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ORIGINAL RESEARCH ARTICLE

# The Effects of Onabotulinum Toxin A Injection into Rectus Femoris Muscle in Hemiplegic Stroke Patients with Stiff-Knee Gait

## A Placebo-Controlled, Nonrandomized Trial

### ABSTRACT

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**Objective:** This study aimed to compare the efficacy of onabotulinum toxin A (onabot) injection into the rectus femoris muscle with that of placebo in the treatment of hemiplegic stroke patients presenting with stiff-knee gait.

**Design:** Twenty-five chronic hemiparetic stroke patients presenting with a stiff-knee gait were included in this study. Fifteen patients received 100–125 U of onabot, and 10 patients received placebo into the rectus femoris muscle. Three-dimensional gait analysis, energy expenditure, 10-m and 6-min walk tests, and spasticity level of the rectus femoris were evaluated at baseline and 2 mos posttreatment.

**Results:** The mean age of patients who received onabot was 53.86 ± 14.74 yrs and of those who received placebo was 59.00 ± 8.11 yrs. At study onset, groups were similar with respect to all parameters ($P > 0.05$). We observed significant improvement in knee flexion (7 degrees average) during swing and a reduction in energy cost of 0.8-J/kg per meter response to injection of 100–125 U of onabot into the rectus femoris muscle. Onabot treatment significantly reduced muscle tone and improved knee kinematics, energy expenditure during walking, and functional assessments at 2 mos ($P < 0.05$); however, placebo had no effects on these parameters. Moreover, maximum knee flexion at swing and energy expenditure in the onabot group was significantly better than placebo at 2 mos ($P < 0.05$).

**Conclusions:** Our results showed the superiority of onabot over placebo in increasing knee flexion during swing phase and decreasing energy expenditure. The application of onabot into the rectus femoris muscle in stroke patients who presented with stiff-knee gait may be a treatment option to provide independent, safe, and less tiring ambulation.

**Key Words:** Stroke, Stiff-Knee Gait, Rectus Femoris, Botulinum Toxin Type A, Three-Dimensional Gait Analysis

Stiff-knee gait (SKG) is characterized by a lack of normal knee flexion during the swing period of gait and is a common result of upper motor neuron injuries resulting from stroke, traumatic brain injury, spinal cord injury, cerebral palsy, and multiple sclerosis. Several mechanisms have been attributed to SKG, the most common being overactivity of the rectus femoris muscle.[1–6] Rectus femoris spasticity has been associated with an increased knee extension moment and decreased knee flexion velocity at toe-off, both of which potentially decrease peak knee flexion during the swing phase.[2]

There are several deleterious consequences of SKG. Above all, toe clearance during swing is reduced, leading to a tendency to totter or fall. In addition, compensatory movements such as ipsilateral hip circumduction or contralateral vaulting are occurred to partially compensate for lack of knee flexion and improve toe clearance; the resulting abnormal spine motion tends the patient to lower back pain and injuries. Other results of SKG include an increased energy expenditure caused by increased vertical displacement of center of gravity.[1–6]

The most common focus of treatment of SKG is rectus femoris muscle spasticity. Surgical procedures such as rectus femoris muscle tenotomy with or without transfer are performed in children with cerebral palsy[7,8] but are not considered as a treatment of choice in adults. Onabotulinum toxin A (onabot) injections are known to be effective in decreasing muscle spasticity in hemiparetic stroke patients.[9,10] It acts locally and temporarily and is not a very invasive procedure. It is usually well tolerated.[11]

Recent publications reported that onabot injection into the rectus femoris muscle was effective in improving knee flexion during swing phase and the energy cost of walking in stroke patients with SKG.[3,4] Robertson et al.[2] also declared significant increase in knee flexion during the swing phase after onabot injection into the rectus femoris muscle. However, none of these studies included a placebo group.[2]

Therefore, the aim of this placebo-controlled trial was to compare the efficacy of onabot injection into that rectus femoris muscle with that of placebo in the treatment of hemiplegic stroke patients presenting with SKG by using three-dimensional gait analysis and indirect calorimeter.

## METHODS

### Subjects

A total of 25 ambulatory hemiplegic stroke patients, 14 men and 11 women, with SKG were enrolled in the present study. The diagnosis of stroke was based on clinical features consistent with stroke and supportive computerized tomography or magnetic resonance imaging. Inclusion criteria were spastic hemiparesis secondary to stroke, at least 6 mos after stroke, lack of knee flexion during the swing phase, and ability to walk without ankle foot orthosis and independently. The exclusion criteria were inability to walk on a treadmill for sufficient time to complete a metabolic analysis, orthopedic surgery or casting to lower limbs, onabot or phenol neurolysis within the past year, presence of other causes of SKG such as considerable hip and knee flexor weakness (as much as to restrain knee flexion at swing), decreased ankle plantar flexion moments and presence of knee, hip, and ankle contracture. None of the patients performed physical therapy during the study. Ongoing medications were kept unchanged throughout the study. This study was approved by the local ethics committee, and all patients provided written informed consent.

The first 15 consecutive patients providing the criteria received 100–125 U of onabot (diluted with 0.09% saline, 100 U/2 ml) into the rectus femoris muscle through four points, with the guidance of electrical stimulation (5 mA), and were regarded as Group 1. The location of needle was also confirmed through flexing and extending the knee. The next ten consecutive patients providing the criteria received 2 ml of 0.09% saline into rectus femoris muscle in the same way and were regarded as Group 2. Only the patients were blinded to group assignment.

All measurements were done 1 to 3 days before and 2 mos after injection.

### Clinical and Functional Assessment

Hip, knee, and ankle joint range of motion was evaluated to check for contractures. Spasticity of the rectus femoris muscle was evaluated using the Modified Ashworth Scale.[12] Functional ability of each subject was assessed using the 10-m walk test[13] and 6-min walk test.[14]

### Gait Measurements

Gait was assessed using a three-dimensional, seven-camera, VICON 512 motion measurement system (Oxford Metrics Ltd., Oxford, UK). The VICON Clinical Manager software was used for calculating and plotting data. Fifteen reflective markers were placed on specific anatomic landmarks bilaterally of the subject's pelvis, thighs, shanks, and feet according to the marker protocol of Davis et al.[15] Anthropometric measures of height, weight, leg length, and

width of ankles and knees were taken for appropriate anthropometric scaling. After three or five times of practice in the laboratory, each subject was instructed to walk at a self-selected speed along a walkway with two force plates embedded in the floor. As many walks as necessary were carried out by each patient to achieve a clean trial on at least three occasions.

Selected kinematic and temporal-spatial parameters were used to determine the effect of treatment on gait. The following items were analyzed as kinematic parameters: maximum knee flexion at swing, knee extension at midstance, and dynamic knee range of motion (ROM) during a gait cycle. The last one was calculated by taking away maximum knee extension at stance from maximum knee flexion at swing. Gait velocity (meters per second), step length (centimeters), stride length (centimeters), and cadence (steps per minute) were recorded as temporal-spatial parameters of three-dimensional gait analysis.

### Energy Expenditure

Walking energy expenditure measurements were performed through breath-by-breath method using an open-circuit indirect calorimeter (Vmax 29c; Sensormedics, USA). After receiving an introduction, each patient practiced using the mask and treadmill beforehand. After an adequate rest period with the facemask, the test was performed for 5 mins of treadmill walking at a speed of 0.5 m/sec. It has been known that after 2 mins of submaximal walking, the patient can attain a steady state condition.[16] Afterward, aerobic demand ($\dot{V}O_2$) was determined from an expired air sample collected during the final 2 mins of each 5-min walk. Gait analysis and energy expenditure measurements were carried out on the same day with enough resting periods.

SPSS v15 for Windows was used for statistical analysis. Mann-Whitney *U* and Wilcoxon tests were used for statistical analysis. In addition, Pearson Correlation was used to analyze correlations. $P < 0.05$ value was accepted for significance.

## RESULTS

The procedure was well tolerated by all patients, and all of them completed the study. None of the subjects in both groups declared adverse events or complications of injection. The mean age of patients who received onabot (seven women and eight men) was 53.86 ± 14.74 yrs and those who received placebo (four women and six men) was 59.00 ± 8.11 yrs. Patient demographics are shown in Table 1. Groups were similar in terms of age, sex, type of stroke, hemiplegic side, and duration of stroke ($P > 0.05$). Group 1 received 113.33 ± 12.90 U of onabot.

**TABLE 1** Patient characteristics

| | Group 1 | Group 2 |
|---|---|---|
| Age, yrs | 53.86 ± 14.74 | 59.00 ± 8.11 |
| Sex, *n* (%) | | |
| Female | 7 (46.7) | 4 (40.0) |
| Male | 8 (53.3) | 6 (60.0) |
| Type of stroke, *n* (%) | | |
| Ischemic | 12 (80.0) | 8 (80.0) |
| Hemoragic | 3 (20.0) | 2 (80.0) |
| Hemiplegic side, *n* (%) | | |
| Right | 9 (60.0) | 5 (50.0) |
| Left | 6 (40.0) | 5 (50.0) |
| Duration of stroke, mos | 14.59 ± 7.15 | 13.41 ± 7.02 |

### Clinical and Functional Assessment

At study onset, no significant differences were observed between the groups with respect to rectus femoris muscle spasticity level, 10-m walk test, and 6-min walk test ($P > 0.05$); however, all of these parameters improved significantly in Group 1 after treatment ($P < 0.05$). Besides, no significant changes were observed in Group 2 after treatment ($P > 0.05$) (Table 2). Moreover, rectus femoris spasticity in onabot group was significantly improved after treatment when compared with placebo ($P < 0.05$) (Table 3). In addition, we did not observe significant difference in muscle weakness according to the Medical Research Council scale in both groups after treatment ($P < 0.05$).

### Gait Measurements

At the study, onset no significant differences were observed between the groups with respect to maximum knee flexion at swing and minimum knee flexion at stance ($P > 0.05$); however, maximum knee flexion at swing increased significantly in Group 1 after treatment ($P < 0.05$). Besides, no significant changes in maximum knee flexion at swing were observed in Group 2 after treatment ($P > 0.05$). Moreover, maximum knee flexion at swing in Group 1 was significantly higher than Group 2 at 2 mos posttreatment ($P < 0.05$). In addition, the ROM of knee joint in a gait cycle increased significantly in Group 1 after treatment ($P < 0.05$), but no significant changes were observed in Group 2 ($P > 0.05$) (Table 3). In addition, improvement of ROM of knee joint is positively

**TABLE 2** Clinical and functional assessments

| | Group 1 | | Group 2 | | Group 1 *vs.* Group 2 |
|---|---|---|---|---|---|
| | Mean ± SD | *P* | Mean ± SD | *P* | *P* |
| Spasticity level (MAS) Of rectus femoris | | | | | |
| Baseline | 2.46 ± 0.63 | | 2.40 ± 0.51 | | 0.087 |
| 2 mos after treatment | 1.40 ± 0.50 | <**0.001**[a] | 2.30 ± 0.82 | 0.739[a] | **0.007** |
| 10-m walk test, secs | | | | | |
| Baseline | 31.00 ± 20.20 | | 28.30 ± 16.55 | | 0.956 |
| 2 mos after treatment | 23.40 ± 16.10 | **0.001**[a] | 28.47 ± 16.47 | 0.336[a] | 0.291 |
| 6-min walk test, m | | | | | |
| Baseline | 165.20 ± 128.27 | | 161.00 ± 111.46 | | 0.222 |
| 2 mos after treatment | 208.20 ± 153.28 | **0.001**[a] | 163.30 ± 117.42 | 0.778[a] | 0.868 |

[a]Baseline *vs.* 2 mos after treatment.
Items in boldface are statistically significant.
MAS, Modified Ashworth Scale.

correlated with the improvement of knee flexion during swing ($P < 0.001$, $r = 0.803$).

Temporal-spatial parameters of both study groups were similar at baseline and 2 mos after treatment; none of the parameters changed after treatment in both groups ($P > 0.05$).

### Energy Expenditure

Table 3 shows the $\dot{V}o_2$ evaluations of the patients. There was no significant difference between the two study groups at the baseline evaluation of oxygen consumption. On the contrary, oxygen consumption rates of Group 1 were significantly decreased compared with Group 2 at 2 mos posttreatment ($P < 0.05$). Oxygen consumption of Group 1 improved significantly ($P < 0.05$); however, no significant changes were observed in Group 2 at the end of follow-up period ($P > 0.05$) (Table 3).

## DISCUSSION

The present study's findings indicate that onabot injected into the rectus femoris muscle had beneficial effects, as compared with placebo in hemiplegic stroke patients with SKG. The primary findings are that onabot treatment significantly improved knee kinematics and decreased energy expenditure during walking and also reduced muscle tone and improved functional assessment findings, whereas the placebo did not.

The effectiveness of onabot in reducing poststroke muscle hypertonia in adults has been reported.[17–20] In addition, the ability of onabot to increase knee flexion during swing and to decrease

**TABLE 3** Knee joint kinematics (in degrees) and oxygen consumption

| | Group 1 | | Group 2 | | Group 1 *vs.* Group 2 |
|---|---|---|---|---|---|
| | Mean ± SD | *P* | Mean ± SD | *P* | *P* |
| Maximum knee flexion at swing | | | | | |
| Baseline | 16.81 ± 6.53 | | 16.34 ± 3.83 | | 0.934 |
| 2 mos after treatment | 23.93 ± 11.60 | **0.002**[a] | 15.10 ± 3.84 | 0.092[a] | **0.033** |
| Maximum knee extension at stance | | | | | |
| Baseline | −1.27 ± 9.50 | | −1.23 ± 6.31 | | 0.598 |
| 2 mos after treatment | −0.74 ± 9.32 | 0.394[a] | −0.82 ± 5.89 | 0.441[a] | 0.739 |
| Knee range of motion in a gait circle | | | | | |
| Baseline | 18.09 ± 10.21 | | 17.09 ± 7.04 | | 0.956 |
| 2 mos after treatment | 24.92 ± 13.90 | **0.003**[a] | 16.80 ± 6.11 | 0.237[a] | 0.134 |
| Oxygen consumption ($\dot{V}o_2$), J/kg per meter | | | | | |
| Baseline | 5.47 ± 1.13 | | 5.68 ± 0.82 | | 0.639 |
| 2 mos after treatment | 4.64 ± 1.56 | **0.010**[a] | 5.74 ± 0.96 | 0.549[a] | **0.026** |

[a]Baseline *vs.* 2 mos after treatment.
Items in boldface are statistically significant.

energy expenditure in stroke patients with SKG has been shown in several studies.[2–4] Stoquart et al.[4] reported a gain of 5 degrees in peak knee flexion during swing and a decrease in energy cost of 0.8 J/kg per meter during walking in response to 200 U of onabot injected into the rectus femoris muscle. Caty et al.[3] reported that 200 U of onabot injected into the rectus femoris muscle resulted in a 5-degree increase in peak knee flexion and a decrease in energy cost of 0.9 J/kg per meter. Furthermore, Robertson et al.[2] reported an increase in knee flexion of 8 degrees during swing after injection of 200 U of onabot. The improvements reported in these studies were all statistically significant.[2–4] Based on these reports of the efficacy of 200 U of onabot, we used 100–125 U of onabot in the present study to determine the effectiveness of the lower dose. We observed significant improvement in knee flexion (7 degrees average) during swing and a reduction in energy cost of 0.8 J/kg per meter in response to an injection of 100–125 U of onabot into the rectus femoris muscle.

The study also demonstrated significant improvements in rectus femoris muscle tone and in 10-m and 6-min walk test scores.[3] Our findings in the onabot group are comparable with the literature. It was reported that walking speed was a reliable and objective yet inexpensive method of monitoring gait rehabilitation in hemiplegic patients.[21–23] Therefore, the increasing gait speed in the onabot group may indicate an improvement of ambulation.

To our knowledge, the present study is the first to compare the efficacy of onabot and placebo injection into the rectus femoris muscle in hemiplegic stroke patients with SKG by using three-dimensional gait analysis and an indirect calorimeter.

Moreover, we introduced the ROM of the knee joint in a gait cycle in this study. To our knowledge, this parameter has not been used previously while evaluating knee kinematics in hemiplegic stroke patients with SKG. According to present study, the ROM of knee joint in a gait cycle improved significantly after onabot injection, but there seems to be no change after placebo injection. In addition, positive correlation between the improvement of ROM of knee joint and the improvement of knee flexion during swing may indicate that this new parameter could also be used in SKG patients for dynamic evaluation of knee joint using three-dimensional gait analysis.

Although the 10-m and 6-min walk test scores of patients who received onabot injection improved significantly, no changes were detected in the temporal-spatial parameters of these patients in three-dimensional gait analysis. This contradiction might stem from the fact that the patients were required to walk as quick as possible but without risking their safety during the 10-m and 6-min walking tests. Similarly, the fact that they were inquired to walk at a self-selected walking speed during three-dimensional gait analysis might be the reason.

Previous studies also reported no significant improvements in temporal-spatial parameters.[2–4] Thus, our results regarding tempo-spatial parameters are comparable with the literature.

The present study does have some limitations, primarily the small patient group and the lack of randomization, as well as the lack of double-blind design. However, a potential bias would have ensued because of the fact that the physician who performed the injections was not blinded. Other limitations are the lack of dynamic electromyographic evaluation of the rectus femoris muscle and long-term follow-up. Dynamic electromyographic evaluation of the rectus femoris muscle during three-dimensional gait analysis could be useful for identifying alterations in muscle activity after onabot injection. Nevertheless, the present study's results are noteworthy.

## CONCLUSIONS

Our results showed the superiority of onabot on placebo in increasing knee flexion during the swing phase and decreasing energy expenditure. The application of onabot into the rectus femoris muscle of stroke patients who presented with SKG caused by rectus femoris muscle spasticity may be a treatment option to provide independent, safe, and less tiring ambulation, which is the most important rehabilitation goal of a patient with stroke. The results of this study should be confirmed by an randomized clinical trial with more subjects.

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