CLINICAL STUDY PROTOCOL

Development of repetitive transcranial magnetic stimulation (rTMS) combined with machine-assisted bimanual therapy (BT) in upper limb rehabilitation.

VERSION NO. 4

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English Synopsis

I. Title of Study

Development of repetitive transcranial magnetic stimulation (rTMS) combined with machine-assisted bimanual therapy (BT) in upper limb rehabilitation.

II. Indication

1. Inclusion Criteria

(1) Age 40-80 years;
(2) First-onset stroke patients;
(3) Patients diagnosed with cerebral infarction or hemorrhage through CT or MRI;
(4) Signed informed consent form by the patient and their family;
(5) Stable physiological parameters;
(6) Stroke occurred within the last 12 months;
(7) Patients with unilateral hand function impairment caused by the stroke;
(8) Upper limb muscle tone (Modified Ashworth Scale, MAS) less than 3 points;
(9) Able to follow two-step commands.

2. Exclusion Criteria

(1) A history of epilepsy or family history of epilepsy;
(2) Presence of suicidal tendencies;
(3) Currently using medications that lower the seizure threshold;
(4) Pregnant or planning to become pregnant;
(5) Co-existing neurological diseases (such as multiple sclerosis, other neurodegenerative diseases, meningitis, brain abscess, or meningioma);
(6) Subjects with uncontrollable migraines caused by elevated intracranial pressure;
(7) Subjects taking antidepressants who cannot discontinue the medication;
(8) Subjects with sleep disorders during rTMS treatment;
(9) Subjects with cerebellar stroke or brainstem stroke;
(10) Cerebral ischemic disorders resulting from traumatic brain injury;
(11) Transient ischemic attacks (TIAs);

(12) History of bleeding tendency and other conditions affecting upper limb function, such as myasthenia gravis, systemic immune neuropathy, severe epilepsy, endocrine system disorders, wearers of external or internal cardiac pacemakers, individuals with metallic implants or orthopedic devices;
(13) Co-existing severe heart, liver, kidney dysfunction, or other serious physical illnesses;
(14) Subjects with impaired consciousness who cannot cooperate with examinations or treatments, such as those with mental disorders, or those with intellectual or cognitive impairments, severe dementia;
(15) Presence of implanted electronic devices in the body;
(16) Co-existing severe liver, kidney, or hematological disorders;
(17) Special vulnerable populations;
(18) Skin disease (e.g., pressure ulcers, trauma, cellulitis, etc.).

III. Phase of Development:

Not applicable.

IV. Study Rationale:

The study aims to establish a therapeutic model that combines Bimanual Therapy (BT) with repetitive transcranial magnetic stimulation (rTMS) to investigate neuroplasticity modulation in stroke patients with upper limb hemiparesis. In the study, inhibitory rTMS will be applied to the unaffected hemisphere, and facilitatory rTMS will be applied to the affected hemisphere during stimulation. Patients will also receive BT concurrently with these rTMS stimulations. Functional assessments of the upper limb will be performed prior to, immediately after, and at 1 and 3 months follow-ups to evaluate rehabilitation outcomes. This study will assess rehabilitation outcomes and explore the associated mechanisms of brain modulation , with the goal of improving clinical applicability.

V. Study Objectives:

This study comprises three main objectives. First, to establish a treatment process and environment for utilizing rTMS to modulate neural activity in patients with upper limb hemiparesis caused by stroke. Second, to investigate the application of inhibitory stimulation, continuous theta burst stimulation (cTBS), to the unaffected hemisphere of the stroke-damaged brain, followed by

facilitatory stimulation, intermittent theta burst stimulation (iTBS), to the affected hemisphere. The intention is to employ the established treatment process in the first part to formulate a clinical treatment model. Third, we will further study functional assessments of the upper limb before treatment, immediately post-treatment, and at 1- and 3-month follow-ups.

VI. Study Design

- Duration of Treatment

A. The experiment for establishment of therapeutic environment.

Participants in the experiment for establishment of therapeutic environment underwent 1-3 evaluations. During this experiment, repetitive Transcranial Magnetic Stimulation (rTMS) was employed for brain modulation, involving two sets of stimuli. Each set consisted of initially administering continuous Theta Burst Stimulation (cTBS) to suppress the healthy side (approximately 600 pulses), followed by intermittent Theta Burst Stimulation (iTBS) to enhance the lesion side (600 pulses), totaling approximately 4 minutes (around 1200 pulses). The intensity of iTBS and cTBS is 80-120% of Motor Threshold.

Patients receiving rTMS treatment concurrently underwent machine-assisted bilateral upper limb training. During treatment sessions, patients were instructed to repeatedly perform grasping-opening tasks or engage in bilateral upper limb activities involving simultaneous shoulder and elbow movements while counting down loudly from 300. Upon completion of all training sessions, patients and therapists were required to complete usability and satisfaction analyses to evaluate equipment usability and operational satisfaction.

B. The experiment for evaluation of therapeutic effects.

Patients will be divided into three groups: a Control group, an rTMS group, and an rTMS+BT group. Each group will receive a 65-minute treatment session, administered once every two days, totaling 10 sessions and completing the entire course within 20 days.

Control group: only received traditional rehabilitation training for 50 minutes and self-stretching training (15 minutes); rTMS group: received rTMS intervention (15 minutes) and 50 minutes of traditional rehabilitation training; rTMS+BT group: received rTMS intervention (15 minutes) along with BT meanwhile and 50 minutes of traditional rehabilitation training.

- Number of Planned Patients

72 participants are expected to be recruited in the trial.

- Investigational Product

1. Robot-assisted palm and finger rehabilitation device
   Device name: "RM" Wearable Powered Hand Rehabilitation Device (Non-Sterile)
   Manufacturer: Rehabotics Medical Technology Corporation
2. Bilateral proximal/distal upper limb training platform
   (1) The name of proximal upper limb training device: Non-powered upper limb proximal training platform
   Manufacturer: Rehabotics Medical Technology Corporation
   (2) The name of distal upper limb training device: Non-powered upper limb distal training equipment
   Manufacturer: developed equipment by the Rehabilitation Department of Chang Gung Hospital
3. Repetitive transcranial magnetic stimulation (rTMS)
   Device name: Repetitive transcranial magnetic stimulation (rTMS)
   Manufacturer: Apollo Powermag 100, Mag & More, Germany.

- Endpoints

The primary endpoint was evaluated through the Fugl-Meyer Assessment, while secondary endpoints encompassed various measures, including the Modified Ashworth Scale (MAS), Manual Muscle Testing (MMT) for the upper extremity, Action Research Arm Test (ARAT), Brunnstrom Recovery Stage, Instrumental Activities of Daily Living Scale (IADLs). Additionally, participants and therapists responded to the System Usability Scale (SUS) questionnaire, and a Satisfaction questionnaire was administered.

- Criteria for Evaluation

1. Inclusion Criteria
   (1) Demographics and baseline characteristics of the participants were all available.
   (2) Participants completed all treatment sessions.
   (3) Functional assessments of the upper limb were performed at multiple time points: prior to, immediately after, and at 1 and 3 months follow-ups, without any omissions.

(4) Both participants and therapists completed the System Usability Scale (SUS) questionnaire and the Satisfaction questionnaire.

2. Exclusion Criteria

(1) Participants with unforeseen psychological issues or significant changes in health conditions to prevent interference with the analysis.

(2) Participants using non-study-related medications that could potentially interfere with the outcomes.

● Statistical Methods

Detailed demographic and medical history records are documented for each subject, including age, gender, time of stroke onset, location of stroke, and types of stroke. The clinical assessment will be conducted by a licensed occupational therapist with experience in treating neurological conditions. Clinical assessment results are being compared between groups using a student-t test. Pre and post-training within each group are being assessed using one-way ANOVA to determine improvement. One-way ANOVA is employed for inter-group comparisons, followed by post-hoc tests. If the data do not follow a normal distribution, non-parametric statistical methods are applied. Correlation analysis is used to explore relationships between clinical assessment results and various factors. Quantitative data are presented as (Mean±SEM), and a 95% confidence interval ($p<0.05$) is considered statistically significant.

● Duration of the Study

The study is scheduled to span a total of three years, commencing on August 1st, 2024, and concluding on July 31st, 2027.

● End of Study

In summary, this three-year study, conducted from August 1, 2024, to July 31, 2027, focuses on establishing an integrated approach using rTMS with BT for treating upper limb hemiparesis in stroke patients. The research credits the collaboration of participants, the medical team, and supporting institutions. We are optimistic that the insights gained will play a crucial role in advancing the field of stroke rehabilitation.