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Decreasing Procedural Pain Over Time of Left Prefrontal rTMS for Depression: Initial Results from the Open-Label Phase of a Multi-site Trial (OPT-TMS)

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Abstract

Background—There is much interest in whether daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) over several weeks may become a clinically useful antidepressant treatment. Although rTMS appears largely safe, many patients report that this procedure is somewhat painful, which may restrict its ultimate appeal and utility. We analyzed interim results from the open-label phase of a multi-site randomized trial of rTMS as a treatment for depression to investigate whether the procedural pain of left prefrontal rTMS changes over time.

Methods—Patients with unipolar depression who had failed to respond during at least three weeks of the sham-controlled double-masked rTMS were then offered three more weeks (15 sessions) of open-label rTMS. Retrospective pain ratings and state emotional factors from 20 subjects were assessed using visual analog scales (VAS) recorded on computers before and after each treatment (289 sessions).

Results—Over the 15 treatment sessions, subjective reports of the painfulness of rTMS decreased 48% from baseline. This reduction, although greatest in the first few days, continued steadily (average 2.11 points per session) over the 3 weeks of treatment. The analysis found a significant effect for rTMS-session ($p < 0.0001$) on rTMS-procedural pain over and above changes in subjective emotional states.

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Conflicts of Interest: MUSC holds several TMS related patents. Drs. George and Sackeim are advisory board members for Neuronetics, Inc.

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Conclusion—The procedural pain of left, prefrontal rTMS decreases over time, apparently independently of other emotional changes. Since rTMS scalp pain may decline over time, physicians and patients may decide to continue treatment despite initial discomfort. These observational data can be better tested once the data from the blinded phase of the trial becomes available.

Introduction

Repetitive transcranial magnetic stimulation (rTMS) is currently being investigated in the treatment of depression; however, many patients report that prefrontal TMS is painful. The exact cause of the focal pain of prefrontal rTMS is not known, but some have reasoned that the magnetic pulses activate nociceptors in the scalp, periosteum, and maybe meninges under the coil.[1] Because prefrontal rTMS for depression is considered painful and requires daily visits for several weeks, we initially hypothesized that there would be high dropout rates in clinical trials. In fact, the dropout rate has been surprisingly low. For example, in a recent multi-site trial of 300 patients, the dropout rate at 4 weeks after randomization was only 7%, lower than in antidepressant medication trials.[2]

Many of our depressed patients in treatment studies state that the painfulness of rTMS declines over time. Although this is a common anecdote among TMS researchers, we are unaware of any formal data in this area. Thus, using the open phase data from a large dataset in an ongoing treatment trial, we sought to test formally whether the painfulness of rTMS diminishes over time, and whether these changes are independent of, or linked to, overall changes in emotional state or general pain perception.

Methods

Study Design

We analyzed data from the ongoing National Institute of Mental Health funded study called the Optimization of TMS for the Treatment of Depression (OPT-TMS; NCT00149838). This is a 4 year, 4 site study of double-blinded, randomized, sham-controlled daily left prefrontal rTMS as an acute clinical treatment for major depression. Two hundred and forty moderately depressed adult subjects are expected to participate in the study.

Phase I of the study employs the double-blind, randomized, sham-controlled use of daily prefrontal rTMS to determine the efficacy and safety of the rTMS (120% of motor threshold, 10 hertz, 4 seconds on, 26 seconds off, 75 trains for 3000 stimuli per day). After three weeks of double-blind rTMS, subjects that do not respond to rTMS have the option of enrolling in Phase II, which consists of open-label treatment.

Phase II data, which we analyzed for this paper, includes subjects who were non-responsive in Phase I, either to the sham or the actual rTMS treatment. They were offered a fixed 3-week open treatment of rTMS followed by rTMS treatment of variable duration over the right prefrontal cortex if they did not remit to left-sided treatment.

TMS Treatments

Prior to Phase II, all subjects had 3 weeks of either real or sham left prefrontal rTMS. The Neuronetics Model 2100 therapy System with a solid iron-filled figure eight coil was used for this randomized trial (Neuronetics Inc., Malvern, Pennsylvania). Sophisticated e-shields that may reduce the discomfort of rTMS were not used. Instead, subjects who complained of pain around the site of stimulation were offered the insertion of a simple foam pad. This thin (0.5mm) 12 × 12 inch packing sheet from Staples, Inc (Framingham, Massachusetts) could be folded to create 4 layers of padding, but no more. Subjects rested in a semi-reclined chair with their head supported by a head-holder frame. The coil was positioned 5 cm anterior and in a parasagittal

line from the location that maximized movement in the right hand abductor pollicis brevis as determined by EMG.[3-5] Baseline magnetic resonance imaging (MRI) scans were performed on all subjects, and approximately 1/3 of subjects had the coil positioned 6 cm forward (rather than 5 cm) based on MRI analysis of where the 5 cm rule resulted in placement, and whether this was over prefrontal, or premotor, cortex.[6,7] Patients were given noise-canceling headphones and were instructed to rest quietly during the treatment, but not to fall asleep. Eyes could be open or closed.

Visual Analog Scales

Immediately before and after each rTMS session, all subjects completed custom-developed visual analog scale (VAS) questionnaire on Windows (REALbasic 5.5, REAL software, Austin, Texas). The questionnaire consisted of 15 pre-treatment questions and 27 post-treatment questions. Subjects were asked to rate the following on a scale from 1 to 100: happy, irritable, angry, excited, confused, calm, sad, anxious, nervous, bored, relaxed, tired, distracted, pain, and discomfort. Included only in the post questionnaire were retrospective measures of pain, unpleasantness, tolerability, and discomfort for the beginning, middle and end of the treatment. Pain of the treatment (beginning, middle and end), discomfort and pain (pre and post) were the main factors examined. Data were stored at the four sites on laptops and then transferred quarterly to a central study server.

Subjects

We accessed centrally stored data from the open label phase of the OPT-TMS database of computerized VAS ratings for data from July 2005 to June 2006. We collected these digital data from 27 patients and then de-linked these from the trial (323 sessions). That is, in order to make sure that this analysis did not compromise the integrity of the blind, we de-linked these from the central database and thus could not ask other questions related to outcome, response, etc. For formal statistical analysis, we chose to analyze 20 patients who had data from at least ten treatment sessions with 15 of these patients completing 15 sessions (289 sessions). It is important to remember that at this particular point in the trial, all 20 subjects had already received 15 sessions of either placebo or active rTMS in phase 1. Therefore they were not prefrontal-stimulation naive.

Statistical Analyses

Data were analyzed using Hierarchical Linear Modeling (proc mixed in SAS v9.1; see Singer, 1999 for details on this approach).[8] TMS-session number was the independent variable used in the models. Dependent variables included subjective VAS ratings of rTMS painfulness, happiness, sadness, nervousness and anxiety. Additionally, non-rTMS-related pain experiences were rated using a VAS after each rTMS session.

Results

Procedural Pain

Average, retrospective VAS procedural pain ratings from session 1 (61.7, SEM=7.14), session 10 (39.76, SEM=5.89) and session 15 (32.22, SEM=6.76) suggest an overall decrease in rTMS procedural pain. Subjects reported a 36% decrease in rTMS-painfulness from session 1 to session 10 and a 48% decrease from session 1 to session 15. A resurgence in subjective procedural pain ratings occurred in sessions 6, 7, and 8. We investigated a possible “weekend effect” but found no significant results.

Overall, there was a significant effect for rTMS-session on rTMS procedural pain ($t(259)=6.23$, $p<.0001$). Further, this effect was observed over and above effects of rTMS-session on anxiety,

nervousness, happiness, and sadness ($t(262)=5.66$, $p<.0001$), none of which were significantly related to rTMS-session. No significant effects were observed for rTMS-session on general, non-rTMS-procedural pain ratings ($t(260)=1.17$, ns).

Discussion

In this multi-site sample of medication-free unipolar depressed patients, the painfulness of left prefrontal rTMS diminished 48% over 3 weeks of daily treatment. This fairly dramatic reduction in the painfulness of rTMS, albeit from an open label trial, appears to be independent of changes in mood and anxiety as assessed by other VAS questions. Since all data analyzed for this paper were delinked from the primary database to maintain the principal study's integrity; it is unknown which subjects received 3 weeks of rTMS in the initial blinded phase of the study and which subjects were TMS naive at the start of open label rTMS in phase II. In addition, we are not able to associate these data with observer ratings, or any other data from the trial.

To our knowledge, this is the first formal description of this accommodation to the painfulness of rTMS. We were struck by the magnitude of the reduction, as well as the fact that the painfulness continues to decline even into the second and third weeks of treatment. Furthermore, many of these subjects received 3 weeks of rTMS in the blinded phase for a total of 6 weeks of active rTMS. The exact number of subjects in this category is unknown since the blind for this study has not been compromised but the ratio is likely 1:1. In previous studies, pain was not meticulously assessed once the subject stopped complaining about discomfort during the first few days of rTMS treatment. Interestingly, Avery and colleagues' recent report suggested that rTMS reduced aches and pains after 1 and 2 weeks of treatment and then lost its durability at 3 weeks.[9] We were thus surprised to see a continued decline in the later weeks of treatment.

There are several aspects of this small study that should be kept in mind in order to properly interpret these findings. First, this is open label and we are not able to determine if the effects are due to actual cortical brain stimulation by rTMS, or due to the stimulation of scalp receptors. We will hopefully be able to address this directly with the data from the blinded phase of the trial, with results available within 2 years.

Second, all subjects had already participated in 3 weeks of the first phase of the study. It is unclear how and to what degree 3 compared to 6 weeks of active treatment influenced these results. For example, someone with extreme pain during rTMS might have dropped out of the earlier phase and thus not be in this dataset. We wondered whether a visual examination of the initial pain ratings might show two groups, with half of the subjects having lower pain ratings from receiving 3 weeks of active treatment in the earlier blinded phase. The data however do not appear strikingly split.

Third, in order to maintain study blind integrity these data were de-linked from the clinical trial dataset and thus there is incomplete information regarding whether these pain changes are related to demographic variables, prior treatments or treatment response to rTMS. Anecdotally, we think these pain accommodation effects are separate from the clinical antidepressant effects. For example, in other studies we have had patients who respond to active rTMS, and have an accommodation to the pain. When they return several weeks later for maintenance rTMS, they have lost their accommodation to the painfulness and the procedure hurts in the same manner as when they began. Their mood however remains good. This is indirect evidence of a disconnect between the accommodation to pain and a clinical antidepressant effect. We also failed to find a correlation between the rTMS pain changes and other VAS measured mood effects.

We are unclear whether these changes in the subjective painfulness of left prefrontal rTMS in depressed patients might relate to other work showing that prefrontal rTMS can cause changes in pain perception. For example, in post-surgical patients, 4000 stimuli immediately after surgery have been shown to cause a 40% reduction in morphine use in the hospital.[10] The time course of this effect has not been explored more than 24 hours.

The current study allowed four sheet of foam padding to be inserted between the TMS coil and the scalp. The use of the foam padding was not recorded for each session so it is unclear how well the foam reduced subjective pain. Borckardt and colleagues have shown that a single foam pad can reduce subjective pain and unpleasantness ratings by 5.3% to 8.4%.[1] The foam padding increases the distance between the TMS coil and the scalp and thus may reduce subjective pain since the intensity of the magnetic field decreases rapidly with distance from the coil. The foam may simply cushion the weight and vibration of the TMS coil yielding a more pleasant experience. The use of foam padding needs further study.

Conclusion

The continuation of the blind in the principle study prevents us from knowing which subjects received 3 weeks of placebo or active rTMS in the first phase of the trial. However, we have found that the painfulness of prefrontal rTMS diminishes over the course of 3 weeks in depressed patients undergoing an open-label treatment trial. This accommodation likely contributes to the high rates of retention in rTMS depression treatment studies. Further studies are needed to understand the mechanisms behind this accommodation. Regardless of the mechanism, clinicians and researchers using rTMS should be aware of this accommodation in designing treatment studies and in working with individual patients within a trial who might find rTMS initially painful.

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Figure 1.

Overall schematic of Optimization of TMS for the treatment of depression study. All subjects begin in Phase I and continue to Phase II if they do not remit.

Figure 2.
The picture shows a model with the TMS coil placed over the site of stimulation with a small packing sheet between the coil and her scalp.

Painfulness of Left Prefrontal rTMS

Figure 3.

Average VAS ratings of painfulness during the beginning, middle and end of 15 treatment sessions (20 subjects, 289 sessions).

Figure 4.
Average VAS ratings of happiness, sadness, nervousness and anxiety of 15 treatment sessions.