Research Ttile:
A randomized controlled clinical trial of upper limb training with bilateral cutaneous electrical stimulation to improve upper limb functions in patients with chronic stroke

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The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project entitled: A randomized controlled clinical trial of upper limb training with bilateral cutaneous electrical stimulation to improve upper limb functions in patients with chronic stroke

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Purpose:

To investigate whether bilateral cutaneous electrical stimulation over both paretic and non-paretic upper limb (bilateral ES) will be more superior to cutaneous electrical stimulation over paretic upper limb (unilateral ES) when combined with task-orientated upper limb training (TOT) respectively.

Methods:

All eligible subjects will be randomly assigned into 4 groups: (1) bilateral cutaneous electrical stimulation over both paretic and non-paretic upper limb (bilateral ES) and (2) unilateral cutaneous electrical stimulation over paretic upper limb (unilateral ES), (3) bilateral placebo electrical stimulation over both paretic and non-paretic upper limb (placebo ES) combined with task-orientated upper limb training (TOT) respectively for 8 weeks, 3 times a week (total 20 treatment sessions). (4) No active treatment. Subjects will

be assessed on improvement of the Wolf Motor Function test, Fugl Meyer Assessment Upper Extremity Portion, and Motor Activity Log Questionnaire.

Potential Risks and Benefits:

The major benefit from participating in this study is that subjects may have the opportunity to know their own level of motor functions of their upper limbs. The results may also be beneficial for planning an intensive rehabilitation program for improving upper limb motor functions in patients with stroke. The electrical stimulation and testing procedures have been well proved to be safe and used with negligible side effects, both clinically and experimentally. A few subjects may feel some exhaustion during assessment and therefore rest will be allowed between assessment procedures.

Informed Consent:

I,_____, understand the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons, and my withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name will not appear on any publications resulted from this study.

I can contact the chief investigator, Dr. Shamay Ng at telephone 2766-4889 for any questions about this study. If I have complaints related to the investigators, I can contact Ms. Gloria Man secretary of Departmental Research Committee, at 2766-4394. I know I will be given a signed copy of this consent form.

Signature (participant):_____Date: _____

Signature (Witness):_____Date: _____

Methods

Design

This study was a single-blinded randomized, placebo-controlled trial. The study was registered on ClinicalTrials.gov (NCT03112473) and conducted in our neurorehabilitation laboratory. Informed consents were obtained before the study began. The study protocol was approved by the ethics committee of the Hong Kong Polytechnic University and conducted in accordance to the Declaration of Helsinki.

As there was no previous study investigating the effect of Bi-TENS+TOT in improving the upper limb motor control in people with stroke, the effect size (Cohen's d=0.314) used for the calculation of sample size in this study was obtained from our pilot trial. The sample size was calculated by using G*power version 3.1.0 (Franz Faul, Universitat Kiet Germany) with α of 0.05, power of 0.80, correlation among measure of 0.5 and non-sphericity correlation of 1. Ninety-six subjects were necessary to detect a significant between-group difference in the improvement of the upper limb motor control measured by FMA-UE. In accordance to our previous clinical trial, dropout rate of was assumed to be 20%, so a buffer of 24 subjects would be included. A sample size of 120 (30 per group) was used to detect the significant between-group difference finally.

The randomization was conducted by a research assistant who did not involve in the intervention and assessment after the baseline measurement. The eligible subjects were stratified into one of the four groups randomly: Bi-TENS+TOT group, Uni-TENS+TOT group, Placebo-TENS+TOT group and Control group. The stratification was conducted by the online software "Minimize". The factors of age (50-60, 60-70,>70), sex (male, female), type of stroke (ischemia, hemorrhage) and side of lesion (left, right) were balanced in the four groups. To achieve concealment, the allocation information was kept by the research assistant. Following the provision of informed consent, subjects were informed of their allocation to one of four groups, but specific group allocation remained concealed to maintain the blinding of treatment.

Subjects

One hundred and twenty subjects (mean age=61.70±5.91 years) were recruited from the local self-help groups. The inclusion criteria of the subjects included: (1) were between 50 and 80 years of age; (2) had been diagnosed with stroke within 1 to 10 years; (3) had volitional control of the non-paretic arm and at least minimal antigravity movement in the paretic shoulder; (4) had at least 5 degrees in wrist extension in the antigravity position; (5) had an Abbreviated Mental Test score $\geq$7. The participants were excluded if they: (1) had any additional medical, cardiovascular or orthopedic condition; (2) had contraindications to TENS, such as implant cardiac pacemaker, skin allergy; (3) had receptive dysphasia; (4) had a significant upper limb peripheral neuropathy; (5) were involved in drug studies or other clinical trials; (6) had severe shoulder, elbow, wrist or finger contractures.

Intervention

TENS protocol

With reference to previous studies, the dosage of 20 sessions of 60-minute TENS could provide sufficient stimulus to elicit recovery of motor function in people with chronic stroke. In the Bi-TENS group, the subjects received TENS on both paretic and non-paretic sides of the upper limbs. In the Uni-TENS group, TENS was only applied on the paretic side of the upper limb while a placebo stimulation (P-STIM) was applied on the non-paretic side. In the Placebo-TENS+TOT group, the P-STIM was applied on both sides of the upper limbs. In the Control group, the subjects did not receive any active treatment. The disposable surface electrodes were applied to stimulate the median nerve (from the carpal tunnel to flexor digitorum superficialis) and superficial radial nerve (from the extensor pollicis longus to extensor digitorum communis).

The stimulator was 120z Dual-Channel TENS Unit (ITO PHYSITHERAPY&REHABILITION CO., LTD, Tokyo, Japan). The parameter (100 Hz, 0.2 ms square pulses, intensity barely below the motor threshold) of TENS followed our previous study (10). The P-STIM was provided by identical-looking TENS devices that electrical circuit has been disconnected.

TOT protocol

The TOT protocol was developed based on the guideline of stroke rehabilitation (40). Under the supervision of a well-trained research assistant with health-related discipline training, the subjects with stroke were required to complete six 10-minute training items in each session of treatment, including stretching exercises, mobilizing exercise, strengthening exercises, seated reaching tasks, dexterity training and bimanual practice. Five minutes' interval for resting was provided between each training item.

Outcome Measure

To eliminate the bias, an experienced rehabilitation therapist who was blinded to the group allocation assessed all outcome measures in a random sequence for 5 times, including baseline, mid-intervention (4th week of study), post-intervention (8th week of study), 1-month follow-up and 3-month follow-up.

Primary Outcome

Fugl-Meyer Assessment of upper extremity (FMA-UE)

FMA-UE was used for evaluating the upper limb motor control in people with stroke. FMA-UE showed an excellent inter-rater (r=0.997) and test-retest (r=0.965) reliability in people with chronic stroke. FMA-UE has 4 subsections: (1) shoulder-arm; (2) wrist; (3) hand; (4) coordination and speed. There was a total score of 66 with 33 items with ordinal scoring from 0 to 2.

Secondary Outcome

The Peak Torque and co-contraction ratio of Maximum Voluntary Contraction (MVC)

Peak torque and co-contraction ratio was used to assess the muscle strength and abnormal muscle activation. The raw force data and electromyography (EMG) signal was record by the custom-built measurement frame mounted with load cell and surface EMG, respectively. At the beginning, the subjects were seated with shoulder flexion 0°, elbow flexion 0° and wrist 0° neutral position placed in the torque measurement. The paretic hand was fixed by stripe and the forearm was fixed by G-clamp. The 2 bar-shaped electrodes were placed on flexor carpi ulnaris and extensor carpi ulnaris. During data collection, the subjects were required to perform 5 seconds isometric MVC of wrist extension/flexion, respectively. Each movement was performed 3 times. The data of the 3 trials were averaged.

The torque of the movement was the product of the force and moment arm, which is the length from the transverse crease of the wrist to the head of the 3rd metacarpal. The peak torque would be recorded by extracting the peak value of torque being produced during MVC. Excellent intra-rater reliability ranged from 0.97 to 0.98 were reported in our pilot study.

The raw EMG was rectified and filtered by a band pass filter (20-450Hz) and a notch filter (49Hz-51Hz) by Butterworth method. Then the EMG signal would be integrated. The time window beginning at 0.25 seconds before and end at 0.25 seconds after the peak torque occurred was captured to calculate the integrated EMG (iEMG) of the agonist and antagonist. The co-contraction ratio would be calculated by the following formula:

$$\text{Co-contraction Ratio} = \frac{\square\square\square\square\ \square\square\square\square\square\square\square\square\square\square\square}{\square\square\square\square\ \square\square\square\square\square\square\square\square + \square\square\square\square\ \square\square\square\square\square\square\square\square\square\square\square} \times 100\%$$

Good to Excellent intra-rater reliability ranged from 0.837 to 0.975 were reported in our pilot study.

ROM of wrist and elbow

The ROM of wrist and elbow were measured by the electrogoniometer (Model SG 110; Biometrics, Gwent, UK). The electrogoniometer showed a high intra-rater (r=0.90-0.92) reliability (44) in people with stroke. The subjects performed maximal ROM of wrist flexion/extension and elbow flexion/extension with their paretic side twice. The mean values of 2 trials were recorded.

Action Research Arm Test (ARAT)

ARAT was an objective scale to assess the upper limb motor function. Previous study showed that ARAT showed an excellent intra-rater (r=0.996-0.997) and inter-rater (r=0.989) reliability in people with chronic stroke. This ordinal scale consists of 19 items with a total score of 57. The quality of the performance on each item was rated from 0 to 3.

Jacket Test (JT)

JT was an objective scale to evaluate the upper limb motor function by completion time of dressing task, which included shoulder abduction, flexion and elbow extension and hand gripping. JT showed a good to excellent intra-rater (r=0.845-0.891), inter-rater (r=1.000-1.000) and test-retest (r=0.781-0.795) reliability in people with chronic stroke. The subjects were required to put on a jacket or cardigan sweater straight on his or her shoulders, and then took it off completely for 3 trials. The completion time of the 3 trials was averaged.

Motor Activity Log (MAL)

The MAL questionnaire was a subjective scale to assess upper limb motor function. Subjects were required to rate the amount of use (AOU) and the quality of movement (QOM) of their paretic upper limb from 0 to 5 in 30 items of ADL. MAL showed a good reliability in both components of AOU (ICC=0.79) and QOM (ICC=0.82) in people with stroke. A higher score of AOU and QOM indicated that higher usage frequency and better performance of their paretic upper limbs, respectively.

Community Integration Measure (CIM)

The Chinese version of CIM was used to assess the community integration level. CIM showed a good test-retest reliability (ICC=0.84) in measuring the people with chronic stroke. CIM consists of 10 items, each item rated from 1 to 5, giving a score ranged from 10 to 50. A higher score indicated a higher level of community integration.

Statistical Analysis

All the quantitative analyses were performed by the SPSS (Version 23.0, IBM, Armonk, NY). Descriptive analysis was used to summarize subjects' demographic information. One-way analysis of variance, Chi-Squared test ($\chi 2$ test) and Kruskal-Wallis test were used to compare the baseline characteristics of the four groups as appropriate. Intention-to-treat analysis (last observation carry forward) was used. The linear mixed models (LMM) were used to compare the changes over time in variables of interest between those in the Bi-TENS+TOT group and those in the Uni-TENS+TOT group, Placebo-TENS+TOT group and Control group. The maximum likelihood estimation was used to selected the best fit model. The first-order autoregressive structure with heterogeneous variances (AR (1): heterogeneous) was used to estimate the

parameters of statistical model. The intervention effect from pre-intervention to post-intervention was analyzed by LMM. The carryover effect from post-intervention to 3-month follow-up assessment was analyzed using the same LMM method. The significant level was set at 0.05. The post-hoc analysis would be conducted by Bonferroni correction when there was an overall significant difference.