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ORIGINAL ARTICLE

How effective is physical therapy for gait muscle activity in hemiparetic patients who receive botulinum toxin injections?

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ABSTRACT

BACKGROUND: Administration of botulinum neurotoxin A (BoNT-A) to the ankle plantar flexors in patients with hemiplegia reduces the strength of knee extension, which may decrease their walking ability. Studies have reported improvements in walking ability with physical therapy following BoNT-A administration. However, no previous studies have evaluated from an exercise physiology perspective the efficacy of physical therapy after BoNT-A administration for adult patients with hemiplegia.

AIM: To investigate the effects of physical therapy following BoNT-A administration on gait electromyography for patients with hemiparesis secondary to stroke.

DESIGN: Non-randomized controlled trial.

SETTING: Single center.

POPULATION: Thirty-five patients with chronic stroke with spasticity were assigned to BoNT-A monotherapy (N.=18) or BoNT-A plus physical therapy (PT) (N.=17).

METHODS: On the paralyzed side of the body, 300 single doses of BoNT-A were administered intramuscularly to the ankle plantar flexors. Physical therapy was performed for 2 weeks, starting from the day after administration. Gait electromyography was performed and gait parameters were measured immediately before and 2 weeks after BoNT-A administration. Relative muscle activity, coactivation indices, and walking time/distance were calculated for each phase.

RESULTS: For patients who received BoNT-A monotherapy, soleus activity during the loading response decreased 2 weeks after the intervention ($P<0.01$). For those who received BoNT-A+PT, biceps femoris activity and knee coactivation index during the loading response and tibialis anterior activity during the pre-swing phases increased, whereas soleus and rectus femoris activities during the swing phase decreased 2 weeks after the intervention ($P<0.05$). These rates of change were significantly greater than those for patients who received BoNT-A monotherapy ($P<0.05$).

CONCLUSIONS: Following BoNT-A monotherapy, soleus activity during the stance phase decreased and walking ability either remained unchanged or deteriorated. Following BoNT-A+PT, muscle activity and knee joint stability increased during the stance phase, and abnormal muscle activity during the swing phase was suppressed.

CLINICAL REHABILITATION IMPACT: If botulinum treatment of the ankle plantar flexors in stroke patients is targeted to those with low knee extension strength, or if it aims to improve leg swing on the paralyzed side of the body, then physical therapy following BoNT-A administration could be an essential part of the treatment strategy.

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KEY WORDS: Botulinum toxins - Electromyography - Stroke - Gait.

Spasticity is a significant sequela in patients with post-stroke hemiplegia, and it occurs in approximately 38% of patients within 12 months of stroke.[1] Numerous randomized, comparative studies have been conducted regarding botulinum therapy for the treatment of spasticity, and a dramatic increase in the use of botulinum neurotoxin type A (BoNT-A) was subsequently noted.[2] According to the guidelines of the American Academy of Neurology and the

Japan Stroke Society, botulinum therapy for leg spasticity not only alleviates spasticity but also promotes improvements in walking and other active functions.[3, 4] Furthermore, a meta-analysis of studies that investigated the effects of botulinum neurotoxin type A (BoNT-A) treatment for equivarus deformity of the foot due to leg spasticity reported improvements in walking speed.[5] However, the meta-analysis included numerous studies in which physical therapy was performed following BoNT-A administration. Conversely, numerous studies reported that walking speed did not increase following botulinum administration to the ankle plantar flexors in patients with chronic phase stroke.[6-8] Furthermore, a previous study in which the only intervention was botulinum administration to the ankle plantar flexors reported no changes in the spatiotemporal parameters of walking.[9]

A meta-analysis that assessed the safety of BoNT-A therapy indicated that the most frequent adverse event was localized muscle weakness.[10] Studies have also reported increases in the frequency of falls associated with muscle weakness following BoNT-A administration to the ankle plantar flexors.[11] In a previous study, some patients reported deterioration in their walking ability following BoNT-A administration to the ankle plantar flexors.[9] Ankle plantar flexors contribute to stability of knee extension during the stance phase;[12] therefore, decreased walking ability following BoNT-A administration is possible. Deteriorations in gait may also be secondary to the physiological mechanism of action of BoNT-A rather than muscle weakness. When BoNT-A is administered to skeletal muscles, it enters the motor neurons in the spinal cord by retrograde axonal transport, thereby affecting Renshaw cells, which control recurrent inhibition.[13] For patients with hemiplegia, the motor neurons of the quadriceps femoris undergo excitatory synaptic stimulation via the soleus recurrent inhibition pathway, resulting in involuntary coactivation.[14] Therefore, following BoNT-A administration to the soleus, the activity of Renshaw cells is suppressed and the H-reflex of vastus lateralis is reduced.[15] As a result of these mechanisms, BoNT-A administration to the ankle plantar flexors in patients with hemiplegia reduces knee extension strength, which in turn increases the risk of falls.

Studies of physical therapy including leg resistance exercises, walking training, functional electrical stimulation of the ankle dorsiflexors, and biofeedback following BoNT-A administration have reported improvements in walking ability.[16-19] However, the improvements were based on simple parameters such as walking speed; therefore, the mechanisms underlying these improvements remain uncertain. No previous study has investigated from the point of view of exercise physiology the efficacy of physical therapy following BoNT-A administration for adult patients with hemiplegia.

This study aimed to investigate the effects of BoNT-A administration to the ankle plantar flexors combined with physical therapy on gait electromyography for adult stroke patients. We hypothesized that this combination therapy would increase the activities of muscles other than the ankle plantar flexors.

Materials and methods

Subjects

Fifty-eight patients with chronic stroke who received botulinum toxin A (BOTOX®; Allergan Pharmaceuticals, Dublin, Ireland) for lower limb spasticity at Fukui General Hospital between September 2014 and October 2016 were recruited for this study. The inclusion criteria were as follows: 1) unilateral cerebral lesions; 2) at least 6 months since the onset of stroke; 3) walking ability of monitoring level or higher (can walk either without help or with a T-shaped cane, without leg braces); 4) walking speed of 0.1-1 m/s; and 5) spasticity of at least 1+ on the modified Ashworth scale (MAS) in the ankle plantar flexors.

The exclusion criteria were as follows: 1) passive ankle dorsiflexion range of motion (ROM) ≤0; 2) higher cognitive dysfunction that can hinder the intervention and/or evaluation; 3) cardiovascular diseases that restrict exercise; and 4) BoNT-A administration within the previous 4 months.

We presented two treatment strategies to 35 patients who were finally included, BoNT-A administration alone (BoNT-A monotherapy) and intensive physical therapy following BoNT-A administration (BoNT-A+PT). Patients were asked to choose their treatment; subsequently, they were administered BoNT-A monotherapy (N.=18) or BoNT-A+PT (N.=17) (Figure 1).

All measurements and interventions were performed at Fukui General Hospital. This study was approved by the Ethical Review Committee of the hospital (approval no.: Nittazuka Ethics 26-4). All subjects provided written informed consent.

BoNT-A administration

The target muscles for BoNT-A administration were the medial head of the gastrocnemius, lateral head of the gastrocnemius, soleus, tibialis posterior, flexor digitorum lon-

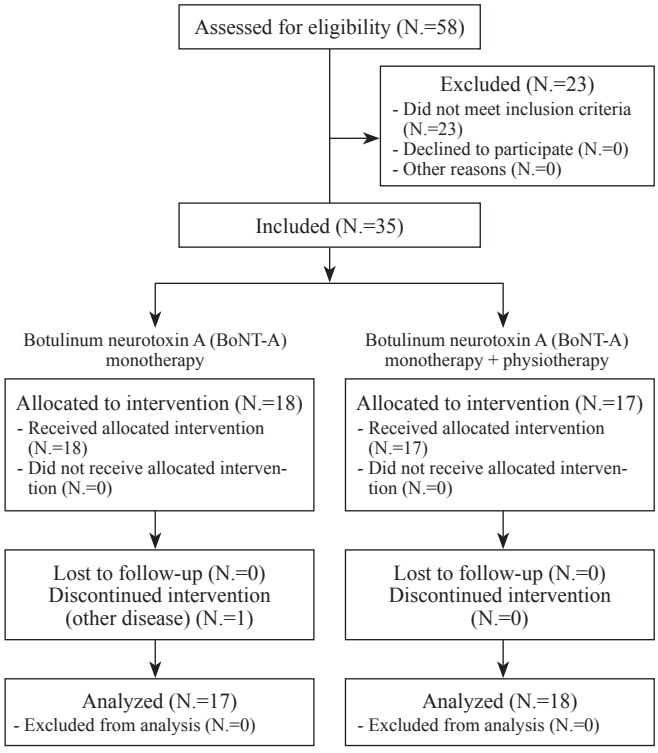

Figure 1.—Flow diagram of the study design and the processes.

gus, and flexor pollicis longus. The administration site was selected according to each patient's condition. A total of 300 units were administered per muscle, with a minimum dose of 50 units. Ultrasound was used to monitor the positions of the needles and muscles during administration to the deep muscles.

Physical therapy intervention

Physical therapy was performed for 2 weeks (two 1-hour sessions per day), starting from the day after BoNT-A administration. All patients were randomly treated by three therapists who were blinded to the purpose of this study. The same physical therapy program was followed for each patient. It included the following: 1) stretching of the ankle plantar flexors; 2) leg resistance exercises; 3) low-frequency electrical stimulation (PAS System GD-601; OG Wellness Technologies Co., Ltd., Okayama, Japan) of the ankle dorsiflexors; 4) electromyographic feedback (MyoTrace; Noraxon Inc., Scottsdale, AZ, USA) for ankle dorsiflexion exercises; and 5) walking exercises, including walking on a level surface and treadmill with body weight support (Unweighing System; Biodex Medical Systems Inc., Shirley, NY, USA).

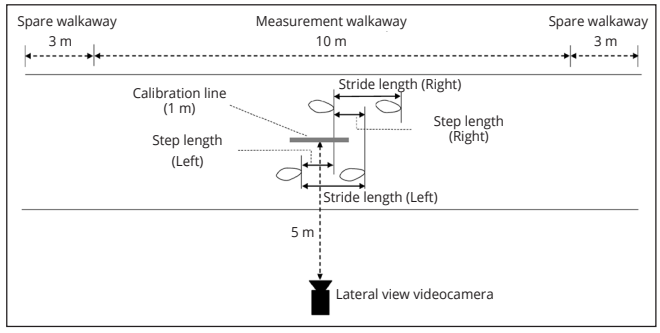

Figure 2.—Layout of the walkway used for measuring electromyography and spatiotemporal parameters during gait.

Evaluation

The evaluations were performed immediately before and 2 weeks after BoNT-A administration by a single examiner. The primary outcome assessment included electromyography and determination of spatiotemporal parameters during gait; the secondary outcome assessment included determination of the spasticity of ankle plantar flexors and patient satisfaction.

Electromyography was performed and spatiotemporal parameters were evaluated at a comfortable walking speed and mode. A straight walkway (16 m) was prepared for measuring the walking distance (including an extra 3 m at each end). A video camera (HD Pro WebCamera; Logicool, Inc., Tokyo, Japan) with a sampling frequency of 30 Hz was set at 5 m lateral to the midpoint of the walkway, and a 1-m line was drawn at the midpoint of the walkway (Figure 2). The time taken by each patient to walk 10 m was measured using a stopwatch. During the measurements, the subjects wore shoes and were allowed to use walking canes, but not leg braces.

TELEmyo DTS (Noraxon Inc.) was used for electromyographic recording. The sampling frequency was 1500 Hz and the bandpass filter was set at 10-500 Hz. Electromyography was assessed in the following five muscles on the paralyzed side of the body: tibialis anterior, soleus, medial head of the gastrocnemius, rectus femoris, and biceps femoris. Muscle action potential was induced using bipolar leads. Skin impedance was reduced to no more than 10 kΩ using alcohol-soaked cotton swabs and Abrasive (Skin Pure; Nihon Kohden Co., Ltd., Tokyo, Japan). Ag-AgCl electrodes (EM-272; Noraxon Inc.) were positioned 2 cm apart and were placed on positions recommended by the SENIAM (Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscle) project.[20] Foot switches were placed on the soles of both feet (4 points

for each foot). Time axes of all devices were matched using synchronization and optical signals.

Spasticity of the ankle plantar flexors was evaluated based on the MAS and clonus scores in the supine position. Scores of 1+ on the MAS were assigned as 2, and scores of 2 and higher were revised upward by 1. The clonus score was recorded in five stages according to the duration of the ankle clonus (0, no clonus can be induced; 1, clonus lasting for 1-4 seconds; 2, 5-9 seconds; 3, 9-15 seconds; 4, >15 seconds.[21] Additionally, ROM of passive and active ankle dorsiflexion were measured using a goniometer with the patient in the supine position and the knee joint flexed to 90°.

Patient satisfaction was evaluated 2 weeks after BoNT-A administration using the global rating of change scale (GRCS).[22] GRCS uses a questionnaire with the following question: "Has your walking changed in comparison with before treatment?," and the patient can choose an answer from 15 possible scores (-7 to 7).

Data analysis

MR3 (Noraxon Inc.) was used for analyzing the electromyographic waveforms. First, full-wave rectification of all raw waveforms was performed. The analysis interval was set to three continuous gait cycles around the middle part of the walkway. Initial contact was defined as the time of electric potential input from the foot switch on the paralyzed side of the body and was determined using synchronized video cameras, with monitoring for abnormal electric potentials from the foot switch due to leg-dragging during the swing phase. The duration of each of the three gait cycles was normalized after considering one gait cycle to be 100%. The arithmetic mean of the three gait cycles was obtained, and 1000-point amplitudes were calculated at intervals of 0.1%, followed by normalization using the mean amplitude of the entire gait cycle.

According to the report by Turns *et al.*,[23] muscle activities in each of the gait phases were distinguished based on the data from the foot switch, *i.e.*, the loading response, single support, pre-swing, and swing phases were calculated from the mean amplitudes of the respective phases (Figure 3). Additionally, according to Chow *et al.*,[24] coactivation indices were calculated for the tibialis anterior and gastrocnemius; they were calculated for the rectus femoris and biceps femoris by dividing the areas of overlaps between the flexor and extensor muscle amplitudes for each gait phase by the duration of the relevant gait phase (Figure 4). The temporal gait parameters were walking speed, which was calculated from the walking time (measured using a stopwatch), and cadence and gait cycle duration, which were calculated from the foot switch data. The asymmetry index for the swing phase duration was calculated as follows:[25]

Asymmetry index = swing phase duration on the paralyzed side / (swing phase duration on the paralyzed side + swing phase duration on the non-paralyzed side)

Spatial gait parameters were measured using the still image extracted from the video data when the subject passed through the intermediate points on the walkway.[26, 27] The image processing software ImageJ (National Institutes of Health, Bethesda, MD, USA) was used. Stride length was measured as the linear distance between successive points of heel contact of the same foot. Step length was measured as the linear distance between corresponding successive points of heel contact of opposite feet. The asymmetry index for step length was calculated as follows:[28]

Asymmetry index = step length on the paralyzed side / (step length on the paralyzed side + step length on the non-paralyzed side)

For all electromyographic data and gait parameters, the means obtained from three walking trials were calculated. Therefore, for electromyographic data and temporal parameters, the means calculated were derived from nine gait cycles (three gait cycles × three trials); for spatial parameters, the means calculated were derived from three gait cycles (one gait cycle × three trials).

Statistical analysis

For all the data evaluated, the differences in each treatment group before and after the intervention were compared using the paired *t*-test or Wilcoxon signed-rank test depending on the normality and scale of the data. In addition, the effect size (ES; ES=r value) and the 95% confidence intervals (95% CI) were calculated.[29] Differences between the treatment groups with respect to preintervention data and proportional changes before and after intervention ([post - pre] / pre) were evaluated using the *t*-test, Welch Test, and Mann-Whitney U Test. The software used for these analyses was SPSS version 20 (IBM Co., Ltd., Armonk, NY, USA), with a significance level of 5%.

Results

One patient who was receiving BoNT-A monotherapy discontinued therapy due to other medical reasons; therefore, a total of 17 patients received BoNT-A monotherapy (13

males and 4 females; mean age, 57.2 years; mean months since stroke onset, 75.2 months) and 17 received BoNT-A+PT (12 males and 5 females; mean age, 58.6 years; mean months since stroke onset, 39.8 months) (Figure 1, Table I). The total volume of BoNT-A administered to each muscle in both groups was approximately the same (Table I).

Baseline

No significant difference between groups was observed for age (P=0.523), but there was a significant difference between groups for mean months since stroke onset (P=0.020) (Table I). No significant differences in the baseline of all electromyogram data for tibialis anterior (loading response: P=0.291; single support: P=0.667; pre-swing: P=0.341; swing: P=0.713), soleus (P=0.300, P=0.437, P=0.262, and P=0.113, respectively), medial gastrocnemius (P=0.143, P=0.223, P=0.069, and P=0.052,

TABLE I.—*Baseline characteristics of patients in each group.*

	BoNT-A monotherapy (N.=17)	BoNT-A+PT (N.=17)
Age	57.2±10.7	58.6±10.5
Sex (female/male)	4/13	5/12
Type of stroke (CI/ICH/SAH)	6/10/1	6/10/1
Months since onset	75.2±51.2	39.8±37.7
Paretic side (L/R)	6/11	7/10
Fugl-Meyer assessment LE	21±3	19±6
Assistive device (none/t-cane/AFO)	3/11/13	2/13/14
Total amount of BoNT-A administered		
MG	1025 U	1025 U
Sol	1075 U	1050 U
FDL	500 U	450 U
LG	1025 U	1025 U
TP	1075 U	1050 U
FHL	400 U	450 U

BoNT-A: botulinum neurotoxin A; PT: physical therapy; CI: cerebral infarction; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; LE: lower extremity; AFO: ankle foot orthosis; MG: medialis gastrocnemius; LG: lateralis gastrocnemius; Sol: soleus; TP: tibialis posterior; FDL: flexor digitorum longus; FHL: flexor pollicis longus.

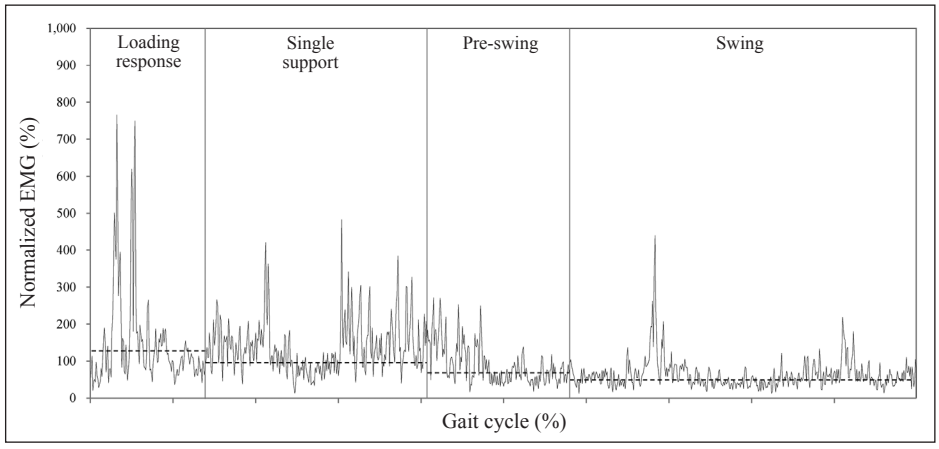

Figure 3.—Calculation of the mean amplitude for each gait phase.
The electromyographic amplitude in soleus, with normalized waveform, is shown. Broken lines indicate the calculated mean amplitudes in each gait phase.

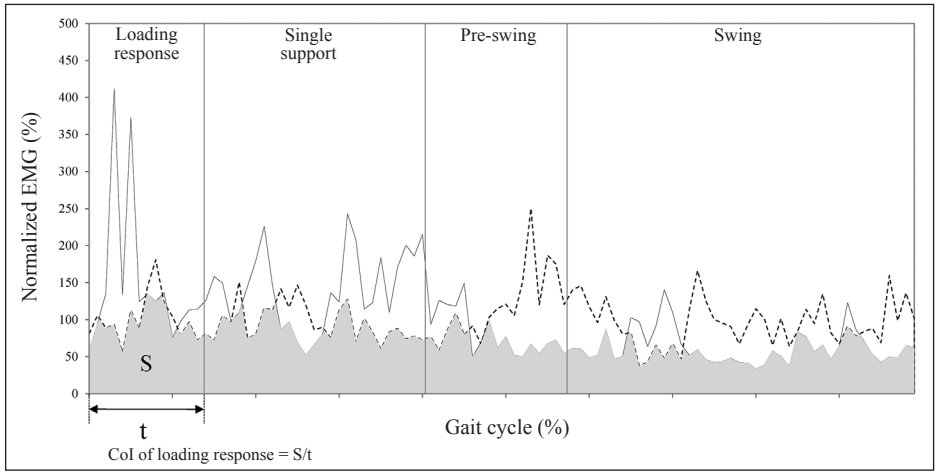

Figure 4.—Calculation of the coactivation indices for each gait phase.
The electromyographic amplitudes with normalized waveforms for the extensor muscles (broken lines) and flexor muscles (unbroken line). The areas of the parts of the two waveforms that overlap in each gait phase (gray: S) were calculated, and the co-activation index for each phase was calculated by dividing the respective area by the duration of each gait phase (t).

TABLE II.—*Comparisons of electromyogram data between BoNT-A monotherapy and BoNT-A+PT groups.*

Muscles	Gait phase	BoNT-A monotherapy (N.=17)			BoNT-A+PT (N.=17)			P value
		Pre	Post	Change rate	Pre	Post	Change rate	
TA	LR	95.9±24.6	104.3±28.8	9.8±20.5	107.8±38.5	99.3±33.3	-5.2±24.9	NS
	SS	67.7±17.8	64.0±26.9	-6.2±31.0	69.6±24.7	58.9±24.4*	-10.6±32.3	NS
	PSw	119.9±29.9	119.6±36.4	-0.7±14.0	110.1±29.4	124.7±40.0*	14.4±22.9	<0.05
	Sw	116.6±26.2	112.1±24.2	-1.4±19.8	112.6±35.9	117.1±23.5	13.7±41.1	NS
Sol	LR	154.8±35.8	140.7±30.3**	-8.0±12.2	142.9±30.0	142.7±29.6	1.4±19.0	NS
	SS	138.5±28.3	134.9±20.9	-1.0±13.6	130.3±32.5	130.3±30.2	2.7±20.6	NS
	PSw	62.4±18.1	75.3±22.0**	23.3±33.8	70.6±23.7	78.8±25.1	16.1±36.1	NS
	Sw	44.2±17.5	49.1±14.1	19.0±32.2	56.2±24.5	48.1±18.5*	-8.2±31.7	<0.05
MG	LR	153.4±31.4	148.5±33.9	-3.0±11.9	133.9±23.8	136.1±22.1	3.7±21.2	NS
	SS	123.8±18.4	127.1±16.7	3.4±11.5	114.1±26.6	120.8±21.0	8.5±18.2	NS
	PSw	62.5±19.4	65.9±20.2	7.7±23.6	74.5±17.9	76.8±15.1	7.0±28.1	NS
	Sw	60.3±19.2	58.5±19.7	-0.4±22.9	77.5±24.9	66.3±21.2*	-11.2±23.3	NS
RF	LR	151.2±27.9	157.9±31.8	6.3±21.5	135.1±43.5	149.6±41.4	7.4±42.3	NS
	SS	92.6±30.4	93.5±27.6	3.7±20.5	85.2±24.4	85.9±22.4	3.7±20.5	NS
	PSw	86.0±33.5	76.5±27.8	-5.4±37.0	96.2±36.8	90.7±36.3	-1.3±35.2	NS
	Sw	70.2±26.1	72.1±23.5	6.8±27.9	83.5±26.9	73.7±21.1*	-9.8±15.5	<0.05
BF	LR	174.0±32.8	169.5±42.9	-3.1±11.9	153.3±35.6	176.0±31.2*	25.6±61.0	<0.05
	SS	125.9±25.2	126.0±30.1	-0.4±8.8	122.0±37.2	109.7±35.2	-9.0±20.0	NS
	PSw	39.1±21.6	42.6±26.6	13.3±53.0	55.0±38.0	43.3±18.0	-5.4±45.5	NS
	Sw	61.0±26.6	61.8±29.7	3.4±24.7	69.7±28.0	71.0±30.7	2.8±24.2	NS

Values are normalized mean amplitudes (%) during each gait phase (mean±standard deviation).
Change rate = (post data - pre data) / pre data × 100.
P value: comparison of the change rate between BoNT-A monotherapy and BoNT-A+PT groups (*t*-test or Welch's *t*-test or Mann-Whitney U Test).
BoNT-A: botulinum neurotoxin A; PT: physical therapy; TA: tibialis anterior; Sol: soleus; MG: medial gastrocnemius; RF: rectus femoris; BF: biceps femoris; LR: loading response; SS: single support; PSw: pre-swing; Sw: swing; NS: no significant difference.
*P<0.05, **P<0.01 (pre *vs.* post, paired *t*-test or Wilcoxon signed-rank test).

TABLE III.—*Comparisons of the coactivation indices between BoNT-A monotherapy and BoNT-A+PT groups.*

Muscles	Gait phase	BoNT-A monotherapy (N.=17)			BoNT-A+PT (N.=17)			P value
		Pre	Post	Change rate	Pre	Post	Change rate	
TA-MG	LR	74.1±19.0	75.2±20.7	2.2±18.2	76.0±27.6	74.5±26.3	1.2±23.9	NS
	SS	56.6±13.1	56.0±20.0	-0.8±30.8	54.5±18.4	51.9±19.5	-0.8±33.2	NS
	PSw	46.3±15.3	48.7±13.9	8.3±20.0	53.7±14.7	54.8±15.0	8.4±51.9	NS
	Sw	48.2±12.1	48.4±10.7	3.5±20.5	55.4±14.2	52.1±13.7	-4.2±19.8	NS
RF-BF	LR	117.5±26.0	120.5±31.5	3.7±19.5	99.9±27.4	122.0±34.1*	32.3±65.8	<0.05
	SS	76.8±25.1	77.1±24.3	2.2±15.1	68.0±20.0	71.8±22.2	7.4±23.4	NS
	PSw	31.6±14.2	32.4±17.9	3.4±27.1	41.9±25.3	35.0±10.4	0.8±54.2	NS
	Sw	38.5±13.4	38.5±13.5	2.5±20.2	45.6±13.3	42.3±14.2	-7.0±16.1	NS

Values are coactivation indices (%) during each gait phase (mean±standard deviation).
Change rate = (post data - pre data) / pre data × 100.
P value: comparison of the change rate between BoNT-A monotherapy and BoNT-A+PT groups (*t*-test or Welch's *t*-test or Mann-Whitney U Test).
BoNT-A: botulinum neurotoxin A; PT: physical therapy; TA: tibialis anterior; Sol: soleus; MG: medial gastrocnemius; RF: rectus femoris; BF: biceps femoris; LR: loading response; SS: single support; PSw: pre-swing; Sw: swing; NS: no significant difference.
*P<0.01 (pre *vs.* post, paired *t*-test or Wilcoxon signed-rank test).

respectively), rectus femoris (P=0.163, P=0.438, P=0.278, and P=0.152, respectively), biceps femoris (P=0.091, P=0.729, P=0.147, and P=0.365, respectively), the co-activation index of the tibialis anterior and gastrocnemius (P=0.813, P=0.705, P=0.162, and P=0.117, respectively), and the coactivation index of the rectus femoris and biceps femoris (P=0.069, P=0.277, P=0.150, and P=0.135, respectively) between the treatment groups were found (Table II, III). No significant differences in the baseline of all spatiotemporal parameters of gait velocity (P=0.098), cadence (P=0.999), single gait cycle period (P=0.835), loading response period (P=0.221), single support period (P=0.161), pre-swing period (P=0.174), double-support period (P=0.134), swing period (P=0.736), swing period asymmetry index (P=0.312), stride length (P=0.053) and step length asymmetry index (P=0.061) between

TABLE IV.—*Comparisons of gait parameters between BoNT-A monotherapy and BoNT-A+PT groups.*

Assessment		BoNT-A monotherapy (N.=17)			BoNT-A+PT (N.=17)			P value
		Pre	Post	Change rate	Pre	Post	Change rate	
Gait velocity	(m/s)	0.57±0.20	0.59±0.18	5.5±17.0	0.46±0.20	0.54±0.16**	21.7±16.0	<0.01
Cadence	(steps/min)	81.3±18.0	81.7±15.7	1.3±7.9	81.3±20.7	87.2±17.3**	9.1±10.8	<0.05
1 stride period	(s)	1.55±0.35	1.52±0.31	-0.8±7.1	1.58±0.43	1.43±0.29**	-7.5±8.7	<0.05
LR period	(s)	0.25±0.16	0.23±0.13	-0.9±16.5	0.28±0.13	0.23±0.09†	-17.5±10.4	<0.01
SS period	(s)	0.41±0.09	0.41±0.06	2.0±10.2	0.37±0.09	0.36±0.06	0.2±12.8	NS
PSw period	(s)	0.28±0.13	0.28±0.12	2.2±14.3	0.34±0.15	0.29±0.11*	-9.9±15.9	<0.05
DS period	(s)	0.53±0.28	0.51±0.23	0.6±14.2	0.62±0.24	0.52±0.17†	-13.8±11.2	<0.01
Sw period	(s)	0.61±0.14	0.60±0.11	-1.0±8.3	0.59±0.17	0.55±0.11*	-5.2±10.1	NS
AI-Sw period		0.60±0.04	0.59±0.04	-1.0±4.0	0.61±0.05	0.60±0.04	-1.8±4.3	NS
Stride length	(cm)	83.4±19.6	83.6±16.6	1.6±10.1	69.6±20.5	76.6±18.4†	12.2±12.1	<0.01
AI-step length		0.51±0.07	0.52±0.06	0.6±6.3	0.57±0.10	0.53±0.06**	-5.7±6.4	<0.01

Values represent the mean±standard deviation.
*P<0.05, **P<0.01, †P<0.001 (pre *vs.* post, paired *t*-test or Wilcoxon signed-rank Test).
Change rate = (post data - pre data) / pre data × 100.
P value = comparison of the change rate between BoNT-A monotherapy and BoNT-A+PT groups (*t*-test or Welch's *t*-test or Mann-Whitney U Test).
BoNT-A: botulinum neurotoxin A; PT: physical therapy; LR: loading response; SS: single support; PSw: pre-swing; Sw: swing; DS: double support; AI: asymmetry index; NS: no significant difference.

TABLE V.—*Comparisons of ankle joint data between BoNT-A monotherapy and BoNT-A+PT groups.*

Assessment	BoNT-A monotherapy (N.=17)			BoNT-A+PT (N.=17)			P value
	Pre	Post	Change	Pre	Post	Change	
Modified Ashworth Scale	3 (0)	2 (0)†	-1 (0)	3 (0)	2 (0)**	-1 (0)	NS
Clonus Score	1 (1)	0 (1)*	0 (-1)	1 (4)	0 (1)**	-1 (3)	P<0.05
ROM-passive df	13.6±6.1	16.7±6.2**	3.1±3.4	13.9±6.9	20.8±6.0†	6.8±5.5	P<0.05
ROM-active df	-9.9±14.8	-4.5±14.1**	5.4±5.6	-6.4±16.2	-1.4±11.7**	5.0±7.0	NS

Values appear as mean±standard deviation or as median (quartile deviation). ROM is expressed in grades.
Modified Ashworth Scale: score of 1+ was assigned as 2, and scores of 2 and higher were revised upward by 1.
*P<0.05; **P<0.01; †P<0.001 (pre *vs.* post, paired *t*-test or Wilcoxon signed-rank Test).
Change = (post data - pre data).
P value: comparison of the change between BoNT-A monotherapy and BoNT-A+PT groups (*t*-test or Welch's *t*-test or Mann-Whitney U Test).
BoNT-A: botulinum neurotoxin A; PT: physical therapy; ROM: range of motion; df: dorsiflexion; NS: no significant difference.

the treatment groups were found (Table IV). No significant differences in the baseline of all ankle joint data for MAS (P=0.843), clonus score (P=0.127), passive ROM (P=0.875), and active ROM (P=0.511) between treatment groups were found (Table V).

Muscle activity during each gait phase

Of the patients who received BoNT-A monotherapy, the electromyographic amplitude in the soleus after the intervention decreased significantly during the loading response phase (P=0.005; ES=0.628; 95% CI: 0.049-0.235) and increased significantly during the pre-swing phase (P=0.002; ES=0.679, 95% CI: -0.203 to -0.055) (Table II). No other significant differences in electromyographic amplitudes were found after the intervention for these patients.

Of the patients who received BoNT-A+PT, the electromyographic amplitude in the tibialis anterior increased significantly during the pre-swing phase (P=0.035; ES=0.497; 95% CI: -0.282 to -0.011), whereas those in the soleus (P=0.047; ES=0.473; 95% CI: 0.001-0.160) and rectus femoris (P=0.022; ES=0.536; 95% CI: 0.016-0.179) decreased significantly during the swing phase, and that in biceps femoris increased significantly during the loading response phase (P=0.033; ES=0.506; 95% CI: -0.434 to -0.021) after the intervention. These rates of change were significantly greater than those for patients who received BoNT-A monotherapy (tibialis anterior: P=0.027; soleus: P=0.019; rectus femoris: P=0.040; biceps femoris: P=0.013) (Table II).

Furthermore, of those who received BoNT-A+PT, the coactivation index of the rectus femoris and biceps femoris after the intervention significantly increased during the loading response phase (P=0.006; ES=0.686; Z=2.741), and the rate of change was significantly greater than that for those who received BoNT-A monotherapy (P=0.048) (Table III).

Spatiotemporal gait parameters

For patients who received BoNT-A monotherapy, there were no significant differences after the intervention. For those who received BoNT-A+PT, gait velocity (P=0.002; ES=0.764; Z=3.148) and cadence (P=0.003; ES=0.663; 95% CI: -9.333 to -2.341) significantly increased after the intervention, and the rates of change for both parameters were significantly greater than those for patients who received BoNT-A monotherapy (gait velocity: P=0.002; cadence: P=0.023) (Table IV). Seven patients who received BoNT-A monotherapy and one who received BoNT-A+PT demonstrated decreased walking speed after the intervention.

For patients who received BoNT-A+PT, the durations of the single gait cycle (P=0.005; ES=0.635; 95% CI: 0.052-0.241), loading response phase (P<0.001; ES=0.856; Z=3.527), pre-swing phase (P=0.019; ES=0.569; Z=2.343), and double support phase (P<0.001; ES=0.810; Z=3.337) significantly decreased after the intervention; these rates of change were significantly greater than those of patients who received BoNT-A monotherapy (loading response: P=0.001; pre-swing: P=0.026; double support: P=0.003) (Table IV).

For patients who received BoNT-A+PT, stride length increased significantly (P<0.001; ES=0.724; 95% CI: -10.480 to -3.442) and step length asymmetry index decreased significantly (P=0.004; ES=0.638; 95% CI = 0.013-0.061) after the intervention, with the rate of change in both parameters being significantly greater than those of patients who received BoNT-A monotherapy (stride length: P=0.003; step length asymmetry index: P=0.007) (Table IV).

Muscle tone and ROM

For both treatment groups, MAS scores (BoNT-A monotherapy: P<0.001; ES=0.827; Z=3.408, BoNT-A+PT: P=0.002; ES=0.772; Z=3.180) and clonus scores (BoNT-A monotherapy: P=0.043; ES=0.491; Z=2.023, BoNT-A+PT: P=0.003; ES=0.712; Z=2.934) after the intervention significantly decreased, whereas passive ROM (BoNT-A monotherapy: P=0.002; ES=0.683; 95% CI: -4.888 to -1.347, BoNT-A+PT: P<0.001; ES=0.790; 95% CI: -9.635 to -4.012) and active ROM (BoNT-A monotherapy: P=0.001; ES=0.708; 95% CI: -8.275 to -2.549, BoNT-A+PT: P=0.010; ES=0.592; 95% CI: -8.613 to -1.387) after the intervention significantly increased compared with those before the intervention. Changes in clonus score and passive ROM due to the intervention were significantly greater for those who received BoNT-A+PT than for those who received BoNT-A monotherapy (P=0.024 and P=0.021, respectively) (Table V).

Patient satisfaction: GRCS

After the interventions, GRCS was higher for those who received BoNT-A+PT than for those who received BoNT-A monotherapy (BoNT-A monotherapy: median, 2; maximum, 4; minimum, -2; BoNT-A+PT: median, 3; maximum, 6; minimum, 0). Two subjects who received BoNT-A monotherapy reported deterioration in walking, whereas none who received BoNT-A+PT did.

Discussion

In this study, improvements in MAS score, clonus score, and ROM for both treatment groups were evaluated, and BoNT-A was found to be effective for inhibiting spasticity. There was a significant difference in the mean number of months since stroke onset between baseline groups, but it was considered that the results were not affected because both groups were in the chronic phase. With respect to gait evaluation, for patients who received BoNT-A monotherapy, changes in muscle activity were found only in the soleus, and no changes in the spatiotemporal parameters were observed. Additionally, approximately 40% of the patients demonstrated decreased walking speed and some reported gait deterioration. For those who received BoNT-A+PT, changes in muscle activity occurred in numerous muscles and changes in spatiotemporal gait parameters were observed; almost all subjects showed improvements in walking speed. Improvements in the spatiotemporal gait parameters in our study were similar to those reported in previous studies in which subjects with approximately the same severity of spasticity as that in our study patients underwent walking training after BoNT-A administration;[16, 30] however, the proportional change was markedly greater in our study, and the increase in walking speed reached 0.06 m/s,[31] which is the minimal difference for clinically significance. The duration of physical therapy in this study was shorter than that in previous studies;[16-19] nevertheless, physical therapy was performed for a longer duration each day. Furthermore, intensive physical therapy immediately after BoNT-A administration could have a greater effect on improving gait parameters than long-term physical therapy such as home exercises or that during hospital visits.

Electromyographic evaluation of gait showed that soleus activity during the loading response phase decreased following BoNT-A+PT, which is consistent with the find-

ings of Hesse *et al.*[32] BoNT-A acts at the terminals of γ-motor neurons and reduces the excitation of type Ia afferent neurons from muscle spindles;[33, 34] therefore, suppression of the stretch reflex during the initial contact time with equine gait is highly probable.

For patients who received BoNT-A+PT, despite receiving the same dose of BoNT-A as those who received BoNT-A monotherapy, no decrease in soleus activity was observed after the intervention. Additionally, increases were noted in biceps femoris activity as well as the coactivation index of the rectus femoris and biceps femoris. These findings, which were considered to be due to physical therapy, were similar to those reported by Mulroy *et al.*[35] The vertical force component of the floor reaction force is highest during the loading response phase; therefore, the stability of the knee joint during this phase is essential.[36] The increase in knee coactivation compensates for the decreased knee joint stability.[37] Therefore, an increase in knee coactivation without a decrease in soleus activity, which contributes to knee stability,[12] could reduce the risk of the knee giving way, which is associated with the adverse effects of BoNT-A.

For patients who received BoNT-A+PT, tibialis anterior activity increased during the pre-swing phase and soleus activity decreased during the swing phase after the intervention. Soleus activity during the pre-swing phase increased after BoNT-A monotherapy, whereas no increase in soleus activity was observed following BoNT-A+PT. Tang *et al.*[38] previously suggested that increased tibialis anterior activity after BoNT-A administration is due to the decreased excitation of type Ia centripetal neurons from the ankle plantar flexors, thereby reducing the reciprocal inhibition of the tibialis anterior. Therefore, the increase in tibialis anterior activity in this study could have been due to reduced reciprocal inhibition. Furthermore, increased tibialis anterior activity during the pre-swing phase may have contributed to the decrease in soleus activity during the swing phase.

Decreased knee flexion angle during the swing phase due to hyperactivation of the rectus femoris is a gait abnormality that generally occurs in stroke patients.[39, 40] BoNT-A is often administered to the rectus femoris to overcome this problem.[39, 40] However, decreased muscle activity during the stance phase after BoNT-A administration to the rectus femoris has been reported.[41] BoNT-A administration to the soleus acts on Renshaw cells at the spinal cord segment level, which reduces the activity of the quadriceps femoris.[15] Hence, there are concerns regarding potential decreased knee stability during the stance phase following BoNT-A administration. In our study, rectus femoris activity decreased during the swing phase for patients who received BoNT-A+PT, suggesting that the required increase in knee flexion angle during the swing phase could be achieved without increasing the risk of decreased knee stability during the stance phase.

Because soleus activity during the stance phase was decreased in patients who received BoNT-A monotherapy, it is possible that there were decreases in knee extension strength, which could result in gait deterioration. Physical therapy following BoNT-A administration could increase the muscle activity associated with knee joint stability, and it possibly has positive effects on muscle activities associated with leg swinging. If botulinum treatment of the ankle plantar flexors in stroke patients is targeted to those with low knee extension strength or aims to improve leg swing on the paralyzed side of the body, then physical therapy following BoNT-A administration could be an essential part of the treatment strategy. Additionally, intensive physical therapy performed immediately after BoNT-A administration is considered effective.

Limitations of the study

BoNT-A was administered to the deep muscles such as the tibialis posterior and flexor digitorum longus in some of the patients in this study, and the subsequent effects could not be confirmed by surface electromyography. Additionally, the effects of the changes in muscle activity on parameters of kinematics are unknown. Because physical therapy included multiple components such as resistance exercises, electrical stimulation, and walking training, the specific treatment that was responsible for the effects is unclear. Most patients in this study had moderately severe spasticity and movement disorders; therefore, the results would not necessarily be similar for stroke patients with mild or severe disabilities.

Conclusions

In this study, marked changes in muscle activity were observed in stroke patients who underwent physical therapy after BoNT-A administration to the ankle plantar flexors. These changes included increased biceps femoris activity and coactivation index of the rectus femoris and biceps femoris during the loading response phase; furthermore, they included increased tibialis anterior activity and decreased soleus and rectus femoris activities in the pre-swing and swing phases. Almost all patients in both treatment groups demonstrated improved walking speed,

and none reported gait deterioration. Physical therapy after BoNT-A administration increased the stability and leg swing capability of the knee. Therefore, it can possibly prevent deterioration in walking ability.

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