TRANSCRANIAL ROTATING PERMANENT MAGNET STIMULATION – STROKE

Study Protocol

This is a two-year randomized double-blind placebo-controlled pilot clinical trial in 30 chronic ischemic stroke patients to assess the safety and efficacy of bilateral multifocal TRPMS treatment. Patients recruited from the stroke clinic at the Houston Methodist Hospital Eddy Scurlock Stroke Center will be randomly assigned in a 1:1 ratio to either the treatment cohort (group 1, 15 patients) or the placebo cohort (group 2, 15 patients). Group 1 and 2 patients will receive active TRPMS treatment and sham treatment (placebo control), respectively. Both patients and investigators evaluating study outcomes will be blinded to treatment assignment. Randomization and coding of patients will be carried out by a research associate who will be involved in constructing, testing, and maintaining the stimulators but will not be participating in any of the evaluation procedures or analysis of data. The research associate will use a list of random numbers generated by a hardware real random number generator for randomization. The research associate will maintain blinding until all data are analyzed by providing real or sham stimulators constructed by the research associate without disclosing their nature to other personnel. Informed consent will be obtained from the patients. They will be compensated for parking. The study will be conducted by the PI Dr. David Chiu with assistance from a study coordinator and a clinical assistant. The sub-investigator Dr. Santosh Helekar will provide technical advice regarding the magnetic stimulator device, guide the operation of the device, and assist with the analysis of the functional MRI data.

Rationale for Using TRPMS in Stroke Recovery and Preliminary Results

The rationale for this treatment is based on the findings and mechanistic insights obtained from published pilot clinical trials with conventional repetitive transcranial magnetic stimulation. In stroke with acute loss of neurons and connections functional recovery may depend on reorganization of connectivity [1-3] . So a technique that strengthens or normalizes brain connectivity is thought to be of high value. Conventional rTMS has shown significant promise in contributing to the recovery of both motor function[4-6] and power[7]. Two approaches using rTMS have been tested in combination with physical or occupational therapy in subacute and chronic ischemic stroke with unilateral deficit. They involve either high frequency (≥5 Hz) cortical stimulation on the side of the lesion believed to cause increase neuronal excitability and facilitation or low frequency (≤1 Hz) on the contralesional side to suppress of local neural activity and block interhemispheric inhibition leading in both cases to enhanced functional cortical reorganization underlying recovery of motor function[8]. The latter strategy with multiple consecutive sessions of rTMS, in particular, has shown efficacy in facilitating functional recovery in chronic stroke [9-11]. High frequency stimulation of the primary motor cortex on the ipsilesional side has also been shown to be safe and effective over a long period after a short treatment schedule[5]. While relaxation of contralateral inhibitory control by contralesional low frequency stimulation has been shown to increase functional connectivity of the primary motor cortex with the ipsilateral lateral premotor and supplementary motor cortices[12], the efficacy of direct stimulation of the latter cortical sites has not been tested. Our multifocal magnetic stimulation method allows us to stimulate all of these ipsilesional and contralesional sites, simultaneously to maximize the benefit. Our preliminary results in a 58 year old chronic

ischemic stroke patient with hemiparesis, who received 2 two-week treatments using the procedure outlined below, are promising. The patient shows significant changes in functional activation in functional MRI accompanied by improvement in grip strength, pinch strength and tone in the affected upper limb, and in gait speed and sensations in the affected lower limb.

Rationale for Use of the New Magnetic Stimulation Device

The new device invented by Drs. Santosh Helekar and Henning Voss is substantially different from conventional TMS devices used in previously published studies. An important difference of this stimulator is that it produces a maximum stimulus strength that is only 6% of the maximum stimulus strength of conventional TMS. Another important difference is that it is much more focal with a spatial spread of about 2 - 3 cm for the stimulus. The frequencies of stimulation used with this device are also lower than those used in conventional stimulation studies. The rationale for using these lower stimulus frequencies is two-fold: 1) We would like to explore whether these reduced stimulus parameters are sufficient to produce the desired effect on recovery from stroke; and 2) This device uses a different mechanism for delivery of each stimulus, namely an oscillatory pulse of 100 ms duration. We believe that this is a more physiological and effective stimulus to bring about restorative neuroplastic changes in stroke, and does not require the higher frequencies of stimulation used in conventional TMS therapy.

Patients

Patients with chronic ischemic stroke with measurable unilateral motor deficit of arm and leg (or arm alone) of more than 3 months duration will be included in the study. Informed consent will be obtained from the patients.

The inclusion criteria for the study are:

1) Patients aged 18 to 80

2) Clinical diagnosis of chronic ischemic stroke recovering for more than 3 months with unilateral motor deficits of arm and leg, or arm alone

***The exclusion criteria are*:**

1) History of seizure

2) Epileptogenic activity (indicative of increased risk of seizures) on EEG

3) Any active unstable medical condition

4) Pregnancy

5) Schizophrenia, bipolar disorder, alcoholism, or substance abuse

6) Medications which in the investigator's clinical judgment significantly lower the seizure threshold

7) Presence of metal or electronic implants in the head (or any in the body that preclude MRI), including pacemakers, defibrillators, aneurysm clips, neuro-stimulators, cochlear implants, metal in the eyes, etc.

8) Any changes in medications prescribed for the treatment of stroke impairment within six weeks prior to inclusion in the study or at any time during the study

9) Botulinum toxin use within 2 months prior to the Screening Visit or any planned use of botulinum toxin during the study

10) Changes in NIHSS and motor assessment scores between Visit 1 and Visit 2 indicating that the patient's impairment is not stable. The following cutoffs, based on research establishing Minimal Clinically Important Differences, will be used for this determination:
    - National Institutes of Health Stroke Scale: A change in total score of more than 2 points in either direction, or a change in the motor extremity score of more than 1 point in either direction.
    - Fugl-Meyer Assessment of Sensorimotor Impairment: A change of more than 5 points in either direction on the upper-extremity motor score for the affected arm.
    - Action Research Arm Test: A change of more than 5 points in either direction on the ARAT score for the affected arm.

11) Any condition that precludes a high quality brain MRI scan.

Study Questionnaire

Each subject will be asked to fill out a questionnaire on an electronic tablet before and after each study session, as we have done in prior studies, in order to assess any subjective effects and adverse reactions to the mild magnetic stimuli delivered during the session.

Evaluation of Patients

Clinical evaluation of patients before (at two time points more than one week apart) and immediately after treatment and at one week, one month and three month follow-up time points will include National Institutes of Health Stroke Scale (NIHSS), grip strength (with hand dynamometer), pinch strength (with pinchmeter), gait speed (Timed Up and Go test), Fugl-Meyer motor arm assessment and Action Research Arm Test (ARAT). All motor function tests will be done by an external physical therapist under the guidance of the PI.

Primary endpoint:

Post-treatment increase in the number of activated voxels in the cortical areas surrounding the lesion, namely precentral gyrus, premotor cortex, supplementary motor cortex, paracentral lobule, and postcentral gyrus, in functional MRI scans conducted at baseline (Visit 2) and immediately post-treatment (Visit 23). The brain voxels are activated by grasping movements performed or attempted by the patient with the affected hand in the MRI machine during acquisition of the functional MRI scan.

Secondary endpoints will be:

1) Change in the Fugl-Meyer motor arm score between baseline (Visit 2) and immediately post-treatment (Visit 23).

2) Change in National Institutes of Health Stroke Scale (NIHSS) score between baseline (Visit 2) and immediately post-treatment (Visit 23).

3) Change in the ARAT score between baseline (Visit 2) and immediately post-treatment (Visit 23).

4) Change in grip strength score between baseline (Visit 2) and immediately post-treatment (Visit 23).

5) Change in pinch strength score between baseline (Visit 2) and immediately post-treatment (Visit 23).

6) Change in Timed Up and Go test score between baseline (Visit 2) and immediately post-treatment (Visit 23).

Schedule of Assessments							
	Visit 1	**Visit 2**	**Visit 3-22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**
	Pre-treatment	Pre-treatment 1week later	Treatments	Immediately Post-treatment	1 week Post treatment	1 month Post treatment	3 months Post treatment
NIHSS	X	X		X	X	X	X
Grip strength	X	X		X	X	X	X
Pinch strength	X	X		X	X	X	X
Timed Up and Go (gait speed)	X	X		X	X	X	X
Fugl-Meyer assessment	X	X		X	X	X	X
ARRT (Action Research Arm Test)	X	X		X	X	X	X
Electroencephalography (EEG)	(X)1	(X)1					
fMRI	(X)1	(X)1		X		X	
Electromyography (EMG)	(X)1	(X)1		X		X	
TRPMS Treatment			X				
1= can be performed at either visit							

Multifocal Transcranial Rotating Permanent Magnet Stimulation (TRPMS) Treatment
TRPMS microstimulators will be attached to a specially chosen tight fitting neoprene cap by Velcro at stimulus sites determined as described below. The patient will be assisted in wearing the flexible cap on his/her head. The cap is essentially similar to a diving or swimming cap, and fits and feels exactly the same when worn. Two microstimulators will be attached to the primary motor cortical (PMC) sites (one medial and one lateral spaced at a distance of 4 cm) on the contralesional side. One the ipsilesional side one microstimulator each will be attached to the lateral premotor cortical (LPC) and supplementary motor cortical (SMC) sites. In addition, on the ipsilesional side two microstimulators will be placed on sites surrounding the lesion on the PMC or the postcentral gyrus spaced 4 cm apart. The stimulus protocol will be preprogrammed and uploaded to a Bluetooth-enabled microcontroller driving the device, to be turned on using a smartphone app. The researcher administering the treatment will turn the stimulator on. The stimulator turns off by itself at the end of the treatment on any given day. But if it needs to be turned off before that then the researcher can easily do so. Treatment will be of four weeks' duration. It will consist of 40 min repeated TRPMS stimulation Monday through Friday. For low frequency stimulation on the contralesional side (PMC) the stimulus pulse duration will be 100 ms and frequency will be 0.2 Hz. The effectiveness of these parameters in modulating cortical neuronal activity has been established by our prior studies[13, 14]. For ipsilesional side (PMC, LPC and SMC) the stimulus duration and frequency will be 25 ms and 5 Hz, respectively.

EEG Recording
EEG recording of 30 min duration will be conducted before the four week treatment using the 10-20 international system EEG. EEG data will be examined visually for the presence of epileptiform activity or other abnormalities. Power spectral analysis of the entire EEG data will be conducted using EEG lab toolbox (Swartz Center for Computation Neuroscience, Institute for Neural Computation, the University of California San Diego, San Diego, CA) to detect the presence of abnormal spectral peaks and changes. This procedure will be done for safety monitoring and will not be included in the statistical analysis.

Anatomical and Functional MRI
Anatomical MRI scan (T1-weighted 3D-MPRAGE) and fMRI (single shot echoplanar imaging[3]; TR = 2000 ms, TE = 30 ms, 36 slices, slice thickness 4 mm, no gap, matrix 64x64, FOV 22 cm) will be carried out on a 3.0 T Philips Ingenia MRI scanner at the HMRI imaging core facility. After the standard anatomical MRI scan a 7.5 minute event-related and a 5 min resting state fMRI scans will be conducted on all patients. The task performed by the patients in the scanner for the event-related scan will be 30 second attempted or actual gripping movements with the affected, unaffected and both hands, sequentially, alternating with 30 second rest periods in a simple block design. The movements and rest periods will be triggered by instructions on the overhead display in the scanner. This will allow us to determine the blood oxygenation level-dependent (BOLD) response in the contralateral PMC on both sides in real time. Each patient will be asked to wear our nylon magnetic stimulation device cap on which EEG 10-20 C3 and C4 fiducial loci will be marked by attached vitamin E capsules that show up on MRI scans. These markings will allow us to pinpoint the sites of stimulation for the subsequent magnetic stimulation treatment. During resting state fMRI the patient will be asked to look at a blank screen displaying a fixation cross. fMRI data will be resampled into 4 mm x 4 mm x 4 mm voxels and preprocessed with SPM12 (Wellcome Department of Cognitive Neurology, London,

UK) using the method of Ashburner and Friston[15]. The analysis of fMRI data will consist of general linear model-based estimation of the event-related BOLD response in each patient using SPM12 software program, as well as fcMRI computation.

Functional Connectivity Analysis

Using in-house MATLAB scripts and functions we will compute the strengths of connections in the fMRI time series data between stimulated volumes (half spheres of 2.4 cm diameter localized in MNI space with MRICRON (Chris Rorden, 2013) and converted to matrix coordinates using mni2cor function (Xu Cui, 2012)) by measuring the partial correlation coefficient (ρ) between pairs of voxel time series. The ρ coefficients will be transformed to z scores, and the high threshold set at $z = 2.5$. ROI coordinates will be obtained from the automated anatomical labeling template[16].

Granger Causality Analysis

In addition to the functional connectivity between cortical regions and their targets we will estimate effective (or directed) connectivity between these regions with the concept of Granger causality [17, 18]. Granger causality will be computed between the average signal in the stimulated region and voxel-wise in the target region, in order to create a causality map for each patient. Statistical significance thresholds will be computed by adaptation of an established test[19] based on random trial perturbations. The maps will be multiple test corrected using a procedure that has been applied to Granger causality testing before[20].

Electromyography

To detect and assess muscle activity during attempted gripping or push down movements with the affected hand and compare it with the normal hand we will perform non-invasive electromyography (EMG) of two intrinsic muscles of each hand, namely abductor policies brevis (APB) and first dorsal interosseous (FDI) muscles. Subjects will be required to follow alternatingly flashed instructions on a computer screen to perform gripping and push down movements with each of their hands at their own pace in a serial block design. Movements of 14 s duration will be alternated with 14 s pauses. The total duration of recording will be ~7.5 min. It will be done on the day of the fMRI scan up to one week before, one day after and one month after the treatment.

We will use self-adhesive surface electrodes (Covidien Kendall 130 foam electrodes, Covidien LLC, Mansfield, MA) attached to the thenar eminence for APB and the dorsal part of the web between the thumb and the index finger for FDI. We will conduct bipolar recordings referenced to the base of the index finger with a ground strap or self-adhesive electrode attached to the wrist. Recordings will be carried out using a wireless EMG system (BioRadio, Great Lakes NeuroTechnologies, Valley View, OH) with a sampling rate of 4 kHz. For counting the number of motor potentials, we will filter the EMG traces using a 20 – 500 Hz digital band pass filter (idealfilter function in MATLAB, Mathworks, Inc., Natick, MA). In our in-house MATLAB graphical user interface program we will then set a cutoff threshold at a level corresponding to positive and negative amplitudes of 15 μV from upper and lower limits of baseline set manually by visually examining each recorded trace one by one. The MATLAB program counts the biphasic or polyphasic peaks that overshoot this threshold. In the computer program peak-to-peak amplitudes are calculated by adding the largest positive and negative peak amplitudes of the

biphasic/polyphasic transients. The peak-to-peak durations correspond to the interval between the peak time points of these largest amplitudes.

Statistical Analysis of Data

For this initial phase clinical trial, sample size power calculation was not performed; rather, a sample size of 30 comparable to that used in prior rTMS stroke Phase 1 trials was chosen. Non-parametric methods of statistical analysis were employed because of the sample size and non-Gaussian distribution of data. The Mann-Whitney U test was applied for comparison of rank ordered values and pre-/post-treatment differences between active and sham treatment arms. Within-subject comparison across time points was done using the Wilcoxon signed rank test. Pair-wise comparison of proportions of subjects between groups involved application of Fisher's exact test. Finally, linear regression models were used to test for significant interactions between treatment effects and age, time in months since the stroke, and cortical versus subcortical infarct location. Level of significance was set at 5%.

Anticipated Results

Based on our prior experience with the device, we anticipated the treatment to be safe with no serious adverse effects. The hypothesis was for significantly greater improvement in the primary endpoint immediately after active treatment compared to sham treatment. We anticipated the improvement to persist at one month and three months post-treatment. The patients are also anticipated to have greater improvement in the clinical scales of motor function after active treatment. These changes are expected to be correlated with functional MRI activity and functional connectivity between stimulated cortical sites on the ipsilesional side, indicating functional cortical reorganization.

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INVESTIGATOR'S AGREEMENT

By signing this protocol, I confirm that I have read it and agree to conduct the trial as outlined herein, complying with the obligations and requirements of clinical investigators and applicable requirements listed in Title 21 of the Code of Federal Regulations.

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David Chiu, M.D. Date