Original Article

Ultrasonographic evaluation of changes in the muscle architecture of the gastrocnemius with botulinum toxin treatment for lower extremity spasticity in children with cerebral palsy

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Abstract

Background

Botulinum toxin A treatment involves injecting botulinum toxin A to relax muscle spasticity. Using ultrasonography, this study examined changes in the muscle architecture before and after treatment to evaluate the influence of botulinum toxin A injection on muscles.

Methods

The participants included 18 children (mean age, 6.2 years) with cerebral palsy who were treated with botulinum toxin A for lower extremity spasticity and 27 healthy children (mean age, 6.4 years) as a control group. In all cases, botulinum toxin A was injected into the gastrocnemius muscle. The muscle length, muscle width, and pennation angle (which indicates the degree of muscle fiber tone), were measured using B-mode ultrasonography before and 12 weeks after injection.

Results

The muscle length and muscle width were shorter in the cerebral palsy group than in the control group. The pennation angle in the cerebral palsy group significantly decreased after injection from 28.2 ± 3.6° to 25.8 ± 2.5° in the resting position of the ankle and from 18.6 ± 2.8° to 15.9 ± 1.7° in the maximum dorsiflexion position of the ankle. In the control group, the pennation angle was 25.9 ± 3.2° in the resting position of the ankle and 15.1 ± 2.5° in the maximum dorsiflexion position of the ankle. The rate of increase of fascicle length during passive movement from the resting position of the ankle to the maximum dorsiflexion position was 143.9% in the cerebral palsy group, which was significantly less than the value of 157.7% in the control group. After botulinum toxin A treatment, the rate of increase of fascicle length in the cerebral palsy group increased to 155.1%.

Conclusions

The decrease in the pennation angle after botulinum toxin A treatment is considered to be the result of a reduction of spasticity and subsequent structural changes in flaccid muscle fibers.

1 Introduction

Spasticity, one of the upper motor neuron signs, is a prominent motor disorder in patients with cerebral palsy [1]. Spasticity is characterized by velocity-dependent increases in tonic stretch reflexes accompanied by increased tendon reflexes [2]. As a result, the condition of the muscle tone changes, and muscle or tendon shortening affects the range of motion and causes contracture.

In recent years, botulinum toxin A (BoNT-A) has played an important role as a pharmacological treatment for spasticity [3]. BoNT-A treatment involves injecting a BoNT-A preparation composed of protein produced by botulinum

toxin, a cause of food poisoning, to relax muscle spasticity [4]. BoNT-A inhibits the release of the neurotransmitter acetylcholine at nerve endings and acts as a muscle relaxant [5]. The range of motion, the Modified Ashworth Scale [6], and the Tardieu Scale [7] are commonly used for the evaluation of BoNT-A treatment. However, these measurements evaluate clinical results, and there have been very few evaluations or reports on changes in the muscle structure after BoNT-A treatment.

BoNT-A treatment has clinical effects, such as reducing spasticity, characterized by velocity-dependent increases and improvements in the range of motion [3,4]. In pennate muscles, such as the gastrocnemius, the muscle fascicles are arranged obliquely and the pennation angle of muscle fascicle arrangement toward the aponeurosis changes during contraction [8,9]. The pennation angle and the fascicle length have a relationship with the muscle physiological cross-sectional area, which eventually affects muscle tension [10]. Evaluating muscle structure of muscle spasticity before and after treatment using ultrasonography allows a clinical understanding of muscle tension [8,11,12]. In this study, we reviewed the impact of BoNT-A treatment on the muscle and on changes in muscle structure by measuring the pennation angle of the gastrocnemius and fascicle length using ultrasonography.

2 Methods

2.1 Patients

The study was conducted on 29 lower extremities of 18 children (8 boys and 10 girls) with cerebral palsy who received BoNT-A treatment for lower extremity spasticity at our hospital (the CP group). Their ages ranged from 3 to 8 years, with a mean age of 6.2 years. Eleven patients had diplegia, and 7 had hemiplegia. According to the Gross Motor Function Classification System (GMFCS) [13], three patients were classified as level I, five as level II, seven as level III, three as level IV, and none as level V. None of the patients had a history of surgical treatment, such as muscle release or treatment such as phenol block, or had received BoNT-A treatment before. The control group consisted of 27 children (11 boys and 16 girls) with typical development. Their ages ranged from 4 to 8 years, with a mean age of 6.4 years. They were normal volunteers who were brothers and sisters of the patients and were accompanying them on outpatient visits. None of the children had a history of neurological or kinematical problems or lower extremity injuries or had received orthopedic treatment.

We explained our study to the participants and/or their families and obtained written informed consent from the families. The contents of the evaluation and protocol performed in this study were approved by the ethics committee of the Department of Miyazaki Prefecture Center for Disabled Children.

The injection site was the gastrocnemius muscle. A dose of 4 units/kg BoNT-A was injected into the proximal one-third of the lower leg under ultrasound guidance [14,15]. The clinical evaluation included age in months, height, weight, spina malleolar distance, fibula length, circumference of the thigh, circumference of the lower leg, dorsiflexion with knee extension, dorsiflexion with knee flexion, and plantar flexion angle.

2.2 Imaging technique and analysis

Ultrasound measurements were performed with the Logiq 7 ultrasonography imaging system (GE Healthcare, Chicago, Illinois, USA), with a linear probe (50 mm, 9 MHz) and B-mode. The measurement site was in the medial head of the gastrocnemius in the prone position. Measurements were performed with the participants in the resting position with their legs hanging down and in the passive maximum dorsiflexion position of the ankle with extended knee. Three measurements were made for each position, and the mean values were used. The pennation angle (θ), an indication of muscle fiber tone, was determined from the angle between deep aponeurosis and gastrocnemius muscle fascicle. The angle was measured using a digital curvimeter (SYNAPSE, FUJIFILM, Japan). Muscle width was measured in the thickest region of the muscle. Fascicle length was calculated from muscle width and pennation angle (fascicle length = muscle width/sinθ), and the change in fascicle length with ankle joint angle was defined as the muscle elongation rate (fascicle length in the dorsiflexion position/fascicle length in the resting position × 100) (Fig. 1) [8,11,12,16–18]. The ultrasonography measurements were performed before and 12 weeks after injection.

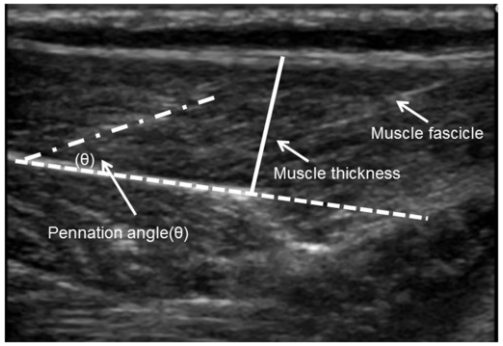

Fig. 1 Ultrasound image showing measurements of muscle structure.

alt-text: Fig. 1

2.3 Statistical methods

Statistical analyses were performed with SPSS, version 21. Values before and 12 weeks after injection were compared by the Wilcoxon signed rank test. Values in the CP group and the control group were compared by the Mann–Whitney U test. A *p*-value less than 0.05 was considered to indicate a significant difference. All results are presented as mean values and standard deviations.

3 Results

3.1 Clinical assessment outcomes

There were no significant differences in age, height, weight, spina malleolar distance, and fibula length between the CP group and the control group, while significant differences between the groups were found in thigh and lower leg circumferences (Table 1). The mean dorsiflexion angle of the ankle with knee extension in the CP group was −14.4 ± 11.0°, indicating talipes equinus, compared to that in the control group. After BoNT-A treatment, the CP group showed a marked improvement, with a mean angle of −3.8 ± 7.9° (Fig. 2).

Table 1 Anthropometric and ankle angle data for the cerebral palsy group and control group.

alt-text: Table 1

	CP	Control	*p*	
	Mean (SD)	Mean (SD)		
Age (mo)	73.1 (22.1)	76.2 (15.9)	0.55	
Height (cm)	113.9 (9.3)	118.3 (9.5)	0.31	
Weight (kg)	20.2 (7.9)	22.9 (5.4)	0.30	
SMD (cm)	55.1 (5.0)	59.0 (6.4)	0.16	
Fibula length (cm)	20.9 (2.1)	22.7 (2.7)	0.07	
COT (cm)	25.7 (4.9)	29.9 (3.2)	<0.01	[a]
COLL (cm)	19.2 (3.4)	23.5 (2.6)	<0.01	[a]
DKE (°)	−14.4 (11.0)	19.2 (7.5)	<0.001	[a]
DKF (°)	15.5 (14.2)	31.3 (6.4)	<0.001	[a]
Plantar flexion~~Planterflexion~~ (°)	39.3 (7.0)	42.8 (6.7)	0.40	

SD: Standard deviation; COT: Circumference of thigh; COLL: Circumference of lower leg; DKE: Dorsiflexion knee extension; DKF: Dorsiflexion knee flexion.

[a] Mann–Whitney ~~U~~ *U* test.

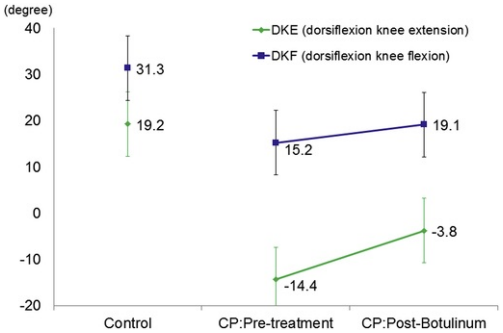

Fig. 2 Ankle angle during passive dorsiflexion before and after treatment. CP, cerebral palsy group.

alt-text: Fig. 2

3.2 Ultrasonographic assessment outcomes

The pennation angle in the resting position in the CP group was 28.2°, which was significantly greater ($p < 0.01$) than the angle of 25.9° in the control group. After BoNT-A treatment, the pennation angle in the CP group significantly decreased from 28.2° to 25.8° in the resting position of the ankle ($p < 0.05$) and from 18.6° to 15.9° in the maximum dorsiflexion position of the ankle ($p < 0.01$). Muscle width and fascicle length were significantly shorter in the CP group than in the control group, both in the resting position and in the dorsiflexion position.

No change was observed in muscle thickness after BoNT-A treatment, but fascicle length significantly increased from 22.5 to 23.9 mm in the resting position ($p = 0.13$) and from 32.2 to 37.0 mm in the dorsiflexion position ($p < 0.05$). The rate of increase of fascicle length during passive movement from the resting position of the ankle to the maximum dorsiflexion position of the ankle was 143.9% in the CP group, which was significantly less than the value of 157.7% in the control group ($p < 0.05$). After BoNT-A treatment, the rate of increase of fascicle length in the CP group increased to 155.1% (Table 2).

Table 2 Ultrasonographic findings of the patients.

alt-text: Table 2

	Resting ankle	P[a]	CP vs Co	maximum dorsiflexion	P[a]	CP vs Co
	Mean (SD)		P[b]	Mean (SD)		P[b]
Pennation angle (°)						
CP Pre-treatment	28.2 (3.6)		<0.01	18.6 (2.8)		<0.01
Post-Botulinum	25.8 (2.5)	<0.05	0.83	15.9 (1.7)	<0.01	0.18
Control	25.9 (3.2)			15.1 (2.5)		
Muscle thickness (mm)						
CP Pre-treatment	10.6 (2.0)		<0.001	10.1 (1.8)		<0.001
Post-Botulinum	10.4 (1.9)	0.70	<0.001	10.1 (1.7)	0.90	<0.001
Control	13.7 (1.6)			12.6 (1.4)		
Fascicle length (mm)						
CP Pre-treatment	22.5 (3.5)		<0.001	32.2 (5.2)		<0.001
Post-Botulinum	23.9 (3.6)	0.13	<0.001	37.0 (5.9)	<0.05	<0.01

Control	31.4 (3.2)			49.6 (9.2)		
Muscle elongation rate (%)						
CP Pre-treatment	143.9 (19.2)		<0.05			
Post-Botulinum	155.1 (13.7)	<0.05	0.61			
Control	157.7 (22.9)					

SD: Standard deviation; CP vs Co: CP group versus Control group.

[a] Wilcoxon signed-rank test.

[b] Mann–Whitney ~~U~~ *U* test.

4 Discussion

In recent years, because of rapid progress in imaging technology, in vivo studies of the musculoskeletal system have advanced to facilitate the evaluation of in vivo information, including ultrasonography, CT, and MRI. When imaging examination is conducted in children, including those with cerebral palsy, the use of ultrasonography does not require sedation and allows brief examination of the patient in any position [12,16]. An additional advantage is that dynamic muscle systems and soft tissue systems can be evaluated in real time [8]. Having said that, normal B-mode ultrasonography allows two-dimensional evaluation only, and three-dimensional evaluation of muscle volume is difficult. On the other hand, CT and MRI allow three-dimensional evaluation, and it is possible to evaluate muscle structure objectively and thoroughly, which is an advantage [19,20]. However, examination using CT or MRI is not always available, and, particularly in children with cerebral palsy, these examinations require preparation, such as setting of infusion and sedation, which takes time. Ultrasonographic examination is a highly effective method of evaluation in outpatients.

Ultrasonography enables noninvasive, real-time evaluation of in vivo information. Many studies using ultrasonography have reported on the structure and characteristics of muscles and tendons [8]. The principle of evaluating the muscle architecture using ultrasound is based on an ultrasonic reflection method, in which sound waves reflect from structures with different in vivo tissue densities, such as collagen fibers. Ultrasonography enables the quantitative evaluation of changes in the muscle architecture associated with contraction [8,9]. In pennate muscles such as the gastrocnemius, muscle fascicles are arranged obliquely, and the pennation angle, which indicates the position of muscle fascicles relative to the aponeurosis, has been reported to considerably affect the muscular force during contraction [9,10]. Muscle contraction leads to an increase in the physiological cross-sectional area following an increase in the pennation angle and a shortening of fascicle length, which results in increased muscle tension [9,21,22].

Previous studies on disuse muscle atrophy have reported decreases in the pennation angle, fascicle length, and muscle volume [23], and studies comparing patients with cerebrovascular disease and healthy individuals have reported a decrease in fascicle length in paralyzed patients [17,18,24]. Findings on changes in the pennation angle vary according to the patients' background; both a decrease due to disuse muscle atrophy and an increase due to hypertonia can coexist. In addition, changes in the muscle structure in patients with spastic paralysis are sensitive to treatment history, follow-up period, and the amount of physical therapy [17,25].

The patients in this study were children with cerebral palsy aged 3–8 years, and the evaluation was performed only for the first BoNT-A treatment. Because all patients were receiving injections for the first time and the treatment evaluation was performed 12 weeks after injection, the evaluation was not markedly influenced by physical growth or by other treatments, and we were able to focus on changes in the gastrocnemius resulting from BoNT-A treatment alone [16].

The typically developing children in the control group in this study did not differ from the children in the CP group in physical characteristics such as age, height, and weight, and they were therefore considered a suitable control group. However, there were significant differences between the groups in thigh and lower leg circumferences, which may have been due to muscle atrophy associated with paralysis in the CP group.

Ultrasonography revealed that the muscle width and fascicle length were significantly shorter in the CP group than in the control group, suggesting muscle atrophy associated with paralysis. In addition, the pennation angle in the resting position was greater in the CP group than in the control group. This finding conflicts with previous studies [23,24]; however, in cases of spastic paralysis, the muscle fibers constantly contract from the influence of muscle tone, which may lead to an increased muscle tone [26].

After BoNT-A treatment, the pennation angle and fascicle length in the CP group became similar to of the values in the control group, both in the resting position and in the maximum dorsiflexion position. The decrease in the pennation angle in the resting position after treatment may have been due to routine reduction in the muscle tone. In addition, the decrease in the pennation angle and the increase in the muscle elongation rate after BoNT-A treatment suggest reductions in the muscle contraction and muscle tone, causing structural changes in flaccid muscle fibers [16]. The decrease in the pennation angle indicates an increase in fascicle length. The increase in fascicle length

indicates that the muscle fiber has elongated, leading to an improvement in the muscular range of motion [17,18]. In many children with spastic paralysis, the gastrocnemius is easily elongated and joint contracture or disuse muscle atrophy has not progressed. At this point, the symptoms are reversible. However, fascicle length declines with physical growth, and if the mobility gradually decreases, secondary muscle contracture or shortening occurs, which eventually leads to irreversible joint contracture. The results of this study indicate that BoNT-A treatment works effectively to help spastic muscles become more dynamic.

In basic studies, such as those using animal models, BoNT-A targeted both type I fibers (slow-twitch) and type II fibers (fast-twitch); existing studies generally reported an increase in type I fibers and a decrease in type II fibers after BoNT-A treatment [27–29]. However, recent results of muscle biopsy in children with cerebral palsy demonstrated that the proportion of type I fibers decreases and that of type II fibers increases after BoNT-A treatment, with a positive correlation between the proportion of type II fibers and the number of injections of BoNT-A [30]. The discrepancy with histological findings may be associated with the targeted muscle, number of injections of BoNT-A preparation, duration of treatment, and existence of disuse muscle atrophy [19,31,32]. In any case, although degeneration of muscle fibers and muscle atrophy after BoNT-A treatment are predicted from these studies, some effects have been observed in clinical practice, including relaxation of muscle tone, improvement of the range of motion, pain relief, and delay in surgical intervention. Muscle atrophy, decrease in muscle strength, and muscle dysfunction were also reported; however, these studies used multiple doses, injections in several muscles with 1.5–2 times the dose used in our study, and combination therapy, such as cast fixation [19]. Our study was limited to the initial injection, fixed dose, and evaluation of the medial gastrocnemius alone after treatment. The results are difficult to compare with those of previous studies; however, no change was noted in muscle width or calf circumference during the 12 weeks of observation. We must evaluate the treatment history with multiple doses and long-term administration. As for the major concern of muscle atrophy, although previous studies reported decreases in muscle length and muscle thickness due to disuse or atrophy, with subsequent decrease in muscle volume [20,33], it is critical to conduct histological examination, such as muscle biopsy, and more quantitative measurements of muscle mass using MRI or CT.

5 Conclusions

This study used ultrasonography to investigate the effect of injecting a BoNT-A preparation into a muscle for lower extremity spasticity on changes in the muscle structure in children with cerebral palsy. An increase in the pennation angle was observed in the resting position, and constant muscle contraction associated with spasticity was suggested. The decrease in the pennation angle and the increase in fascicle length were considered to be the results of a reduction of spasticity and subsequent structural changes in flaccid muscle fibers.

Conflict of interest

The authors declare that they have no conflict of interest.

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