

Combined transcranial magnetic stimulation and ketamine for treatment of refractory mood disorder, anxiety, and pain: A case report

Steve Best^{1*} and Dan G. Pavel²

¹The Neuroscience Center 440 Lake Cook Road, Bldg 2, Deerfield, IL 60015, USA

²PathFinder Brain SPECT Imaging, 440 Lake Cook Road, Suite 3, Deerfield, IL 60015, USA

Abstract

Treatment resistant depression (TRD) is a major public health problem, with approximately one third of patients failing to respond to multiple antidepressant medications. Depression occurring alongside a comorbid anxiety disorder and/or chronic pain may be especially likely to be resistant to treatment. A factor underlying TRD is dysregulation of a thalamo-cortical circuit including the anterior cingulate cortex. Recent research has shown the efficacy of transcranial magnetic stimulation, and of ketamine I.V., as therapeutic approaches in treatment resistant depression and anxiety. We hypothesized that stimulating the ACC with TMS would facilitate improved entrainment of this circuit, thereby improving response to ketamine. We describe the combination therapy of Transcranial Magnetic Stimulation (TMS) and ketamine for an adult female patient with severe, long-term depression, comorbid with anxiety and chronic pain. Pre- and post-treatment assessments indicated that this approach resulted in substantial symptom reductions in all three comorbid disorders. This was corroborated by the significant functional improvement seen at follow-up on brain imaging with Single Photon Emission Computed Tomography (SPECT).

Keywords: Ketamine, Transcranial magnetic stimulation, Depression, Panic disorder, Agoraphobia, Pain, Brain SPECT functional imaging.

Accepted January 25, 2017

Abbreviations

ACC: anterior cingulate cortex

BPI-SF: Brief Pain Inventory-Short Form

Ceretec: 99mTechnetium-HMPAO

HMPAO: hexamethylpropyleneamineoxime

NMDA: N-methyl-D-aspartate

OASIS: Overall Anxiety Severity and Imap

PHQ-9: Patient Health Questionnaire

SPECT: Single Photon Emission Computed Tomography

TRD: Treatment Resistant Depression

TMS: Transcranial Magnetic Stimulation

Introduction

Treatment resistant depression (TRD) is a major public health problem, with approximately one third of patients failing to respond to multiple antidepressant medications [1]. In addition, TRD is associated with general medical

costs estimated to be approximately 20 times greater than those stemming from depression that is responsive to treatment [2]. Depression occurring alongside a comorbid anxiety disorder and/or pain may contribute to treatment resistance [1-3]. To address these challenges, recent research has investigated the efficacy of transcranial magnetic stimulation (TMS) and its variant (r TMS) as a treatment for TRD and anxiety [4,5]. Most studies have used TMS to apply electromagnetic stimulation to the dorsolateral prefrontal cortex, a region implicated in both depression and anxiety [6-8]. Unfortunately, few studies have demonstrated full remission with TMS alone. A parallel body of research suggests a positive effect of ketamine, an N-methyl-D-aspartate (NMDA) antagonist, on both depression [9] and anxiety [10]. A primary benefit of ketamine is that it provides rapid albeit short-term relief from TRD symptoms relating to suicidality within approximately two hours. To date, little is known about the possible synergistic effects of combined TMS/ketamine for TRD alone, or comorbid with anxiety and/or pain.

Research suggests that a factor involved in TRD is

dysregulation of a thalamo-cortical circuit including the anterior cingulate cortex (ACC), among other areas [11]. Research has also shown abnormalities in ACC neuronal functioning in anxiety [12]. Accordingly, we hypothesized that stimulating the ACC with TMS would facilitate improved reactivity of this circuit, thereby improving response to ketamine. We report on a patient with refractory major depressive disorder comorbid with panic disorder with agoraphobia and chronic pain who had not responded to numerous antidepressant medications, but showed very pleasing results after treatment with the novel TMS/ketamine combination therapy [3,13-14].

Case Presentation

The patient was a 55-year-old Caucasian female who presented with major depressive disorder, panic disorder with agoraphobia, anosmia, frequent headaches, and long-term back pain. The neurological exam was within normal limits and did not suggest focal neurological dysfunction of the Central Nervous System. In addition, she had previously been diagnosed with schizoaffective disorder, although no psychotic symptoms were observed at our clinic. Intermittently, she had been treated with varied pharmacological interventions and psychotherapy for 24 years before coming to our Clinic. During this time, her symptoms did not respond to Wellbutrin, Lexapro, Abilify, Viibryd, Paxil, Nardil, or conventional psychotherapy. Before beginning TMS/ketamine treatment the patient was assessed for depression, anxiety, pain, and life satisfaction. The assessment included the Patient Health Questionnaire-9 (PHQ-9), the Overall Anxiety Severity and Impairment Scale (OASIS), the Brief Pain Inventor-Short Form (BPI-SF), and the Satisfaction With Life Scale (SWLS). At the pre-treatment assessment, she exhibited severe levels of depression (PHQ-9 = 25) and anxiety (OASIS = 18), moderate back pain (BPI-SF = 19), and extremely low levels of life satisfaction (SWLS = 5). She also underwent functional brain imaging with SPECT [15-17] using 99mTc Ceretec (HMPAO). Resulting images showed extensive bilateral hypoperfusion in the dorsolateral prefrontal as well as in orbitofrontal areas (Figure 1), as is frequently seen in depression, and occasionally in chronic pain.

The treatment initiated was based on the patented therapy developed by one of us [3]. Prior to the combination treatment, the patient was given two days of TMS pretreatment (4 treatments per day of 30 minutes each with 45 minutes of rest between treatments). Combined TMS/ketamine infusion treatment [3,13,14] began the following day and continued once per week for 30 weeks. Three years of observational evidence from our clinic suggested that this duration would produce clinically significant results. Combined treatment consisted of 40 minutes of 1 Hz continuous TMS with a concurrent intravenous ketamine infusion bracketed within the middle 30 minutes of TMS, resulting in five minutes of TMS alone pre- and post-infusion. The dosage of infused ketamine increased

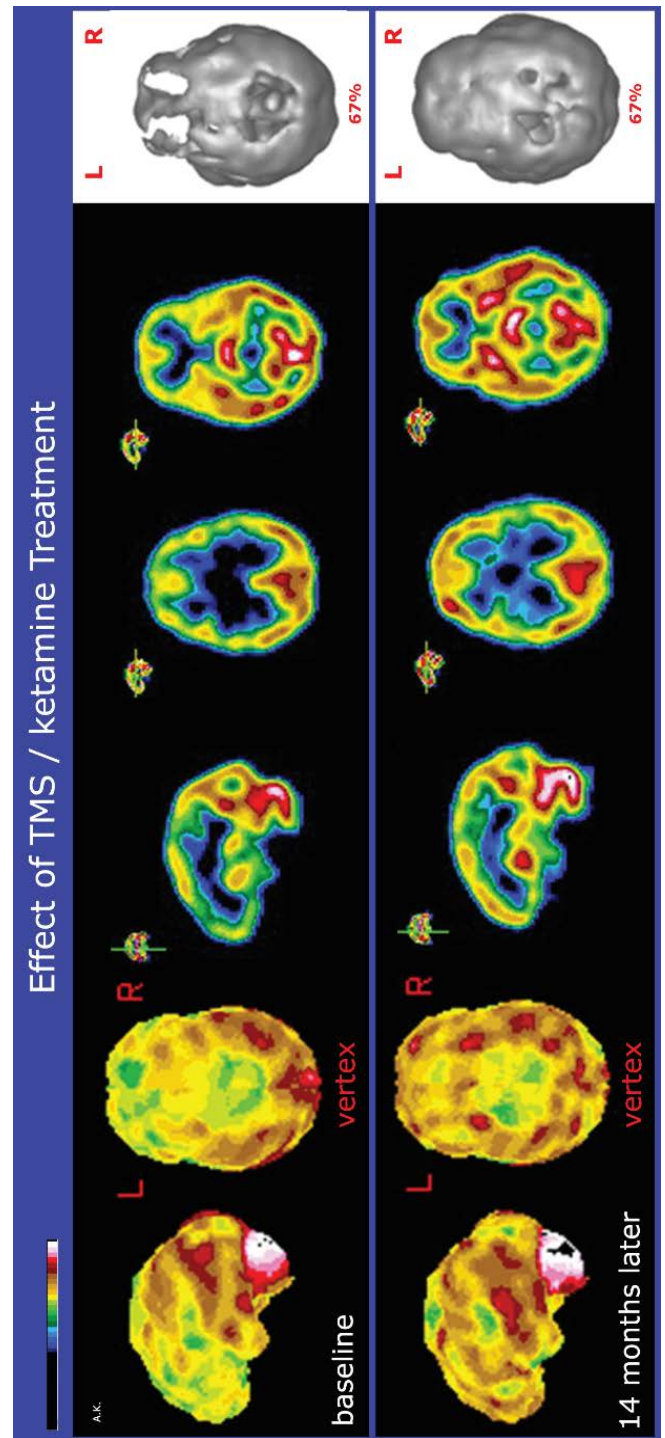


Figure 1. Brain SPECT functional imaging results, pre and post treatment

The first two columns show 2/8 images from the stereotactic surface projections obtained via the Neurostat software (16) with our own color code. The next three columns are representative of the orthogonal sections display. The last column shows one of the thresholded volumetric displays (threshold=67%). In the upper row is the baseline display (before treatment). The lower row shows the follow-up display, 14 months later. In the meantime the patient underwent a series of 30 TMS/ketamine combination treatments. At post-treatment there are major perfusion improvements in the frontal convexities, fronto-parietal and anterior cingulate areas as well as bilateral increase in the basal ganglia.

gradually from 50 mg at the first treatment to a peak of 250 mg at the tenth treatment, and tapered down to 225 mg at the last treatment. To attenuate anxiety during treatment, anxiolytics were given on an as-needed basis. During pretreatment and combined treatment, the TMS head coil (manufactured by Neotonus) was positioned at the midline of the anterior scalp to achieve maximal stimulation of the medial prefrontal area that overlays the anterior cingulate cortex, a region implicated in depression and anxiety [6-7,12]. TMS treatments were administered at 115% of motor threshold at 1 Hz continuous pulsation settings established to be within safety guidelines and consistent with our protocol in use for over three years. Using this method, we hypothesized that the effects of the combination therapy of ketamine along with TMS would facilitate more normal oscillatory rhythms in this region, leading to a decrease in depression and anxiety symptoms.

After four months of weekly treatments, the patient reported markedly improved symptoms and was again assessed for depression, anxiety, pain, and life satisfaction. At this assessment, she reported greatly decreased levels of depression (PHQ-9 = 2), anxiety (OASIS = 5), and back pain (BPF-SF = 0), and greatly increased levels of life satisfaction (SWLS = 22). At long-term follow-up the patient had been practically free of suffering for two years.

A repeat post-treatment brain SPECT showed substantial improvement (increased perfusion) in both frontal lobes, and slightly increased perfusion in the anterior cingulate (Figure 1). There was also significantly increased perfusion in the thalamus and bilaterally in the striatum.

Discussion

This case report presents the therapeutic strategy aimed at addressing complex cluster of symptoms occurring in comorbidity of psychiatric and somatic disorders (depression, anxiety and pain). While existing research has indicated that TMS is somewhat effective in treating depression and anxiety [4-5,8], and that ketamine produces short-term relief from depression and anxiety [9-10], it is the combination therapy using concurrent TMS and ketamine infusion that achieved the results in this case. We believe that modulation of the known dysfunctional cortico-thalamo-cortical circuit via the entraining effect of electromagnetic stimulation rendered this patient more responsive to the ketamine infusion. This resulted in more efficacious relief from the refractory depression and comorbid anxiety, as well as improvement of the somatic component (chronic pain). The result appears to be enduring, as the patient has been free of suffering for two years.

This latter effect is substantiated by our present clinical experience with similar cases as well as by a recent review that points to the relation between mental disorders and chronic physical conditions, as well as the need to integrate their treatment [18].

The favorable effect of the combination therapy is further emphasized by the substantial improvement of cortical perfusion on brain SPECT functional imaging. Future work is in progress to further evaluate the efficacy of this treatment on a larger patient population.

Conclusion

This case presentation points to the clinical efficacy of a novel combination therapy of concurrent TMS along with ketamine infusion in a case of treatment refractory mood disorder with comorbidities including chronic pain. The favorable results were obtained despite years of unsuccessful previous treatments. The clinical improvements were also substantiated by the increases in cortical and subcortical perfusion, seen on brain SPECT.

Ethics Approval and Consent to Participate

This is a retrospective case report based on treatment with FDA approved procedures and medications. Nonetheless the patient has signed a consent for publication which is available to the Editor if needed.

Funding

No external funding sources were involved in any aspect of this case study: its conception or design, the acquisition of data, the analysis and interpretation of data, or the drafting or revising of the manuscript.

Acknowledgements

There are no acknowledgements to be made.

References

1. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psych.* 2001; 62: 10-17.
2. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psych.* 2002; 63: 963-971.
3. Best SRD. Rapid relief of treatment resistant depression by facilitated ketamine infusion: A preliminary report. *Activitas Nervosa Superior.* 2014; 56: 28-36.
4. Gross M, Nakamura L, Pascual-Leone A, et al. 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.* 2007; 116: 165-73.
5. Zwanger P, Minov C, Ella R, et al. Transcranial magnetic stimulation for panic. *Am J Psych.* 2014; 159: 315-326.
6. Chang CC, Yu SC, McQuoid DR, et al. Reduction of dorsolateral prefrontal cortex gray matter in late-life depression. *Psychiatry Res Neuroimaging.* 2011; 193: 1-6.
7. Smith R, Chen K, Baxter L, et al. Antidepressant effects of sertraline associated with volume increases in dorsolateral prefrontal cortex. *J Affect Disord.* 2013; 146: 414-419.
8. Cohen H, Kaplan Z, Kotler M, et al. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *Am J Psych.* 2004; 161: 515-24.

9. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000; 47: 351-354.
10. Ionescu DF, Luckenbaugh DA, Niciu MJ, et al. A single infusion of ketamine improves depression scores in patients with anxious bipolar depression. *Bipolar Disorders*. 2014; 17: 438-443.
11. Linas RRL, Ribary U, Jeanmond D, et al. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci*. 1999; 96: 15222-15227.
12. Etkin A, Prater KE, Hoeft F, et al. Failure of anterior cingulate activation and connectivity with the amygdala during implicit regulation of emotional processing in generalized anxiety disorder. *Am J Psych*. 2010; 167: 545-554.
13. Best SRD. Combined ketamine/transcranial magnetic stimulation treatment of severe depression in bipolar I disorder. *Journal of ECT*. 2014; 30: e50-e51.
14. Best SRD. Combined ketamine and transcranial magnetic stimulation for treatment resistant depression in the context of chronic OCD: A case report. *Neuropsychiatric Electrophysiology*. 2015; 1: 1-4.
15. Catafau AM. Brain SPECT in clinical practice. Part I: perfusion. *J Nucl Med*. 2001; 42: 259-271.
16. Minoshima S, Koeppe RA, Frey KA, et al. Anatomical standardization: linear scaling and nonlinear warping of functional brain images. *J Nucl Med*. 1994; 35: 1528-1537.
17. Juni JE, Waxman AD, Devous MD, et al. Procedure guidelines for brain perfusion SPECT using 99mTc radiopharmaceuticals 3.0. *J Nucl Med Tech*. 2009; 37: 191-195.
18. Scott KM, Lim C, Al-Hamzawi A, et al. Association of mental disorders with subsequent chronic physical conditions: World mental health surveys from 17 countries. *JAMA Psych* 2015.