Journal of Psychiatric Research 114 (2019) 113–119

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Efficacy of repetitive transcranial magnetic stimulation using a figure-8-coil or an H1-Coil in treatment of major depressive disorder; A randomized clinical trial

Igor Filipčić[a,b,c,*], Ivona Šimunović Filipčić[d], Željko Milovac[a], Strahimir Sučić[a], Tomislav Gajšak[a], Ena Ivezić[a,b], Silvio Bašić[b,e], Žarko Bajić[a], Markus Heilig[f]

[a] Psychiatric Hospital "Sveti Ivan", Zagreb, Croatia
[b] Faculty of Dental Medicine and Health, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia
[c] School of Medicine, University of Zagreb, Zagreb, Croatia
[d] Department of Psychological Medicine, University Hospital Center Zagreb, Zagreb, Croatia
[e] Department of Neurology, Dubrava University Hospital, Zagreb, Croatia
[f] Department of Clinical and Experimental Medicine, Center for Social and Affective Neuroscience, Linköping University, Linköping, Sweden

ARTICLE INFO

Keywords:
Repetitive transcranial magnetic stimulation
rTMS
Deep TMS
Major depressive disorder

ABSTRACT

Repetitive transcranial magnetic stimulation (rTMS) is an evidence-based treatment option for major depressive disorder (MDD). However, comparisons of efficacy between the two FDA-approved protocols of rTMS modalities are lacking. The aim of this industry-independent, randomized-controlled, single-blind trial was to evaluate clinical outcome of the two FDA-approved rTMS protocols delivered by H1-coil and the figure-8-coil, in MDD patients. A total of 228 MDD patients were randomized to 20 sessions of H1-coil or 8-coil as an adjunct to standard-of-care pharmacotherapy, or standard-of-care pharmacotherapy alone. Baseline MDD symptom severity was almost the same in the three groups. Hamilton depression rating scale (HAM-D17) mean score was 17 (5.3) in H1-coil, 17 (5.4) in 8-coil, and 19 (6.1) in control group. The primary outcome was the proportion of patients achieving remission defined as HAM-D17 score ≤ 7 at end-of-treatment at week-4. In the intention-to-treat analysis odds ratio for remission was 1.74 (CI95% 0.79–3.83) in H1-coil compared to the 8-coil group. The difference between two rTMS protocols was not significant. Remission rate was significantly greater in both HF-rTMS groups compared to the control: 60% (CI95% 48–71%), 43% (CI95% 31–55%) and 11% (CI95% 5–20%) respectively. The response was significantly better in H1-coil, than in 8-coil group OR = 2.33; CI95% 1.04–5.21 (P = 0.040). The HAM-D17 was lowered by 59% in the H1-coil, 41% in the 8-coil (P = 0.048), and 17% in the control group (P < 0.001 vs H1-coil; P = 0.003 vs 8-coil). Safety, tolerability, and the changes in quality of life were comparable. We confirmed the safety and efficacy of both FDA-approved protocols as adjunctive treatments of MDD. Better response rate and greater reduction of depression severity were observed in the H1-coil group, but without a significant difference in the remission rate between the two rTMS modalities.
Clinical trials registration: Clinicaltrials.govNCT02917499

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling disorder in which resistance to treatment is a substantial problem (De Carlo et al., 2016; World Health Organization, 2016). It has been estimated that 20%–40% of patients do not benefit adequately from available interventions, including pharmacotherapy and psychotherapy (Murphy et al., 2017). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive treatment method that modulates brain electrical activity by electromagnetic induction (Milev et al., 2016). High frequency rTMS (HF-rTMS) applied at 10–20 Hz to the left dorsolateral prefrontal cortex (DLPFC) is an approved MDD treatment with an efficacy comparable to pharmacological MDD therapy (Brunoni et al., 2017; Lefaucheur et al., 2014; Milev et al., 2016; Rush, 2007).

Considerable antidepressant effects of HF-rTMS with a figure-8-coil over the DLPFC compared to sham were shown in medication-free patients with treatment-resistant depression (TRD) (George et al., 2010; O'Reardon et al., 2007). Recently, a novel form of HF-rTMS therapy,

* Corresponding author. Psychiatric hospital "Sveti Ivan", Jankomir 11, pp68, HR-10 090, Zagreb, Croatia.
E-mail address: igor.filipcic@pbsvi.hr (I. Filipčić).

https://doi.org/10.1016/j.jpsychires.2019.04.020
Received 3 January 2019; Received in revised form 21 March 2019; Accepted 23 April 2019

"deep rTMS" (dTMS) has been approved by the FDA as a treatment for unipolar MDD in adults who have not responded to antidepressant medications in the current episode (Levkovitz et al., 2015; Perera et al., 2016). dTMS delivered with the H1-coil (designed to target the PFC bilaterally with preference for the left hemisphere) allows non-invasive stimulation of brain regions to a depth that has been estimated to reach approximately 4 cm (Roth et al., 2007; Zangen et al., 2005). Roth et al. (2007) have demonstrated a clear preference for the left hemisphere for H1-coil, where at any depth the model field is higher in the left relative to the right hemisphere (Roth et al., 2007).

Previous studies have shown safety and efficacy of dTMS in treatment-resistant depression (Kedzior et al., 2015). However, there has been only one large industry-sponsored randomized-controlled trial (RCT) of the acute efficacy and tolerability of dTMS, in antidepressant medication–free adults, and none to compare the efficacy and tolerability of these two HF-rTMS modalities conventional FDA approved protocols (Levkovitz et al., 2015; McClintock et al., 2017).

A recent systematic review with a network meta-analysis by Brunoni et al. (2017) found few differences in clinical efficacy and tolerability for the acute treatment of MDD between the different HF-rTMS modalities (Brunoni et al., 2017). However, the findings were inconclusive for most comparisons between active interventions, and therefore did not provide any definitive evidence of superiority for either of the interventions (Feifel, 2017; Roth et al., 2017). Nevertheless, the tolerability of all active interventions were similar to sham, confirming that they were well tolerated (Brunoni et al., 2017). Thus, while differences in clinical efficacy and tolerability between HF-rTMS modalities with the figure-8-coil and the H1-coil in the treatment of MDD might exist, it has not been possible to confirm those from data available to date (McClintock et al., 2017).

To address this knowledge gap, we conducted an industry-independent, pragmatic, RCT in which we evaluated and compared the efficacy and safety of the two protocols that led to the FDA-approval of HF-rTMS with the respective device, the H1-coil and the figure-8-coil. We evaluated both interventions as an augmentative treatment in the acute treatment of treatment resistant MDD. We hypothesized that H1-coil HF-rTMS would be more effective than figure-8-coil HF-rTMS as adjunctive treatments of MDD. We based this hypothesis on two premises: i) H1-coil directly stimulates larger volumes and deeper into the prefrontal cortex compared to the figure-8-coil rTMS (Zangen et al., 2005) and therefore is more likely to hit projections affecting the subgenual anterior cingulate cortex, ii) the original large multicenter double blind sham controlled studies that led to FDA clearance of the figure- 8 coil and the H1-coil indicated greater remission and response rates for the H1 coil (Levkovitz et al., 2015) than for the figure- 8 coil (O'Reardon et al., 2007).

2. Participants and methods

2.1. Study design

We undertook a pragmatic RCT at the neurostimulation laboratory at Psychiatric Hospital "Sveti Ivan", Croatia between December 5, 2016 and January 15, 2018.

The study was approved by the institutional Ethics Committee, registered at ClinicalTrials.gov (NCT02917499), and reported according to CONSORT guidelines (Boutron et al., 2008). All participants gave written informed consent for the participation. The study protocol was previously published and executed with no major changes (Filipcic et al., 2018).

2.2. Participants

Eligible patients were recruited through physician referrals in the order of their arrival at the hospital neurostimulation center. All participants were screened on site by trained, board-certified psychiatrists through a structured clinical interview based on DSM-5 criteria. The targeted population included patients diagnosed with MDD (ICD-10: F32, F33), and with at least one prior disease episode. Inclusion criteria were as follows: a confirmed Mini-International Neuropsychiatric Interview diagnosis of MDD, aged 20–70 years, meeting standardized criteria for failure to receive clinical benefit from antidepressant medication treatment in the current illness episode, and with psychopharmacological treatment unchanged for the 4-weeks preceding entering the study. Exclusion criteria were: previous treatment with TMS, ferromagnetic material close to the head, having a cardiac pacemaker and/or implanted electronic device, the presence of neurological disorders (uncontrolled epilepsy, previous significant head injuries, brain surgery), pregnancy and/or lactation, significant medical and/or psychiatric comorbidities, substance abuse in the last three months, acute psychosis, or acute suicidality.

2.3. Sample size determination

A power analysis was performed before the start of enrollment. While developing the protocol, we were not aware of any RCT comparing HF-rTMS with the H1-coil and the figure-8-coil. Therefore, the power analysis was based on the expected "medium effect size", with Cohen's $d = 0.50$ set a-priori. A sample size of 64 was determined sufficient to achieve 80% power at $P < 0.05$ and to detect a standardized effect of this size or larger. To account for the expected $\leq$15% of drop out and missing data, this number was increased to 76 in each group. Power analysis was done in PASS 14 Power Analysis and Sample Size Software (2015) (NCSS, LLC, Kaysville, Utah, USA).

2.4. Outcomes

The primary outcome was the proportion of patients achieving remission defined as Hamilton depression rating scale (HAM-D17) score $\leq$7 after the 4-week therapy (20 treatments) (Hamilton, 1960). Experienced psychiatrists conducted the semi-structured interviews and scored the baseline HAM-D17 at enrollment. Secondary outcomes were: a) change in symptoms as measured by HAM-D17, b) treatment response (HAM-D17 $\geq$ 50% decrease), c) change in the quality of life measured by WHOQOL-BREF ("Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group.," 1998), d) safety, and tolerability. The outcomes assessment was performed by independent experienced psychiatrists who were unaware of the modality of intervention. All patients were instructed not to mention their ongoing treatment to the psychiatrists who did the clinical assessment. Patients were monitored daily during the HF-rTMS sessions in order to assess safety and tolerability of the procedure, using spontaneously reported adverse events. Patients from the control group who were treated by standard pharmacotherapy alone were monitored only at baseline, and after the 4-weeks.

2.5. Intervention

Patients were randomized to the 4-week treatment by HF-rTMS with H1-coil (H1-coil group) or figure-8-coil (8-coil group), and received standard treatment with pharmacotherapy in both groups, or to the control group treated only with pharmacotherapy. Modifications of pharmacotherapy were not allowed in any group during the study period. The stimulation protocol, including stimulation parameters and positioning over the left DLPFC, followed the multicenter trials that led to FDA approval of this treatment of MDD (Levkovitz et al., 2007; O'Reardon et al., 2007). Both protocols were administered 5-days per week (total of 20 sessions).

HF-rTMS with both coils was performed using a Magstim Rapid^2 (Magstim Company, Spring Gardens, UK) at stimulation intensity of 120% of the abductor pollicis brevis (APB) motor threshold (MT). HF-rTMS with the figure-8-coil included 40-min sessions of 10 Hz

stimulation (4-s trains separated by 26-s inter-train intervals, 75 trains totaling 3000 pulses/session), while HF-rTMS with the H1-coil device (Brainsway Ltd., Jerusalem, Israel) included 20-min sessions of 18 Hz (2-s trains separated by 20-s inter-train intervals, 55 trains totaling 1980 pulses/session).

2.6. Randomization

Enrolled patients were randomized into three groups in a 1:1:1 ratio by stratified, permuted-block randomization. Stratification was done for age (three age groups) and gender. We used three blocks of random sizes: 3, 6, and 9. Randomization was performed by an independent research institution (Biometrika Healthcare Research, Croatia), only after the successive enrollment of participants and the allocation was concealed from the physicians and nurses who did the enrollment. The randomization sequence was generated by Sealed Envelope on-line service.

2.7. Possible confounders

In addition to the randomization, we attempted to control for the possible confounding effects of gender, age, education, marital status, work status, diagnosis, duration of MDD, and treatment with particular antidepressants, antipsychotics, and benzodiazepines by multivariable logistic regression and analysis of covariance.

2.8. Statistical analysis

Analysis was conducted in both intention-to-treat (ITT) and per-protocol (PP) populations. Missing values for the ITT analysis were imputed assuming failure. For remission and response rates they were set at failure to achieve these two outcomes. For continuous variables: decrease in HAM-D17, and WHOQOL-BREF, they were set at the baseline values indicating no change after the therapy. We chose this strategy in order to perform a more conservative analysis that increase the null hypothesis likelihood of no effect. The primary analysis of proportion of patients achieving remission was performed by multivariable binary logistic regression. We used the multivariable analysis in order to control the effects of possible confounders. The changes in secondary outcomes: HAM-D17 and WHOQOL-BREF were analyzed by the analysis of covariance. In all analyses, preplanned possible confounders and the baseline scores of the respective outcomes were included as covariates. The homogeneity of variances across treatment groups were checked by Levene's test. The homogeneity of regression slopes was checked by testing the significance of the interaction between treatment group and the preplanned covariates. Partial Eta squared (η^2) was given as the standardized effect size. Sensitivity analysis of the difference between two rTMS modalities in the decrease of HAM-D17 score was done by Quade's rANCOVA procedure. The values of baseline and after-treatment HAM-D17 and covariates were first ranked. Than we did the linear regression of the ranks of the outcome, the ranks of the covariates and the baseline HAM-D17 scores. Finally, the Mann-Whitney test was done using the unstandardized residuals from the previously described regression analysis as the dependent variable, and rTMS modality as the independent variable. As the standardized effect size measure for the Mann-Whitney test, we presented r, calculated as: Z/(SQRT(n)) where Z was a standardized U statistic, and n was the number of participants. The statistical significance of the results of sub-group analysis and sensitivity analysis of HAM-D17 score decrease were corrected for multiple testing by sequential Holm-Bonferroni correction. In all instances, we used two-tailed tests. The level of statistical significance was set at $P < 0.05$, and we gave all confidence intervals at 95% level. No data monitoring committee oversaw the study. Statistical data analysis was done by NCSS 12 Statistical Software (2018) (NCSS, LLC. Kaysville, Utah, USA).

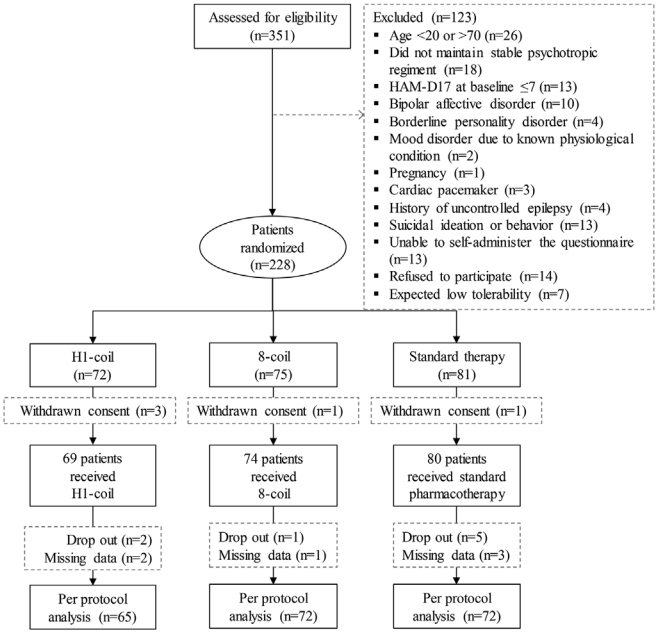

Fig. 1. CONSORT statement flow diagram.

3. Results

From December 2016, to January 2018, a total of 351 patients were assessed for eligibility. After assessment, 228 patients were randomly assigned to the H1-coil (n = 72), 8-coil (n = 75) or control group (n = 81). Ultimately, 65 patients treated with H1-coil and standard pharmacotherapy, 72 treated with figure-8-coil HF-rTMS and standard pharmacotherapy who received 20 sessions, and 72 treated with standard pharmacotherapy alone came for clinical evaluation at the end of treatment (Fig. 1). All-cause discontinuation rates were 7/72 (9.7%) in the H1-coil, 3/75 (4%) in the 8-coil, and 11.1% (9/81) in the control group. All randomized study participants received TMS treatment and standard pharmacotherapy as outpatients throughout the duration of their participation in the study. The majority of participants' socio-demographic and clinical characteristics were comparable between treatment groups (Table 1). Baseline MDD symptom severity was almost the same in the three groups (Table 2). Treatment resistance (TRD) was not systematically recorded, but post-hoc review of the files indicated that all patients met the criteria of TRD, defined as at least two previous adequately given (dose-duration) antidepressant treatments without response.

In ITT population, remission rate was grater in both HF-rTMS groups compared to the control group (Table 2, Fig. 3). The odds ratio for remission was OR = 11.3; CI95% 4.00–32.10; $P < 0.001$ in H1-coil and standard pharmacotherapy and OR = 7.20; CI95% 2.30–22.54; P = 0.001 in 8-coil and standard pharmacotherapy group compared to the standard pharmacotherapy only control group. Number of patients achieving remission was 43/72 (60%; CI95% 48–71%) in H1-coil, 32/75 (43%; CI95% 31–55%) in 8-coil, and 9/81 (11%; CI95% 5–20%) in the control group. After the adjustment for all preplanned confounders, the remission rate measured by HAM-D17 ≤ 7 was not significantly different between two rTMS modalities, neither in the ITT nor the PP populations. The odds ratio for remission in ITT analysis of H1-coil group compared to the referent 8-coil group was OR = 1.74; $CI_{95\%}$ 0.79–3.83; P = 0.17. In ITT population, patients with baseline moderate/severe depression (HAM-D17 ≥ 17) patients treated with H1-coil and standard pharmacotherapy had significantly higher odds for remission than patients treated with figure-8-coil and standard pharmacotherapy (OR = 4.59; $CI_{95\%}$ 1.69–12.48; P = 0.003). We did not observe significant differences in odds ratios for remission between

Table 1
Participants baseline characteristics in intention-to-treat population.

	H1-coil (n = 72)		8-coil (n = 75)		Control (n = 81)	
Gender						
man	31	(43.1)	41	(54.7)	36	(44.4)
women	41	(56.9)	34	(45.3)	45	(55.6)
Age (years), median (IQR)	50	(44–60)	51	(42–59)	53	(48–61)
Education						
primary or secondary	51	(70.8)	57	(76.0)	69	(85.2)
university	21	(29.2)	18	(24.0)	12	(14.8)
Marital status						
single	28	(38.9)	26	(34.7)	34	(42.0)
in a relationship	44	(61.1)	49	(65.3)	47	(58.0)
Work status						
employed	26	(36.1)	35	(46.7)	32	(39.5)
unemployed	23	(31.9)	17	(22.7)	16	(19.8)
retired	23	(31.9)	23	(30.7)	33	(40.7)
Body mass index (kg/m^2)	28	(25–31)	28	(25–28)	28	(27–30)
Clinical characteristics						
Diagnosis						
depressive episode (F32)	13	(18.1)	18	(24.0)	8	(9.9)
recurrent depressive disorder (F33)	59	(81.9)	57	(76.0)	73	(90.1)
Duration of MDD (years), median (IQR)	10	(5–17)	7	(3–13)	9	(3–14)
Number of previous psychiatric hospitalizations, median (IQR)	3	(1–8)	3	(1–7)	4	(1–9)
Pharmacotherapy in the present episode						
SSRI	28	(38.9)	32	(42.7)	30	(37.0)
SNRI	32	(44.4)	31	(41.3)	28	(34.6)
Other antidepressants	20	(27.8)	14	(18.7)	21	(11.1)
Antipsychotics	15	(20.8)	15	(20.0)	12	(14.8)
Benzodiazepines	29	(40.3)	24	(32.0)	25	(30.9)

Data are presented as number (percentage) of participants if not stated otherwise.
Abbreviations: IQR = interquartile range; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin and norepinephrine reuptake inhibitors.

patients with mild depression (HAM-D17 < 17) or other socio-demographic and clinical characteristics.

Both HF-rTMS modalities and standard pharmacotherapy were significantly superior to the standard pharmacotherapy alone (Table 2, Fig. 2). In both ITT and PP analysis, after the adjustment for all pre-planned confounders the baseline to endpoint change in the HAMD-17 score yielded a significant main effect of treatment group favoring the H1-coil over the figure-8-coil ($F_{1,132} = 3.97$; $P = 0.05$; $\eta^2 = 0.03$). This finding was confirmed by the sensitivity analysis (Mann-Whitney test, $U = 1780$; $Z = -2.41$; $P = 0.02$; $r = -0.20$).

The response rate (HAM-D17 ≥ 50% decrease) was significantly better in H1-coil and standard pharmacotherapy than in 8-coil and standard pharmacotherapy group after the adjustment for all pre-planned confounders, and in both ITT and PP analysis. The odds ratio for response in ITT analysis of H-1 coil group compared to the referent 8-coil group was OR = 2.33; $CI_{95\%}$ 1.04–5.21; P = 0.04. Responders were 48/72 (67%; CI95% 55–78%) in the H1-coil, 44% (CI95% 33–56%) in the 8-coil, and 24% (CI95% 15–35%) in the control group. In H1-coil and standard pharmacotherapy group, the response rate was significantly better compared with control (Table 2, Fig. 3). The odds ratio for response was OR = 9.29; CI95% 3.29–26.26 in H1-coil and standard pharmacotherapy compared to the control. Odds ratio for response was not significantly different between 8-coil and the control group; OR = 2.09; CI95% 0.87–5.06; P = 0.10.

There was no significant differences in the change of WHOQOL-BREF score between the three study groups (Table 2).

The safety population consisted of all enrolled patients who received at least one application of treatment (H1-coil n = 69; 8-coil n = 74); 96% (137/143) of these completed all treatments. Both HF-rTMS modalities were generally well tolerated, and for the 143 patients who received at least one session, no serious adverse events were reported. A headache was the most prevalent adverse event in both groups, reported by 15 (20%) patients in the 8-coil, and 20 (29%) in the H1-coil group. Within the H1-coil group, 3 (4%) patients reported application site discomfort, 5 (7%) application site pain, 8 (12%) muscle twitching/spasms or jaw pain, 4 (6%) lightheadedness or dizziness, and 5 (7%) insomnia. Within the 8-coil group, 1 (1%) patient reported application site discomfort, 2 (3%) lightheadedness or dizziness, 1 (1%) anxiety, and 5 (7%) insomnia; no patients in this group reported application site pain or muscle twitching. Within the control group (n = 80), 3 (4%) patients reported headache, 1 (1%) dizziness, 2 (3%) anxiety, 2 (3%) fatigue, 1 (1%) nausea and 4 (5%) insomnia.

4. Discussion

To the best of our knowledge, the present study is the first pragmatic, RCT assessing the antidepressant effects between two conventional FDA approved protocols of these two rTMS modalities. The results of this industry-independent, randomized controlled, single-blinded, single-center study showed that two HF-rTMS FDA-approved protocols with the H1-coil and standard pharmacotherapy and the figure-8-coil and standard pharmacotherapy are both effective as augmentative treatment for TRD MDD in a population of patients recruited from clinical practice. The results demonstrated a remission rate of 60% in the H1-coil and standard pharmacotherapy and 43% in the 8-coil and standard pharmacotherapy group in the intention-to-treat population, compared to 11% in the control group treated with pharmacotherapy alone at endpoint. Although the primary outcome did not separate significantly the two TMS protocols, secondary analyses support a significantly greater efficacy of HF-rTMS delivered using the H1-coil compared with figure-8-coil in a population of MDD patients, although H1-coil protocol uses a smaller number of pulses and has a shorter duration of session. Both HF-rTMS modalities were comparably safe with no dropouts for the adverse events.

Reduction of HAM-D17 scores and the remission rate in both HF-rTMS groups, were somewhat higher than in the multicenter studies that compared the efficacy of HF-rTMS and sham monotherapy (Levkovitz et al., 2015; O'Reardon et al., 2007). These differences could primarily be explained by the differences in study interventions. More importantly, these studies were multicenter double-blind, sham-controlled trials and in such studies, the efficacy results are usually lower, in part due to the increased variance introduced by multiple study sites.

Table 2
Outcomes of H1-coil compared to 8-coil and control group.

	H1-coil (n = 72)					8-coil (n = 75)					Control (n = 81)						
	Baseline		After 4 weeks	Δ	Δ%	Baseline		After 4 weeks	Δ	Δ%	Baseline		After 4 weeks	Δ	Δ%	p1	p2	p3
Intention-to-treat population																		
Primary outcome																		
Remission (≤7), n (%)	0	(0.0)	43	(59.7)		0	(0.0)	32	(42.7)		0	(0.0)	9	(11.1)		0.17	< 0.001	0.001
Secondary outcomes																		
HAM-D17, mean (SD)	17	(5.4)	7	(5.6)	−10	17	(5.4)	10	(6.9)	−7	18	(6.2)	15	(6.4)	−3	−17%	0.05	< 0.001	0.003
Response (≥50% decrease), n (%)			48	(66.7)				33	(44.0)				19	(23.5)			0.04	< 0.001	0.10
WHOQOL-BREF, mean (SD)	49	(12.5)	49	(11.5)	0	48	(12.7)	49	(14.0)	1	46	(13.6)	45	(13.8)	−1	−2%	0.47	0.69	0.95
Per-protocol population[a]																		
Primary outcome																		
Remission (≤7), n (%)	0	(0.0)	42	(64.6)		0	(0.0)	31	(43.1)		0	(0.0)	9	(12.5)		0.06	< .001	0.002
Secondary outcomes																		
HAM-D17, mean (SD)	17	(5.3)	6	(5.1)	−11	17	(5.4)	10	(6.9)	−7	19	(6.1)	14	(6.6)	−5	−26%	0.01	< 0.001	0.02
Response (≥50% decrease), n (%)			47	(72.3)				32	(44.4)				19	(26.4)			0.01	0.001	0.27
WHOQOL-BREF, mean (SD)	48	(12.4)	50	(11.4)	2	47	(13.0)	49	(13.9)	2	45	(13.3)	45	(14.2)	0	0%	0.92	0.93	0.65

Abbreviations: HAM-D17 = Hamilton Depression Scale; SD = standard deviation; WHOQOL-BREF = Word Health Organization Quality of Life Brief Questionnaire dimensions; Δ = absolute difference between the baseline and measurement after 4 weeks; Δ% = relative difference calculated as absolute difference divided by the baseline value; p = for remission and response: multivariate binary logistic regression; for the change in HAM-D17, and WHOQOL-BREF: analysis of covariance; all statistical significances are adjusted for baseline values of the respective outcomes and for age, gender, education, marital status, working status, diagnosis, duration of illness, particular antidepressants, antipsychotics, benzodiazepines; p_1 = comparison of H1-coil and figure-8-coil; p_2 = comparison of H1-coil and control; p_3 = comparison of figure-8-coil and control.

[a] Sample sizes in per-protocol analysis: H1-coil n = 65, 8-coil n = 72, control n = 72.

Fig. 2. HAM-D17 score at baseline and at 4th week follow up in intention-to-treat population; error bars represent 95% confidence intervals.

Fig. 3. Response and remission rates in intention-to-treat population; error bars represent 95% confidence intervals; star represent significant difference between H1-coil and figure-8-coil.

In addition, the baseline HAM-D17 scores in this study were lower relative to the sham-controlled multi-center studies. It should be pointed out that patients included in our study had lower HAM-D17 baseline mean score than those in previous large, multi-center TMS studies (Levkovitz et al., 2015; O'Reardon et al., 2007). Therefore, it is possible that the higher remission rates in both groups resulted from the fact that these were patients with less severe MDD.

On the other hand, a sample of patients with less severe MDD might have decreased the sensitivity of the study to detect differences between the experimental groups. Finally, we did not use a sham-control TMS coil so the outcomes we observed might be somewhat overoptimistic due to placebo effects caused by the differences in additional clinical attention and number of meetings in both TMS groups compared to our pharmacotherapy control group. Our main clinical findings compare well to those reported by previous open-label HF-rTMS trials (Berlim et al., 2014; Filipcic et al., 2017). The remission rate of 19% after the treatment with HF-rTMS found by Brunoni et al. in their meta-analysis is not comparable to our study as the approximate mean number of TMS sessions was 13 in the 29 included studies, which is markedly lower than in our trial (Brunoni et al., 2017). Nevertheless, results of this study are similar to the first meta-analysis exploring the efficacy of augmentative HR-rTMS for TRD (Liu et al., 2014).

We did not observe any significant change in the patients' overall quality of life; and thus could not confirm findings from previous studies which reported significant improvements after a 4-week treatment (Janicak et al., 2013; Solvason et al., 2014). However, our results are in accordance with the results of our previous open-label study with figure-8-coil (Filipcic et al., 2017).

Furthermore, although not specifically designed to address questions about rTMS tolerability, the high retention rate (93%) observed in our study and the absence of serious adverse events underscore the

safety profile associated with both rTMS modalities. In addition, we did not observe any relevant differences in tolerability between the two HF-rTMS groups. The all-cause discontinuation rate for treatment with figure-8-coil and H1-coil was comparable to previous studies(Downar et al., 2016; Levkovitz et al., 2015). The standard pharmacotherapy all-cause discontinuation rate of 11.1% was comparable with both rTMS modalities.

We followed an FDA-approved and commonly performed protocol for both modalities; the treatment session duration in the H1-coil group was 20-min, compared to 40-min in the 8-coil group. The shorter duration of treatment sessions with H1-coil may have some advantages in clinical practice (e.g., the number of patients treated per device may be doubled, more practical for patient and medical staff). In addition, although the standard H1-coil protocol uses a smaller number of pulses and has a shorter duration of session, it seems to induce a clinical effect that is at least of the same magnitude, and is in fact likely to be greater, as indicated by our outcome measures.

It is important to recognize that we did not match treatment parameters of rTMS modalities (pulse frequency, number of pulses per session, train duration, etc.) because our study was pragmatic, with an intent to assess the effectiveness of commonly used FDA-approved protocols in clinical practice.

Our study had several important strengths, as well as limitations. Among the former, it is worth noting that the study is manufacturer-independent, and free of any commercial incentives to investigators or patients. rTMS treatment of MDD in Croatia is reimbursed by the National Insurance Fund and available for all patients by indication. Advertisement of drugs and medical treatments such as TMS to the general population and patients is not allowed in Croatia. Patients represent a consecutive series of individuals with an MDD diagnosis seen at a public hospital. Treatment was delivered in a regular care setting, and evaluations were carried out by blinded raters. Because of these factors, our efficacy findings may approach those of effectiveness in a real-world clinical setting. Our control condition has limitations. Patients treated with either of the rTMS modalities were monitored daily, while the control group was monitored only at baseline and after the 4-weeks of treatment. This difference in the number of visits might have induced a bias against the null hypothesis. For this reason, our findings might overestimate the efficacy of both TMS interventions. Optimally controlling for this would have required a sham coil, of a configuration that could control for both active devices. This was not available. Further limitations are the lack of longer-term outcomes and neurocognitive assessments. Also, this was a single-center trial, which may reduce the generalizability of our findings. A more substantive study, presumably to be conducted on a multi-site basis, is clearly required to definitively demonstrate the superior efficacy of a H1-coil over figure-8-coil.

Another potential strength is the use of a scalp-measurement-based heuristic known as BeamF3 which has been made available in a free online tool as this is feasible or cost-efficient for most rTMS clinics.

In conclusion, we report the augmentative HF-rTMS treatment resulted in increased response and remission rates at the end of acute treatment. These effects were favorable compared to short-term efficacy of other treatment approaches, especially considering the high level of treatment resistance of this population. These findings suggest an additive and clinically meaningful effect of concurrent HF-rTMS and pharmacotherapy greater than either treatment alone. We also found evidence that HF-rTMS FDA-approved protocol for treatment-resistant depression, delivered with the H1-coil may be more effective for treatment of MDD severity than with a figure-8-coil, although it uses a smaller number of pulses and has a shorter duration of session. While some questions remain for future studies, clear clinical implications can already be derived from these findings. Firstly, both modalities of HF-rTMS can be safely combined with pharmacotherapy to achieve a higher likelihood of remission. Secondly, both HF-rTMS modalities are equally safe and tolerable.

4.1. Contributors

IF and IŠF conceived and designed the study. All authors provided on the study design and data interpretation. ŽM, SS, and TG provided medical care and determined the motor thresholds of participants. ŽB, IF and IŠF developed the plan for statistical analysis. ŽB completed the statistical analysis. IF, IŠF, ŽB and EI drafted the paper. All other authors provided critical revision of the manuscript. IF had final responsibility for submission of the manuscript.

Declaration of interests

No financial relationships with commercial interests.

Funding

Psychiatric Hospital “Sveti Ivan”, Zagreb, Croatia.

Role of the funding source

The funding sources had no role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication. The corresponding author (IF) and statistician (ŽB) had full access to all the data and the corresponding author (IF) had final responsibility for the decision to submit for publication.

Acknowledgments

Authors wish to acknowledge the work of all patients, physicians, and medical nurses who took part in the data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.04.020.

References

Berlim, M.T., Van den Eynde, F., Tovar-Perdomo, S., Chachamovich, E., Zangen, A., Turecki, G., 2014. Augmenting antidepressants with deep transcranial magnetic stimulation (DTMS) in treatment-resistant major depression. World J. Biol. Psychiatr. 15, 570–578. https://doi.org/10.3109/15622975.2014.925141.

Boutron, I., Moher, D., Altman, D.G., Schulz, K.F., Ravaud, P., CONSORT Group, 2008. Extending the CONSORT statement to randomized trials of nonpharmacologic treatment: explanation and elaboration. Ann. Intern. Med. 148, 295–309.

Brunoni, A.R., Chaimani, A., Moffa, A.H., Razza, L.B., Gattaz, W.F., Daskalakis, Z.J., Carvalho, A.F., 2017. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA psychiatry 74, 143–152. https://doi.org/10.1001/jamapsychiatry.2016.3644.

De Carlo, V., Calati, R., Serretti, A., 2016. Socio-demographic and clinical predictors of non-response/non-remission in treatment resistant depressed patients: a systematic review. Psychiatr. Res. 240, 421–430. https://doi.org/10.1016/j.psychres.2016.04.034.

Development of the World Health Organization WHOQOL-BREF quality of life assessment The WHOQOL Group, 1998. Psychol. Med. 28, 551–558.

Downar, J., Blumberger, D.M., Daskalakis, Z.J., 2016. Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression. CMAJ (Can. Med. Assoc. J.) 188, 1175–1177. https://doi.org/10.1503/cmaj.151316.

Feifel, D., 2017. Network meta-analysis in mental Health research. JAMA psychiatry 74, 850–851. https://doi.org/10.1001/jamapsychiatry.2017.1164.

Filipcic, I., Milovac, Z., Sucic, S., Gajsak, T., Filipcic, I.S., Ivezic, E., Aljinovic, V., Orgulan, I., Penic, S.Z., Bajic, Z., 2017. Efficacy, safety and tolerability of augmentative rtms in treatment of major depressive disorder (mdd): a prospective cohort study in Croatia. Psychiatr. Danub. 29.

Filipcic, I., Šimunović Filipčić, I., Gajšak, T., Milovac, Ž., Sučić, S., Ivezić, E., S, Z.P., I, O., I, Š., Bajić, Ž., Jeleč, V., 2018. Efficacy and safety of repetitive transcranial magnetic stimulation using an H1-coil or figure-8-coil in the treatment of unipolar major depressive disorder: a study protocol for a randomized controlled trial. Psychiatr. Danub. 30, 79–84.

George, M.S., Lisanby, S.H., Avery, D., McDonald, W.M., Durkalski, V., Pavlicova, M.,

Anderson, B., Nahas, Z., Bulow, P., Zarkowski, P., Holtzheimer, P.E., Schwartz, T., Sackeim, H.A., 2010. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch. Gen. Psychiatr. 67, 507–516. https://doi.org/10.1001/archgenpsychiatry.2010.46.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23.

Janicak, P.G., Dunner, D.L., Aaronson, S.T., Carpenter, L.L., Boyadjis, T.A., Brock, D.G., Cook, I.A., Lanocha, K., Solvason, H.B., Bonneh-Barkay, D., Demitrack, M.A., 2013. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of quality of life outcome measures in clinical practice. CNS Spectr. 18, 322–332. https://doi.org/10.1017/S1092852913000357.

Kedzior, K.K., Gellersen, H.M., Brachetti, A.K., Berlim, M.T., 2015. Deep transcranial magnetic stimulation (DTMS) in the treatment of major depression: an exploratory systematic review and meta-analysis. J. Affect. Disord. 187, 73–83. https://doi.org/10.1016/j.jad.2015.08.033.

Lefaucheur, J.-P., André-Obadia, N., Antal, A., Ayache, S.S., Baeken, C., Benninger, D.H., Cantello, R.M., Cincotta, M., de Carvalho, M., De Ridder, D., Devanne, H., Di Lazzaro, V., Filipović, S.R., Hummel, F.C., Jääskeläinen, S.K., Kimiskidis, V.K., Koch, G., Langguth, B., Nyffeler, T., Oliviero, A., Padberg, F., Poulet, E., Rossi, S., Rossini, P.M., Rothwell, J.C., Schönfeldt-Lecuona, C., Siebner, H.R., Slotema, C.W., Stagg, C.J., Valls-Sole, J., Ziemann, U., Paulus, W., Garcia-Larrea, L., 2014. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin. Neurophysiol. 125, 2150–2206. https://doi.org/10.1016/j.clinph.2014.05.021.

Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S.H., Bystritsky, A., Xia, G., Tendler, A., Daskalakis, Z.J., Winston, J.L., Dannon, P., Hafez, H.M., Reti, I.M., Morales, O.G., Schlaepfer, T.E., Hollander, E., Berman, J.A., Husain, M.M., Sofer, U., Stein, A., Adler, S., Deutsch, L., Deutsch, F., Roth, Y., George, M.S., Zangen, A., 2015. Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. World Psychiatr. 14, 64–73. https://doi.org/10.1002/wps.20199.

Levkovitz, Y., Roth, Y., Harel, E.V., Braw, Y., Sheer, A., Zangen, A., 2007. A randomized controlled feasibility and safety study of deep transcranial magnetic stimulation. Clin. Neurophysiol. 118, 2730–2744. https://doi.org/10.1016/j.clinph.2007.09.061.

Liu, B., Zhang, Y., Zhang, L., Li, L., 2014. Repetitive transcranial magnetic stimulation as an augmentative strategy for treatment-resistant depression, a meta-analysis of randomized, double-blind and sham-controlled study. BMC Psychiatry 14, 342. https://doi.org/10.1186/s12888-014-0342-4.

McClintock, S.M., Reti, I.M., Carpenter, L.L., McDonald, W.M., Dubin, M., Taylor, S.F., Cook, I.A., O'Reardon, J., Husain, M.M., Wall, C., Krystal, A.D., Sampson, S.M., Morales, O., Nelson, B.G., Latoussakis, V., George, M.S., Lisanby, S.H., National Network of Depression Centers rTMS Task Group, American Psychiatric Association Council on Research Task Force on Novel Biomarkers and Treatments, 2017. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J. Clin. Psychiatry. https://doi.org/10.4088/JCP.16cs10905.

Milev, R.V., Giacobbe, P., Kennedy, S.H., Blumberger, D.M., Daskalakis, Z.J., Downar, J., Modirrousta, M., Patry, S., Vila-Rodriguez, F., Lam, R.W., MacQueen, G.M., Parikh, S.V., Ravindran, A.V., CANMAT Depression Work Group, 2016. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 4. Neurostimulation treatments. Can. J. Psychiatr. 61, 561–575. https://doi.org/10.1177/0706743716660033.

Murphy, J.A., Sarris, J., Byrne, G.J., 2017. A review of the conceptualisation and risk factors associated with treatment-resistant depression. Depress. Res. Treat. 2017, 4176825. https://doi.org/10.1155/2017/4176825.

O'Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., McDonald, W.M., Avery, D., Fitzgerald, P.B., Loo, C., Demitrack, M.A., George, M.S., Sackeim, H.A., 2007. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol. Psychiatry 62, 1208–1216. https://doi.org/10.1016/j.biopsych.2007.01.018.

Perera, T., George, M.S., Grammer, G., Janicak, P.G., Pascual-Leone, A., Wirecki, T.S., 2016. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimul 9, 336–346. https://doi.org/10.1016/j.brs.2016.03.010.

Roth, Y., Amir, A., Levkovitz, Y., Zangen, A., 2007. Three-dimensional distribution of the electric field induced in the brain by transcranial magnetic stimulation using figure- 8 and deep H-coils. J. Clin. Neurophysiol. 24, 31–38. https://doi.org/10.1097/WNP.0b013e31802fa393.

Roth, Y., Pell, G.S., Zangen, A., 2017. Network meta-analysis in mental Health research. JAMA psychiatry 74, 851. https://doi.org/10.1001/jamapsychiatry.2017.1161.

Rush, A.J., 2007. STAR*D: what have we learned? Am. J. Psychiatry 164, 201–204. https://doi.org/10.1176/appi.ajp.164.2.201.

Solvason, H.B., Husain, M., Fitzgerald, P.B., Rosenquist, P., McCall, W.V., Kimball, J., Gilmer, W., Demitrack, M.A., Lisanby, S.H., 2014. Improvement in quality of life with left prefrontal transcranial magnetic stimulation in patients with pharmacoresistant major depression: acute and six month outcomes. Brain Stimul 7, 219–225. https://doi.org/10.1016/j.brs.2013.10.008.

World Health Organization, 2016. Depression: Fact Sheet Number 369 [WWW Document].

Zangen, A., Roth, Y., Voller, B., Hallett, M., 2005. Transcranial magnetic stimulation of deep brain regions: evidence for efficacy of the H-coil. Clin. Neurophysiol. 116, 775–779. https://doi.org/10.1016/j.clinph.2004.11.008.