

ORIGINAL ARTICLE

Factors Influencing Gait Velocity Improvement Following Botulinum Toxin Injection for Spasticity of the Plantar Flexors in Patients with Stroke

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Objective: In patients with hemiplegia, botulinum toxin type A injection for ankle spasticity of the plantar flexors reportedly improves walking speed. This improvement may be affected by background factors and patient baseline physical performance. This study aimed to clarify the factors affecting gait velocity improvement after botulinum toxin type A injection. **Methods:** Background and evaluation data were collected for 60 patients with stroke who received botulinum toxin type A injection for spasticity of the plantar flexors. The patients were divided into improvement (n=27) and non-improvement (n=33) groups based on the gait velocity change from before injection to 2 weeks after injection. Logistic regression analysis was performed with the improvement and non-improvement groups as response variables and background data and evaluation data at baseline as explanatory variables. **Results:** The presence or absence of physical therapy following botulinum toxin type A injection (odds ratio: 7.82) was the only significant explanatory variable for gait velocity change. **Conclusion:** Background factors and physical performance at baseline did not affect gait velocity improvement after botulinum toxin type A injection. If botulinum treatment of the ankle plantar flexors in patients with stroke is targeted at walking performance improvement, then physical therapy following botulinum toxin type A injection should be an essential part of the treatment strategy.

Key words: rehabilitation; spasticity; walking speed

INTRODUCTION

According to the American Academy of Neurology and the Japan Stroke Society guidelines, botulinum therapy for leg spasticity not only alleviates spasticity but also improves walking and other active functions.^{1,2)} However, numerous studies have reported that walking speed does not increase following botulinum injection to the ankle plantar flexors in patients in the chronic phase of stroke.³⁻⁵⁾ A previous meta-analysis of studies that investigated the effects of botulinum neurotoxin type A (BoNT-A) treatment on

equinovarus deformity of the foot resulting from spasticity of the plantar flexors reported an improvement in walking speed; however, the change was small.⁶⁾ In contrast, other studies have reported a reasonable improvement in walking speed with physical therapy following BoNT-A injection to the ankle plantar flexors in chronic-phase stroke patients.⁷⁻¹⁰⁾ However, the mechanisms underlying the improvement in walking speed remain unclear.

Previously, we assigned patients who received BoNT-A injection alone to a monotherapy group and those who received BoNT-A injection followed by intensive physical therapy

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to a combination therapy group. We analyzed changes in electromyography and spatiotemporal parameters associated with gait in relation to the treatment intervention.¹¹⁾ We found that soleus activity decreased during the stance phase in the monotherapy group, along with a possible decrease in knee extension strength, which could have resulted in gait deterioration. In the combination therapy group, muscle activity associated with knee joint stability increased during the stance phase, and almost all patients showed an improvement in walking speed. However, the current study was a nonrandomized controlled trial; consequently, there was a bias in patient characteristics between the two treatment groups.

The gait velocity improvement following BoNT-A injection may be affected by patient characteristics and baseline physical performance; however, the type of factor that may be relevant is unclear. For example, the time since stroke onset may affect the changes in gait and spasticity associated with BoNT-A injection. Skeletal muscle atrophy and a shift to type II muscle fibers that occur after stroke can worsen walking performance.^{12,13)} Spasticity worsens with the contraction of soft tissue caused by relative immobilization and chronic disuse of paralyzed body parts.¹⁴⁾ It is assumed that these issues will worsen further over time. Furthermore, the number of BoNT-A injections previously administered may affect gait velocity improvement. In an earlier study that considered the effect of repeated botulinum therapy for spasticity of the plantar flexors in patients with stroke, the improvement rates of gait velocity and range of motion (ROM) of ankle dorsiflexion differed after the first and second or third injections.¹⁵⁾

The primary purpose of the current study was to determine whether the improvement in walking speed after BoNT-A injection for ankle spasticity of the plantar flexors is associated with physical therapy. The secondary purpose was to determine whether the background factors of the subjects are also associated with improved walking speed. We hypothesized that the relevant factors would include physical therapy following BoNT-A injection, physical function, the time since stroke onset, and the number of previous BoNT-A injections.

MATERIALS AND METHODS

Subjects

This study included 71 patients with chronic stroke who received BoNT-A (BOTOX; Allergan Pharmaceuticals, Dublin, Ireland) injections to improve talipes equinovarus resulting from ankle plantar flexor spasticity at Fukui Gen-

eral Hospital between September 2014 and October 2017. Patients were presented with the following two treatment options: BoNT-A injection monotherapy or BoNT-A injection followed by intensive physical therapy during hospitalization (**Fig. 1**). We did not recommend the physical therapy option; patients chose which of the two treatments to undergo based on their financial situation, family considerations, and employment status, among others. Subjects who chose BoNT-A monotherapy received no self-training or self-care instructions and were instructed to discontinue their usual outpatient rehabilitation until the efficacy of the monotherapy was evaluated 2 weeks after BoNT-A injection.

The inclusion criteria were as follows: (i) unilateral cerebral lesion; (ii) at least 6 months since stroke onset; (iii) walking ability of monitoring level or higher (could walk either without help or with a T-shaped cane); and (iv) spasticity of 1–3 points on the Modified Ashworth Scale (MAS)¹⁶⁾ for the ankle plantar flexors. The exclusion criteria were as follows: (i) a BoNT-A injection within the previous 4 months; (ii) diagnosed with cognitive impairment by a doctor (Mini-Mental State Examination [MMSE] score of less than 24 points); and (iii) under treatment for cardiovascular or orthopedic diseases.

All measurements and interventions were performed at the Nittazuka Medical Welfare Center. All subjects provided written informed consent for participation. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Nittazuka Medical Welfare Center (Nittazuka Ethics 30–43). This study used data from prospective studies registered for clinical trials (UMIN000030102).

BoNT-A Injection

The target muscles for BoNT-A injection were the medial head of the gastrocnemius, the lateral head of the gastrocnemius, the soleus, the tibialis posterior, the flexor digitorum longus, and the flexor hallucis longus. Injections to the flexor digitorum longus and the flexor hallucis longus were administered only to patients with marked involuntary toe flexion in the standing position. A total of 300 units of BoNT-A was administered via doses of 50 or 75 units per muscle for all patients. Ultrasound was used to monitor the positions of the needles and muscles during deep muscle injections. Immediately after injection, no treatment was performed to boost the effect of BoNT-A (e.g., electrical stimulation).

Physical Therapy Intervention

Physical therapy was performed for 2 weeks (two 1-h ses-

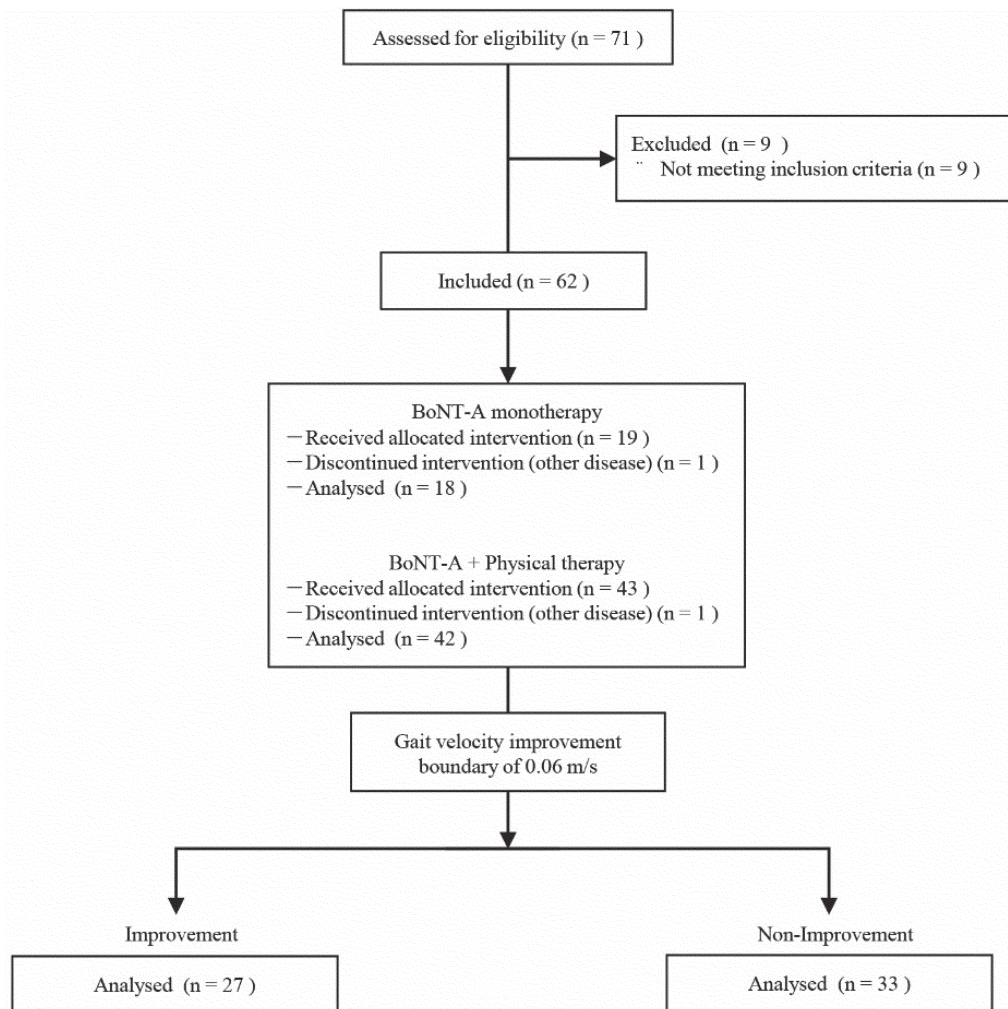


Fig. 1. Flow diagram of subject selection.

sions per day) starting from the day after BoNT-A injection. The patients who chose to receive intensive physical therapy following BoNT-A injections were treated by five randomly selected therapists who were blinded to the purpose of this study. The patients undergoing physical therapy followed the same physical therapy program. The program included (i) ankle plantar flexor stretching; (ii) leg resistance exercises; (iii) low-frequency electrical stimulation of the ankle dorsiflexors (PAS System GD-601; OG Wellness Technologies, Okayama, Japan); (iv) electromyographic feedback for ankle dorsiflexion exercises (MyoTrace; Noraxon, Scottsdale, AZ, USA); and (v) walking exercises, including walking on a level surface and on a treadmill with body weight support (Unweighing System; Biodex Medical Systems, Shirley, NY, USA).

Data Collection

Background data for each patient, including age, sex, body mass index, MMSE, paretic side, stroke type, number of months since stroke onset, Fugl-Meyer assessment of the lower limbs,¹⁷⁾ previous number of BoNT-A injections, and the total amount of BoNT-A administered per muscle were collected. The evaluation data were assessed by a single examiner for gait velocity and spasticity immediately before and 2 weeks after the BoNT-A injection. A straight walkway (16 m) was prepared for measuring gait velocity (including an additional 3 m at each end). The time required for each patient to walk 10 m was measured using a stopwatch. During the measurements, the patients were allowed to use walking canes, but use of a brace was only allowed if walking without a brace was not possible. Ankle plantar flexor spasticity was evaluated according to the MAS with the subject in the supine position with knee extension. A score of

1+ on the MAS was assigned as 2, and a score of 2 or higher was revised upward by 1. Additionally, the ROM of passive ankle dorsiflexion was measured in the supine position with knee extension, and the ROM of active ankle dorsiflexion was measured in the supine position with knee flexion to 90° using a goniometer.

Data Analysis

The change in gait velocity from before BoNT-A injection to 2 weeks after injection was calculated, and the patients were divided into improvement and non-improvement groups using a cutoff gait velocity change value of 0.06 m/s (Fig. 1). This value was used because the minimum detectable change in customary gait velocity for older adults with stroke ranges from 0.05 to 0.08 m/s in most studies.^{18–20} The background and evaluation data at baseline were compared between the improvement and non-improvement groups using the *t*-test, Mann–Whitney *U*-test, or chi-square test. The *d* values for the *t*-test, *r* values for the Mann–Whitney *U*-test, and Cramer's *V* for the chi-square test were calculated as effect size (ES) indices.²¹

To identify the factors affecting gait velocity improvement, logistic regression analysis was conducted with the improvement and non-improvement groups as response variables and the presence or absence of physical therapy following BoNT-A injection, the number of months since stroke onset, the number of previous BoNT-A injections, the gait velocity at baseline, and the MAS score at baseline as explanatory variables; the explanatory variables were chosen after consideration of previous studies.^{11–15} All analyses were performed using SPSS version 25 (IBM, Armonk, NY, USA), and the significance level was set at 5%. The sample size was determined using G* Power 3.1 (ES (f^2): 0.35; significance level: 5%; statistical power: 80%; number of predictors: 5; calculated total sample size: 43) (Heinrich Heine University, Düsseldorf, Germany).

RESULTS

Although 62 patients met the eligibility criteria, two dropped out because of poor physical health. Consequently, 60 patients were included in the current study (Fig. 1).

Of the 60 study patients, 27 were included in the improvement group and 33 were included in the non-improvement group based on the meaningful minimum change in walking speed (Fig. 1). The number of patients who underwent physical therapy following BoNT-A injection was significantly higher in the improvement group than in the non-improvement

group (improvement group: 25 of 27 patients, non-improvement group: 17 of 33 patients; $P < 0.001$, $ES = 0.446$). Additionally, the number of months since stroke onset was significantly lower in the improvement group than in the non-improvement group ($P = 0.008$, $ES = 0.690$) (Table 1). With regard to baseline data, gait velocity was significantly lower in the improvement group than in the non-improvement group ($P = 0.027$, $ES = 0.510$), and the MAS score ($P = 0.040$, $ES = 0.266$) was significantly higher in the improvement group than in the non-improvement group (Table 1).

Logistic regression analysis identified the presence or absence of physical therapy following BoNT-A injection as the only statistically significant explanatory variable for gait velocity change ($P < 0.05$; odds ratio: 7.824; 95% confidence interval: 1.389–44.060) (Table 2). No multicollinearity was detected, and goodness-of-fit was corroborated for the resulting one-variable model with the chi-square test at $P < 0.001$ and a Hosmer–Lemeshow test result of $P = 0.657$ (Table 2).

DISCUSSION

This study used prospective study data from those undergoing BoNT-A monotherapy and those undergoing BoNT-A injection followed by physical therapy. To examine the factors affecting gait velocity improvement after BoNT-A injection, the patient characteristics and evaluation data at baseline were compared between the improvement and non-improvement groups. Compared to the non-improvement group, the number of patients who underwent physical therapy following BoNT-A injection was higher, the number of months since stroke onset was lower, the gait velocity at baseline was lower, and the MAS scores at baseline were higher in the improvement group. These results had been predicted in previous studies,^{11–14} and these factors may affect gait velocity improvement. However, these findings could have been influenced by the non-random grouping of treatment methods because many patients in the improvement group received physical therapy. Logistic regression analysis was used to overcome this problem. The analysis indicated that the presence or absence of physical therapy following BoNT-A injection was the most significant factor affecting gait velocity improvement, and the statistical suitability of the logistic regression analysis was high.

The results of the current study indicate that patient characteristics and the evaluation data at baseline did not affect gait velocity improvement after BoNT-A injection to ameliorate plantar flexor spasticity. In a previous study¹⁵ in which BoNT-A was repeatedly injected four times in succes-

Table 1. Comparisons of background and baseline data between the improvement and non-improvement groups

			Improvement group (n=27)	Non-improvement group (n=33)	P-value	
Physical therapy following BoNT-A injection	(yes/no)		25/2	17/16	<0.001	^c
Age	(years)	Mean (SD)	56.5 (11.7)	56.5 (10.1)	n.s.	^a
Sex	(female/male)		8/19	7/26	n.s.	^c
BMI		Mean (SD)	23.4 (4.2)	24.0 (2.9)	n.s.	^a
MMSE		Median (QD)	30 (2)	30 (2)	n.s.	^b
Paretic side	(L/R)		13/14	11/22	n.s.	^c
Stroke type	(CI/ICH/SAH)		8/17/2	13/18/2	n.s.	^c
Number of months since onset		Mean (SD)	39.2 (31.3)	68.4 (49.8)	<0.01	^a
Assistive device (for assessment)	(none/T-cane/AFO)		4/18/3	7/22/4	n.s.	^c
Fugl-Meyer assessment LE		Median (QD)	19 (5)	20 (5)	n.s.	^b
Number of previous BoNT-A injections		Median (QD)	0 (0)	0 (1)	n.s.	^b
Total amount of BoNT-A administered	(units (n))	MG	1750 (27)	2025 (33)	n.s.	^c
		LG	1750 (27)	2025 (33)		
		Sol	1775 (27)	2100 (33)		
		TP	1775 (27)	2100 (33)		
		FDL	500 (10)	900 (18)		
		FHL	550 (11)	750 (15)		
Gait velocity	(m/s)	Mean (SD)	0.44 (0.19)	0.55 (0.24)	<0.05	^a
Modified Ashworth Scale		Median (QD)	3 (1)	3 (0)	<0.05	^b
ROM-passive df	(degrees)	Mean (SD)	2.8 (9.3)	3.5 (5.8)	n.s.	^a
ROM-active df	(degrees)	Mean (SD)	-9.1 (15.2)	-9.3 (14.7)	n.s.	^a

Comparisons between the improvement and non-improvement groups were carried out using the ^a*t*-test, the ^bMann-Whitney *U*-test, and the ^cchi-squared test.

BMI, body mass index; CI, cerebral infarction; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; AFO, ankle-foot orthosis; LE, lower extremity; MG, medialis gastrocnemius; LG, lateralis gastrocnemius; Sol, soleus; TP, tibialis posterior; FDL, flexor digitorum longus; FHL, flexor hallucis longus; df, dorsiflexion; n.s., no significant difference.

Table 2. Factors related to gait velocity improvement according to logistic regression

	OR	95%CI	P-value
Physical therapy following BoNT-A injection	7.824	1.4–44.1	<0.05
Number of months since onset	1.011	1.0–1.1	n.s.
Number of previous BoNT-A injections	1.339	0.4–4.0	n.s.
Baseline gait velocity	1.002	1.0–1.0	n.s.
Modified Ashworth Scale	0.453	0.2–1.3	n.s.

Cox-Snell R²: 0.274; Nagelkerke R²: 0.367.

Model chi-square test: P < 0.01; Hosmer-Lemeshow test: P = 0.657.

OR, odds ratio.

sion at 3- to 5-month intervals, the gait velocity improvement gradually decreased. We hypothesized that the number of previous BoNT-A injections would be a factor affecting gait velocity improvement. One of the exclusion criteria in this

study was receipt of a BoNT-A injection within the previous 4 months, and there were no criteria for continuous repetitive injections. Therefore, the number of previous BoNT-A injections may not affect gait velocity improvement unless

the injections are continuous and repeated.

The proportion of the overall amount of BoNT-A injected to each of the treated muscles did not differ between the improvement group and the non-improvement group. The unaffected side step length could be longer in patients who received the BoNT-A injection in the gastrocnemius because of improved ankle dorsiflexion; moreover, claw toe during the stance phase could be improved in patients who received the BoNT-A injection in their toe flexors. However, for patients who received BoNT-A monotherapy to treat plantar flexor spasticity in our previous study,¹¹⁾ the MAS and ankle dorsiflexion ROM of the affected side at rest improved, whereas, regardless of the injection site, the single-leg support time during walking, muscle activity of the affected side, and the step length of the unaffected side did not change. Although the ankle and toe alignment may be affected by the site of injection, its influence on walking performance may be small.

Because spasticity worsens over time,^{12–14)} we considered that BoNT-A as a spasticity therapy could be affected by the time since stroke onset. However, gait velocity improvement after BoNT-A injection was not affected by the time since stroke onset; furthermore, gait velocity improvement was not affected by the degree of spasticity of the plantar flexors at baseline. Essentially, the degree of spasticity of the plantar flexors may not affect walking performance in stroke patients. Spasticity is considered to be a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes,²²⁾ but the hyperactivation of short latency stretch reflexes from type Ia afferent neurons during walking, which is a characteristic of patients with hemiplegia, has little effect on lower limb functionality.²³⁾ In fact, there was no significant correlation between spasticity of the plantar flexor and walking speed.²⁴⁾ BoNT-A acts at the terminals of γ -motor neurons and reduces excitation of type Ia afferent neurons from muscle spindles,²⁵⁾ and there is a high possibility that BoNT-A has the effect of decreasing short latency stretch reflexes. Consequently, spasticity reduction by BoNT-A injection may have only a minor effect on walking performance. Therefore, it is reasonable that the time since stroke onset and the degree of spasticity at baseline did not affect gait velocity improvement following BoNT-A injection.

BoNT-A injection as a spasticity therapy is used to improve walking ability; however, it is possible that the result of BoNT-A injection may be the impairment of walking performance. The ankle plantar flexors, which are often the targets of BoNT-A injection, contribute to knee extension stability during the stance phase.²⁶⁾ Consequently, a decrease in walking speed¹¹⁾ and an increase in the frequency of falls²⁷⁾ could

result after BoNT-A injection to the plantar flexors. Indeed, some patients reported a deterioration in their walking ability following BoNT-A administration to the ankle plantar flexors.¹¹⁾ Walking speed was found to improve following 4 weeks of physical therapy (lower limb strengthening with resistive exercises, balance training, and gait training) in patients with chronic-phase stroke.²⁸⁾ After 2 weeks of resistance exercise for the lower limbs and walking exercises after BoNT-A injection to ameliorate plantar flexor spasticity, the co-activities of knee extensors and flexors during the walking stance phase increased along with an increase in the walking speed.¹¹⁾ After BoNT-A injection to the plantar flexors, performing resistance training and walking exercises is considered to be effective in preventing a decrease in knee joint stability. Although BoNT-A injection has a spasticity suppression effect, it may not improve walking performance by itself, and it is important to undergo physical therapy after injection. Additionally, intensive physical therapy performed immediately after BoNT-A administration is considered to be effective.

The present study had some limitations. All patients were in the chronic phase after stroke onset. Even if patients in the acute or recovery phase are considered, it is unclear whether background factors will influence the improvement in gait velocity following BoNT-A injection. Although it is advisable to include age and sex as confounding factors in the logistic regression analysis, the suitability of the analysis decreased as the number of variables increased; therefore, we prioritized the inclusion of those variables with a high possibility of improving gait velocity. Whether the subject underwent physical therapy following BoNT-A injection was chosen by the subjects themselves. Therefore, it is possible that those who underwent physical therapy were originally highly motivated to exercise, and this factor may have affected the improvement of gait velocity. Moreover, physical therapy in this study was intensively performed for 2 weeks. Even if the duration and frequency of physical therapy were changed, it is unknown whether these variables would be selected as factors affecting gait velocity improvement following BoNT-A injection. Finally, no group received physical therapy alone. Consequently, we cannot clarify the synergistic effects of BoNT-A injection and physical therapy following injection.

In this study, logistic regression analysis identified only the presence or absence of physical therapy after injection as a factor affecting gait velocity improvement after BoNT-A therapy; gait velocity improvement was not influenced by any background factors. The results of this study underline

the reliability of gait velocity improvement in those who receive physical therapy following BoNT-A injection. If botulinum treatment of the ankle plantar flexors in patients with stroke is targeted at improved walking performance, then physical therapy following BoNT-A injection appears to be an essential part of the treatment strategy.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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