Significant Reduction in Phantom Limb Pain After Low-Frequency Repetitive Transcranial Magnetic Stimulation to the Primary Sensory Cortex

COL Geoffrey G. Grammer, MC USA; Sonya Williams-Joseph, PMHNP-BC†; CPT Ashley Cesar, MC USA†; MAJ David K. Adkinson, MC USA‡; Christopher Spevak, MD, MPH, JD§*

ABSTRACT Objective: Phantom limb pain (PLP) is believed to be linked to the reorganization of the deafferented sensory cortex. We present a case of a patient with upper extremity PLP who was successfully treated with repetitive transcranial magnetic stimulation (rTMS). Methods: We treated an active duty service member who suffered an amputation of his right upper extremity after sustaining a blast injury in Afghanistan. He had 28 sessions of alternating sequences of rTMS to the left dorsolateral prefrontal cortex and primary sensory cortex of the left cerebral hemisphere. Pain intensity was assessed with the Visual Analogue Scale. Results: We delivered 1 Hz stimulation to the sensory cortex corresponding to the area of amputation five times a week. After 4 sessions, the patient's pain decreased from a Visual Analogue Scale of 5 to 2. Left 10 Hz stimulation was added and after 28 sessions, the pain decreased from 2 to 1. Conclusions: Our findings support that rTMS was an effective modality for this patient in treating his PLP. The significance of 10 Hz stimulation is unknown because of the lack of an effect size and is possibly associated with a floor effect.

INTRODUCTION

Wars in Iraq and Afghanistan have led to a significant increase in traumatic injuries of military personnel such as extremity amputation.[1] Phantom limb pain (PLP) can occur after amputation and affects up to 80% of those with this type of injury.[2] Treatment of PLP can be difficult with traditional pain control measures. Repetitive transcranial magnetic stimulation (rTMS) is currently Food and Drug Administration approved for the treatment of major depression.[3–6] rTMS offers either inhibitory or excitatory neuromodulation and may present a unique opportunity to treat central nervous system–mediated pain syndromes, such as PLP. Several clinical trials have supported the role of rTMS in the treatment of other pain disorders, such as neuropathic pain and fibromyalgia[7–10]; however, the utility of rTMS in PLP has not been conclusive.[11] rTMS has been found to be safe,[12] has been well tolerated by patients, causes minimal discomfort, and is easily administered without requirements for sedation.[13,14] rTMS involves placing a magnetic coil on a patient's scalp and pulsing a magnetic field down to the cortex which, through Faraday's Law, leads to electrical stimulation of- and subsequent depolarization of cortical neurons.[14–18]

PLP has been described as a pain syndrome that results following amputation of an extremity. Patients can describe their limb feeling as if it is malpositioned or in pain, and it can be quite debilitating. Although the exact cause of PLP is unknown, one theory is that deafferation of the sensory cortex, resulting from the amputation, causes cortical reorganization.[19,20] When an extremity is amputated, that area of the sensory cortex no longer receives afferent input. The consequence of such a loss may then be a redistribution of the surrounding sensory cortical activity. For example, if a patient were to lose a hand to amputation, sensory signal corresponding to the face might then distribute into that area[21] given the proximity of these regions on the homunculus mapping of the brain. This inappropriate signal may then result in abnormal sensations inappropriately attributed to the missing limb.

RESULTS

We present a 24-year-old active duty soldier who sustained a severe blast injury to his right upper extremity in early 2010 while deployed in Afghanistan. After surgical amputation of the affected limb, the soldier complained of constant PLP rated as 5/10 per the Visual Analog Scale (VAS). Five months after his injury, he was referred to the Procedural Psychiatry Transcranial Magnetic Stimulation (TMS) Clinic at Walter Reed Army Medical Center to see if nonpharmacologic pain control could be achieved after conventional pain management did not offer adequate relief. Before his presentation for TMS, he had been on a stable medication regimen for 3 months consisting of oxycodone IR 10 mg qid,

*Department of Research, National Intrepid Center of Excellence, Walter Reed National Military Medical Center, 4860 South Palmer Road, Bethesda, MD 20889.

†Department of Psychiatry, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, MD 20889.

‡Department of Psychiatry, Fort Carson, 6105 Wetzel Avenue, Building 1435, Fort Carson, CO 80913.

§Department of Anesthesia, Georgetown University's School of Medicine, 3900 Reservoir Road, Washington, DC 20057.

doi: 10.7205/MILMED-D-14-00236

pregabalin 200 mg tid, amitriptyline 75 mg qhs, celecoxib 100 mg bid, duloxetine 60 mg qd, and fentanyl 50 mcg patch q72 hours. Before this regimen, trials of methadone, hydromorphone, and clonazepam had not offered significant relief. Three weeks after starting rTMS, fentanyl was discontinued, and oxycodone ER 10 mg bid was initiated because of difficulties with fentanyl patch adhesion.

Motor threshold (MT) determination was obtained from the right cerebral hemisphere and thus left upper extremity, since the patient had a right extremity amputation. The left dorsolateral prefrontal cortex (DLPFC) was estimated to be 5.5 cm anterior to this location, and the sensory cortex was estimated to be 1.5 cm posteriorly. Since much of the patient's PLP centered on sensations that corresponded to his wrist, we moved the coil 10 degrees toward the vertex for the superior oblique angle. These reference points were then translated to the left cerebral hemisphere for treatment.

High-frequency pulse administration was at 120% of the MT, delivered at 10 Hz, with a stimulation time of 4 seconds, in 26 second intervals, for a total of 3000 pulses per treatment to the left DLPFC. Low-frequency pulses were at 100% of the MT, delivered at 1 Hz, with a stimulation time of 26 seconds, in 4 second intervals, for a total of 2000 pulses per treatment session to the sensory cortex. Treatment utilizing high-frequency pulses to the DLPFC has been found to be beneficial in alleviating pain.[22] Treatment utilizing low-frequency pulses has demonstrated an inhibitory effect.[23,24]

A total of 28 treatments were administered over 6 weeks. The first five treatments were low-frequency treatments targeting the primary sensory cortex (PSC), after which treatment proceeded in an alternating pattern, between low and high frequency. The patient received 17 low-frequency treatments to the PSC and 11 high-frequency treatments to the DLPFC. The goal was to inhibit sensory cortical activity while augmenting DLPFC function.

The patient reported a pain rating of 5/10 on the VAS before beginning the treatments. By the fourth treatment (the first three treatments were all low frequency), the patient reported significant improvement in his PLP, and rated his pain as 2/10. At the conclusion of 28 treatments, the patient rated his pain as 1/10, which represents an 80% decrease in the pain rating score per VAS. Our findings support that rTMS was an effective modality for this patient in treating his PLP.

DISCUSSION

We targeted inhibitory, slow rTMS over the sensory cortex in the hope that this would attenuate inappropriate cortical activity brought about by deafferation and inappropriate processing of sensory input by this brain region from areas other than the amputated extremity. By inhibiting this area, inappropriate signal processing may result in decreased symptoms of PLP and lead to ultimate remapping of cortical regions, so that signal processing from other body regions are not being attributed to the missing limb.

The effect of a single TMS pulse into superficial cortex can have secondary effects on millions of neurons remote from the TMS site, which has also been supported by animal research.[25] For this particular patient, treatment of the sensory cortex resulted in a definite and rapid improvement in symptoms of PLP. The addition of treatment to the DLPFC was well tolerated, but offered little additional benefit perhaps because of a floor effect.

A treatment energy of 100% of the MT at the sensory cortex was chosen, instead of 120%, to minimize the chance of generalized seizure induction since this region may be more epileptogenic.[25] Although this patient's upper extremity amputation allowed for targeting the affected cortical area, lower extremity amputations may not be as amenable to study or treatment because of corresponding cortical areas that are located further from the scalp, along the medial aspect of the cerebral hemispheres. Presumption of synonymous effects of stimulating the medial cerebral hemisphere is premature until there is a better understanding of the impact of TMS in this area. A consequential larger area of spread of the magnetic field would be expected in the medial cerebrum compared to the lateral cerebral area corresponding to the upper extremities, because of physical properties of magnetic fields and the anatomically greater distance from the treatment coil.

With this case, placebo effects as well as therapeutic attention cannot be excluded. However, they are both less likely to have contributed to the clinical response given the temporal improvement of symptoms with treatment despite ineffective prior pain treatments. The synergistic and confounding contributions of his pharmacotherapy regimen on the effects of rTMS are unknown, a limitation amplified by the variety of classes of pharmacologic agents he was receiving.

Transcranial magnetic stimulation has a potentially favorable risk/benefit ratio that makes its use for this condition appealing. rTMS is a focal treatment that affects local brain activity and avoids systemic side effects that may be inherent to pharmacologic treatments. rTMS is generally well tolerated and considered safe[26] and devoid of a detrimental impact on alertness or cognition. rTMS has the advantage of not contributing to drug interactions in this population that often finds itself affected by polypharmacy because of the frequently severe and resistant nature of PLP. There is a risk of secondary generalization of stimulation activity, and when using a 10 Hz pulse sequence for depression, a rate of one seizure per 30,000 treatments has been observed[27] with the iron core figure-8 coil design device used in this case. Using a pulse sequence at 1 Hz should have a lower risk of seizure than that seen when treating depression, because of a lower energy delivery associated with the slower frequency. rTMS may not be an option for patients with retained metal or implanted devices in proximity to the treatment coil or in those patients with known recurrent seizures. Use of rTMS is limited by significant expense of delivery and labor intensity of daily treatments lasting approximately 30 to 60 minutes per session.

A recent case series using 20 Hz rTMS stimulation at an intensity of 80% of the MT over the motor cortex, described clinical improvement in patients with PLP.[28] Our case suggests that treatment with 1 Hz rTMS over the sensory cortex may be effective for upper extremity PLP. Treatment with 1 Hz stimulation may have favorable tolerability and safety when compared to high-frequency stimulation. This is the first case of PLP successfully treated with rTMS over the PSC that we could find in the literature.

ACKNOWLEDGMENTS

We are grateful to the U.S. service member who provided permission to share the details of his combat-related trauma and treatment experience with rTMS. We are grateful to Ms. Shalini Mehta, MPH and Jeffrey T. Cole, PhD of Booz Allen Hamilton for their writing and editorial assistance.

REFERENCES

1. Weeks SR, Anderson-Barnes VC, Tsao JW: Phantom limb pain: theories and therapies. Neurologist 2010; 16(5): 277–86.
2. Flor H: Phantom-limb pain: characteristics, causes, and treatment. Lancet Neurol 2002; 1(3): 182–9.
3. Holtzheimer PE 3rd, Russo J, Avery DH: A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. Psychopharmacol Bull 2001; 35(4): 149–69.
4. Anderson IM, Delvai NA, Ashim B, et al: Adjunctive fast repetitive transcranial magnetic stimulation in depression. Br J Psychiatry 2007; 190: 533–4.
5. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J: A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. Am J Psychiatry 2006; 163(1): 88–94.
6. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, de Castella A, Kulkarni J: Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. Arch Gen Psychiatry 2003; 60(10): 1002–8.
7. Johnson S, Summers J, Pridmore S: Changes to somatosensory detection and pain thresholds following high frequency repetitive TMS of the motor cortex in individuals suffering from chronic pain. Pain 2006; 123(1–2): 187–92.
8. André-Obadia N, Mertens P, Gueguen A, Peyron R, Garcia-Larrea L: Pain relief by rTMS: differential effect of current flow but no specific action on pain subtypes. Neurology 2008; 71(11): 833–40.
9. Hirayama A, Saitoh Y, Kishima H, et al: Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain 2006; 122(1–2): 22–7.
10. Khedr EM, Kotb H, Kamel NF, Ahmed MA, Sadek R, Rothwell JC: Longlasting antalgic effects of daily sessions of repetitive transcranial magnetic stimulation in central and peripheral neuropathic pain. J Neurol Neurosurg Psychiatry 2005; 76(6): 833–8.
11. Töpper R, Foltys H, Meister IG, Sparing R, Boroojerdi B: Repetitive transcranial magnetic stimulation of the parietal cortex transiently ameliorates phantom limb pain-like syndrome. Clin Neurophysiol 2003; 114(8): 1521–30.
12. Loo CK, McFarquhar TF, Mitchell PB: A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. Int J Neuropsychopharmacol 2008; 11(1): 131–47.
13. Barker AT, Jalinous R, Freeston IL: Non-invasive magnetic stimulation of human motor cortex. Lancet 1985; 1(8437): 1106–7.
14. Rossini PM, Rossi S: Transcranial magnetic stimulation: diagnostic, therapeutic, and research potential. Neurology 2007; 68(7): 484–8.
15. Currà A, Modugno N, Inghilleri M, Manfredi M, Hallett M, Berardelli A: Transcranial magnetic stimulation techniques in clinical investigation. Neurology 2002; 59(12): 1851–9.
16. Griškova I, Höppner J, Rukšėnas O, Dapšys K: Transcranial magnetic stimulation: the method and application. Medicina (Kaunas) 2006; 42(10): 798–804.
17. Maeda F, Pascual-Leone A: Transcranial magnetic stimulation: studying motor neurophysiology of psychiatric disorders. Psychopharmacology 2003; 168(4): 359–76.
18. Post A, Keck ME: Transcranial magnetic stimulation as a therapeutic tool in psychiatry: what do we know about the neurobiological mechanisms? J Psychiatr Res 2001; 35(4): 193–215.
19. Flor H, Nikolajsen L, Staehelin Jensen T: Phantom limb pain: a case of maladaptive CNS plasticity? Neuroscience 2006; 7(11): 873–81.
20. Karl A, Birbaumer N, Lutzenberger W, Cohen LG, Flor H: Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci 2001; 21(10): 3609–18.
21. Ramachandran VS, Altschuler EL: The use of visual feedback, in particular mirror visual feedback, in restoring brain function. Brain 2009; 132(Pt 7): 1693–710.
22. Borckardt JJ, Reeves ST, Frohman H, et al: Fast left prefrontal rTMS acutely suppresses analgesic effects of perceived controllability on the emotional component of pain experience. Pain 2011; 152(1): 182–7.
23. Gerschlager W, Siebner HR, Rothwell JC: Decreased corticospinal excitability after subthreshold 1 Hz rTMS over lateral premotor cortex. Neurology 2001; 57(3): 449–55.
24. Hoffman RE, Cavus I: Slow transcranial magnetic stimulation, long-term depotentiation, and brain hyperexcitability disorders. Am J Psychiatry 2002; 159(7): 1093–102.
25. George MS, Belmaker RH: Transcranial Magnetic Stimulation in Clinical Psychiatry. Arlington, TX, American Psychiatric Publishing, 2006.
26. O'Reardon JP, Solvason HB, Janicak PG, et al: Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007; 62(11): 1208–16.
27. Neuronetics: NeuroStar TMS Therapy System User Manual. Available at http://neurostar.com/wp-content/uploads/NeuroStar-Prescribing-Information.pdf; accessed May 30, 2014.
28. Ahmed MA, Mohamed SA, Sayed D: Long-term antalgic effects of repetitive transcranial magnetic stimulation of motor cortex and serum beta-endorphin in patients with phantom pain. Neurol Res 2011; 33(9): 953–8.