Title

Combination therapy with Repetitive Facilitative Exercise Program and Botulinum Toxin Type A to improve motor function for the upper-limb spastic paresis in Chronic Stroke: A Randomized Controlled Trial

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Keywords: stroke, rehabilitation, hemiplegia, muscle spasticity, botulinum toxin, exercise therapy

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Running title: Repetitive Facilitative Exercise combined with botulinum toxin

Conflict of interest: The authors have no conflicts of interest directly relevant to the content of this article.

- Forty chronic stroke patients with upper-limb spastic paresis were enrolled an RCT.
- Control group (CG) received repetitive facilitative exercise (RFE) program only.
- Intervention group (IG) received BoNT-A injection combined with the RFE program.
- Motor control and motor functions were evaluated during 4-week study period.
- IG evidenced significantly greater improvement in the outcome measures than CG.

ABSTRACT

Study Design: An open-label, randomized, controlled, observer-blinded trial.

Introduction: Repetitive facilitative exercise (RFE) is a movement therapy to recover from hemiparesis after stroke. However, improvement is inhibited by spasticity. Recently, botulinum toxin type A (BoNT-A) injection has been shown to reduce spasticity.

Purpose: To examine the combined effect of an RFE program and BoNT-A treatment on upper-limb spastic paresis in chronic stroke.

Methods: Forty chronic stroke inpatients with upper-limb spastic paresis (Brunnstrom stage ≥III and Modified Ashworth Scale (MAS) score ≥1) were enrolled. Subjects were randomized into two groups of 20 each and received 4 weeks of treatment. The intervention group received RFE and BoNT-A injection; the control group underwent RFE only. Assessments were performed at baseline and at study conclusion. The primary outcome was change in Fugl–Meyer Assessment score for the upper extremity (FMA). The Action Research Arm Test (ARAT), active range of motion, Box and Block Test, and MAS were also evaluated.

Results: All participants completed this study. After 4 weeks, the intervention group evidenced a significantly greater increase in FMA score [median 11.0 (range 4 to 20)] than the control group [median 3.0 (range 0 to 9)] ($p<0.01$, $r=0.79$); as well as improvements in the other measures such as ARAT [median 12.5 (range 4 to 22) vs. 7 (0 to 13)] ($p<0.01$, $r=0.6$), and MAS in the elbow flexors [median −1.5 (range −2 to 0) vs. −1 (−2 to 0)] ($p<0.01$, $r=0.45$).

Discussion: A high degree of repetitive volitional movement induced by the facilitative technique with concomitant control of spasticity by BoNT-A injection might increase efficiency of motor learning with continuous movement of the affected upper-limb. *Conclusions*: The combination of RFE and BoNT-A for spastic paresis might be more effective than RFE alone to improve upper-limb motor function and to lessen impairment in chronic stroke.

Keywords: stroke, rehabilitation, hemiplegia, muscle spasticity, botulinum toxin, exercise therapy

Introduction

To promote recovery from a paretic upper limb after stroke, various rehabilitation approaches have been effective.[1] Regardless of the kind of training, a previous neurophysiological study suggests that repeating identical movements is important for motor relearning.[2] In accordance with that observation, Kawahira[3] developed the repetitive facilitative exercise (RFE) program, which combines repetitive volitional flexion and extension movements with modified traditional neurofacilitation approaches.[4]

The RFE approach is aimed at achieving the intended movements and lessening synergistic movement patterns by reconstruction and strengthening of the injured nerve tract related to the intended movements.[4] In this approach, therapists use repetitive elicitation of the limb or finger by physical stimulation such as muscle spindle stretch or skin-muscle reflex induced by tapping or rubbing the targeted muscle (Figure 1).[4] A previous randomized controlled trial (RCT) showed that RFE is beneficial for improvement of not only motor impairment but also manipulating objects.[5] According to the Japanese Guidelines for the Management of Stroke,[6] RFE is recommended as grade B for the exercise therapy of an affected upper limb after stroke. However, improvement with RFE is often inhibited when the patient has spasticity in the paretic limb.

Spasticity is a motor disorder caused by an upper motor neuron lesion and is characterized by an increase in muscle tone resulting from hyper-excitability of the stretch reflex.[7] This symptom is observed in approximately one-third of stroke survivors.[8,9] The excessive tension of the muscle decreases motor function and there is a negative correlation between them.[10] Spasticity in affected limbs often worsens with

repeated arm movements such as flexing and extending. It also hinders occupational therapy because of restricted range of motion (ROM) or pain. Joint contracture and pain caused by limb spasticity limit voluntary motor control of the arm and inhibit activities of daily living (ADL), including hygiene and dressing.[11,12] For these reasons, controlling muscular hypertonicity is important for improving intended movements, especially in the arm and fingers. To treat spasticity, traditional approaches—including muscle stretching and thermotherapy—are effective for treating spasticity, but the effects are only temporary. Therefore, it is often necessary for a therapist to stretch the patient's spastic muscles for a certain amount of time before each training session.

Recently, treatment with botulinum toxin type A (BoNT-A) injection has been widely used to reduce and control focal spasticity after stroke. Several studies showed that the BoNT-A injection reduces muscle tone and increases passive ROM,[13,14] but it is unclear whether the injection alone improves voluntary motor control and upper-limb function in chronic stoke suvivors.[15]

Therefore, it has been considered that some kind of rehabilitation (adjuvant therapy) should be combined with BoNT-A injection to improve arm and finger motor function.[16,17] Although several RCTs have investigated the effects of combined adjunct exercise therapies following BoNT-A injection, there are few reports showing improvement in affected upper-limb ability.[18-22] In addition, as far as we know no study of the combined effect of RFE and BoNT-A treatment has yet been reported.

The aim of this trial was therefore to examine whether the RFE program combined with BoNT-A injection achieves better improvement than the RFE program alone in regard to voluntary motor control and function in chronic stroke patients with upper-limb spastic paresis.

Methods

Participants

Participants were recruited from among patients admitted to a university hospital rehabilitation center in Japan from December 2012 to May 2014 (Figure 2).

Inclusion criteria were: (1) patients (>10 years and <90 years old) who suffered a first unilateral stroke; (2) chronic stroke (>6 months from the onset); (3) mild-to-moderate upper-limb motor paralysis (Brunnstrom recovery stage ≥III)[23]; (4) muscle tone ≥1 measured with the Modified Ashworth Scale (MAS)[24] (at either elbow, wrist, or finger flexors); and (5) ability to understand tasks such as evaluations in the intervention.

Exclusion criteria were the following: (1) patients who had previously received one or more BoNT-A injections; (2) pregnant or lactating; (3) clinically unstable medical status; (4) contracture or profound atrophy in the arm or finger; and (5) conditions making it difficult to comprehend oral instructions, such as severe higher brain dysfunction, severe dementia, or loss of consciousness.

All participants provided written informed consent, and the study protocol conformed to the Helsinki Declaration as revised in 2008. Approval for this trial was obtained from the university ethics committee (24-119) and the trial was registered with the UMIN Clinical Trial Registry (UMIN000009640).

Design

This was an open-label, randomized, observer-blinded trial conducted for 4 weeks. Forty inpatients participated who had stroke-related upper-limb spasticity with MAS greater than or equal to 1 and Brunnstrom stage of motor paralysis more than III. Lesion sites due to stroke were confirmed with computed tomography or magnetic resonance imaging (MRI). Participants were randomized into two groups: one group received BoNT-A injection combined with RFE program, the other group received RFE only. Randomization was accomplished with a computer-generated number and was managed by an independent researcher who did not take part in the recruitment or measurement. This study was open-label; although participants were not blinded to receiving BoNT-A injection or not, all outcome measures were assessed by a trained and experienced evaluator who was blinded to treatment assignment. Assessment measurements were made at the initiation and at the end of the 4-week intervention period. Participants were told that, if assigned to RFE program only, they might receive BoNT-A injection after the study conclusion if necessary.

Intervention

Participants received either RFE program combined with BoNT-A injection (combination group) or RFE program only (control group), for a 4-week hospitalization period. All participants received RFE training for 40 minutes per day, 6 days a week, for the entire 4 weeks. After each treatment session, participants moved to the occupational therapy area and performed about 20 minutes of dexterity(object-)related self-training: affected upper-limb activities including reaching to grasp then release sponges of different sizes, using an arm skateboard, or the wiping exercise. In addition,

they participated in the usual inpatient rehabilitation program, including ADL training or speech language therapy, throughout the trial period.

The theory and training methods of the RFE have been reported.[3-5] Repetitive facilitative techniques are used to minimize synergy patterns and to achieve isolated control of the paretic upper-limb movement primarily for shoulder flexion, elbow extension and flexion, wrist extension, extension of each finger (in a supine position), supination and pronation, and extension and flexion of each finger (in a seated position). Each of these targeted articular movements (i.e. a "movement pattern") was repeated frequently within a short time. The patients underwent exercises performed as 2 sets, with 50 repetitions in each set for one movement pattern and 1–2 minutes of rest between patterns. Thus, 100 repetitions of each of five-to-eight specific patterns for at least five joints of the paretic limb were undertaken in daily sessions. During the RFE sessions in both groups, concurrent low-amplitude continuous neuromuscular electrical stimulation (NMES)[25] was applied to more easily induce targeted movement such as elbow extension or finger extension.

The combination group began the same 4-week RFE program immediately after admission, and received BoNT-A injections in the affected (targeted) upper-limb muscles (maximum dose, 240 U), administered by the attending physician within 10 days after admission (Figure 2). Onabotulinumtoxin A (Botox®, GlaxoSmithKline K.K., Tokyo), a botulinum neurotoxin (concentration, 25 U per mL; reconstituted with 0.9% normal saline), was injected into the muscles whose hypertonicity disturbed the patient's intended movements and ADL. Injections were given together with CHB-101 (Unique Medical Co., Ltd. Tokyo) as electromyography (EMG) guidance for muscle selection. During the study period, additional neural blocks were not administered and the dose of oral muscle relaxant was not changed.

Outcome measures

Each evaluation was performed at the initiation of trial (baseline) and at week 4 (end of the intervention period). The primary outcome measure was the upper extremity scale of the Fugl–Meyer Assessment (FMA) used to assess motor control such as sensation, ROM, coordination, and speed.[26] FMA in upper limb includes 33 items and ranges from 0 to 66; a maximum score indicates complete recovery of the limb, and the reliability and the validity of the FMA is well established.[26]

Subjects were also assessed with the Action Research Arm Test (ARAT),[27] active ROM, Box and Block Test (BBT),[28] and MAS. The ARAT, used to evaluate motor function, i.e. mainly the ability to manipulate objects, consists of 4 subscales: grasp, grip, pinch, and gross movement in the horizontal and vertical planes.[27] Each task is scored from 0 (no movement) to 3 (normal performance): the total score ranges from 0 to 57. The active ROM of extension at the elbow and wrist were evaluated using a protractor goniometer. BBT is a simple and low-cost test of ability to manipulate objects with very high validity.[28] Subjects moved blocks one by one from one compartment to another over a partition 12 cm in height. The score was the total number of blocks successfully moved in 1 minute. The MAS was used to evaluate spasticity—i.e., muscle tone in the elbow, wrist, and finger flexors. Reliability of the MAS has been verified by using a 6-point scale to evaluate spasticity in each joint.[24] To facilitate data analysis, each of the MAS scores (0, 1, 1+, 2, 3, and 4) was replaced with a numerical value (0, 1, 2, 3, 4, and 5, respectively) which is referred to as "computed MAS score".[29]

Statistical analysis

A sample size of 20 patients in each group was estimated to give 80% power ($\alpha = 0.05$, 2-tailed test) to detect a mean difference of 6.6 in the FMA score, assuming a standard deviation of 7 points. Non-parametric procedures were used because the data could not be assumed to be normally distributed. The Mann-Whitney U-test for continuous variables and the chi-square test for frequencies were used to compare baseline characteristics between treatment groups. To calculate change scores for all outcome measures (FMA, ARAT, active ROM, BBT, and MAS), we computed the difference between baseline and week 4 values; change scores between the 2 groups were compared with the Mann-Whitney U-test. Data are summarized as median and range. The effect size *r* was calculated for each scale to reflect the size of the differences between groups of the change over 4 weeks. Cohen[30] suggested $r \geq 0.10$, $r \geq 0.30$, and $r \geq 0.50$ as indicative of a small effect, a moderate effect, and a large effect, respectively. *P* values < 0.05 were considered to be statistically significant. SPSS version 20.0 for Windows was used for the analyses.

Results

Sixty-three (63) patients with chronic stroke were screened as potential participants during the recruitment period. Figure 2 illustrates the process of recruitment. Fifteen patients did not satisfy the inclusion criteria (6 patients once received a BoNT-A injection) and 8 declined to give consent. Forty adults (25 males and 15 females; median age 62 [range 19-80] years) with upper-limb spastic paresis after chronic stroke

were enrolled and available for analysis. There were no dropouts during the 4-week study period, and no adverse events were observed during the trial. Table 1 shows characteristics of the participants. Thirteen patients had cerebral infarctions and 27 had cerebral hemorrhages. Seventeen patients had right hemiplegia and 23 had left hemiplegia, and none of the patients presented with absence of functional sensation. No significant differences were seen between the two treatment groups in demographic characteristics or baseline outcome measures.

Details of BoNT-A injection frequency and mean dosage are shown in Table 2. Injections into the biceps brachii muscle and the flexor digitorum superficialis muscle occurred with high frequency.

Table 3 shows the median and range of differences in FMA, ARAT, active ROM, BBT, and MAS scores between baseline and 4 weeks. Crude mean increase in FMA in the combination group was 10.9 points (median: 11) at the end of the trial. In contrast, crude mean increase in FMA in the control group was 3.5 points (median: 3) over the same period. Table 3 also displays results of the Mann-Whitney U-test of the combined effects of RFE program and BoNT-A injection relative to RFE only: there was a significant difference between the two groups in the increase in the primary outcome, FMA ($p < 0.01$, $r = 0.79$).

Increases in the other outcome scores were also observed at week 4 in both groups. At the end of treatment, the combination group showed significantly greater increases than the control group on scores for upper-limb ability such as ARAT ($p < 0.01$, $r = 0.60$) and BBT ($p < 0.01$, $r = 0.48$). Similarly, significantly greater increases in the active ROM for each joint were observed in the combination therapy group than in the control group: extension of elbow joint ($p < 0.01$, $r = 0.52$) and extension of wrist

joint ($p < 0.01$, $r = 0.62$). It is noteworthy that all of the ARAT subscales displayed significant increases in the combination group (Table 3).

MAS in the elbow flexors showed decreases in both groups; moreover, the combination group displayed a greater decrease than the control group ($p < 0.01$, $r = 0.45$). However, no significant difference between the two groups was observed in MAS scores in the wrist flexors or finger flexors at 4 weeks; this might be due to the fact that the control group also showed improvement on these scores.

Discussion

The present study is the first RCT to examine the effectiveness of combined RFE and BoNT-A treatment for upper-limb spastic paresis in chronic stroke. It demonstrated that the combination approach is more effective than the RFE program alone for improving upper-limb motor control and motor function in patients with stroke-related spasticity.

The combination therapy produced on average a statistically significant 10.9 point increase in FMA by the end of the trial, which is clinically significant because the minimal clinically important difference (MCID) is from 4.25 to 7.25.[31] In participants who received BoNT-A injections, spasticity—measured by MAS—was further reduced, while active ROM in the upper-limb and ability to manipulate objects—measured by ARAT and BBT—showed greater improvement. The combination group displayed a mean increase of 12.9 points (median; 12.5) on ARAT at the end of training, which is greater than the MCID (5.7).[32]

Although FMA and ARAT improved in both groups in this trial, the changes differed significantly between the two groups. Furthermore, all of the ARAT subscales

in the combination group displayed significantly greater increases than those in the control group. The greater improvement in the combination group could be related to the high degree of repetitive volitional movement induced by the facilitative technique while spasticity is controlled by BoNT-A injection. In addition, all subjects in the combination group underwent BoNT-A injection with EMG guidance. Thus, using an injection-guiding technique for BoNT-A injection might also contribute to increasing the effect of BoNT-A treatment for focal spasticity.[33]

One of the aims of the RFE approach is to normalize muscle tone and to realize and repeat a practical movement pattern of the upper limb.[3] Evolutional facilitation methods are repeated smoothly, and therapists could perform about 100 repetitions of each of five to eight patterns within 40 minutes.[5] This approach improves the intended motor control and dexterity of the affected upper limb.[4,5] However, enhancement of muscle tone with repeated motion in patients with spasticity often worsens and inhibits the movement. The improvement in outcome measures in the control group was small, suggesting that spasticity might inhibit efficacy of RFE in the promotion of movement recovery.

Many other studies related to RFE have been reported. RFE achieves further improvement in combination with additional modalities, such as low amplitude electrical stimulation as in the current study,[25] direct application of vibratory stimulation (DAViS),[34] or low-frequency repetitive transcranial magnetic stimulation (rTMS).[35] Further, the RFE combined with DAViS and electrical stimulation might provide greater benefit than RFE combined with rTMS in terms of motor recovery of the affected upper limb.[36] DAViS is a minimally invasive and inexpensive therapy and has been proven to reduce upper-limb spasticity.[37] However, duration of the anti-spastic effect after treatment is relatively short, lasting only around 30 minutes. Therefore, to

control the muscle tonus this treatment must be given immediately before the initiation of RFE.

Depressed muscle spasticity lasts around 3 months after BoNT-A injection, so there is no need to control spasticity before every movement therapy session. Nowadays BoNT-A therapy is widely applied in clinical practice to treat and control focal spasticity. Nevertheless, there are only a few studies that demonstrate improved motor ability of the affected upper limb with BoNT-A therapy, and the intervention reported in most of those studies was BoNT-A injection only, not BoNT-A combined with adjunctive physiotherapy.[16] To our knowledge, there are few reports of RCTs showing significant recovery of motor function after combination with BoNT-A injection and rehabilitation.[18,38] Recently it has been proposed that some kind of rehabilitation should be performed after the injection to improve motor functions of the affected limb.[16] To improve functions in the upper paretic spastic limb and realize the patient's intended movements, it is desirable to repeat identical movements and encourage motor learning while controlling muscle tone.[2,39] Therefore, modified constraint-induced movement therapy (mCIMT)—where the patient intensively uses the affected limb by performing variable tasks for 2 hours or more—is surely effective in terms of increasing intensity, and combining this therapy with BoNT-A injection (after injection) should improve spasticity and motor function of the paretic extremity.[18,40] On the other hand, RFE itself has the advantage of repeated identical voluntary movements, which are important for motor recovery, during a shorter intervention period (within 40 minutes).

Additionally, hand strengthening exercises,[41] mirror therapy,[42] and robot training[43] are candidates for effective exercise hand therapy in combination with BoNT-A injection. To our knowledge, however, no comparative study has been conducted on their effects, including what extent of intensive training should be provided to stroke

patients with spastic hemiplegia or after BoNT-A treatment. Although muscle strengthening exercises had once been presumed to induce spasticity in stroke, they are now regarded as the main rehabilitation strategy to improve motor impairments.[16] Vinstrup et al. reported that, for the paretic hand, electromyographic activity of flexor muscles (flexor digitorum superficialis) is higher than that of extension muscles (extensor digitorum) during finger flexion and extension exercises using elastic resistance.[41] In addition, a dose-response relationship between resistance and muscle activity was observed for the flexor musculature during finger extension exercise. In general, therefore, motor control of finger extension might be more difficult than that of finger flexion for patients with hemiparesis after stroke. In the RFE, to obtain a wider active range of finger extension, the tip of the therapist's ring finger is gently placed on the fingernail of the patient to give slight resistance (see Fig. 1 (3)). Further, to achieve intentional movement, manual stretch reflex synchronized with the patient's intention to move for each individual finger, and low-amplitude continuous NMES, were used in the current RFE program. In contrast, mirror therapy uses a mirror box to achieve bilateral symmetrical training under a visual illusion that the hemiplegic hand is moving in the same way as the unaffected hand,[42] and the robot training uses mechanical and assistive, partial assistive, or resistive motion under visual- or bio- feedback.[43] Intensive repetition of voluntary or assisted movements would be common among these three candidates and RFE, though the nature of the method is different. Besides, a single case report introduced rTMS as a noninvasive neuromodulation technique, and described a combined therapy of rTMS with repetitive task training 'immediately' after BoNT-A injection.[17] In the future, accordingly, studies need to clarify from when and what adjuvant exercise therapy or additional neuromuscular modulation techniques are

beneficial for the individual patient to improve hand function after treatment with BoNT-A injections.

In the current study, RFE alone also led to significant improvement in motor function in the spastic upper limb. Regarding the change score of ARAT at the end of training (4 weeks), the control group archived a mean increase of 6.3 points (median: 7), which is greater than the MCID of ARAT. Reduction in spasticity was also seen in the control group (without BoNT-A treatment). As a result, no significant difference between groups was seen in MAS scores for the wrist joint or the fingers. We used MAS scores to measure spasticity; a change of 1 point in MAS score is considered clinically significant.[13,44] One explanation for the significant decrease in MAS scores is that there might be an anti-spastic effect of RFE on antagonist muscles induced by reciprocal innervation. Because we studied chronic stroke patients, decreased motor ability before the trial might be caused by "learned non-use"[45] in their affected upper limbs with spasticity. With the improvement in voluntary movement due to the RFE program, spasticity might decrease. In fact, Etoh et al.[46] reported that neurophysiological parameters related to spasticity—reduction of F-wave parameters—are induced by 4 weeks of RFE in patients after subacute stroke.

An RCT reported by Meythaler et al.,[38] in which BoNT-A injection and exercise therapy was compared with placebo injection and exercise therapy, showed improvement of spasticity measured by MAS even in the placebo control group. However, significant improvement of upper-limb function was found only in the BoNT-A combination group in their study, so they concluded that most of the improvement in function of the affected limb was caused by control of spasticity during active motion.[38] That result is similar to the result of the current study; although the MAS scores in both groups decreased and no significant difference in decrease of MAS was seen in the

wrist joints and fingers, there were significant differences between the two groups in improvement of functions in the affected upper limb. On the other hand, the present result—that MAS of the elbow in the combination group decreased to a greater extent than in the control group—might contribute further to improved function in the affected upper limb. However, we might have to pay more attention to increasing spasticity during repetitive active action, as suggested by Meythaler et al.[38] So it could be important to use the measurement that reflects functional performance to more accurately evaluate the practical effect of the decrease in spasticity.

While measuring MAS, evaluation is done statically after a short rest. However, spasticity often induces a problem by increasing muscle tone with continuing motion; a good indicator is to observe how the elbow and fingers are repeatedly flexing and extending. In that sense, examinations to evaluate repetitive article operations, such as the BBT, might reflect the results, including the degree of spasticity, especially repetitive pinch-and-release movements. Although an increase in the BBT score in the current study was observed in both groups, the improvement was greater with combination therapy ($p<0.01$, $r=0.48$). Kinematic analysis by computer would be beneficial for evaluating active function affected by spasticity. Bensmail et al.[15] used electromagnetic fields and showed improvements in kinematic parameters of the affected arm during reaching movements after BoNT-A treatment. However, in their study measures of the ability to manipulate objects, such as ARAT and BBT, did not improve compared to before the BoNT-A injection. Accordingly, to obtain improvements of both motor impairment and motor function, the addition of intensive rehabilitation on the paretic upper limb and hand, such as mCIMT or RFE, might be needed after BoNT-A injection.

Recently, evaluation of neural activity and reorganization by image analysis has become possible. Neuroplasticity is thought to affect functional recovery from various movement disorders. Research on intra-cortical suppression[47] and changes in brain activity[48] after BoNT-A is progressing. Further study is required to confirm the combined effects of RFE after BoNT-A injection on plasticity and to explore changes in the central nervous system by functional MRI or TMS.

Limitations

This study has some limitations. First, it was an open-label trial. Although a double-blind study is ideal, we did not plan to use placebo and avoided, as much as possible, unnecessary invasiveness for patients with spasticity. In addition, we did not make a comparison with BoNT-A injection only or with conventional rehabilitation paired with BoNT-A injection. Most of the chronic stroke patients who were admitted to our hospital had known that RFE improves motor function of the affected upper limb more effectively than conventional rehabilitation, so it would have been difficult to set up such groups because it might have reduced participation in the trial if patients were randomly assigned to the control group. Second, the sample size was small, which might cause imbalance at baseline. Third, it is unclear how long the observed improvements will persist after the 4-week trial conclusion. It is possible that the peak effect of current intervention could have occurred towards the end of the treatment period because the effect of BoNT-A injection on suppressing spasticity lasts at least 4 to 6 weeks.[13,14] It is therefore necessary to continue observing patients over a longer period in a large-scale study to determine whether the beneficial effect of combination therapy continues. Fourth, although both groups underwent RFE under low-amplitude

continuous NMES, it is possible that the use of NMES could also have affected the current results. This is because adjunct use of electrical stimulation after BoNT-A has been reported to reduce spasticity[20] or improve active hand function.[49] Furthermore, we should examine additional dosing effects of BoNT-A injection because repeated administration of BoNT-A combined with rehabilitation led to better improvement of spasticity and motor function.[50]

Conclusions

The present randomized, controlled study revealed that the combination of RFE and BoNT-A injection might be more effective than RFE alone in improving motor functions and lessening motor impairment in the stroke-related chronic paretic upper limb with spasticity. Adverse events were not observed with this treatment, so it can be presumed to be safe. Accordingly, RFE may be applied actively after BoNT-A injection especially to improve motor functions for the post-stroke spastic upper limb. Further investigation into the long-term effect of BoNT-A injections paired with RFE, and to compare this effect with other types of rehabilitation combined with BoNT-A treatment, are needed in the future.

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Figure legends

Figure 1.

A method of repetitive facilitative exercise (RFE) aiming to extend the right forefinger. (1) The patient lies supine and the upper limb is held while the wrist is flexed. The therapist quickly flexes the patient's second finger immediately (the direction arrowed in the figure) before the patient makes an effort to extend his/her finger. (2) At the same time as when the patient extends the finger, the therapist says, 'straighten' and taps forward around the proximal interphalangeal joint (the direction arrowed in the figure), facilitating the finger's extension. (3) To obtain a wider range of motion, the tip of the therapist's ring finger is gently placed on the fingernail of the patient (the direction arrowed in the figure) to give slight resistance against the intended movement. Repetitions, in 2 sets of 50 times, of this pattern are performed in each daily session.

Figure 2.

Study recruitment, randomization and allocation.

Abbreviations: BoNT-A, botulinum toxin type A; Duration, elapsed time following stroke; RFE, Repetitive facilitative exercise program

Table 1. Baseline characteristics and demographics of the participants (n = 40)

	Combination group (n=20)	Control group (n=20)	*p* value
Age, years	60.5（19-75）	66（41-80）	0.09[a]
Sex, male (%)	11（55）	14（70）	0.33[b]
Months since first stroke	40.5（12-209）	32.5（7-157）	0.58[a]
Side of motor deficit, right (%)	6（30）	11（55）	0.11[b]
Type of stroke (%)			0.74[b]
Infarction	7（35）	6（30）	
Hemorrhage	13（65）	14（70）	
Stroke location (%)			0.98[b]
Corona radiata or internal capsule	5（25）	6（30）	
Putamen	7（35）	7（35）	
Thalamus	6（30）	6（30）	
Territory of middle cerebral artery	1（5）	0（0）	
Brainstem	1（5）	1（5）	
FMA	34.5（18-50）	45 (11-55)	0.16[a]
ARAT	10.5 (0-41)	14 (0-42)	0.27[a]
BBT	6 (0-37)	6 (0-25)	0.97[a]
Active ROM			
Extension of elbow joint	-10 (-95-0)	-10 (-70-0)	0.31[a]
Extension of wrist joint	14.5 (-50-50)	21 (-40-60)	0.26[a]

MAS			
Elbow flexors	2 (0-4)	2 (1-3)	0.35[a]
Wrist flexors	1.5 (0-3)	2 (0-4)	0.8[a]
Finger flexors	2 (0-3)	2 (0-4)	0.91[a]

Combination group received the repetitive facilitative exercise (RFE) program and botulinum toxin type A (BoNT-A) injection. Control group received only the RFE program. Abbreviations: FMA, Fugl–Meyer Assessment; ARAT, Action Research Arm Test; BBT, Box and Block Test; ROM, Range of motion; MAS, Modified Ashworth Scale.

Values are medians (range or frequencies in parentheses).

[a]Mann-Whitney *U*-test

[b]Chi-square test

Table 2. Frequency and dose of BoNT-A injections to each targeted muscle

Muscle	Frequency, n (%)	Dose (units)
Pectoralis major	8 (40)	46.9±15.0
Latissimus dorsi	1 (5)	50.0±0
Biceps brachii	16 (80)	49.4±14.6
Brachialis	7 (35)	35.7±12.4
Pronator teres	3 (15)	35.0±10.8
Flexor carpi radialis	12 (60)	35.6±12.2
Flexor carpi ulnaris	12 (60)	34.4±11.7
Extensor carpi radialis	1 (5)	30.0±0
Flexor digitorum superficialis	18 (90)	37.8±11.7
Flexor digitorum profundus	8 (40)	31.9±12.2
Flexor pollicis longus	7 (35)	21.4±6.9
Flexor pollicis brevis	2 (10)	17.5±2.5
Adductor pollicis	4 (20)	22.5±2.5

Abbreviations: BoNT-A, botulinum toxin type A

frequency, the number of patients (percentage); dosage, mean dosage and standard deviation of BoNT-A injection for each of the muscles injected.

Table 3. Changes in outcome measures after 4 weeks of treatment

	Combination group (n=20)			Control group (n=20)			Group comparison[a]	effect size
	Baseline	Week 4	Difference	Baseline	Week 4	Difference	*p value*	*r*
FMA total	34.5 (18-50)	46 (26-58)	11 (4-20)**	45 (11-55)	47 (12-59)	3 (0-9)**	<0.01	0.79
ARAT total	10.5 (0-41)	26.5 (7-54)	12.5 (4-22)**	14 (0-42)	22 (3-53)	7 (0-13)**	<0.01	0.6
Grasp	3 (0-12)	8.5 (1-17)	3.5 (1-10)**	4 (0-14)	7 (0-17)	2 (0-5)**	<0.01	0.45
Grip	2.5 (0-9)	5 (0-12)	2 (0-4)**	3.5 (0-9)	5.5 (0-11)	1 (-1-5)**	0.024	0.36
Pinch	1 (0-13)	4 (1-17)	4 (0-8)**	2 (0-14)	3 (0-17)	1 (0-4)**	<0.01	0.61
Gross movement	4 (0-7)	6 (2-9)	2.5 (0-4)**	6 (0-9)	6 (3-9)	1 (0-3)**	<0.01	0.54
Active ROM								
Extension of elbow joint	-10 (-95-0)	0 (-72-0)	10 (0-24)**	-10 (-70-0)	-6 (-70-0)	0 (0-20)*	<0.01	0.52
Extension of wrist joint	14.5 (-50-50)	32 (0-58)	15.5 (5-58)**	21 (-40-60)	28 (-20-62)	2 (0-20)**	<0.01	0.62
BBT	6 (0-37)	12.5 (0-47)	6 (0-12)**	6 (0-25)	9 (0-30)	3 (0-8)**	<0.01	0.48
MAS								

Elbow flexors	2 (0-4)	0 (0-2)	-1.5 (-2-0)**	2 (1-3)	1 (0-2)	-1 (-2-0)**	<0.01	0.45
Wrist flexors	1.5 (0-3)	0 (0-2)	-1 (-3-0)**	2 (0-4)	1 (0-3)	-1 (-2-0)**	0.051	0.31
Finger flexors	2 (0-3)	0 (0-2)	-1 (-3-0)**	2 (0-4)	0.5 (0-3)	-1 (-2-0)**	0.068	0.29

Combination group received the RFE program combined with BoNT-A injection. Control group received only the RFE program. Abbreviations: FMA, Fugl–Meyer Assessment; ARAT, Action Research Arm Test; BBT, Box and Block Test; ROM, Range of motion; MAS, Modified Ashworth Scale. Values are median and range in parentheses.

*p<0.05, **p<0.01; comparisons are between values at baseline and 4 weeks in each group according to the Wilcoxon's signed-rank test.

[a]p-values indicate the significance level of changes in outcome measures between the groups according to the Mann-Whitney U test.

Figure 1

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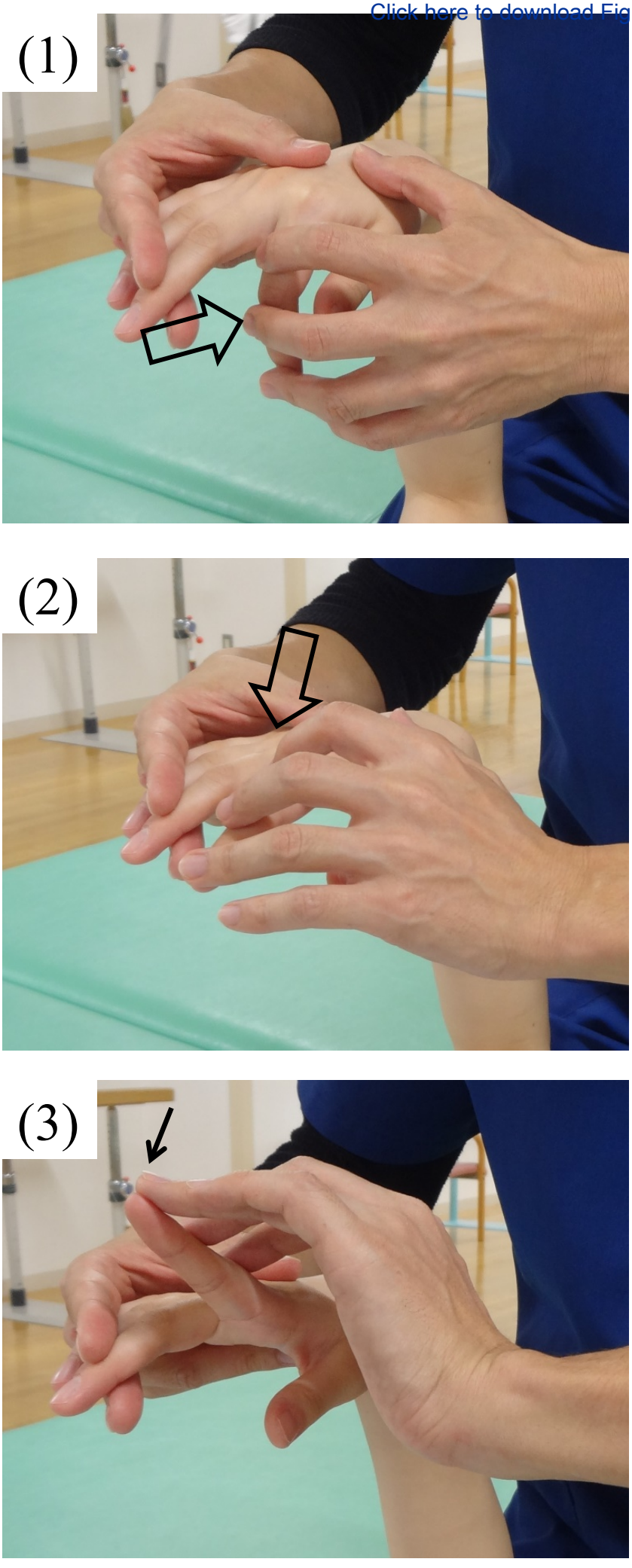

Figure 1

Figure 2

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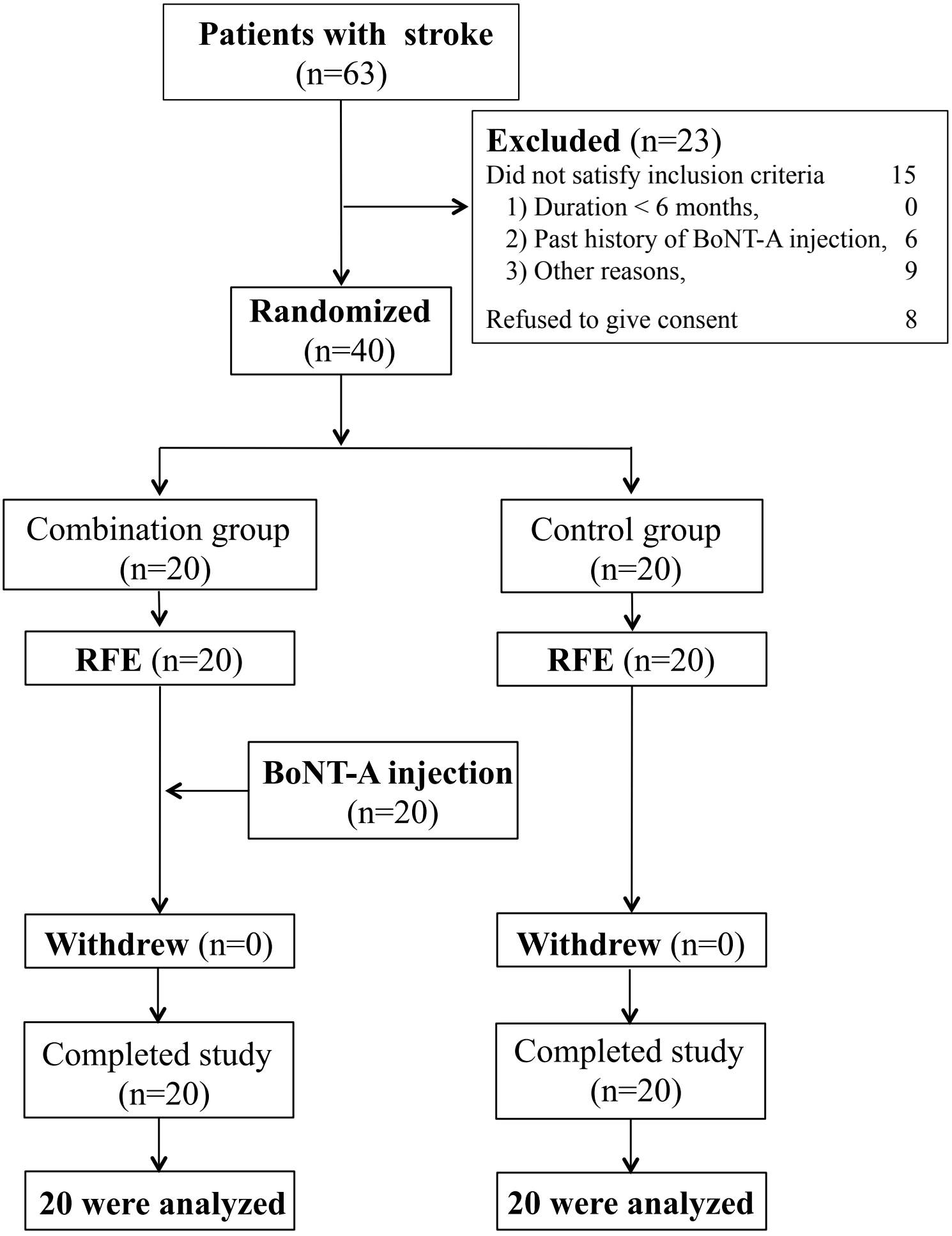

Figure 2