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Upper Limb Motor Function Affects the Outcome after Treatment with Botulinum Toxin A

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Spasticity · Botulinum toxin therapy · Upper limb · Motor function · Fugl-Meyer Assessment

Abstract
Background: Treatment with Botulinum toxin A (BoNT-A) is effective in decreasing upper limb spasticity. ***Objective:*** This study aimed to determine the differences in the outcome based on the upper limb motor function before BoNT-A treatment. ***Methods:*** The subjects were 61 patients who underwent BoNT-A treatment for upper limb spasticity. Limb function was evaluated using the Fugl-Meyer Assessment upper extremity (FMA-UE), modified Ashworth scale, passive range of motion and disability assessment scale before treatment as well as 2, 6, and 12 weeks after treatment. We divided the total and each subscale of FMA-UE before BoNT-A administration into beyond-the-mean-score group (higher score group) and below-the-mean-score group (lower score group). ***Results:*** In both the higher and lower score groups of the FMA-UE total and modified Ashworth scale scores improved significantly after treatment. In FMA-UE, the higher score group of subscale A improved significantly, but subscale C decreased significantly at 2 and 6 weeks after the administration. The lower score group of total, subscale A, and B improved significantly. In the disability assessment scale, the self-dressing capability at 6 weeks and limb position at 2, 6 and 12 weeks after the administration improved significantly in the higher score group. In the lower score group, the hygiene capability at 2 weeks as well as the dressing capability and limb position improved significantly at 2, 6 and 12 weeks after administration. ***Conclusions:*** The time course after administration of BoNT-A differed based on upper limb motor function before injection. When administering BoNT-A into the finger flexor muscles of a patient, we should carefully judge the indications for administration.

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Introduction

Spasticity is defined as a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex; it is a component of upper motor neuron syndrome [1]. It also includes symptoms such as spastic dystonia, co-contractions and association reactions [2]. Recently, the Support Program for Assembly of a Database for Spasticity Measurement project defined spasticity as disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles [3]. Spasticity after stroke is reported to be approximately 43% at 6 months [4] and 38% at 12 months [5] after onset. The severity of upper limb spasticity is seen to increase over time, until 18 months after stroke [6].

Upper limb spasticity tends to occur predominantly in the shoulder adductor, elbow flexor, forearm flexor, wrist flexor, and finger flexor muscles; it causes pain and abnormal positions in the upper limb. Approximately 60–70% of the patients with upper limb spasticity face difficulties in maintaining hygiene, dressing and maintaining limb position [7]. Spasticity significantly reduces upper limb motor function and activity [8]. A moderate correlation is also seen between spasticity and motor function [6]. Therefore, we can deduce that spasticity affects not only passive motion but also active motion in the upper limbs along with hindering the recovery of motor function.

Botulinum toxin A (BoNT-A) has commonly been used to treat spasticity and spastic dystonia. BoNT-A administration is effective for decreasing spasticity, expanding the joint range of motion (ROM), improving abnormal position of the upper limbs during gait, and recovering activities of daily living such as hygiene and dressing [7, 9–12]. The International Consensus Statement stated that motor function improved in some patients after BoNT-A injections, but further research was needed to clarify the effects (Recommendation C) [13]. Recently, BoNT-A administration, combined with rehabilitation measures such as constraint-induced movement therapy [14], intensive occupational therapy, repetitive transcranial magnetic stimulation [15], and home-based functional training [16, 17] has been reported to improve active motor function. In these circumstances, the existing upper limb motor function before BoNT-A administration may affect the final treatment outcome. However, to the best of our knowledge, there are no reports on how the differences in existing upper limb motor function before BoNT-A administration affect the outcome. Therefore, the purpose of this study was to evaluate the upper limb motor function before and after BoNT-A administration and to determine the differences in the outcome according to the upper limb motor function before BoNT-A treatment.

Materials and Methods

Subjects

The subjects were 61 patients who underwent BoNT-A treatment between January 2012 and April 2016 for upper limb spasticity resulting from cerebrovascular damage. There were 37 men and 24 women, with an age of 54 ± 16 (mean ± SD) years. Twenty-five patients had right hemiplegia and 36 had left hemiplegia. The aetiology was cerebral infarction in 22 cases, cerebral haemorrhage in 38 and subarachnoid haemorrhage in 1. The time after onset until BoNT-A administration was 1,375 ± 1,211 (mean ± SD) days. Before administration, 58 of the 61 patients had received physical and/or occupational therapies such as stretching of spastic muscles and upper limb function exercises at a rate of 1.9 ± 1.4 (mean ± SD) times per week.

BoNT-A Treatment

In Japan, due to insurance-related regulations, the maximum BoNT-A injection in the upper limbs on a single occasion is limited to 240 units. BoNT-A (Botox, GlaxoSmithKline, Tokyo, Japan) was diluted with saline to a concentration of 12.5–25.0 U/mL. Experienced physiatrists evaluated muscle tone in each muscle, determined the indications, and selected the target muscles. We performed the injection under the guidance of ultrasound and/or electrical stimulation. Because 240 units are not always enough dose for patients with severe spasticity, the dose to each muscle was determined based on patient need and recommendation by experienced physiatrists. After administration, an occupational therapist individually instructed each patient regarding stretching of the spastic muscles and exercises to be performed for 30 min/day. Two patients who had not had rehabilitation before administration started outpatient occupational therapy 2 times per week after administration, while 58 patients who had received rehabilitation before administration continued physical and/or occupational therapies at the same frequency. After administration, all patients were instructed to perform stretching of spastic muscles and exercises individually until 12 weeks.

Assessment

Assessments were performed 4 times: just before the administration and 2, 6 and 12 weeks after the administration, by the same investigator. Written informed consent was obtained from all patients. This study was approved by the institutional review board of our institute.

Motor function was assessed using the total Fugl-Meyer Assessment [18] upper extremity (FMA-UE) score and its subscales (A: shoulder/elbow/forearm, B: wrist, C: fingers, D: coordination/speed).

The modified Ashworth scale (MAS) [19] was used to assess the spasticity. The subjects were seated in a relaxed state. The passive range of motion (P-ROM) of the shoulder, elbow, forearm, wrist, thumb, and fingers was assessed. The MAS was evaluated by providing resistance during passive motion in the maximum ROM of the

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joint. The positions of the shoulder, elbow and forearm were unified at the time of evaluation. Difficulties in activities of daily living associated with upper extremity spasticity were assessed by using the disability assessment scale (DAS) [20]. The DAS includes hand washing, changing clothes, abnormal limb position and pain associated with spasticity. Patients were evaluated in an interview format.

We divided the total and each subscale of FMA-UE before BoNT-A administration into beyond-the-mean-score group (higher score group) and below-the-mean-score group (lower score group).

Statistical Analysis

At 2, 6 and 12 weeks patients after BoNT-A administration were compared with those before the administration. The unpaired *t* test was used to compare P-ROM before BoNT-A administration in both groups. The paired *t* test with Bonferroni correction was used to compare P-ROM measurements. The Wilcoxon signed-rank test with Bonferroni correction was used to compare FMA-UE, MAS and DAS scores. The MAS score 1+ was set to 1.5. The statistical analyses were performed using SPSS Statistics version 23 (IBM, Armonk, NY, USA). p values <0.05 were considered statistically significant.

Results

The injection site and the administered doses were as follows: the pectoralis major and 47.5 ± 12.1 units in 30 patients, the biceps brachii and 55.5 ± 12.9 units in 40 patients, the brachialis and 25.8 ± 7.6 units in 13 patients, the brachioradialis and 22.5 ± 2.5 units in 2 patients, the triceps brachii and 62.5 ± 12.5 units in 2 patients, the pronator teres and 44.5 ± 14.4 units in 11 patients, the flexor carpi radialis and 29.9 ± 9.5 units in 48 patients, the flexor carpi ulnaris and 27.0 ± 6.0 units in 44 patients, the palmaris longus and 25 units in 1 patient, the flexor digitorum profundus and 41.4 ± 25.6 units in 7 patients, the flexor digitorum superficialis and 53.6 ± 10.6 units in 55 patients, the extensor indicis and 25 units in 1 patient, and the flexor pollicis longus and 27.1 ± 6.4 units in 24 patients (mean ± SD).

The mean total FMA-UE score was 23.7. The patients with a score of 24 or more were classified into the higher score group, while patients with a score of 23 or less were placed into the lower score group. The mean score of the subscale A was 16.7 (higher score ≥17, lower score ≤16), the mean score of the subscale B was 1.5 (higher score ≥2, lower score ≤1), the mean score of the subscale C was 5.2 (higher score ≥6, lower score ≤5), and the mean score of the subscale D was 0.3 (higher score ≥1, lower score of 0).

The P-ROM of the higher score group and lower score group are shown in Table 1. The P-ROM of thumb interphalangeal and fingers were within normal values in both groups. The P-ROM of shoulder flexion, abduction, external rotation and elbow flexion was significantly restricted in the lower score group, but were still enough to evaluate MAS.

In the higher score group of the FMA-UE total, the MAS scores for all muscles improved significantly at 2 weeks after the administration. The scores for the forearm pronators, distal interphalangeal joint flexors and proximal interphalangeal joint flexors improved significantly at 6 weeks. In the lower score group, the MAS scores for all muscles improved significantly at 2 and 6 weeks after the administration, while scores for the forearm pronators, wrist flexors, finger distal interphalangeal joint flexors, and thumb interphalangeal joint flexors improved significantly at 12 weeks (Table 2).

The self-dressing capability (measured with the DAS) at 6 weeks and limb position (based on the DAS) at 2, 6 and 12 weeks after the administration improved significantly in the higher score group of the FMA-UE total. In the lower score group, the hygiene capability DAS at 2 weeks as well as the dressing capability and limb position DAS improved significantly at 2, 6 and 12 weeks after administration (Table 3).

In FMA-UE, the higher score group in subscale A improved significantly at 2 weeks after the administration. However, subscale C decreased significantly at 2 and 6 weeks after the administration. The lower score group in total and of subscale B improved significantly at 2, 6 and 12 weeks, while subscale A improved significantly at 2 and 6 weeks after the administration. There were no significant changes in subscales C and D (Fig. 1).

Discussion

We divided the FMA-UE before administration into the higher score group and lower score group. We found that the higher score group showed significant improvements in subscale A and deterioration in subscale C, while the lower score group improved in total, including subscales A and B.

Till date, several studies have assessed the motor function of the upper limbs after the administration of BoNT-A by using the FMA-UE. One study reported that the total score at 4 weeks after BoNT-A administration significantly improved in 9 subacute and 9 chronic stroke patients [21]. Another study showed significant improvement in total, subscale A, and subscale B scores at 4 weeks after BoNT-A administration in 80 patients with chronic stroke that had occurred at least 10 months before [16]. These results are consistent with the results of our study. On the other hand, in our study, the higher score group of subscale C showed temporary deterioration in muscle func-

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Table 1. Changes in P-ROM according to FMA-UE total score before injection

FMA-UE	*n*	Joint	Motion	Before		2 weeks	6 weeks	12 weeks
Higher score	21	Shoulder	Flexion	152±19		152±23	152±24	153±20
			Abduction	159±23		154±27	155±30	154±28
			Adduction	0		0	0	0
			Internal rotation	80±0		80±0	80±0	80±0
			External rotation	41±21		45±17	46±17	41±16
		Elbow	Flexion	143±5		142±6	141±7	141±7
			Extension	1±7		2±6	1±8	3±6
		Forearm	Pronation	90±2		90±2	90±2	90±2
			Supination	86±9		87±7	87±7	85±10
		Wrist	Flexion	74±15		71±18	71±17	73±18
			Extension	55±18		60±14	61±12	57±15
Lower score	40	Shoulder	Flexion	115±32		127±31**	128±31**	125±36*
			Abduction	113±45		119±44	122±42	122±45
			Adduction	0		0	0	0
			Internal rotation	78±6		79±6	78±8	79±4
			External rotation	23±29		28±30	28±27	28±29
		Elbow	Flexion	135±15		131±37	136±14	134±17
			Extension	−5±22		−3±16	−4±15	−5±16
		Forearm	Pronation	88±8		85±26	84±28	82±30
			Supination	73±32		83±15	85±16	83±17
		Wrist	Flexion	71±27		71±27	73±27	73±26
			Extension	43±26		57±17**	57±18**	54±20**

n = 61, values are presented as mean ± SD, non-paired *t* test and paired *t* test.
* $p < 0.05$.
** $p < 0.01$.
P-ROM, passive range of motion; FMA-UE, Fugl-Meyer Assessment upper extremity.

tion after administration of BoNT-A. The subscale C of FMA-UE evaluates 7 exercises [18], mainly using finger flexion. Subjects who used their spastic finger flexor muscles daily showed a decreased ability to flex their finger after the injection and lost the function provided in subscale C. Fortunately, they recovered function at 12 weeks. In the lower score group, the patients could not flex their fingers in the first place (mean score of 2.6) and did not use their fingers daily. Therefore, the spasticity did not affect upper motor function. One report showed that the subscale B plus subscale C significantly improved at 2, 4 and 12 weeks after BoNT-A administration in 23 stroke patients from 3 months to 1 year after onset [22]. We therefore hypothesize that the decrease of subscale C may be masked in their study.

The P-ROM was maintained enough to evaluate MAS in both groups, but the shoulder flexion, abduction, external rotation and elbow flexion were restricted more in the lower score group. The spasticity and low frequency of use due to impairment often cause joint contractures. However, the decrease of spasticity after BoNT-A administration and rehabilitation may have contributed to improvement in P-ROM and FMA-UE in this group.

The DAS score showed significant improvement in both groups with regard to dressing capability and limb position, whereas hygiene improved only in the lower score group. This may be attributed to a decrease in spasticity after BoNT-A treatment, an increase in P-ROM of shoulder flexion and wrist extension, and a greater improvement in FMA-U/E in the lower score group.

This study has several limitations. The number of subjects was insufficient. The dose of BoNT-A injections and the injected muscles were not consistent, due to which it was difficult to examine the influence of BoNT-A administration in detail. Although MAS was used to assess spasticity, there is no consensus on its inter-rater reliability [23]. In addition, MAS may evaluate elements other than spasticity, such as viscoelasticity of muscles or contracture of soft tissues [24–27]. In the near future, we need multicentre collaborative research using unified conditions in a large sample.

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Table 2. Changes in the MAS according to FMA-UE total score before injection

FMA-UE	*n*	Muscles	Before	2 weeks	6 weeks	12 weeks
Higher score	21	Shoulder adductors	1+ (1 – 2)	1 (0 – 1)**	1 (1 – 1+)	1+ (1 – 1+)
		Elbow flexors	1+ (1 – 2)	1 (0 – 1+)**	1 (1 – 1+)	1 (1 – 1+)
		Forearm pronators	1+ (1+ – 1+)	1 (1 – 1+)**	1 (0 – 1+)**	1 (1 – 1+)
		Wrist flexors	1+ (1 – 2)	1 (1 – 1+)*	1 (1 – 1+)	1+ (1 – 1+)
		Finger DIP joint flexors	1+ (1 – 1+)	1 (0 – 1)**	1 (0 – 1)*	1 (0 – 1+)
		Finger PIP joint flexors	1+ (1 – 2)	1 (1 – 1)**	1 (1 – 1+)*	1 (1 – 1+)
		Thumb IP joint flexors	1 (1 – 1+)	1 (0 – 1)*	1 (0 – 1)	1 (1 – 1+)
Lower score	40	Shoulder adductors	2 (1 – 2)	1 (1 – 1+)**	1+ (1 – 1+)**	1+ (1 – 2)
		Elbow flexors	2 (1+ – 2)	1 (1 – 1+)**	1+ (1 – 1+)**	1+ (0 – 1)
		Forearm pronators	1+ (1 – 2)	1 (0 – 1+)**	1 (0 – 1+)**	1 (1 – 1+)*
		Wrist flexors	2 (2 – 3)	1+ (1 – 1+)**	1+ (1 – 1+)**	1+ (1+ – 2)**
		Finger DIP joint flexors	1+ (1 – 2)	1 (1 – 1+)**	1 (1 – 1+)**	1 (1 – 1+)*
		Finger PIP joint flexors	2 (1+ – 2)	1 (1 – 1+)**	1+ (1 – 1+)**	1+ (1 – 2)
		Thumb IP joint flexors	1+ (1 – 2)	1 (0 – 1)**	1 (0 – 1+)**	1 (0 – 2)**

n = 61, median (interquartile range), Wilcoxon signed-rank test with Bonferroni correction.
* $p < 0.05$.
** $p < 0.01$.
MAS, modified Ashworth scale; FMA-UE, Fugl-Meyer Assessment upper extremity; DIP, distal interphalangeal; IP, interphalangeal; PIP, proximal interphalangeal.

Table 3. Changes in DAS according to FMA-UE total score before injection

FMA–UE	*n*	DAS	Before	2 weeks	6 weeks	12 weeks
Higher score	21	Hygiene	1 (0–2)	0 (0–1)	0 (0–1)	1 (0–1)
		Dressing	1 (0–2)	0 (0–1)	0 (0–1)*	1 (0–1)
		Limb position	2 (1–2)	0 (0–1)*	0 (0–1)*	0 (0–1)*
		Pain	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–0)
Lower score	40	Hygiene	1 (0–2)	0 (0–2)*	1 (0–2)	1 (0–2)
		Dressing	1 (1–2)	1 (0–2)**	1 (0–2)**	1 (0–2)*
		Limb position	2 (0.75–3)	0.5 (0–1)**	1 (0–2)*	1 (0–2)*
		Pain	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–1)

n = 61, median (inter quartile range), Wilcoxon signed-rank test with Bonferroni correction.
* $p < 0.05$.
** $p < 0.01$.
DAS, disability assessment scale; FMA-UE, Fugl-Meyer Assessment upper extremity.

Conclusions

This study showed that administration of BoNT-A in spastic muscles of the upper limb reduced spasticity, improved motor function, P-ROM, positioning and dressing capability. In addition, the time course and degrees of improvement after administration of BoNT-A differed considerably based on pre-treatment upper limb motor function. When finger flexion or pinching was possible before administration, it was found that finger function may temporarily decrease after administration. These results are very important for using BoNT-A in the upper limb muscles. In particular, when considering BoNT-A administration to the finger flexor muscles of a

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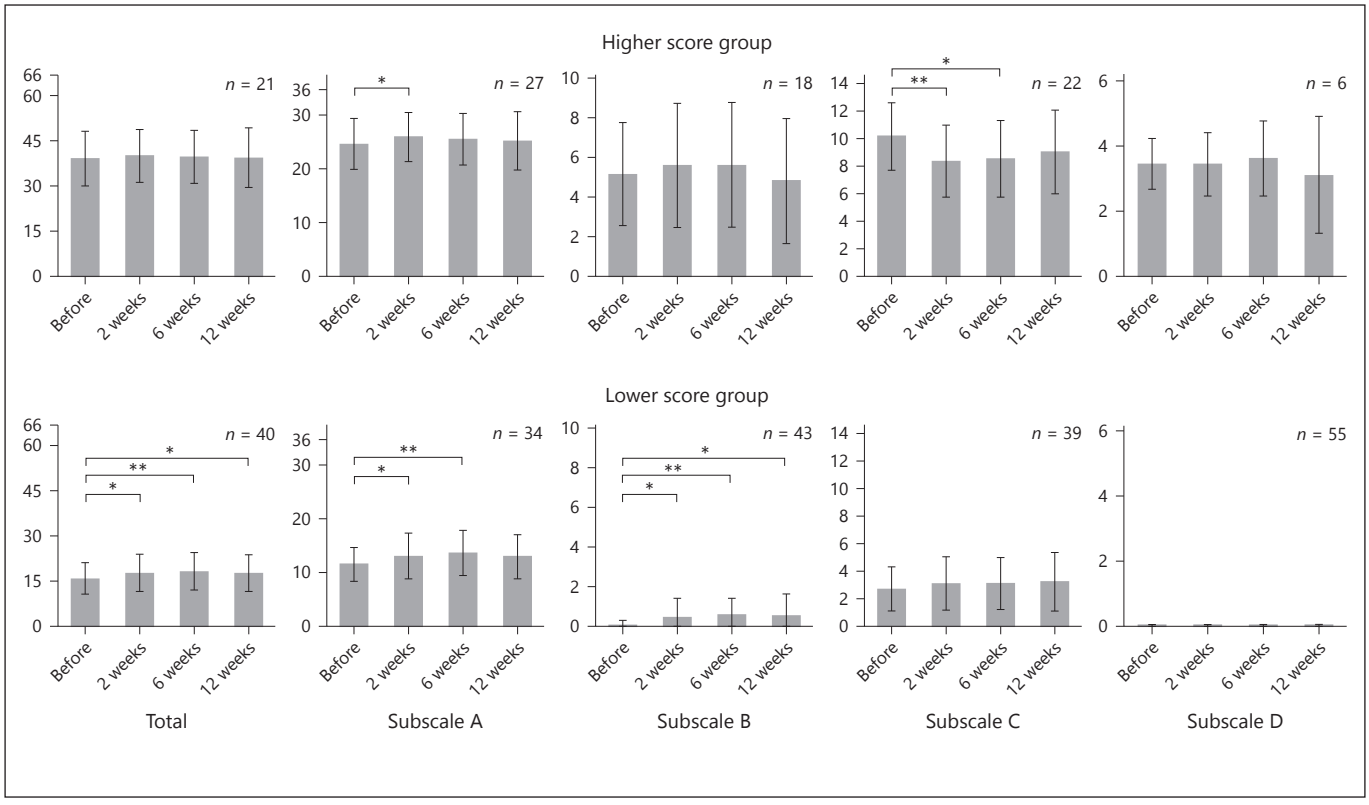

Fig. 1. Changes in FMA-UE. In the higher score group, subscale A improved significantly at 2 weeks, but subscale C decreased significantly at 2 and 6 weeks after BoNT-A administration. In the lower score group, total and subscale B improved significantly at 2, 6, and 12 weeks, while subscale A improved significantly at 2 and 6 weeks after BoNT-A administration. Data is presented as mean ± SD. Wilcoxon signed-rank test with Bonferroni correction, * $p < 0.05$, ** $p < 0.01$.

patient with relatively good voluntary motor function, we should carefully judge the indications for administration.

Statement of Ethics

Patients (or their parents or guardians) gave written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors declare that they have no conflicts of interest to disclose.

Authors Contribution

K.F.: contributed to research planning and writing the manuscript. H.K., Y.K., and E.S.: contributed to research planning, implementation and analysis. H.O., N.N., A.I., Y.O., M.Y., and H.T.: contributed to the collection of research data.

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