Psychiatria Danubina, 2022; Vol. 34, Suppl. 3, pp 7-9 *Conference paper*

OVERVIEW OF STUDIES ON THE EFFICACY OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION ON THE SEVERITY OF SYMPTOMS OF MAJOR DEPRESSIVE DISORDER, CONDUCTED IN UNIVERSITY PSYCHIATRIC HOSPITAL SVETI IVAN 2016-2022

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SUMMARY

This brief report presents the studies on HF rTMS efficacy on major depressive disorder (MDD) symptoms conducted in University Psychiatric Hospital Sveti Ivan from 2016 to 2022. We assessed the clinically relevant effects of rTMS delivered by H1-coil and the figure-8-coil on MDD symptoms severity in the pooled sample of patients. During the last seven years, we enrolled in the studies on MDD 336 patients with a median (interquartile range; IQR) age of 53 (45-61) years, 181 (54%) of them women. We performed interventions with two different coils (8-coil and H1-coil) at 120% of the motor threshold, approximately half with 10 and half with 18 Hz frequency, and > 90% with one daily session during 20 workdays. We offer considerations on how the bulk of our research informed the future direction of our laboratory's studies and clinical work.

Key words: *transcranial magnetic stimulation - major depressive disorder*

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INTRODUCTION

Depression is a complex condition associated with a great deal of disability and suffering. A high percentage of patients receiving proper antidepressant medication remain treatment resistant to various psychopharmacological interventions (Fagiolini & Kupfer 2003). Adding to available therapeutic strategies for depression, high-frequency (HF) rTMS of the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-8 or an H1-coil (deep TMS) is definitely an efficient method of treatment for depression, with A level evidence of efficacy, approved for treating Major Depressive Disorder (MDD) in adults who have not responded to prior antidepressant medications (Lefaucheur et al. 2020, Perera et al. 2016, Baeken et al. 2016).

University psychiatric hospital „Sveti Ivan" - TMS laboratory has been treating patients suffering from depression with rTMS since the beginning of 2016. In this report, we aim to present the highlights of studies on HF rTMS efficacy on symptoms of MDD conducted in our TMS laboratory in the period 2016-2022, through which the clinically relevant effects on MDD symptoms severity in the pooled sample of patients were assessed. We then discuss how the findings from these studies informed the ongoing and future research and the day-to-day clinical work in our TMS laboratory.

SUBJECTS AND METHODS

All studies were designed with detailed protocols and registered on public clinical trial registries. We conducted all primary analyses in intention-to-treat populations. The primary outcome in all studies was Hamilton Depression Rating Scale-17 (HDRS-17) total score. The secondary outcome was Beck Depression Inventory-II (BDI-II) total score. We analysed the safety and tolerability of the samples of patients who received at least one dose of the planned intervention in all studies, but these data were not presented here. Allocations were concealed from the physicians who enrolled the participants, and outcome assessments were blinded and performed by psychiatrists who did not participate in the interventions. The primary analysis in all studies was multivariable, adjusted mix, within-between subject analysis of covariance. We controlled different important prognostic factors as covariates and regularly corrected the statistical significances using Benjamini-Hochberg procedure with a false discovery rate set at < 5%.

RESULTS

During the last seven years, we enrolled 336 patients with a median (interquartile range; IQR) age of 53 (45-61) years, 181 (54%) of them were women. The majority of participants were included in randomized controlled trials (93%), while the rest were part of prospective cohort

Table 1. Clinical characteristics

	Total, (n=336)	H1-coil, (n=125)	8-coil, (n=107)	Control, (n=104)
Depressive episode (F32), n (%)	75 (23.9)	27 (23.9)	26 (26.3)	22 (21.6)
Recurrent depressive disorder (F33), n (%)	211 (67.2)	78 (69.0)	65 (65.7)	68 (66.7)
Age at onset, median (IQR)	43 (33-52)	41 (27-50)	42 (34-51)	45 (38-53)
Age at onset, n (%)				
<25	32 (10.7)	19 (17.8)	5 (5.6)	8 (7.8)
25-34	49 (16.4)	19 (17.8)	19 (21.1)	11 (10.8)
35-44	85 (28.4)	25 (23.4)	29 (32.2)	31 (30.4)
45-54	83 (27.8)	29 (27.1)	23 (25.6)	31 (30.4)
55-64	44 (14.7)	12 (11.2)	13 (14.4)	19 (18.6)
≥65	6 (2.0)	3 (2.8)	1 (1.1)	2 (2.0)
Duration of disorder (years), median (IQR)	8 (3-16)	9 (4-17)	7 (3-16)	7 (2-12)
Duration of disorder (years), n (%)				
≤1	49 (15.6)	10 (8.8)	18 (18.4)	21 (20.6)
2-4	62 (19.7)	22 (19.3)	18 (18.4)	22 (21.6)
5-9	62 (19.7)	25 (21.9)	19 (19.4)	18 (17.6)
10-19	87 (27.7)	35 (30.7)	29 (29.6)	23 (22.5)
≥20	54 (17.2)	22 (19.3)	14 (14.3)	18 (17.6)
HDRS-17 at baseline, median (IQR)	18 (13-22)	19 (15-23)	17 (13-20)	17 (13-22)
HDRS-17 at baseline, n (%)				
mild (≤13)	82 (26.2)	27 (23.7)	29 (29.0)	26 (26.3)
moderate (14-18)	92 (29.4)	28 (24.6)	34 (34.0)	30 (30.3)
severe (19-22)	71 (22.7)	30 (26.3)	20 (20.0)	21 (21.2)
very severe (≥23)	68 (21.7)	29 (25.4)	17 (17.0)	22 (22.2)
BDI-II at baseline, median (IQR)	27 (19-37)	26 (17-35)	27 (22-37)	29 (19-38)
BDI-II at baseline, n (%)				
mild (≤20)	85 (28.1)	37 (33.3)	22 (22.2)	26 (28.0)
moderate (21-30)	97 (32.0)	33 (29.7)	37 (37.4)	27 (29.0)
severe (31-40)	73 (24.1)	23 (20.7)	27 (27.3)	23 (24.7)
extreme (≥41)	48 (15.8)	18 (16.2)	13 (13.1)	17 (18.3)

Abbreviations: IQR - interquartile range; HDRS-17 - Hamilton Depression Rating Scale-17; BDI-II - Beck Depression Inventory-II

and non-randomized historical control studies. More than two-thirds (211 (67%)) of participants were diagnosed with recurrent depressive disorder. The median (IQR) duration of MDD was 8 (3-16) years, and 204 (65%) of patients had at least one psychiatric comorbidity. The most frequent comorbidities were neurotic, stress-related somatoform disorders, adult personality and behaviour disorder, and organic mental disorders. Two-thirds of patients (211 (63%)) participated in randomized controlled trials, 93 (28%) in prospective cohort studies, and 32 (10%) in non-randomized trials with historical control. Due to the different studies' different eligibility criteria and objectives, in total, we enrolled patients with baseline median (IQR) HDRS-17 of 18 (13-22), 68 (22%) with very severe MDD, 71 (23%) with severe, 92 (29%) with moderate and 82 (26%) with mild MDD symptoms severity (Table 1).

We allocated in random or non-random fashion 125 (37%) patients in the treatment arm with H1-coil, 107 (32%) with 8-coil, and 104 (31%) in control groups not treated with active HR rTMS but with a sham-coil or standard therapy only. We performed all interventions at 120% of the motor threshold, approximately half with 10 and a half with 18 Hz frequency and > 90% with one daily session during 20 workdays.

DISCUSSION

We reported how the augmentative HF-rTMS treatment resulted in increased response and remission rates at the end of acute treatment of depression, which was favorable compared to the efficacy of other treatment approaches, especially considering how often the resistance is in this population (Filipčić et al. 2019). All rTMS protocols as an adjunct to standard-of-care pharmacotherapy was superior to treatment with standard pharmacotherapy alone across our studies.

Our results showed significantly better response rates with H1-coil treatment relative to 8- coil treatment in 228 patients with major depressive disorder, though the study found no differences in remission rates (Filipčić et al. 2019). Besides using the H1-coil regularly in our clinical work, we are researching on comparing the efficiency between the H1 and the newer, H7-coil and sham coil. The H7-coil (and its stimulation target) are significantly different from the H1-coil, and is cleared for the treatment of refractory MDD (Tringali et al. 2012). Through our future research, we will contribute to explain the benefit of deep TMS treatment of MDD with the H7-coil.

Accelerated rTMS protocols are being increasingly studied because of their potential to enhance treatment efficacy and shorten treatment time. We performed the first assessment of the accelerated deep TMS protocol with H1-coil (Filipčić et al. 2021). Our research found that the accelerated deep TMS with an H1-coil regimen twice daily for 10 days or 15 days can be a safe and effective alternative for the treatment of MDD (Filipčić et al. 2021). With future larger randomized sham-controlled trials, we aim to determine whether a course of this accelerated protocol is equally effective and tolerable as the standard dTMS protocol, using both the H1 and the H7- coil. In our future work, we also aim to investigate how the *theta-burst* stimulation might show similar results and efficiency, as previously demonstrated with both 8-coil and deep TMS.

Our investigative efforts were focused on identifying reliable characteristics for selecting of optimal parameters for treatment and the prediction of outcome to establish rTMS as a safe and efficient treatment for the increased number of patients suffering from depression (Milovac et al. 2017). We demonstrated that in women, the reduction of symptoms over treatment with 8-coil TMS was more effective than in the group of men when combined with antidepressants (Milovac 2021). In our future research, we will try to produce protocol adjustments, considering the hormonal status of our patients, primarily investigating how the status of sex hormones (along with other covariates) may or may not confound the efficiency of rTMS as treatment method.

Our previous studies provided new insight for deep TMS approaches for possible future avenues to treat depression, but also other indications, especially anxious depression, OCD, negative symptoms in schizophrenia, addiction, anorexia/bulimia and PTSD, as well as neurological conditions, including tinnitus, multiple sclerosis and post-CVI neuropathic pain (Lefaucheur et al. 2012, 2020, Isserles et al. 2021, Pell et al. 2022).

CONCLUSION

To conclude, major developments are to be expected through the work of our laboratory, including innovative stimulation patterns, targets, and coils; treatment of specific populations, and combinatory treatments and personalization and stratification of rTMS parameters.

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Acknowledgements: None

Conflict of interest: None to declare.

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