Time to remission analysis for major depressive disorder after repetitive transcranial magnetic stimulation (rTMS)

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Abstract

We previously examined the efficacy of rTMS for major depressive disorder in an applied clinical practice. Clinical response was related to severity of depression as well as the rTMS instrument utilized suggesting a relationship to instrument or magnetic field parameters and individual factors. The effectiveness of repetitive transcranial magnetic stimulation (rTMS) in the treatment of major depressive disorder was further evaluated using Log-Rank statistics for time to remission outcomes. A follow-up retrospective medical records study was carried out on patients with major depressive disorder undergoing rTMS therapy at AwakeningsKC Clinical Neuroscience Institute (CNI), a suburban tertiary psychiatric clinic. Cox Proportional Hazard with Log-Rank statistics were applied and the time course to clinical remission was evaluated over a 6-week period with respect to age, gender, and depression severity. Clinical response was observed referencing two different rTMS instruments (MagVenture; NeuroStar). Time to remission studies of 247 case reports (N=98 males; N=149 females) showed consistently greater clinically defined remission rates after 6 weeks of rTMS treatment for patients using the MagVenture *vs* NeuroStar instrument. Patients previously admitted for inpatient psychiatric hospitalization exhibited higher response rates when treated with the MagVenture rTMS unit. Stepwise Cox Proportional Hazards Regression final model of time to remission included rTMS unit, inpatient psychiatric hospitalization and obese body habitus. Response to rTMS in applied clinical practice is related to severity of psychiatric illness and may require consideration of magnetic field parameters of the rTMS unit with respect to individual factors such as sex or body composition.

Introduction

Major Depressive Disorder (MDD) can be characterized by neurobiological abnormalities in regulatory feedback pathways involving select brain regions and neurotransmitter systems.[1,2] Repetitive Transcranial Magnetic Stimulation (rTMS) was developed to treat subjective symptoms of depression through the modulation of activity within orbital frontal corticostriatal (OFC) circuits involving the medial prefrontal cortex (mPFC), the hippocampus, the limbic system, amygdala, and other regions.[3-5] Transcranial Magnetic Stimulation has proven to be efficacious at alleviating depression symptoms over a wide range of settings particularly for treatment-resistant cases of MDD.[6-12] The technology is widely utilized in clinical practice but the practical application to ethnically, financially, and geographically diverse patient groups with complex comorbidities require further characterization.[13-15]

We recently examined the effectiveness of rTMS in combination with cognitive behavioral therapy (CBT) in the treatment of MDD using data derived from a retrospective review of medical records from patients with MDD undergoing rTMS therapy at a suburban tertiary psychiatric clinic, AwakeningsKC Clinical Neuroscience Institute (CNI).[16] Our investigation found clinically rated remission rates of 72% achieved in an average of 3.1±1.0 weeks of rTMS therapy. The rates of clinical remission were related to individual factors including history of psychiatric hospitalization, suicide attempts, obesity status and comorbid substance use disorder. Our investigation identified several unexpected factors that appeared to moderate clinical response, most notably, a proportionately greater clinical response was identified among patients treated using the MagVenture over the NeuroStar rTMS instrument. The various rTMS instruments do possess qualitative differences in select features particularly the coil design and pulse width with perceptible differences in functional and side effects profiles. A direct, side-by-side comparison of clinical response rates was carried out by Oliveira-Maia AJ *et al.*[17] utilizing Neurostar (N=41) and Magstim (N=113, Eden Prairie, MN), for up to 6 weeks therapy with 20 Hz stimulation but no significant differences in response rate were identified. The present study extends the analysis of our midwestern cohort using Cox Proportional Hazards regression and Log-Rank statistics to investigate time to clinically rated remission from depression.

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Materials and Methods

AwakeningsKC Clinical Neuroscience Institute (CNI)

AwakeningsKC CNI is a tertiary health care center for outpatient psychiatric treatment located in Prairie Village, Kansas. The center is Kansas State Certified for Cognitive Behavioral Therapy (CBT) with three clinics for Medication-Psychotherapy, repetitive Transcranial Magnetic Stimulation (rTMS), and intensive outpatient CBT. AwakeningsKC CNI has applied clinical data utilizing two similar rTMS stimulators, Mag Vita (MagVenture, Alpharetta, GA) and NeuroStar (Neuronetics, Malvern, PN).[18] Both instruments utilize a magnetic coil with a figure eight configuration but differ in several technical parameters such as coil composition and thermoregulation and pulse width of stimulation described in detail elsewhere.[19]

Repetitive Transcranial Magnetic Stimulation (rTMS) parameters

rTMS treatments were administered by psychiatrists or trained technicians closely overseen by an experienced psychiatrist. The rTMS treatment followed established

guidelines with a single daily session 37 minutes in duration for 6 weeks with a maximum of 30 treatments. Treatment sessions were carried out in an isolated room with an adjustable chair and a large screen television with multiple viewing options. The patients were advised to wear earplugs during the treatment due to the loud noise produced by the instrument. Individual treatment times and instruments were applied consistently to maximize outcomes. The stimulator coil was positioned over the dorsolateral prefrontal cortex, located approximately 2.2 inches below the center line of the head on the interauricular line from the ear through the center of the head at the top. The motor threshold (MT) was identified for each patient prior to treatment and reassessed weekly throughout the treatment phase based upon the activation of the Abductor Pollicis Brevis (APB) motor cortex.

Data collection and assessments

This study was conducted under the authority of the University of Kansas Medical Center Office of Research Compliance who reviewed the study protocol and monitored study activities to ensure that appropriate steps were taken to protect the rights and welfare of humans participating as research subjects. Electronic medical records (Bestnotes, Twinfalls, ID) from patients of AwakeningsKC CNI were searched to identify adult men and women aged 18-80 years with Major Depressive Disorder who received up to 6 weeks of rTMS treatment as a component of their psychiatric treatment for depression. All study patients completed an 11-page downloadable assessment form prior to their initial visit. This form includes self-reported patient demographic information, detailed substance abuse history, psychiatric self-assessment, past psychiatric treatment, medical history, current and past medications, family medical history, and family psychiatric history. Clinician defined remission was assessed based on changes in depressive symptomology, such as noted interest in activities, feelings of hope and positivity for the future, improved sleeping and appetite disturbances, a presence of volition in the patient's speech, an improved self-esteem, improved cognitions, improved lethargy, and presentation of brighter affect. Clinician rated remission was assessed independently of psychometric testing results. Time to remission from depression was the primary outcome with medical, psychiatric and family history and demographics including age, sex, education, socio-economic status, marital status, and employment evaluated as co-variates.

Data analysis

SAS statistical software version 9.4 (SAS Institute Inc. Cary, North Carolina, USA) was used to generate summary data for formal presentation and carry out all primary and secondary data analyses. Log-Rank statistics were applied to assess time to clinical remission based upon the clinician defined week of remission with hazard ratios calculated for time to clinical remission. Stepwise Cox proportional hazard regression modeling was applied to the identified clinically meaningful variables to identify a parsimonious model of time to remission with rTMS therapy.

Results

We examined data from the electronic medical records at AwakeningKC CNI for patients experiencing up to 6 weeks of rTMS therapy for MDD. Our cohort consisted of 247 adult men (N= 98) and women (N=149) with a mean age of 42.9±13.9 years (18 to 78 years) of mostly Caucasian (97%) race with high rates of prior psychiatric hospitalization (62%) and previous suicide attempts (36%) previously described in Davila *et al*.[16]

Time to remission status

Log-Rank statistics were employed to further characterize and support the influence of identified parameters on the time course of clinical response to rTMS therapy. The week of clinician rated remission was modeled for patients treated using the two different rTMS instruments. A significant difference was found in the average time to remission for patients treated using the MagVenture (3.5±0.1 weeks) compared to the NeuroStar (3.8±0.1 weeks) instrument (Log-Rank χ^2 =5.7; P=0.02; Figure 1). This corresponded with higher clinician rated response rates after 6 weeks of 81% for patients treated using the MagVenture instrument compared to 64% observed for patients treated with the NeuroStar instrument. Patients reporting a previous hospitalization in a psychiatric facility showed an enhanced clinical response profile (Figure 2A) compared to individuals without a previous psychiatric hospitalization supporting our previous findings. Patients with a previous hospitalization showed a mean time to remission of 3.5±0.1 weeks compared to 3.9±0.1 weeks for patients without a previous psychiatric hospitalization (Log-Rank χ^2 =5.7; P=0.02). Further, this relationship appeared to be moderated by the rTMS unit utilized for treatment with greater remission rates observed among patients with a previ-

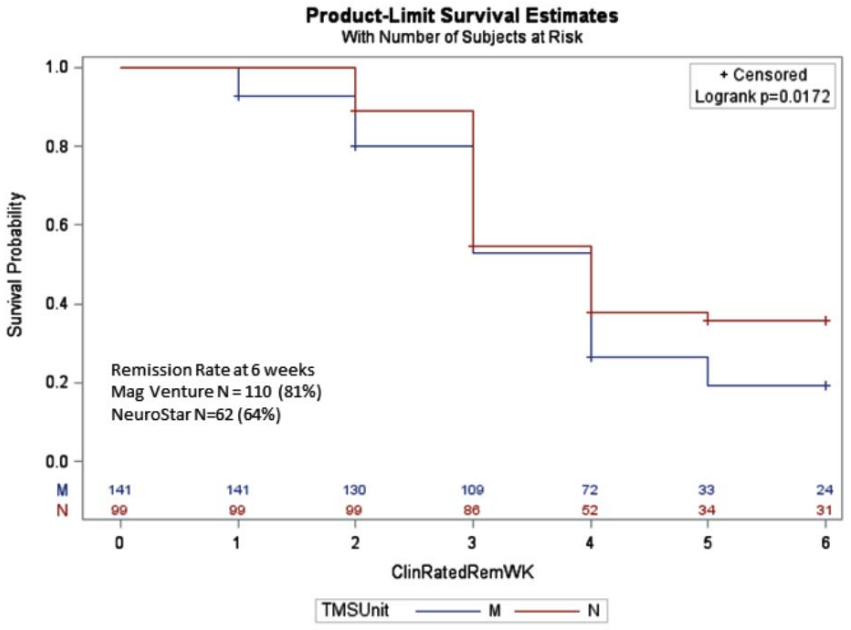

Figure 1. Time to remission for patients with major depressive disorder treated using MagVenture or Neurostar TMS Units. Logrank test of time to remission from depression for MagVenture compared to Neurostar TMS units showed higher remission rates for patients treated using the MagVita TMS unit than those treated using the Neurostar unit. Legend indicates the four comparison groups with TMS Units, M=MagVenture and N= NeuroStar. The number (%) for patients remitted at week 6 are shown. The number of non-remitted, non-censored patients are shown for each group at each time point. Seven patients were censored for MagVenture and six for NeuroStar.

ous psychiatric hospitalization treated using the MagVenture rTMS unit (86% for MagVenture *vs* 67% for NeuroStar; Log-Rank χ^2 =12.0; P=0.001; Figure 2B). This corresponded with a slightly shorter mean time to remission of 3.3±0.1 weeks for previously hospitalized patients treated using the MagVenture instrument compared to the 3.4±0.1 weeks for patients treated using the NeuroStar instrument.

Stepwise Cox proportional hazards modeling of time to remission status was applied to identify the most parsimonious model to predict clinical remission to rTMS therapy. The initial model parameters were based upon findings from our examination and included: MagVenture rTMS instrument relative to NeuroStar, obesity status, age, sex, presence of substance abuse history, previous suicide attempts and previous inpatient psychiatric hospitalization. The criteria for model entry was defined as P=0.5 and the criteria to stay were set at P=0.1. The global model converged and was significant (likelihood ratio test χ^2=11.1, df=3, P=0.01; Table 1). The final model included MagVenture TMS instrument (χ^2=3.4, P=0.06, hazard ratio=1.3), obesity status (χ^2=4.3, P=0.04, hazard ratio=1.7) and prior inpatient psychiatric hospitalization (χ^2=3.6, P=0.06, hazard ratio=1.4).

Discussion and Conclusions

Our continuing investigation of the effectiveness of repetitive transcranial magnetic stimulation (rTMS) and CBT in the treatment of major depressive disorder and other related psychiatric co-morbidities and conditions supported the efficacy of rTMS in an applied clinical setting (Awakening KC, CNI).[16] Our present analysis of time to remission from depression symptoms further supported a differential effect of rTMS unit with higher remission rates observed for MagVenture over NeuroStar. Patients treated using the MagVenture instrument also showed shorter mean time to remission and higher overall remission rates at 6 weeks with augmented response rates to CBT. Our previous report demonstrated a >70% clinical response rate as assessed by clinician defined remission and change in PHQ9 scores.[16] The strongest predictors of clinical response pertained to severity of MDD as indicated by prior hospitalization and suicide attempts. Our investigation also identified several unexpected factors impacting response that may be clinically relevant including influences of individual

Table 1. Stepwise cox proportional hazards regression final model.

Testing Global Null Hypothesis: BETA=0			
Test	**Chi-Square**	**DF**	**Pr > ChiSq**
Likelihood Ratio	11.1	3	0.01
Odds Ratio Estimates			
Effect	**Point Estimate**	**P-value**	**HR**
MagVenture *vs* NeuroStar rTMS Unit	3.9	0.05	1.3
Obesity	3.9	0.05	1.7
Inpatient Hospitalization	3.6	0.06	1.4
Residual Chi-Square Test			
Chi-Square	**DF**	**Pr > ChiSq**	**Chi-Square**
5.2	4	0.26	5.2

Stepwise Cox Proportional Hazards regression final model of clinical remission from depression symptoms after 6 weeks of treatment using rTMS. The model includes three co-variates with related odds ratios. Hosmer-Lemeshow goodness-of-fit testing showed no significant lack of fit.

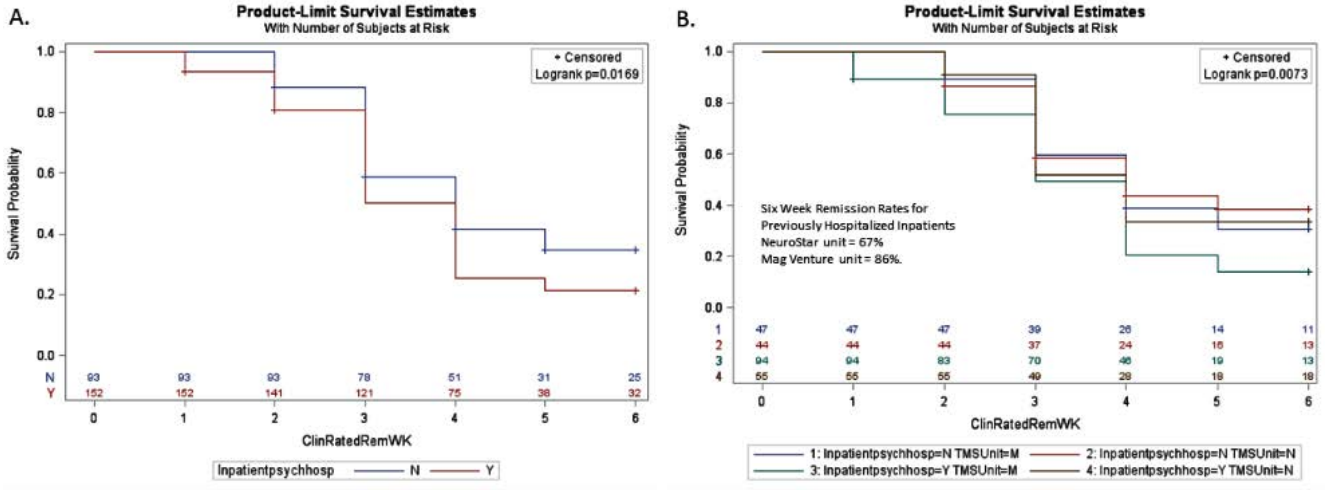

Figure 2. time to remission for patients with major depressive disorder and previous inpatient psychiatric hospitalization treated with rTMS. Logrank test of time to remission for up to 6 weeks of rTMS treatment for patients with and without a previous inpatient hospitalization (A). Inpatientpsychhosp = Y denotes patients with a previous psychiatric hospitalization; Inpatientpsychhosp = N denotes patients without a previous psychiatric hospitalization. B) shows results incorporating rTMS unit with TMSUnit = M for MagVenture and TMSUnit N= for NeuroStar. Survival probability plots the proportion of patients remaining unremitted at each week. The numbered legends at the bottom indicate the number of patients remaining unremitted per group at each study week.

factors such as age, sex and body composition. The rTMS instrument utilized for treatment consistently showed higher overall efficacy for the MagVenture over the NeuroStar instrument. As reported, AwakeningKC-NCI purchased the NeuroStar instrument prior to the MagVenture;[16] thus, there is a time course difference in the collected data between the two instruments. Differences in the familiarity and experience of the provider with the technology could have impacted the selection of patients or patient care leading to differences in clinical response. Patients treated using the MagVenture instrument did possess significantly higher baseline PHQ9 scores which may reflect non-random distribution based upon severity of illness. However, the relationship of clinical efficacy for TMS instruments to specific sub groups (age, gender, obesity status) would not be expected to vary by the experience of the individual provider.

As described, the various TMS instruments do possess qualitative differences in coil design, pulse width leading to perceptible differences such as pain more commonly reported for the NeuroStar instrument. Further, the absence of a cooling mechanism on the NeuroStar instrument limits performance parameters requiring downtime to avoid overheating. It is possible that repeated high-volume application of either TMS instrument in a daily practice setting, over time, might produce fluctuations in signal or performance not yet identified. However, the relationship to select patient subgroups suggests a mechanistic difference in performance worthy of further exploration.

Electrical and magnetic fields applied to pure water induce a dipole associated with persistent changes in the chemical properties of water including reduced hydrogen bonding, increased Van der Waals forces and viscosity and altered solubility.[20-23] Application of a magnetic weak field of 45 μT on a glutamic acid solution causes a change in the pH shifting towards the deprotonated species.[24] These electromagnetic influences on the degree of structuring in water observed in vitro have interesting implications if applied to in vivo settings with the potential to impact on cellular signaling, activity and functioning.[25] Non-thermal effects of microwaves, for example, can re-orient water at the surfaces of biomolecular structures such as membranes.[26] *In vivo* induction of magnetic fields in brain imaging results in anisotropic movement of fluids underpinning diffusion tensor imaging. rTMS could, theoretically, augment anisotropic movement of water in the brain enough to induce electrochemical changes and modulate neuronal excitability. Further, if the distribution of total fat or water composition in the brain parallels that of the body then factors such as obesity and female sex with proportionally greater body fat and lower body water composition could augment neural response to rTMS.[27] Similarly, variations in rTMS parameters could differentially impact these dipoles leading to variation in efficacy. The findings raise interesting novel questions regarding the mechanism of action of rTMS and the possible role of extracellular water structuring in biological systems for further exploration.

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