Official title: Scrambler therapy improves pain in neuromyelitis optica: a randomized controlled trial

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Standard protocol approvals, registrations, and patient consents:

We enrolled 22 patients with NMOSD (11 per arm) at the Johns Hopkins Neuromyelitis Optica Clinic. Participants with severe limitations to mobility or sight due to their disease were given the option to have study visits conducted in their homes. The protocol was approved through the Johns Hopkins Institutional Review Board (IRB00115699) and launched on March 2, 2018. Written informed consent was obtained from each participant prior to study enrollment. The study was registered through ClinicalTrials.gov (NCT03452176). The Food and Drug Administration granted Scrambler therapy (FDA) 510(k) approval for acute, chronic and post-operative pain, "Scrambler ST 5 TENS Device," (K081255) in February 2009.

Participants:

Participants with self-reported neuropathic pain caused by NMOSD were recruited through the Johns Hopkins Neuromyelitis Optica Clinic. For participation eligibility, patients were aged 18 years or older with an NMOSD diagnosis based on the 2015 international consensus diagnostic criteria,[20] regardless of anti-aquaporin 4 (AQP4) serostatus. For inclusion, neuropathic pain needed to be attributable to an inflammatory spinal cord lesion, indicated by MRI from a previous clinical myelitis event. Persistent pain needed to be rated at a level of 4 or higher on an 11-point numeric rating scale (NRS), with persistent pain defined by presence for >3 months. Patients needed to be stable in their disease, such that they had no spinal cord relapses within 6 months prior to enrollment. Patients were eligible to use any combination of standard of care medications for pain treatment, including anti-epileptic, antidepressant, opioid or non-steroidal

anti-inflammatory medications, with no adjustments to the regimen within 30 days of enrollment. Patients with a known or suspected concomitant diagnosis of peripheral neuropathy were excluded. Patients with an ongoing concomitant central neurologic disorder were excluded, as were those who used an investigational agent for pain control within 30 days of enrollment, were pregnant or breastfeeding, were cognitively or mentally incompetent, or had implantable pain management or arrhythmia devices.

Randomization and Masking:

Following consent and screening, participants were randomly assigned to receive Scrambler treatment versus sham at a 1:1 ratio for 10 consecutive weekdays. Recruitment was batched using a randomized block design stratifying across medication class (anti-epileptic, antidepressant, opioid or none) and pain level at screening (moderate 4-6, or severe 7-10) to promote similar distributions across groups in this small study. The rationale was to increase homogeneity between groups due to limited data that suggest response to Scrambler therapy may differ due to interference of medications used for pain.[23] Randomization assignments were assigned by a third-party utilizing www.randomizer.org.

Scrambler therapy was administered via the GEOMC Pain Scrambler, model MC-5A. Electrodes were placed on participants receiving treatment within the dermatome above and below the level of injury, in a sufficiently sensitive area closest to the pain. For instance, if the patient had pain in the back from C3 to C8, a set of electrodes would be placed at C2 (above the pain) and T1 (below the pain.) Stimulation intensity was increased until a maximum tolerable threshold

was reached without being painful, per the established protocol. If the patient felt a constant burn, sting or feeling of discomfort, electrodes were repositioned. The exact electrode positioning depended on the demarcation of the surface pain area, and analgesic response of the patient. Once the channel was regulated to the patient's maximum intensity, pain was assessed by asking the patient how s/he felt in the area of pain covered by the electrodes and adjusted for desired effect of reduced pain and/or analgesic response. Additional channel-pairs were similarly implemented as necessary based on size of pain area, up to 5 pairs in total. Electrodes remained in the established position and intensity for 35 minutes from the time of proper placement was instituted. As central pain is often more pervasive as compared with peripheral neuropathy, more than one area was often targeted.

For the sham group, small motors (<1 cm) which produce a vibratory sensation similar to a wearable activity tracker (i.e., FitBit) were connected to each electrode to simulate Scrambler stimulation but without electrical charge. Channel-pairs were similarly applied in a sufficiently sensitive dermatome closest to the pain, surrounding the level of spinal cord injury. The sham sensation was applied for 35 minutes.

For both groups, the Scrambler machine was kept behind a curtain to help preserve masking. The machine itself was turned on for all participants, though without emitting any stimulation in those receiving sham, so that the alert indicating termination of treatment would be heard by all participants regardless of treatment assignment. Because treatment effect has been shown to vary across technicians, one technician was trained in the proper delivery of Scrambler treatment and performed all interventions.

Study objectives and measures:

Our primary objective was to test the hypothesis that Scrambler therapy is an effective, acceptable, feasible and safe treatment of persistent central neuropathic pain for patients with NMOSD. To test this hypothesis, we performed a randomized single blind, sham-controlled trial testing Scrambler therapy in patients with NMOSD. The primary outcome was feasibility and acceptability. Secondary endpoints included both safety and effectiveness at the end of the 10-day treatment period. Feasibility of treatment was examined to determine whether the intervention was appropriate for this patient population, toward the effort of informing a larger, Phase III study. This was measured by assessing the following: 1) adherence to visit schedule and 2) response to the following question asked directly after completion of the 10-day treatment period: "Do you think you received treatment?" (Yes/No). Acceptability was measured by assessing response to the following question, also asked directly following the treatment course: "Would you want to continue treatment in clinic, if available?" (Yes/No).

Safety of the intervention was evaluated by comparing Adverse Events (AEs) and Serious Adverse Events (SAEs) in the treated versus sham groups. These were monitored and documented prior to initiation of each treatment daily, at termination of final treatment, and at 30- and 60-day follow-up.

Effectiveness was evaluated based on degree of improvement in pain, comparing the treatment group to sham. Prior to initiation of Scrambler therapy and at completion of treatment, patients were asked to rate their pain by the 11-point NRS score. Patients additionally reported NRS pain

scores at 30- and 60- days following therapy completion to assess sustainability of treatment effect.

Although not powered appropriately, an exploratory objective aimed to assess the relationship between improved pain and other co-occurring symptoms. Prior to initiation of Scrambler therapy, patients were asked to complete each of the following measurement tools to determine baseline pain severity and interference, anxiety, depression, and sleep disturbance, respectively: Brief Pain Inventory (BPI), Neuro-QoL [Quality of Life in Neurological Disorders] Short Form v1.0 - Anxiety, Neuro-QoL Short Form v1.0 - Depression, and Neuro-QoL Short Form v1.0 - Sleep Disturbance. Measurement tools were accessed by participants via a secure online portal. Participants were provided with an alphanumeric code that enabled their responses to be linked to their demographic and clinical data in a confidential manner. Questionnaires were mailed to participants without internet access with a postage-paid envelope provided for return of questionnaires. Patients again completed all measurement tools at end of treatment, and at 30- and 60-days following end of treatment.

Statistical analysis:

As one measure of feasibility of treatment, adherence to visit schedule was ascertained. We report the number of patients in each group who were able to complete all treatments. Fisher's exact test was performed to assess if adherence is independent of group assignment. For each of the two survey questions used to assess feasibility and acceptability, as described above, a 95% confidence interval for the proportion of participants answering "Yes" was calculated.

Given the small number of patients in the study, exact binomial confidence intervals were calculated since normal distribution could not be assumed.

Descriptive statistics were used to report AEs and SAEs. Incidence and severity were compared between groups.

Effectiveness was based on degree of improvement of pain and compared NRS pain scores in the treatment group and sham group using the Friedman One-Way Repeated Measure Analysis of Variance by Ranks test at baseline, following treatment, and at 30- and 60-day follow-up. Wilcoxon signed-rank testing was used to determine sustainability over time by comparing scores at baseline to those following treatment, at 30-day follow-up and at 60-day follow-up. A chi-squared analysis comparing the number of treated patients who thought they received treatment versus the number of sham patients who thought they received treatment was performed to determine if masking was effective.

The target sample size of 22 (11 per arm) was based on previous studies which suggest that the average pain value at baseline is at least 4 on the 0-10 NRS with a standard deviation of the original pain value expected to fall in the range of 1-1.5 in this patient population. A conservative estimate of the standard deviation of the change across patients from Day 1 to Day 10 was approximately up to 2. With 11 patients in each arm and under these assumptions, we were able to detect a change of 2.5 points in the Scrambler group at 80% power, with a difference in proportions of 60% between the two groups.

To explore the impact on co-occurring symptoms when intervening on pain, scores were tabulated for each of the following based on measurement tool data: anxiety, depression, sleep

disturbance and pain interference. Friedman One-Way Repeated Measure Analysis of Variance by Ranks was tabulated for each symptom, comparing the change at baseline, following treatment, and at 30- and 60-day follow-up timepoints in each arm. A subanalysis was similarly conducted in those patients who “responded” to Scrambler treatment versus sham. Based on a cohort of adult patients with spinal cord injury who reported clinically meaningful change in pain over time, “response” was defined as patients with a decrease in NRS pain scores of 1.80 points between baseline and end of treatment.

Demographic and clinical characteristics were compared between Scrambler and sham groups using Mann-Whitney *U* and Chi-squared testing, as appropriate.

Data availability:

Public Law 110-85 (also known as the FDA Amendments Act of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. We support efforts to promote data sharing toward the advancement of science and registered this clinical trial, providing trial design, eligibility criteria and outcomes measures.

Classification of evidence:

This study provides Class II evidence of Scrambler therapy use in patients diagnosed with NMOSD who have central neuropathic pain.