) strip attached from the heel to each head of the gastrocnemius muscle;
- (prone) strip placed at the arch and stretched slightly above both the medial and lateral malleolus;
- (prone) strip stretched across the anterior ankle, covering both the medial and lateral malleolus [17].

3.3. Casting

For managing spasticity, casting should be considered in order to reduce excitatory input of muscle spindles, preventing changes in muscle length and reducing contractures [10,18]. Casting is usually applied to the affected (upper or lower) limb to immobilize it in a predetermined position with molded casts made of plasters or tape materials [8,19]. In addition, serial casting allows for progressively increasing the angle of stretch in order to improve ROM by changing passive mechanical properties of the muscle and increasing the number of sarcomeres [20]. It has been proposed as adjuvant treatment after BoNT-A injection in children with cerebral palsy and adults with acquired brain injury [21,22]. In particular, for children with cerebral palsy, delayed serial casting after BoNT-A injection compared to immediate serial casting had a significantly better effect on spasticity at 3 and 6 months after treatment in a pilot study of 12 children (PEDro score 5/10) [22]. With respect to post-stroke spasticity, a pilot study of 13 stroke patients (PEDro score 5/10) found that Neofrakt® night casting may lead to prolonged stretching of spastic muscles with long-lasting therapeutic benefit due to enhancing the BoNT-A

effects [23]. Moreover, a retrospective analysis of 10 chronic stroke patients found significant improvements in ROM and functional profile after a serial casting program combined with BoNT-A injection [24]. An RCT (PEDro score 7/10) compared the effect of taping, casting and stretching after BoNT-A injection in plantar-flexor muscles of 69 stroke patients with spastic equinus [25]. Combining BoNT-A with casting or taping may lead to better and longer lasting effects on spasticity, gait function and ankle passive ROM (PROM) than stretching procedures alone [25].

3.4. Splinting and orthoses

A splint is a removable device designed to support weak and ineffective joints or muscles [26]. For managing spasticity, splinting is mainly based on 2 approaches: the biomechanical approach, which aims to prevent deformity by aligning, mobilizing and stabilizing joints, and the neurophysiological approach, which aims to reduce spasticity by sustained stretch and reflex-inhibiting positions [8]. Orthoses are orthopedic devices aimed to replace or substitute for the loss of muscle function; to correct, compensate or prevent abnormal postures or deformities; and to aid movements of an injured limb. Orthoses are often used in conjunction with other interventions such as physical therapy and/or BoNT-A treatment [27,28]. The literature is sparse on the use of splinting and orthoses as adjuvant treatment to BoNT-A injection in patients with spasticity.

A recent case-control study found a significantly greater reduction of upper-limb spasticity in 39 stroke patients who received BoNT-A plus (volar-dorsal wrist/hand immobilization) splinting as compared with BoNT-A or splinting alone [29]. However, an RCT of 70 stroke patients (PEDro score 8/10) found that palmar splinting combined with manual stretching and passive joint mobilization was less effective than adhesive taping for enhancing the outcome (muscle hypertonia, disability and position) of BoNT-A treatment in stroke patients with wrist and finger flexor muscle spasticity [14].

For orthoses, a retrospective chart review found no difference between 2 small groups of chronic stroke patients in terms of spasticity when using a dynamic wrist-hand orthosis combined or not with BoNT-A injection in the spastic upper limb [30]. Conversely, a case-control study of 103 stroke patients reported that (color Doppler) ultrasound-guided BoNT-A injection combined with ankle foot orthosis might effectively reduce muscle spasm and thus promote movement, balance and daily life activities [31].

3.5. Physical modalities

The usefulness of physical modalities as adjuvant treatments for managing spasticity has been widely described in the literature. This section reports the antispastic effects of extracorporeal shock wave therapy (ESWT), therapeutic ultrasound (US), vibration therapy (VT), ES, and transcutaneous electrical nerve stimulation (TENS).

3.5.1. Extracorporeal shock wave therapy (ESWT)

ESWT is defined as a sequence of single sonic pulses characterized by high peak pressure (100 MPa), fast pressure rise (< 10 ns), and short duration (10 μs) conveyed by an appropriate generator to a specific target area with an energy density from 0.003 to 0.890 mJ/mm^2 [8]. Radial ESWT uses a type of pneumatically generated shock wave with low to medium energy that disperses eccentrically from the applicator tip without focusing the energy on a targeted spot [32,33].

ESWT is thought to produce a "neurological" effect on spastic muscles by inducing enzymatic and non-enzymatic nitric oxide synthesis, which allows for modulation of neurotransmission at the neuromuscular junctions [34]. Nitric oxide is involved in neuromuscular junction formation at the peripheral nervous system and in essential physiological functions of the central nervous system, including neurotransmission, memory, and synaptic plasticity [34,35]. In addition, ESWT has been suggested to have a direct "non-neural rheological" effect on hypertonic muscles in terms of the documented therapeutic effects of shock waves on bone and tendon diseases [35]. Both focused and radial ESWT were recently found to similarly improve spasticity of the gastrocnemius muscle in patients with stroke [36].

3.5.2. Therapeutic ultrasound (US)

According to its thermal (deep heat) and mechanical effects, US has been reported to lead to increased local metabolism, blood flow, extensibility of connective tissue and tissue regeneration at the target tissues [37,38]. For healthy muscles, US combined with stretching significantly improved the extensibility of muscular tissue as compared with static stretch only [39]. For spastic muscles, US may allow for changes of viscoelastic properties and also decrease the sensitivity of the muscle spindle to stretch and alpha motoneuron excitability by increasing the tissue temperature [37,38]. This reasoning comes from 2 small-sample studies (PEDro score 5/10) finding a significant reduction in alpha motoneuron excitability (as measured by Hmax/Mmax ratio) and ankle plantar flexor spasticity (measured by the MAS) in patients with post-stroke spasticity after fifteen 10-min sessions of continuous US (intensity 1.5 W/cm^2) [37,38]. Unfortunately, the antispastic effect of US was not further confirmed by subsequent studies. First, a cross-sectional study (PEDro score 4/10) comparing the efficacy of US and infrared therapy for managing spasticity found that neither infrared therapy nor US could modify the clinical and electrophysiological features of spasticity [40]. Furthermore, an RCT of 50 patients with post-stroke spasticity (PEDro score 6/10) reported no adjuvant effect of continuous US (intensity 1.5 W/cm^2) on passive muscle stretching in minimizing spasticity of the ankle plantar flexors [41]. Finally, a pilot RCT (PEDro score 6/10) found no significant effect of continuous US (intensity 1.5 W/cm^2) on spasticity (measured by the MAS) and ankle passive ROM in 30 patients with spastic equinus due to chronic stroke [42].

3.5.3. Vibration therapy (VT)

Vibratory stimulus modulates primary (Ia) afferent-motoneuron synaptic transmission by inducing presynaptic inhibition [43]. In whole-body VT, the vibratory stimulus is delivered to the whole body from the feet, which contact the vibration platform (static or dynamic exercises are usually performed while standing on the platform) [44]. Whole-body VT has been found to depress the H-reflex, increase the excitability of corticomotor pathways and intracortical inhibition while decreasing intracortical facilitation, and increase temperature and blood flow in both skin and lower-limb muscles [45]. In terms of muscle spasticity with central nervous system disorders, a recent systematic review found insufficient evidence to support (or refute) the use of whole-body vibration in patients with stroke, spinocerebellar ataxia or multiple sclerosis [45]. In terms of duration, only one study of children with cerebral palsy reported that an 8-week intervention normalized muscle tone, improved active joint range and enhanced ambulatory performance for at least 3 days [46].

Focal muscle vibration preferentially activates primary (Ia) spindle afferents, thereby inhibiting the monosynaptic reflex [47]. Hence, focal VT has been proposed as a potential therapy for spasticity. In particular, focal VT was found effective in reducing upper- and lower-limb spasticity in adult patients and lower-limb spasticity in children with cerebral palsy [48–53].

An RCT of 42 individuals (PEDro score 8/10) reported that the addition of segmental muscle VT to BoNT-A injection (as compared with VT or BoNT-A alone) might lead to further advantages, mostly in terms of prolonging the effect on muscle tone over time in patients with multiple sclerosis and spasticity [54].

3.5.4. Electrical stimulation (ES)

Previous studies found that ES might enhance the BoNT-A neuromuscular blockade effect by increasing and accelerating the BoNT-A uptake at the motor nerve terminals in animal models [55]. ES is the most frequently studied adjunct therapy to BoNT-A injection in humans [1]. Several studies reported that ES enhanced the effect of BoNT-A, but the best ES procedure to couple with BoNT-A for spasticity lacks agreement [1]. In particular, a cohort study of 12 patients (PEDro score 4/10) found that in muscles injected with BoNT-A, the compound muscle action potential might be reduced more with low-frequency (4 Hz) than high-frequency (25 Hz) ES [56]. Furthermore, a pilot study of 20 individuals (PEDro score 5/10) observed that ES of the injected muscles delivered immediately after BoNT-A treatment might be more effective than delayed ES on boosting BoNT-A action. [57]. The authors explained their findings according to the internalization process of BoNT-A, described to rapidly occur after BoNT-A administration [57].

Also, functional electrical stimulation (FES) was investigated as adjunct therapy to BoNT-A treatment. In particular, a preliminary investigation of 18 patients (PEDro score 6/10) found improvements in the walking speed of stroke patients with a spastic drop foot treated with BoNT-A plus FES [58]. However, an RCT of 23 individuals (PEDro score 6/10) reported no gains in hand grasp function with cyclic FES combined with OnabotulinumtoxinA in patients with chronic spastic hemiparesis [58]. More recently, an open-label, prospective clinical trial of 15 patients observed that task-orientated therapy with electromyography-controlled FES after BoNT-A injection effectively reduced spasticity and improved upper-limb motor function in patients with spastic paresis [59].

3.5.5. Transcutaneous electrical nerve stimulation (TENS)

TENS may have 2 different effects (production of β-endorphin or gate control effect) depending on the frequency (5 vs 80–100 Hz). The antispastic effect of TENS has been hypothesized to relate to the production of β-endorphins, which may decrease the excitability of the motor neurons and (based on the gate control theory) cause a reduction in nociceptive inputs [60]. Furthermore, TENS has been suggested to facilitate cortical synaptic reorganization and motor output by increasing sensory input due to stimulation by larger-diameter A α,β fibers [60].

For patients with stroke, the recent literature recommends the use of TENS to reduce spasticity, improve static balance and increase walking speed because of its low cost, ease of use, and lack of adverse reactions [61]. From a clinical viewpoint, comparison with other spasticity interventions suggests that TENS is equivalent to or better than oral baclofen and task-related training, equivalent or inferior to exercise, and superior to cryotherapy [1].

4. Discussion

Patients with spasticity are disabled by 3 main features: paresis (reduced voluntary recruitment of skeletal motor units due to a disruption of central voluntary motor command as a consequence of upper motor-neuron disorders), soft tissue contracture and muscle overactivity [62]. BoNT-A reduces muscle overactivity by acting in the cytosol of nerve endings and inhibiting the release of acetylcholine at neuromuscular junctions (it cleaves the 25 kDa synaptosomal-associated protein, which is required for vesicle docking and, consequently, neurotransmitter release [63]). Currently, a number of adjuvant (rehabilitation) treatments have been proposed to be combined with BoNT-A to potentiate its effect (boosting or combined "neurological" effect) and reduce soft-tissue contracture (non-neurological, rheological, effect).

Adhesive taping was found to effectively improve the BoNT-A effect in the upper and lower limb in terms of spasticity, disability and muscle activity [13–16]. However, from a daily practice viewpoint, it might be difficult to apply (costly and time-consuming), especially for outpatients (daily checking might reduce compliance). With regard to (serial) casting, progressively increasing stretch of the spastic muscle might be useful despite the few high-quality studies [18–25]. From a clinical perspective, casting might be complicated in patients with sensory deficit (risk of pressure sores). Finally, there is level 1 evidence that casting is better than taping and taping is better than stretching for outcomes including the MAS, ROM and gait [1]. Conversely, consensus is lacking on taping and casting duration (days of application), timing (early or delayed application), target (most appropriate for upper or lower limbs or functional or non-functional limbs) and material (kinesiotaping or wearable casts).

For physical modalities to combine with BoNT-A for treating limb spasticity, a recent systematic review showed level 1 evidence that ESWT is better than ES for some post-injection outcomes including the MAS, spasm frequency and pain [1]. Furthermore, ES of the injected muscles had a boosting effect on BoNT-A injection [1,55–57]. From a clinical point of view, although the best ES protocol has not been defined, it should include the lowest number of sessions as possible (to improve compliance) and in line with the internalization process of BoNT-A (which has been reported to occur rapidly after injection) [64]. In addition, there is level 2b evidence that whole-body VT might be useful in reducing leg muscle spasticity of patients with cerebral palsy [45]. However, the current literature overview found no study investigating BoNT-A plus TENS [58]. Furthermore, to the best of our knowledge, we have no evidence supporting the use of US as an adjuvant approach to enhance the effects of BoNT-A treatment [8].

Unfortunately, the most appropriate adjuvant treatment protocol after BoNT-A injection has not been defined, probably because it should be based on the quality of evidence (which is affected by the great variability of methods, study designs, different populations/spasticity etiology, sample size, intervention protocols, and outcomes considered, as shown in the current literature overview) but also on several clinical and organizational issues such as the goal to achieve, timing, setting, cost and duration. Future research should focus on investigating the most appropriate post-injection treatment protocol for each goal.

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Disclosure of interest

The authors declare that they have no competing interest.

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