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Original Article

Effect of two doses of botulinum toxin type A on maximum plantar contact area in hemiplegic stroke patients with pes equinovarus

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ABSTRACT

Wada Y, Otsuka N, Kawate N, Moriyama H, Ezure H, Inoue Y. Effect of two doses of botulinum toxin type A on maximum plantar contact area in hemiplegic stroke patients with pes equinovarus. Jpn J Compr Rehabil Sci 2020; 11: 85–90.

Objectives: To quantitatively demonstrate the therapeutic effects of two doses of botulinum toxin type A (BoNT-A) on pes equinovarus in hemiplegic stroke patients.

Methods: The subjects of this study included eight chronic stroke patients who received two BoNT-A doses (mean dose interval: 136.0 (10.5) days) from April 2011 to March 2013 and underwent a sheet-type weight-bearing lower limb test. The maximum plantar contact area on the paralyzed side, ratio of maximum plantar contact areas on the paralyzed and non-paralyzed sides, and Modified Ashworth Scale (MAS) were measured before BoNT-A administration and 4 weeks after both the first and second doses.

Results: A significant increase in the maximum plantar contact area was observed after administration of the second dose compared to that of the first dose on the paralyzed side. Additionally, a significant increase was observed in the ratio of paralyzed/non-paralyzed maximum plantar contact areas after the administration of both the first and second doses compared to that before BoNT-A administration. MAS was observed to decline significantly after the administration of both the first and second doses compared to that prior to BoNT-A administration.

Conclusions: We suggest that comparison of the plantar contact area is useful for assessing the therapeutic effects of BoNT-A doses on pes equinovarus in hemiplegic stroke patients.

Key words: spasticity, botulinum therapy, equinovarus, stroke, plantar contact area

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Introduction

Spasticity is a symptom of upper motor neuron damage, defined as "a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex" [1]. It is notable that spasticity was observed in 19% of patients at 3 months after a stroke and 38% of patients at 12 months after a stroke [2, 3]. In Japan, botulinum toxin type A (BoNT-A) is often used to treat spasticity. BoNT-A acts on the neuromuscular junctions of the skeletal muscles to suppress the release of acetylcholine at nerve endings and reduces spasticity by inhibiting muscle contractions [4]. It takes 2 to 3 days for BoNT-A to exhibit an effect, which is maintained for about 3 months and then attenuates [5]. The Japanese guidelines for stroke therapy from 2015 [6] state that, "Botulinum therapy is strongly recommended for spasticity of the upper and lower limbs (grade A)," and "botulinum therapy and 5% phenol are recommended (grade A) as an intramuscular nerve block of the tibial nerve or lower leg muscles when pes equinovarus due to spasticity inhibits walking or other everyday activities." Severe lower limb spasticity can exhibit an extension synergy pattern accompanied by pes equinovarus that affects walking functions [7, 8]. Botulinum therapy is expected to reduce lower limb spasticity, improve pes equinovarus, and improve the gait and walking ability [9, 10].

In clinical practice, botulinum therapy is often performed multiple times and not just as a single dose. Although the effectiveness of multiple doses of BoNT-A has been demonstrated [11], there are only a

few reports on repeated doses in the lower limbs compared to the upper limbs [12−14]. In addition, the effects of multiple BoNT-A doses on pes equinovarus in hemiplegic stroke patients have not been demonstrated. Generally, the Modified Ashworth Scale (MAS) [15] is used to evaluate spasticity. Nevertheless, MAS assesses the resting muscle tone and is not suitable for evaluating the muscle tone during movement. Assessing the muscle tone while standing and walking as well as at rest would help to create more appropriate treatment plans and improve the assessments of efficacy. The therapeutic effects on pes equinovarus can be judged by the increase in the area of plantar contact with the first metatarsal bones and heel of the foot [16]. We believe that by assessing the effects of BoNT-A using MAS and the plantar contact area during movement, we can comprehensively examine the usefulness of repeated BoNT-A doses on pes equinovarus.

Therefore, the objective of this study was to quantitatively examine the therapeutic effects of repeated BoNT-A doses on hemiplegic stroke patients presenting with lower limb spasticity by comparing the changes in the maximum plantar contact area, the ratio of paralyzed/non-paralyzed maximum plantar contact areas, and MAS before the first dose, 4 weeks after the first dose, and 4 weeks after the second dose.

Subjects and methods

1. Subjects

This study was a retrospective observational study. Patients with hemiplegia who received botulinum therapy at the Showa University Hospital from April 2011 to March 2013 and who underwent a sheet-type weight-bearing lower limb test before and after the doses were eligible for the study. The criteria for inclusion were patients who did not have subarachnoid hemorrhage, did not have recurrences, did not consume oral antispasmodics, and could walk independently in their daily life. Consequently, eight chronic stroke patients who fulfilled these criteria were included as subjects. We obtained approval from the Showa University ethics committee for research on human subjects (approval No. 2974) for this series of studies; notably, informed consent was waived.

2. BoNT-A administration

BoNT-A was dissolved in physiological saline for administration. The site of administration was decided by the physician in charge and was selected from among the gastrocnemius, soleus, tibialis posterior, and flexor digitorum longus muscles. The gastrocnemius and soleus were identified by palpation, while the tibialis posterior and flexor digitorum longus were identified by electrical stimulation. The paralyzed leg was evaluated 4 weeks after BoNT-A (BOTOX®, GlaxoSmithKline) administration and the physician in charge evaluated it again at least 12 weeks after administration of the BoNT-A dose. If the physician in charge decided that another BoNT-A dose was required after the examination, a second dose was administered after obtaining consent from the patient.

3. Assessments

The weight-bearing lower limb test was performed using a sheet-type foot pressure sensor (Anima, WalkWay MW-1000). Each measurement was performed on a sheet-type sensor of length 4.8 m without shoes, cane or foot orthosis. The maximum plantar contact area was calculated as the mean of the maximum plantar contact areas for all the steps on the sheet. The ratio of the paralyzed/non-paralyzed maximum plantar contact areas was calculated using the maximum plantar contact areas of the paralyzed and non-paralyzed sides. At the same time, the physician in charge used MAS to evaluate the paralyzed ankle joint. The measurements and assessments were performed three times: before BoNT-A administration, 4 weeks after the first dose, and 4 weeks after the second dose.

4. Statistical processing

It is notable that MAS 1+ was treated as 1.5. The Shapiro-Wilk normality test was used to confirm normal distributions. The Friedman test was used as an analysis of variance of repeated measurements to compare the maximum plantar contact areas on the paralyzed and non-paralyzed sides, the ratio of paralyzed/non-paralyzed maximum plantar contact areas, and MAS. Multiple comparisons between groups were performed using the Wilcoxon signed-rank test with Bonferroni correction. Two-sided p-values <0.05 were considered statistically significant. JMP® 14 (SAS Institute Inc., Cary, NC, USA) was used as the statistical software.

Results

Table 1 shows the subjects' characteristics. Table 2 shows the sites of administration and doses. The mean interval between the first and second BoNT-A doses (mean (SD)) was 136.0 (10.5) days. The total dose was altered in two cases between the first and second doses. Additionally, there were changes in the site of administration and dosage with respect to the second dose in five cases.

1. Paralyzed side maximum plantar contact area

The maximum plantar contact area on the paralyzed side (mean (SD)) was 128.1 (29.8) cm^2 before the first dose, 137 (27.8) cm^2 4 weeks after the first dose, and 146.9 (21.8) cm^2 4 weeks after the second dose ($p = 0.044$ using the Friedman test). The maximum plantar contact area on the paralyzed side increased significantly after the first and second doses ($p < 0.05$) (Figure 1).

Table 1. Subject characteristics.

Sex	Male 6/Female 2
Age at injection, years	57.8 (10.3)
Cerebral hemorrhage/Cerebral infarction, *n*	5/3
Side of hemiparesis, *n*	Right 2/Left 6
Brunnstrom Recovery Stage (lower limb), *n*	III 5/IV 2/V 1
Time between onset and treatment, years	9.0 (7.2)

Data are mean (SD) or number.

Table 2. BoNT-A doses and administration site.

	Muscle	Patients	Injected dosage of botulinum toxin type A
The first dose	Gastrocnemius	7	150
	Soleus	6	58.3(11.8)
	Tibialis posterior	8	62.5(12.5)
	Flexor digitorum longus	5	40 (12.2)
	Total	8	262.5(69.6)
The second dose	Gastrocnemius	8	131.3(24.2)
	Soleus	7	60.7(12.2)
	Tibialis posterior	8	59.4(12.4)
	Flexor digitorum longus	3	50 (10.8)
	Total	8	262.5(72.8)

Data are mean (SD) or number.

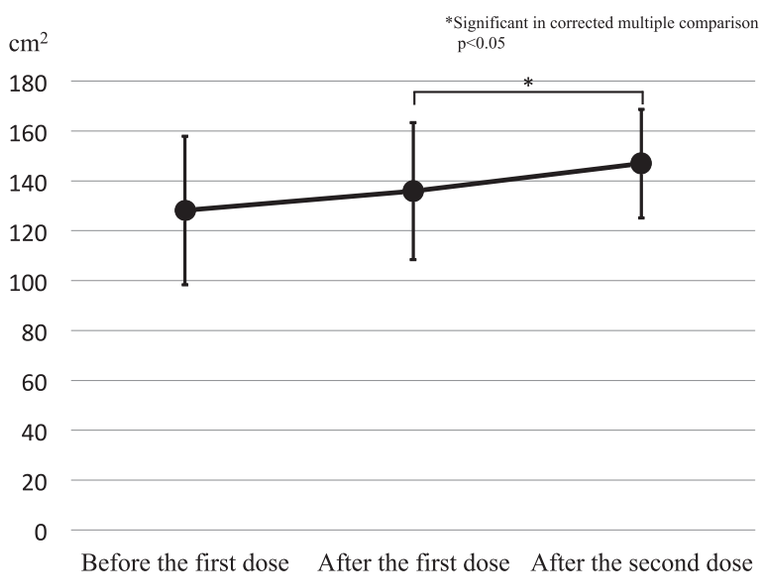

Figure 1. Changes in maximum plantar contact area on the paralyzed side before BoNT-A administration, 4 weeks after the first dose, and 4 weeks after the second dose.

2. Non-paralyzed side maximum plantar contact area

The maximum plantar contact area on the non-paralyzed side (mean (SD)) was 165.4 (23.3) cm^2 before the first dose, 167.8 (20.9) cm^2 4 weeks after the first dose, and 164.1 (19.9) cm^2 4 weeks after the second dose. No significant differences were observed from the Friedman test ($p = 0.65$).

3. Ratio of paralyzed/non-paralyzed maximum plantar contact areas

The ratio of the maximum planted ground contact area between the paralyzed and non-paralyzed sides (mean (SD)) was 0.78 (0.14) before the first dose, 0.80 (0.14) weeks after the first dose, and 0.89 (0.05) 4 weeks after the second dose ($p = 0.00037$ using the

Friedman test). Significant increases were observed 4 weeks after the first dose compared to before, and 4 weeks after the second dose compared to before ($p < 0.05$) (Figure 2).

4. MAS

The median MAS was observed to be 4 before the first dose, 1.75 at 4 weeks after the first dose, and 1 at 4 weeks after the second dose ($p = 0.00014$ using the Friedman test). Significant decreases were observed after the first dose compared to before, and after the second dose compared to before ($p < 0.05$).

Discussion

The results of this study suggest that comparison of the plantar contact area is useful for assessing the therapeutic effects of repeated administration of BoNT-A for pes equinovarus in hemiplegic stroke patients. Significant improvements were observed in the MAS and the ratio of paralyzed/non-paralyzed maximum plantar contact areas at 4 weeks after the first dose and 4 weeks after the second dose compared with the values prior to the first BoNT-A dose. Significant increases in the maximum plantar contact area on the paralyzed side were observed 4 weeks after the first dose and 4 weeks after the second dose. The methods of quantitatively assessing pes equinovarus after botulinum therapy include using a plantar pressure distribution sensor to perform measurements in the standing position [17], measuring the ratio of maximum plantar contact areas during walking using a sheet-type plantar pressure sensor [18], and using a 3-dimensional motion analyzer [19]. However, previous studies analyzed the comparisons before and after a single dose. To our knowledge, our study is the first to use a sheet-type plantar pressure sensor to evaluate the effects of repeated BoNT-A doses on hemiplegic stroke patients with a focus on pes equinovarus.

Pes equinovarus is mainly caused by spasticity, contracture, weakness of the ankle dorsiflexors, and instability of the tibial and peroneal muscles [20, 21]. The effects of contracture are particularly evident in the chronic phase and the evaluation of spasticity with MAS alone is insufficient [22]. Hypertonia is divided into reflexive elements based on stretch reflexes and non-reflexive elements based on the viscoelasticity of the tissues that make up a joint [23]. Bakheit et al. [22] and Takeuchi et al. [24] suggested that MAS measures the non-reflexive elements of hypertonic states. In the subjects of the present study, a mean of 9.0 (7.2) years had elapsed from the onset to the administration of BoNT-A, indicating that the effects of the non-reflexive elements cannot be ignored. Tanikawa et al. [19] evaluated the effect of botulinum therapy on ankle varus during walking using a 3D motion analyzer. They reported that while MAS had returned to the pre-dose levels 12 weeks after BoNT-A administration, the maximum foot varus angle during the swing phase had improved significantly, indicating that the spasticity at rest and improvements in movement are not always consistent. While the effects of BoNT-A on spasticity attenuate over time, promoting continuous weight-bearing on the paralyzed side throughout its duration of effectiveness is thought to improve the factors besides spasticity. We believe that in addition to using MAS, the therapeutic effects on pes equinovarus can be examined in more detail if quantitative assessments during movements are also performed using a sheet-

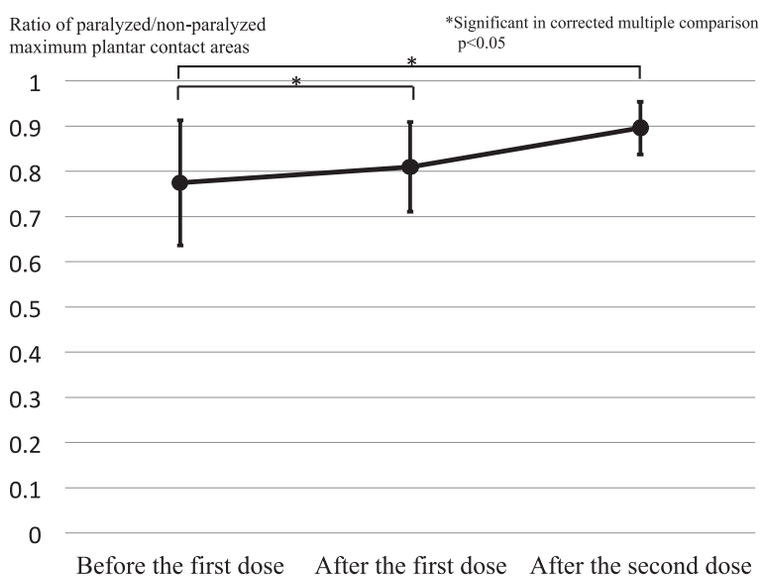

Figure 2. Changes in the ratio of paralyzed/non-paralyzed maximum plantar contact areas before BoNT-A administration, 4 weeks after the first dose, and 4 weeks after the second dose.

type weight-bearing lower limb test.

Previous studies have demonstrated the usefulness of repeated administration of BoNT-A to the lower limbs. In a study of repeated BoNT-A doses performed in Japan, the mean interval between the doses was 133.2 days, with the dose interval in the upper limbs not markedly different from that in the lower limbs [25]. The dose and administration interval in the present study were similar to those in previous research. Takekawa et al. showed that with multiple BoNT-A doses, spasticity gradually lessened with each one to create a greater therapeutic effect. They reported that even if the effect of a single dose is insufficient, repeated doses should be given [26]. Hara et al. reported that the combination of four BoNT-A doses and intensive inpatient rehabilitation significantly improved the ankle MAS, ankle dorsiflexion angle, 10-Meter Walk Test, Functional Reach Test, and the Timed Up and Go Test after the fourth dose [12]. We believe that the treatment should be judged not merely by the effects of a single dose, but should be examined continuously by assessing the effects of multiple BoNT-A doses. The results of the present study support findings that repeated BoNT-A doses lead to a continuous improvement of pes equinovarus. To assess the plantar contact area, we could quantitatively assess the improvement of spasticity and the non-reflexive elements of hypertonic states after repeated BoNT-A doses. In our study, while the effect of the second BoNT-A dose was equivalent to that of the first dose, a continuous improvement in factors other than spasticity was observed. However, the improvement was not sufficient to produce a significant difference compared to the improvement after the first dose. For analyzing treatment plans and improving the assessments of efficacy, the assessment of the plantar contact area is better than MAS which is an ordinal scale. Adding rehabilitation to botulinum therapy has been shown to be effective. Additionally, while the subjects of this study received outpatient stretching guidance and other forms of rehabilitation, the amount of stretching they actually performed during the study remains unclear. In our future study, we plan to research the changes in pes equinovarus by adding constant exercise therapy after BoNT-A dose using a sheet-type foot pressure sensor.

The limitations of this study include the following. First, the sample size was small. Second, the amount of rehabilitation performed during the study was not standardized. Third, there was no comparison of the changes in walking abilities such as speed and maximum distance. Fourth, it was a retrospective observational study using medical records without a control group. Furthermore, although an increased maximum plantar contact area indicates an improvement in pes equinovarus, it is unclear how much this improvement was reflected in improved abilities, which is a topic for future research. In the future, we would like to examine the mid- to long-term effects of BoNT-A on spasticity, walking ability, and range of activity when rehabilitation is included in the study period.

Conclusion

Our study suggested that comparison of the maximum plantar contact area is useful for judging the effect of the BoNT-A doses on pes equinovarus. This study was the first to use a sheet-type plantar pressure sensor to evaluate the effects of repeated BoNT-A doses on hemiplegic stroke patients with pes equinovarus. We believe that in addition to MAS, the therapeutic effects on pes equinovarus can be examined in more detail if quantitative assessments are also performed using a sheet-type foot contact sensor.

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