

Letters

One-Year rTMS Treatment for Refractory Trigeminal Neuralgia

To the Editor:

Repetitive transcranial magnetic stimulation (rTMS) is emerging as an interesting tool in the relief of chronic pain.¹ Indeed, numerous groups have independently demonstrated analgesic effects after a single session of stimulation when the rTMS coil is applied over the motor cortex.² The question remains, however, whether rTMS can be used to induce long-lasting pain relief.

In investigating the effects of five daily sessions of active rTMS vs. sham in 24 patients with chronic pain from trigeminal neuralgia, Khedr et al. report an average pain relief of 45% among the participants in the active rTMS group, with 79% of participants acknowledging significant pain relief. These effects were noted to persist for at least two weeks after the end of stimulation.³

In this context, we aimed to determine whether rTMS could indeed be used to induce reliable pain relief when applied repeatedly and longitudinally in a clinical setting. A single patient with refractory trigeminal neuralgia was invited to participate in our trial of maintenance rTMS if the patient demonstrated a positive response to an initial regimen of 10 sessions of active rTMS. A total of 35 sessions were administered over a one-year period, with various intervals between the sessions. The aim of reporting this case is to provide initial data to design further studies to determine whether long-term rTMS (in this case, for up to one year) could be used to generate meaningful and long-lasting pain relief.

Patient

B.H. is a 62-year-old woman who presented to us in October 2007 complaining of a 15-year

history of chronic pain in relation to trigeminal neuralgia and anesthesia dolorosa. She noted that when her symptoms first began, she experienced lancinating pain shooting from the corner of the mouth to the angle of the jaw. The patient initially sought dental care, including refitting of dentures, which only made the pain worse. After failing conservative medical treatment with carbamazepine, phenytoin, gabapentin, and clonazepam, she elected to undergo microvascular decompression (MVD) in March 2000, about eight years after the initial presentation of the trigeminal pain. Although the MVD surgery helped to remove the “terrible blazing pain that traversed her face,” she continued to describe atypical left-sided facial pain. During the following two years, she underwent two more MVD surgeries and glycerol rhizotomy—all without any success. In January 2006, the patient underwent surgical neurectomy to sever the second division of the trigeminal nerve; the procedure left her with numbness in the face and pain within the numb area (anesthesia dolorosa). The neurosurgeon suggested treatment with epidural motor cortex stimulation, an invasive modality that could perhaps reduce the pain by 50%. The patient declined consent after considering the risks associated with the neurosurgery. For the next year and half, the pain was uncontrollable; she reported that she “lived on narcotics and various nerve medications without any real relief” and spent more time in bed than not.

She presented to our Center for Noninvasive Brain Stimulation expressing strong interest in treatment with rTMS. She noted persistent daily left facial pain that felt like “a nagging pain in the upper palate, in the area above the upper tooth line” of at least seven years’ duration. She said that the pain had been getting worse over the years, and that it

felt worst when she was tired, anxious, or upset. She also noted that the pain could be exacerbated by talking on the phone or chewing gum. On physical exam, the patient was 5'6" and 260 pounds; she appeared generally fatigued and complained of facial pain but otherwise was in no acute distress. Oropharynx was pink and moist with no apparent lesions. She had no rashes or erythema on her face or skin. Her cranial nerves were intact in detail with the exception of V2; the patient acknowledged sensation of dull touch but not pinprick. Strength was normal, reflexes were normal, and sensation to touch and pinprick were otherwise intact throughout. The patient's medical records were reviewed: she was being treated for hypertension and hypothyroidism. She had no other cardiovascular, endocrine, or neurological comorbidities.

Methods

The patient received stimulation with 10 Hz rTMS applied over the hand region of the motor cortex, as previously described.^{4,5} There were a total of four treatment periods: #1–10 sessions, four-month interval; #2–10 sessions, two-week interval; #3–5 sessions, three-month interval; and #4–10 sessions one-month follow-up. Each daily session of M1 rTMS consisted of 30 trains of stimulation applied at 10 Hz for a four-second duration (1,200 pulses); each train was separated by 26 seconds; the total stimulation period was 15 minutes. Thus, the patient received a total of 35 individual rTMS sessions over a one-year period, separated by various intervals.

The primary outcome was self-reported overall daily pain. Pain was assessed by means of a numerical scale, rated from 0 to 10, where 0 corresponds to "no pain" and 10 corresponds to "worst possible" pain. The patient was instructed to record her overall pain for the past 24 hours into a daily pain diary and she was instructed to do so around the same time every afternoon. The secondary outcome was pain medication use, as recorded in the daily diary. Finally, we recorded the adverse effects during this treatment period.

To analyze change in pain, we averaged daily pain scores in periods of up to 12 days and then compared them using a paired comparison

analysis with a *t*-test. We performed a similar analysis for medication use during the trial. As the patient was taking four different types of medications (pregabalin 75 mg, 4–8 tablets; clonazepam 1 mg, 1–4 tablets; meperidine 50 mg, 0–9 tablets; and hydromorphone 8 mg, 0–2 tablets), we calculated a weighted average of the daily pain medications that she was taking. We summed the number of individual tablets she was taking each day, considering the opioid drugs with twice the weight as other medications; we divided by six to calculate the "Medication Units," a weighted average of the number of pain tablets she took each day. Because this is a case report and not a confirmatory study, pair-wise comparisons were not corrected for multiple comparisons.

To evaluate and screen for potential cognitive side effects, the following neuropsychiatric assessments were administered at the first, fifth, and tenth sessions of each treatment period: Mini-Mental State Exam, digit span forward, digit span backward, Beck Depression Index, and questionnaire regarding ability to concentrate and self-perceived cognition.

This protocol was approved by the Committee for Clinical Investigation at Beth Israel Deaconess Medical Center.

Results

We show the results organized by the rTMS treatment periods in text below, and graphically in the accompanying figure (Fig. 1).

First rTMS Treatment Period (Day 1 to Day 44)

Prior to the first rTMS treatment, the baseline pain was 5.79 ± 1.71 (mean \pm standard deviation [SD]) and the weighted mean of medications was 3.26 ± 0.32 units of medications (mean \pm SD). After the first rTMS treatment, there was a significant reduction in pain (to 4.06 ± 2.28 , $P = 0.025$) and in medication use (2.46 ± 0.62 , $P = 0.0002$). However, this effect was short lived as, after the first follow-up, pain returned (7.33 ± 1.77) and medication use increased again (3.69 ± 0.41).

First Interval (Day 45 to Day 175)

During this interval, pain remained elevated (within the range of first follow-up), ranging from 6.36 ± 1.02 to 7.83 ± 1.16 . In fact, there

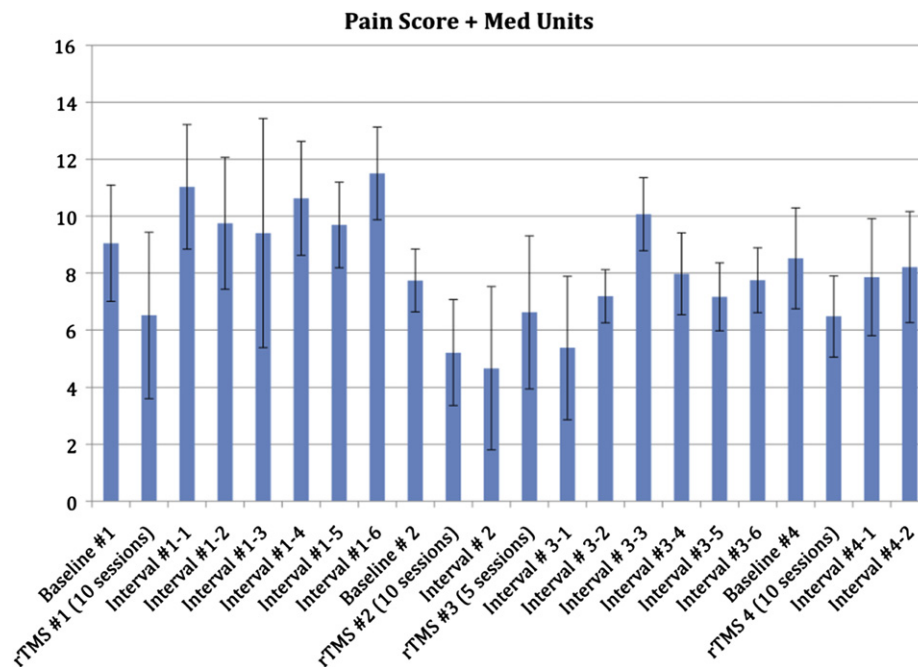


Fig. 1. Medication-adjusted pain scores for the one-year period, as divided into intervals of approximately 10–16 days. Total intervals between treatment Periods #1, #2, #3, and #4 were four months, two weeks, and three months, respectively. Treatment #4 was followed by a one-month period of evaluation. Medication-adjusted pain scores were calculated by sum of average pain score visual analogue scale (VAS, 0–10) and weight-adjusted medication usage. For medication usage, we averaged the number of individual tablets the patient was taking from each of her four pain medications, considering the narcotic class drugs with twice the weight as other medications. VAS = Visual analogue scale.

was no difference when comparing pain scores by interval periods ($P=0.1$).

Second rTMS Treatment Period (Day 176 to Day 210)

For the second TMS treatment, the baseline pain was 5.57 ± 0.97 (mean \pm SD) and the weighted mean of medications was 2.16 ± 0.12 (mean \pm SD). After the first rTMS treatment, there was again a significant reduction in pain (to 3.38 ± 1.66 , $P=0.0052$) and medication use (1.83 ± 0.19 , $P=0.0003$). Interestingly, in contrast to the first session, pain reduction lasted for at least two weeks in this second application (3.25 ± 2.31 , $P=0.012$), and similarly, medication use continued to be reduced (3.69 ± 0.41 , $P=0.0033$).

Third rTMS Treatment (Day 211 to Day 231)

For the third rTMS treatment, the baseline pain was 3.25 ± 2.31 (mean \pm SD) and the weighted mean of medications was 1.79 ± 0.27 (mean \pm SD). Although there was no significant reduction in pain (likely because of

the low baseline due to carry-over effect of treatment 2) (after treatment—first follow-up: 3.57 ± 2.31 , $P=0.75$), there was a significant reduction in medication use (to 1.13 ± 0.20 , $P<0.0001$).

Third Interval (Day 232 to Day 291)

Similarly to the other applications of rTMS, the effects lasted only for two weeks and pain returned after this period. There was an interval of 60 days in which pain returned to her baseline levels (6.64 ± 1.51) and also there was an increase in medication use (1.97 ± 0.26).

Fourth rTMS Treatment (Day 291 to Day 342)

For the fourth rTMS treatment, B.H. again had a reduction in her pain levels from a baseline of 6.54 ± 1.52 (mean \pm SD) to 4.46 ± 1.19 ($P=0.0008$); however, there was no reduction in her medication levels (from 2.01 ± 0.22 to 2.07 ± 0.19 , $P=0.46$). Similarly, pain improvement was short lived. One week after stimulation, the patient's pain had returned to 5.78 ± 1.86 and after two weeks her average pain

score was 6.07 ± 1.85 . However, interestingly, she was taking significantly less medications toward the end of the trial as compared with when she started the treatment: 3.26 ± 0.33 vs. 1.91 ± 0.15 , a 41% reduction.

Adverse Effects

Throughout this year, B.H. reported very few adverse effects. She occasionally reported episodes of transient mild headache and mild neck pain following certain treatment sessions; these sensations lasted only for a few minutes and resolved spontaneously. There were no reports of any other more serious adverse reactions. There were no significant changes in any of the neuropsychiatric assessments that were administered.

Other Subjective Results

In retrospect, the patient reports that she obtained significant relief from the program for short periods of time. She strongly asserts that rTMS does in fact work to reduce her pain, with a meaningful improvement in quality of life, but acknowledges that the stimulation appears to have no long-term effects on permanently reducing her pain, as the chronic pain, tends to return toward baseline weeks after the end of each stimulation cycle.

Discussion

In this case report, we discuss our one-year experience in applying 10 Hz (motor cortex) rTMS in an experimental clinical setting to a patient with chronic orofacial pain. Our results show that, although individual treatment periods could result in significant and meaningful pain relief, the observed effects were limited to about two weeks and a maximum of four weeks after the end of each stimulation period. This longitudinal study, however, demonstrated some interesting points: (1) long-term treatment with rTMS appears safe, with adverse effects limited to those similar to single-session use; (2) effects of back-to-back stimulation sessions (i.e., Treatment Periods #2 and #3, separated by two weeks) may be cumulative and propagative in effect; (3) application of rTMS in the acute setting may be helpful in reducing pain medication use; (4) monthly sessions of rTMS (two weeks on, two weeks

off) could potentially be an effective (yet costly) treatment strategy; and (5) withdrawal of therapy for patients with chronic pain might result in rebounding of pain and medication use. Therefore, this case report suggests that rTMS may be helpful in the acute treatment of pain (especially with respect to decreased medication use), but is unlikely to leave any long-lasting permanent effects on pain relief unless accompanied by additional daily sessions applied within two weeks. The strategy of separating stimulation sessions for three to four months is unlikely to be effective.

One important aspect here is that there are currently no guidelines or data showing an optimal strategy for maintenance of rTMS treatment. Studies of rTMS in patients with depression suggest that 10 consecutive sessions is more effective than five sessions at perpetuating antidepressant effects and that the mean duration to relapse is about four to five months;⁶ Demirtas-Tatlidede et al. use relapse as an indication for maintenance therapy. We, therefore, decided to test the strategy of an initial period of 10 consecutive daily rTMS sessions followed by a four-month interval. However, this might not be the best strategy. In fact, in patients with depression, adjunctive sessions of rTMS have the greatest effects when applied within a one-week period,⁷ and O'Reardon et al. report positive results with maintenance therapy at a frequency of 1–2 per week for six months to six years.⁸ Our data from Treatment Periods #2 and #3 suggest that five daily sessions administered two weeks after an initial application of 10-daily sessions may be effective in extending the efficacy of stimulation and time to relapse.

This report is limited by the fact that it is possible for our results to have been confounded by the placebo effect or otherwise uncontrolled variables, such as personal occurrences in the patient's life. However, this seems unlikely, as the patient had no response to alternative forms of therapy and in fact reported to us that she was skeptical to receive any benefits from this therapy because of unsuccessful experiences with other treatment modalities. Furthermore, during the first trial of 10 sessions of rTMS (when the patient was naïve to rTMS), the patient was blinded, as she was in fact told that she would be receiving either sham or active rTMS for the first

treatment session, and she demonstrated a response to stimulation, nonetheless. Finally, the results demonstrated here are consistent with results from other groups.²

Acknowledgments

The authors would like to acknowledge the patient and her husband for the commitment to this trial and for their assistance in providing medical history data for the preparation of this article.

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doi:10.1016/j.jpainsymman.2009.04.020

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Intravenous Naloxone Plus Transdermal Buprenorphine in Cancer Pain Associated with Intractable Cholestatic Pruritus

To the Editor:

The complex and unpredictable series of symptoms that comes with the terminal stage of neoplastic disease significantly compromises patients' quality of life, and poses harsh therapeutic challenges for clinicians. Good control of severe cancer-related cholestatic pruritus seems to be hard to achieve and pruritus still undermines the remaining physical and relational capabilities of seriously ill cancer patients. Its pathogenesis remains substantially unknown and its treatment mostly empirical.

An increased central opioidergic tone seems to be an important component of cholestatic pruritus, with hyperactivity of the serotonergic system playing a primary role. These elements were the basis for the therapeutic choice successfully applied in the following clinical case.

Case

A 65-year-old woman, about 40 kg in weight, had advanced stage colon carcinoma with liver metastases, and was receiving both chemotherapy (systemic and locoregional) and (palliative) radiotherapy. She had severe nociceptive