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● *Original Contribution*

SBOTE STUDY: EXTRACORPOREAL SHOCK WAVE THERAPY VERSUS ELECTRICAL STIMULATION AFTER BOTULINUM TOXIN TYPE A INJECTION FOR POST-STROKE SPASTICITY—A PROSPECTIVE RANDOMIZED TRIAL

ANDREA SANTAMATO,* ANGELA NOTARNICOLA,[†] FRANCESCO PANZA,[‡] MAURIZIO RANIERI,[§]
 MARIA FRANCESCA MICELLO,* PAOLO MANGANOTTI,^{||} BIAGIO MORETTI,[†] FRANCESCA FORTUNATO,[¶]
 SERENA FILONI,[#] and PIETRO FIORE*

*Department of Physical Medicine and Rehabilitation, University of Foggia, Foggia, Italy; [†]Department of Neuroscience and Organs of Sense, Orthopaedics and Traumatology Units, University of Bari, Bari, Italy; [‡]Geriatric Unit and Gerontology-Geriatric Research Laboratory, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; [§]Department of Neurological and Psychiatric Sciences, University of Bari, Bari, Italy; ^{||}Department of Neurological Sciences and Vision (E.A.), Verona Hospital, University of Verona, Italy; [¶]Section of Hygiene, Department of Medical and Occupational Science, University of Foggia, Foggia, Italy; and [#]Fondazione Padre Pio Rehabilitation Center San Giovanni Rotondo, Foggia, Italy

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Abstract—Research is on-going to identify new methods of biostimulation to increase the effect of botulinum toxin type A (BTX-A) in the treatment of spasticity. The Spasticity treated by Botulinum Toxin and ESWT (SBOTE) study is a prospective, randomized controlled trial assessing the effectiveness of extracorporeal shock wave therapy (ESWT) given immediately after BTX-A injections compared with electrical stimulation (ES) given immediately after BTX-A therapy for the management of focal upper limb spasticity in stroke patients. ES was given for 30 min twice a day for 5 days starting at 5 Hz; ESWT was given once a day for 5 days. At study follow-up, patients treated with BTX-A injections and ESWT showed a statistically greater significance and continuous decrease of spasticity measure (modified Ashworth scale [MAS]: 1.37, 1.75 and 1.58 at 15, 30 and 90 days post-treatment, respectively), of spasms (spasm frequency scale [SFS]: 0.8 and 0.25 at 30 and 90 days post-treatment, respectively) and of pain (visual analogue scale [VAS]: 1.94 and 1.87 at 30 and 90 days, respectively) compared with patients treated with BTX-A injections and ES (MAS: 2.37, 2.18 and 2.18, respectively) ($p < 0.05$) (SFS: 1.5 and 1.06, respectively) ($p < 0.05$) (VAS: 2.44 and 2.69 respectively) ($p < 0.05$). ESWT enhances the effect of BTX-A to a greater extent than ES, probably by modulating rheology of the muscle and neurotransmission at the neuromuscular junction. (E-mail: angelanotarnicola@yahoo.it) © 2013 World Federation for Ultrasound in Medicine & Biology.

Key Words: Spasticity, Botulinum toxin type A, Electrical stimulation, Extracorporeal shock wave therapy.

INTRODUCTION

Spasticity is estimated to occur in up to 38% of patients post-stroke (Watkins et al. 2002). The common clinical picture of upper limb spasticity includes flexed wrist, clenched fist, flexed elbow, pronated forearm and thumb in palm. Prolonged abnormal limb posture can lead to substantial deformity, affecting mobility, transfer and hygiene. This contributes to pressure sores and pain, and interferes with activities of daily living (Lieber

et al. 2004). In the rehabilitation setting, the main objective of post-stroke spasticity management is the reduction of hypertonia, thereby increasing mobility and articular range of motion and improving personal hygiene and functional activities.

Botulinum toxin type A (BTX-A), one of the most potent biologic toxins known to man, acts by blocking neuromuscular transmission *via* the inhibition of acetylcholine release. Since early reports on the use of BTX-A to treat spasticity in 1989 (Das and Park 1989), there have been more than 900 articles assessing its employment for neurologic diseases. Actually, BTX-A represents the gold standard therapy for focal spasticity after stroke: many studies and meta-analyses demonstrated that BTX-A injections are safe and effective with low

Address correspondence to: Angela Notarnicola, MD, PhD, Department of Neuroscience and Organs of Sense, Orthopaedics and Traumatology Units, University of Bari, Piazza G.Cesare 11, 70124 Bari, Italy. E-mail: angelanotarnicola@yahoo.it

prevalence of complications, reversibility and efficacy in reducing spastic hypertonia (Das and Park 1989; Brashear et al. 2002; Simpson et al. 1996; Rosales and Chua-Yap 2008; Wissel et al. 2009). In spasticity, the effect of the toxin starts several days after injection and persists for around 90 days, with the greatest effect observed within the first month (Jost et al. 2005). Several studies have supported the possibility of increasing the effect of BTX-A with different physical therapies, although there remains no general agreement as to which of these supportive treatments is the most effective (Baricich et al. 2008; Hesse et al. 1998; Carda and Molteni 2005; Wissel et al. 2009). Recently, the efficacy of BTX-A combined to electrical stimulation (ES) was reported for spasticity reduction (Bayram et al. 2006; Kang et al. 2007; Santus et al. 2011; Picelli et al. 2011). It has been shown that ES induces the merging of numerous synaptic vesicles with neuronal membrane releasing acetylcholine (Zhu and Xu 2009). Considering that motor units are able to internalize a larger quantity of toxin, ES applied after BTX-A injections increases the efficacy of BTX-A. Different ES application times of nerve stimulation have been used in previous studies (Eleopra et al. 1997; Frasson et al. 2005; Esquenazi and Mayer 2007), even if there is no clear agreement concerning the optimum frequency of ES and duration time of application.

Other physical therapies without the employment of BTX-A injections, such as vibrotactile stimulation and extracorporeal shock wave therapy (ESWT), have been suggested as methods of improving post-stroke spasticity and other movement disorders (Liepert and Binder 2010; Lohse-Busch et al. 1997; Manganotti and Amelio 2005; Trompetto et al. 2009; Amelio and Manganotti 2010). The employment of ESWT alone to treat spasticity of various etiologies was investigated in some reports: the first published paper showed the safety and effectiveness of 500 non-focused pulses of low-energy ESW administered in the treatment of hypertonic muscles of young people (Lohse-Busch et al. 1997). After one session, the patients reported a statistically significant improvement of their clinical picture that persisted for several weeks (Lohse-Busch et al. 1997). Few years later, other researchers monitored the safety and effectiveness of one ESWT session in reducing muscle hypertonia and movement disorder (Manganotti and Amelio 2005). They demonstrated a reduction of wrist and finger flexor spasticity in stroke patients with no adverse effects or nerve damage with effects persisting for least 12 weeks (Manganotti and Amelio 2005). In a more recent study, a single ESWT stimulation was employed to treat children affected by cerebral palsy with spastic equinus foot (Amelio and Manganotti 2010). The patients reported a significant decrease in the Ashworth scale, an

increase of the articular ankle range of motion and an improvement of whole plantar surface area of the treated limb for 4 weeks (Amelio and Manganotti 2010). In another study, four sessions of ESWT were administered to treat secondary dystonia and idiopathic writer's cramp: the improvement lasted 1 month for secondary dystonia patients, whereas the results were less consistent for writer's cramp (Trompetto et al. 2009).

To the best of our knowledge, at present, no papers cite the effect of ESWT combined with BTX-A to treat spasticity after stroke. The SBOTE (Spasticity treated by Botulinum Toxin and ESWT) study is the first prospective, randomised controlled trial assessing the effectiveness of BTX-A combined with ESWT and assessing the efficacy of BTX-A with ESWT compared with BTX-A with ES in the treatment of focal upper limb spasticity in post-stroke patients with a 90-day follow-up period.

MATERIALS AND METHODS

Ethical approval

The SBOTE study was conducted according to the Declaration of Helsinki, the guidelines for Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT) Statement guidelines (available at URL <http://www.consort-statement.org>). The study was approved by the Institutional Review Board (IRB) of the University of Bari, Italy (Prot. n. 977/C.E.). Written informed consent was received from all study participants and/or their relatives.

Inclusion criteria

The inclusion criteria at screening and at the baseline visit (t_0) were: focal spasticity of finger flexors measured as ≥ 2 on the modified Ashworth scale (MAS) (Bohannon and Smith 1987), at least a 6-month period from stroke, daily painful muscle spasms measured as ≥ 2 on the spasm frequency scale (SFS) (Snow et al. 1990), and pain at rest and during limb mobilization measured as ≥ 3 on the visual analogue scale (VAS) (Price et al. 1994).

Exclusion criteria

Patients were excluded from the study if they met any of the following criteria: fixed contractures and/or deformities at the wrist and elbow, previous fractures of the paretic upper limb, cognitive impairment, peripheral nervous system disorders/myopathies, pacemaker, pregnant or taking medications that could have an impact on the study or on response to ESWT or ES (e.g., previous BTX-A treatment, GABAergic medications, benzodiazepines, anticoagulants, or muscle relaxants). Patients with structural alterations in the soft tissue (e.g., fibrosis) were

also excluded. A sonographic measurement was performed on the spastic muscle of the forearm during the first evaluation to identify these exclusions.

Recruitment and randomization

Patients were enrolled from referrals to the Departments of Physical Medicine and Rehabilitation at the Universities of Bari and Foggia, Italy.

Patients recruited were randomly allocated to receive either BTX-A with ES (group A) or BTX-A with ESWT (group B) after stratification using a software-generated randomization tool.

Study protocol

Patients were evaluated according to the MAS for spasticity, VAS for pain and SFS for muscle spasms:

- The MAS is a scale used to assess muscle spasticity, from 0 indicating normal muscle tone up to 4 indicating a rigid flexion (Bohannon and Smith 1987). For statistical purposes, a MAS score of '1' was considered as 1, MAS score '1+' as 2, and so on until 5.
- The SFS is a scale used to assess the frequency of muscle spasms daily in hypertonic muscles. The score ranges from 0 indicating no spasms up to 4 indicating ≥ 10 spasms per day, or continuous contraction (Snow *et al.* 1990).
- The VAS is a scale used to measure pain, from a 10 cm horizontal axis where 0 means no pain and 10 is the worst pain possible (Price *et al.* 1994).

Each patient was examined at every visit by the same investigator who was blinded to the treatment regimen. Adverse effects of BTX-A (weakness) or ESWT (bruise) were monitored.

After screening, patient assessments occurred before treatment (baseline, t_0), and also after 15 (t_1), 30 (t_2) and 90 days (t_3) after BTX-A with ES and BTX-A with ESWT for MAS, and at 30 and 90 days for VAS and SFS.

BTX-A injections

After clinical evaluation, patients were treated under ultrasound guidance with one dose of BTX-A injected IM into the flexor digitorum superficialis muscle in the forearm. To avoid differences in dose calculation, all patients received BTX-A as Botox® (Allergan Inc., Irvine, CA, USA), diluted with 2 mL of 0.9% saline.

Electrical stimulation

Immediately after BTX-A injection, electrical stimulation (ES) was administered using the Endomed 482 device (Enraf-Nonius, Rotterdam, The Netherlands). Surface electrodes were positioned over the motor points, directly on the belly of the flexor digitorum superficialis

muscle and 5 Hz of rectangular biphasic balanced current was applied for 30 min twice a day for 5 days. Intensity was adjusted according to the patient's tolerance (50–90 mA).

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) was administered immediately after BTX-A injection once a day for 5 days. An electromagnetic coil lithotripter (Minilith SL1; Storz Medical, Switzerland) equipped with an on-line sonographic axial probe of 7.5 MHz was used. Pressure pulses were focused on the forearm; at each session 1000 impulses were administered on the belly of the flexor digitorum superficialis muscle (Fig. 1) and 1000 on the proximal muscle-tendon junction (elbow) (Fig. 2). An energy flux density (EDF) of 0.030 mJ/mm² was applied and the repetition frequency of shock wave irradiation was 4 Hz; anesthesia was not required.

Study end-points

The primary end-point of the SBOTE study was the response to the two treatments defined as a decrease in spasticity (MAS), spasms (SFS) and pain (VAS) from baseline to the follow-up time points. The secondary end-point was a comparison between the results of the two groups.

Power analysis

A sample of 16 patients in each group would achieve a power $>80\%$ to detect a difference of 3.5 points of VAS between the two measurements, assessing SD = 1, correlation = 0.7 and alpha = 0.05; a sample of 16 patients in each group would achieve a power $>80\%$ to detect a difference of 3.5 points of MAS between the two measurements, assessing SD = 1, correlation = 0.7 and alpha = 0.05; a sample of 16 patients in each group would achieve a power $>80\%$ to detect a difference of 2



Fig. 1. The administration of a session of extracorporeal shock wave therapy (ESWT): the probe is put on flexor superficialis digitorum muscle's belly.



Fig. 2. The administration of a session of extracorporeal shock wave therapy (ESWT): the probe is put on proximal muscle-tendon junction of flexor superficialis digitorum muscle.

points of SFS between the two measurements, assessing SD = 1, correlation = 0.7 and alpha = 0.05.

Statistical analysis

At baseline, differences in age, stroke duration, MAS, SFS and VAS between treatment groups were analyzed using the Mann-Whitney U Test. MAS, SFS and VAS are shown as mean \pm standard deviation (SD). Sex differences were analyzed using the Pearson's χ^2 with Yates correction. All parameters were monitored clinically at baseline (t_0), and then after 15 (t_1), 30 (t_2) and 90 days (t_3) of administered therapy for MAS, and after 30 (t_2) and 90 (t_3) days for SFS and VAS. Differences between baseline (t_0) and post-treatment outcome measures (t_1 - t_2 - t_3) for each group were calculated using the Wilcoxon signed-rank test. The difference between each treatment group was calculated using the Mann-Whitney U test. GPower 3.1.10 software (Microsoft Corporation, Redmond, WA, USA) was used for power analysis and sample size estimation. Regression test was used to evaluate any statistical relationships between MAS, SFS and VAS for both groups, at 30 and 90 days of follow-up. All other analyses were performed using SPSS for Windows, v. 6.1 (Microsoft Corporation). The level of statistical significance was set as $p < 0.05$.

RESULTS

A total of 64 consecutive patients (39 women; 25 men) were screened for study eligibility. At the end of the evaluation, 32 patients (18 women; 14 men; mean age \pm SD: 63.75 ± 6.43 years) with post-stroke upper limb spasticity met the inclusion criteria and were enrolled into the study. All 32 patients enrolled completed the trial and were included in the analysis. Sixteen participants (group A) received ES after

BTX-A for 30 min and continued twice a day for 5 days, and 16 participants (group B) received ESWT starting after BTX-A and given once a day for 5 days.

The mean dose of BTX-A injected was 118.6 (± 26.4) (range 80–140) UI in group A and 112.4 (± 22.7) (range 80–140) UI in group B ($p = 0.8$).

Table 1 summarizes the baseline clinical and demographic characteristics of the 32 patients enrolled in the SBOTE study. At baseline, there were no significant between-group differences in age distribution, sex, stroke duration, MAS, SFS and VAS.

Table 2 shows the mean MAS, SFS and VAS in both groups at baseline and during the follow-up time points. In group A, there was a statistically significant decrease in MAS at 15 days ($p = 0.0000$). In the SFS and VAS scores, there was a statistically significant reduction at 30 days ($p < 0.05$). In group B, there was a statistically significant reduction in MAS at 15 and 30 days ($p < 0.05$); in SFS there was statistically significant reduction at 30 and 90 days ($p < 0.05$). VAS improved after 30 days ($p < 0.05$).

Table 3 shows results of the between-group analysis. The decrease in MAS was statistically significant in group B vs. group A at 15 days ($p = 0.0001$), and at 30 ($p = 0.01$) and 90 days ($p = 0.0007$). SFS and VAS reductions were statistically greater in group B in comparison with group A after 30 and 90 days ($p < 0.05$). No statistically significant correlation among MAS, SFS and VAS in both groups was found at 30 and 90 days of follow-up ($p > 0.05$). None of the patients reported adverse effects during the study period.

DISCUSSION

The SBOTE study confirmed that both BTX-A combined with ESWT or ES are effective to reduce upper limb spasticity after stroke and that BTX-A combined with ESWT was more effective than BTX-A with ES. Statistically significant improvements from baseline to follow-up were achieved in the BTX-A with ES group

Table 1. Demographic and clinical characteristics at baseline (t_0) of patients with post-stroke upper limb spasticity who received BTX-A with ES (group A) or BTX-A with ESWT (group B)

	Group A	Group B	<i>p</i> value
Mean age, y (SD)	63.1 \pm 7.03	64.4 \pm 6.09	0.07*
Sex (F/M)	10/6	9/7	0.97 [†]
Mean time (SD) since onset of stroke in months	9.3 \pm 3.97	10.5 \pm 2.12	0.74*

BTX-A = botulinum toxin type A; ES = electrical stimulation; ESWT = extracorporeal shock wave therapy; SD = standard deviation.

* Mann-Whitney U-test.

[†] Pearson's χ^2 with Yates correction.

Table 2. Outcome measures [MAS, SFS and VAS] in patients with post-stroke upper limb spasticity who received BTX-A with ES (group A) or BTX-A with ESWT (group B) at the different time points. MAS, SFS and VAS are shown as mean ± SD

	MAS		SFS		VAS	
	Mean ± SD	<i>p</i> value	Mean ± SD	<i>p</i> value	Mean ± SD	<i>p</i> value
Group A						
t ₀	3.62 ± 0.5	–	2.56 ± 1.03	–	5.25 ± 1.34	–
t ₁	2.37 ± 0.5	0.0000*	–	–	–	–
t ₂	2.18 ± 0.4	0.2521	1.5 ± 0.82	0.0030*	2.44 ± 0.89	0.000*
t ₃	2.18 ± 0.4	1	1.06 ± 0.77	0.1298	2.69 ± 0.79	0.4088
Group B						
t ₀	3.5 ± 0.52	–	2.37 ± 1.15	–	5 ± 1.21	–
t ₁	1.37 ± 0.5	0.0000*	–	–	–	–
t ₂	1.75 ± 0.45	0.0329*	0.81 ± 0.65	0.0000*	1.94 ± 0.68	0.000*
t ₃	1.58 ± 0.52	0.1536	0.25 ± 0.44	0.0081*	1.87 ± 0.62	0.7876

BTX-A = botulinum toxin type A; ES = electrical stimulation; ESWT = extracorporeal shock wave therapy; SD = standard deviation; MAS = modified Ashworth scale; SFS = spasm frequency scale; VAS = visual analogue scale; t₀ = before treatment; t₁ = 15 days after treatment; t₂ = 30 days after treatment; t₃ = 90 days after treatment.

Values after 15 (t₁), 30 (t₂), and 90 days (t₃) of administered treatment for MAS and after 30 (t₂) and 90 days (t₃) for SFS and VAS were compared with baseline (t₀) in groups A and B.

* Statistically significant.

at 15 days for MAS and at 30 days for SFS and VAS; in the BTX-A with ESWT group, statistically significant improvements from baseline to follow-up were achieved at 15 days for MAS, at 30 days for MAS, SFS and VAS, and at 90 days for SFS.

The injection of BTX-A is a safe and effective procedure in spasticity, able to decrease muscle tone and to increase articular range of motion (Brashear *et al.* 2002; Rosales and Chua-Yap 2008). In a randomized, double-blind, placebo-controlled, multicenter trial, the patients who received BTX-A reported a statistically significant improvement in muscle spasticity at all of the 12-week follow-up visits compared with placebo (Brashear *et al.* 2002). Another published paper, concern-

ing an evidence-based systematic review on the efficacy and safety of BTX-A therapy in post-stroke spasticity, demonstrated that BTX-A is considered a safe therapeutic agent that improves muscle tone in upper and lower limb spasticity following stroke measuring with MAS (Rosales and Chua-Yap 2008). Recently, a group of clinicians from across Europe experienced in the use of BTX-A, gathered to develop a consensus statement on best practice in managing adults with spasticity: they considered BTX-A a valuable tool in the multi-modal treatment of adult spasticity (Wissel *et al.* 2009). The effect of BTX-A should be improved by different physical therapies, for example by ES (Baricich *et al.* 2008; Hesse *et al.* 1998; Carda and Molteni 2005; Wissel *et al.* 2009). When ES is applied alone, it is able to reduce muscle tonicity *via* the reduction of the stretching reflex, allowing a larger range of motion and preventing soft tissue stiffness and contracture (Hazlewood *et al.* 1994). In a randomized controlled clinical trial study, patients treated for spasticity with ES combined with Bobath therapy reported an increase of passive joint range of motion and a reduction of muscle tone measured by MAS (Bakhtyary and Fatemy 2008). When BTX-A and electrical stimulation were associated, it was verified as a reduction of the amount of BTX-A required and as an improvement of the relationship between therapeutic outcome and side effects attributable to an enhancement of motor recovery (Santus *et al.* 2011; Picelli *et al.* 2011). It has been shown that ES induces the merging of numerous synaptic vesicles with neuronal membrane releasing acetylcholine (Zhu and Xu 2009). Considering that motor units are able to internalize a larger quantity of toxin, ES applied after BTX-A may increase the efficacy of BTX-A. In the SBOTE study, we confirmed the efficacy of this combined treatment in post-stroke spasticity.

Table 3. Baseline and follow-up results for all outcome measures [MAS, SFS and VAS] in patients with post-stroke upper limb spasticity who received BTX-A with ES (group A) or BTX-A with ESWT (group B)

Time	Scale	Group A	Group B	<i>p</i> value
		Mean ± SD	Mean ± SD	
t ₀	MAS	3.62 ± 0.5	3.5 ± 0.52	0.2722
	SFS	2.56 ± 1.03	2.37 ± 1.15	0.2828
	VAS	5.25 ± 1.34	5 ± 1.21	0.3013
t ₁	MAS	2.37 ± 0.5	1.37 ± 0.5	0.0001*
	MAS	2.18 ± 0.4	1.75 ± 0.45	0.0147*
t ₂	SFS	1.5 ± 0.82	0.81 ± 0.65	0.0033*
	VAS	2.44 ± 0.89	1.94 ± 0.68	0.0359*
	MAS	2.18 ± 0.4	1.58 ± 0.52	0.0007*
t ₃	SFS	1.06 ± 0.77	0.25 ± 0.44	0.0014*
	VAS	2.69 ± 0.79	1.87 ± 0.62	0.0007*

BTX-A = botulinum toxin type A; ES = electrical stimulation; ESWT = extracorporeal shock wave therapy; SD = standard deviation; MAS = modified Ashworth scale; SFS = spasm frequency scale; VAS = visual analogue scale; t₀ = before treatment; t₁ = 15 days after treatment; t₂ = 30 days after treatment; t₃ = 90 days after treatment.

* Statistically significant.

Different ES application times of nerve stimulation have been used in previous studies (Eleopra et al. 1997; Frasson et al. 2005; Esquenazi and Mayer 2007). In almost all of them, ES has been applied after BTX-A injection (Bayram et al. 2006; Grumelli et al. 2005; Ravichandran et al. 2006; Montecuccio et al. 2004). Many studies support the use of repetitive nerve stimulation (Eleopra et al. 1997; Frasson et al. 2005; Torii et al. 2010; Detrembleur et al. 2002), while others conclude that there is no significant increase of the efficacy of BTX-A after initial application (Kang et al. 2007; Rha et al. 2008). There is also no clear agreement concerning the optimum frequency of ES and duration time of application: for example, the lower efficacy of high frequency stimulations can be explained by the hypothesis that prolonged high-frequency stimulation may reduce excitability at the site of nerve fibre stimulation (Frasson et al. 2005). In our study, we chose an application time of 30 min after BTX-A administered twice a day for 5 days and we applied a low-frequency of stimulation (starting at 5 Hz).

To the best of our knowledge, we were the first to evaluate the BTX-A combined with ESWT in the treatment of spasticity. Previously, the safety and the effectiveness of ESWT in the treatment of muscles spasticity were verified (Lohse-Busch et al. 1997; Manganotti and Amelio 2005; Amelio and Manganotti 2010). In the SBOTE study, we employed the same mean number of ESWT impulses applied in previous experimental studies (Lohse-Busch et al. 1997; Manganotti and Amelio 2005; Amelio and Manganotti 2010). In accordance with the literature, at least 500 impulses are necessary to induce a cellular stimulation effect, whereas >2500 impulses could generate necrotic effects (Kamelger et al. 2010). We treated the muscle belly and muscle-tendon junction considering that spasticity is characterized by muscle hypertonia and tendon retraction (Brown 1994). The EDF managed at different points of the hypertonic muscle was 0.030 mJ/mm². We excluded applying medium and high levels of ESWT, which cause cruentation and are useful for delayed union, whereas we chose a low energy level (0.030 mJ/mm²) because we needed a neo-angiogenic effect (Rompe et al. 1998). Unlike previous studies, we chose to administer ESWT once a day for 5 days, as suggested by the ISMST guidelines, which recommend between 3 and 6 ESWT sessions for muscle-tendon injuries (Tiele 2009). The follow-ups were at 15, 30 and 90 days: it is known that the maximum biologic response of BTX-A occurs within 15 days after the injection (Jost et al. 2005). However, we did not assess the VAS and SFS score at 15 days: in upper and lower limb spasticity, the clinical improvement after BTX-A combined with several supportive therapies is reported not before the 30th day of follow-up (Brashear A et al. 2002).

In our study, we found in both groups a statistically significant score reduction of outcome measures; however, the patients treated with BTX-A and ESWT reported a statistically significant greater decrease in MAS, SFS and VAS compared with patients submitted to BTX-A and ES therapy. Patients treated with BTX-A combined with ESWT showed statistically greater significance and continuous decrease of spasticity at 15, 30 and 90 days, reducing spasms and pain at 30 and 90 days in comparison with patients treated with BTX-A injections and ES.

The mechanisms behind the positive effects of ESWT on spastic muscles remain unknown. It is supposed that on spastic muscles the action of ESWT is similar to ultrasound therapy (Ansari et al. 2006, 2007). Ultrasound produces vibrations that act on fibrosis and other intrinsic components of chronically over-activated muscles. Besides, ESWT induces important cellular metabolic effects, promoting enzymatic and nonenzymatic nitric oxide (NO) synthesis (Mariotto et al. 2005). NO-induced angiogenesis increases muscle and tendon neovascularization, thereby improving muscle stiffness. ESWT may modify muscle spindle excitability, modulating muscle input directed to the spinal cord, thereby decreasing the resistance to passive lengthening by allowing an increased muscle tendon unit. ESWT may also act by inhibiting the stretch reflex (Manganotti and Amelio 2005; Amelio and Manganotti 2010; Trompetto et al. 2009). We noted a medium-term effect of ESWT, as occurs in the treatment of tendinopathies (Schofer et al. 2009; Notarnicola et al. 2010; Moretti et al. 2009).

In stroke patients, spasticity-related pain has been described by several authors (Sjölund 2002; Pham and Lafforgue 2003). Sjölund suggested that pain is due to processes in sensory systems equivalent to those causing spasticity in motor systems (Sjölund 2002). Another author has suggested that pain in spasticity could be generated in cases of complex regional pain syndrome (Schwartzman et al. 2006). This theory is based on central sensitization of pain transmission neurons throughout the nervous system. Such a process is effected by N-methyl-D-aspartic acid complex mechanisms and is maintained and augmented by a major immune contribution from activated glial and astrocyte secretion of chemokines and cytokines (Schwartzman et al. 2006). The entire concept of maintained chronic pain is now viewed as a neuronal activity-dependent process. One hypothesis is an exaggerated localized neurogenic inflammation that can induce peripheral nerve sensitization and abnormal sensory input integration by the cerebral cortex (Pham and Lafforgue 2003). An abnormal sympathetic response may cause vasodilatation alternating with episodes of arterial spasms, edema, pain and hyperhidrosis (Pham and Lafforgue 2003). Pizzi et al. (2005) supposed in upper-limb spasticity post-stroke the pain appears to be related to range of

motion reduction. [Wissel et al. \(2010\)](#) verified spasticity is associated with pain in the shoulder in 60%, in the elbow in 100% and in the wrist in 33% of patients after stroke. However, the exact causal relationship among muscle spasticity (MAS), spasms (SFS) and pain (VAS) is still unclear. In our experience, we did not verify a correlation among all outcome measures at follow-up time. Both groups showed a progressive pain reduction at the follow-up visits. This result can be explained with the BTX-A effect on pain management: several studies have demonstrated the analgesic effect of BTX-A on central pain, inhibiting neurogenic inflammation by the attenuation of neurotransmitter release (glutamate, substance P and calcitonin-gene related peptide). This prevents capsaicin receptor increase, thereby resulting in the inhibition of peripheral sensitization reducing transmission of nociceptive signals in to the spinal cord ([Aoki 2005](#)).

The clinical effects of both protocols of therapy were assessed by considering the minimal clinically-important difference (MCID) for VAS; that is, the smallest difference in an outcome score that a patient perceives as beneficial ([Jaeschke et al. 1989](#)). [Lin et al. \(2011\)](#) suggested in stroke rehabilitation the clinically meaningful improvement of the VAS is within 10% to 15% change. Therefore, in the current study, patients of both groups were considered as having experienced a clinically important change (in group A and B, respectively, 48.8% and 62.6%).

To account the best result on pain reduction in patients submitted to ESWT after BTX-A compared with patients treated with BTX-A and ES, we can consider also the action of ESWT on pain. This can be explained by assuming a reduction in mechanical stimulation and tissue inflammation with a following decrease in stimulation of mechanoreceptors and nociceptors in muscle and tendon tissues. Pain reduction may be caused by inhibition of the synthesis of painful and proinflammatory cytokines ([Iannone et al. 2009](#); [Moretti et al. 2008](#); [Mariotto et al. 2005](#)). NO is involved in neuromuscular junction formation in the peripheral nervous system ([Molina et al. 1998](#)) and in important physiological functions of the central nervous system, including neurotransmission, memory and synaptic plasticity ([Blottner and Luck 2001](#)). NO synthesis has been suggested as being one of the most physiologically important mechanisms that could explain analgesic and anti-inflammatory effects in various tendon diseases ([Rompe et al. 1996](#)).

One limitation of this study is the absence of a sham stimulation for ES and ESWT. The absence of inclusion of a placebo group is often found in similar published studies for ethical reasons ([Marconi et al. 2011](#); [Harvey et al. 2009](#)). Other limitations are the relatively small study population, the single injection of BTX-A or the absence of comparison with a group of patients treated

with BTX-A alone ([Brashear et al. 2002](#); [Simpson et al. 1996](#); [Rosales and Chua-Yap 2008](#); [Wissel et al. 2009](#); [Hazlewood et al. 1994](#); [Bakhtiary and Fatemy, 2008](#); [Lohse-Busch H et al. 1997](#); [Manganotti and Amelio 2005](#); [Amelio and Manganotti 2010](#)).

The SBOTE study confirmed that ESWT appears to be a clinically relevant supplement to BTX-A injections in the treatment of spasticity. The greater effect of BTX-A with ESWT compared with BTX-A with ES can be explained by considering the different site of action of ESWT and ES: ES increases the diffusion of BTX-A, thereby improving its effect, whereas our team proposes that ESWT acts mechanically (reducing muscle hypertonia) and trophically (imposing neovascular effects) on treated muscles. These results add to the growing number of positive reports that substantiate the efficacy of ESWT as an effective treatment in spasticity. Recent improvements in technology have helped to make ESWT a less expensive and faster procedure.

CONCLUSION

This is the first randomized study to demonstrate the efficacy of combined treatment of BTX-A with ESWT, as well the greater efficacy of BTX-A with ESWT respect to BTX-A with ES in the management of post-stroke spasticity of the upper limb (measured as MAS, SFS and VAS). Given the putative mechanisms of action of these combined interventions, both could be considered in the treatment of post-stroke spasticity. However, further larger studies are needed to investigate the biologic and cellular effects of ESWT on spasticity and to confirm these study findings.

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