

ORIGINAL REPORT

EFFECTS OF BOTULINUM TOXIN-A ON THE MUSCLE ARCHITECTURE OF STROKE PATIENTS: AN ULTRASONOGRAPHIC STUDY\*

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**Objective:** The aim of this study was to explore *in vivo* the effects of botulinum toxin-A treatment on the muscle architecture of patients with stroke, using musculoskeletal ultrasonography.

**Methods:** This prospective clinical trial included 26 adult stroke sufferers with a mean age of 55 years (standard deviation 14). Pennation angles between the fascicle path and the deep aponeurosis of the muscle, fascicle length, muscle thickness and muscle compressibility were scanned at the bulkiest part of the medial gastrocnemius on both limbs. Sonographic evaluations were performed initially before botulinum toxin-A injection and repeated on day 10 and after 2 months.

**Results:** On the hemiplegic sides, anterior pennation angle and muscle thickness decreased ( $p=0.014$ ,  $p=0.010$ , respectively), fascicle length increased ( $p=0.025$ ) and muscle compressibility did not change after 2 months of treatment compared with the baseline values.

**Conclusion:** The results confirm that muscle structure changes due to botulinum toxin-A. Long-term effects of botulinum toxin-A, timing for disappearance of the toxin effects, or evaluations for repeat injections, remain to be studied. The use of musculoskeletal ultrasonography appears to be promising in this regard.

**Key words:** botulinum toxin-A; muscle architecture, stroke; ultrasonography.

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INTRODUCTION

With the use of musculoskeletal ultrasonography (MSUS), morphological changes in the architecture of paretic muscles have been reported in patients with stroke (1, 2). However, there is no information on whether those changes are further altered with botulinum toxin-A (BoNT-A) injection, which is a widely used treatment for focal spasticity in this group of

patients (3). Previous studies have mainly investigated the effects of BoNT-A on clinical and functional outcome (4–9).

The aim of the present study was to explore *in vivo* the effects of BoNT-A treatment on the muscle architecture of patients with stroke. Given its myriad advantages (non-invasive, inexpensive, repeatable, does not contain ionizing radiation, provides dynamic imaging and comparison), we reasoned that MSUS can be a prompt method for measuring anterior pennation angle, fascicle length, thickness and compressibility of the gastrocnemius muscle. To the best of our knowledge, this study is the first to show the effects of BoNT-A on muscle architecture.

MATERIAL AND METHODS

Participants

Twenty-six consecutive adult stroke patients (14 male, 12 female) with a mean age of 55 years (standard deviation (SD) 14.04) were recruited. Inclusion criteria were: presence of hemiparesis and clinically detectable spasticity in the gastrocnemius muscle (with a score > 1+ according to Modified Ashworth Scale; MAS); and the absence of previous surgery on the lower limbs and injection (BoNT-A, phenol or alcohol) to the gastrocnemius muscle within the last year. All participants were informed about the study procedure and gave informed consent. The study protocol was approved by the Institutional Review Board.

Protocol

Data regarding age, height, weight, date of stroke onset, aetiology of stroke, dominant hemisphere, affected arterial territory, MAS scores, Brunnstrom stage of lower limb and leg circumference were noted.

Ultrasonographic evaluations of the medial head of the gastrocnemius muscle were performed bilaterally with a linear probe (7.5 MHz, Aloka Prosound 5000, Japan) while subjects were in a supine position on the examination table. Hip joints were kept in external rotation, knee joints in extension and ankle joints in a resting position. Pennation angles between the fascicle path and the deep aponeurosis of the muscle, fascicle length and muscle thickness were scanned at the most bulky part of the medial gastrocnemius (Fig. 1). These parameters were measured with minimum compression (in order to obtain a whole screen image rapidly with no shadowing). Thereafter, muscle thicknesses were also determined with maximum compression (Fig. 2) in order to calculate muscle compressibility (%) using the following formula:

$$\frac{\alpha - \beta}{\alpha} \times 100$$

where  $\alpha$  = muscle thickness with minimum compression (mm);  $\beta$  = muscle thickness with maximum compression (mm).

BoNT-A was delivered to both medial and lateral heads of the gastrocnemius muscle with a ratio of 50%. Injections were performed while the patient was in supine position and the knee in 90° flexion.

\*This study has been accepted for oral presentation in ISPRM 2011.

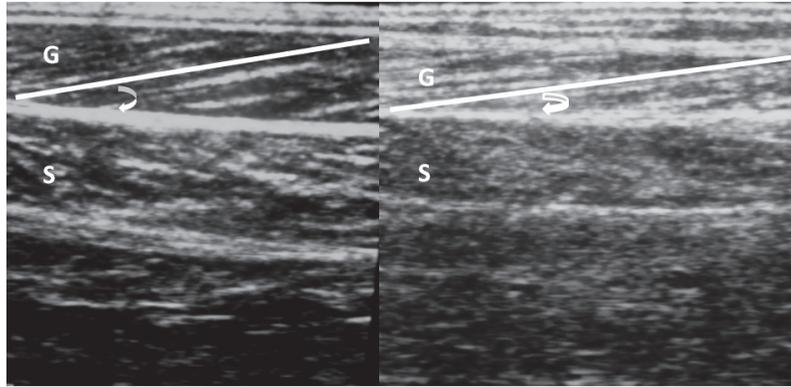


Fig. 1. Ultrasonographic imaging (longitudinal view) of the medial head of the gastrocnemius muscle in (A) a normal and (B) a hemiplegic subject demonstrating the pennate structure of the muscle. The curved arrows correspond to the pennate angle and the white lines correspond to single fascicles. G: gastrocnemius muscle, S: soleus muscle.

Physical examination (passive ankle plantar and dorsiflexion) was used as guidance for injections.

All clinical and ultrasonographic evaluations were performed initially before BoNT-A injection and repeated on day 10 and after 2 months.

#### Statistical analyses

Data were analysed using SPSS 16.0. Descriptive statistics are given as mean (SD) and quantities. Wilcoxon signed-rank test was used for comparison of measurements (baseline, day 10 and month 2). Differences between the paretic and healthy lower limbs were assessed with a Mann-Whitney *U* test. Spearman's rank correlation coefficient was used to discover the strength of an association between 2 sets of data. The level of significance was set at  $p < 0.05$ .

## RESULTS

Mean duration after stroke onset was 861 (SD 1237) (range 67–5,761) days. Mean weight (kg) and height (cm) of the patients were 70.2 (SD 10.4) and 166.7 (SD 6.9), respectively. Twenty-two patients had ischaemic and 4 had haemorrhagic type of stroke. A mean of 128.46 (SD 24.28) (100–150) units of BoNT-A was used. Mean MAS scores decreased from 2.65 (SD 0.56) to 1.61 (SD 0.69) 2 months after treatment ( $p < 0.001$ ).

On the hemiplegic sides, anterior pennation angle, muscle thickness and leg circumference decreased ( $p = 0.014$ ,  $p = 0.010$ ,  $p = 0.014$ , respectively), fascicle length increased ( $p = 0.025$ ) and muscle compressibility did not change on the second month of treatment compared with baseline values

(Table I). All of these parameters were statistically similar between baseline and day 10 measurements. Moreover, no significant differences were observed concerning the unaffected side either on day 10 or after 2 months.

Compared with the unaffected sides, the hemiplegic sides had similar angles of anterior pennation at baseline and on day 10 ( $p > 0.05$ ), but smaller angles after 2 months of BoNT-A injection ( $p = 0.024$ ). Values pertaining to fascicle length and muscle compressibility of the hemiplegic sides were significantly smaller than the unaffected sides at baseline, day 10 and month 2 (all  $p < 0.001$ ). Muscle thickness and leg circumference values were similar between sides at any time of measurement (all  $p > 0.05$ ). Duration after stroke onset was positively correlated with unaffected side muscle thickness, and negatively correlated with hemiplegic side anterior pennation angle and muscle compressibility ( $r = 0.494$ ,  $p = 0.010$ ;  $r = -0.497$ ,  $p = 0.011$  and  $r = -0.760$ ,  $p = 0.000$ , respectively). However, duration after stroke onset was not correlated with any of the ultrasonography measurements on either day 10 or 2 months after treatment (all  $p > 0.05$ ).

## DISCUSSION

This study describes the effects of BoNT-A on muscle architecture in stroke patients. The findings revealed that muscle thickness and anterior pennation angle decreased, and fascicle length increased 2 months after BoNT-A injection.

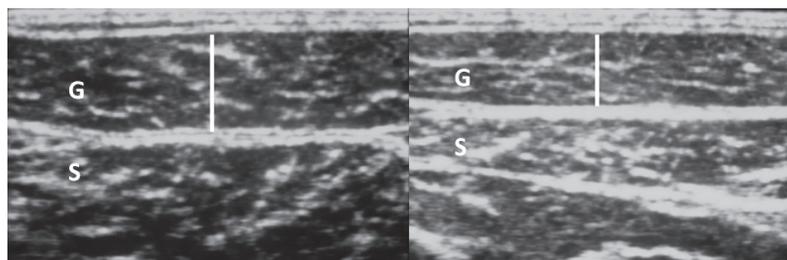


Fig. 2. Ultrasonographic imaging (axial view) of the medial head of the gastrocnemius muscle during (A) minimum and (B) maximum compression. G: gastrocnemius muscle, S: soleus muscle.

Table I. Ultrasonographic findings of the patients

	Healthy side		Hemiplegic side		Healthy side vs hemiplegic side <i>p</i>
	Mean (SD)	<i>p</i>	Mean (SD)	<i>p</i>	
Anterior pennation angle, degree					
Baseline	21.53 (1.88)		21.26 (1.30)		0.297
10 days post-treatment	21.60 (2.20)	0.262 <sup>a</sup>	21.26 (1.19)	0.962 <sup>a</sup>	0.321
2 months post-treatment	21.59 (2.14)	0.586 <sup>b</sup>	20.94 (1.57)	0.014 <sup>b</sup>	0.024
Muscle thickness, mm					
Baseline	15.55 (2.54)		14.76 (2.40)		0.313
10 days post-treatment	15.35 (2.32)	0.234 <sup>a</sup>	14.60 (2.20)	0.104 <sup>a</sup>	0.247
2 months post-treatment	15.58 (2.39)	0.612 <sup>b</sup>	14.43 (2.22)	0.010 <sup>b</sup>	0.065
Fascicle length, mm					
Baseline	48.94 (4.35)		39.86 (4.84)		<0.001
10 days post-treatment	48.50 (3.98)	0.138 <sup>a</sup>	39.98 (4.98)	0.530 <sup>a</sup>	<0.001
2 months post-treatment	49.25 (4.18)	0.201 <sup>b</sup>	40.20 (4.75)	0.025 <sup>b</sup>	<0.001
Muscle compressibility, %					
Baseline	37.97 (8.52)		24.77 (8.99)		<0.001
10 days post-treatment	38.24 (9.94)	0.948 <sup>a</sup>	24.68 (9.71)	0.821 <sup>a</sup>	0.001
2 months post-treatment	39.13 (8.68)	0.073 <sup>b</sup>	24.60 (10.01)	0.841 <sup>b</sup>	<0.001

<sup>a</sup>Baseline vs 10 days post-treatment; <sup>b</sup>baseline vs 2 months post-treatment. SD: Standard deviation.

Although muscle atrophy after BoNT-A injection was reported in some studies, none of them have evaluated changes with respect to anterior pennation angle and fascicle length which, *per se*, have association with muscle tension/length and eventual joint contractures (10–12). Furthermore, those studies used magnetic resonance imaging, or muscle biopsy, which are quite expensive and inconvenient methods. Our study have used MSUS to evaluate the muscle structure *in vivo*. Yet, it has been shown previously that MSUS is a potentially useful tool to quantify certain parameters of the skeletal muscle (13, 14). Given its several advantages, MSUS is convenient for physicians to perform and is easily accepted by their patients (15, 16). Likewise, it has also been used for imaging of the spastic muscle architecture in stroke patients (1, 2, 17). Compared with healthy controls, Gao et al. (1) have reported smaller pennation angles, shortened fascicle length and thinner muscle thickness in chronic stroke survivors. Although baseline fascicle length values for our patients were also found to be shortened on the hemiplegic sides, anterior pennation angle and muscle thickness values were similar on both sides of our patients. We believe that the latter disparity could stem from the difference between the durations after stroke onset in the two studies. Yet, Gao et al. included chronic patients who had at least one year duration after stroke onset (1). However, 12 (46.1%) of our patients had less than one year history of stroke, and in most of those patients increased muscle thickness and anterior pennation angle were observed.

In the current study, we additionally used “muscle compressibility” as a new sonographic parameter in order to evaluate muscle elasticity, which is known to be negatively affected in spastic muscles (18, 19). Our findings showed that compressibility of the gastrocnemius muscle was significantly impaired either before or after BoNT-A injection. Moreover, compressibility displayed negative correlations with duration after stroke onset; indicating decreased muscle elasticity in chronic stroke survivors. Another finding of our study was the positive correlation between healthy side muscle thickness and duration

after stroke onset. This may be due to the relative overuse of the unaffected lower limb during the interim.

The present study has some limitations, primarily the lack of control group receiving placebo injection. Addition limitations are the lack of long-term follow-up and blinding. Nevertheless, our results appear to be significant.

In conclusion, muscle thickness and anterior pennation angle decrease, but fascicle length increases after BoNT-A injection in stroke patients. Long-term effects of BoNT-A, i.e. the exact timing for disappearance of the toxin effects or evaluation of the effects of repeat injections, remain to be deciphered in further studies. The use of MSUS would be particularly noteworthy in this regard.

*The authors declare no conflicts of interest.*

## REFERENCES

- Gao F, Grant TH, Roth EJ, Zhang LQ. Changes in passive mechanical properties of the gastrocnemius muscle at the muscle fascicle and joint levels in stroke survivors. *Arch Phys Med Rehabil* 2009; 90: 819–826.
- Gao F, Zhang LQ. In vivo biomechanical evaluations of the medial gastrocnemius: changes in muscle properties in stroke survivors. *Conf Proc IEEE Eng Med Biol Soc* 2006; 1: 2083–2086.
- Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M; GSK1358820 Spasticity Study Group. Botulinum toxin type A in post-stroke lower limb spasticity: a multicenter, double-blind, placebo-controlled trial. *J Neurol* 2010; 257: 1330–1337.
- Brashear A, Gordon MF, Elovic E, Kasscieh VD, Marciniak C, Do M, et al. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Engl J Med* 2002; 347: 395–400.
- Shaw L, Rodgers H, Price C, van Wijck F, Shackley P, Steen N, et al. BoTULS investigators. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol Assess* 2010; 14: 1–113.
- Cousins E, Ward A, Roffe C, Rimington L, Pandyan A. Does low-

- dose botulinum toxin help the recovery of arm function when given early after stroke? A phase II randomized controlled pilot study to estimate effect size. *Clin Rehabil* 2010; 24: 501–513.
7. Yaşar E, Tok F, Safaz I, Balaban B, Yilmaz B, Alaca R. The efficacy of serial casting after botulinum toxin type A injection in improving equinovarus deformity in patients with chronic stroke. *Brain Inj* 2010; 24: 736–739.
  8. Bakheit AM, Zakine B, Maisonobe P, Aymard C, Fhedoroff K, Hefter H, et al. The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: an international survey. *Int J Rehabil Res* 2010; 33: 199–204.
  9. Elia AE, Filippini G, Calandrella D, Albanese A. Botulinum neurotoxins for post-stroke spasticity in adults: a systematic review. *Mov Disord* 2009; 24: 801–812.
  10. Schroeder AS, Ertl-Wagner B, Britsch S, Schröder JM, Nikolin S, Weis J, et al. Muscle biopsy substantiates long-term MRI alterations one year after a single dose of botulinum toxin injected into the lateral gastrocnemius muscle of healthy volunteers. *Mov Disord* 2009; 24: 1494–1503.
  11. Glass GE, Hussain M, Fleming AN, Powell BW. Atrophy of the intrinsic musculature of the hands associated with the use of botulinum toxin-A injections for hyperhidrosis: a case report and review of the literature. *J Plast Reconstr Aesthet Surg* 2009; 62: 274–276.
  12. Shen J, Ma J, Lee C, Smith BP, Smith TL, Tan KH, et al. How muscles recover from paresis and atrophy after intramuscular injection of botulinum toxin A: study in juvenile rats. *J Orthop Res* 2006; 24: 1128–1135.
  13. Ohata K, Tsuboyama T, Ichihashi N, Minami S. Measurement of muscle thickness as quantitative muscle evaluation for adults with severe cerebral palsy. *Phys Ther* 2006; 86: 1231–1239.
  14. Abe T, DeHoyos DV, Pollock ML, Garzarella L. Time course for strength and muscle thickness changes following upper and lower body resistance training in men and women. *Eur J Appl Physiol* 2000; 81: 174–180.
  15. Özçakar L, Malas FU, Kara G, Kaymak B, Haşçelik Z. Musculoskeletal sonography use in physiatry: a single-center one-year analysis. *Am J Phys Med Rehabil* 2010; 89: 385–389.
  16. Özçakar L, Tok F, Kesikburun S, Palamar D, Erden G, Ulaşlı A, et al. Musculoskeletal sonography in physical and rehabilitation medicine: results of the first worldwide survey study. *Arch Phys Med Rehabil* 2010; 91: 326–331.
  17. Li L, Tong KY, Hu X. The effect of poststroke impairments on brachialis muscle architecture as measured by ultrasound. *Arch Phys Med Rehabil* 2007; 88: 243–250.
  18. Fridén J, Lieber RL. Spastic muscle cells are shorter and stiffer than normal cells. *Muscle Nerve* 2003; 27: 157–164.
  19. Kamper DG, Schmit BD, Rymer WZ. Effect of muscle biomechanics on the quantification of spasticity. *Ann Biomed Eng* 2001; 29: 1122–1134.