Multifocal Transcranial Rotating Permanent Magnet Stimulation in Chronic Ischemic Stroke: A Phase 1 / 2A Randomized Clinical Trial

Rajan Gadhia, MD, C. David McCane, BA, Jason Lee, BS, Blessy John, MS, Lisa Nguyen, BS, Kayla Butler, PT, Vivek Misra, MD, John J. Volpi, MD, Amit Verma, MD, Santosh A. Helekar, MD, PhD, David Chiu, MD

David Chiu, MD
Elizabeth Blanton Wareing Chair in the Eddy Scurlock Stroke Center, Houston Methodist Hospital
Professor of Neurology, Weill Cornell Medical College
Disclosures

- Trial funded by a grant from the Houston Methodist Research Institute Translational Research Initiative and Seraya Medical LLC.

- *SA Helekar* listed as an inventor on U.S. patent numbers 9456784 and 10398907.

- Patent licensed to Seraya Medical LLC.
Previous clinical studies of repetitive magnetic brain stimulation in chronic ischemic stroke have generally evaluated single site brain stimulation.

Treatment consisted of either high frequency excitatory stimulation of the ipsilesional cortex or low frequency inhibitory stimulation of the contralesional primary motor cortex.

Greater benefit suggested for contralesional hemispheric or bilateral hemispheric stimulation.

A recent large multicenter randomized controlled trial (NICHE) of single site stimulation yielded negative results.
Novel Aspects of Transcranial Rotating Permanent Magnet Stimulation (TRPMS)

- Simultaneous stimulation at 6 sites, 4 ipsilesional and 2 contralesional
- Non-invasive, portable, wearable, battery-operated device
- Prolonged oscillatory pulses of stimulation
- Focal stimulation unaffected by head movement
- Active stimulation indistinguishable from sham
1. Neoprene cap with microstimulators

2. Stimulator console device controller box
Methods: Study Design

- Phase I / 2A single center randomized double blind sham-controlled clinical trial
  - Evaluating safety of therapy
  - Assessing restorative reorganization of brain function
  - Studying recovery of motor function
- 1:1 randomization active treatment and sham
- 30 planned subjects

- Inclusion criteria
  - Chronic ischemic stroke (>3 months)
  - Persistent stable unilateral weakness affecting at least the upper extremity
  - Age 18-80

- Key exclusion criteria
  - History of seizure or epileptogenic activity on EEG
  - Any active unstable medical condition
  - Any condition precluding MRI
  - Botulinum toxin use within 2 months of screening
**Methods: Treatment**

- **Treatment:** 40 minutes stimulation 5 days per week x 4 weeks

- **6 stimulators**
  - 4 on the lesional hemisphere (25 ms stimuli every 200 ms)
  - 2 on the contralesional hemisphere (100 ms stimuli every 5s)

- **On the lesional hemisphere**
  - 2 on the normal cortex surrounding the lesion in case of cortical lesion, or on the intact primary motor cortex in case of subcortical lesion
  - 1 on lateral premotor cortex
  - 1 on supplementary motor cortex

- **On the contralesional hemisphere**
  - 2 on the primary motor cortex
Methods: Outcome Evaluations

- **Safety Endpoint**
  - Incidence of adverse events

- **Primary Efficacy Endpoint**
  - Change in the ipsilesional hemisphere active voxel number on BOLD fMRI immediately after end of treatment in active compared to sham-treated patients

- **Secondary Efficacy Endpoints (change in scale immediately after end of treatment)**
  - Fugl-Meyer motor arm score
  - ARAT (Action Research Arm Test)
  - Hand dynamometer score (grip strength on affected side)
  - Pinch dynamometer score (pinch strength on affected side)
  - Timed Up and Go Test (gait velocity)
  - NIH Stroke Scale
Methods: Subjects

- 31 patients randomized
  - One patient withdrew after 2 days of treatment because of inability to obtain transportation
  - One patient excluded from efficacy analysis because of uninterpretable pre- and post-treatment functional MRI

- 30 patients included in safety analysis
- 29 patients completed treatment and were evaluated in efficacy analysis
- Of the 29 patients, 14 received active treatment and 15 received sham treatment
The two treatment arms did not significantly differ in:

- Age (median 66)
- Gender (48% male)
- Race (14% non-white)
- Lesional side (59% left)
- Cortical versus subcortical lesion location (45% cortical)
- Stroke chronicity (range 4 months to 16 years)
- Pre-treatment functional MRI BOLD profile
## Results: Safety Endpoint - Adverse Events

<table>
<thead>
<tr>
<th>Subject Index</th>
<th>Active Group</th>
<th>Sham Group</th>
<th>Meets SAE Criteria</th>
<th>Relationship to Active TRPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Transient tinnitus</td>
<td></td>
<td>No</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
<td>No</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Acute ischemic stroke</td>
<td></td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td>Seizure (3 weeks post-treatment)</td>
<td></td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>2</td>
<td>Urinary tract infection</td>
<td></td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>3</td>
<td>Migraine</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Fall</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Renal stone</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Fatigue</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Muscle cramps</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Results: Safety Endpoint

- In the active group: 2 patients had 5 adverse events (3 serious AEs)
- In the sham group: 5 patients had 6 adverse events (2 serious AEs)
- A patient in the active group with severe intracranial arterial stenosis had multiple AEs including stroke recurrence
- All AEs were judged unrelated to treatment
- TRPMS was safe and well-tolerated, without any clear device-related adverse effects
**Results: Primary Efficacy Endpoint**

Number of Active Voxels in the Ipsilesional Hemisphere on BOLD fMRI

- Significantly greater increase immediately after active TRPMS compared to sham
  - median +48.5 vs -30, p=0.038
- Significant difference maintained on repeat fMRI one month after treatment
  - p=0.024
- Significantly greater active voxel number immediately after active TRPMS compared to sham
  - median 227.5 vs 26, p=0.016
- Significantly higher proportion of subjects with >15% increase in active voxel number immediately after active TRPMS compared to sham
  - 64% vs 20%, p=0.025
## Results: Primary Efficacy Endpoint

**Number of Active Voxels**

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment Group</th>
<th>Sham Treatment Group</th>
<th>P-value (Sham vs Active)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 14</td>
<td>N = 15</td>
<td></td>
</tr>
<tr>
<td><strong>Number of Active Voxels (rows 1 – 5)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Treatment</td>
<td>133.5 (4-589)</td>
<td>242 (0-443)</td>
<td>0.982</td>
</tr>
<tr>
<td>Post-Treatment Day 1</td>
<td>227.5 (173-601)</td>
<td>26 (0-206)</td>
<td><strong>0.016</strong></td>
</tr>
<tr>
<td>Post-Treatment Day 30</td>
<td>262.0(76-615)</td>
<td>113 (0-176)</td>
<td>0.058</td>
</tr>
<tr>
<td>Post-Treatment Day 1 minus Pre-Treatment</td>
<td>48.5 (-60-81)</td>
<td>-30 (-405-0)</td>
<td><strong>0.038</strong></td>
</tr>
<tr>
<td>Post-Treatment Day 30 minus Pre-Treatment</td>
<td>5.5 (-48-166)</td>
<td>-87.5 (-280-0)</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Subjects showing increase at Post-Treatment Day 1</td>
<td>9 (64%)</td>
<td>3 (20%)</td>
<td><strong>0.025</strong></td>
</tr>
<tr>
<td>Subjects showing increase at Post-Treatment Day 30</td>
<td>7 (50%)</td>
<td>2 (14%)</td>
<td>0.103</td>
</tr>
</tbody>
</table>

Values in rows 1 – 5 are medians (1st – 3rd quartiles). Significant P values are shown in red.
Results: Other fMRI Outcomes

Mean Intensity of Active Voxels on BOLD fMRI

- Significantly greater increase immediately after active TRPMS compared to sham
  - median +0.21 vs -0.33, p=0.024
- Significantly greater mean intensity of active voxels immediately after active TRPMS compared to sham
  - median 5.87 vs 4.86, p=0.008
- Significantly higher proportion of subjects with increase in mean intensity of active voxels immediately after active TRPMS compared to sham
  - 71% vs 20%, p=0.009
- In post hoc analysis, mean intensity of active voxels showed significant positive correlation to 5 of the 6 clinical motor scales
## Results: Other fMRI Outcomes

### Mean Intensity of Active Voxels

<table>
<thead>
<tr>
<th></th>
<th>Active Treatment Group</th>
<th>Sham Treatment Group</th>
<th>P-value (Sham vs Active)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 14</td>
<td>N = 15</td>
<td></td>
</tr>
<tr>
<td>Mean Intensity of Active Voxels (T val., rows 1 – 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Treatment</td>
<td>6.01 (5.03-6.45)</td>
<td>5.38 (0-6.17)</td>
<td>0.415</td>
</tr>
<tr>
<td>Post-Treatment Day 1</td>
<td>5.87 (5.59-6.63)</td>
<td>4.86 (0-5.84)</td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Post-Treatment Day 30</td>
<td>5.84 (5.73-6.4)</td>
<td>5.20 (0-6.22)</td>
<td>0.127</td>
</tr>
<tr>
<td>Post-Treatment Day 1 minus Pre-Treatment</td>
<td>0.21 (0-0.6)</td>
<td>-0.33 (-1.76-0)</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Post-Treatment Day 30 minus Pre-Treatment</td>
<td>0.00 (-0.39-0.75)</td>
<td>-0.25 (-0.63-0)</td>
<td>0.097</td>
</tr>
<tr>
<td>Subjects showing increase at Post-Treatment Day 1</td>
<td>10 (71%)</td>
<td>3 (20%)</td>
<td><strong>0.009</strong></td>
</tr>
<tr>
<td>Subjects showing increase at Post-Treatment Day 30</td>
<td>6 (43%)</td>
<td>2 (14%)</td>
<td>0.209</td>
</tr>
</tbody>
</table>

Values in rows 1 – 5 are medians (1st – 3rd quartiles). Significant P values are shown in red.
Active Group Subject #1

Right hand gripping

Pre-treatment

Post-treatment day 1

Post-treatment day 30

Increased activation
Active Group Subject #2

Right hand gripping

Pre-treatment

Post-treatment day 1

Post-treatment day 30

Increased activation
Sham Group Subject

Right hand gripping

Pre-treatment

Post-treatment day 1

Post-treatment day 30

No activation
A significant increase was observed in TUG (gait velocity) immediately after active TRPMS treatment.

A non-significant numerical improvement was seen in 4 of the 5 other clinical scales of motor function (FM-UE, ARAT, grip strength, and NIHSS).

- 43% of active subjects improved >4.25 (MCID) on FM-UE
- 33% of sham subjects improved >4.25 on FM-UE

There was no improvement observed in pinch strength.

Persistent numerical improvement was observed over the 3-month follow up, including a significant increase in TUG gait velocity.
Clinical Outcomes

Fugl-Meyer Upper Extremity
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90

Action Research Arm Test
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90

Grip Strength
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90

Pinch Strength
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90

Timed Up and Go
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90

NIH Stroke Scale
- Pre-Treatment
- Post-Treatment Day 1
- Post-Treatment Day 90
Fugl-Meyer Motor Arm Score

Fugl-Meyer Upper Extremity

Motor Function Score (Median)

Pre-Treatment
Post-Treatment Day 1
Post-Treatment Day 7
Post-Treatment Day 30
Post-Treatment Day 90
TUG Gait Velocity

Timed Up and Go

Active

Velocity (ft/s, Median)

Pre-Treatment
Post-Treatment Day 1
Post-Treatment Day 7
Post-Treatment Day 30
Post-Treatment Day 90
Conclusions

- This study was the first bilateral multifocal transcranial rotating permanent magnet stimulation (TRPMS) trial in chronic ischemic stroke patients using a novel wearable device.

- TRPMS was safe and well-tolerated.

- TRPMS induced significant functional cortical activation in the injured brain as demonstrated by BOLD functional MRI.

- Clinical scales suggested possible improvement of motor function which persisted for 3 months after treatment.

- The treatment effect on the primary endpoint was not significantly influenced by age, time after stroke, or cortical vs subcortical lesion location.
The trial was positive for the primary efficacy outcome

Improvement of clinical motor function will need to be verified

Next step: Phase IIB multicenter randomized clinical trial with 100 - 200 subjects

- Sponsor: Seraya Medical LLC
- Enrichment of trial with earlier chronic patients?

TRPMStrial@houstonmethodist.org