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Early physiotherapy after injection of botulinum toxin increases the beneficial effects on spasticity in patients with multiple sclerosis

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Objective: To determine whether additional physiotherapy increases botulinum toxin type A effects in reducing spasticity in patients with multiple sclerosis.
Design: A single-blind, randomized, controlled pilot trial with a 12-week study period.
Subjects: Thirty-eight patients with progressive multiple sclerosis affected by focal spasticity and who were observed at the Multiple Sclerosis Centre operating in the S. Andrea Hospital in Rome.
Interventions: For intervention all patients received botulinum toxin type A; the treatment group also received additional physiotherapy to optimize management through passive or active exercise and stretching regimens.
Main measures: To measure objective and subjective level of spasticity, patients were assessed at baseline, 2, 4 and 12 weeks post treatment by Modified Ashworth Scale and visual analogue scale.
Results: When compared with the control group, we found a significant decrease of spasticity by Modified Ashworth Scale ($P<0.01$ by *t*-test) in the treatment group at week 2 (2.73 versus 3.22), week 4 (2.64 versus 3.33) and week 12 (2.68 versus 3.33). The mean (%) difference in Modified Ashworth Scale score between baseline and the end of follow-up was –0.95 (26.1) in the treatment group and –0.28 (7.7) in the control group ($P<0.01$). The combined treatment proved also to be more effective by visual analogue scale ($P<0.01$) at week 4 (6.95 versus 5.50) and at week 12 (7.86 versus 6.56) but not at week 2 (5.18 versus 5.50; $P=0.41$).
Conclusions: Our data suggest that physiotherapy in combination with botulinum toxin type A injection can improve overall response to botulinum toxin.

Introduction

Multiple sclerosis is a common demyelinating disease that affects young adults. Spasticity is one of the most important symptoms experienced by patients, both because of its frequency, but also because of the impact on daily life. It is only when spasticity interferes with function that it needs to be treated. Several oral anti-spasticity agents are available for multiple sclerosis patients, such as baclofen, dantrolene, tizanidine, benzodiazepine, gabapentin and cannabinoids.[1] These drugs are mainly used in the early stages of the disease or in patients who are still ambulant, and can have side-effects, the commonest of which are drowsiness and weakness. Parenteral medications are generally given to non-ambulant patients. The most

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commonly used are botulinum toxin type A and intrathecal baclofen.[2]

Some randomized clinical trials have shown botulinum toxin type A to be effective in the management of spasticity related to multiple sclerosis.[3–7] Moreover, one of these studies reported that botulinum toxin type A injection into the adductor muscle group resulted in statistically significant improvement in nursing care, particularly in most severely disabled multiple sclerosis patients.[3]

Botulinum toxin type A is rarely a treatment in isolation; in clinical practice it is often given in combination with physiotherapy to obtain the maximum benefit. However, no randomized controlled trials have been performed to investigate the potential efficacy of botulinum toxin type A in combination with neurological rehabilitation to treat multiple sclerosis-related spasticity.

Methods

Participation in the study was considered in 130 consecutive outpatients affected by a progressive form of multiple sclerosis,[8,9] who were seen in routine follow-up at the Centre for the Diagnosis and Therapy of multiple sclerosis operating in the S. Andrea Hospital in Rome. Inclusion criteria were as follow: aged 18–65 years, secondary progressive disease course, anti-spastic/anti-epileptic treatment stable for at least three months prior the study entry, spasticity scores >3 points as measured by the Modified Ashworth Scale[10] in the lower and/or upper limbs and written informed consent.

The Modified Ashworth Scale grades the level of resistance encountered during manual passive stretching (score from 0 to 5: 0 indicating no increase in muscle tone, 5 corresponding to joint fixed rigid in a position). All patients agreed to receive the full course of treatment and to perform all assessments as specified in the protocol. Caregivers also agreed to assist the patient in complying with study requirements if necessary (e.g. visits to Centre on weekend).

Exclusion criteria were: any form of multiple sclerosis other than secondary progressive multiple sclerosis; any other disabling condition interfering with the clinical evaluation; pregnancy or breastfeeding; any psychiatric disorders or severe cognitive disturbances that could preclude safe participation in the study; known history of alcohol or substance abuse; previous botulinum toxin type A injections.

The study design was planned as a single-blind, randomized controlled trial: patients eligible were randomized in a 1:1 ratio into two counterbalanced groups: a treatment group received a physiotherapy programme after botulinum toxin type A injection (group I) and a control group receiving botulinum toxin type A injection but not physiotherapy (group II). Randomization was accomplished using simple block randomization in groups of four. Treatment assignment was randomly generated by the study statistician who had no contact with study subjects.

For intervention all patients received by a well-trained neurologist who was aware of group allocation. Botulinum toxin type A (Botox; Allergan, Irvine, CA, USA) 100 U diluted (50 U/mL) and injected in flexor digitorum superficialis (two sites), flexor carpi radialis (two sites) and flexor carpi ulnaris (two sites) of the upper limbs. For the lower limbs, botulinum toxin type A 100–300 U diluted (50 U/mL) was injected in the tibialis posterior (one site), gastrocnemius medial and lateral (three sites) and soleus (two sites). The dose was modified for less spastic muscle but the total amount and site of botulinum toxin type A injections were similar in the two groups. Injections were given under electromygraphic (EMG) guidance.

The physiotherapy was performed daily for 15 consecutive days after botulinum toxin type A injection, including weekends. Patients underwent specific and regular activity designed to maintain muscle length through passive or active exercise and a stretching regimen on the injected area (40 min for each session), consisting of soft movements of joints with short pauses at the final position and reciprocal movements to prevent contractures and permanent shortening of muscles. Clinical data were collected at baseline, at 2, 4 and 12 weeks after botulinum toxin type A injection. The assessing neurologist conducted the neurological exam by using Expanded Disability Status Scale (EDSS)[11] and Modified Ashworth Scale measurement. He was unaware of the treatment allocation of the individual patients. At each time interval after baseline, patients had to self-evaluate evolution of spasticity using a visual analogue scale. The scale estimates satisfaction in the degree of relief from

spasticity in injected muscles with a score from 0 (not satisfied) to 10 (clearly satisfied).

Statistical analysis

Statistical analysis of the data was carried out using a two-way ANOVA for repeated measures followed by uncorrected paired Student's *t*-test in comparing the two group data at each time point.

Results

From 110 screened patients, 46 patients satisfied entry criteria. Six patients were excluded for difficulties to attending the Centre for the entire duration of the study as proposed by the informed consent at the study entry. The remaining 40 patients (34 women and six men) were enrolled in the study (Figure 1). Thirty-eight patients completed the study and constituted the per-protocol population, two patients (control group) discontinued the trial and were not regularly assessed. Table 1 summarizes baseline demographic and clinical characteristics of patients according to the treatment allocation. No significant differences occurred between the two groups with respect to gender, age, and level of disability as determined by the EDSS score.

All patients suffered severe spasticity as measured by the Modified Ashworth Scale (a score of 3 was detected in 15 patients and a score of 4 in 25 patients). All patients received a single botulinum toxin type A treatment. Botulinum toxin injection was without serious adverse events in all patients. A decrease of spasticity measured by Modified Ashworth Scale was detected in both groups of treatment after botulinum toxin injection ($P < 0.01$ by ANOVA). A significant differences between the two groups was observed at each time point ($P < 0.01$ by *t*-test). In group I, we observed a reduction of spasticity at week 2 that persisted at 4 and 12 weeks post treatment, while in group II, Modified Ashworth Scale score showed a transient decrease at week 2 and a slight increase at week 4 and week 12 (Table 2).

A significant improvement of spasticity over time in both groups was also observed by visual analogue scale score ($P < 0.05$ by ANOVA). Differences between the two groups were detected at four weeks and at 12 weeks ($P = 0.01$ by *t*-test) but not at two weeks ($P = 0.41$) (Table 3).

Discussion

Few controlled studies have been performed up to now to evaluate the effect of botulinum toxin type A on spasticity in multiple sclerosis,[3–7] and none have assessed the effect of physiotherapy after botulinum toxin type A injection, although pharmacological interventions are usually supported by physiotherapy.

The present single-blind, controlled randomized designed study represents a first demonstration of benefit of combination therapy consisting in botulinum toxin type A injection plus strengthening exercises in the treatment of spasticity in multiple sclerosis. In spite of these considerations, the study suffers from some limitations. The sample size was small and functional outcome measures, usually employed in clinical practice, such as the range of motion, spasm frequency scale and joint resting angles have not been applied.

Spasticity measurement is a complicated issue.[12] Research is ongoing into different assessment strategies including neurophysiological methods, biomechanical techniques and new clinical scales which have been recently proposed to satisfy criteria for a reliable and valid measurement of the impact of spasticity on people with multiple sclerosis.[13–16]

In order to catch both doctor and patient experience in this study we opted for a standardized clinical assessment of spasticity using the Modified Ashworth Scale and a visual analogue scale. Although the Modified Ashworth Scale score could be influenced by subjective physician's evaluation and a visual analogue scale score may depend on the psychological burden of the patient at the time of each assessment, both of them are well known in clinical practice and appreciated for their validity.

Our results confirm the striking success of botulinum toxin type A in reducing spasticity as previously reported.[3–7] Muscle tone was reduced at the two week evaluation by Modified Ashworth Scale, and persisted for the observational period of three months after injection. With local spasticity suddenly reduced, the patient may present with a different functional ability that permits other therapeutic interventions,

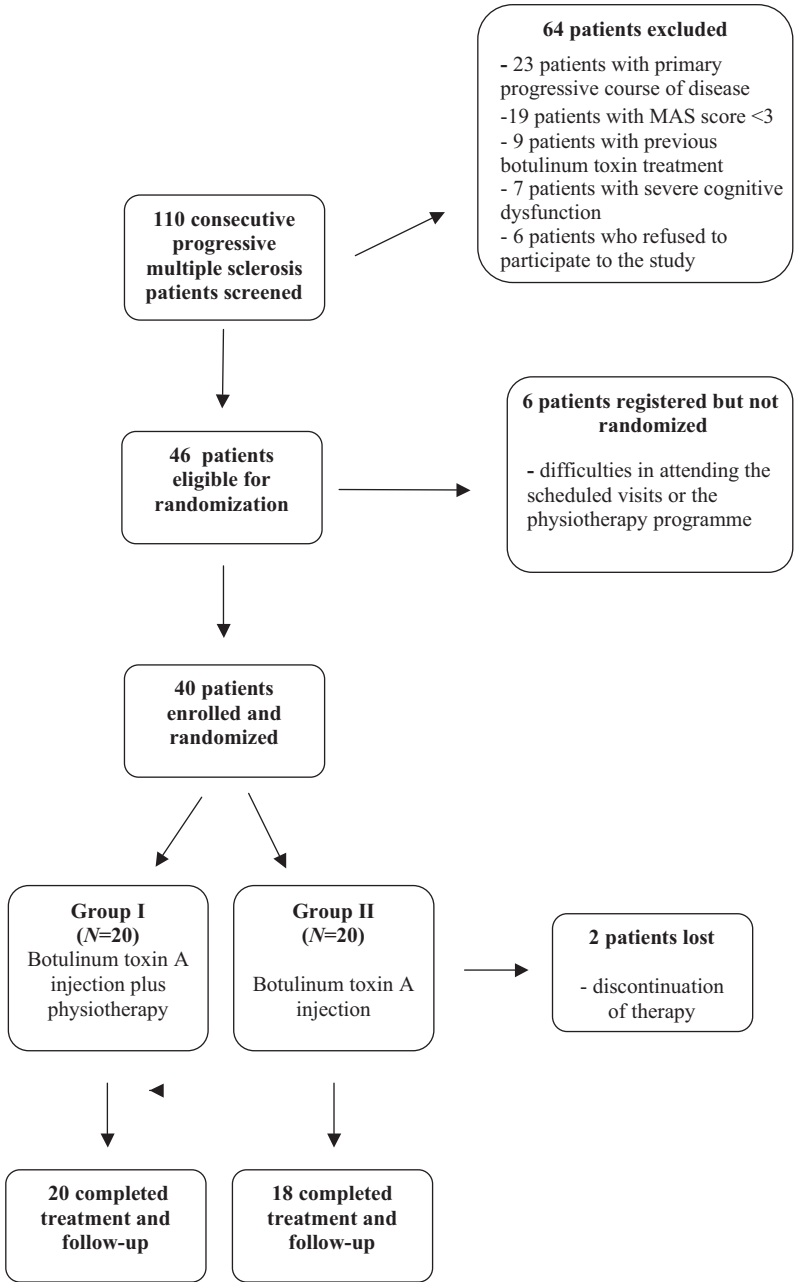

Figure 1 Trial profile.

Table 1 Demographics and clinical characteristics of study population

	Group I Physiotherapy ($N=20$)	Group II Control ($N=18$)
Gender (male/female)	2/18	2/16
Age (years), mean (SD)	46.4 (9.0)	48.1 (7.5)
Range	36–60	38–62
EDSS, mean (SD)	5.8 (1.3)	6.0 (1.1)
Median; range	6.0; 3.5–7.5	6.0; 3.5–7.5
Walking without assistance ($N=16$)	9	7
Walking with device ($N=9$)	4	5
Unable to walk ($N=13$)	7	6

EDSS, Expanded Disability Status Scale.

Table 2 Modified Ashworth Scale (MAS) scores in the two groups of multiple sclerosis patients measured at different time points from botulinum toxin type A injection

	Group I Physiotherapy ($N=20$)	Group II Control ($N=18$)	*P*-value[a]
Baseline, mean (SD)	3.63 (0.49)	3.61 (0.50)	0.87
Week 2	2.73 (0.55)	3.22 (0.55)	<0.01
Week 4	2.64 (0.58)	3.33 (0.60)	<0.01
Week 12	2.68 (0.64)	3.33 (0.60)	<0.01
Δ change from baseline to week 2, mean (SD)	−0.91 (0.52)	−0.39 (0.50)	<0.01
Δ change from baseline to week 4	−1 (0.69)	−0.28 (0.46)	<0.01
Δ change from baseline to week 12	−0.95 (0.78)	−0.28 (0.46)	<0.01

[a]*P*-value was calculated by unpaired Student's *t*-test.

Table 3 Visual analogue scale scores in the two groups of multiple sclerosis patients measured at different time points from botulinum toxin type A injection

	Group I Physiotherapy ($N=20$)	Group II Control ($N=18$)	*P*-value[a]
Week 2, mean (SD)	5.18 (1.10)	5.50 (1.38)	0.41
Week 4	6.95 (1.00)	5.50 (1.20)	0.01
Week 12	7.86 (0.64)	6.56 (0.78)	0.01
Δ change from week 2 to week 4, mean (SD)	1.77 (0.87)	0 (1.08)	<0.01
Δ change from week 4 to week 12	2.68 (1.08)	1.06 (1.16)	<0.01

[a]*P*-value was calculated by unpaired Student's *t*-test.

such as increasing range of motion, retraining of ambulation and gait, and improving ability in ADLs. The sudden decrease in muscle tone brought on by botulinum toxin type A enables the physiotherapist to focus on functional treatment goals that were not possible previously.[12]

We demonstrated a relevant role for physiotherapy in combination with botulinum toxin type A injection. These findings indicate that stretching exercises may improve the diffusion of botulinum toxin type A in the injected muscles, leading to more effective uptake of the toxin, given the correlation between terminal nerve end activity and toxin uptake. In addiction, acting in synergy with botulinum toxin type A, repetitive stretch exercises decrease muscle contracture, promoting functional recovery and re-education on the altered

spastic muscles in the affected limb. As they become more able in their movements, patients experience less difficulty. This has a positive effect on mood, which might account for the delayed beneficial effect of the combination of botulinum toxin type A plus physiotherapy observed on the visual analogue scale.

In recent years, some articles have discussed the usefulness of treatment of upper and lower limb spasticity in neurological rehabilitation derived by tonic stretching or other combined therapy, such as botulinum toxin type A plus electrical stimulation or a tracking system for training of grip force control.[17–20] Structured rehabilitation, consisting of physiotherapy and occupational therapy for six months, for children with hemiparetic cerebral palsy previously treated with botulinum toxin type A injections led to reduced impairment for at least nine months.[21]

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Competing interests

None declared.

Clinical messages

- Botulinum toxin type A confirms its beneficial effect on spasticity in patients with multiple sclerosis, as evaluated subjectively by visual analogue scale and objectively by Modified Ashworth Scale.
- The beneficial effect of botulinum toxin type A is evident after two weeks and persists for at least three months after a single injection.
- A physiotherapy programme consisting of strengthening exercises improves the effect on spastic muscles when combined with botulinum toxin type A injection.

Contributors

GM (neurologist confident with botulinum toxin type A treatment) contributed to following the study procedures and in writing the manuscript. BG (resident in neurology certified in EDSS training) assessed the EDSS and Modified Ashworth Scale in all patients and gave an important contribution to the study design and in writing the manuscript. CP (PhD student) performed the study randomization and carried out the statistical analysis. PL (resident in neurology) helped in the planning and organization of the study and helped to revise the manuscript. PC (Director of the Multiple Sclerosis Centre) designed and supervised the study, discussed the results and helped in preparing and revising the manuscript. He is guarantor for the accuracy and honesty of the report and the morality of the study.

References

1 Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev* 2003; CD001332.
2 Thompson AJ, Jarrett L, Lockley L, Marsden J, Stevenson VL. Clinical management of spasticity. *J Neurol Neurosurg Psychiatry* 2005; **76**: 459–63.
3 Snow BJ, Tsui JK, Bhatt MH, Varelas M, Hashimoto SA, Calne DB. Treatment of spasticity with botulinum toxin: a double blind study. *Ann Neurol* 1990; **28**: 512–15.
4 Grazko MA, Polo KB, Jabbari B. Botulinum toxin A for spasticity, muscle spasms, and rigidity. *Neurology* 1995; **45**: 712–17.
5 Hyman N, Barnes M, Bhakta B *et al.* Botulinum toxin (Dysport) treatment of hip adduttor spasticity in multiple sclerosis: a prospective, randomised, double-blind, placebo controlled, dose ranging study. *J Neurol Neurosurg Psychiatry* 2000; **68**: 707–15.
6 Dunne JW, Heye N, Dunne SL. Treatment of chronic limb spasticity with botulinum A. *J Neurol Neurosurg Psychiatry* 1995; **58**: 712–17.
7 Finsterer J, Fuchs I, Mamoli B. Automatic EMG-guided botulinum toxin treatment of spasticity. *Clin Neuropharmacol* 1997; **20**: 195–203.
8 Mc Donald WI, Compston A, Edan G *et al.* Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol* 2001; **50**: 121–27.
9 Lublin FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. National Multiple Sclerosis Society

(USA) advisory committee on clinical trials of new agents in multiple sclerosis. *Neurology* 1996; **46**: 907–11.
10 Bohannom RW, Smith MB. Inter-rater reliability of a modified Ashworth Scale of muscle spasticity. *Phys Ther* 1987; **67**: 206–207.
11 Kurtzke J. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1984; **33**: 1444–52.
12 Priebe MM, Sherwood AM, Thornby JI *et al.* Clinical assessment of spasticity in spinal cord injury: a multidimensional problem. *Arch Phys Med Rehabil* 1996; **77**: 713–16.
13 Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assesment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. *Disabil Rehabil* 2005; **27**: 33–68.
14 Wood D, Burridge J, van Wijck F *et al.* Biomechanical approaches applied to the lower and upper limb for the measurement of spasticity: a systematic review of the literature. *Disabil Rehabil* 2005; **27**: 19–32.
15 Platz T, Eickhof C, Nuyens G, Vuadens P. Clinical scales fort he assessment of spasticity, associated phenomena, and function: a systematic review of the literature. *Disabil Rehabil* 2005; **27**: 7–18.
16 Hobart JC, Riazi A, Thompson AJ *et al.* Getting the measure of spasticity in multiple sclerosis: the Multiple Sclerosis Spasticity Scale (MSSS-88). *Brain* 2006; **129**: 224–34.
17 Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. *Am J Phys Med Rehabil* 2000; **79**: 44–47.
18 Hesse S, Werner C, Bardeleben A, Brandl-Hesse B. Management of upper and lower limb spasticity in neuro-rehabilitation. *Acta Neurochir Suppl* 2002; **79**: 117–22.
19 Johnson CA, Burridge JH, Strike PW, Wood DE, Swain ID. The effect of combined use of botulinum toxin type A and functional electric stimulation in the treatment of spastic drop foot after stroke: a preliminary investigation. *Arch Phys Med Rehabil* 2004; **85**: 902–909.
20 Kurillo G, Gregoric M, Goljar N, Bajd T. Grip force tracking system for assessment and rehabilitation of hand function. *Technol Health Care* 2005; **13**: 137–49.
21 Speth LA, Leffers P, Janssen-Potten YJ, Vles JS. Botulinum toxin A and upper limb functional skills in hemiparetic cerebral palsy: a randomized trial in children receiving intensive therapy. *Dev Med Child Neurol* 2005; **47**: 468–73.