学位論文

表題

Spasticity and Range of Motion Over Time in Stroke Patients who Received Multiple-Dose Botulinum Toxin Therapy

（複数回ボツリヌス療法を実施した脳卒中患者における痙縮および関節可動域の経時的変化）

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Title

Spasticity and Range of Motion Over Time in Stroke Patients who Received Multiple-Dose Botulinum Toxin Therapy

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Abstract

Objective

This study examined how the effects of botulinum toxin therapy changed over time by sequential evaluation of clinical improvements in spasticity and contracture in 24 chronic-stage stroke patients on repeated botulinum toxin therapy who were receiving fewer rehabilitation interventions.

Methods

Botulinum toxin injection was administered into the spastic muscle of the paralyzed upper or lower limb 5 times with at least 3-month intervals. Modified Ashworth Scale and range of motion were measured before and 2 weeks after each dose in the extremities to compare the first measurement value with subsequent values. Each pre-dose value was also compared with the first pre-dose value.

Results

Compared with pre-dose scores, Modified Ashworth Scale significantly improved in all flexors after 2 weeks from the first to fifth doses. Range of motion significantly improved in wrist dorsiflexion and ankle dorsiflexion. Comparison of values before each dose versus the first pre-dose value showed significant improvement both in the Modified Ashworth Scale score of wrist flexors, finger flexors, and ankle planter flexors, and the range of motion of elbow extension, wrist dorsiflexion, and ankle dorsiflexion.

Conclusion

The comparison of pre-dose values versus 2-week post-dose values indicated that the effect of botulinum toxin formulation would not lessen after repeated injections with continuous improvements of Modified Ashworth Scale and range of motion. The

comparison of pre-dose values versus the first pre-dose value also suggested that multiple injections of botulinum toxin formulation could be more effective in reducing spasticity and increasing the range of motion than a single injection.

Keywords

Spasticity; stroke; botulinum toxin A therapy; Modified Ashworth Scale; Range of Motion

Introduction

The number of disorders related to stroke is increasing worldwide with the aging of the population.[1] Spasticity associated with stroke is a chronic disorder requiring treatment for many years. It is reported that spasticity occurs in 40% of stroke patients,[2] of which 4% to 20% will have disability with severe spasticity.[3,4] The incidence of spasticity is higher in patients who visit rehabilitation facilities and that of severe or symptomatic spasticity seems to be from 30% to 36%.[5] In patients with spasticity, the upper limbs present the Wernicke-Mann posture with a predominance of flexor synergy, and the lower limbs often present the equinovarus position of the ankle. This condition is not only undesirable in appearance, it can also affect the patient's activities of daily living (ADL), complicate nursing care, and cause pain and secondary complications.[6,7]

Different types of treatments are available for spasticity, including drug therapy, physical therapy, and surgical procedures. Among these, botulinum toxin therapy using botulinum toxin type A (BoNT-A) represents a typical local treatment of spasticity that is less invasive than motor point block or surgical treatment with fewer side effects compared with oral antispasticity drugs.[8-12] It is commonly used overseas as a treatment for post-stroke sequelae and other spasticity symptoms. In Japan, the benefit of BoNT-A has been demonstrated against spasticity in patients with stroke[13,14] and BoNT-A injections were approved for insurance coverage in the indication for upper and lower limb spasticity in October 2010. The use of BoNT-A injections to relieve spasticity prior to rehabilitation interventions allows medical professionals to provide stretching and exercise therapy to patients with increased joint flexibility, and work positively for appropriate control of spasticity.

Simpson et al.[15] proposed the possible effects of repeated injections of BoNT-A as a research subject that should be followed up over a long period in the future. There are a few case reports[16-18] and studies[19-22] on the use of multiple injections of BoNT-A for spasticity. However, to our knowledge, no studies have investigated the possible effects of long-term, repeated-dose BoNT-A therapy on spasticity and range of motion in a setting less accessible to rehabilitation. Some articles report on the usefulness of the BoNT-A injection and intensive rehabilitation exercise. However, the clinical course of patients who had the BoNT-A injection with minimal exercise is uncertain. We suppose that in a region in which there are few hospitals and therapists, for example in largely rural areas of Japan like Hokkaido, many patients would not have sufficient rehabilitation exercise to improve their physical condition. So, it is important to clarify the effectiveness of the BoNT-A injection in patients who could not participate in intensive rehabilitation exercise. In this study, we retrospectively reviewed the effectiveness of multiple-dose BoNT-A therapy on relieving spasticity and range of motion with minimal amount of exercise in patients with chronic stroke patients.

Methods

This therapy and study were conducted in compliance with the Helsinki Declaration to ensure due protection of the subjects. All study subjects provided consent after being given sufficient information on this study. The conduct of this study and therapy was approved by the Asahikawa Medical University Ethics Committee.

The subjects of this study had to fulfill the following criteria: (1) Patients with upper or lower limb spasticity associated with stroke (spasticity of Modified Ashworth Scale grade 1 or higher), (2) The time from the onset of stroke to the study treatment is more than 2 years, (3) Outpatients of the Asahikawa Medical University Hospital or the

Asahikawa Rehabilitation Hospital who desire to receive further rehabilitation for upper or lower limb spasticity, (4) Absence of contraindications for BoNT-A injections,[7] (5) Have a history of 2 or more injections of BoNT-A between November 2012 and April 2016; (6) Spasticity and range of joint motion had been evaluated before and after treatment with BoNT-A injection. We set the evaluation schedule before and 2 weeks after BoNT-A injection in order to determine the positive pharmacological effects. After that, we usually evaluated the patient's condition every month; and (7) Physical therapy or occupational therapy is performed once a week or less. The Japanese insurance system does not support chronic stroke patients in receiving frequent rehabilitation exercise at outpatient clinics, and in our hospital, chronic stroke patients are rarely able to participate in frequent rehabilitation exercise. It is meaningful to know the features of patients who have insufficient exercise, such as at least once a month, and up to 3 times a month.

Forty patients were evaluated before the first dose of BoNT-A and 2 weeks after the injection. Sixteen out of the 40 patients dropped out due to difficulties in visiting the hospital. Fifteen patients changed their doctors to nearby physicians, and 1 patient had financial problems in paying for the treatment. Evaluations before 5 doses of BoNT-A and 2 weeks after each dose were available from 24 out of 40 patients (treatment group). The patients' backgrounds are shown in Table 1. Mean age ± SD of 59.9 ± 13.1 years, disease duration after onset of 7.0 ± 3.1 years. The stroke types of these patients were cerebral infarction for 9 (37.5%) and cerebral hemorrhage for 15 (62.5%). The current oral medications being taken by the patients were not changed during this study.

Patients received BoNT-A injections into more than one affected muscle of the paralyzed upper or lower limb in at least 3-month intervals and training for self-

rehabilitation exercises. Evaluation of spasticity and range of motion was performed before each dose and 2 weeks after the dose in the paralyzed upper or lower limb. Post-dose evaluation included constant follow-up of patients to decide whether BoNT-A therapy should be continued or discontinued and training of self-rehabilitation exercises. More than 3 months after the former injection, the date, injection site, and the dosage of the next injection were decided according to the degree of spasticity and the patient's request. Multiple injections were allowed only when both objective and subjective treatment responses were observed and the patient's consent was obtained. Multiple injections were not given to patients who reported no perceived effects of treatment and did not wish to continue the therapy or those who did not appropriately follow the instructions on self-rehabilitation exercises after treatment.

We were not able to set a control group for ethical reasons because most spasticity can become severe without appropriate treatment. However, MAS and ROM data were available over time from 3 patients among those who dropped out of BoNT-A therapy and these are shown as a reference (drop-out group). The patients' backgrounds are shown in Table 1. Mean age ± SD of 56.0 ± 34.6 years, disease duration after onset of 6.2 ± 4.1 years. The stroke types of these patients were cerebral infarction for 2 (66.6%) and cerebral hemorrhage for 1 (33.3%). Mean pre-dose MAS and ROM values were compared with those observed from 2 to 49 weeks after dosing.

1. Evaluation

Evaluation procedures were standardized to avoid the influence of changes in spasticity occurring before and after motions on evaluation. One specialist from the rehabilitation department evaluated patients to ensure reproducibility.

(1)Modified Ashworth Scale (MAS).

Ashworth Scale, a semi-quantitative scale developed by Ashworth, is used to assess the severity of spasticity. Bohannon et al.[23] further revised the Ashworth Scale to a 6-point scale and published it as the Modified Ashworth Scale (MAS) with documented high reliability and validity.[24] In the assessment of MAS, passive exercise was applied to the site to be tested in a sitting position and resistance against the motion was measured to estimate the severity of spasticity. This test was performed on elbow flexors, wrist flexors, finger flexors, and ankle planter flexors.

(2)Range of Motion (ROM).

A plastic goniometer (Sakai Medical, Tokyo) was used to measure ROM. Passive ROM was measured for each of elbow extension, wrist dorsiflexion (fingers in a flexed position), wrist dorsiflexion (fingers in an extended position), finger extension, and ankle dorsiflexion (knee in an extended position).

2. Injection of BoNT-A

Several injection sites were selected from the following muscles: greater pectoral, biceps, triceps, brachioradialis, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum superficialis, flexor digitorum profundus, flexor pollicis longus, adductor muscle of the thumb, lumbricales in the upper extremities; and medial gastrocnemius, lateral gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, extensor hallucis longus, and flexor digitorum longus in the lower extremities. BoNT-A was injected according to the guidelines published by Sheean et al.[6] The concentration of BoNT-A injection was set at 2.0 U/0.1 ml. Following the specified dosage and administration, the dosage was ≤100 units per muscle, below a total of 360 units for the upper and lower limbs combined.

Injection was consistently performed under electrical nerve stimulation to ensure accurate injection into the target muscle.

3. Training of self-rehabilitation and activities of daily living

Patients received training on the stretching methods of the elbow flexors, wrist flexors, finger flexors, and ankle planter flexors once a week or less because in our region, there are no rehabilitation services that can provided exercise more than once a week due to there being few therapists and few hospitals. At every medical examination, we asked patients whether their home exercise programs were performed correctly. On the injection day, 20 minutes ROM exercise was performed on a one-to-one basis after the injection. Patients were requested to stretch their paretic upper and lower limbs as a home exercise, but it seemed to be difficult for them to do so by themselves, and it was also difficult for their family to help them in some cases. In that situation, we recommended them to make a brace in order to assist their stretching. A continuous joint extension brace with a Taumel mechanism for the elbow joint was prescribed for 2 patients in order to assist continuous extension of shortened flexor muscles. A wrist and finger joints extension brace was prescribed for one patient. We instructed patients to wear the brace once or twice a day for about 20 to 30 minutes each.

The patients received conventional rehabilitation in the hospital about twice a month. The purpose of the rehabilitation was to improve ADL, gait performance, and ROM of the paretic limbs.

4. Statistical processing

The evaluation parameters were compared at every treatment before the dose and 2 weeks after the dose of BoNT-A. Evaluation before the first dose was compared with

the second to fifth evaluations. According to the method described by Kaji et al.,[13,14] an additional one point (1+) in MAS score was converted to 1.5 for statistical testing.

Furthermore, improvement was calculated by subtracting the value 2 weeks after the dose from the pre-dose value, and compared between the first dose and the second to fifth doses.

In addition, the number of days between each treatment was compared with the number of days from the first to the second BoNT-A injection up to the fifth dose.

Wilcoxon's signed rank sum test was used to test MAS scores and improvement in MAS scores, and paired *t*-test was used to test ROM, improvement in ROM, and dosing intervals with a significance level of <5% ($P < 0.05$). SPSS 12.0J software (SPSS, Tokyo) was used for statistical analysis.

Results

The first, second, third, fourth, and fifth doses were administered to 40, 38, 36, 31, and 24 patients, respectively.

Table 2 shows injected muscles, mean units of dose, and the percentage of patients who were followed up throughout 5 doses. The total units of dose were 272.6 ± 82.1 U for the first, 302.6 ± 63.8 U for the second, 303.9 ± 67.7 U for the third, 326.3 ± 55.3 U for the fourth, and 339.1 ± 33.9 U for the fifth dose.

1. Comparison between pre-dose and 2-week post-dose MAS/ROM (pre-dose vs. 2-week post-dose from the first to fifth dose) (Table 3 and Fig.1)

MAS

Overall, MAS scores measured 2 weeks after each dose significantly improved compared with each pre-dose score for all doses from the first to fifth treatment ($P < 0.05$).

ROM

Wrist dorsiflexion (finger extension position) and ankle dorsiflexion measured 2 weeks after each dose significantly improved compared with each pre-dose range for all doses from the first to fifth treatment ($P < 0.05$). A significant improvement was observed in elbow extension at the second dose and wrist dorsiflexion (finger flexion position) at the second and third doses ($P < 0.05$). No change was observed for finger extension.

2. Comparison of pre-dose MAS/ROM (first pre-dose vs. second to fifth pre-dose) (Table 4 and Fig.1)

MAS

Compared with first pre-dose scores, muscle tension significantly decreased in wrist flexors before the second and third doses, in finger flexors before the second, third, and fourth doses, and in ankle planter flexors before the second dose ($P < 0.05$). No change was observed for elbow flexors.

ROM

Compared with the first pre-dose ranges, joint angles significantly improved in elbow extension before the fourth dose, in wrist dorsiflexion (finger flexion position) before the second, third, and fourth doses, in wrist dorsiflexion (finger extension position) before the second and fourth doses, in ankle dorsiflexion before the second dose ($P < 0.05$). No change was observed for finger extension because most fingers were capable of extension at the baseline.

3. Improvement of MAS and ROM (initial improvement vs. improvement after the second to fifth dose) (Table 5)

MAS

The degree of improvement decreased in wrist flexors at the second dose and in finger flexors at the second and third doses compared with the initial improvement. No change was observed for other flexors in the improvement from the second to fifth dose relative to the initial improvement.

ROM

The degree of improvement decreased in wrist dorsiflexion (finger flexion and extension positions) at the second, third, and fourth doses and in ankle dorsiflexion at the second and third doses compared with the initial improvement. No change was observed for other joints in the improvement from the second to fifth dose relative to the initial response.

4. Treatment intervals (the number of days between the first dose and the second dose vs. days between subsequent doses)

The treatment interval was 106.2 days from the initial to the second dose, 114.2 days from the second to third dose, 119.4 days from the third to fourth dose, and 139.0 days from the fourth to the fifth dose. There was no significant difference in treatment intervals up to the fifth dose compared with the days between the initial and the second dose.

5. Drop-out group (Fig. 2)

MAS

Before starting injection, MAS scores were 2.3±1.2 in wrist flexors, 2.7±0.6 in finger flexors, and 1.5±0.0 in ankle planter flexors. The following improvement was observed in all flexors 2 weeks after dosing, MAS scores became worse or returned to the pre-dose level at 49 weeks with 2.0±1.0 in wrist flexors, 3.0±0.0 in finger flexors, and 1.5±0.0 in ankle planter flexors.

ROM

ROM before starting injection was as follows: wrist dorsiflexion, 43.3±28.9° (finger flexion position); wrist dorsiflexion (finger extension position), 31.7±27.5°; finger extension, 0.0±0.0° ; and ankle dorsiflexion, 2.5±3.5°. All ROM except finger extension improved 2 weeks after dosing. However, measurements at 49 weeks also became worse or returned to the pre-dose level except for finger extension: wrist dorsiflexion (finger flexion position), 35.0±21.8°; wrist dorsiflexion (finger extension position), 21.7±20.2°; finger extension, 0.0±0.0°; and ankle dorsiflexion, 2.5±3.5°.

Discussion

The total units of injected BoNT-A doses tended to increase with the number of injections from 272.6 ± 82.1 U at the initial dose to 302.6 ± 63.8 U, 303.9 ± 67.7 U, 326.3 ± 55.3 U, and 339.1 ± 33.9 U at the second, third, fourth, and fifth doses, respectively. This could be due to incremental dose escalation of BoNT-A paced with the onset of the therapeutic effect, which was selected instead of bolus injection to prevent ADL or quality of life (QOL) from worsening by decreased muscle contractions at the injection site as a result of excessive effects of BoNT-A injection.

Comparison of pre-dose MAS and 2-week post-dose MAS scores revealed significant improvements for all doses from the first to fifth dose ($P < 0.05$). This indicates that MAS score may improve at every treatment even if BoNT-A is injected repeatedly. Although it is suggested that multiple injections may attenuate the effect, its pharmacological effects seemed to have endured. In the comparison of ROM, while wrist dorsiflexion (finger extension position) and ankle dorsiflexion improved similarly every time, improved elbow extension was observed at the second dose and wrist dorsiflexion (finger flexion position) at the second and third doses. It is likely that the

baseline ROM had been raised at the initial dose and maintained the condition from the fourth to fifth pre-dose evaluations, narrowing the range of improvement. The lack of changes in finger extension could be related to a ceiling effect caused by the less limited extension angle of finger joints. Overall, both MAS and ROM showed a general tendency toward improvement. Picelli et al.[25] reported that the effects of BoNT-A injection decreased when muscular fibrosis is more severe. Since both spasticity and ROM were improved, our patients might be less affected by muscular fibrosis and this may have contributed to the overall good response. We would be able to know the situation more precisely if we could evaluate patients' muscles with an ultrasonic diagnostic method.

Each pre-dose MAS score was compared with the initial pre-dose score. A significant decrease in muscle tension was observed in wrist flexors before the second and third doses, in finger flexors before the second, third, and fourth doses, and in ankle planter flexors before the second dose. There was no change in elbow flexors. Compared with ROM measured before the first dose, joint angles significantly improved in elbow extension before the fourth dose, in wrist dorsiflexion (finger flexion position) before the second, third, and fourth doses, in wrist dorsiflexion (finger extension position) before the second and fourth doses, and in ankle dorsiflexion before the second dose. This suggests that multiple injections of BoNT-A could promote relief of spasticity and joint angle more than a single injection could do. However, no change was observed for finger extension. This was also considered due to the ceiling effect.

The comparison of improvements suggests that muscle tension could be relieved in a similar way every time BoNT-A injections are administered repeatedly. In the assessment using MAS, the degree of improvement decreased in wrist flexors at the

second dose and in finger flexors at the second and third doses compared with the initial improvement. Pre-dose MAS scores lower than the initial score were thought to be the cause of this result, rather than an attenuation of effect. The degree of ROM improvement also decreased in wrist dorsiflexion (finger flexion and finger extension positions) at the second, third, and fourth doses and in ankle dorsiflexion at the second and third doses compared with the initial improvement. Similarly to MAS, this could be due to the improvement of pre-dose ROM compared with the initial range, which relatively decreased the range of improvement between pre-dose ROM and 2-week post-dose ROM.

Treatment intervals were 106.2 days from the first to second doses, 114.2 days from the second to third doses, 119.4 days from the third to fourth doses, and 139.0 days from the fourth to fifth doses. Although treatment intervals tended to be prolonged with increasing number of injections, there was no significant difference in the number of days for each interval. In chronic stroke patients administered BoNT-A injections, reduced muscle tonus would recover within several months. So, some patients want to have the next injection before 3 months. The tendency to elongate the injection interval in our study may suggest the effectiveness of repeated BoNT-A injections. It may be possible to reduce patients' spasticity without intensive rehabilitation therapy by repeating BoNT-A injections. According to previous studies, relief of muscle tension occurs within 2 weeks of BoNT-A injection and disappears in 3 to 4 months.[14,26-29] Therefore, the pharmacological effects can last from 3 to 4 months and another injection of BoNT-A is needed when the pharmacological effects wear off. Ashford et al.[30] reported a significant response in MAS score at the 16-week evaluation in patients who were being treated with BoNT-A while on rehabilitation. Farina et al.[31] reported that

botulinum toxin therapy combined with casting could be effective for extending the duration of treatment effect. Takekawa et al.[32] pointed out the importance of rehabilitation after BoNT-A injection, describing that daily exercises such as stretching would be needed in addition to the rehabilitation provided in facilities; in contrast, BoNT-A therapy would not be suitable for people who may be unable to commit to self-rehabilitation, including home care training of the family members, because the effects of BoNT-A therapy are unlikely to last long in such a case. Roche[33] et al. divided patients with chronic stoke into 2 groups of either botulinum therapy + standardized self-rehabilitation program or botulinum therapy alone and performed evaluation before the botulinum injection and 1 month after the injection. The authors reported that MAS had no significant difference between groups, but maximum walking speed, 6-min walk distance, and the time of stepping up and down stairs improved in the patient group with a self-rehabilitation program, suggesting its adjunctive role for gait improvement when used in combination with botulinum injection. Hara et al.[22] reported functional improvement of the lower extremities by repeated doses, but under the condition of hospitalized intensive rehabilitation. The subjects of this study were only able to receive rehabilitation with physical or occupational therapy at a limited frequency as low as once a week. In such a situation, however, it is possible to improve MAS and ROM outcomes by repeated-dose botulinum toxin therapy in combination with self-rehabilitation training, which is also expected to increase ADL and QOL. We believe that self-rehabilitation training is important since, in the current rehabilitation system of Japan, continued use of outpatient physical and occupational therapy services is difficult during the home-based maintenance phase.

Spasticity after cerebrovascular disorder affects as much as a half of patients with motor dysfunction.[2] In patients with clinical spasticity, the activities of daily living can decrease with pain, gait disorder, and impairment of joint movement. Spasticity also causes difficulty in providing effective rehabilitation for patients. Despite a strong urgent need for clear explanation of the underlying mechanism in this context, basic research on spasticity has not progressed until recent years. One of the reasons may be that there have been few experimental reports that used spasticity model animals. After Fulton et al.[34] reported the development of spasticity in primates such as monkeys from which the motor cortices of the cerebrum and prefrontal area were removed, only a few studies with spasticity model animals have been published.[35-37] Long-term observation studies like ours are scarce. Future advancement of basic spasticity research may expand the possibilities of drug development and effective rehabilitation by reflecting the pathogenetic mechanism.

We were not able to set a control group for ethical reasons because most spasticity can become severe without appropriate treatment. However, MAS and ROM data were available over time from 3 patients among those who dropped out of BoNT-A therapy and these are shown as a reference. Both the MAS and ROM of these patients improved 2 weeks after dosing, but returned to the pre-dose level or became negative at 49 weeks in the drop-out group. This represents the clinical course of untreated patients. Meanwhile in the repeated BoNT-A therapy group combined with minimum exercise therapy, spasticity showed remission 2 weeks after every treatment, even a few years after onset. Many of the MAS and ROM values were improved before the second to fifth doses compared with the first pre-dose values. It is possible that patient satisfaction increased with improvement in spasticity, although we did not measure it in this study.

These results, therefore, suggest that multiple BoNT-A injection therapy plus minimum exercise therapy could be an effective treatment for spasticity. Most previous studies have focused on a combination with intensive rehabilitation[22,38] and there have been no reports on patients who have no ability to undertake full rehabilitation. Hence, we believe our study results to be important.

The limitations of this study include the time of development of spasticity after stroke and heterogeneity in the timing of BoNT-A injections. MAS can measure muscle tension, but strictly speaking, it is not an assessment scale specific to spasticity. Most of the studies on spasticity may involve a fundamental defect related to tendinous compliance[39] and physiological, morphological, and histochemical changes in muscle fibers,[40] which can cause resistance at the time of stretching exercises and may overestimate spasticity. While MAS is an ordinal scale, many studies commonly use descriptive statistics as the primary analysis method for statistical judgment. Even with these methodological limitations of this study, our study results showed definite improvement from the baseline and we believe that this is clinically meaningful.

Conclusions

This study followed up the treatment of spasticity with long-term multiple injections of BoNT-A with minimal exercise and confirmed that it was beneficial for relieving spasticity and improving ROM with minimal exercise.

MAS measured 2 weeks after dosing significantly improved from the first to fifth doses in all flexors compared with the pre-dose scores. ROM also significantly improved in wrist dorsiflexion and ankle dorsiflexion. This indicates that the effect of botulinum toxin formulation would not lessen after repeated injections with continuous improvements of MAS and ROM. When each pre-dose value was compared with the

first pre-dose value, significant improvement of MAS was observed in wrist flexors, finger flexors, and ankle planter flexors, and that of ROM was noted in elbow extension, wrist dorsiflexion, and ankle dorsiflexion, suggesting multiple injections of botulinum toxin formulation could be more effective in reducing spasticity and increasing the range of motion than a single injection. In contrast, no improvement occurred after 19 weeks of treatment in the drop-out group. Therefore, repeated administration of botulinum toxin could promote recovery from spasticity and correct the range of joint motion with infrequent rehabilitation, and the effect is likely to be maintained for a long period of time.

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Tables and Figures

Table 1 Backgrounds of patients

Table 2 The number of units of BoNT-A injection and the percentage of patients injected

Mean ± SD (units). The percentages indicate the percentage of patients who received injections to the relevant muscle in the entire patient population (%).

Table 3 Comparison of pre-dose and 2-week post-dose MAS and ROM

Values before injection vs. 2 weeks after injection. Mean ± SD. 1 pre, before the first dose:1 post, 2 weeks after the first dose; 2 pre, before the second dose; 2 post, 2 weeks after the second dose; 3 pre, before the third dose; 3 post, 2 weeks after the third dose; 4 pre, before the fourth dose; 4 post, 2 weeks after the fourth dose; 5 pre, before the fifth dose; 5 post, 2 weeks after the fifth dose; MAS, Modified Ashworth Scale; ROM, Range of Motion

* Wilcoxon signed rank sum test ($P < 0.05$)

† Wilcoxon signed rank sum test ($P < 0.01$)

‡ Paired t-test ($P < 0.05$)

§ Paired t-test ($P < 0.01$)

Table 4 Changes in MAS and ROM values before the first dose and before the second to fifth dose with BoNT-A

Values before the first dose vs. before the second to fifth dose. Mean± SD. 1 pre, before the first dose; 2 pre, before the second dose; 3 pre, before the third dose; 4 pre, before the fourth dose; 5 pre, before the fifth dose; MAS, Modified Ashworth Scale; ROM, Range of Motion

* Wilcoxon signed rank sum test ($P < 0.05$)

† Wilcoxon signed rank sum test ($P < 0.01$)

‡ Paired t-test ($P < 0.05$)

§ Paired t-test ($P < 0.01$)

Table 5 Improvement before and after each dose

The degree of improvement was calculated by subtracting values 2 weeks after the dose from each pre-dose value. Initial improvement vs. improvement at the second and fifth dose. Mean ± SD. 1st, first dose; 2nd, second dose; 3rd, third dose; 4th, fourth dose; 5th, fifth dose; MAS, Modified Ashworth Scale; ROM, Range of Motion.

* Wilcoxon signed rank sum test ($P < 0.05$)

‡ Paired t-test ($P < 0.05$)

§ Paired t-test ($P < 0.01$)

Figure 1 Comparison of MAS score

1 pre, before the first dose; 1 post, 2 weeks after the first dose; 2 pre, before the second dose; 2 post, 2 weeks after the second dose; 3 pre, before the third dose; 3 post, 2 weeks after the third dose; 4 pre, before the fourth dose; 4 post, 2 weeks after the fourth dose; 5 pre, before the fifth dose; 5 post, 2 weeks after the fifth dose. MAS, Modified Ashworth Scale.

* Wilcoxon signed rank sum test ($P < 0.05$)

† Wilcoxon signed rank sum test ($P < 0.01$)

Figure 2 MAS and ROM of drop-out group

A

wrist, wrist flexors; finger, finger flexors; ankle, ankle planter flexors

B

wrist (FF), wrist dorsiflexion (finger flexion position); wrist (FE), wrist dorsiflexion (finger extension position); finger, finger extension; ankle, ankle dorsiflexion

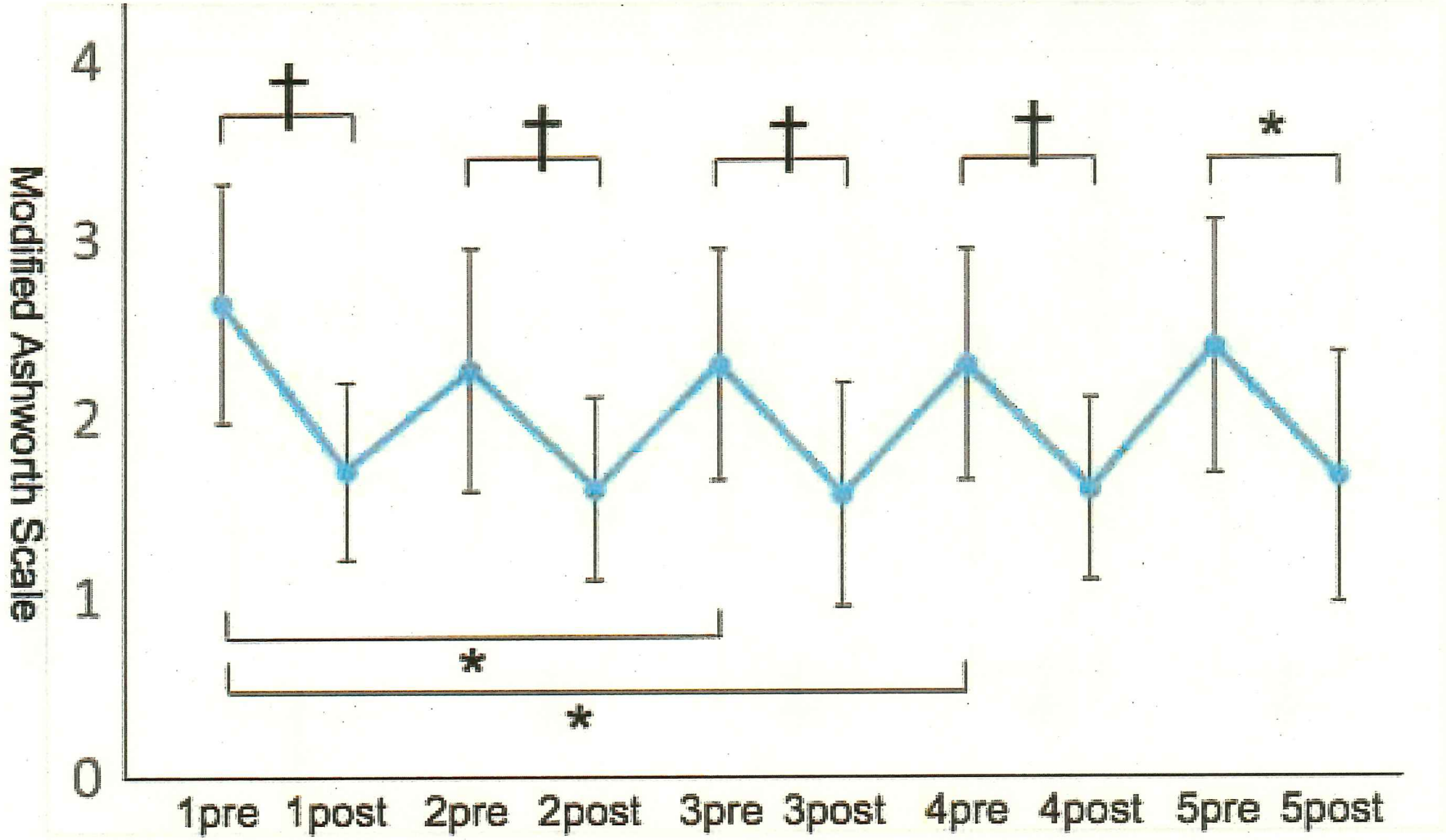

Fig. 1 A M A S (elbow flexors)

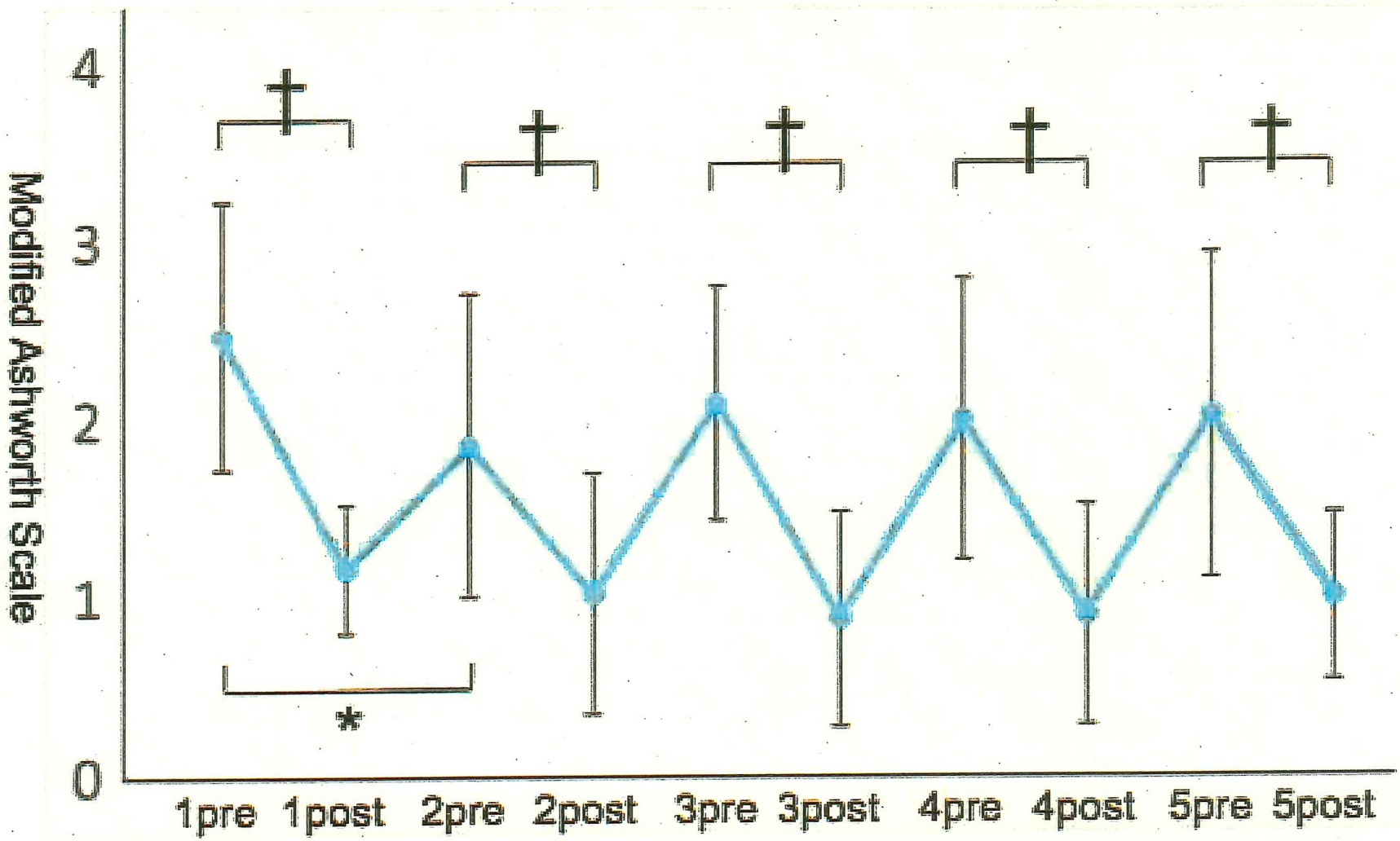

Fig. 1 B M A S (wrist flexors)

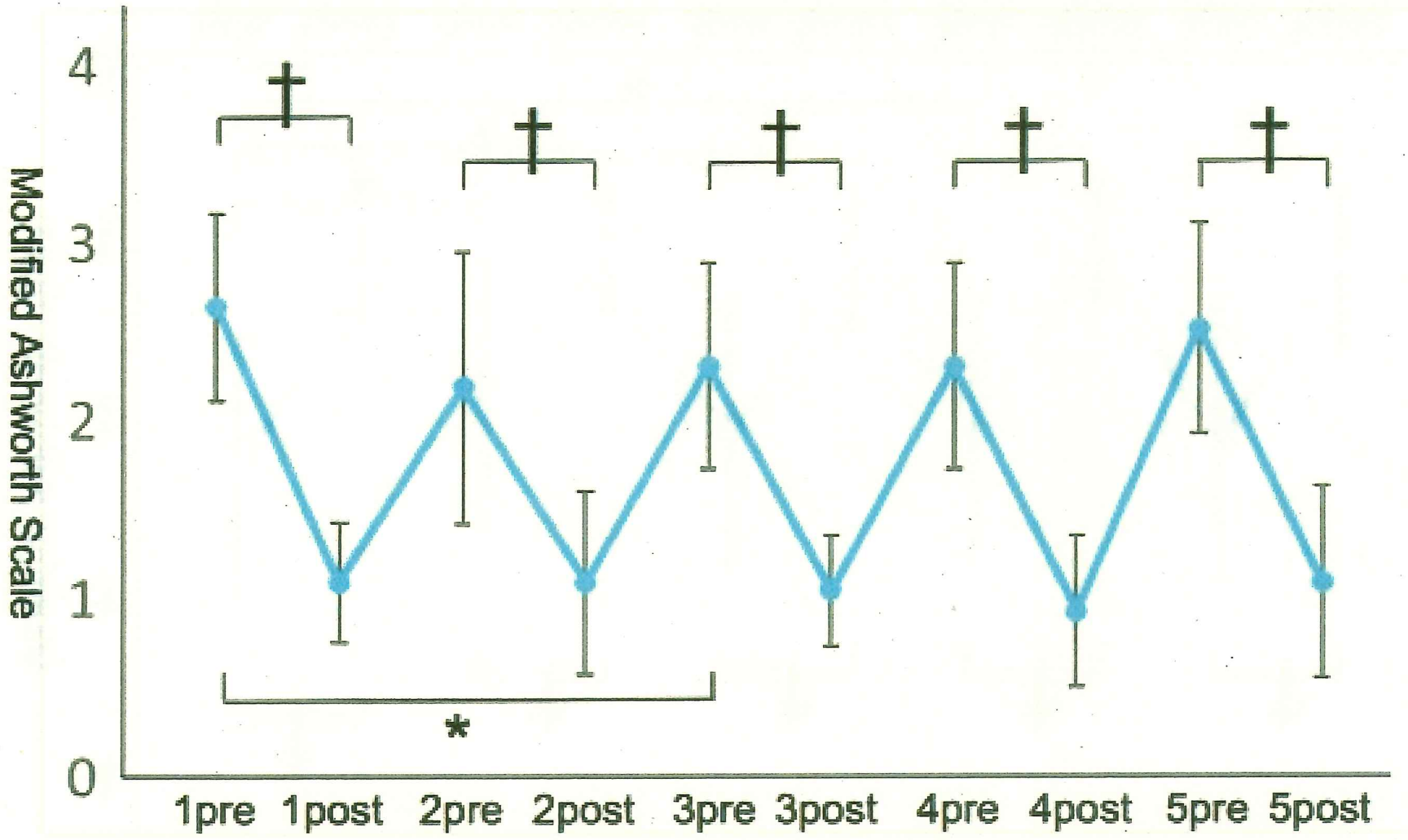

Fig.1 C M A S (finger flexors)

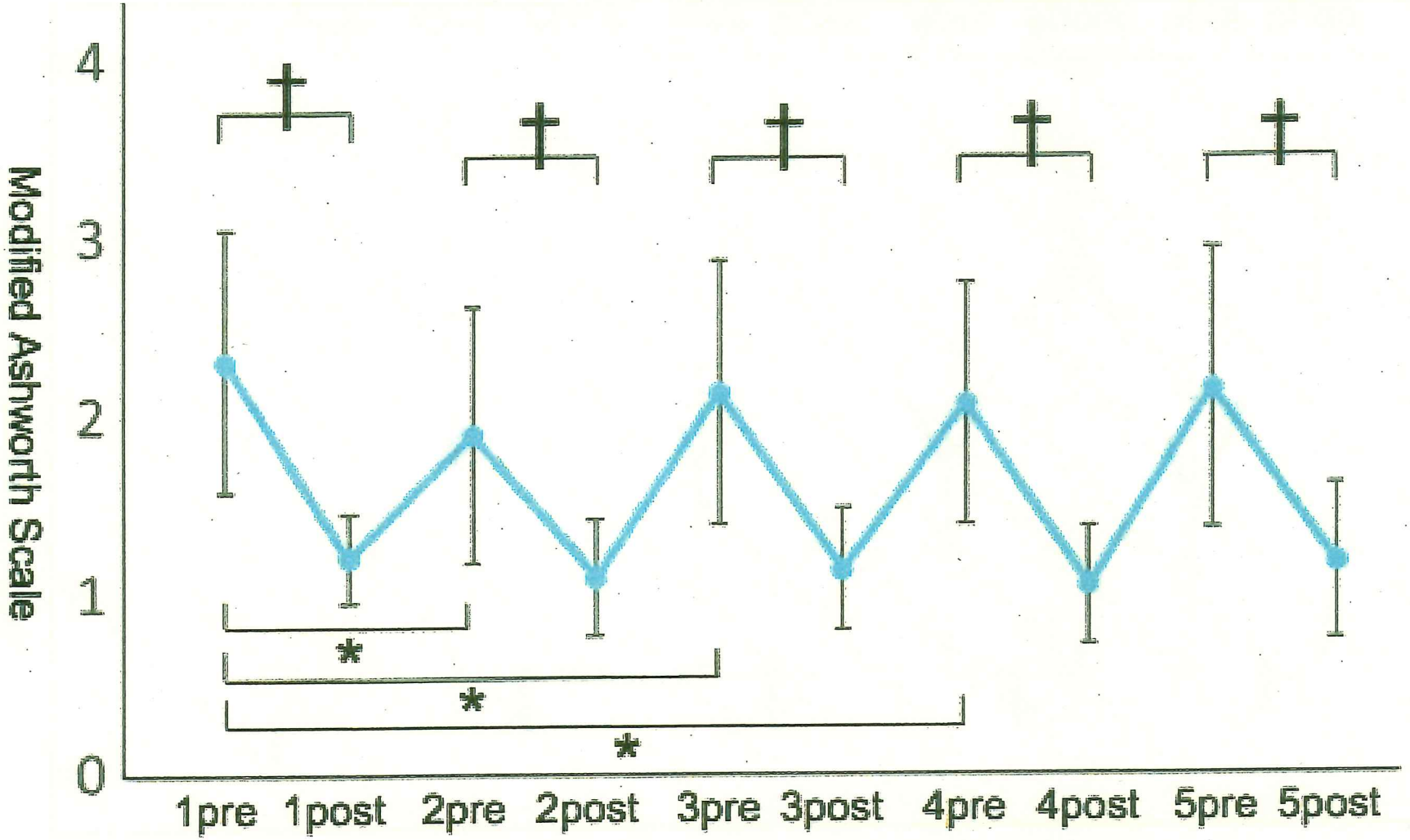

Fig. 1 D M A S (ankle plantarflexors)

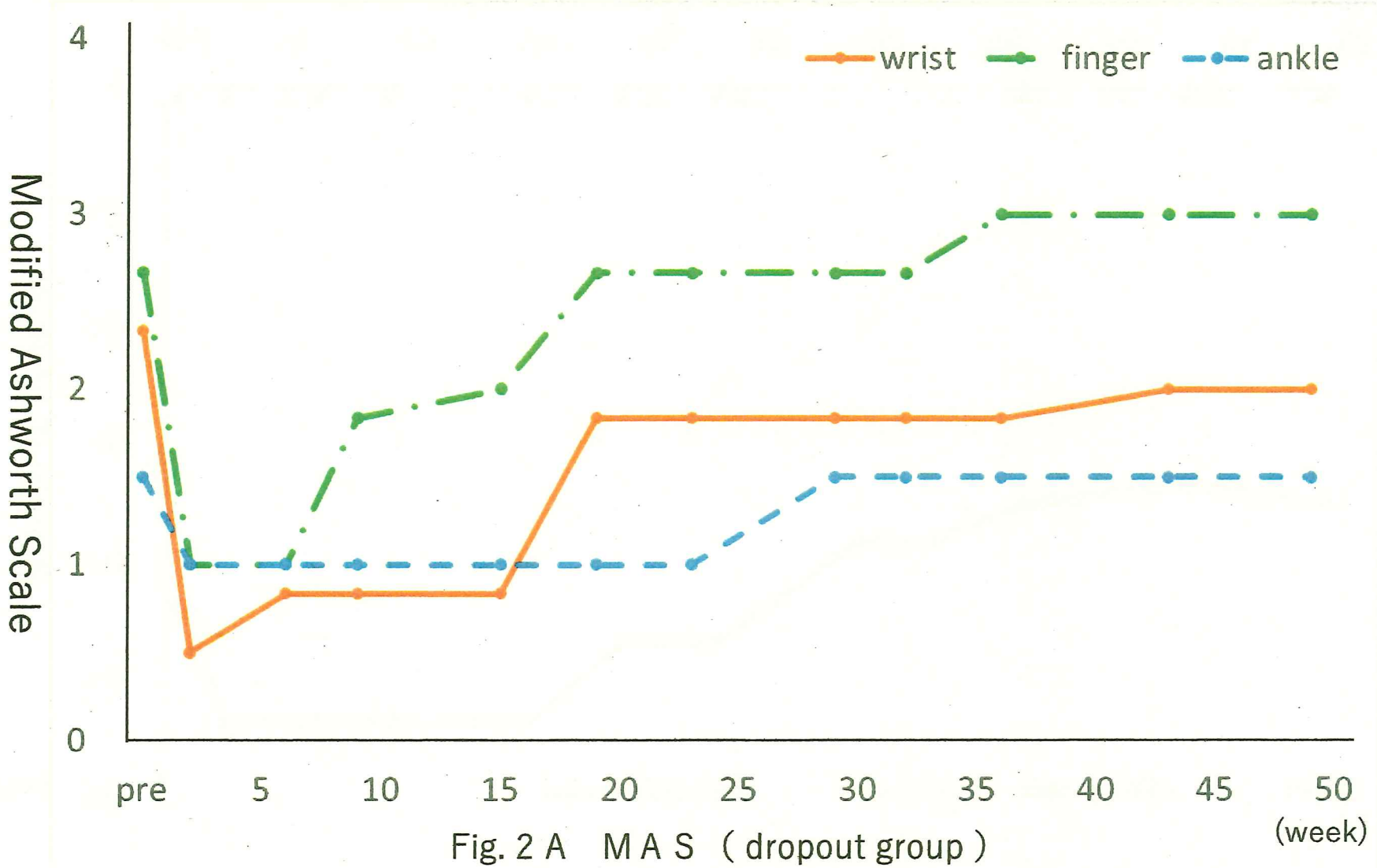

Fig. 2 A M A S (dropout group)

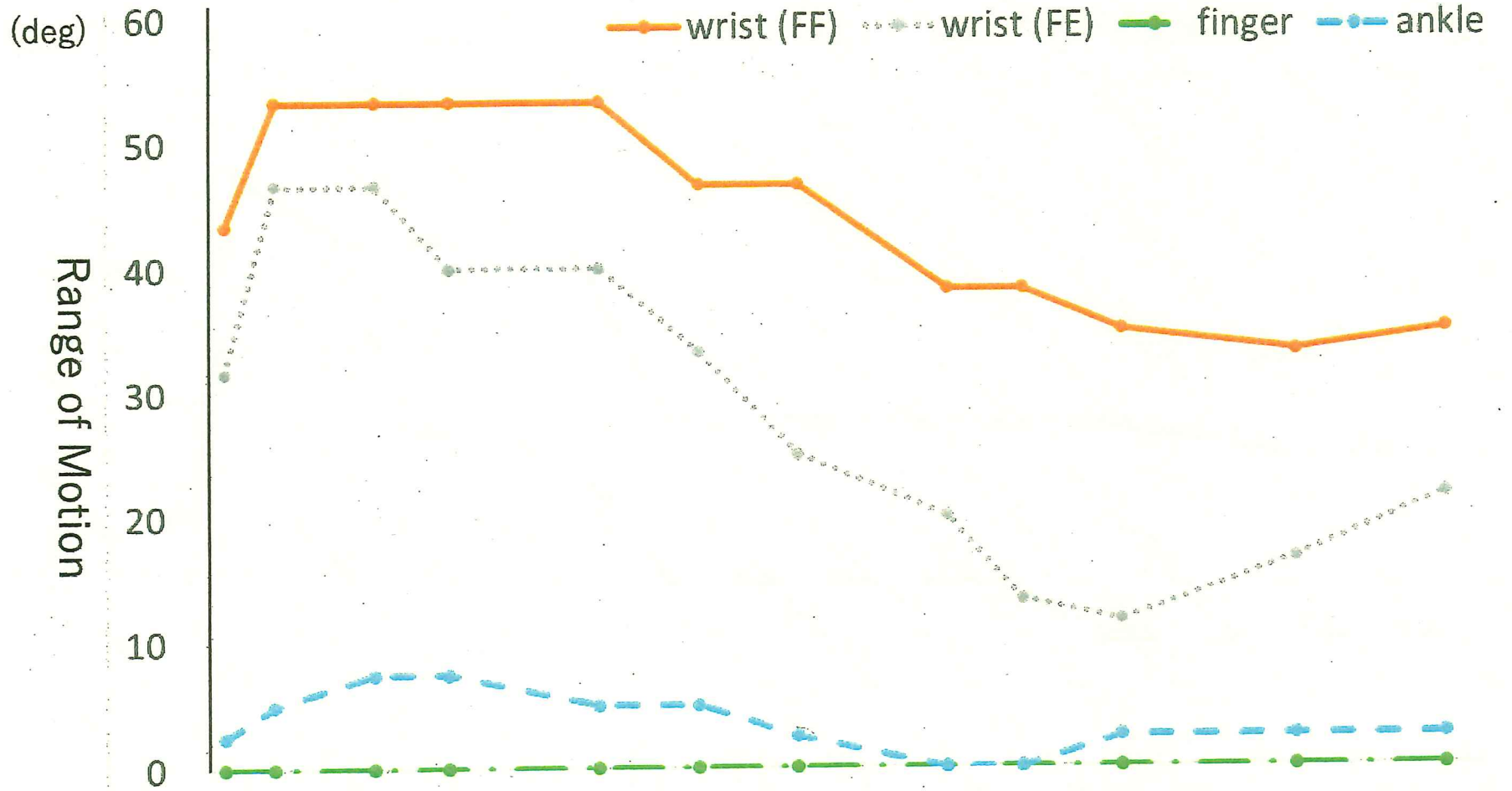

Fig. 2 B ROM (dropout group)

Table 1. Backgrounds of patients		
	treatment group (n=24)	drop-out group (n=3)
Age (years, mean±SD)	59.9±13.1	56.0±34.6
Gender (No. of men/women, %)	Men: 13(54.2)	3(100.0)
	Women: 11(45.8)	0(0.0)
Stroke type (No. of cases, %)	Cerebral infarction: 9(37.5)	2(66.6)
	Cerebral hemorrhage: 15(62.5)	1(33.3)
Time after stroke onset (years, mean±SD)	7.0±3.1	6.2±4.1
Paralyzed side (No. of cases, %)	Right: 11(45.8)	1(33.3)
	Left: 13(54.2)	2(66.6)

Table 2 The number of units of BoNT-A injection and the percentage of patients injected

First dose (24 patients)	Mean (U)	SD	Percentage (%)
Total	272.6	82.1	
Greater pectoral	42.5	10.6	8.7
Biceps	61.4	21.9	47.8
Brachioradialis	60.0	0.0	4.3
Flexor carpi radialis	42.3	10.8	47.8
Flexor carpi ulnaris	42.5	9.2	43.5
Flexor digitorum superficials	41.8	12.7	60.9
Flexor digitorum profundus	39.2	12.6	56.5
Flexor pollicis longus	18.0	4.5	21.7
Adductor muscle of the thumb	20.0	0.0	13.0
Lateral gastrocnemius	52.5	19.4	52.2
Medial gastrocnemius	52.5	19.4	52.2
Soleus	58.1	17.1	34.8
Tibialis posterior	60.0	14.7	60.9
Flexor digitorum longus	52.5	20.8	52.2
Flexor hallucis longus	60.0	0.0	8.7

Second dose (24 patients)	Mean (U)	SD	Percentage (%)
Total	302.6	63.8	
Biceps	54.2	18.7	52.2
Brachioradialis	44.5	20.5	8.7
Flexor carpi radialis	33.2	12.2	60.9
Flexor carpi ulnaris	33.9	12.9	60.9
Flexor digitorum superficials	33.2	11.7	73.9
Flexor digitorum profundus	35.3	13.0	78.3
Flexor pollicis longus	21.1	7.8	39.1
Extensor hallucis longus	30.0	0.0	4.3
Adductor muscle of the thumb	12.5	10.6	8.7
Lateral gastrocnemius	59.3	12.2	65.2
Medial gastrocnemius	59.3	12.2	65.2
Soleus	58.8	7.9	34.8
Tibialis posterior	57.5	14.8	69.6
Flexor digitorum longus	48.5	15.6	43.5
Flexor hallucis longus	45.0	12.9	17.4

Third dose (24 patients)	Mean (U)	SD	Percentage (%)
Total	303.9	67.7	
Biceps	52.5	25.6	52.2
Triceps	60.0	28.3	8.7
Brachioradialis	45.0	12.9	17.4
Flexor carpi radialis	32.5	10.8	69.6
Flexor carpi ulnaris	32.5	10.8	69.6
Flexor digitorum superficials	34.2	10.2	82.6
Flexor digitorum profundus	33.7	10.7	82.6
Flexor pollicis longus	14.3	5.3	30.4
Extensor hallucis longus	27.5	3.5	8.7
Adductor muscle of the thumb	16.7	5.8	13.0
Lateral gastrocnemius	50.7	15.3	60.9
Medial gastrocnemius	52.9	11.6	60.9
Soleus	54.2	13.6	26.1
Tibialis posterior	51.2	11.8	73.9
Flexor digitorum longus	47.0	15.8	65.2
Flexor hallucis longus	43.8	14.9	17.4

Fourth dose (24 patients)	Mean (U)	SD	Percentage (%)
Total	326.3	55.3	
Biceps	44.3	11.8	65.2
Triceps	35.0	7.1	8.7
Brachioradialis	47.0	8.4	21.7
Flexor carpi radialis	29.7	12.7	69.6
Flexor carpi ulnaris	29.7	12.7	69.6
Flexor digitorum superficials	29.5	12.0	91.3
Flexor digitorum profundus	27.9	11.3	82.6
Flexor pollicis longus	16.7	5.2	26.1
Extensor hallucis longus	25.0	7.1	8.7
Adductor muscle of the thumb	10.0	0.0	8.7
Lateral gastrocnemius	54.4	16.4	78.3
Medial gastrocnemius	54.4	16.4	78.3
Soleus	64.2	9.2	26.1
Tibialis posterior	50.3	7.8	78.3
Flexor digitorum longus	51.6	8.9	69.6
Flexor hallucis longus	38.0	13.0	21.7

Fifth dose (24 patients)	Mean (U)	SD	Percentage (%)
Total	339.1	33.9	
Greater pectoral	50.0	0.0	9.1
Biceps	47.8	10.9	40.9
Triceps	40.0	10.0	13.6
Brachioradialis	50.0	0.0	13.6
Flexor carpi radialis	36.5	9.9	59.1
Flexor carpi ulnaris	36.5	9.9	59.1
Flexor digitorum superficials	39.0	8.4	90.9
Flexor digitorum profundus	40.0	7.3	86.4
Flexor pollicis longus	21.1	9.3	40.9
Extensor hallucis longus	20.0	0.0	4.5
Adductor muscle of the thumb	20.0	0.0	4.5
Lumbricales	20.0	0.0	4.5
Lateral gastrocnemius	49.1	14.9	72.7
Medial gastrocnemius	49.1	14.9	72.7
Soleus	52.9	15.0	31.8
Tibialis posterior	54.2	8.4	86.4
Flexor digitorum longus	52.9	6.1	63.6
Flexor hallucis longus	42.0	13.0	22.7

Table 3 Changes in MAS and ROM before and after each dose

		1 pre	1 post	2 pre	2 post	3 pre	3 post	4 pre	4 post	5 pre	5 post
MAS	Elbow flexors (n=15)	2.6±0.7	1.7±0.5 †	2.3±0.7	1.6±0.5 *	2.3±0.7	1.6±0.6 †	2.3±0.7	1.6±0.5 †	2.4±0.7	1.7±0.7 †
	Wrist flexors (n=21)	2.5±0.8	1.2±0.4 †	1.9±0.9	1.0±0.7 †	2.1±0.7	0.9±0.6 †	2.0±0.8	0.9±0.6 †	2.0±0.9	1.0±0.5 †
	Finger flexors (n=21)	2.6±0.5	1.1±0.3 †	2.2±0.8	1.1±0.5 †	2.3±0.6	1.1±0.3 †	2.3±0.6	0.9±0.4 †	2.5±0.6	1.1±0.5 †
	Ankle plantar flexors (n=23)	2.3±0.7	1.2±0.3 †	1.9±0.7	1.1±0.3 †	2.1±0.7	1.1±0.3 †	2.1±0.7	1.0±0.3 †	2.2±0.8	1.2±0.4 †
ROM	Elbow extension(n=15)	-7.0±11.6	-4.7±11.1	-4.7±8.1	-1.7±5.2 ‡	-4.0±7.4	-2.3±6.5	-3.3±8.4	-2.3±5.3	-5.3±12.3	-4.0±11.2
(degrees)	Wrist dorsiflexion (finger flexion position) (n=21)	49.8±16.2	61.2±7.7 §	59.3±10.4	61.7±8.0 ‡	57.9±10.4	61.7±9.3 ‡	59.1±14.4	61.0±9.4	56.0±14.7	59.1±8.2
	Wrist dorsiflexion (finger extension position) (n=21)	27.9±35.5	50.7±21.9 §	42.1±23.5	52.6±16.4 §	41.7±23.4	54.5±14.7 §	47.1±20.8	55.5±12.6 §	39.3±23.0	54.5±12.1 §
	Finger extension (n=21)	-1.0±3.0	-1.0±3.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
	Ankle dorsiflexion (n=23)	4.1±5.2	10.0±4.5 §	6.3±6.8	8.9±6.4 §	5.7±6.3	9.1±5.3 §	4.1±5.4	9.1±5.4 §	3.3±4.9	7.9±6.2 §

Table 4 Changes in MAS and ROM before the first dose and before the second to fifth dose of BoNT-A

		1 pre	2 pre	3 pre	4 pre	5 pre
MAS	Elbow flexors (n=15)	2.6±0.7	2.3±0.7	2.3±0.7	2.3±0.7	2.4±0.7
	Wrist flexors (n=21)	2.5±0.8	1.9±0.9 †	2.1±0.7 *	2.0±0.8	2.0±0.9
	Finger flexors (n=21)	2.6±0.5	2.2±0.8 *	2.3±0.6 *	2.3±0.6 *	2.5±0.6
	Ankle plantar flexors (n=23)	2.3±0.7	1.9±0.7 *	2.1±0.7	2.1±0.7	2.2±0.8
ROM	Elbow extension(n=15)	-7.0±11.6	-4.7±8.1	-4.0±7.4	-3.3±8.4 ‡	-5.3±12.3
(degrees)	Wrist dorsiflexion (finger flexion position) (n=21)	49.8±16.2	59.3±10.4 §	57.9±10.4 ‡	59.1±14.4 ‡	56.0±14.7
	Wrist dorsiflexion (finger extension position) (n=21)	27.9±35.5	42.1±23.5 ‡	41.7±23.4	47.1±20.8 ‡	39.3±23.0
	Finger extension (n=21)	-1.0±3.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
	Ankle dorsiflexion (n=23)	4.1±5.2	6.3±6.8 ‡	5.7±6.3	4.1±5.4	3.3±4.9

Table 5 Pre-dose improvement and two-week post-dose improvement at each treatment with BoNT-A						
		1st	2nd	3rd	4th	5th
MAS	Elbow flexors (n=15)	0.9±0.5	0.7±0.5	0.7±0.6	0.7±0.6	0.7±0.7
	Wrist flexors (n=21)	1.3±0.7	0.8±0.8 *	1.2±0.6	1.1±0.7	1.0±0.7
	Finger flexors (n=21)	1.6±0.5	1.1±0.7 *	1.3±0.5 *	1.4±0.6	1.4±0.8
	Ankle plantar flexors (n=23)	1.1±0.7	0.8±0.6	1.0±0.7	1.0±0.6	1.0±0.7
ROM	Elbow extension(n=15)	2.3±4.6	3.0±4.1	1.7±4.1	1.0±3.9	1.3±9.0
(degrees)	Wrist dorsiflexion (finger flexion position) (n=21)	11.4±14.0	2.4±4.9 ‡	3.8±7.4 §	1.9±7.7 ‡	3.1±9.6
	Wrist dorsiflexion (finger extension position) (n=21)	22.9±23.2	10.5±14.0 ‡	12.9±14.3 ‡	8.3±13.1 §	15.2±17.8
	Finger extension (n=21)	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
	Ankle dorsiflexion (n=23)	5.9±4.7	2.6±4.0 §	3.0±3.9 ‡	5.0±3.4	4.6±3.4