Devore Best *Neuropsychiatric Electrophysiology* (2015) 1:2
DOI 10.1186/s40810-015-0003-y

NEUROPSYCHIATRIC ELECTROPHYSIOLOGY

CASE REPORT Open Access

Combined ketamine and transcranial magnetic stimulation for treatment resistant depression in the context of chronic OCD: a case report

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Abstract

Treatment resistant depression (TRD) is a major public health issue, with comorbid OCD contributing to the general medical costs and severity associated with TRD. Recent research has investigated the efficacy of transcranial magnetic stimulation (TMS and its variant rTMS) in ameliorating the symptoms of depression and OCD. Most studies have used TMS to facilitate electromagnetic stimulation of the dorsolateral prefrontal cortex, a region implicated in depression, or the supplemental motor area, a region implicated in OCD. However, it is difficult to achieve full remission with TMS alone. A parallel line of research has examined the effects of ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, on both depression and OCD. A primary benefit of ketamine is that it provides short-term but rapid relief from certain grave TRD symptoms within approximately two hours. As of yet, little is known about the possible synergistic effects of combined TMS/ketamine for comorbid TRD and OCD. Thus, I report on the case of a 32-year-old male who presented with chronic OCD with somatic fixation, depression, and generalized anxiety disorder, who was treated with a novel combined TMS/ketamine treatment for 12 weeks. Measures of depression and OCD symptoms were administered pre and post treatment. The patient showed significant reductions in depression, but not OCD symptoms, which is consistent with previous research.

Keywords: Ketamine, Transcranial magnetic stimulation, Depression, OCD

Background

Treatment resistant depression (TRD) is a major public health issue, with at least 20% of patients failing to respond to more than one traditional antidepressant (Crown et al. 2002; Sackeim 2001). In addition, TRD is associated with general medical costs estimated to be 19 times greater than those stemming from treatment responsive depression (Sackeim 2001). A factor that may contribute to treatment resistance is the high degree of comorbidity with a variety of mental disorders. For example, approximately 33% of depressed individuals also meet diagnostic criteria for OCD (Masellis et al. 2003). To address these challenges, recent research has investigated the efficacy of transcranial magnetic stimulation (TMS and its variant rTMS) in ameliorating the symptoms of depression and OCD (Gross et al. 2007; Mantovani et al. 2010). Most studies have used TMS to facilitate electromagnetic stimulation of the dorsolateral prefrontal cortex, a region implicated in depression (Mayberg et al. 2005; Chang et al.

2011; Smith et al. 2013), or the supplemental motor area (SMA), a region implicated in OCD. However, it is difficult to achieve full remission with TMS alone. A parallel line of research has examined the effects of ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, on both depression (Berman et al. 2000; Diazgranados et al. 2010; Murrough et al. 2012; Zarate et al. 2006; Zarate et al. 2012; Ibrahim et al. 2012) and OCD (Bloch et al. 2012). A primary benefit of ketamine is that it provides short-term but rapid relief from certain grave TRD symptoms within approximately two hours. As of yet, little is known about the possible synergistic effects of combined TMS/ketamine for comorbid TRD and OCD.

One study suggested that a factor implicated in TRD is dysregulation of a thalamocortical circuit encompassing the anterior cingulate cortex (ACC) and other areas (LLínas et al. 1999). Research has also shown abnormalities in ACC neuronal functioning in OCD (Ursu et al. 2003). In addition, research has shown that the ACC can be affected by TMS directed to the medial frontal cortex which overlays the ACC (Hayward et al. 2007). Accordingly, I hypothesized that transcranial magnetic stimulation of the medial frontal cortex would affect the ACC and thereby facilitate a less abnormal level of functioning in the relevant thalamocortical circuit, and thus improve the response to ketamine. I report on a chronically depressed patient with comorbid OCD first diagnosed in childhood who did not respond to numerous antidepressant medications, and who was then treated with a novel combined ketamine/TMS technique. The patient showed substantial improvement in depression symptomatology, though not in OCD symptomatology, after 4 months of weekly treatments. An IRB exemption was obtained from an independent accredited agency.

Case presentation

Patient X is a 32-year-old male who presented with chronic obsessive-compulsive disorder with somatic fixation, depression, and generalized anxiety disorder. Patient X was treated with pharmacological interventions and psychotherapy for 50 months before beginning ketamine/TMS treatment. During this initial treatment phase, Patient X's symptoms did not respond to treatment with the mood stabilizers (olanzapine and valproic acid), antidepressants (desvenlafaxine, sertraline, and fluvoxamine), anti-anxiety medication (chlorazepate), psychostimulants (lis-dexamphetamine, and methylphenidate), gabapentin, or conventional psychotherapy. Before beginning ketamine/TMS treatment, Patient X had been coincidentally referred to a licensed psychologist for a comprehensive pretreatment assessment of symptomatology. The assessment included the Beck Depression Inventory-2 (BDI-II), the Beck Anxiety Inventory (BAI), the Beck Hopelessness Scale (BHS), and the Personality Assessment Inventory (PAI), which includes subscales measuring a variety of psychopathology domains. PAI subscale scores greater than 70 indicate clinically significant difficulties. At the pretreatment assessment, Patient X exhibited severe levels of depression (BDI-II = 48) in terms of cognitions (PAI DEP-C = 81), affect (PAI DEP-A = 77), and appraisals of hopelessness (BHS = 18). In addition, Patient-X reported severe anxiety (BAI = 52). Related to these symptoms, Patient X reported a high degree of suicidal ideation (PAI SUI = 89). Patient X also demonstrated clinically significant levels of obsessive-compulsive symptoms (PAI ARD-O = 78). The OCD symptoms included engaging in behavioral rituals to decrease anxiety, fear of losing control of impulses and handling contaminated objects, a heightened need for order, high

anxiety in messy or disordered environments, being excessively detailed and pedantic, a strong need to control his feelings and thoughts, and overarching perfectionism.

Prior to beginning combined treatment, Patient-X was given 2 days of rTMS pretreatment (4 treatments per day of 30 minutes each with 45 minutes of rest between treatments). Combined ketamine/TMS treatment began the following day and continued twice per week for 10 weeks. Combined treatment consisted of 50 minutes of 1Hz continuous TMS with an intravenous ketamine infusion administered concurrent to and bracketed within the middle 40 minutes of TMS, resulting in 5 minutes of TMS pre and post infusion. The dosage of infused ketamine increased gradually from 40 mg at the first treatment to a peak of 425 mg at the 12^{th} treatment, and tapered down to 225 mg at the last treatment. The dose increases occurred in order to assist the patient in reaching a mildly dissociated and cataleptic state. I hypothesized that greater dosages were needed until central nervous system function reached a point of maximal health. I defined this point as when both the patient and a close family member rated the patient's functioning as normal. Once normal functioning was achieved, I began to taper the dosage. During combined treatment, the TMS head coil (manufactured by Neotonus) was positioned at the midline (Fz on 10/20 positioning system) of the anterior scalp to achieve maximal stimulation of the medial prefrontal area that overlays the anterior cingulate, a region implicated in depression (Gross et al. 2007). TMS treatments were administered at 115% of motor threshold (threshold of comfort for this patient) at 1Hz continuous pulsation given that these settings were within safety guidelines and consistent with my usual method. Using this method, I hypothesized that the dissociative effects of ketamine along with TMS activation of the anterior cingulate would help reestablish normal oscillatory rhythms in this region, leading to a decrease in depression and OCD symptoms.

After 8 twice-weekly treatments, Patient X began to report improvements in mood that increased throughout treatment. At post-treatment, Patient X was again evaluated, by the same licensed psychologist for comprehensive assessment. At this assessment, Patient X reported greatly decreased levels of depression (BDI-II = 13) in terms of cognitions (PAI DEP-C = 61), affect (PAI DEP-A = 66), and appraisals of hopelessness (BHS = 4). In addition, Patient X reported reduced anxiety (BAI = 24) and no ongoing evidence of suicidal ideation (PAI SUI = 51). However, Patient X's obsessive-compulsive symptoms remained elevated (PAI ARD-O = 84).

Conclusions

This case report adds to the literature on improving the efficacy of brain electromagnetic stimulation by administering pharmacological agents that modulate glutamatergic transmission. Whereas previous research suggests that TMS is somewhat effective in treating depression and OCD, and that sub-anesthetic doses of ketamine are temporarily helpful with depression and OCD; the present case report suggests that a combined ketamine/TMS treatment may be a more efficacious treatment for refractory depression than either infused ketamine or TMS alone. However, this combined treatment did not affect the OCD symptoms, which is partially consistent with a previous study showing that ketamine had no lasting effect on OCD symptoms. Despite the promising findings in this case report, one limitation is that I was not able to establish that placement of the TMS coil stimulated the ACC as was hypothesized. Future research should

evaluate this hypothesis using confirmatory imaging. In addition, subsequent studies should examine combined ketamine/TMS treatment in a randomized controlled trial.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interest
The author declares that he has no competing interest.

Received: 22 November 2014 Accepted: 14 January 2015
Published online: 06 May 2015

References

Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47:351–354

Bloch MH, Wasylink S, Landeros-Weisenberger A, Panza KE, Billingslea E, Leckman JF, Pittenger C (2012) Effects of ketamine in treatment-refractory obsessive-compulsive disorder. Biol Psychiatry 72(11):964–970

Chang CC, Yu SC, McQuoid DR, Messer DF, Taylor WD, Singh K, Payne ME (2011) Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. Psychiatry Res Neuroimaging 193:1–6

Crown WH, Finkelstein S, Berndt ER, Ling D, Poret AW, Rush AJ, Russell JM (2002) The impact of treatment-resistant depression on health care utilization and costs. J Clin Psych 63:963–971

Diazgranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, Machado-Viera R, Zarate CA (2010) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 71:1605–1611

Gross M, Nakamura L, Pascual-Leone A, Fregni F (2007) Has repetitive transcranial magnetic stimulation (TMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier TMS studies. Acta Psychiatrica Scandinavica 116:165–173

Hayward G, Mehta MA, Harmer C, Spinks TJ, Grasby PM, Goodwin GM (2007) Exploring the physiological effects of double-cone coil TMS over the medial frontal cortex on the anterior cingulate cortex: an H215O PET study. Eur J Neurosci 25(7):2224–2233

Ibrahim L, Diazgranados N, Franco-Chaves J, Brutsche N, Henter ID, Kronstein P, Moaddel R, Wainer I, Luckenbaugh DA, Manji HK, Zarate CA (2012) Course of improvement in depressive symptoms to a single intravenous infusion of ketamine vs add-on riluzole: results from a 4-week, double-blind, placebo-controlled study. Neuropsychopharmacology 37:1526–1533

LLínas RR, Ribary U, Jeanmond D, Kronberg E, Mitra PP (1999) Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci 96(26):15222–15227

Mantovani A, Westin G, Hirsch J, Lisanby SH (2010) Functional magnetic resonance imaging guided transcranial magnetic stimulation in obsessive-compulsive disorder. Biol Psychiatry 67(7):e39–e40

Masellis M, Rector NA, Richter MA (2003) Quality of life in OCD: differential impact of obsessions, compulsions, and depression comorbidity. Canadian J Psychiatry 48(2):72–77

Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, Schawlb JM, Kennedy SH (2005) Deep brain stimulation for treatment-resistant depression. Neuron 45:651–660

Murrough JW, Perez AM, Pillemer S, Stern J, Parides MK, Aan HR, Collilns KA, Mathew SJ, Charney DS, Iosifescu DV (2012) Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment-resistant major depression. Biol Psychiatry 74(4):250–256

Sackeim HA (2001) The definition and meaning of treatment-resistant depression. J Clin Psych 62:10–17

Smith R, Chen K, Baxter L, Fort C, Lane RD (2013) Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. J Affect Disord 146:414–419

Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS (2003) Overactive action monitoring in obsessive-compulsive disorder evidence from functional magnetic resonance imaging. Psychological Science 14(4):347–353

Zarate CA Jr, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK (2006) A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 63(8):856–864

Zarate CA Jr, Brutsche NE, Ibrahim L, Franco-Chaves J, Diazgranados N, Cravchik A, Selter J, Marquardt CA, Liberty V, Luckenbaugh DA (2012) Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol Psychiatry 71:939–946