Effect of Simultaneous Botulinum Toxin Injections Into Several Muscles on Impairment, Activity, Participation, and Quality of Life Among Stroke Patients Presenting With a Stiff Knee Gait

Gilles D. Caty, MD; Christine Detrembleur, PhD; Corinne Bleyenheuft, MD; Thierry Deltombe, MD; Thierry M. Lejeune, MD

Background and Purpose—Walking is an essential activity for daily life and social participation, and it is frequently limited after stroke. A lack of knee flexion during the swing phase (stiff knee) is one of the impairments that restrict walking ability among patients with hemiparetic spasticity. Our purpose was to study the effect of Botulinum toxin type A (BoNT A) injections in several spastic muscles on the impairment, activity, participation, and quality of life of patients with chronic stroke presenting with a stiff knee gait.

Methods—Twenty chronic hemiparetic poststroke patients with stiff knee gait and ability to walk on a treadmill were recruited. BoNT A was injected into several spastic muscles: the rectus femoris (200 U), semitendinosus (100 U) and triceps surae (200 U). Patients’ neurological impairments (Ashworth scale, Duncan-Ely test, Stroke Impairment Assessment Set, and instrumented gait analysis), activity (ABILOCO and 10-m walking test), and participation (SATISPART-Stroke and 36-item Short-Form Health Survey) were assessed before and 2 months after the injection.

Results—BoNT A injection reduced the impairments. It improved Stroke Impairment Assessment Set (56.5 [52.5 to 63] to 56.5 [52.5 to 63]; P<0.001), reduced rectus femoris muscle tone (2 [1 to 2.5] to 0 [0 to 1]; P<0.001), and reduced semitendinosus muscle tone (1 [1 to 1.5] to 1 [0 to 1]; P<0.001). Gait analysis demonstrated increased knee flexion during the swing phase (22°±19° to 27°±16°; P=0.03), decreased external mechanical work (0.66±0.38 to 0.59±0.25 J kg⁻¹ m⁻¹; P=0.04), and demonstrated a lower energy cost (5.8±1.9 to 4.9±1.9 J kg⁻¹ m⁻¹; P=0.03). The patients’ locomotion ability was improved (2.2±1.9 to 3.2±2.1 logits; P=0.03). The participation and quality of life remained unchanged.

Conclusions—BoNT A injections in several muscles improved the stiff knee gait and the locomotion ability in adult stroke patients. (Stroke. 2008;39:000-000.)

Key Words: Botulinum toxin ■ muscle spasticity ■ stroke

One third of the people who experience a stroke¹ present with disorders in the 3 international classification of functioning (ICF)² domains: permanent neurological impairment, activity limitation restraining their participation, and quality of life. Spastic hemiparesis is the classical clinical picture of neurological impairment that limits walking ability. Walking is essential for daily life activities and social participation; therefore, it is considered the most important activity of daily life by stroke patients.³ Stiff knee gait is a common pattern of impaired kinematics in these patients; it is characterized by a lack of knee flexion during the swing phase of the gait cycle. The physiopathology and treatment of stiff knee gait has not been clearly established. The overactivity of the rectus femoris (RF) is often cited,⁴,⁵ but the altered activity of other muscles could also take place in the physiopathology.⁶ In a previous study, Stoquart et al⁷ demonstrated that 200 U of Botulinum toxin type A (BoNT A, Botox) injected into the RF was effective at improving knee movement and the energy cost of walking. These authors focused on gait analysis and explored only the first ICF domain. They demonstrated that RF chemodenervation was ineffective for patients with no knee flexion during the swing phase (<10°). This may be related to the involvement of other underactive (iliopsoas) or overactive (triceps surae or vasti) muscles in the stiff knee physiopathology.⁶ In this case, simultaneous BoNT A injections into several spastic muscles could be an adequate treatment. To our knowledge, no previous study has evalu-
ated BoNT A injections in multiple muscles for the treatment of stiff knee gait.

BoNT A injections have been increasingly used to manage spasticity among hemiparetic stroke patients. Dose-related BoNT A injection efficacy was clearly demonstrated by a placebo-controlled randomized controlled trial on muscle tone, commonly assessed by the Ashworth scale.\(^6,7\) Specifically, the effects of BoNT A injection have been shown only to improve impairments. The impairment reduction may lead to a reduced burden of care, eg, an increase in the passive range of motion facilitating dressing. The effect of BoNT A injection on patient activity and participation in social activities remains uncertain for 2 reasons.\(^8\) First, the activity and participation are not systematically evaluated or assessed with an insensitive tool. For instance, locomotion activities are frequently measured by ordinal scales, and there is no standard method of appraising participation. Recently, new questionnaires were developed after Rasch analysis to assess locomotion ability\(^9\) and social participation\(^10\) in stroke patients. These linear, unidimensional scales should assess these domains with high sensitivity. Second, the relationship between impairment and disability is not straightforward in spastic patients. The disability may be more associated with negative upper motor syndrome signs (paresis and loss of dexterity) than positive signs (spasticity and abnormal postures). A significant reduction in spasticity may not lead to a functional improvement in activity or participation. In some patients, the increased tone of spastic muscle may be useful, for instance, in spastic quadriceps femoris used for maintaining an upright position.

The main aim of this study was to investigate the efficacy of BoNT A injections in several muscles on stiff knee gait in stroke patients following the ICF framework. The secondary aim was to analyze whether simultaneous BoNT A injections into several spastic muscles are more useful in the treatment of stiff knee gait, as opposed to 1 single injection into the RF.\(^7\)

**Methods**

**Subjects**

Twenty chronic poststroke patients, 15 males and 5 females, with spastic hemiparesis and stiff knee gait are enrolled in the present study. The selection criteria are based on clinical examination and visual gait observation. The inclusion criteria are spastic hemiparesis secondary to stroke, >6 months since stroke, lack of knee flexion during the swing phase, and ability to walk independently without an assistive device. The exclusion criteria are inability to walk on a treadmill for sufficient time to complete a metabolic analysis (\(\approx\)2 minutes) and any cognitive deficit that would prevent the completion of the questionnaires. Their mean age is 52.3 \pm 16.1 years (range, 23 to 81), and the mean time since stroke is 45.9 \pm 32.9 months (range, 7 to 118). Ongoing treatments are kept unchanged (physical therapy and medication) throughout the study. This study is approved by the Local Ethics Committee and all patients provide written informed consent.

**Body Function and Structure Assessment**

Neurological impairments are assessed using the Stroke Impairment Assessment Set\(^11\), which is a Rasch-validated scale. The Duncan-Ely test\(^12\) is used to quantify RF muscle tone, and the Ashworth scale\(^13\) is used to quantify semitendinosus and triceps surae muscle tone.

Gait analysis is performed after the protocol described by Stoquart et al.\(^7\) Three-dimensional kinematic analysis and energetic measurements are conducted while patients walk on a force-measuring treadmill (Mercury LTmed; HP Cosmos).\(^16\) Segmental kinematics are measured using the Elite system (BTS). At 100 Hz, 6 infrared cameras measure the 3 spatial coordinates of 20 reflective markers positioned on specific anatomic landmarks. These measurements allow computation of the angular displacement of the hip, knee, and ankle during the walking cycle.\(^17\) The amplitude of knee flexion (\(d_k\)) is computed as the difference between the minimum knee flexion at the end of the stance phase (\(d_s\)) and the maximum knee flexion during the swing (\(d_d\)). Ground reaction forces are recorded by 4 strain gauges located under each corner of the treadmill.\(^18\) The total positive mechanical work (\(W_{pos}\)) performed by muscles during walking is divided into the external work (\(W_{ext}\)) performed to move the center of body mass (COM\(_b\)) relative to the surroundings and the internal work (\(W_{int}\)) performed to move body segments relative to the COM\(_b\).\(^18\) The \(W_{ext}\) and \(W_{int}\) are computed after the method described by Detrembleur et al.\(^19\) The metabolic cost of walking is determined by the patient’s oxygen consumption (\(O_2\)) and carbon dioxide production (\(CO_2\)) measured throughout the treadmill test. The energy expended above the resting value (standing subtracted from walking consumption) is divided by the walking speed to obtain the net energy cost of walking (\(C; J kg^{-1} m^{-1}\)).

**Activity Assessment**

Locomotion ability is assessed using ABILOCO.\(^11\) This 13-item questionnaire, validated by Rasch analysis, is a linear interval, unidimensional, and invariant scale assessing locomotion ability in adult stroke patients, and it can be used regardless of age, sex, cerebral lesion type, and time since the stroke occurred. Walking ability is also assessed by standard ordinal scales: the Functional Walking category,\(^20\) the Functional Ambulation categories,\(^21\) and the 12th item of the Functional Independence Measure\(^22\) evaluating walking ability. The patient’s spontaneous walking speed is measured using the 10-meter walk test.

**Participation and Quality of Life Assessment**

Patient participation is assessed with the SATISPART-Stroke\(^12\) questionnaire, and the quality of life is assessed with the 36-item Short-Form Health Survey.\(^23\) SATISPART-Stroke, validated by Rasch analysis, is a linear, unidimensional scale assessing the stroke patient satisfaction in participation.

**BoNT A Treatment**

Selection of muscles to be injected is based on clinical assessment and gait analysis. All the BoNT A injections are performed by the same experienced physician (C.B.) with EMG guidance or electrostimulation. BoNT A (100 U Botox in 1 mL saline; Allergan) is injected into the RF (200 U, 6 sites\(^2\)), the semitendinosus (100 U, 4 sites), and the triceps surae (TS; 200 U, 6 sites), including the gastrocnemius medialis, the gastrocnemius lateralis, and the soleus. The total BoNT A dose for a patient ranges from 300 to 500 U. Seven patients underwent a selective tibial neurotomy to treat a spastic equinus foot. Their TS is no longer spastic and is not injected. Table 1 shows the BoNT A dose for each patient. Note that a BoNT A injection (100 U) into the flexor digitorum longus is performed in 2 patients to treat spastic toes.

**Study Protocol**

The same physician (G.C.) performs all clinical examinations, tests, and analyses. Each subject is assessed before and 2 months after BoNT A treatment. The walking speed on the treadmill is determined before BoNT A treatment as the most comfortable speed and is similar for both gait analyses. The patients walk on the treadmill at 62.5\% to 100\% of their spontaneous walking speed as measured at the 10-meter walk test.

**Statistics**

In a previous study, Stoquart et al\(^7\) showed that the benefit of RF BoNT A injection is influenced by knee flexion amplitude. For this reason, the patients are divided into 2 groups as a function of \(d_k\), the
pre-BoNT A amplitude of knee flexion during swing (Table 1): group 1 (n = 8) includes patients with pre-BoNT A knee flexion <10° (5 ± 2°), and group 2 (n = 12) includes patients with pre-BoNT A knee flexion >10° (33 ± 16°). A 2-way repeated-measures ANOVA is computed to study the effects of BoNT A treatment and groups on parametric data (mean ± SD). A signed rank test (Wilcoxon) is used to compare the nonparametric data after BoNT A treatment (median [range]) for 20 patients and in each group.

Results

The results are presented successively for each ICF domain. The treatment is well-tolerated, and no side effects are reported.

Body Function and Structure: Neurological Impairments

BoNT A injection reduces neurological impairments (Table 2). Despite the fact that the Stroke Impairment Assessment Set median value has not changed, the neurological impairments are significantly improved, as evidenced by the increase in the lowest values (56.5 [48 to 63] to 56.5 [52.5 to 63]; P < 0.001). BoNT A injections have beneficial effects on spasticity, leading to a decreased muscle tone of the RF, semitendinosus, and TS. The median Duncan-Ely score decreases from 2 [1 to 2.5] to 0 [0 to 1]; P < 0.001), and the median and range for the semitendinosus Ashworth scale remains and decreases, respectively, from 1 [1 to 1.5] to 0 [0 to 1]; P < 0.001). The median TS Ashworth scale tends to decrease from 3 [0 to 3] to 0 [0 to 3]; P = 0.06.

Body Function and Structure: Gait Analysis

Figure 1 presents the knee angular displacement during stride in the sagittal plane. In healthy subjects, a slight knee flexion occurs during the loading phase at the beginning of the stance phase. A second large knee flexion occurs during the swing phase to allow for foot clearance. Typical traces of knee angular displacement are presented for both groups. In patient 2, before BoNT A, the knee is permanently flexed at ~15°, and no additional knee flexion occurs during the swing phase (d3 = 3°). This patient belongs to group 1. After BoNT A, knee flexion is normalized at ~45° during the swing phase (d3 = 25°). In patient 16, before BoNT A, the amplitude of knee flexion is reduced during the swing phase (d3 = 44°).

Moreover, the shape of the curve is abnormal. Knee flexion stops at the beginning of the swing phase, and the curve presents a characteristic double-bump shape. This patient belongs to group 2. After BoNT A, knee flexion increases, and this double bump disappears. Before BoNT A, d3 is markedly reduced in both groups: 5.1 ± 2.6° in group 1, corresponding to 10% of the normal value, and 33.3 ± 16.6° in group 2, corresponding to 66% of the normal value. The treatment improves the knee flexion movement (P = 0.029; Table 2, Figure 2). In group 1, the mean d3 increases by 2.4-times from 5 ± 2° to 12 ± 7°; in group 2, the mean d3 increases by 1.12-times from 33 ± 17° to 37 ± 13°.

Figure 2 characterizes the energetic of walking for all patients. The mechanical work performed by the muscles during walking is markedly increased in all patients. Before BoNT A, the external mechanical work (Wext) is on average 2-times greater than in healthy subjects. After treatment, mean Wext decreases 0.9-times from 0.66 ± 0.38 to 0.59 ± 0.25 J kg⁻¹ m⁻³ (P = 0.04; Table 2, Figure 2). Before BoNT A, the
internal mechanical work ($W_{\text{int}}$) is on average 1.5-times greater than in healthy subjects. After treatment, $W_{\text{int}}$ does not change (0.28±0.09 to 0.26±0.07 J kg$^{-1}$ m$^{-1}$; $P=0.3$; Table 2). Before BoNT A, the total mechanical work ($W_{\text{tot}}$) is on average 2-times greater than in healthy subjects. After treatment, $W_{\text{tot}}$ decreases from 0.94±0.44 to 0.86±0.3 J kg$^{-1}$ m$^{-1}$ ($P=0.06$; Table 2). Because of the high mechanical work performed by the muscles during walking, the energy cost is markedly increased before BoNT A and is on average 2.2-times greater than in healthy subjects. After treatment, the energy cost decreases 0.85-times from 0.93±0.45 to 0.7±0.32 J kg$^{-1}$ m$^{-1}$ ($P=0.007$; Table 2), and $W_{\text{int}}$ decreases 0.8-times from 1.23±0.56 to 0.96±0.39 J kg$^{-1}$ m$^{-1}$ ($P=0.03$; Table 2).

### Activity

The inclusion criterion (ability to walk independently at any speed and without an assistive device) explains the high score on the 12th item of the Functional Independence Measure, Functional Walking Category, and Functional Ambulation Categories scales. No significant changes between pre- and post-BoNT A treatment are detected on the 12th item of the Functional Independence Measure, Functional Walking Category, and Functional Ambulation Categories (Table 2). In contrast, the ABILOCO score increases from 2.2±1.9 to 3.2±2.1 logits ($P=0.03$; Figure 2). This corresponds to a 1.12-times increase in the range of locomotion ability explored by ABILOCO.

The patient’s spontaneous walking speed measured with the 10-meter walk test is initially low and remains unchanged after BoNT A treatment (0.63±0.29 to 0.66±0.30 m s$^{-1}$; $P=0.19$).

### Figure 1

Typical traces of knee angular displacement during the stride of patient 2 of group 1 (left) and of patient 16 of group 2 (right). The dotted lines represent values of healthy subjects. The gray lines and dark lines represent respectively pre- and post-BoNT A data of the patients. The amplitude of knee flexion ($d_1$) is computed as the difference between the minimum knee flexion at the end of stance phase ($d_1$) and the maximum knee flexion during the swing ($d_2$).
Participation and Quality of Life
The treatment has no effect on the quality of life as measured by the 36-item Short-Form Health Survey questionnaire (92 [86.5 to 96.8] to 94 [90.3 to 98]; \(P=0.35\)) or on the participation satisfaction assessed by the SATISPART-Stroke (0.39 ± 0.85 to 0.21 ± 1.26 logits; \(P=0.4\); Figure 2).

Discussion
This study demonstrates the beneficial effects of simultaneous Botulinum toxin injections into several spastic muscles for stiff knee gait among adult patients with chronic stroke. BoNT A treatment significantly reduces muscle tone, improves knee kinematics, decreases energy cost (Body Function and Structure ICF domain), and improves locomotion ability (Activity ICF domain); however, the treatment has no impact on satisfaction with respect to participation and quality of life (Participation ICF domain).

Body Function and Structure
The decrease in RF, semitendinosus, and TS muscle tone after BoNT A injection in the present study is expected and corresponds to the well-known chemodenervation effect of the BoNT A injection.\(^8,9\)

The gait analysis demonstrates that BoNT A injection improves knee flexion during the swing phase: disappearance of the double-bump shape and increase of \(\approx 5^\circ\) in knee flexion amplitude. Stoquart et al.\(^7\) found similar results after 200-U BoNT A injection in the RF, and Sung et al.\(^5\) found similar results after phenol injection of the RF motor branch. The improvement in knee movement reduces the energy cost of walking, similar to that observed by Stoquart et al.\(^7\) However, these authors reported an improvement of cost of energy only in patients who flexed their knee >10° before the injection (group 2). In the present study, cost of energy is improved in all patients irrespective of their group. The BoNT A injection program should be adapted for each patient depending on the clinical examination and walking pattern. In group 1 patients, only 200-U BoNT A injected in the RF is ineffective; however, 500-U BoNT A injected into several spastic muscles is effective at improving gait analysis variables, which supports the hypothesis that the stiff knee gait physiopathology is variable and several muscles may be involved.\(^6\) In group 1, stiff knee would be related to the overactivity of several muscles (RF, semitendinosus, TS), whereas in group 2 it seems to be mainly related to RF overactivity. The patients in group 1 have more severe neurological impairment (median Stroke Impairment Assessment Set, 50.5) than group 2 (median Stroke Impairment Assessment Set, 61) patients. In group 2 patients, a 500-U BoNT A injection in several muscles is not more effective than 1 single 200-U BoNT A injection in the RF. Given the high cost of Botulinum toxins and the risk of a paresis induced by excessive BoNT A dosage, the BoNT A injection should be as focused as possible.

Activity
The locomotion ability, assessed by the Functional Walking Category, Functional Ambulation Categories, and the 12th item of the Functional Independence Measure scales, are not modified by the treatment. This may be related to a ceiling effect; indeed, the pre-BoNT A Functional Walking Category, Functional Ambulation Categories, and the 12th item of the Functional Independence Measure scores are high because of the inclusion criterion, ie, the subjects have to be able to walk independently. This may also be related to a lack of sensibility to change (responsiveness) of these ordinal scales. In contrast, ABILOCO detects a functional improvement in walking ability. This scale was developed after Rasch analysis to measure walking ability (Activity ICF domain) and presents the fundamental properties, such as linearity,
unidimensionality, and invariance.11 ABILICO can assess walking abilities among stroke patients with a wide range of locomotion capacities. The ABILICO results can be submitted to arithmetic and parametric statistics.11 These results and their relation to gait analysis illustrate the responsiveness of ABILICO and support its use in clinical practice and research. It also underlines the interest of Rasch-built questionnaires for the outcome assessment of neurological rehabilitation.24–26

In a recent review, Francisco10 stated that until recently, “... studies have not demonstrated unequivocally that Botulinum toxin injection is effective in improving function ...”. The present study is the first to our knowledge to report a functional improvement induced by BoNT A injections. The increased amplitude of knee flexion during the swing phase and the decreased energetic cost can explain the improvement in locomotion ability. Some locomotion activities assessed by ABILICO become feasible after BoNT A, such as “going up an escalator alone” and “going upstairs putting each foot on the next step.” A 1-logit increase means that, on average, the patients are able to perform 3 more locomotion ABILICO items as a result of treatment.

**Participation and Quality of Life**

The BoNT A treatment has no impact on subject participation and quality of life. Several hypotheses can be advanced to explain this phenomenon. First, participation is the most difficult ICF domain to tackle, and there is no gold standard methodology to assess it. The 36-item Short-Form Health Survey13 is a generic questionnaire to assess the health-related quality of life and may lack specificity to evaluate stroke patients. SATISPART-Stroke12 is specifically dedicated to stroke patients. However, some SATISPART-Stroke items, such as “using knife, fork, and spoon in all circumstance” and “reading and understanding a document in all circumstance,” bear no relationship to locomotion. Second, the power of the treatment may be below patient expectations: the physician’s goal is an improvement, whereas the patient’s hope is often complete recovery, even months after the stroke. The improvement in walking ability may be insufficient to improve patient quality of life or to reach the level of participation improvement they hope for. Third, the 2-month delay in assessing the outcome may be insufficient to obtain a modification of participation and quality of life. Repeated BoNT A injections could be necessary to allow patients to modify their social life. Fourth, participation is also dependent on contextual factors that cannot be modified by the treatment.

**Conclusion**

This study demonstrates that BoNT A injections are effective for a stiff knee gait among stroke patients. For the first time to our knowledge, a functional improvement in walking is demonstrated after a reduction in impairment induced by BoNT A.

**Acknowledgments**

The Botox was offered by Allergan. The authors thank the patients for their participation in this study.

**Disclosures**

None.

---

**References**

Effect of Simultaneous Botulinum Toxin Injections Into Several Muscles on Impairment, Activity, Participation, and Quality of Life Among Stroke Patients Presenting With a Stiff Knee Gait

Gilles D. Caty, Christine Detrembleur, Corinne Bleyenheuft, Thierry Deltombe and Thierry M. Lejeune

Stroke. published online July 17, 2008;

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2008/07/17/STROKEAHA.108.516153.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/