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Original article

Electrical stimulation of antagonist muscles after botulinum toxin type A for post-stroke spastic equinus foot. A randomized single-blind pilot study

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ABSTRACT

Background: Botulinum toxin type A (BoNT-A) injection is an effective treatment for lower-limb spasticity and should be offered as first-line treatment for focal manifestations. Although its possible role has been hypothesized, the efficacy of electrical stimulation (ES) of antagonists of the injected muscles for improving clinical outcome after BoNT-A injection remains to be established.
Objectives: This randomized single-blind pilot study aimed to investigate the efficacy of ES of antagonist muscles as adjunct treatment after BoNT-A injection to plantar flexor muscles in hemiplegic patients with spastic equinus foot.
Methods: After BoNT-A injection at triceps surae, patients were randomly allocated to 2 groups: group 1, single ES session on injected muscles plus 5 sessions of ES on antagonist muscles, and group 2, single ES session on injected muscles alone. Both groups underwent daily physical therapy for 60 min for 2 weeks (5 days/week). Assessments were performed before treatment (T_0) and at 10 days (T_1), 20 days (T_2), and 90 days (T_3) after treatment. Our primary outcome was gait velocity at a comfortable speed at T_2 (10-m walk test [10MWT]). The following were secondary outcomes: triceps surae spasticity (Modified Ashworth Scale), ankle passive range of motion (pROM), strength of tibialis anterior muscle, and 2-min walk test (2MWT).
Results: The 30 patients enrolled were randomly allocated to the 2 groups: 15 in group 1 and 15 in group 2. At T_1, T_2 and T_3, both groups showed a significant reduction in muscle tone and an increase in ankle pROM ($P < 0.05$). At T_2 and T_3, both groups showed a significant increase in 10MWT and 2MWT. The groups did not significantly differ in tibialis anterior strength or primary or secondary outcome measures.
Conclusions: ES of antagonist muscles does not improve clinical outcomes in the post-stroke spastic equinus foot after BoNT-A injection.

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1. Introduction

Stroke is a leading cause of disability that has significant socio-economic consequences [1–3]. In fact, stroke survivors could show several sequelae of the acute event, including hemiparesis/hemiplegia, spasticity, and walking dysfunction [4,5]. In particular, post-stroke spasticity (PSS) is a common clinical problem after stroke, affecting 4% to 42.6% of individuals, with the prevalence of disabling spasticity ranging from 2% to 13% [6]. Spasticity of the plantar flexor muscles is related to the equinovarus foot deformity, one of the most relevant factors involved in walking impairments in stroke survivors [7–10].

Botulinum toxin type A (BoNT-A) is effective for treating lower-limb spasticity and should be offered as first-line treatment for focal manifestations [11–16]. Different techniques have been proposed to improve the clinical effects of BoNT-A, including electrical stimulation (ES) [17], taping [18], casting [19], extracorporeal shock waves [20] and self-rehabilitation programmes [21]. However, although the benefits related to the associations between BoNT-A and post-injection rehabilitative treatments are widely accepted, we lack agreement on the most effective approach [22,23]. In particular, the use of ES of injected muscles may be effective for enhancing the duration of the BoNT-A effect [24,25]. More recently, Picelli et al. reported a significant increase in chemodenervation after a single ES session of injected muscles immediately after BoNT-A injection versus repeated sessions beginning the day after injection [26]. However, although several authors have hypothesized a possible role of ES of muscles acting as antagonists to those injected with BoNT-A to improve clinical outcomes [23–25,27], the efficacy remains to be established. Notably, more recently, a systematic review highlighted the critical issue regarding the stimulation of antagonist muscles, concluding that further research should be planned to clarify whether only the injected muscle should be stimulated or whether antagonist muscles should also be involved [28].

The aim of this randomized single-blind pilot study was to evaluate whether ES of the tibialis anterior muscle as adjunct treatment after BoNT-A injection to plantar flexor muscles in hemiplegic patients with spastic equinus foot has can improve outcomes.

2. Material and methods

2.1. Participants

All participants signed a written informed consent for participation in the research study. The aims and modalities were explained to all patients, and every precaution was taken to protect their privacy. The institutional review board approved the study, which was conducted in accordance with the guidelines of the Declaration of Helsinki for Human Research. We recruited patients among those referred to the Physical and Rehabilitation Medicine Unit of University Hospital "Maggiore della Carità", Novara, Italy, from May to December 2016. Inclusion criteria were hemiplegia after ischemic or hemorrhagic stroke; documented by CT scan and/or available case history; time since stroke at least 6 months; equinovarus foot with disabling spastic hypertonia of triceps surae graded at least 1+ with the Modified Ashworth Scale (MAS), interfering with normal gait [29]; presence of muscular activity of the tibialis anterior muscle on the hemiparetic side, graded at least 1 on the Medical Research Council (MRC) scale [30]; ability to walk without assistance; and last BoNT-A treatment and/or any rehabilitative treatment at least 3 months before the evaluation. Exclusion criteria were fixed contractures (passive range of motion [pROM] $<$ 5 degrees) [19] and/or bony deformities at the ankle; cognitive impairments limiting the ability to understand motor tasks required during treatment; concomitant progressive central nervous system disorders or peripheral nervous system disorders/myopathies; and previous surgery of the plantar flexor muscles on the affected side.

2.2. Study design

In this randomized single-blind pilot study, we used specific software (http://www.randomization.com) to randomly allocate participants to one of the 2 treatment arms by using a digitally generated randomization algorithm with a 1:1 distribution and no blocks. The scheme was given to physical therapists who were not involved in participants' evaluation or treatment to allocate participants according to the randomization list. An intention-to-treat approach was chosen, and missing data were considered participants who did not achieve the outcome.

2.3. Treatment

BoNT-A administration was considered appropriate when clinical assessment highlighted the presence of spasticity in triceps surae, confirmed by dynamic surface electromyography (sEMG). The muscles considered potentially responsible for the equinovarus foot deformity were analyzed by sEMG during gait. BoNT-A was considered an appropriate treatment when stretch-induced EMG activity was recorded (spasticity), with presence of continuous resting activity (spastic dystonia), or with evidence of co-contraction [31]. When tone increase was not associated with muscle overactivity, it was considered to mainly depend on soft-tissue alterations, and BoNT-A treatment was not considered. BoNT-A (Botox, Allergan, 100 U diluted with 2 ml saline 0.9%) was injected into the lateral and medial head of the gastrocnemius and into the soleus muscle of the affected side, according to clinical and ultrasonography findings. The BoNT-A dose was adjusted to between 50 and 120 U for each muscle, according to the participant and muscle size, degree of activation during dynamic EMG, presence of weakness, risk of side effects, and prior response to injections, when performed [32,33]. The target muscles were located by using ultrasonography (Esaote MyLabSix, Genoa, Italy). BoNT-A injections were always administered by the same investigator who was blinded to participants' allocation. After injection, participants were assigned to one of treatment groups: group 1, ES of injected muscles plus ES of tibialis anterior muscle, and group 2, ES of injected muscles. Participants in both groups underwent ES (0.2 ms, 4 Hz, rectangular biphasic balanced current, (Fisioline Winner, Fisioline Biomedical Instrumentation, Verduno (CN), Italy) of the injected muscles immediately after the injection; the single session duration was 60 min each day [25]. Intensity was adjusted to the participant's tolerance in order to elicit a visible contraction of the muscles. The session was followed by stretching the calf muscles for 20 min. Group 1 also received ES (0.2 ms, 20 Hz, rectangular biphasic balanced current, using the Fisioline Winner, Fisioline Biomedical Instrumentation, Verduno (CN), Italy) of the ipsilateral tibialis anterior muscle (daily sessions lasting 60 min for 5 days) in the first week after the injection. Intensity was adjusted to the participant's tolerance in order to elicit a visible contraction of the muscles. Moreover, all participants received daily physical therapy (strengthening exercises, stretching, gait training, aerobic exercises) for 60 min, according to clinical needs.

2.4. Outcome measures

Clinical evaluations were performed at baseline, before the BoNT-A injection (T_0) and at 10 (T_1), 20 (T_2) and 90 days (T_3) after injection. The assessments were performed by a trained medical

physician and senior physical therapist with blinding to the subsequent rehabilitative regimen. The primary outcome was gait velocity at a comfortable speed at T_2 by using the 10-m walk test (10MWT). Secondary outcomes were spasticity of the injected muscles (measured with the MAS); pROM of the ankle joint, measured with the knee fully extended by using a hand-held goniometer; strength of the tibialis anterior muscle by the MRC scale; and gait endurance by the 2-min walk test (2MWT) [34–36]. We quantified the sensitivity of the measurement of pROM in 5 degrees, considering the dorsiflexion angle as positive and the plantar flexion angle as negative, with neutral position of the ankle joint as 0 degrees [19]. Any adverse events occurring after treatment were recorded.

2.5. Statistical analysis

As previously proposed for stage III demonstration-of-concept pilot studies, we included 30 individuals, 15 allocated to each arm by using random assignment with blinded outcome measures [37]. According to the Shapiro–Wilk test, data were not normally distributed. Differences between groups at baseline were evaluated by the Mann-Whitney U test for both demographic and outcome measure. Differences between single-variable measurements in each group at T_1, T_2, and T_3 (intra-group analysis) were evaluated with Friedman's test for repeated measures with Dunn's multiple comparison test. We analyzed differences between groups (inter-group analysis) for our primary outcome (10MWT at T_2) with the Mann–Whitney U test. Finally, we analyzed differences between groups for secondary outcome variables at T_1, T_2, and T_3 with the Mann–Whitney U test. For statistical purposes, an MAS score of 1 was considered as 1, 1+ as 2, and so on until 5. $P < 0.05$ was considered statistically significant. Statistical analysis was performed with Prism 6.0 (GraphPad Software Inc.) for Macintosh OS 10.11.

3. Results

From May to December 2016, 102 hemiplegic individuals with triceps surae post-stroke spasticity were evaluated and received BoNT-A injection; 30 met our inclusion criteria and were enrolled in the study, randomized and allocated to one of the treatment arms: 15 in group 1 (mean age 60.7 [SD 8.9] years) and 15 in group 2 (mean age 57.5 [SD 6.3] years). The groups did not differ in demographic data and outcome measures at baseline (Table 1). No adverse events were reported during the study period, and all participants completed the scheduled assessments (Fig. 1).

The groups did not differ in inter-group analysis of the primary outcome measure (10MWT) or all secondary outcome measures. We observed a significant increase in mean (SD) speed (10MWT) vs T_0: group 1 at T_2 [0.7 (0.4) vs 0.6 (0.4); $P = 0.035$] and T_3 [0.8 (0.5) vs 0.6 (0.4); $P < 0.001$] and group 2 at T_2 [0.7 (0.3) vs 0.6 (0.3); $P = 0.001$] and T_3 [0.8 (0.3) vs 0.6 (0.3); $P < 0.001$] (Table 2).

Table 1
Baseline characteristics of study population ($n = 30$).

	Group 1 ($n = 15$)	Group 2 ($n = 15$)
Age (years)	60.7 (8.9)	57.5 (6.3)
Sex (male/female)	8/7	9/6
Hemiparesis (right/left)	6/9	7/8
Stroke (ischaemic/haemorrhagic)	11/4	10/5
Time from stroke (months)	45.2 (51.9)	48.3 (39.1)
Mean BoNT-A dose (U)	270.0 (31.6)	273.3 (53.0)
Previous BoNT-A treatment (naïve/non-naïve)	5/10	4/11

Data are mean (SD) or number. Group 1: single electrical stimulation (ES) of botulinum toxin type A (BoNT)-injected muscles plus 5 ES sessions on antagonist muscles; Group 2: ES of BoNT-injected muscles.

All participants showed a significant reduction in MAS at T_1, T_2, and T_3 vs T_0: group 1 at T_1 [2.0 (1.0) vs 3.0 (2.0); $P < 0.001$], at T_2 [2.0 (1.0) vs 3.0 (2.0); $P < 0.001$], and T_3 [2.0 (1.0) vs 3.0 (2.0); $P = 0.001$] and group 2 at T_1 [2.0 (1.0) vs 3.0 (1.0); $P < 0.001$], T_2 [2.0 (1.0) vs 3.0 (1.0); $P < 0.001$], and T_3 [2.0 (1.0) vs 3.0 (1.0); $P < 0.001$].

All participants showed a significant increase in pROM in ankle dorsal flexion vs T_0: group 1 at T_2 [6.7 (3.6) vs 1.3 (4.0); $P < 0.001$] and T_3 [6.3 (5.2) vs 1.3 (4.0); $P < 0.001$] and group 2 at T_2 [6.7 (3.1) vs 0.7 (4.2); $P < 0.001$] and T_3 [8.0 (3.2) vs 0.7 (4.2); $P < 0.001$].

We found no significant intra-group differences for both groups in MRC score for the tibialis anterior muscle; both groups showed a significant improvement in endurance (2MWT) at T_2 and T_3 vs T_0: group 1 at T_2 [73.1 (43.7) vs 63.5 (42.3); $P = 0.004$] and T_3 [76.4 (49.1) vs 63.5 (42.3); $P < 0.001$] and group 2 at T_2 [85.5 (32.3) vs 75.5 (31.9); $P < 0.001$] and T_3 [89.5 (32.9) vs 75.5 (31.9); $P < 0.001$].

4. Discussion

Our data do not support the routine application of ES on the antagonists of the injected muscles as adjunct treatment after BoNT-A injection to improve the clinical outcome of stroke survivors affected by spastic equinovarus foot. As discussed above, there is no agreement on the possible role of ES and, to the best of our knowledge, this is the first study to specifically analyze its clinical use after BoNT-A injection in a routine clinical setting.

As previously reported, the ES of antagonist muscles was reported as possible adjunct treatment post BoNT-A injection to enhance the clinical effect of BoNT-A and improve functional outcome. The rationale considers a supposed effect on reinforcing reciprocal inhibition facilitation by stimulating the Renshaw cells [38]. However, its effect is still debated, and comparison with the published literature is difficult because of the paucity of studies published on this topic.

In a pilot study, Hesse et al. (1995) proposed a 3-day additional, repetitive, alternating ES of plantarflexors and tibialis anterior muscles; as compared with BoNT-A injection alone, ES conferred a significant increase in muscle tone reduction, gait velocity, stride length, and stance and swing symmetry [25]. In a more recent paper, Bayram et al. (2006) added ES of flexor and extensor muscles of the ankle for 3 days after BoNT-A injection. The authors found no significant difference between low-dose BoNT-A injection plus ES and high-dose BoNT-A injection alone [27]. However, in these papers, the authors proposed a stimulation protocol involving both injected and antagonist muscles, matching their results with a control group that received BoNT-A alone. Therefore, the specific impact of ES on the antagonist cannot be separated from the previously described effect of ES on the injected muscles in increasing BoNT-A efficacy [18,26].

Moreover, as remarked by Mills et al., in previously published literature, each study used different dosing and stimulation parameters, with significant differences in timing, duration, frequency and intensity [23]. To date, it appears that low-frequency ES may be better than high-frequency ES, and immediate ES better than delayed ES [25,27]. Therefore, we considered these parameters to define our ES protocol of injected muscles but considered the previously proposed protocol to stimulate antagonists, adjusting the intensity to elicit a visible contraction [25,27].

Johnson et al. (2004) proposed a 16-week functional ES (FES) program with a portable, single-channel, neuromuscular stimulator (Odstock Dropped Foot Stimulator mark IIIc) after BoNT-A injection [39]. The rationale for applying an FES protocol after BoNT-A sounds reasonable, even if different from ES: the authors

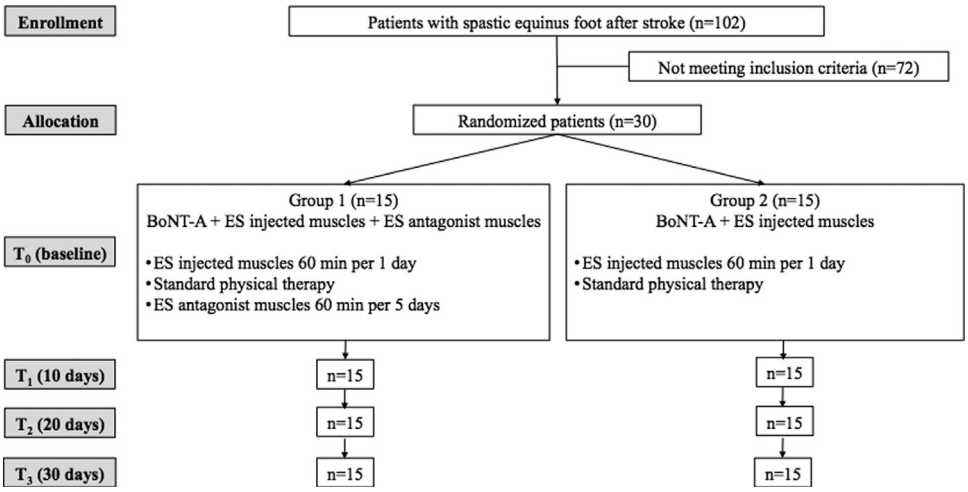

Fig. 1. Study flow chart. ES: electrical stimulation; BoNT-A: botulinum toxin type A.

Table 2
Intra-group differences in outcome measures at different time points.

Variables	Groups	T_0	T_1	*P* value T_0–T_1	T_2	*P* value T_0–T_2	T_3	*P* value T_0–T_3
10MWT (m/s)	1 ($n=15$)	0.6 (0.4)	0.6 (0.4)	$P=0.141$	0.7 (0.4)	$P=0.035$	0.8 (0.5)	$P<0.001$
	2 ($n=15$)	0.6 (0.3)	0.7 (0.3)	$P=0.142$	0.7 (0.3)	$P=0.001$	0.8 (0.3)	$P<0.001$
MAS	1 ($n=15$)	3.0 (2.0)	2.0 (1.0)	$P<0.001$	2.0 (1.0)	$P<0.001$	2.0 (1.0)	$P=0.001$
	2 ($n=15$)	3.0 (1.0)	2.0 (1.0)	$P<0.001$	2.0 (1.0)	$P<0.001$	2.0 (1.0)	$P<0.001$
pROM in ankle dorsal flexion (degrees)	1 ($n=15$)	1.3 (4.0)	4.7 (4.4)	$P=0.053$	6.7 (3.6)	$P<0.001$	6.3 (5.2)	$P<0.001$
	2 ($n=15$)	0.7 (4.2)	4.0 (3.9)	$P=0.203$	6.7 (3.1)	$P<0.001$	8.0 (3.2)	$P<0.001$
MRC score of tibialis anterior muscle	1 ($n=15$)	1.0 (0.0)	1.0 (1.0)	$P=0.269$	2.0 (1.0)	$P=0.143$	1.0 (1.0)	$P=0.269$
	2 ($n=15$)	1.0 (0.0)	1.0 (1.0)	$P=0.999$	2.0 (1.0)	$P=0.472$	1.0 (1.0)	$P=0.999$
2MWT (m)	1 ($n=15$)	63.5 (42.3)	71.2 (43.2)	$P=0.203$	73.1 (43.7)	$P=0.004$	76.4 (49.1)	$P<0.001$
	2 ($n=15$)	75.5 (31.9)	81.9 (30.8)	$P=0.396$	85.5 (32.3)	$P<0.001$	89.5 (32.9)	$P<0.001$

Data are mean (SD) for continuous variables and medians (interquartile ranges) for categorical variables. Group 1, single electrical stimulation (ES) of botulinum toxin type A (BoNT)-injected muscles plus 5 ES sessions on antagonist muscles; Group 2, ES of BoNT injected muscles. MAS, Modified Ashworth Scale; pROM, passive range of motion; MRC: Medical Research Council; 10MWT: 10-m walk test; 2MWT: 2-min walk; test.

suggested that the protocol might further reinforce calf inhibition and provide a mechanical stretching effect while strengthening the stimulated muscles, also providing a greater orthotic benefit during walking. In fact, FES was applied to elicit ankle dorsiflexion and eversion during the swing phase of walking. Unfortunately, only a short-term increase in velocity, not statistically significant, was observed in the experimental group, which did not completely support the authors' hypothesis. In addition, the authors proposed a very complex stimulation protocol, which is difficult to apply in a standard clinical setting. However, future research should also focus on this topic.

Our study has several limitations. The major one is the small sample size, although this is common to other studies of similar patients [25,27]. The clinical outcome measures (10MWT, 2MWT) showed limited inter-observer variability. MAS and pROM might be considered slightly inaccurate measurements, potentially sensitive to subjective interpretation. However, they were considered as secondary outcomes, and these assessments were performed by investigators who were blinded to subsequent treatment regimen. Moreover, the total amount of ES applied to antagonist muscles might be considered too limited to elicit a clinical effect. However, the dose of ES in the present study was higher than that reported in previous works [25,27], showing its global efficacy. To compare our results with previously published ones and to define the specific role of ES in antagonist muscles, we used a similar duration of treatment. Moreover, this was a proof-of-concept study, and our aim was to test a protocol that could be easily applied as adjunct treatment in a routine clinical setting [25,27]. We cannot exclude that an increase in total amount of ES could lead to different clinical outcomes. These aspects must be considered in future research studies.

We did not focus on instrumental evaluation of participants' gait. These measures could be interesting to demonstrate improvement in gait parameters, but we deliberately excluded this analysis. For this purpose, we hypothesized that clinical outcomes such as 10MWT and 2MWT could provide more robust insights into the clinical impact of this treatment. In addition, to the best of our knowledge, these clinical measures show good sensitivity in evaluating the treatment's efficacy, without being affected by subjective judgement. Finally, to avoid any potentially confusing factors, we excluded other adjunct treatments that could improve participants' outcome, such as taping, casting, extracorporeal shock waves and self-rehabilitation programmes [20,21,40]. In addition, casting and taping could require a delay after BoNT-A injection for ES to be applied to antagonist muscles proposed by previous protocols [25,27]. Further research might focus on late ES on antagonist muscles after taping or casting.

5. Conclusions

To our best knowledge, this is the first paper exploring the specific clinical impact of ES in antagonist muscles after BoNT-A injection to the plantar flexor muscles in individuals affected by post-stroke spasticity. Our study does not bring any evidence supporting the use of ES applied to antagonist muscles (ankle

dorsiflexors) as adjunct therapy to BoNT-A injection of the triceps surae in individuals with spastic equinus foot after stroke.

Authors' contribution

Dr Baricich: conception and design of the work; data acquisition, analysis and interpretation; work draft.

Dr. Picelli: conception and design of the work; data analysis and interpretation; work revision.

Dr. Carda: conception of the work; data interpretation; work revision.

Prof. Smania: conception of the work; data interpretation; work revision.

Prof. Cisari: conception of the work; data interpretation; work revision.

Dr. Santamato: conception and design of the work; data analysis and interpretation; work revision.

Dr. de Sire: data analysis and interpretation; work draft.

Dr. Invernizzi: conception and design of the work; data acquisition, analysis and interpretation; work revision.

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