EPILEPSY CURRENTS

Current Literature

In Clinical Science

TMS: A Tailored Method of Stimulation for Refractory Focal Epilepsy?

Low-Frequency Repetitive Transcranial Magnetic Stimulation for the Treatment of Refractory Partial Epilepsy: A Controlled Clinical Study.

Sun W, Mao W, Meng X, Wang D, Qiao L, Tao W, Li L, Jia X, Han C, Fu M, Tong X, Wu X, Wang Y. *Epilepsia* 2012;53:1782–1789.

PURPOSE: This study was designed to evaluate the therapeutic effect of low-frequency repetitive transcranial magnetic stimulation (rTMS) on patients with refractory partial epilepsy. METHODS: Sixty-four patients with refractory focal epilepsy were screened and 60 patients were randomly divided into two groups by stimulation intensity: 90% (group 1) or 20% (group 2) of resting motor threshold (rMT). Seizure frequency and interictal EEG epileptic discharges were compared between the baseline and follow-up periods. KEY FINDINGS: Seizures significantly decreased following 2-weeks high intensity (90% rMT) rTMS treatment compared with baseline level ($p < 0.05$). rTMS also decreased interictal epilepsy discharges and improved the scales of Symptom Checklist-90 significantly ($p < 0.05$). Seizures and spikes in the follow-up period in the patients who received low intensity (20% rMT) rTMS did not show any difference compared with baseline data ($p > 0.05$, respectively). SIGNIFICANCE: Low-frequency high intensity rTMS (90% rMT) delivered into the epileptogenic zone had a significant antiepileptic effect on patients with refractory partial seizures. rTMS treatment can also reduce the interictal epileptic discharge frequency and improve the psychological condition of these patients.

Commentary

Neurostimulation-based treatments for epilepsy are an alternative for the many patients who remain refractory to standard antiepileptic drugs (AEDs), but modalities such as vagus nerve stimulation, deep brain stimulation, and responsive neurostimulation require surgical implantation of hardware and are accompanied by attendant risks (1). Transcranial magnetic stimulation (TMS), by contrast, is a noninvasive painless method of modulating cortical function, which requires no surgical intervention, is safely repeatable, and can be applied to multiple different targets in the same individual. TMS has quickly attained an important role as a research tool in clinical neuroscience owing to its ability to both probe and modulate cortical physiology and has an FDA-approved clinical indication in the treatment of refractory major depression (2). The potential therapeutic effect of TMS on focal epilepsy, however, has been much less clear. Controlled clinical trials of low-frequency repetitive TMS (rTMS) in refractory epilepsy patients have yielded disparate outcomes, with seizures and interictal epileptiform discharges (IEDs) reduced in some studies but not in others (3–5). Differences in subject selection, location of TMS target, and stimulation parameters could all potentially have played a role in the variability of outcomes. The question remains: Is there a population of refractory epilepsy patients for whom low-frequency rTMS could be a useful therapeutic option?

The recent report by Sun and colleagues from Beijing provides quite striking results from what appears to be the largest controlled clinical study to date of low-frequency rTMS in epilepsy. The investigators randomized 60 patients (mostly adolescents and young adults) with refractory focal epilepsy (mostly extratemporal in origin) to receive either high-intensity 0.5-Hz rTMS treatment (delivered at 90% of the resting motor threshold) or low-intensity treatment (20% of motor threshold) for 2 weeks, using a paradigm totaling 1,500 pulses of stimulation delivered each day. Outcomes included seizure frequency, IED frequency as measured on routine EEG, and scores on a psychologic symptom checklist.

The results, frankly, are startlingly positive. The high-intensity treatment group had an approximately 80% reduction in seizure frequency during the 8 weeks of follow-up following the 2-week treatment period, and this magnitude of improvement was achieved quite quickly and remained remarkably steady during the follow-up period. A surprising 35% of these patients, who on average had been having nearly nine seizures per week during the baseline period, became seizure-free for the entire follow-up period. The median time to first seizure was more than 6 weeks for the high-intensity treatment group. The comparison group with low-intensity treatment, meanwhile, had no significant change in their seizure frequency following rTMS, included no subjects who became seizure-free, and had a median time of 1 week to first seizure.

Epilepsy Currents, Vol. 13, No. 4 (July/August) 2013 pp. 162–163

Not only was seizure frequency dramatically reduced, but IED frequency on a 60-minute EEG was decreased by about 50% in the high-intensity treatment group (from a baseline of about 1.25 spikes/min), and scores on most dimensions of the psychologic Symptom Checklist (SCL)-90 were significantly improved at the end of the follow-up period, though there was no correlation between seizure-frequency reduction and the effect on spikes or psychologic symptoms. No significant changes on these measures were seen in the low-intensity treatment group.

These findings need to be reproduced in another comparable patient cohort in another set of investigators' hands. If seizure outcomes anywhere close to these are seen consistently, not only would this be the most positive result of a TMS therapeutic trial in epilepsy so far, but this would represent a degree of antiepileptic effect far beyond what is typically seen with essentially any other available intervention in use for refractory epilepsy today, aside from surgical resection.

What do such strongly positive results imply, in the setting of conflicting prior data? One very distinct possibility is that the proper selection of patients most likely to benefit from rTMS based on localization of their seizure onset is critical.

Prior evidence suggests that patients with neocortical epilepsy, and particularly those with visible cortical lesions, have the greatest chance of benefit. Stimulation from standard TMS coils in current use is unlikely to be able to reach medial temporal lobe structures, and indeed Sun and colleagues report that the small number of patients with medial temporal lobe epilepsy in their cohort showed "poor efficacy," although individual subject responses are not provided. The anatomic distribution of their subjects' seizure foci suggests that they may have been selected based on likelihood of TMS response, though this is not explicitly described either. Among the prior studies with conflicting results, the proportions of subjects with medial temporal versus neocortical epilepsy and nonlesional versus lesional etiology are also tellingly different, with the best results seen among those with focal cortical malformations, for whom TMS targeting is perhaps most straightforward, and confidence in being able to reach the desired target is high.

Other modifiable TMS variables include the frequency of stimulation (0.3 Hz, 0.5 Hz, and 1 Hz have been studied) as well as the intensity, exact paradigm, and number/duration of sessions, but there are not enough data from the literature to judge the optimal protocol at this point. Both the prior controlled study with positive seizure outcomes and the current report showed sustained benefits 8 weeks after the TMS treatment, but neither provided longer follow-up than that.

The article by Sun and colleagues has a number of limitations, including a lack of presented data on individual responses and some manifest errors and imprecisions in the manuscript text. Nevertheless, it is an important publication because its efficacy findings are so striking that they need to be reproduced for the epilepsy community to determine whether rTMS can really have such a salutary effect on seizures, even if only in a selected population. Anything that even approaches the reported level of benefit and carries as low a risk as TMS deserves further investigation, though the durability of any benefit in the long term remains unclear.

Broadly speaking, the question going forward may ultimately be not the simple one of whether TMS "works for epilepsy," but rather the more refined one of how TMS usage might be best tailored to the epilepsy patients who are most likely to benefit from it. In the sense that a goal of all epilepsy treatment is to identify the best personalized approach, TMS may not be that different after all.

by Bernard S. Chang, MD

References

1. Fisher RS. Therapeutic devices for epilepsy. *Ann Neurol* 2012;71:157–168.
2. Najib U, Bashir S, Edwards D, Rotenberg A, Pascual-Leone A. Transcranial brain stimulation: Clinical applications and future directions. *Neurosurg Clin N Am* 2011;22:233–251.
3. Fregni F, Otachi PT, Do Valle A, Boggio PS, Thut G, Rigonatti SP, Pascual-Leone A, Valente KD. A randomized clinical trial of repetitive transcranial magnetic stimulation in patients with refractory epilepsy. *Ann Neurol* 2006;60:447–455.
4. Cantello R, Rossi S, Varrasi C, Ulivelli M, Civardi C, Bartalini S, Vatti G, Cincotta M, Borgheresi A, Zaccara G, Quartarone A, Crupi D, Lagana A, Inghilleri M, Giallonardo AT, Berardelli A, Pacifici L, Ferreri F, Tombini M, Gilio F, Quarato P, Conte A, Manganotti P, Bongiovanni LG, Monaco F, Ferrante D, Rossini PM. Slow repetitive TMS for drug-resistant epilepsy: Clinical and EEG findings of a placebo-controlled trial. *Epilepsia* 2007;48:366–374.
5. Theodore WH, Hunter K, Chen R, Vega-Bermudez F, Boroojerdi B, Reeves-Tyer P, Werhahn K, Kelley KR, Cohen L. Transcranial magnetic stimulation for the treatment of seizures: A controlled study. *Neurology* 2002;59:560–562.

American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.

Enter your full name. If you are NOT the main contributing author, please check the box "no" and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.

This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships

Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.

American Epilepsy Society

Epilepsy Currents Journal

Disclosure of Potential Conflicts of Interest

Section #1 Identifying Information

1. Today's Date: 7/30/2013

2. First Name Bernard Last Name Chang Degree M.D., M.M.Sc.

3. Are you the Main Assigned Author? ☒ Yes ☐ No

   If no, enter your name as co-author:

4. Manuscript/Article Title:

5. Journal Issue you are submitting for:

Section #2 The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Grant	☒				
2. Consulting fee or honorarium	☒				
3. Support for travel to meetings for the study or other purposes	☒				
4. Fees for participating in review activities such as data monitoring boards, statistical analysis, end point committees, and the like	☒				
5. Payment for writing or reviewing the manuscript	☒				
6. Provision of writing assistance, medicines, equipment, or administrative support.	☒				
7. Other	☒				

* This means money that your institution received for your efforts on this study.

** Use this section to provide any needed explanation.

Section #3 Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add" box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information. If you have more than one relationship just add rows to this table.

Type of relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments**
1. Board membership	☒				
2. Consultancy	☒				
3. Employment	☒				
4. Expert testimony	☒				
5. Grants/grants pending	☒				
6. Payment for lectures including service on speakers bureaus	☒				
7. Payment for manuscript preparation.	☒				
8. Patents (planned, pending or issued)	☒				
9. Royalties	☒				
10. Payment for development of educational presentations	☒				
11. Stock/stock options	☒				
12. Travel/accommodations/meeting expenses unrelated to activities listed.**	☒				
13. Other (err on the side of full disclosure)	☒				

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☒ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.
Epilepsy Currents Editorial Board