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Full Length Research Paper

Feasibility study of deep-TMS add-on treatment for major depression in elderly patients

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Major depressive disorder (MDD) in the elderly is a major clinical problem. Depressed elderly subjects have shown modest antidepressant responses to transcranial magnetic stimulation (TMS) compared to younger adults. Deep TMS enables non-invasive stimulation of deep layers of the prefrontal cortex, and was approved for the treatment of MDD. The aim of this study was to examine the safety and efficacy of deep TMS add-on treatment for elderly MDD patients. Twenty daily H1-coil deep TMS treatments (18 Hz, 120% MT) were delivered in fifteen (15) elderly depressive patients. Clinical assessments were carried throughout the study and for an additional two weeks follow-up period. At the end of treatment period, there was a significant reduction on depression and anxiety rating scales. One subject reached remission and two reached response bordering remission. A trend toward significant improvement was found in the quality indicator disparity scale (QUIDS). At follow up, cognitive improvement was noted and treatment was well tolerated. In conclusion, an add-on H1-coil deep TMS treatment protocol in elderly MDD subjects indicated improvement in depressive symptoms.

Key words: Psychiatry, geriatric, affective disorders, depression, brain stimulation.

INTRODUCTION

Depression is a common, recurrent and chronic disorder and a leading contributor to functional impairment and disability (Ustun et al., 2004). Depression in ageing adults is often under-recognized and undertreated and is complicated by comorbid medical conditions and cognitive decline (Alexopoulos, 2005). Furthermore, late-onset depression is associated with greater brain structural changes (Dahabra et al., 1998). Findings suggest that antidepressant treatment may be less efficient in the elderly (Nelson et al., 2008; Tedeschini et al., 2011), supported by association between older age and lower rate of response to all classes of antidepressants (Calati et al., 2013). In many instances, older patients do not respond to or cannot tolerate the dosage of antidepressant medication needed to produce response, due to side effects or to drug-drug interactions (Lyness et al., 1996).

Transcranial magnetic stimulation (TMS) is a non-invasive treatment, with minimal side effects, making it particularly attractive as a potential treatment in the elderly. However, TMS studies designed specifically for older populations are surprisingly sparse (Abraham et al., 2007; Manes et al., 2001; Mosimann et al., 2004; Nahas et al., 2004). Utilizing various TMS techniques and protocols, those studies yielded response rates of 26-30% with a 30-35% reduction in the Hamilton depression rating scale (HDRS). Trials in elderly patients proved Repetitive transcranial magnetic stimulation (rTMS) treatment safe, while cognitive abilities were preserved and occasionally even improved. Nonetheless, previous trials found older age to be correlated with poor response (Aguirre et al., 2011; Figiel et al., 1998; Jorge et al., 2008;

Su et al., 2005).

Deep TMS (dTMS) enables a safe non-invasive stimulation of deep layers of the pre-frontal cortex (Levkovitz et al., 2007, 2009), with favorable results in the treatment of MDD (Harel et al., 2014) and other psychiatric disorders (Bersani et al., 2013).

Its higher penetration ability compared to other TMS coils (Roth et al., 2007, 2014) may provide a stronger stimulation and therefore more efficient in treating older patients. The aim of this study was to examine the safety and efficacy of H1-coil dTMS add-on treatment for elderly MDD patients.

MATERIALS AND METHODS

Subjects

Patients signed a written informed consent to a protocol approved by the local ethics board. Inclusion criteria included: Age 64 or above; DSM-IV diagnosis of current major depression episode (unipolar or a bipolar); Score of Hamilton depression rating scale (HDRS-21) ≥ 20 (Hamilton, 1960); Resistant depression, as defined by failed treatment of at least 6 weeks with at least one antidepressant in accepted dose, and/or intolerance to two or more antidepressants; Negative answers on safety screening questionnaire for TMS (Keel et al., 2001). Exclusion criteria included: substantial suicidal risk or attempted suicide in the past year; psychotic depression; previous negative response to electroconvulsive therapy (ECT); dementia; any major neurological disorder; use of hearing aids; history of drug abuse or alcoholism; and an active unstable medical condition. Patients continued anti-depressant medication, on which they were stable for at least 6 weeks prior to the trial. If they were not on psychiatric medication, none was started. Bipolar patients had to continue previous treatment with a mood-stabilizer in an adequate dose.

Objectives and outcome measures

Primary outcomes were safety and remission, judged by HDRS-21 <9 score. Secondary objectives were mood response, evaluated by 50% reduction in HDRS-21, Hamilton anxiety rating scale (HAM-A; Hamilton, 1959), Quick Inventory of Depressive Symptomatology (QIDS; Rush et al., 2003), Geriatric depression scale (GDS; Yesavage et al. 1982), Clinical global impression scale (CGI; Guy 1976) and cognitive ability, evaluated by The mini mental state examination (MMSE) (Folstein et al., 1975). Measurements were assessed at baseline, mid-treatment, end of treatment and two weeks following completion of trial. The initial clinical evaluation was performed by the primary investigator and a research assistant, while follow-up assessments were completed by the research assistant.

dTMS Protocol

All subjects received pre-frontal deep rTMS using the H1L-Coil, placed 6 cm anterior to point of minimal motor threshold, i.e. position where the stimulator power output, required to produce a motor evoked-response (MEP), was minimal. Treatment included 55 trains of 18 Hz at 120% of motor threshold with a 2 s pulse train and 20 s inter-train interval. Subjects received treatment for 4 weeks, 5 days a week, resulting in 20 sessions in total.

Statistical analysis

The means and standard deviations (SD) of continuous variables were compiled. Changes from baseline were analyzed using paired-samples t-test. Also, P-values of ≤0.05 were considered significant and Nominal P-values are presented.

RESULTS

Between April 2012 and March 2014, fifteen subjects participated in the trial (an additional subject was excluded from analyses due to receiving smaller number of trains per session (42 vs. 55). One subject dropped out after 2 weeks due to non-improvement. Fourteen subjects completed the treatment and were analyzed for efficacy. The mean age was 72.4 years (SD 4.8). Six participants were male and 8 were female. Furthermore, the mean duration of the current depressive episode was 9.4 months (SD 7 months). Four were diagnosed with bipolar depression, and the rest had unipolar disease.

A paired-samples t-test showed that mean HDRS-21 score was significantly reduced between screen visit (Mean=23.14, SD=3.30) and Visit 20 (Mean=18.07, SD=5.93) ($t(14) = 2.626$, $P = 0.0210$), with a mean change of - 5.07 (SD=7.23; Figure 1). Scores of only 10 patients were received at the follow up, and the difference was not significant ($t(10) = 1.585$, $P = 0.1485$), with a mean change of -3.60 (SD=7.18). Notably, of the fourteen patients eligible for analysis, one reached full remission and two showed clinical response bordering remission (with final HDRS scores of 8 and 9).

HAM-A score was also significantly reduced between screen visit (M=18.64, SD=6.27) and visit 20 (M=13.36, SD=4.99) ($t(14) = 2.844$, $P = 0.0138$), with a mean change of -5.29 points (SD=6.96; Figure 2). At the follow up, the difference was not significant ($t(10) = 1.549$, $P = 0.1558$), with a mean change of -4.20 (SD=8.57).

The mean QIDS score showed a trend toward significant difference between Screen visit (M=21.92, SD = 4.11) and Visit 20 (M = 1 8.08, SD = 7.39) ($t(13) =$

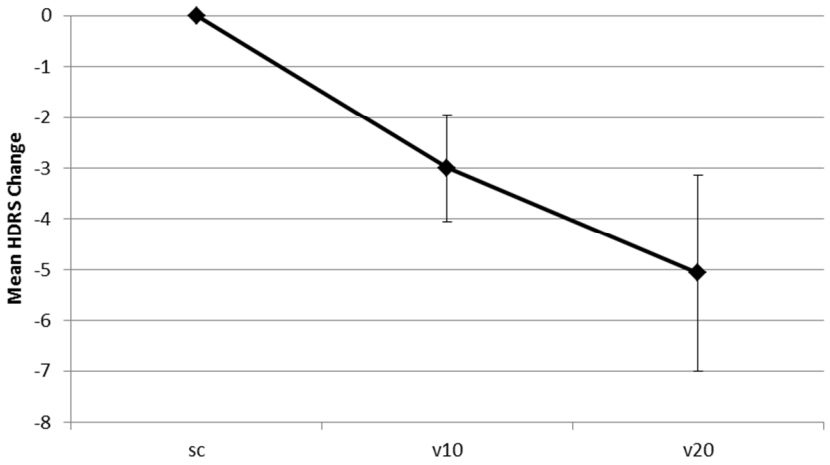

Figure 1. Change in HDRS-21 score between screening visit (sc), after 10 sessions (v10) and after 20 sessions (v20). Shown are mean±SE.

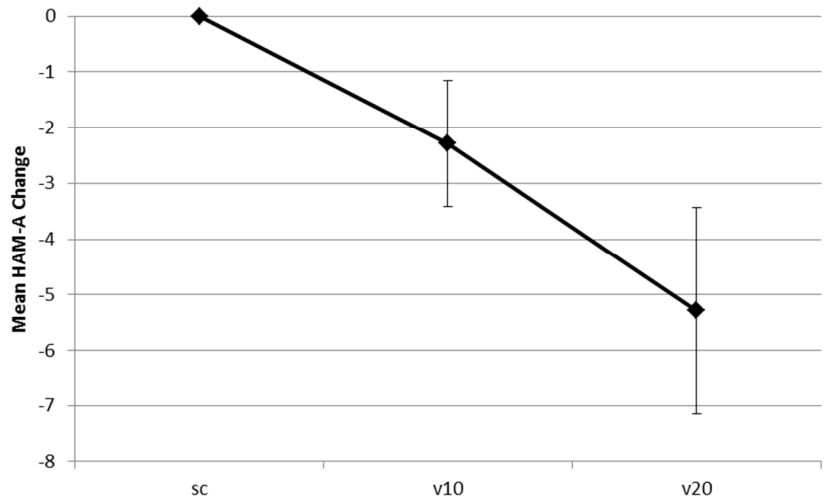

Figure 2. Change in HAM-A score between screening visit (sc), after 10 sessions (v10) and after 20 sessions (v20). Shown are mean±SE.

2.031, P =0.065). At follow up, the results were M=17.50, SD=7.96, compared to Screen visit t(10) = 1.589, P =0.1466. No significant changes were found in the GDS score (P =0.7418 at visit 20 and P=0.1026 at follow-up).

There were no significant differences in MMSE score between baseline and visit 20 (t(11) = 0.2479, P =0.8088). Yet there was a significant average improvement at the 2 weeks follow up of 1.11 points compared to baseline (t(8) = 2.443, P =0.0404) and of 1.0 points compared to visit 20 (t(8) = 2.449, P =0.0400).

DISCUSSION

This study examined safety and efficacy of H1-coil dTMS add-on treatment for elderly depression. Following a 20 session protocol on 14 elderly patients, a statistically and clinically significant reduction was found in depression and anxiety scores on the HDRS-21 and HAM-A. Yet, of the fourteen patients, one reached full remission and two showed clinical response bordering remission. A trend toward significant improvement was found in the quality indicator disparity scale (QUIDS) score. Upon follow up, cognitive improvement was noted and treatment was well tolerated, without serious adverse events.

Previous superficial rTMS trials in the elderly were somewhat disappointing (Aguirre et al., 2011; Figiel et al., 1998; Jorge et al., 2008; Manes et al., 2001; Mosimann et al., 2004), hypothetically due to high scalp-to-PFC distance. Brain atrophy at old age is a well-known phenomenon (Earnest et al., 1979; Yamaura et al., 1980), which results in increased distance between the

skull and cortex. Consequently, older age is correlated with increased pre-frontal cortex (PFC) distance (Kozel et al., 2000). Moreover, microstructural white matter abnormalities may be linked to lower rates of remission in geriatric depression (Alexopoulos et al., 2002). Since the strength of the magnetic field generated by TMS coils decreases exponentially, high distance between the coil and cortex is associated with an increase in the motor threshold, in a linear fashion (Stokes et al., 2007, 2013).

Greater antidepressant efficacy is associated with higher stimulation intensity (Padberg et al., 2002) and higher frontal gray matter volumes (Jorge et al., 2008). Greater coil-PFC distance, resulting in decreased stimulation, may be responsible for the lower responsiveness of elderly patients. Mosimann et al. (2002) showed that increased distance between the PFC and skull is associated with a poor anti-depressant response. By adjusting TMS intensity to PFC distance, the coil-cortex distance was no longer a variable and the negative correlation between age and clinical response disappeared (Nahas et al., 2004). Hence our theory was that the deeper stimulation provided by dTMS may overcome increased cortex-scalp distance in the aged. Study results were similar to previous figure 8 coil trials, though we presume adjustment of dTMS stimulation intensity with amount of pre-frontal atrophy in-mind may increase the clinical efficacy of this technique in the future.

Electroconvulsive therapy (ECT) is prevalent and effective in elderly depression. Even so, it is associated with cardiac and pulmonary complications (Kerner and Prudic, 2014) and may induce cognitive harm (Rose et al., 2003) in this already cognitively fragile population. TMS on the contrary, is less distressful for the patients as it does not involve anesthesia or post-treatment confusions and is not associated with medical complications (Janicak et al., 2008; Loo et al, 2008). TMS was successful in the maintenance of ECT (Cristancho et al., 2013) and its treatment was as effective at 6-months follow-up (Dannon et al., 2002). In addition, rTMS alone offers an economic benefit over ECT alone in treating resistant depression (Kozel et al., 2004). All of the above suggests deeper understanding, and further research into the TMS technique could make TMS the treatment of choice for drug resistant elderly MDD.

As this is a pilot study, its major limitations include its size and the absence of a sham-treatment arm. Nevertheless, although the small number of participants prevents clear delineation of patient and disease-specific response factors, dTMS was shown to be safe and effective in elderly patients suffering from MDD.

Conclusion

An add-on H1-coil deep TMS treatment protocol in elderly MDD subjects indicated improvement in depressive symptoms. Our results support the need for a larger-scale sham-controlled study with adjustment of dTMS stimulation intensity with amount of pre-frontal atrophy to further evaluate dTMS efficacy in old age MDD.

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Statement of Interest

Professor Levkovitz was a consultant from Brainsway Ltd. until 01/07/2014. Dr. Yiftah Roth is the chief scientist for Brainsway Ltd.

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