THE EFFECTIVENESS OF COMBINATION OF LOW FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION AND STRUCTURED PHYSIOTHERAPY TRAINING PROGRAM ON RESTORING UPPER EXTREMITY FUNCTION FOR PATIENTS AFTER STROKE

STUDY PROTOCOL

NCT02490371

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Chapter

Methodology

2.1. Study design

This was a double-blind randomized controlled trial; both assessors and patients were blinded to group allocation. Figure 1 illustrates the overall study design. The study was registered in the clinical trial system at registry.gov (reference number: NCT 02490371).

2.2. Participant recruitment

2.2.1 Inclusion and exclusion criteria

A convenient sampling method was adopted. Patients who were diagnosed with their first-ever stroke and referred to the Physiotherapy Department at Queen Elizabeth Hospital for post-stroke rehabilitation between November 2015 to December 2016 were screened for eligibility by an independent physiotherapist using criteria shown in Table 1.

Figure 1: Experimental design and patient flow

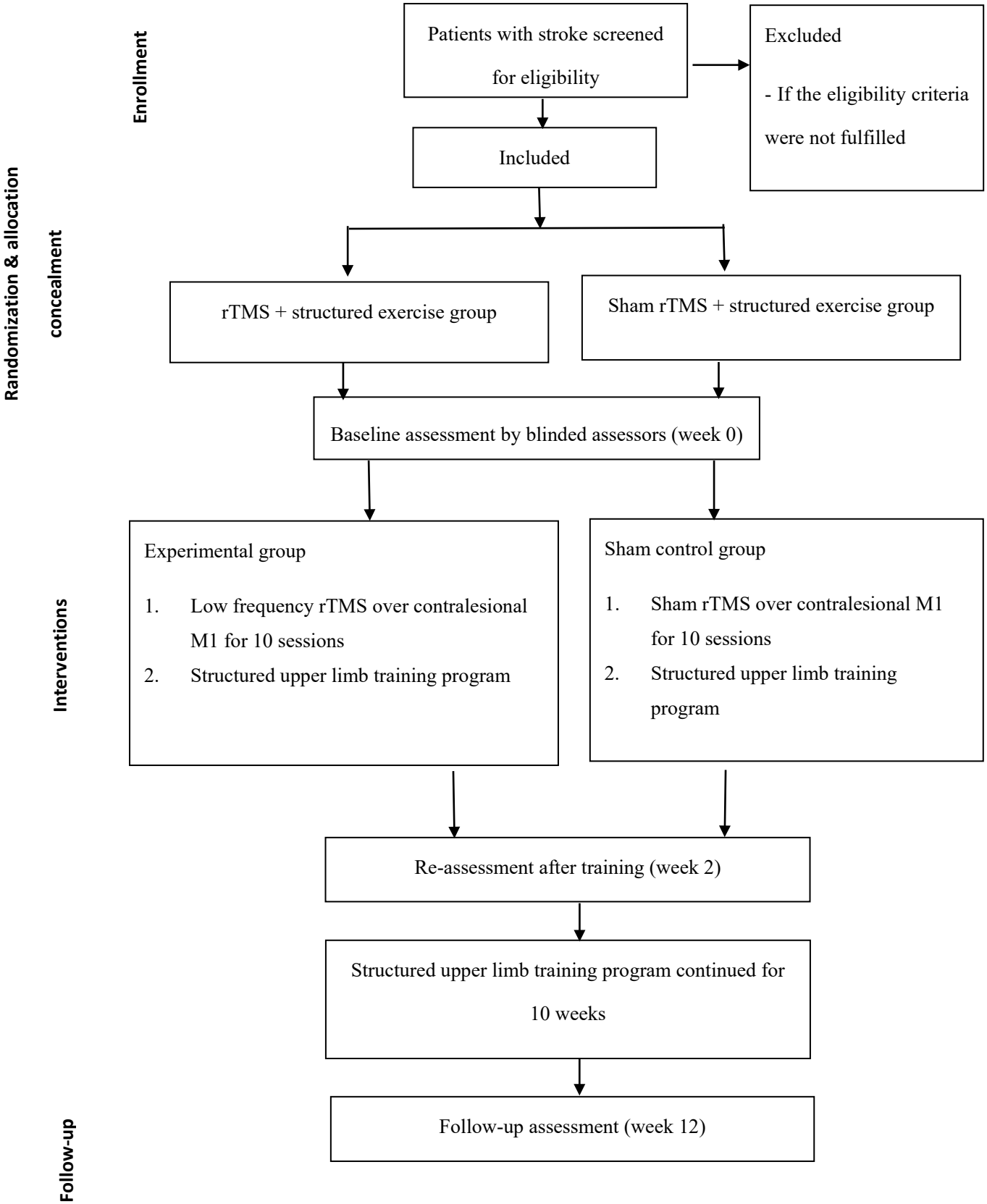


Table 1. Inclusion and exclusion criteria

Inclusion criteria:	**Exclusion criteria:**
1. First episode of stroke; 2. Aged 60 or more; 3. Muscle strength of grade <5 and >2 based on manual muscle testing of the hand or fingers on the paretic side; 4. Time since stroke onset > 1 month and < 6 months;	1. Mini Mental State Test score ≤ 24; 2. Mental illness; 3. Contra-indications to rTMS according to guidelines formulated by Wassermann (e.g., intracranial implants, epilepsy, cardiac pacemaker, implanted medication pumps); 4 Unstable cardio-pulmonary condition.

2.2.2. Sample size estimation

The sample size was estimated from previously published data on one of the primary outcome measures, the motor-evoked potential (MEP). In a study involving a sample of 20 people by Takeuchi et al. (Takeuchi et al. 2008), a significant improvement in MEP was shown in the intervention group. The estimated effect size was about 0.6. Based on this, with the power set at 90% and $p < 0.05$, the minimum estimated sample size would be 22. When considering a 10% attrition rate, the minimum sample size required would be 24 individuals with stroke.

2.3 Randomization and allocation concealment

The recruited individuals were randomly assigned to either the experimental group or the sham group by drawing a pre-set sealed opaque envelope. The group allocation was determined by the results of a randomized table set with 4 × 6 blocks with an allocation ratio of 1:1. The results were printed and placed in separate envelopes. The envelopes were then numbered and put in sequence. Once the individual was recruited, he or she was assigned the next envelope in the sequence. The randomization was done by a researcher who was not involved in the outcome assessments.

The details of the clinical trial were explained to the potential participants by the investigators, and written informed consent was obtained before the commencement of data collection (Appendix I, II, III and IV). This trial protocol was approved by the Research Ethics Committee (Kowloon Central/Kowloon East) of the Hospital Authority (Appendix V), and the Human Research Ethics Subcommittee of the Hong Kong Polytechnic University (Appendix VI).

2.4. Intervention protocol

The experimental group received 10 sessions of rTMS treatment and a structured upper limb training program, whereas the sham control group received sham rTMS and structured upper limb training only. In addition, both groups received the structured upper limb physiotherapy training program 2 sessions per week for another 10 weeks after the 10 sessions of rTMS or sham stimulation had ended. The details of the treatment protocol for each group are described below.

2.4.1 Preparation of participants for brain stimulation

The brain stimulation was conducted by a trained physiotherapist in Queen Elizabeth Hospital who had received formal training on brain stimulation and had more than 5 years of experienced in neurological in rehabilitation field. All participants had been screened for TMS safety at the time of recruitment using a standardized screening form (Appendix VII). All TMS procedures took place in the TMS suite located in the Physiotherapy Department of Queen Elizabeth Hospital.

The participants were seated in an inclined chair with both the hand and the neck well supported with a cushion. The hotspots over the primary cortical regions in both hemispheres were identified in the initial assessment session. The hotspot was identified using the Magstim Rapid Stimulator (Magstim Company, Whitland, UK). The stimulator was equipped with figure-of-eight stimulating electrodes that were connected to the neuronavigation system. The skin around the first dorsal interosseous (FDI) muscles of both hands was rubbed with an alcohol swab for at least one minute to prepare the skin for electromyographic (EMG) measurement. Two EMG positive and negative electrodes were placed over the muscle belly while the ground electrode was placed over the ulnar styloid process.

The hotspot and motor threshold of the contralesional or ipsilesional primary motor cortex were determined by placing the coil tangentially to the scalp over the hand area of the respective M1. The stimulation site (hotspot) was determined as the location where application of TMS at a slightly suprathreshold intensity induced the highest amplitude of MEP in the FDI muscle. The resting motor threshold (rMT) was defined as the intensity that elicited the MEP at a level of > 50 mV in at least 5 of 10 consecutive stimulations. The rMT was set as the baseline for the stimulation intensity. Once the

hotspot was determined, the placement of the coil on the hotspot was marked as the target point in the navigation system so that the accuracy of site stimulation for subsequent treatment sessions could be ensured. The electromyography signals were amplified (2500V/V), bandpass filtered (-1-5k Hz), and digitized for recording with ADC sampling rate of 3kHz by a built-in EMG device in Brainsight 2 (Brainsight 2, Rogue Research Inc., Montreal, Canada).

2.4.2 Experimental group

The participants in the experimental group underwent transcranial magnetic stimulation over hotspot at contralesional M1 region on weekdays over a 2-week period (i.e., 10 sessions), using a Magstim Rapid Stimulator (Magstim Company, Whitland, UK). We used a figure-of-eight coil (each loop 70 mm in diameter) for delivering the stimulation. The stimulation protocol of rTMS used was at a low frequency of 1 Hz with a stimulus intensity of 90% of rMT for a total of 1200 pulses in each session. This low-frequency protocol was adopted because the stimulation parameters were shown to result in down-regulation of motor cortical excitability over the contralesional cortex (Boggio et al., 2006). For frequencies from 0.2 to 1 Hz (low frequency), which favor the manifestation of the long-lasting inhibitory phase, may lead to cortical inhibition. Conversely, frequencies >2 Hz can mask the inhibitory phase of the preceding pulse,

thereby maintaining the neurons in a state of excitation (Moliadze et al. 2003). A meta-analysis by Zhang et al. (2017) found that low frequency rTMS was more beneficial than high frequency rTMS, and that rTMS administered to the contralesional hemisphere elicited better improvements in upper limb motor recovery than when applied to the lesioned hemisphere (Zhang et al., 2017).

The participants in the experimental group also underwent structured upper limb exercise training conducted by a registered physiotherapist in Queen Elizabeth Hospital. Each participant exercised at his or her own pace and was encouraged to perform the exercise continuously for thirty minutes in each session. In the treatment sessions during the first 2 weeks, the participants performed the 30-minute exercise training immediately after the brain stimulation. For the subsequent 10 weeks, the participants continued to receive exercise training twice per week. In each exercise session, two modes of exercises with 15 minutes for each were offered to improve task performance and dexterity of the paretic upper limb. The specific exercises included: 1. reach and grasp exercises: stacking cones or placing cones, and 2. fine motor control exercises of the hand .

2.4.3 Sham group

The sham group received sham rTMS with a trained physiotherapist. All procedures were exactly the same (identifying the hotspot, etc.), except that sham rTMS was given. Sham stimulation was conducted by positioning the coil at an angle of 90 degrees relative to the scalp instead of tangentially to the hotspot, but the coil produced the same sounds as in real rTMS. This strategy allowed the magnitude of the field delivered to be decreased but did not eliminate it (Lisanby et al., 2001) and created a similar sensation. The participants in the sham control group underwent the same upper limb exercise program as those in the experimental group.

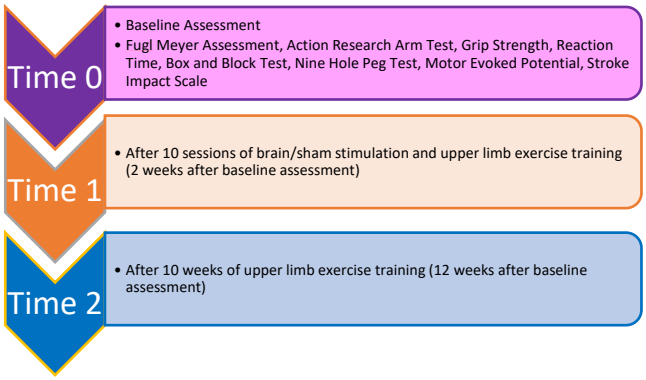
2.5. Outcome assessment

2.5.1 Blinded assessors

Two independent physiotherapists with more than 3 years of relevant experience in neurological rehabilitation were responsible for conducting the evaluations at different time points. These assessors were blinded to group allocation. Evaluations were performed at 3 different time points (figure 6): baseline measurement (Time 0), post-brain stimulation (Time 1), and 12-week follow-up (Time 2) (Figure 6).

A meeting and workshop conducted by the chief investigator were conducted to familiarize the two assessors with the assessment tools and procedures before the trial officially commenced. Regular discussions were conducted at three-month intervals for quality assurance purpose.

Figure 6: Measurement schedule



2.6 Outcome measures

A battery of assessment tools was chosen to evaluate the participants across the domains of International Classification of Function, Disability, and Health endorsed by the World Health Organization (i.e., body functions/structures, activity and participation WHO Disability Assessment Schedule (WHO 2010). The upper-extremity portion of the Fugl-Meyer Motor Assessment Scale (FMA) (Fugl-Meyer et al., 1975) was the primary behavioral measure outcome of arm function, whereas the motor evoked potential (MEP) was the primary physiological measure. Secondary measures included grip force (Takeuchi et al., 2008), the Action Research Arm Test (ARAT), the Nine Hole Pegboard test (NHPT), the Box and Block test, the reaction time test, and the Stroke Impact Scale (SIS).

2.6.1. Measures of body structures/function

2.6.1.1 Fugl-Meyer assessment (FMA)

In the upper-extremity portion of the Fugl-Meyer Motor Assessment Scale (FMA) (Appendix VIII), 25 test items included measurement of movement, coordination, and reflex action of the different parts of the paretic upper extremity. The score could range

from 0 to 66. Better motor function was reflected by a higher FMA score (Fugl et al., 1975). The FMA scores have been shown to have high construct validity, test-retest and interrater reliability (Platz et al., 2005). The minimum clinically important difference MCID of FMA was 5.2 points for the upper extremity portion (Wagner et al., 2008).

2.6.1.2 Motor evoked potential (MEP)

To obtain the MEP of the FDI, EMG activity was measured using silver–silver chloride (Ag-AgCl) electrodes placed on the skin overlying the FDI. The peak-to-peak MEP amplitude was recorded, which reflects cortical excitability (Malcolm et al., 2007) (Figure 7). Ten averaged MEPs evoked from the M1 hotspot on both the ipsilesional and contralesional sides of dies at 120% rMT were recorded using the Magstim 200 (Magstim Company, Whitland, UK). If the EMG could not be triggered at 100% of the resting motor threshold, the MEP was defined as “cannot be triggered” and set at zero.

If the MEP was absent when stimulating the lesioned hemisphere by the stroke, the motor hotspot was defined as being symmetrical to the contra-lesional hemisphere. The signal was amplified, bandpass filtered (1-5k Hz), and digitized for off-line analysis with ADC sampling rate of 3kHz by a built-in EMG device in Brainsight 2 (Brainsight 2, Rogue Research Inc., Montreal, Canada).

2.6.1.3 Grip strength

Isometric hand grip strength was evaluated using the Jamar dynamometer for the paretic hand. The test was conducted in accordance with the standard position of the American Society of Hand Therapists (Figure 8) (i.e., sitting, shouldered in neutral rotation and adducted, elbow flexed at 90 degrees, forearm and wrist in neutral). Participants were instructed to grasp the dynamometer with maximal effort and sustain for 5 seconds (Chen et al., 2009). The force generated (in kg) was registered. Three trials were conducted and a brief rest period was provided between trials. The mean value of three trials was used for subsequent analysis. According to Bohannon (1986), the grip test has excellent test-retest reliability (ICC = 0.84-0.99) in the measurement of patients with neurological dysfunction. The MCID for stroke patients was 5.0kg and 6.2kg for the affected dominant and non-dominant hands (Lang et al, 2008).

2.6.2 Measures of activity

2.6.2.1 Action research arm test (ARAT)

The 19-item ARAT has four subscales that assess various aspects of upper limb function (i.e., pinch, grip, grasp, and gross motor) (Appendix XI) (Figure 9). Each item was rated on a 4-point scale from 0 to 4. A higher ARAT score was indicative of better upper limb function. The intra-rater and inter-rater reliability of ARAT have been found to be good (Platz et al., 2005). The MCID for chronic stroke was 10% of the measure of the total range (i.e., 5.7 points) (Lee et al., 2001).

2.6.2.2 Nine-Hole peg test (NHPT)

The NHPT measures finger dexterity. A nine-hole peg board was positioned in midline of the participant. The container consisting of the pegs was oriented towards the paretic hand. The participants were asked to remove the pegs from the container, one at a time, and place them into the holes on the board as fast as able (Figure 10). They were then required to take each peg from the hole, one at a time, and put it back into the

container. The time taken to complete the test (in seconds) was recorded using a stopwatch. The NHPT has excellent test-retest reliability when used in individuals with stroke (ICC = 0.85) (Platz et al., 2005). The minimal detectable change (MDC) of the NHPT was 32.78 seconds (Chen et al., 2009). For those who were unable to perform the test within 10 minutes despite the best effort, and a value of 600s would be entered for these cases for data analysis purpose.

2.6.2.3 Box and Block test

The Box and Block test measures the gross manual activity of the upper limb. The number of blocks transferred over the partition from one side of the compartment to the other within a one-minute time period was recorded (Figure 11). A higher number indicated better function. The interrater reliability of the Box and Block test was high (ICC = 0.99) with an MDC value of 5.5 blocks per minute and a percentage change of 18% (Chen et al., 2009).

2.6.2.4 Reaction time test

The simple reaction time was tested using a software program designed by the Hong Kong Polytechnic University. Two pictures (apple and dragon fruit) were shown on the screen and appeared for random periods of time (ranging from 180 ms to 200 ms). The image of the apple appeared first as a cue to prepare the participant before the image of the dragon fruit was displayed. Participants were required to press the space bar of the computer once the picture of the dragon fruit appeared on the screen. This same process was repeated until the data for five trials were obtained. The time gap between the appearance of the visual signal and the participant pressing the space bar was recorded by the system. The average of five trials was used for analysis.

2.6.3. Measure of participation

2.6.3.1. Stroke Impact Scale (SIS)

The 59-item Stroke Impact Scale (SIS) is a self-reported measure of health status (Appendix X). It is designed to measure various domains of stroke outcomes, including activities of daily living/instrumental activities of daily living (ADL/IADL), strength, mobility, hand function, memory and thinking, communication, emotion, and participation. Each item was rated on a 5-point scale, yielding a possible score range

from 0 to 100. Lower scores were indicative of increasing difficulty experienced by the participants in accomplishing the tasks described in the test. The MCID of the strength, ADL/IADL, mobility and hand function domains was 9.2, 5.9, 4.5 and 17.8 respectively (Lin et al., 2010).

2.7 Procedures for reporting and monitoring adverse events

During the treatment procedures, one case physiotherapist was responsible for the participant, monitoring changes, rectifying the intervention, recording any change of condition, and reporting any adverse events. According to the Hospital Authority regulations and guideline, the physiotherapist reported adverse events to the supervisor who reported it through the Accident or Incident Reporting System within 48 hours.

2.8. Statistical analysis

The software package SPSS 21.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analysis. The demographic characteristics of the participants and outcome variables at baseline were compared using the Chi-square test (for nominal data), Mann-Whitney U test (for ordinal data), and independent t-test (for continuous

data). Next, for each continuous outcome measure (FMA, MEP, GS, ARAT, B&B, RT), a 2 × 3 two-way repeated measures ANOVA (mixed design; within-subject factor: time; between-subject factor: group) was used to determine whether there was a significant treatment effect on each of the outcome variables (i.e., significant group × time interaction effect). If any substantial difference was found in particular baseline characteristics between the two groups, the variables would be entered as covariates in the above ANOVA model. Post-hoc analysis was then performed to examine the within-group changes over time using paired t-tests and between-group differences in change score at week 2 and week 12 using independent t-tests.

For analysis of the NHPT, because the failure cases were assigned a value of 600s, non-parametric statistics was used. Friedman test and post-hoc Wilcoxon test were used to examine the within-group changes over time, while Mann-Whitney U test was used to examine the difference between the two groups at week 2 and 12.

Next, for those clinical outcome variables that yielded a significant treatment effect (i.e., significant group × time interaction effect), Pearson's product moment correlation coefficients were used to determine the degree of correlation between changes in these variables and those in MEP on both sides.

Intention to treat analysis was first conducted. Any missing data would be substituted using the last-observation-carried-forward (LOCF) method. This was followed by on-protocol analysis, in which only those participants who completed all outcome assessments were included.

The alpha was set at 0.05, except for post-hoc tests where the alpha was adjusted to 0.025 (i.e., Bonferroni correction) because of the 2 comparisons made (within-group analysis: baseline Vs week 2; week 2 Vs week 12; between-group comparison of change score: week 2 and week 12).