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Original Research

Comparing the Effect of Repetitive Transcranial Magnetic Stimulation Therapy and Aerobic Exercise as an Add-on Therapy on the Cognitive Function of Patients with Depression

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ABSTRACT

Background: Cognitive disturbances are a major cause of disability in depression. The antidepressant medication effectively improves cognitive function. However, its adverse effect limits its use, so add-on treatment is needed to support its effectiveness.

Aim: This study aims to compare the efficacy of aerobic exercise and repetitive transcranial magnetic stimulation (rTMS) as an add-on treatment for improving cognitive function.

Material and Methods: Twenty-seven patients with first episodes of moderate and severe depression were recruited from the outpatient psychiatry clinic to join this randomized controlled trial. Participants were allocated to three groups: antidepressant only, antidepressant with add-on aerobic exercise, and antidepressant with add-on rTMS therapy. All participants received 2 weeks of intervention. Cognitive functions were assessed using *Montreal Cognitive Assessment* (MOCA).

Results: No differences were found in baseline characteristic data between groups. Total MOCA score increased after intervention in a group with no add-on treatment (p=0.007), with add-on aerobic exercise (p=0.011), and with add-on rTMS therapy (p=0.017). Hence, there was no between-group difference (p=0.222). The MOCA subtest analysis revealed between-group differences in changes in delayed recall subtest score (p=0.01). The group with add-on rTMS therapy improved better than the group with antidepressants only (p=0.005).

Conclusion: The addition of rTMS therapy resulted in better improved delayed recall function than the addition of aerobic exercise or without any add-on treatment. This finding supports the application of rTMS therapy as an add-on treatment to improve the cognitive function of patients with depression.

Keywords: *transcranial magnetic stimulation, antidepressant, aerobic exercise, depression, cognitive.*

INTRODUCTION

Depression is ranked first as a cause of disability and third in the global burden of disease in the world, exceeding the burden caused by other diseases such as cerebrovascular disease and coronary heart disease.[1] More than 300 million people worldwide suffer from depression. There are about early five percent of the world's population and one-third are from Southeast Asia.[2] Suffering from depression was the most outpatient visitor in the psychiatric clinic, dr. Soetomo Academic General Hospital. Depression is a frequent comorbid of chronic physical illnesses aggravating dysfunction and disability.[3,4]

Cognitive deficit is considered one of the factors causing decreased functional capacity and disability in people with depression, and is often associated with disrupted brain circuitry.[5,6,7] The prescription of antidepressants as a standard treatment effectively improves cognitive function. However, their use are limited due to occurrence of adverse effects, primarily in high doses prescription.[8,9] This findings highlight the need of supporting therapy to improve the cognitive function deficits so that decreased functional activity and the onset of disabilities can be prevented. Two modalities that have been previously studied as adjunctive therapy in the management of depression are repetitive transcranial magnetic stimulation (rTMS)[10,11,12] and aerobic exercise.[13] Repetitive TMS therapy is known to improve cognitive function by increasing levels of brain-derived neurotrophic factor (BDNF) and increasing the neurotransmitter monoamine, which is commonly disrupted in depression.[10] The use of rTMS has been recommended as a safe and effective therapeutic tool for depression cases by various institutions.[11,12] In addition, aerobic exercise is also known to improve cognitive function in patients with depression through the mechanism of increasing brain-derived neurotrophic factor levels, increasing monoamine neurotransmitters, and decreasing hyperactivity of the hypothalamus-pituitary-adrenal (HPA) axis.[13,14,15]

There has not yet been a study that contrasts the benefits of aerobic exercise and rTMS therapy when used in conjunction with antidepressant, particularly in Indonesia. Thus, researchers intend to compare the effectiveness of adding rTMS therapy and aerobic exercise to antidepressant on the cognitive function of patients with depression.

MATERIAL AND METHODS

Participants for this randomized controlled trial were sampled from patients in the outpatient psychiatry clinic of Dr. Soetomo Academic General Hospital. Inclusion criteria were males and females, aged between 21 - 59 years old, with clinical signs of first episode major depressive disorder in moderate or severe level. Patients with poor state of general health, history of seizures, metal implants, visual disturbance, balance disturbance, lower extremity problems, or pregnancy were excluded. Twenty-seven selected participants agreed to give consent and were recruited into the study. Participants were randomly assigned to receive 2 weeks of either antidepressant only, antidepressant with add-on rTMS therapy, or antidepressant with add-on aerobic exercise.

Participants in the group with add-on rTMS therapy received 10 sessions of rTMS therapy using Neuro MS/D TMS device. Each treatment session was begun by determining the resting motor threshold (RMT) area and intensity. Each subject received 3000 pulses of stimulation per session, delivered in 75 trains of 10 Hz rTMS stimulation at 120% of RMT to the left dorsolateral prefrontal cortex (DLPFC). Each train lasted 4s with 26s inter-train interval. Participants in the group with add

on aerobic exercises were asked to exercise using Monark Ergometer static cycle. Each exercise session consisted of 5 minutes of warm up phase, 20 minutes of training phase with moderate intensity (65-75% of maximum heart rate), and 5 minutes of cool down phase.

The study's outcome was evaluated using *Montreal Cognitive Assessment* (MOCA).[16] *Montreal Cognitive Assessment* has a sensitivity value of 0.9 and a specificity value of 0.87 in detecting cognitive disorders. The test components included assessments of delayed recall, visuospatial, executive function, attention, language skills, and time and place orientation.[17] The level of depression severity was assessed using the *Hamilton Depression Rating Scale* (HDRS). HRDS is a standard instrument commonly used to measure the therapeutic effect of antidepressants.[17] The HDRS instrument included variables assessed to affect depression, including depressive mood, guilt, suicidal thoughts, work and interest disorders, insomnia (early, middle, delayed), retardation, agitation, anxiety (psychological, somatic), symptoms. gastrointestinal somatic symptoms, genital somatic symptoms, hypochondriasis, insight, and weight loss.[17] Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS version 20.0). The characteristics baseline was compared using analysis of variance (ANOVA) and Kruskal Wallis Test.

We evaluated the differences in the MOCA test before and after the treatment of both groups using Paired T-Test and Wilcoxon Signed Rank Test. We compared the MOCA test's between-group differences (delta) using ANOVA and the Kruskal Wallis Test. The differences were considered statistically significant at $p<0.05$. Ethical clearance was provided by ethical committee of Dr. Soetomo Academic General Hospital, number 1304/KEPK/VII/2019.

RESULTS

Twenty-four subjects completed the study. Three participants dropped out for not attending one or more therapy sessions for various reasons; two from the group with add-on rTMS, and one from the aerobic exercise. The homogeneity test of subjects' characteristics (age, sex, educational level) across groups found no significant differences. Baseline characteristic data showed no difference between the three groups in terms of age, sex, education level, and HDRS score; therefore, these characteristics may not influence the result. The MOCA score before intervention showed cognitive impairment (score<26) in all groups but no difference across groups.

Table 1. Baseline characteristics

Characteristics	Group			Total	P
	Antidepressant	Antidepressant + aerobic exercise	Antidepressant + rTMS therapy		
Mean age (years)	30 ±8.66	28.38 ±11.083	35.43 ±12.218	31.04 ±12.218	0.231
Sex					0.56
Male	1 (11.1%)	0	1 (14.3%)	2 (8.3%)	
Female	8 (88.9%)	8 (100%)	6 (85.7%)	22 (91.7%)	
Education					0.135
Primary school	1 (11.1%)	0	0	1 (4.2%)	
Junior high school	0	1 (12.5%)	0	1 (4.2%)	
Senior high school	6 (66.7%)	6 (75%)	3 (42.9%)	15 (62.5%)	
Undergraduate	2 (22.2%)	1 (12.5%)	4 (57.1%)	7 (29.2%)	
HDRS	23 ±5.074	25.5 ±5.928	30.57 ±7.721	26.04 ±6.721	0.073

HDRS= Hamilton Depression Rating Scale

Table 2. Comparison of MOCA score before and after intervention

Groups	Pre (*Mean*±SD)	Post (*Mean*±SD)	P
Antidepressant	23.78±3.032	26.56±1.333	0.007*
Antidepressant + aerobic exercise	23.75±1.909	27.13±0.354	0.011*
Antidepressant + rTMS therapy	23.43±1.272	27.29±0.488	0.017 *
P	0.43		

MOCA = Montreal Cognitive Assessment; * p < 0.005

Table 3. Between-group comparison of delta total MOCA score

Group	Δ MOCA
Δ Antidepressant	2.56±1.590
Δ Antidepressant + aerobic exercise	3.38±1.847
Δ Antidepressant + rTMS therapy	3.86±1.345
P	0.222

MOCA = Montreal Cognitive Assessment

Table 4. Between-group comparison of delta MOCA subtest score

Δ MOCA subtest	Groups			p
	Antidepressant	Antidepressant + aerobic exercise	Antidepressant + rTMS therapy	
Δ Visuospacial	0	0.13±0.354	0.14±0.378	0.53
Δ Naming	0	0	0	1
Δ Language	0.11±0.333	0.13±0.354	0	0.647
Δ Abstraction	0.11±0.333	0	0	0.435
Δ Delayed recall	0.44±0.527	1±0.756	1.86±0.9	0.01*
Δ Orientation	0.11±0.333	0.25±0.463	0.29±0.488	0.664
Δ Attention	1.78±0.667	1.88±0.641	1.57±0.535	0.645

MOCA = *Montreal Cognitive Assessment*; * p < 0.05

There was a significant increase in total MOCA score in the group receiving antidepressant only (from 23.78 ± 3.032 to 26.56 ± 1.333, p=0.007), the group receiving

the combination of antidepressant and rTMS therapy (from 23.75 ± 1.909 to 27.13 ± 0.354, p=0.011), and the group receiving the combination of antidepressant and aerobic exercise (from 23.43 ± 1.272 to 27.29 ± 0.488, p=0.017). However, there was no difference in changes in the total MOCA score between the three groups (p=0.222). Further analysis of the subtest of MOCA showed a difference in changes in the delayed recall subtest between groups (p=0.01). Post hoc analysis showed improvement of delayed recall subtest score in the group with additional rTMS therapy was significantly different compared to the group that only had antidepressants (p=0.005).

DISCUSSIONS

Patients with depression are known to experience a decrease in the neurotransmitter monoamine, including serotonin. They play an important role in cognitive function.[18] Nearly, every brain circuit is innervated by the serotonergic system, which is responsible for serotonin production.[19] Based on its importance, the serotonergic system becomes one of the main targets in antidepressant therapy. It inhibits serotonin transport, thereby increasing the number of these neurotransmitters in the synapse cleft.[20] This study showed significant improvement in cognitive function in all groups. It is in line with previous studies that showed cognitive improvements in depression patients either with antidepressant treatment as a single therapy[21] or with a combination of aerobic exercise[22] or TMS therapy.[23]

Further analysis of the MOCA subtest score showed that the group receiving a combination of antidepressant and rTMS therapy improved delayed recall function more than the other two groups. It implies the benefit of rTMS therapy as an add-on treatment. The addition of rTMS therapy in this study improved cognitive function compared to aerobic exercise. This result is in line with Huang,[23] who found that rTMS therapy in the dorsolateral prefrontal cortex (DLPFC) for 2 weeks (frequency 10 Hz, 20 stimulations/session, duration per stimulation 4 seconds, duration between stimulations 56 seconds, intensity 90% resting motor threshold) improved cognitive function test (Trail-Making Test (TMT) and Wisconsin Card Sorting Test (WCST)). After 5 days of rTMS stimulation (frequency 20 Hz, 80% intensity of resting motor threshold, duration of train. 2 seconds, 1 minute inter train duration, 20 trains/session, location of DLPFC area stimulation), Moser et al,[24] also observed an improvement in the results of executive function tests (Stroop Test and Trail-Making Test) in patients with recurrent depression. The mechanism for improving cognitive function after rTMS therapy is associated with increased BDNF, which is associated with increased nerve excitability and synapse efficacy and accelerated signal transmission in the brain,[24] Wang found a significant increase in BDNF levels, activation of tyrosine receptor kinase B (TrkB) and signal transmission between BDNF and TrKB. The relationship between active TrKB and NMDA receptors also increases which are neuroplasticity mediators after rTMS stimulation.[25]

In addition, the magnetic field generated by rTMS over the DLPFC area of the brain induces depolarization in that area, generates an electric current, increases the activity of monoamine neurotransmitters, and activates the circuit,[25] The fact that there was no change in the subtest of language, naming, visuospatial, and abstraction in the groups may be due to the ceiling effect and the inability of MOCA to detect subtle changes in cognitive function. The addition of aerobic exercise to antidepressants in this study failed to provide benefits in cognitive function compared.

This contrasts with Kubesch,[22] who investigated the effects of a single 30-minute aerobic exercise using a stationary bicycle in patients with depression on medication. There was a significant decrease in the mean reaction time of the Stroop test (p = 0.02) and GoNogo (p = 0.048) in the post-aerobic depression patient group. It showed the improvement in cognitive function[22]. In another study, Vasques,[26] found similar results when examining the effects of moderate-intensity aerobic exercise (65-75% maximum heart rate) using a treadmill

for 30 minutes. After the intervention, an increase in attention function and inhibitory control was found, as seen through the results of the Stroop Color-Word Test,[26]. Aerobic exercise is thought to increase Brain-Derived Neurotrophic Factor (BDNF), which plays an important role in neurogenesis and neuroplasticity[27] by increasing the number and activity of platelets,[28] which is the main source of BDNF in the peripheral circulation,[29] The bi-directional nature of BDNF allows BDNF in the peripheral circulation to cross the blood-brain barrier after physical exercise,[30] Aerobic exercise also suppresses hyperactivity of the Hippothalamus-Pituitary-Adrenal (HPA) axis, which indirectly worsens cognitive function through its negative effect on BDNF and stimulates serotonin production,[31] The failure of aerobic exercise in this study to gain similar results may be due to the short term of the study and the patient compliance in following exercise instructions.

CONCLUSIONS

Antidepressants improve general cognitive function as a single therapy or with additional aerobic exercise and rTMS therapy. A combination of antidepressant and rTMS therapy was more statistically significant in improving delayed recall function than a combination of antidepressant and aerobic exercise or antidepressant only. This finding supports the application of rTMS therapy as an add on treatment to improve the cognitive function of patients with depression.

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