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Effect of Dual Therapy with Botulinum Toxin A Injection and Electromyography-controlled Functional Electrical Stimulation on Active Function in the Spastic Paretic Hand

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Background: Many previous studies have demonstrated that botulinum toxin A (BTX-A) injections satisfactorily reduce spasticity. Nevertheless, BTX-A, with or without an adjuvant therapy, effectively improves the direct functional movement in few patients with spastic upper extremity paralysis. Therefore the present study aimed to determine the effectiveness of task-orientated therapy on spasticity and functional movement by using electromyography-triggered functional electrical stimulation (EMG-FES) after BTX-A injections.

Design: Open-label, prospective clinical trial

Method: The subjects were 15 patients with spastic paresis (12 male, 3 female; age range, 17–74 years; 14 due to stroke, 1 due to spinal cord injury) who received BTX-A injections. Before the study was started, all subjects had undergone task-orientated therapy sessions with EMG-FES for 4 months. Despite all patients showing a various extent of improved upper extremity function, upper extremity function reached a plateau because of upper extremity spasticity. After BTX-A injection, all patients underwent task-orientated therapy sessions with EMG-FES for 4 months. The outcomes were assessed with the modified Ashworth scale, the simple test for evaluating hand function, box and block test, grip and release test, finger individual movement test, and grip strength. Assessments were performed at baseline and 10 days and 4 months after BTX-A injection.

Results: The median modified Ashworth scale score decreased from 2 at baseline to 1 at 10 days and 4 months after BTX-A injection. The finger individual movement test score increased slightly at 10 days (p =0.29) and further increased at 4 months (p<0.05). The simple test for evaluating hand function, grip and release test, box and block test, and grip strength decreased after 10 days (p<0.05, p=0.26, p<0.01, and p<0.01, respectively) but increased after 4 months (p<0.01, p<0.05, p<0.01, and p=0.18, respectively).

Conclusion: Task-orientated therapy with EMG-FES after BTX-A injection effectively reduced spasticity and improved upper limb motor function. Our results also suggest that spasticity occurs as a compensation for the force of the affected muscles and leads to misuse movements and ostensible dexterity in many patients. In addition, we hypothesize that BTX-A injection initializes the abnormal adapted movement pattern and that more active hand movements with facilitation of the paretic muscles when using EMG-FES induce an efficient muscle reeducation of the inherent physiological movement pattern that ultimately could prove useful in the activities of daily living. (J Nippon Med Sch 2016; 83: 15–23)

Key words: botulinum toxin, functional electrical stimulation, rehabilitation, muscle spasticity, upper limb

Introduction

Spasticity is a common sequela associated with lesions of the central nervous system. Spasticity of the upper extremity can interfere with the activities of daily living.

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Although patients receive many traditional antispasticity treatments, including conventional physical and occupational therapy, systemic medication, tendon surgery, and the use of orthosis and focal neurolysis such as phenol injections, determining which is optimal is difficult. In the early 1990s, botulinum toxin A (BTX-A) emerged as a commonly used clinical drug. Its use for treating spasticity leads to significant improvement in many patients.

Many previous studies[1–8] have demonstrated that after patients with spastic paralysis receive a BTX-A injection, they have better scores of the modified Ashworth scale and better range of motion (ROM). Nevertheless, the direct effects on upper extremity motor function[5,7,9] and grip strength[6] after BTX-A injection have been observed in few studies. Although BTX-A can reduce spasticity, BTX-A alone does not lead to a complete recovery from paralysis. Therefore, to facilitate the function of paretic muscles after spasticity is reduced, determining if there are more efficient therapies or rehabilitation is important.

Spasticity also activates abnormal synergy patterns (i.e., mass flexion) of the upper extremities, with both the spasticity and synergy contributing to the powerful performance of grip strength. Although compensation movements can appear to cause an early recovery of function, such movements can lead to misuse movements due to the lack of accuracy and efficiency.

For example, the "thumb in palm" hand posture is sometimes observed in patients with spastic paralysis. With this position, the thumb is acutely flexed into the palm and lies under the flexed fingers. These patients are able to pick up a small block by pushing it into the small ulnar space that results from the middle, ring, and little fingers exhibiting spasticity and the abnormal synergy pattern of the upper extremity. However, this abnormal grasp is of little value for the activities of daily living.

The administration of BTX-A in these patients reduces the spasticity of the upper extremities and leads to their hands becoming flaccid. Subsequently, muscular reeducation of the useful hand allows the patient to develop effective and stabile prehensile pinch movements, such as the power grip and the precision grip. (The power grip involves holding an object in a "clamp" that is formed by the partly flexed fingers and the palm, with counter pressure applied by the thumb that lies more or less in the plane of the palm. The precision grip involves pinching the object between the flexor aspects of the fingers and the opposing thumb[10].) The efficient facilitation of the paralysis and muscle reeducation are critical for a patient's rehabilitation; otherwise the patient would not be able to effectively achieve these actions simply from a BTX-A injection alone.

Thus, to achieve neurorehabilitation, therapies such as electromyography (EMG)-triggered functional electrical stimulation (FES) should be applied after BTX-A is injected. Patients with chronic spasticity paralysis who undergo phenol motor point block and task-oriented therapy with EMG-FES are reportedly more likely to have reduced spasticity and enhanced upper extremity functional improvement[11]. These findings suggest that a more active movement therapy, such as task-orientated therapy with EMG-FES, might be an effective treatment for patients with spastic paralysis after BTX-A is injected. Thus, the aim of the present open-label, prospective study was to assess the effectiveness of task-orientated therapy with EMG-FES after a BTX-A injection to improve upper extremity function in patients with spastic paralysis.

Materials and Methods

Subjects were eligible for inclusion in the study if they had had a stroke or spinal cord injury at least 6 months earlier and had motor impairment of the upper extremity due to paresis and focal spasticity. Exclusion criteria included presentation with fixed contractures, previous BTX-A injections or nerve blocks, dementia, severe depression, severe aphasia, and pregnancy or lactation at the time of enrollment. Fifteen patients with upper extremity spastic paresis (due to stroke in 14 patients and due to spinal cord injury in 1 patient) who met the inclusion criteria were recruited from the outpatient rehabilitation services of the Nippon Medical School Chiba Hokusoh Hospital. Patients were enrolled if they did not meet the exclusion criteria. Before starting the study, all subjects underwent occupational therapy sessions with EMG-FES for unilateral paretic upper extremity function, with each session lasting from 40 to 60 minutes, once or twice weekly, for approximately 4 months. Although upper extremity function improved to some extent in all patients, it reached a plateau due to upper extremity spasticity during the EMG-FES therapy.

This study was approved by the Institutional Ethical Review Board of the Nippon Medical School Chiba Hokusoh Hospital and was performed in accordance with the Declaration of Helsinki. All subjects provided informed consent before participating in the study.

The dose of BTX-A (Botox®, Glaxo Smith Kline, Middlesex, UK) was administered according to each patient's individual pattern and severity of spasticity, with the to-

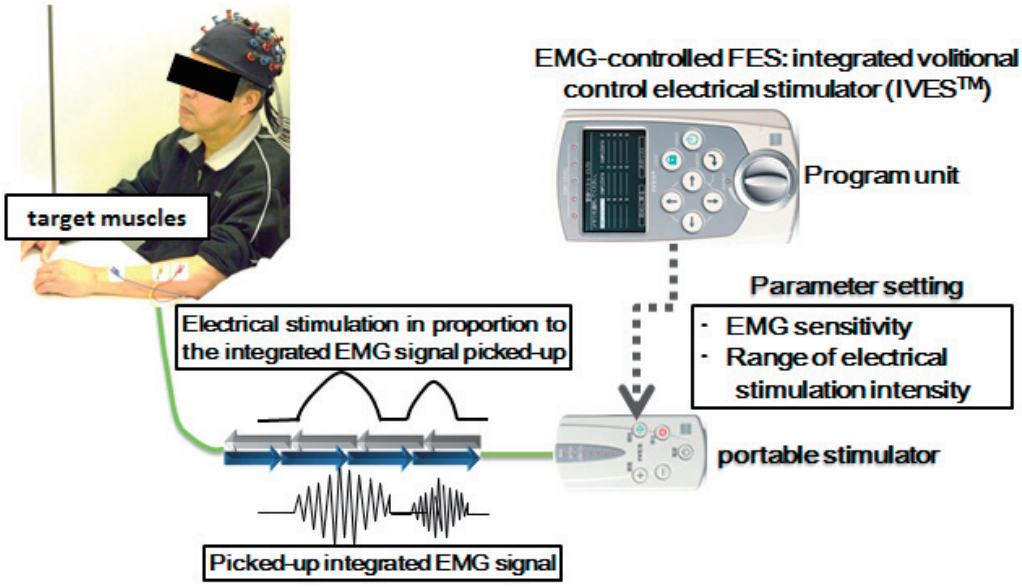

Fig. 1 EMG-FES apparatus and instrumentation
Because the EMG-FES unit is an auto-driven system without an on-off switch, no operation of the EMG-FES system was required after it had been set.

tal dose not exceeding 240 U per session. The Japanese Pharmaceutical Affairs Law states that the maximum applied dose of BTX-A that can be given during a session to treat upper limb spasticity in adult patients is 240 U. In this study, the dilution of BTX-A was standardized, with 1 vial (100 U) diluted with 4 mL of normal saline (2.5 U/0.1 mL). The injections were administered on the basis of anatomical landmarks determined under the guidance of EMG (Neuropack MEB-9104: Nihon Kohden Co., Tokyo, Japan) and ultrasonography (Viamo SSA-640A: Toshiba Medical Systems Co., Tochigi, Japan). The use of these devices ensured the accuracy of needle placement by recording the muscle activity during active or passive movements or by observing the movements during muscle electrical stimulation. Injections were performed with special needle electrodes (Myoject™: Natus Neurology Inc., Middleton, WI, USA).

After receiving injections of BTX-A, all patients underwent regular occupational therapy sessions with EMG-FES for 4 months. Patients practiced task-orientated exercises, which included wiping and picking up small balls and blocks.

The EMG-FES system (IVES+® GD-611, IVES® GD-612: OG Giken Co., Ltd, Okayama, Japan) used in this study was a novel EMG-controlled electrical stimulator device that is referred to as an integrated volitional control electrical stimulator[12]. This device is a portable, 2-channel neuromuscular stimulator that can be used to elicit wrist and finger extension or shoulder flexion during coordinated movements (**Fig. 1**). The system uses a 3-electrode format to allow EMG-FES of the muscles. Two self-adhesive electrodes (3 cm in diameter and separated by 3 cm) were placed over the belly of the target muscles. The stimulation promotes finger, wrist, and/or elbow extension or shoulder flexion during coordinated movement but will not work when the muscles are quiescent. Therefore, all subjects in the study were asked to start a voluntary contraction of the finger extensors. Surface electrodes detected the EMG signal at the target muscle. The target muscle was electrically stimulated with the same surface electrodes. The amplitude of stimulation was proportional to the amplitude found 25 milliseconds after a stimulation pulse in which the stimulus artifacts and M-wave are present. Because the EMG-FES device is able to continuously record from the stimulated muscles, the contraction of a wrong muscle can be avoided. Details of this EMG-FES device have been previously discussed[13,14].

Outcomes for motor function and spasticity were measured at baseline, before the injection of BTX-A, and at 10 days and 4 months after the injection. The action of BTX-A generally occurs at 1 to 2 weeks after an injection and continues until 3 to 4 months. On the other hand, a previous study[11] and our clinical practice suggest that facilitation of the paretic muscles by occupational therapy with EMG-FES requires approximately 4 months to sig-

nificantly improve upper extremity motor function. Outcomes measured included muscle tone, grip strength, the simple test for evaluating hand function (STEF), the box and block test (BBT), the grip and release test, and the finger individual movement test (FIMT). The modified Ashworth scale is a common measure for grading muscle spasticity. Grip strength, STEF, BBT, the grip and release test, and FIMT are sensitive for detecting changes in dexterity. These scales can be easily performed and are widely used in clinical practice in Japan.

The modified Ashworth scale was used to evaluate the tone of the finger flexors. The modified Ashworth scale spasticity grades have been previously defined as follows: 0=no increase in muscle tone; 1=slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part(s) is moved in flexion and extension; 1+=slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM; 2=more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved; 3=considerable increase in muscle tone, passive movement difficult; and 4=affected part(s) rigid in flexion or extension[15]. For statistical analysis the "1+" grade of the modified Ashworth scale was treated as 1.5. The modified Ashworth scale for the fingers was obtained by first having the subject seated with the elbows placed so that 90° of flexion was exhibited while the forearm was pronated, and the wrist was in a neutral position in relation to the proximal and distal interphalangeal joints of fingers 2 through 5, which allowed isolated movement in the metacarpophalangeal joint.

The grip strength of the unilaterally more-affected hand was measured with a grip strength dynamometer (GRIP-D, Takei Co., Tokyo, Japan). Dexterous hand function was measured with the STEF, BBT, grip and release test, and FIMT.

The STEF[16,17] analysis (STEF: Sakai Medical Co., Tokyo, Japan), which is widely used in Japan, was designed to evaluate the speed of manipulation of objects using an upper limb. Subjects were instructed to catch or pinch objects of 10 different shapes and sizes and then carry them to a designated area. The objects used in this test included spheres (70, 40, and 5 mm in diameter); disks (20 mm in diameter×10 mm in height, and 20 mm in diameter×2 mm in height); boxes (100×100×47 mm, 35×35×35 mm, and 14×14×14 mm); thin pieces of cloth (90×80 mm), and pins (3 mm in diameter×42 mm in length). Scoring considered the number of objects carried during the required time period, with the STEF score ranging from 0 (low function) to 100 (high function). Normal ranges for this test are dependent upon the subject's age and sex.

The BBT[18,19] is a valid and reliable measurement of gross manual dexterity. This test requires that the subject pick up a single 1-inch block at a time, lift it over a partition, and then release it within a target area as many times as possible during 60 seconds.

The grip and release test is a useful tool for evaluating hand disability. Subjects were asked to use their fingers to grip and release as rapidly as possible while maintaining their forearm in pronation and their wrist in mild extension. The number of complete cycles of movement performed within 10 seconds was then counted. The grip and release test quantitatively reflects the motor disability of the upper extremity.

For the FIMT, subjects are asked to flex their fingers as quickly as possible over a 10-second period, starting from the thumb and continuing toward the little finger, with the fingers then extended in the reverse order from the little finger and toward the thumb. To simplify the requirements for our subjects we modified the FIMT in accordance with the method reported by Hatanaka et al.[20]. We counted the flexion of the fingers from the thumb toward the little finger as one movement and counted the extension in the reverse order from the little finger toward the thumb as the second movement. This modification allowed flexion and extension of fingers to be counted over only half of the full range of motion.

For statistical analysis, a paired *t*-test was used to analyze the grip strength, BBT, grip and release, and the FIMT tests. The Wilcoxon signed-rank test was used to analyze the STEF and modified Ashworth scale. The modified Ashworth scale scores were analyzed as changes from baseline. Statistical analysis was performed with Microsoft Excel 2013 version 15.0.4771.1004 software (Microsoft Corp., Redmond, WA, USA). A *p*-value of less than 0.05 was considered to indicate statistical significance.

Results

The subjects were 15 patients (12 male and 3 female) ranging in age from 17 to 74 years (mean age, 51.7 years). Of these 15 patients, 14 had had a stroke (9 due to intracerebral hemorrhage and 5 due to cerebral infraction) and 1 had had a spinal cord injury (central cord syndrome) at least 6 months earlier. The mean time inter-

Table 1 Clinical characteristics of the study population

Subject	Sex	Age (years)	Disease type	botulinum toxin A units	Injection site	Time since disease (month)
1	M	74	hemorrhage	50	FDS, FDP	28
2	F	28	hemorrhage	135	FDS, FDP, FPL, Add pol	61
3	M	65	hemorrhage	180	FCU, FCR, FDS, FPL	56
4	M	36	ischemia	100	FDS, FPL	36
5	M	29	hemorrhage	100	FDS, FPL	57
6	F	65	ischemia	100	Biceps, FDP, FPL, Add pol	29
7	M	61	hemorrhage	150	FCR, FCU, PT, FDS, FDP	54
8	M	73	ischemia	150	FDS, FDP, FPL, Add pol	27
9	M	43	hemorrhage	150	FCR, FCU, FDS, FDP	37
10	M	51	ischemia	200	FCR, FCU, FDS, FPL, Add pol	16
11	M	69	spinal cord injury	100	FDS, FDP	11
12	F	52	CVT	50	FPL, Add pol	44
13	M	46	hemorrhage	200	Biceps, FDS, FDP, FPL, Add pol	13
14	M	66	hemorrhage	150	FCR, FCU, FDS, Biceps	95
15	M	17	hemorrhage	60	FDS, FDP	7

Abbreviations: CVT, cerebral venous thrombosis; Biceps, biceps brachii; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; PT, pronator teres; FDS, flexor digitorum profundus; FPL, flexor pollicis longus; Add pol, adductor pollicis; F, female; M, male.

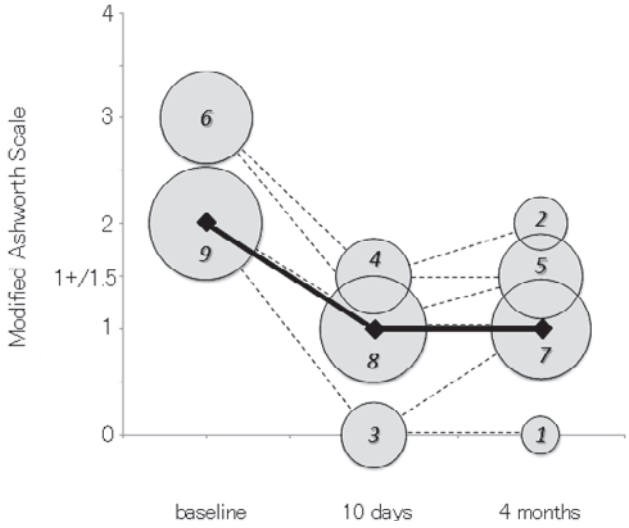

Fig. 2 The scores of the modified Ashworth scale at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
The modified Ashworth scale score of finger flexors improved significantly from baseline to 10 days and 4 months after injection. The solid line shows the median value, and the dotted line shows the individual changes. The size of the circle (numbers in italics) represents the number of patients with the corresponding modified Ashworth scale at each time point.

val since the stroke or spinal cord injury was 37.9 months (range, 7–61 months) (**Table 1**). All 15 subjects completed the study, and none had adverse events.

The median scores for the modified Ashworth scale decreased from 2 at baseline to 1 at both 10 days and 4 months (**Fig. 2**). The mean FIMT score improved slightly but not significantly from 5.1 at baseline to 5.5 at 10 days (p=0.29) (**Fig. 3**) but increased significantly from earlier dates to 7.5 at 4 months (p<0.05; p=0.01). Baseline mean values for STEF and BBT (17.1 and 14.5) decreased after 10 days (13.3 and 12.4, respectively, p<0.05 and p<0.01) and then improved greatly after 4 months (23.3 and 17.7, respectively, p<0.01 and p<0.01) (**Fig. 4 and 5**). All changes of the STEF and BBT were statistically significant.

A similar response pattern was noted between the grip and release test and the grip strength (**Fig. 6 and 7**). For the grip and release test, the score decreased slightly but not significantly from baseline (4.7) to 10 days (4.2, p= 0.26) and then increase significantly at 4 months (5.9, p< 0.05). The grip strength decreased significantly from baseline (14.5) to 10 days (10.8, p<0.01) and then increased slightly but not significantly at 4 months (15.1, p =0.18).

Discussion

Although many studies have examined the efficacy of BTX-A, only a few studies have reported any changes in the detailed dexterity. A study by Hurvitz et al.[6] observed the movement of 9 children who had spastic upper extremity during the 24 weeks after receiving a BTX-A injection; however, the Ashworth scale measurement

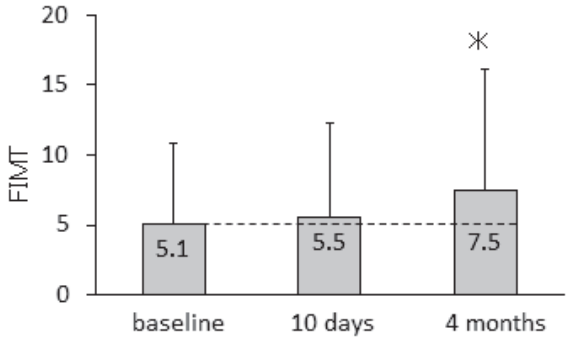

Fig. 3 Finger individual movement test (FIMT) at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
The FIMT score increased slightly but not significantly at 10 days (mean, 5.1 at baseline and 5.5 at 10 days; p=0.29) but increased significantly at 4 months (mean, 7.5; *p<0.05 and **p=0.01). The histograms show the means of the assessment score. The bars represent the standard deviation. The dotted lines represent the mean of the initial score of each assessment.

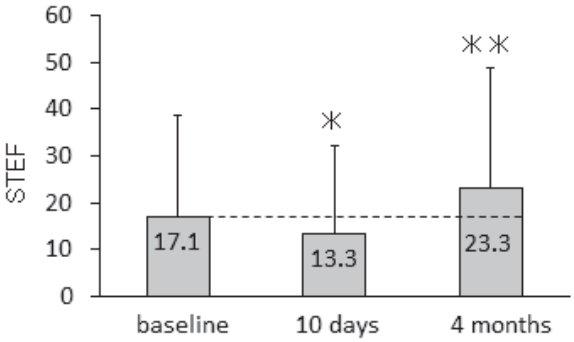

Fig. 4 The simple test for evaluating hand function (STEF) at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
The STEF score decreased significantly from baseline after 10 days (from 17.1 to 13.3 *p<0.05) and then improved significantly after 4 months (23.3, **p<0.01).

showed no obvious correlation with the ROM, site of injection, or pinch force. The improvement in the less complex tasks, such as hand tapping, generally occurred at an earlier time point, whereas the more complex movements, such as forward reaching tasks, improved either later or not at all. The authors of the study concluded that the improvement seen in the pinch force after BTX-A was injected was due to the presence of more active hand usage[6]. Our results also support the hypothesis that more active hand usage is an important factor in the rehabilitation of such patients. Moreover, the active hand

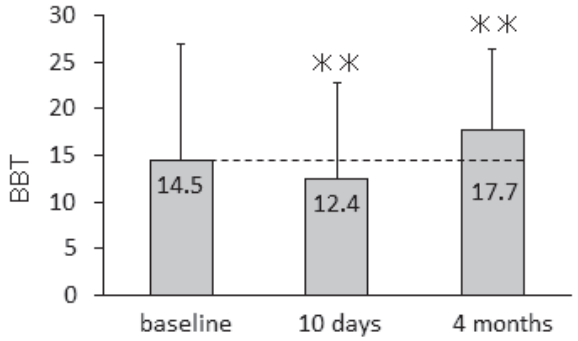

Fig. 5 Box and block test (BBT) at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
Similar to the STEF, the BBT decreased significantly from baseline after 10 days (14.5 to 12.4, **p<0.01) and then significantly increased after 4 months (17.7, **p<0.01).

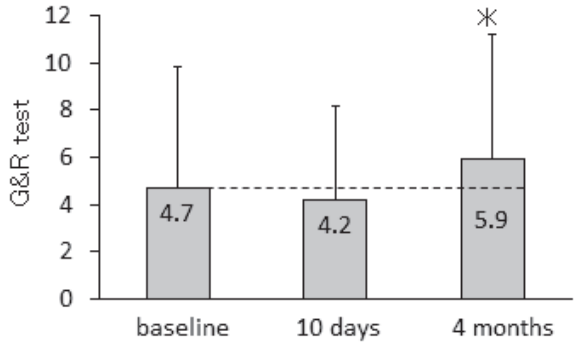

Fig. 6 Grip and release test (G&R test) at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
The G&R test score decreased only slightly from baseline at 10 days (4.7 to 4.2, p=0.26) but then increase significantly at 4 months (5.9, **p<0.05).

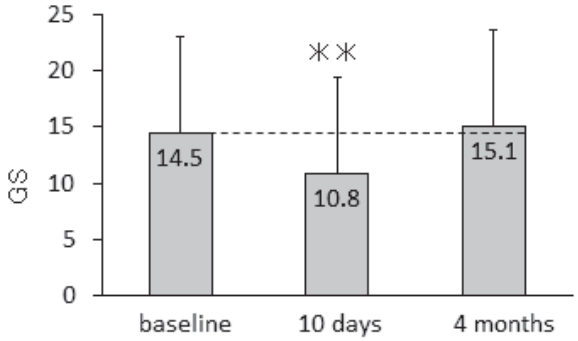

Fig. 7 Grip strength (GS) at baseline (before injection) and 10 days and 4 months after botulinum toxin injection
The GS decreased significantly from baseline after 10 days (14.5 to 10.8, **p<0.01) and returned to near baseline after 4 months (15.1, p=0.18). The change from baseline to 4 months was not significant.

usage in our present study resulted in effective facilitation of the paretic muscles when EMG-FES was used. In addition, some of the task-orientated training movements that patients could not perform without EMG-FES were volitionally enabled with EMG-FES.

Our EMG-FES differs from the other types of FES[7,9], especially with regard to volitional movements. While an injection of BTX-A usually directly improves the spasticity, it occasionally reduces muscle strength via the transsynaptic mechanism. In contrast, the addition of EMG-FES to treatment with BTX-A improves muscle weakness via the transsynaptic mechanism, thereby being of benefit by improving upper extremity motor function.

It should be noted, however, that BTX-A has been reported to have several adverse effects, with a large concern regarding the relaxation of nontargeted muscles. An almost equal transport of BTX-A to the contralateral muscle via the neural pathways and the circulation has been demonstrated[21,22]. Furthermore, BTX-A is carried from the peripheral to the central nervous system by dual anterograde and retrograde axonal transport by either the motor or sensory neurons. After 2 of our patients received BTX-A injections in their finger flexors, extensor weakness developed in these fingers, and upper extremity function was briefly decreased. We hypothesize that transsynaptic transport of the BTX-A had occurred in these patients. When the untargeted muscles have been weakened, especially the agonist muscles because of transsynaptic inhibition of the spinal transmission by BTX-A, a patient has difficulty performing the task practice on their own to facilitate the voluntary contraction in their agonist muscles. Therefore, EMG-FES is extremely useful for facilitating the voluntary contraction of the agonist muscle and for improving motor performance during task practice training in patients in whom BTX-A transsynaptic transport symptoms have developed.

In the present study, grip strength decreased 10 days after the BTX-A injection. Previous studies[6] have demonstrated that the temporary decrease at 10 days might be due to the excessive muscle weakness that is a side effect of the BTX-A injection. However, at 4 months the grip strength had been regained and was not noted to have significantly changed from baseline. Because BTX-A is thought to act for 3 to 4 months in many cases, its effect would be expected to have stopped by 4 months, thereby resulting in the same values that were originally noted at baseline.

Although the FIMT remained improved for our entire study, a transient decline in the dexterous hand function was observed after BTX-A was injected. These observations may indicate that many patients misuse the spasticity and flexor synergy as a way of compensating. For example, as spasticity decreased in these patients, the optimal fine movements of the hand (i.e., picking up small balls and blocks) became clumsy, with a significant decrease in the STEF and BBT found until 10 days after BTX-A injection. However, it should be noted that of all of the tests used in the study, only the FIMT evaluation does not require pinch force or a precision grip while dexterous hand function is measured. Despite grip strength not improving significantly between baseline and 4 months after BTX-A injection, FIMT, STEF, BBT, and grip and release tests significantly improved during this period. This difference might be due to both the recovery of the muscle weakness from the original BTX-A effect and the positive effect of the dexterity related to the EMG-FES.

Although BTX-A reduces spasticity within a few days and an abnormal adapted movement pattern is rapidly initialized, a longer time is needed to reeducate the inherent physiological movement pattern. Task-orientated therapy with EMG-FES after an injection has been shown to effectively reduce the spasticity and improve upper limb motor function. Our study suggests that spasticity occurred as a compensation for the force of the affected muscles, thereby leading to misuse movements and ostensible dexterity in many of the patients. In addition, BTX-A injection might initialize the abnormal adapted movement pattern. Moreover, when facilitation of the paretic muscles has occurred because of more active hand movements, the further use of EMG-FES can induce efficient muscle reeducation of the inherent physiological movement pattern, which was useful in activities of daily living.

A previous study[23] has found evidence of a moderate treatment effect based on 10 randomized controlled trials that examined the effectiveness of BTX-A for treating spasticity-related disability in upper extremities after stroke. However, these studies had substantially varied effect sizes, which ranged from negligible to large. Thus, these findings suggest that treatment with BTX-A after stroke may be of greater benefit for improving passive functions, such as measures of spasticity, rather than active functions, such as motor function and activities of daily living. In addition, BTX-A has been suggested[24] to be an effective treatment option for reducing muscle tone and improving passive function in adults with spasticity (level A, A indicates it should be offered) or to be consid-

ered as a possible method for improving active function (level B, B indicates it should be considered). (Passive function is defined as tasks involving the nonaffected hand, dressing oneself, or hygiene performed by the caregiver; the active function is defined as activities that the patient can voluntarily perform with the spastic limb.) Our results show that neurorehabilitation is necessary to improve active function in patients with spastic paresis.

In conclusion, our findings demonstrate that EMG-FES after BTX-A is effective for improving the spasticity and dexterity of the upper extremities of patients with spastic paresis. The benefit of using task-orientated exercise after BTX-A injection and EMG-FES is that facilitation of the target muscle is more reliable than that observed without EMG-FES.

One limitation of the present study was the small number of subjects. Another limitation was that the study was not blinded because of the clinical ethics of withholding treatments from these patients. Even with these limitations, our results are meaningful with regard to rehabilitation being detected when BTX-A is used to counteract upper extremity spastic paralysis. In most cases the spasticity of the participants gradually deteriorated beyond 4 months after a BTX-A injection, but wide individual differences due to the extent of the hand usage were also observed. After this study some of the subjects received repeated rehabilitation cycles of occupational therapy with BTX-A injection and EMG-FES. This cycle might induce more reeducation of the inherent physiological movement pattern and better dexterity. Further studies should involve a large population and establish the long-term effects of our program.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Yablon SA, Agana BT, Ivanhoe CB, Boake C: Botulinum toxin in severe upper extremity spasticity among patients with traumatic brain injury: an open-labeled trial. Neurology 1996; 47: 939–944.
2. Bhakta BB, Cozens JA, Bamford JM, Chamberlain MA: Use of botulinum toxin in stroke patients with severe upper limb spasticity. J Neurol Neurosurg Psychiatry 1996; 61: 30–35.
3. Brashear A, Gordon MF, Elovic E, Kassicieh VD, Marciniak C, Do M, Lee CH, Jenkins S, Turkel C: Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. N Engl J Med 2002; 347: 395–400.
4. Simpson DM, Alexander DN, O'Brien CF, Tagliati M, Aswad AS, Leon JM, Gibson J, Mordaunt JM, Monaghan EP: Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. Neurology 1996; 46: 1306–1310.
5. Slawek J, Bogucki A, Reclawowicz D: Botulinum toxin type A for upper limb spasticity following stroke: an open-label study with individualised, flexible injection regimens. Neurol Sci 2005; 26: 32–39.
6. Hurvitz EA, Conti GE, Brown SH: Changes in movement characteristics of the spastic upper extremity after botulinum toxin injection. Arch Phys Med Rehabil 2003; 84: 444–454.
7. Rodríguez-Reyes G, Alessi-Montero A, Díaz-Martínez L, Miranda-Duarte A, Pérez-Sanpablo AI: Botulinum toxin, physical and occupational therapy, and neuromuscular electrical stimulation to treat spastic upper limb of children with cerebral palsy: a pilot study. Artif Organs 2010; 34: 230–234.
8. Jahangir AW, Tan HJ, Norlinah MI, Nafisah WY, Ramesh S, Hamidon BB, Raymond AA: Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after stroke. Med J Malaysia 2007; 62: 319–322.
9. Weber DJ, Skidmore ER, Niyonkuru C, Chang CL, Huber LM, Munin MC: Cyclic functional electrical stimulation does not enhance gains in hand grasp function when used as an adjunct to onabotulinumtoxinA and task practice therapy: a single-blind, randomized controlled pilot study. Arch Phys Med Rehabil 2010; 91: 679–686.
10. Napier JR: The prehensile movements of the human hand. J Bone Joint Surg Br 1956; 38-B: 902–913.
11. Hara Y, Ogawa S, Muraoka Y: Hybrid power-assisted functional electrical stimulation to improve hemiparetic upper-extremity function. Am J Phys Med Rehabil 2006; 85: 977–985.
12. Muraoka Y: Development of an EMG recording device from stimulation electrodes for functional electrical stimulation. Front Med Biol Eng 2002; 11: 323–333.
13. Hara Y, Ogawa S, Tsujiuchi K, Muraoka Y: A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. Disabil Rehabil 2008; 30: 296–304.
14. Hara Y, Obayashi S, Tsujiuchi K, Muraoka Y: The effects of electromyography-controlled functional electrical stimulation on upper extremity function and cortical perfusion in stroke patients. Clin Neurophysiol 2013; 124: 2008–2015.
15. Bohannon RW, Smith MB: Interrater reliability of a modified Ashworth scale of muscle spasticity. Phys Ther 1987; 67: 206–207.
16. Kaneko T, Muraki T: Development and standardization of the hand function test. Bull Allied Med Sci Kobe 1990; 6: 49–54.
17. Shindo K, Oba H, Hara J, Ito M, Hotta F, Liu M: Psychometric properties of the simple test for evaluating hand function in patients with stroke. Brain Inj 2015; 29: 772–776.
18. Desrosiers J, Bravo G, Hébert R, Dutil E, Mercier L: Validation of the Box and Block Test as a measure of dexterity of elderly people: reliability, validity, and norms studies. Arch Phys Med Rehabil 1994; 75: 751–755.
19. Mathiowetz V, Volland G, Kashman N, Weber K: Adult norms for the Box and Block Test of manual dexterity. Am J Occup Ther 1985; 39: 386–391.
20. Hatanaka T, Koyama T, Kanematsu M, Takahashi N, Matsumoto K, Domen K: A new evaluation method for upper extremity dexterity of patients with hemiparesis after

stroke: the 10-second tests. Int J Rehabil Res 2007; 30: 243–247.
21. Akaike N, Shin MC, Wakita M, Torii Y, Harakawa T, Ginnaga A, Kato K, Kaji R, Kozaki S: Transsynaptic inhibition of spinal transmission by A2 botulinum toxin. J Physiol 2013; 591: 1031–1043.
22. Torii Y, Akaike N, Harakawa T, Kato K, Sugimoto N, Goto Y, Nakahira S, Kohda T, Kozaki S, Kaji R, Ginnaga A: Type A1 but not type A2 botulinum toxin decreases the grip strength of the contralateral foreleg through axonal transport from the toxin-treated foreleg of rats. J Pharmacol Sci 2011; 117: 275–285.
23. Foley N, Pereira S, Salter K, Fernandez MM, Speechley M, Sequeira K, Miller T, Teasell R: Treatment with botulinum toxin improves upper-extremity function post stroke: a systematic review and meta-analysis. Arch Phys Med Rehabil 2013; 94: 977–989.
24. Simpson DM, Gracies JM, Graham HK, Miyasaki JM, Naumann M, Russman B, Simpson LL, So Y: Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology: Assessment: Botulinum neurotoxin for the treatment of spasticity (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2008; 70: 1691–1698.

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