Kinematic improvement following Botulinum Toxin-A injection in upper-limb spasticity due to stroke

Esteban A Fridman,[1,2,3] Marcos Crespo,[1] Santiago Gomez Argüello,[1] Lorena Degue,[1] Mirta Villarreal,[1,3] Stephan Bohlhalter,[2] Lewis Wheaton,[2] Mark Hallett[2]

[1]Neurorehabilitation Section and Spasticity Clinic, Institute for Neurological Research-FLENI, Buenos Aires, Argentina
[2]Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland, USA
[3]CONICET, Buenos Aires, Argentina

Correspondence to
Dr Esteban A Fridman, Neurorehabilitation Section and Spasticity Clinic, Neurology Department, Institute for Neurological Research, FLENI, Montaneses 2325, Buenos Aires C1428AQK, Argentina; efridman@fleni.org.ar

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ABSTRACT

Background Focal spasticity is a significant motor disorder following stroke, and Botulinum Toxin Type-A (BoNT-A) is a useful treatment for this. The authors evaluated kinematic modifications induced by spasticity, and whether or not there is any improvement following injection of BoNT-A.

Methods Eight patients with stroke with upper-limb spasticity, showing a flexor pattern, were evaluated using kinematics before and after focal treatment with BoNT-A. A group of sex- and age-matched normal volunteers acted as a control group.

Results Repeated-measures ANOVA showed that patients with stroke performed more slowly than the control group. Following treatment with BoNT-A, there was a significant improvement in kinematics in patients with stroke, while in the control group, performance remained unchanged.

Conclusions Focal treatment of spasticity with BoNT-A leads to an adaptive change in the upper limb of patients with spastic stroke.

INTRODUCTION

Two major concerns in the medical community are whether the presence of spasticity by itself interferes with the patient's functionality and how treatment benefits the rehabilitation process. There are multiple reasons for this concern. For instance, to test the response to different antispastic treatments, a static scale such as the Ashworth scale has long been used.[1] Unfortunately, improvements in the Ashworth scale have not always represented functional improvements in spastic patients.[2] On the other hand, scales that evaluate functional disability have a large, nonlinear interval between the rating scores that may be misleading.[3] Additionally, the neurological deficit in patients with spastic stroke is broad, ranging from a severely paretic and spastic arm to mild spastic paresis, with correspondingly different treatment objectives. These limitations are particularly problematic in that subgroup of patients with upper-limb spasticity showing a flexor pattern and a disproportionate impediment to extension due to exaggerated flexor tone but with good distal control. This population rarely improves their motor functionality with oral medications, and may have medication side effects that affect cognitive abilities.[4 5] Thus, a focal intervention with Botulinum Toxin Type-A (BoNT-A) seems more suitable.[5–8]

In this study, we used upper-limb kinematics during a task with reaching, grasping and transport of an object to evaluate specific measures of movement (eg, peak velocity, distance, time). We tested the hypothesis that motor performance would be improved by BoNT-A injection in patients with upper-limb spasticity due to stroke presenting a flexor pattern with residual extensor capabilities.

METHODS

Subjects

We studied eight patients with a single clinical ischaemic stroke event dating back more than 1 year (53.7±16.6 years old, six of them females, all right-handed[9]). They were initially hemiplegic and, by testing time, had experienced a marked motor recovery and 3+ or more on the MRC scale (Medical Research Council 1976), showed complete independence on Functional Independence Measurement (FIM)[10] (table 1), and had been thought to have achieved maximal benefit from standard physical and occupational therapy. They also showed focal flexor spasticity compromising elbow, wrist and fingers (Ashworth 2). Additional inclusion criteria at testing time included full passive hand range motion, presence of selective motor control of finger extensors when tested at maximum wrist flexion (90°), adequate strength of finger flexors and a partial limitation of finger extensors due to the dynamic spastic flexor pattern, and ability to perform the reaching, grasping and transport task at baseline. We excluded those patients with moderate to severe sensory deficit.

Eight normal volunteers (NV) (48.7±8.3 years old, five of them females, all right-handed) participated as sex- and age-matched controls. Since BoNT-A is standard of care for spasticity due to stroke for its benefits on muscle tone,[5–7] there was no placebo group in this study. All subjects gave their written informed consent according to the declaration of Helsinki, and the FLENI Institutional Review Board approved the study protocol.

Experimental design

Kinematics

Subjects sat comfortably in a chair with their tested wrist in a resting position, elbow at 90° of flexion and shoulder in a neutral position. There were no trunk restrictions. The task involved reaching a functional object positioned on one side of the desk (either right or left, depending on the evaluated arm) that was located 35 cm from the body. Subjects were told to grab the object and transport it to a centre spot in the middle of the desk (figure 1). An auditory signal acted as a 'GO' instruction. Subjects were encouraged to perform the task as accurately as possible at the most comfortable

Table 1 Demographics

Patient	Age (years)	Time (years) after cerebrovascular accident	Lesion location	Medical Research Council score (flexor digitorum superficialis)	Functional Independence Measurement score
1	53	5	Left PLIC-subinsular	3^+/5	126
2	29	2	Right PLIC	3^+/5	126
3	58	2	Left MCA	4^+/5	126
4	64	4	Right PLIC	4	126
5	77	4.5	Right mesencephalic	4^+/5	126
6	35	1	Right MCA	3^+/5	126
7	45	1	Left MCA	4/5	126
8	69	3	Right MCA	3^+/5	126

MMCA, middle cerebral artery; PLIC, posterior limb of the internal capsule.

speed. Five trials were acquired at two time points for each subject: before BoNT-A injection and 1 month after the procedure in patients with stroke. The control group performed the same task at two different times (baseline and 30 days) without any pharmacological intervention.

Data acquisition

Kinematic data were obtained using a movement-analysis system (ELITE-BTS, Milan, Italy). Six infrared cameras were located in a circular position around the experimental desk. Reflective markers were positioned at the right and left acromial end, seventh cervical vertebrae, sacrum, epicondyle of the humerus, styloid process of the radius and ulna. The sampling rate during acquisition was 100 Hz.

Statistical analysis

In order to analyse the data, we divided each trial in three different phases. The reaching phase began once the marker located at the styloid process of the radius reached a tangential velocity of 0.01 m/s and ended when the velocity decreased to less than 0.15 m/s. The tangential velocity was calculated from the magnitude of the velocity vector of the temporal derivative of the marker in the x, z and y axes. Second, the grasping phase was the time between the reaching phase and the transport phase. Third, the transport phase began when the same marker displayed a velocity above 0.15 m/s and ended when the velocity was below 0.1 m/s. After separating these three phases, we analysed three variables: the peak velocity, the displayed distance and the phase duration. During the grasping phase, the only possible variable to measure was the phase duration.

Between groups, age differences were analysed using unpaired two-way t statistics. The endpoint measures of the study were the peak velocity, distance and time during kinematics. The software package StatView 5.0 (SAS Institute, Cary, North Carolina) was used for all statistical comparisons. A repeated-measure analysis of variance (ANOVA) design with the dependent variable being peak velocity, distance and time and the independent variable GROUP (NV/patients with stroke) was used. Post-hoc pairwise comparisons were implemented using the Scheffe test. Results were considered significant at a level of $p<0.05$.

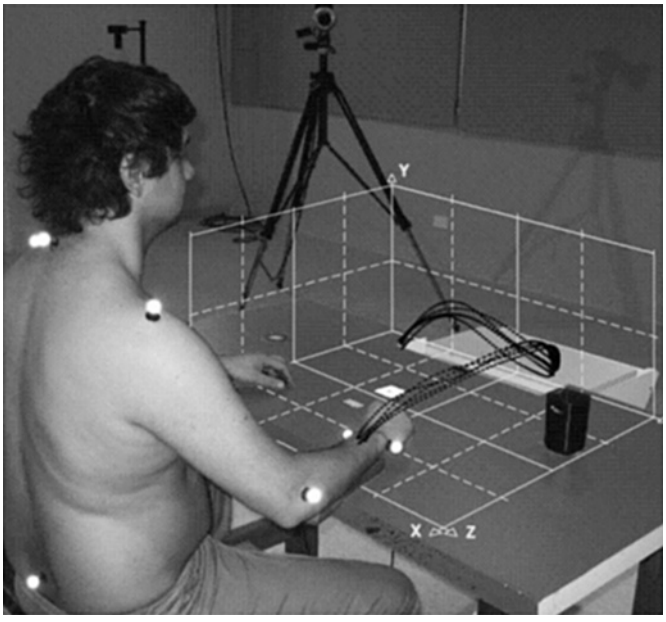

Figure 1 Motion analysis setup: a normal volunteer sitting in the initial position on the work table. The figure shows the expected path of the wrist during reaching, grasping and transport trials (black dots) over a superimposed white x—y—z axis.

Botulinum toxin-A injection

The dose of BoNT-A (BOTOX, Allergan, Irvine, California) was administered according to each patient's individual pattern of spasticity and the consensus between therapists (SGA, LD) and the specialist (EAF), with doses not exceeding 400 U and not more than 50 U per single injection site. The mean dosage of BoNT-A was 305±41.8 U (range 162.5 to 362.5 U) (table 2). The dilution was standardised: one phial (100 U) was diluted with 2 ml of normal saline (5 U/0.1 ml). The injections were administered using anatomical landmarks and under EMG-electrical stimulation guidance (Keypoint, Medtronic, Minneapolis, Minnesota), with identification of target muscles by recording the muscle activity during active or passive movements or observing the movements during muscle electrical stimulation. Injections were performed using special needles/electrodes (Myoject) and 3 ml volume syringes.

Rehabilitation programme

In addition to the BoNT-A treatment, patients received 1 h of standard physical therapy and occupational therapy twice a week (eg, stretching, passive and active movement guidance).

RESULTS

All patients completed the kinematics experimental protocol.

Effects of spasticity in motor control after stroke and consequences of BoNT-A injection

Kinematics during reaching

Overall, the repeated-measures ANOVA of peak velocity during reaching demonstrated significant effects of GROUP ($F=322.630$, $p\leq0.0001$), as well as the group×evaluation interaction ($F=5.535$, $p\leq0.05$). Patients with spastic stroke showed a markedly slower mean peak velocity in both sessions compared with the group of NV (stroke before 0.40 m/s±0.02 and stroke after 0.43 m/s±0.02; NV first 0.83±0.02 m/s and second 0.80 m/s±.01). However, the increment of the peak velocity after BoNT-A injection was not statistically significant in patients with stroke ($p=0.07$). There were significant effects of group ($F=128.021$, $p\leq0.0001$), evaluation ($F=17.104$, $p\leq0.0001$) and the group×evaluation ($F=8.773$, $p\leq0.005$) interaction in the amount of time required to perform the reaching.

Table 2 Application data

Muscle and Botulinum Toxin Type-A U/patient	1	2	3	4	5	6	7	8	Mean U	SD
Biceps	125	40	75	100	100	100	75	100	79.4	38.2
Brachiradialis	50	25	50	75	50	25	50	50	41.7	21.7
Pronator teres	37,5	50	0	0	0	0	50	0	15.3	23.2
Pronator quadratus	25	25	0	0	0	0	25	0	8.3	12.5
Flexor carpi radialis	0	0	37,5	50	50	0	0	0	20.8	25.0
Flexor carpi ulnaris	0	0	0	25	25	0	0	0	8.3	12.5
Flexor digitorum superficialis	75	60	50	25	40	0	75	75	50.0	25.5
Flexor digitorum profundus	50	75	25	25	50	25	0	75	36.1	28.3
Flexor pollicis longus	0	20	0	0	0	12,5	0	25	9.2	11.5
lumbrical	0	0	25	0	0	0	0	0	2.8	8.3
Total									305	41.8

Patients with stroke were slower than NV in both sessions (stroke before 1.18±0.06 s, stroke after 0.98±0.03 s; NV first, 0.61±0.01 s, NV second, 0.58±0.01 s). Although there was a significant improvement in both groups between sessions, the improvement was greater in the spastic stroke group (19% vs 5%, p=<0.05). There were no significant differences within and between groups in distance (stroke before 0.27±0.01 m, after 0.26±0.01 m; NV first 0.27±0.01 m, second 0.27±0.01 m). Figures 2, 3 summarise the results of the kinematics during reaching.

Kinematics during grasping

A repeated-measures ANOVA of amount of time during grasping demonstrated significant effects of GROUP (F=46.666, p≤0.0001), evaluation (F=9.886, p≤0.005), as well as group×evaluation interaction (F=9.115, p≤0.005). Patients with spastic stroke required a longer time than NV to grab the object during both sessions (stroke before 1.90±0.29 s, stroke after 1.07±0.16 s, healthy first 0.16 s±0.03, healthy second 0.14 s±0.02). However, after injection, the spastic stroke group clearly improved their time (stroke before vs stroke after, p≤0.005), while there was no modification in the control group between sessions (p=0.337). Figures 2, 3 summarise the results of the kinematics during grasping.

Kinematics during transport

Similar to the reaching phase, a repeated-measures ANOVA of peak velocity during transport demonstrated significant effects of group (F=130.324, p≤0.0001), of evaluation (F=7.366, p≤0.01), as well as group×evaluation interaction (F=9.304, p≤0.005). Patients with spastic stroke were significantly slower in transporting the object in both sessions compared with NV (stroke before 0.41±0.02 m/s, stroke after 0.48±0.02 m/s; healthy first 0.71 m/s±0.02; healthy second 0.71 m/s±0.01). Additionally, there was a marked acceleration in the peak velocity after BoNT-A injection in the treated group (stroke before vs stroke after, p≤0.001) that was not seen in the control group (healthy first vs healthy second, p=0.79). Similarly, there was a significant effect of group (F=8.833, p≤0.005) and evaluation (F=5.632, p≤0.05) but not group×evaluation interaction (F=1.280, p=ns). Although the distance to transport the object was longer in patients with stroke at both evaluations compared with healthy patients (stroke before 0.30±0.01 m; stroke after 0.28±0.01 m and NV first, 0.27±0.01 m, NV second, 0.26±0.01 m), there was no modification after BoNT-A injection (stroke before vs stroke after, p=0.07) and no modification in NV between sessions (healthy first vs healthy second, p=0.06). Lastly, repeated-measures ANOVA of the amount of time during transport demonstrated significant effects of group (F=74.339, p≤0.0001), evaluation (F=21.858, p≤0.0001) and group×evaluation interaction (F=13.669, p≤0.0005). Patients with spastic stroke required a greater time to transport the object in the both sessions compared with NV (stroke before 1.10±0.07 s, stroke after 0.88±0.03 s and healthy first 0.59 s±0.02, healthy second 0.57 s±0.01), and showed a marked improvement after BoNT-A injection (stroke before vs stroke after, p≤0.0001) not seen in the control group (healthy first vs healthy second, p=0.126). Figures 2, 3 summarise the results of the kinematics during transport.

DISCUSSION

First, we will discuss the clinical, kinematic and functional differences between NV and patients with stroke. Then, we will

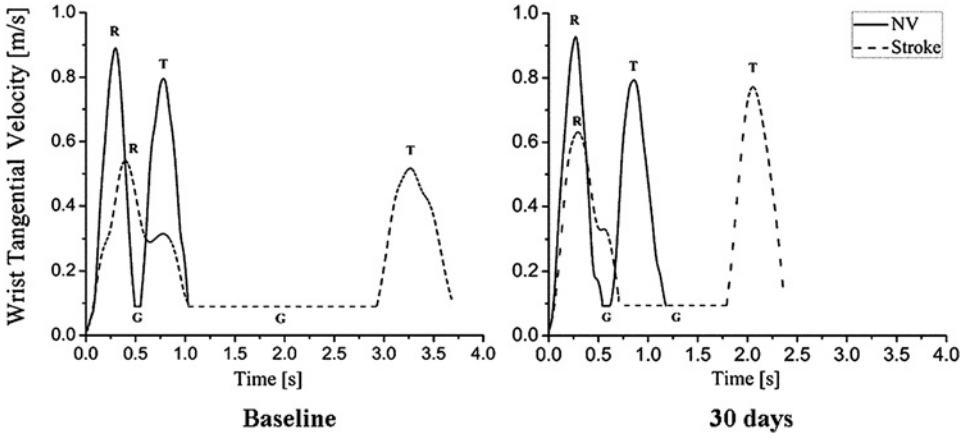

Figure 2 Row curves of wrist tangential velocity during reaching (R), grasping (G), and transport (T), dotted lines in patients with stroke and continuous lines in normal volunteers (NV). NV perform faster than patients with stroke, but patients with stroke significantly improved following treatment, while NV performance remained stable.

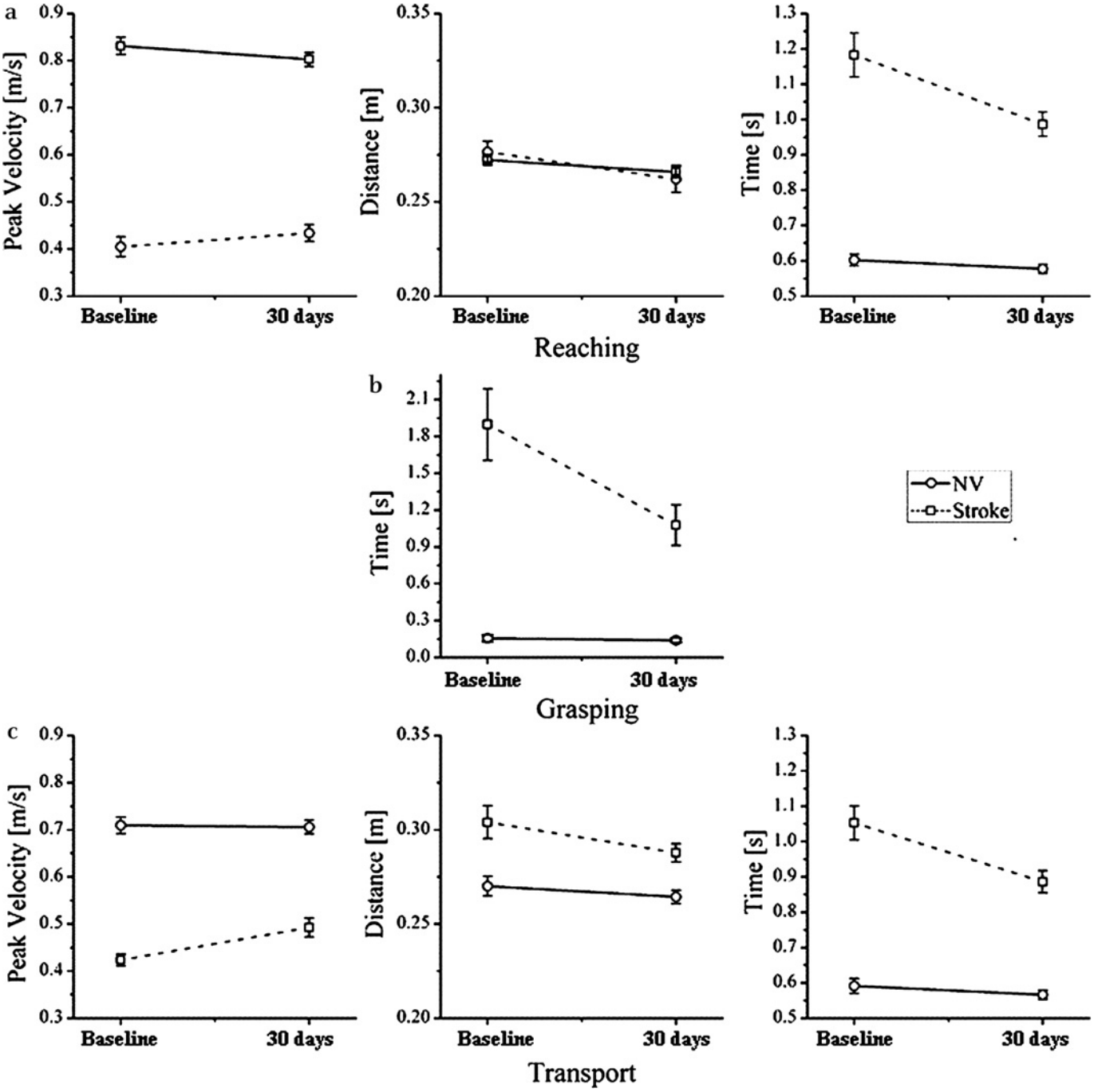

Figure 3 Repeated-measures ANOVA of peak velocity, distance and time during reaching (a), grasping (b) and transport (c) phases. Box plots show the results for normal volunteers (NV) and patients with stroke before and after treatment with BoNT-A. Significance: ^group; ^1, ^2group×evaluation interaction; *evaluation ($p<0.05$).

discuss the modification in these aspects induced by BoNT-A in patients with stroke.

Evaluation-restricted kinematics and functional differences between patients with spastic stroke and NV

In patients with stroke, the peak velocity and time of reaching showed slowness and a delay, respectively; grasping was more prolonged; and transport showed a decrease in peak velocity, with an increment in the distance and time. All these findings demonstrate a dysfunction of selective motor control of the whole upper limb due to the interaction of weakness[11] and spasticity.[12 13] Spasticity of the elbow flexors might explain impairments in reaching and transport in patients with stroke, while spasticity of the finger flexors may be responsible for the prolongation of grasping.

Similarly, after treatment, patients with stroke showed a diminished motor performance compared with the second session of normal volunteers with almost comparable kinematics differences, as described before the treatment (see above).

Longitudinal changes induced by BoNT-A injection during motor execution of the spastic arm

BoNT-A injection induced kinematic modifications in patients with spastic stroke who were absent in normal volunteers when the first and second sessions were compared. Although learning might differ in patients and normals, this provides some

evidence that the improvement in the patients was due to therapy. These modifications were observed during each of the three different phases (reaching, grasping and transport). In the case of the reaching phase, patients with spastic stroke showed a significantly decreased amount of time required to perform the task. However, they did not differ in the peak velocity and distance required to perform it. Thus, it is possible that the reduction in the spastic elbow flexor pattern by BoNT-A injection disrupted the previous segmental misbalance of reciprocal inhibition as in the case of dystonic patients[14 15] and counterbalanced the activity of agonists–antagonists, making the dynamic resistance of the spastic flexor pattern less problematic.[16 17] This hypothetical framework was more evident during the grasping phase of the movement. While NV utilised a similar time between the two separate sessions in order to grasp the object, patients with spastic stroke significantly improved after treatment. Again, BoNT-A injection induced a decrement of the spastic pattern of the finger flexors, and allowed a more suitable recruitment of the finger extensors to accomplish the grip aperture. Lastly, the transport phase of the movement also showed a peak velocity improvement and a decreased time to transport the object after treatment in patients with spastic stroke, without any modification between the two evaluations in NV. We speculate that BoNT-A decreases the negative influence of the spasticity of the injected muscle at the spinal cord level and may influence more proximal parts of the motor system as well. Thus, patients in neurorehabilitation training may regain better cortical control of motoneurons of muscles antagonist to those muscles injected, similarly to patients with stroke without spasticity.[18 19] In other words, for our experiment, a decrease in the flexor tone by BoNT-A elicits better recruitment of the extensor muscles at a segmental level (ie, spinal cord) allowing a more suitable supraspinal control by the fast conducting fibres from the cortex, as seen in recovered paretic patients with stroke.[20]

BoNT-A is widely used to treat focal upper-limb spasticity due to stroke. Its usefulness has been demonstrated in a large double-blind clinical design using a static evaluation such as the five-point Ashworth scale and a wide functional disability scale.[7] However, quality of movements measured by kinematics was not assessed in this previous work. Indirect evidence of the effectiveness of BoNT-A injection to improve the quality of movement in the spastic upper-limb comes from children with spasticity due to cerebral palsy[21 22] but has never been evaluated in adults with upper-limb spastic stroke. We demonstrated that in a group of patients who previously had reached a 'plateau' with standard therapy, we could improve performance by BoNT-A injection combined with additional physical and occupational therapy. Since the task we studied is a typical situation of daily life, we speculate that this improvement in velocity and time required to perform the task might be translated to countless situations in a patient's life, which is difficult to objectify in functional scales (eg, less time required and better quality of movements). In this sense, patients after BoNT-A, even if able to perform similar tasks before, will now perform it with less effort. A further evaluation with more suitable functional scales will clarify this view.

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Competing interests None.

Ethics approval Ethics approval was provided by the Institute for Neurological Research-FLENI-IRB.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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