Crossover to Bilateral Repetitive Transcranial Magnetic Stimulation

A Potential Strategy When Patients Are Not Responding to Unilateral Left-Sided High-Frequency Repetitive Transcranial Magnetic Stimulation

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Abstract: Clinical trials using left-sided repetitive transcranial magnetic stimulation (rTMS) report remission rates of 14% to 32.6%. A large percentage of patients would not achieve remission with standard rTMS treatment. The question of what clinicians should do when a patient is not responding to standard high-frequency (HF) left-sided rTMS remains unanswered. This prospective case series examines whether crossover to bilateral stimulation enhances antidepressant outcomes in patients not responding to unilateral rTMS. Patients in a major depressive episode received an rTMS clinical protocol of 4 to 6 weeks' duration. Stimulation began with HF rTMS (10 Hz) over the left dorsolateral prefrontal cortex (range, 3000–5000 pulses per session). A total of 17 patients without sufficient clinical improvement early in their rTMS course received 1-Hz rTMS (range, 600–1200 pps) over the right dorsolateral prefrontal cortex (added to the HF left-sided stimulation). Hamilton Depression Rating Scale scores decreased from 13.9 ± 3.9 (mean ± SD) from the start of augmentation to 12.2 ± 5.8 at the end of acute treatment, a 1.7-point change, Cohen d effect size = −0.35, 95% confidence interval, −1.01 to − 0.34, suggesting improvement. Remission rate in this sample was 24% (4/17). This case series indicates that crossover to bilateral stimulation is a feasible and potentially effective strategy when patients are not improving with standard rTMS. A randomized controlled trial comparing crossover versus standard rTMS is needed to determine the efficacy of this paradigm.

Key Words: antidepressant, augmentation, depression, rTMS, slow rTMS, slow frequency

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What should clinicians do when a depressed patient is not responding to high-frequency (HF) left unilateral repetitive transcranial magnetic stimulation (rTMS) treatment? Clinical trials using left dorsolateral prefrontal cortex (DLPFC) rTMS reported remission rates of 14% to 32.6%,[1–3] suggesting that most patients will not achieve remission with standard rTMS; moreover, real-world patients have a great variation in disease severity, comorbidities, and often a high degree of treatment resistance. Therefore, strategies to optimize rTMS in clinical practice are needed.

Beneficial strategies include extending the duration of the rTMS course[4] or switching the stimulation site to the right DLPFC.[5] This prospective case series examines another potential but unstudied strategy: crossing over to bilateral stimulation, with the addition of low-frequency (LF) right-sided rTMS, when patients are not responding to unilateral rTMS. This strategy is biologically supported because LF (1 Hz) rTMS over the right DLPFC decreases blood flow in circumscribed regions of the right prefrontal cortex, left medial temporal cortex, left basal ganglia, and left amygdala[6] and has demonstrated efficacy and tolerability in major depression.[7] Besides, crossover to bilateral rTMS has been empirically used by clinicians.[8,9]

MATERIALS AND METHODS

From 2012 to 2016, patients in a major depressive episode who consented to research participation received a clinical rTMS protocol administered 5 days a week for 4 to 6 weeks. Stimulation began with HF rTMS (10 Hz) over the left DLPFC (range, 3000–5000 pulses per session [pps]; intertrain interval range, 15–20 seconds). Patients without sufficient clinical improvement early in their rTMS course received "off-label" (not US Food and Drug Administration approved) 1-Hz rTMS over the right DLPFC (in addition to and sequentially after the HF left-sided stimulation). Low-frequency stimulation typically began at 600 pps and was increased up to 1200 pps as per clinician's judgment. Every 600 pulses of LF rTMS added 11 minutes to the total duration of the rTMS session. We used a Magpro R30 stimulator (MagVenture Tonica Elektronik, Denmark) with a figure-of-eight coil. Motor threshold (MT) was determined for each left and right hemispheres, and stimulation intensity was set at 110% to 120% of the MT. The DLPFC was localized for each hemisphere at 6 cm anterior to the motor cortex or by using the Beam F3 system.[10] To localize the right DLPFC using the Beam F3 system, we positioned the X and Y software values on the right hemisphere.

Primary outcome was change in the 17-item Hamilton Depression Rating Scale (HAM-D); secondary outcomes included depression remission rates (HAM-D ≤7) and change in scores on the Quick Inventory of Depressive Symptoms (QIDS), the Generalized Anxiety Disorder-7 scale (GAD-7), and the Work and Social Adjustment Scale (WSAS) (measuring functional impairment). Clinical improvement was determined by the Clinical Global Impressions (CGI) Scale. Burden of adverse effects was assessed

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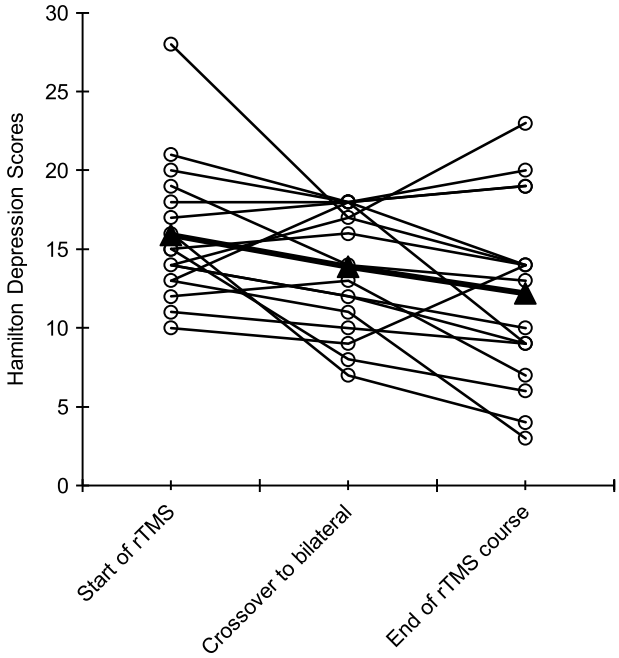

FIGURE 1. Trajectory of HAM-D scores for each patient crossing over to bilateral rTMS. Triangles denote mean HAM-D scores trajectory.

with the Frequency, Intensity, and Burden of Side Effects Rating. Patients lost to follow-up without postbaseline mood assessments were excluded from analysis. We described continuous variables using means and SD, and categorical variables using total number and percentages. We compared baseline to treatment-end depression scores, anxiety, and functional impairment scores and calculated Cohen d effect sizes.

RESULTS

Demographic and clinical characteristics of the 17 patients were as follows: mean age, 48.7 (SD, 13.3) years, 9 (52.9%) were female, and all were white. All patients had at least 3 previous antidepressant trials without response. Four patients (23.5%) had a lifetime history of electroconvulsive therapy, 8 patients (47%) had previous psychiatric hospitalizations, 3 (17.6%) had a previous suicide attempt, and 8 (47%) had a history of anxiety disorder. Baseline MT values were a mean of 52.2 (±8.3) for the left hemisphere and mean of 52.3 (±7.5) for the right.

All except for 1 patient were taking antidepressants. A total of 41% patients (7/17) had medication changes during their rTMS course; however, HAM-D scores at the end of treatment did not differ between the group with medication changes (mean, −2.1 [SD, ±2.8]) and those without medication changes (mean, −1.4 [SD, ±4.8]), $t_{15} = 0.37$, $P = 0.71$.

Figure 1 shows individual data on HAM-D scores changes throughout the rTMS course. A total of 14 patients crossed over to bilateral rTMS after 2 weeks of rTMS, CGI 3 to 4 (minimal improvement or no change); 2 patients after 3 weeks, CGI = 2 and 5 (much improved and minimally worse), and 1 patient after 4 weeks, CGI = 3. Group results show decreased scores on the HAM-D from the time of crossover to the end of rTMS, indicatingantidepressant effects (Table 1). The group's remission was 24% (4/17), and 41.1% patients (7/17) had at least 25% decrease in HAM-D scores. The 2 patients with bipolar disorder did not remit. The QIDS also showed improvement from the time of crossover to the end of treatment. Similarly, the GAD-7 anxiety scale and the WSAS scales also showed improvement (Table 1). Reported adverse effects were mild and minimally burdensome, including headache, 35% (6/17); anxiety, 18% (3/17); and fatigue, tooth pain, sleep disturbance, and scalp soreness, each 12% (2/17).

DISCUSSION

To our knowledge, this is the first report of crossover to bilateral rTMS in patients with insufficient clinical improvement in their rTMS course. With this bilateral "augmentation" strategy, patients showed a meaningful decrease in depression scores with a medium effect size, and 24% remitted. These outcomes are comparable with a 24% remission rate with aripiprazole augmentation in patients minimally responsive to antidepressants.[11] Adverse effects were minimally burdensome. One controversial aspect of this strategy was our decision to cross over to bilateral treatment before the completion of a full left-side rTMS course. The rationale of this early change is supported by literature documenting depression improvement in clinical trials using a 2-week rTMS (10 sessions) course.[12] Likewise, changes in brain metabolism occurred within 2 weeks of rTMS.[6] Nonetheless, it is possible that the improvements we saw would have been obtained simply by continuing the unilateral rTMS. Other limitations include potential confounding effects of concomitant medications and the lack of randomization with a control group.

Nevertheless, we demonstrated that crossover to bilateral stimulation is a feasible and potentially effective strategy when patients are not improving with standard rTMS. A randomized controlled trial comparing crossover versus standard rTMS is needed to determine the efficacy of this paradigm.

TABLE 1. Changes in Depression, Anxiety, and General Functioning Scores in Patients Crossing Over to Bilateral Stimulation (n = 17)

Scale	Baseline Mean (±SD)	Illness Severity	Treatment End Mean (±SD)	Score Change, Units	Illness Severity	Cohen *d* Effect Size	95% Confidence Interval
HAM-D	13.9 (3.9)	Moderate–mild	12.2 (5.8)	−1.7	Mild	−0.35	−1.01 to 0.34
QIDS	12.5 (4.0)	Moderate	9.6 (5.7)	−2.9	Mild	−0.60	−1.26 to 0.11
GAD-7	7.9 (5.2)	Mild	5.9 (5.1)	−2.0	Mild	−0.39	−1.36 to 0.61
WSAS	25.9 (8.2)	Moderately severe	21.6 (10.0)	−4.3	Moderately severe	−0.47	−1.15 to 0.23

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