Synergic use of botulinum toxin injection and radial extracorporeal shockwave therapy in Multiple Sclerosis spasticity

Cinzia Marinaro¹, Cosimo Costantino², Oriana d’Esposito¹, Marianna Barletta¹, Angelo Indino¹, Gerardo de Scorpio¹, Antonio Ammendolia¹

¹Department of Medical and Surgical Sciences, Magna Græcia University, Catanzaro, Italy; ²Department of Medicine and Surgery, University of Parma, Parma, Italy

Abstract. Background and aim: In Multiple Sclerosis (MS) spasticity worsens the patient's quality of life. Botulinum NeuroToxin TypeA (BoNT-A) is extensively used in focal spasticity, frequently combined with physical therapies. Radial extracorporeal shock waves (rESW) were already used in association with BoNT-A. Considering that loss of efficacy and adverse events are determinants of BoNT-A treatment interruption, this study aimed to evaluate the possibility to prolong BoNT-A's effect by using rESW in MS focal spasticity. Methods: Sixteen MS patients with spasticity of triceps surae muscles were first subjected to BoNT-A therapy and, four months later, to 4 sections of rESWT. Patients were evaluated before, 30, 90 days after the end of the treatments, by using Modified Ashworth Scale (MAS), Modified Tardieu Scale (MTS), and kinematic analysis of passive and active ankle ROM. Results: BoNT-A determined a significant reduction of spasticity evaluated by MAS with a reduction of positive effects after 4 months (p<0.05); MTS highlighted the efficacy only 90 days after injection (p<0.05). rESWT decreased MAS values at the end and 30 days later the treatment (p<0.01); MTS values showed instead a prolonged effect (p<0.01). BoNT-A determined a gain of passive and active ankle ROM, persisting along with treatment and peaking the maximum value after rESWT (p<0.05). Conclusions: rESWT can prolong BoNT-A effect inducing a significant reduction of spasticity and improvement in passive and active ankle ROM in MS patients. The use of rESWT following BoNT-A injection is useful to avoid some limitations and to prolong the therapeutic effects of BoNT-A therapy. (www.actabiomedica.it)

Key words: Spasticity, Multiple Sclerosis, rESWT, BoNT-A

Introduction

Multiple Sclerosis (MS) is a chronic inflammatory autoimmune disease characterized by fatigue, poor balance, muscle weakness and spasticity. The term “spasticity” indicates involuntary muscle hyperactivity triggered by rapid passive joint movements, frequently responsible for worsening of the life's quality in MS. Spasticity management involves different approaches including spasmolytic drugs, surgery, physiotherapy and Botulinum Neuro Toxin Type A (BoNT-A) (1).

BoNT-A is a neurotoxin that paralyzes muscles by inhibiting presynaptic release of acetylcholine at the neuromuscular junction. BoNT-A is the reference treatment in focal spasticity offering highly effective and well tolerated common indications; its main limitation is the relatively short duration with an average reinjection interval between three and six months.
Besides, about 44% of patients non-responders to botulinum toxin develop antibodies to neurotoxin, requiring increased dosing to achieve paralysis (4). Prolonging BoNT-A’s clinical efficacy should decrease the number of injections needed for patient hypertonic muscle relief, decreasing the risk of negative side effects and changes in drug effectiveness that often occurs over a lifetime of neurotoxin exposure. Several studies have supported the possibility of increasing the effect of BoNT-A by using physical therapies, such as electrical stimulation or radial extracorporeal shock waves treatment (rESWT), although there remains no general agreement (5–9).

The employment of rESWT alone to treat spasticity was investigated in Stroke, Cerebral Palsy (CP) and MS, with good results (10–13). rESWs are a pneumatically actuated pressure with direct mechanical stimulation, developing maximum energy at the skin surface and diffusing radiantly into the tissues. rESWT in spastic muscle determined improvements of rheological and trophic characteristics of the muscle with reduced muscle extensibility able to modify muscle spindles excitability and production of biological mediators (14–16).

In literature rESWs were first used soon after BoNT-A injection to obtain a combinatory effect on post-stroke spasticity, no data were produced on the efficacy of rESWT when previous treatment effects are decreasing (6). Considering that loss of efficacy and adverse events are determinants of interruption in BoNT-A treatment between MS patient (17), the goal of our study is to evaluate rESWT as a treatment able to prolong the duration of BoNT-A effects in MS patients, potentially decreasing the number of “life-time” injections needed by patients.

Materials and Methods

Study design

This is a prospective non-randomized study conducted in outpatient regimen, approved by the Regional Ethics Committee. All participants provided informed consent according to the Declaration of Helsinki before study enrollment.

Patients were first inoculated with BoNT-A and both clinical and instrumental examinations were performed, by a trained PMR specialist, just before (T0-BoNT-A), thirty days (T1- BoNT-A) and ninety days after BoNT-A therapy (T2- BoNT-A). Four months after BoNT-A injection, the same spastic muscles were subjected to rESWT and examined just before the first session (T0-rESWT), after the fourth session (T1’ - rESWT), thirty days (T1 - rESWT) and ninety days after the end of rESWT (T2 - rESWT) (Fig.1).

Participants

MS patients with spasticity of triceps surae muscles and MAS values range 1–4, an EDSS=5-7.5, plantar flexed and inverted foot were recruited. Patients involved in ongoing physiotherapy treatments or treatment for focal spasticity in the last year, severe cognitive impairment (MMSE<24), neuromuscular

![Figure 1. Experimental timeline.](image)
junction disease, malignant tumor in the treatment area, coagulopathy or pregnancy were excluded. Of 27 subjects examined for study eligibility, 16 patients met the inclusion criteria and joined the study (Tab.1). They were evaluated using Ashworth Modified Scale (MAS) and Modified Tardieu Scale (MTS). No changes in pharmacological therapy or signs of disease progression were detected during the study.

Interventions

BoNT-A and rESWT treatments were conducted in outpatient regimen and treated only on one side; when both sides met the inclusion criteria, treatment was performed on the most hypertonic side. BoNT-A (onabotulinumtoxinA - BOTOX®, Allergan Inc., USA), according to guidelines and clinical assessment, was injected into the muscle belly of medial and lateral gastrocnemius and soleus muscles in a range between 50-300 IU divided into 3 sites/muscle, diluted to 3% in physiological saline solution (18,19). For greater accuracy, the procedure was performed by using ultrasound guidance (ESAOTE MyLab50 ultrasound).

rESWT was conducted using Swiss Dolorclast® device (EMS – Switzerland) one session weekly, for a total of 4 sessions. During each session, 500 shots were administered to each muscle belly by using an energy density flux of 1.8 bars at a frequency of 4 Hz.

After each treatment (BoNT-A and rESWT), patients were not subjected to physiotherapy or other additional procedures.

Outcome measures

The primary outcome was the reduction of the muscle tone of triceps surae, measured by MAS and MTS. For minimal intra-rater and inter-rater variability, a PMR specialist assessed the MAS and MTS scores at the initial and follow-up visits. During measurements, the patient lay in the supine position and had to move their ankle from a position of maximal plantar flexion to maximal dorsal flexion.

The MAS measures resistance during passive muscle stretching with scores ranging from 0 to 4, where 0 indicates no increase in muscle tone and 4 indicates that the affected limb is rigid during flexion or extension (20).

The MTS assesses muscle response to stretch applied at specified velocities. Practically, the joint was turned by using different velocities (V1, V2, V3) and the respective angle of muscle reaction was recorded (R2, R1). The quality of muscle reaction, rated at V3, has been quantified by using 5 different levels, where 0 corresponds to no resistance to passive movement and 5 to no joint movement (21). The secondary outcome was an increase of the active and passive ROM measured with kinematic analysis. An optoelectronic acquisition system with two infrared cameras (BTS SMART-DX 100®, BTS Bioengineering Corp.) was used, allowing the creation of a 2D-model of the bone segment and the reconstruction of its movement in space. Markers were positioned on the head of the fibula, external malleolus, head of the fifth metatarsal bone and the angle was registered. The procedure involved three repetitions of both ankles passive dorsal flexion for passive ROM and ankle active plantar flexion for active ROM measurements.

Statistical analysis

Data were analyzed using the Friedman and Wilcoxon tests, shown as mean ± standard error and statistical significance level settled at p <0.05. Statistical Package for Social Science software (SPSS Ver.25.0, IBM USA) was used.

Results

Twenty-seven patients have been screened; 16 subjects met the inclusion criteria, joined and completed the study (Fig.2).
At baseline patients had MAS mean score of 2.56±0.81 and an EDSS mean value of 5.93±0.75 (Tab.1).

After BoNT-A injection, muscle tone assessed by MAS significantly decreased at all post-BoNT-A follow up, with a maximal effect 90 days post-injection (T2- BoNT-A) when the main decreased from 2.56±0.81 to 1.90±0.84. After the last session of rESWT (T1'- rESWT), patients showed a significant reduction of hypertonia, with a statistically significant decrease of MAS values compared to T0- BoNT-A. Values registered at T1'- rESWT were not maintained one month (T1- rESWT) and three months later (T2- rESWT).

MTS showed a significant decrease only 90 days post-injection (T2-BoNT-A). A further significant reduction of MTS value was observed after rESWT.

During treatment and follow-up no side effects were recorded.

Discussion

In the study presented BoNT-A was considered the gold standard treatment and rESWT a synergistic therapy finalized to extend BoNT-A efficacy on ankle extensor spasticity in MS. The main findings were that both BoNT-A and rESWT can yield significant reduction of spasticity and improvement in passive and active ankle ROM in MS patients with consequent walking improvement. BoNT-A injection induced a persistent effect for 3 months, an additive effect was obtained treating patients with rESWT four months later the BoNT-A injection, extending the therapeutic effect for at least two months.

MS patients present severe quality of life alterations determined by spasticity (22). Among therapeutic approaches, BoNT-A, widely used for post-stroke spasticity, has recently gained widespread confirmation of its efficacy in MS (23). This therapy was proved to be safe and efficient until 90 days (24). Nevertheless, it is invasive and painful at the injection site (25). In order to avoid its erroneous diffusion in adjacent tissues and for better accuracy, echo-guidance is required (3). Furthermore, commercially available BoNT-A preparations contain human and non-human proteins that may behave as antigens and elicit an immune response, generally dose-dependent and positively correlated with the cumulative dose (4). Indeed, shorter injection intervals (i.e., 2 months apart) may increase the risk for neutralizing antibody formation and treatment non-response, suggesting longer injection intervals...
Table 2. Outcome measures at different time points. Statistical values are referred to T0-BoNT-A.

| Subjects treated with BoNT-A | MAS (mean ± SD) | MTS (mean ± SD) | PASSIVE ROM (mean ± SD) | ACTIVE ROM (mean ± SD) |
|------------------------------|------------------|------------------|-------------------------|------------------------|
| T0- BoNT-A                   | 2,56±0,81        | 2,87±0,80        | 17,5±8,75                | 6,43±7,50               |
| T1- BoNT-A                   | 1,96±0,95        | 2,43±0,96        | 26,87±7,71               | 10,31±8,45              |
|                              | P=0,011          |                  | P=0,001                  |                         |
| T2- BoNT-A                   | 1,90±0,84        | 2,18±0,98        | 24,06±6,11               | 9,62±5,96               |
|                              | P=0,013          |                  | P=0,019                  |                         |

| Subjects treated with rESW   |                  |                  |                         |                         |
| T0- rESWT                    | 2,09±0,95        | 2,37±0,95        | 24,06±6,11              | 10,25±6,50              |
| T1'- rESWT                   | 1,43±0,77        | 2±1,09           | 30,62±4,42              | 12,5±9,48               |
|                              | P=0,002          |                  | P=0,011                  |                         |
| T1- rESWT                    | 2,09±0,87        | 2,06±0,85        | 28,75±6,95              | 11,87±7,93              |
|                              | P=0,004          |                  | P=0,012                  |                         |
| T2- rESWT                    | 2,25±0,65        | 2,43±0,89        | 22,81±6,57              | 9,37±6,80               |

Figure 3. Clinical outcome measures at different time points in subjects treated first with BoNT-A following by rESWT. Statistical analysis was performed between different timepoints with reference to T0- BoNT-A. * indicates the statistical significance with p<0.05; ** indicates the statistical significance with p<0.01.
in standard clinical practice (26). For these reasons, BoNT-A has a limit of presenting a maximum dose of injection requiring a long interval between two injections (>4 months).

The long-term persistence of BoNT-A treatment in MS is limited by loss of efficacy, adverse events and lack of regular rehabilitation (17). Currently, different adjuvant treatments have been proposed to be combined with BoNT-A to potentiate its effect, as boosting “neurological” effect, and to reduce soft-tissue contracture, as non-neurological effect. For physical modalities to be combined with BoNT-A for the treatment of limb spasticity in stroke, rESWT was considered to be better than electrical stimulation for some post-injection results, including MAS, spasm frequency and pain (8,27,28). The rESWT has the advantage of being a simple and non-invasive therapy, repeatable over time without limits of safety doses with effect in focal treatment of spasticity in stroke, infantile CP and MS (10,29,30).

In this study MS patients with spasticity of triceps surae muscles were first treated with BoNT-A and the effect on muscle hypertonia, assessed by MAS, was clinically evident at every time point of the therapeutic window. Nevertheless, follow-up evaluation 4 months later BoNT-A treatment registered the loss of therapeutic effect with an increase of spasticity (Tab.2). It is already described that patients should be re-treated when the clinical effect of the previous injection has diminished but no sooner than 3 months from the prior injection (31). Considering the described limits of BoNT-A injection, participants underwent four sessions of rESWT, a non-invasive and less expensive therapy, achieving a reduction in muscle tone, assessed by MAS, already evident at the end of the treatment (T1’- rESWT) and until to one month after the last session. MTS evaluation highlights a more lasting effect of rESWT that persists up to 1 month after treatment (Fig. 3a-b). This discrepancy could lie in the different meanings that the two scales assume in the evaluation of spasticity. The Tardieu scale is often considered better than MAS because it uses slow and fast speeds based on the definition of spasticity, and it can differentiate between neural and biomechanical contributions to passive motion resistance (32,33). In Stroke and CP, Tardieu Scale can differentiate elements of movement restriction caused by non-neural phenomena, such as contractures (34,35). We can therefore hypothesize that the prolonged effect of rESWT, highlighted by MTS, may derive from a direct effect on muscle stiffness and, therefore, also on contractures. Joint contractures involving ankle joint are widespread among MS patients implying that their prevention is essential to enable rehabilitation (36,37).

The short duration of the effect of rESWT, although in disagreement with the literature on Stroke and CP, are perfectly in line with data in MS (10) and could be explained by intrinsic characteristics of the pathology coupled to the mechanism of action of rESWT. Furthermore, the more limited effect of rESWT over time could not be attributed to a small number of treatment sessions considering that efficacy on spasticity seemed to grow exponentially with the number of sessions, reaching the maximum effect at 4 sessions (38).

In our study rESWT was delivered to muscle belly and not to tendon structures considering that there was no consensus on what type of structure must be included in this kind of treatment (39–41).

rESWT could increase ankle passive range of motion in Stroke, effect never investigated in MS (40). Our study shows a significant gain in passive movement, already present 30 days after the BoNT-A injection, decreasing 90 days later. The synergistic use of rESWT, when BonT-A efficacy decrease, enhances the passive movement up to 90 days from the last treatment (Fig. 3c).

As known passive ROM, due to its execution characteristics, highlights the presence of contractures and rigidity. The IAB-Interdisciplinary Working Group of Movement Disorder consensus suggests that BoNT-A has no effect on mechanical alterations of hypertonia (1). On the other hand, shock wave therapy plays a role in passive ROM by breaking the functional link between actin and myosin, reducing the intrinsic rigidity of connective tissue and increasing the extensibility of the gastrocnemius muscle (42,43). Therefore, our results could derive from an overlap between the effect on the neurological component obtained by BoNT-A and the effect on the biomechanical component induced by rESWT; hence the importance of synergistic use of the two types of treatment.
Instrumental evaluation of active plantar flexion showed BoNT-A effect only after 1 month, with a doubling of ROM values soon after rESWT. This increase, although limited, is also observed 1 month after the treatment with rESWT (Fig. 3d). Considering that ankle plantar flexors spasticity implies motor performance reduction associated with a higher energy cost of walking, the improvement of active movement means the improvement of the patient autonomy and therefore modification of the degree of disability (44).

BoNT-A injection in rabbit’s eyelids demonstrated that terminal sprouting and formation of new neuromuscular junctions explain the return of function after muscle paralysis (45). On the other hand, the experimental application of the shock wave therapy determined the damage to endplates inducing a transient dysfunction of nerve conduction at neuromuscular junctions (46,47). We hypothesized that during the transition between treatments, rESWT induced neuromuscular plaque destruction occurs on newly formed neuromuscular junctions gradually regenerated following the loss of BoNT-A effectiveness. This result might explain the major effect observed 1 month after rESWT followed by a loss of efficacy in the following months.

**Limitations**

The present study has some limitations and the results should be interpreted in light of these:

- The design of the study lacked a control group because it was based on observations made on a series of individuals receiving the same treatment;
- Patients were not subjected to physiotherapy in order to obtain results derived exclusively from BoNT-A and rESWT treatments.

It is already known that, to obtain functional results, any physical treatment should be integrated as part of a rehabilitation program. In the future, this study could be conducted introducing physiotherapy, a control group with an adequate sample power and neurophysiological evaluation such as electromyography.

**Conclusion**

The study highlights the possibility to prolong the therapeutic efficacy of BoNT-A treatment of focal spasticity in a cohort of MS patients by using rESWT. The use of rESWT after BoNT-A is useful to avoid some limitations of this therapy (pain, high dose, loss of effectiveness, immunogenicity, etc.) and to prolong the time span between injections, favoring patient compliance to therapy and improving the quality of walking.

**Clinical message:** rESWT is a non-pharmacological, non-invasive and less painful treatment of spasticity in MS. It is able to prolong the duration of BoNT-A effects in MS patients and it could be used to potentially decrease the number of “lifetime” injections needed by patients.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

**References**

1. Dressler D, Bhidayasiri R, Bohlega S, Chana P, Chien HF, Chung TM, et al. Defining spasticity: a new approach considering current movement disorders terminology and botulinum toxin therapy. J Neurol. 2018;265(4):856–62.
2. Cameron MH, Bethoux F, Davis N, Frederick M. Botulinum toxin for symptomatic therapy in multiple sclerosis. Curr Neurol Neurosci Rep. 2014 Aug 22;14(8):463.
3. Fonfria E, Maignel J, Lezmi S, Martin V, Splevins A, Shuber S, et al. The expanding therapeutic utility of botulinum neurotoxins. Toxins (Basel). 2018;10(5):1–27.
4. Naumann M, Boo LM, Ackerman AH, Gallagher CJ. Immunogenicity of botulinum toxins. J Neural Transm. 2013;120(2):275–90.
5. Picelli A, Smania N, Storti I, Munari D, Fontana C, Fiaschi A, et al. Immediate versus delayed electrical stimulation boosts botulinum toxin effect: A pilot study. Mov Disord. 2011 Aug 1;26(9):1785–6.
6. Santamato A, Notarnicola A, Panza F, Ranieri M, Micello MF, Manganotti P, et al. SBOTE study: Extracorporeal shock wave therapy versus electrical stimulation after botulinum toxin type a injection for post-stroke spasticity-a prospective randomized trial. Ultrasound Med Biol. 2013;39(2):283–91.
7. Stieger M, Schmid JP, Yawalkar N, Hunziker T. Extracorporeal shock wave therapy for injection site panniculitis in multiple sclerosis patients. Dermatology. 2015 Feb 17;230(1):82–6.

8. Marisa M, Riccardo M, Giacomo F, Giulia G, Franca D, Pietro F, et al. Pain and Muscle Properties Modifications After Botulinum Toxin Type A (BTX-A) and Radial Extracorporeal Shock Wave (rESWT) Combined Treatment. Endocrine, Metab Immune Disord - Drug Targets. 2019 Nov 11;19(8):1127–33.

9. Picelli A, La Marchina E, Gajofatto F, Pontillo A, Vangelista A, Filippini R, et al. Sonographic and clinical effects of botulinum toxin type A combined with extracorporeal shock wave therapy on spastic muscles of children with cerebral palsy. Dev Neurorehabil. 2017 Apr 3;20(3):160–4.

10. Marinelli L, Morì L, Solaro C, Uccelli A, Pelosi E, Curra A, et al. Effect of radial shock wave therapy on pain and muscle hypertonia: A double-blind study in patients with multiple sclerosis. Mult Scler J. 2015;21(5):622–9.

11. Xiang J, Wang W, Jiang W, Qian Q. Effects of extracorporeal shock wave therapy on spasticity in post-stroke patients: A systematic review and meta-analysis of randomized controlled trials. J Rehabil Med. 2018;50(10):852–9.

12. Vidal X, Marti-Fàbregas J, Canet O, Roqué M, Morral A, Tur M, et al. Efficacy of radial extracorporeal shock wave therapy compared with botulinum toxin type A injection in treatment of lower extremity spasticity in subjects with cerebral palsy: A randomized, controlled, cross-over study. J Rehabil Med. 2020;52(6):jrmm0076.

13. Ammendolia A, D’Esposito O, Barletta M, Dicorato R, Fratto L, Iocco M. Treatment of spasticity in multiple sclerosis: Botulinum toxin A injection versus radial shockwave therapy. Ann Phys Rehabil Med. 2018 Jul 1;61(6):364–5.

14. Gracies JM. Pathophysiology of spastic paresis. I: Paresis and soft tissue changes. Vol. 31, Muscle and Nerve. Wiley-Blackwell; 2005. p. 535–51.

15. Romeo P, Lavanga V, Pagani D, Sansone V. Extracorporeal shock wave therapy in musculoskeletal disorders: A review. Med Princ Pract. 2013;23(1):7–13.

16. Leone JA, Kukulka CG. Effects of tendon pressure on alpha motoneuron excitability in patients with stroke. Phys Ther. 1988 Apr;68(4):475–80.

17. Latino P, Castelli L, Fratteo L, Marchetti MR, Pozzilli C, Giovannelli M. Determinants of botulinum toxin discontinuation in multiple sclerosis: a retrospective study. Neurol Sci. 2017 Oct 1;38(10):1841–8.

18. RCP. Royal College of Physicians, British Society of Rehabilitation Medicine, Chartered Society of Physiotherapy, Association of Chartered Physiotherapists Interested in Neurology. Spasticity in adults: management using botulinum toxin. National guidelines. 2009.

19. Esquenazi A, Alfaro A, Ayoub Z, Charles D, Dashmitaur K, Graham GD, et al. OnabotulinumtoxinA for Lower Limb Spasticity: Guidance From a Delphi Panel Approach. PM R. 2017 Oct;9(10):960–8.

20. Meseguer-henarejos A-B, Sánchez-Meca J, López-Pina J-A, Carles-Hernández R. Inter- and intra-rater reliability of the Modified Ashworth Scale: a systematic review and meta-analysis. Eur J Phys Rehabil Med. 2017;(August):576–90.

21. Li F, Wu Y. LX. Test-retest reliability and inter-rater reliability of the Modified Tardieu Scale and the Modified Ashworth Scale in hemiplegic patients with stroke. Eur J Phys Rehabil Med. 2014;50(1):9–15.

22. Rizzo MA, Hadjimichael OC, Preiningerova J, Vollmer TL. Prevalence and treatment of spasticity reported by multiple sclerosis patients. Mult Scler. 2004 Oct 2;10(5):589–95.

23. Dressler D, Bhidayasiri R, Bohlega S, Chahidi A, Chung TM, Ebke M, et al. Botulinum toxin therapy for treatment of spasticity in multiple sclerosis: review and recommendations of the IAB-Interdisciplinary Working Group for Movement Disorders task force. J Neurol. 2017 Jan 27;264(1):112–20.

24. Jost WH, Kohl A, Brinkmann S, Comes G. Efficacy and tolerability of a botulinum toxin type A free of complexing proteins (NT 201) compared with commercially available botulinum toxin type A (BOTOX®) in healthy volunteers. J Neural Transm. 2005 Jun 3;112(7):905–13.

25. Paracka L, Kollewe K, Wegner F, Dressler D. Strategies to decrease injection site pain in botulinum toxin therapy. J Neural Transm. 2017 Oct 24;124(10):1213–6.

26. Lange O, Bigalke H, Dengler R, Wegner F, Degroort M, Wohlfarth K. Neutralizing antibodies and secondary therapy failure after treatment with botulinum toxin type A: Much ado about nothing? Clin Neuropharmacol. 2009 Jul 1;32(4):213–8.

27. Picelli A, Santamato A, Chemello E, Cinone N, Cisari C, Gandolfi M, et al. Adjuvant treatments associated with botulinum toxin injection for managing spasticity: An overview of the literature. Annals of Physical and Rehabilitation Medicine. 2018 Sep 13;

28. Mills PB, Finlayson H, Sudol M, O’Connor R. Systematic review of adjunct therapies to improve outcomes following botulinum toxin injection for treatment of limb spasticity. Vol. 30, Clinical Rehabilitation. 2016. p. 537–48.

29. Cabanas-Valdés R, Calvo–Sanz J, Urrútia G, Serra-Llobet P, Pérez-Bellmunt A, Germán-Romero A. The effectiveness of extracorporeal shock wave therapy to reduce lower limb spasticity in stroke patients: a systematic review and meta-analysis. Topics in Stroke Rehabilitation. 2019. p. 1–21.

30. Lin Y, Wang G, Wang B. Rehabilitation treatment of spastic cerebral palsy with radial extracorporeal shock wave therapy and rehabilitation therapy. Medicine (Baltimore). 2018 Dec;97(51):e13828.

31. Wein T, Esquenazi A, Jost WH, Ward AB, Pan G, Dimitrova R. OnabotulinumtoxinA for the Treatment of Post-stroke Distal Lower Limb Spasticity: A Randomized Trial. PM R. 2018;10(7):693–703.

32. Abdollahi I, Azarnia S, Dorebati SN, Salavati M. Inter-rater reliability of the modified Tardieu scale for the assessment of knee extensor spasticity in patient with multiple sclerosis. Koomesh. 2017 Jan 12;19(1):220–6.
33. Banky M, Williams G. Tardieu Scale. J Physiother. 2017;63(2):126.
34. Patrick E, Ada L. The Tardieu Scale differentiates contracture from spasticity whereas the Ashworth Scale is confounded by it. Clin Rehabil. 2006 Feb 1;20(2):173–81.
35. Alhusaini AAA, Dean CM, Crosbie J, Shepherd RB, Lewis J. Evaluation of spasticity in children with cerebral palsy using ashworth and tardieu scales compared with laboratory measures. J Child Neurol. 2010 Oct 10;25(10):1242–7.
36. Hoang PD, Gandevia SC, Herbert RD. Prevalence of joint contractures and muscle weakness in people with multiple sclerosis. Disabil Rehabil. 2014 Sep 18;36(19):1588–93.
37. Picelli A, Vallies G, Chemello E, Castellazzi P, Brugnera A, Gandolfi M, et al. Is spasticity always the same? An observational study comparing the features of spastic equinus foot in patients with chronic stroke and multiple sclerosis. J Neurol Sci. 2017 Sep;380:132–6.
38. Mori L, Marinelli L, Pelosin E, Curra A, Molfetta L, Abbruzzese G, et al. Shock Waves in the Treatment of Muscle Hypertonia and Dystonia. Biomed Res Int. 2014;2014.
39. Oh JH, Park HD, Han SH, Shin GY, Choi KY. Duration of treatment effect of extracorporeal shock wave on spasticity and subgroup-analysis according to number of shocks and application site: A meta-analysis. Ann Rehabil Med. 2019;43(2):163–77.
40. Wu Y-T, Chang C-N, Chen Y-M, Hu G-C. Comparison of the effect of focused and radial extracorporeal shock waves on spastic equinus in patients with stroke: a randomized controlled trial. Eur J Phys Rehabil Med. 2017;(August):1–27.
41. Taheri P, Vahdatpour B, Mellat M, Ashari F, Akbari M. Effect of Extracorporeal Shock Wave Therapy on Lower Limb Spasticity in Stroke Patients. Arch Iran Med. 2017 Jun;20(6):338–43.
42. Vettrano M, D’Alessandro F, Torrisi MR, Ferretti A, Vulpiani MC, Visco V. Extracorporeal shock wave therapy promotes cell proliferation and collagen synthesis of primary cultured human tenocytes. Knee Surgery, Sport Traumatol Arthrosc. 2011 Dec 27;19(12):2159–68.
43. Notarnicola A, Moretti B. The biological effects of extracorporeal shock wave therapy (eswt) on tendon tissue. Vol. 2, Muscles, ligaments and Tendons Journal. 2012.
44. Jeng B, Sandroff BM, Motl RW. Energetic cost of walking and spasticity in persons with multiple sclerosis with moderate disability. NeuroRehabilitation. 2018 Oct 31;Preprint(Preprint):1–7.
45. Harrison AR, Berbos Z, Zaldivar RA, Anderson BC, Semmer M, Lee MS, et al. Modulating neuromuscular junction density changes in botulinum toxin-treated orbicularis oculi muscle. Invest Ophthalmol Vis Sci. 2011;52(2):982–6.
46. Kenmoku T, Nemoto N, Iwakura N, Ochiai N, Uchida K, Saisu T, et al. Extracorporeal shock wave treatment can selectively destroy end plates in neuromuscular junctions. Muscle and Nerve. 2018 Mar;57(3):466–72.
47. Kenmoku T, Ochiai N, Ohtori S, Saisu T, Sasho T, Nakagawa K, et al. Degeneration and recovery of the neuromuscular junction after application of extracorporeal shock wave therapy. J Orthop Res. 2012;30(10):1660–5.

Correspondence
Received: 25 November 2020
Accepted: 9 December 2020
Cinzia Marinaro, MD PhD
Campus “Salvatore Venuta” - Viale Europa, Loc. Germaneto, Catanzaro
Italy
Phone: +390961712816
E-mail: cinziamarinaro83@gmail.com