Original Research

Comparison of the Effects of Repetitive Transcranial Magnetic Stimulation and Aerobic Exercise as an Adjunct Therapy in Depressed Patients on Activity of Daily Living and Quality of Life

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ABSTRACT

Background: Depression is one of the most common causes of disabilities and poor quality of life worldwide. One-fifth of patients fail to respond to antidepressant therapy. Hence, adjunct therapy is urgently needed.

Aim: This study aims to compare the effectiveness of repetitive transcranial magnetic stimulation (rTMS) and aerobic exercise as adjunct therapy on activity of daily living and quality of life in depressed patients.

Material and Methods: A randomized-controlled experiment was conducted between May 2019 and January 2020. Twenty-seven depressed patients were divided into three groups for two weeks: antidepressant-only, antidepressant-and-aerobic exercise, and antidepressant-and-rTMS. The Barthel Index and SF-36 were used to assess the activity of daily living and quality of life.

Results: After the intervention, there were no appreciable changes in the Barthel Index scores in any of the three groups ($p>0.05$). Following therapy, SF-36 results for physical function, bodily discomfort, public health, vitality, social function, emotional role functioning, and mental health all showed substantial improvements across groups (p 0.05). Patients in the antidepressant and rTMS groups improved more than those in the other two groups in the areas of overall health (15.71±6.075, $p=0.009$), emotional role functioning (20.29±11.940, $p=0.049$), and mental health (14.29±6.075, $p=0.041$). However, the Barthel Index score changes did not differ between groups ($p=0.664$).

Conclusion: Better quality of life improvement in the rTMS group compared to the other two groups supports the use of rTMS as an additional therapy. It aims to enhance quality of life in patients with moderate and severe first-episode depression.

Keywords: *Depression, repetitive transcranial magnetic stimulation, aerobic exercise, the activity of daily living, quality of life.*

Introduction

Depression is one of the biggest causes of disability, creating a global burden.[1] Depression is a frequent comorbid of chronic physical illnesses aggravating dysfunction and disability. More than 300 million people worldwide suffer from depression. Nearly five per cent of the world's population and one-third are from Southeast Asia.[2] There are 9,162,886 or 3.7 % of the population in Indonesia.[2]

Wide ranges of treatment options are available for depression ranging from biological treatments to psychotherapy. Nevertheless, despite all available therapeutic alternatives, a sizeable minority of patients do not improve with these medications, and nearly a fifth still experience depressive symptoms.[3]

Decreased functional capacity in depressed patients is associated with abnormal front-subcortical circuit function, which causes symptoms of depression and cognitive disturbance.[4-8] Antidepressant medication as standard management can reduce depression and improve cognitive function[9,10] and potentially provide side effects[11]. Thus, adjunct therapy is urgently needed so that a decrease in the activity of daily living and quality of life can be prevented.

Repetitive transcranial magnetic stimulation (rTMS) and aerobic exercise are two techniques that have been previously investigated as adjuvant therapies for treating depression. Both therapies are known to be effective in reducing levels of depression[12,13] which may be associated with improved activity of daily living and quality of life and have been recommended in various depression management guidelines.[14,15] However, absent studies compare interventions specifically toward the activity of daily living and quality of life in a depressed patient. Thus, the present study aimed to compare the efficacy of rTMS and aerobic exercise as adjunctive therapy in depressed patients on ADL and QoL in improving activity of daily living and quality of life as an adjunct therapy in a depressed patient. The hypothesis: there is a difference in the effect of rTMS and aerobic exercise on ADL and QoL in depressed patients receiving antidepressant treatment.

Material and Methods

The subjects were 27 patients with first-episode depression recruited from the outpatient psychiatry clinic of Dr Soetomo Academic General Hospital. Inclusion criteria used in this study were: 1.) males and females, 2.) aged between 21-59 years old, and 3.) met the clinical criteria of moderate or severe major depressive disorder. The exclusion criteria were: 1.) poor state of public health, 2.) history of seizure, 3.) metal implants, 4.) visual disturbance, 5.) balance disturbance, 6.) lower extremity problem, and 7.) pregnant. All subjects signed an informed consent form, were given standard antidepressant medication, and then divided randomly into three groups, namely group 1 (antidepressant), group II (antidepressant+aerobic exercise), and group III (antidepressant+rTMS). Subjects in groups II and III received 10 sessions of therapy for 2 weeks.

Repetitive TMS treatment was performed using a Neuro MS/D TMS device. At the beginning of each session, the resting motor threshold (RMT) area and intensity were determined. Each subject received 3000 pulses of stimulation per session and 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. Aerobic exercises were performed using a static cycle Monark Ergometer with moderate intensity (65-75% of maximum heart rate) for 30 minutes.

The outcome measurement tools used in this study were the Barthel Index and SF-36, evaluated before and after the intervention. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS). The characteristic baselines were compared using ANOVA and Kruskal-Wallis Test. The change in the Barthel Index and SF-36 before and after the treatment were analyzed using Paired T-Test and Wilcoxon Signed Rank Test. Between-group differences (delta) were analyzed using ANOVA and Kruskal

Wallis Test, and a p-value < 0.05 was considered significant. The ethical committee of Dr Soetomo Academic General Hospital approved this study.

Results

Twenty-four subjects completed the sessions and study protocol. Three participants dropped out due to conflicting schedules and could not attend the therapy sessions, two from group III and one from group II. The homogeneity test of subjects' characteristics, whether age, sex, and educational level across groups found no significant differences.

The results of the Barthel Index assessment showed no significant difference after therapy in each group ($p<0.05$) and between the groups ($p=0.664$). However, the result of the SF-36 assessment showed significant improvement in domains of physical function, public health, vitality, social function, emotional role function, and mental health after intervention in each group ($p<0.05$). Furthermore, between-group comparison analysis showed that patients in group III had better improvement in the domain of public health (15.71±6.075, $p=0.009$), emotional role functioning (20.29±11.940, $p=0.049$) and mental health (14.29±6.075, $p=0.041$) compared to the other two groups.

Image 1. Research flow chart

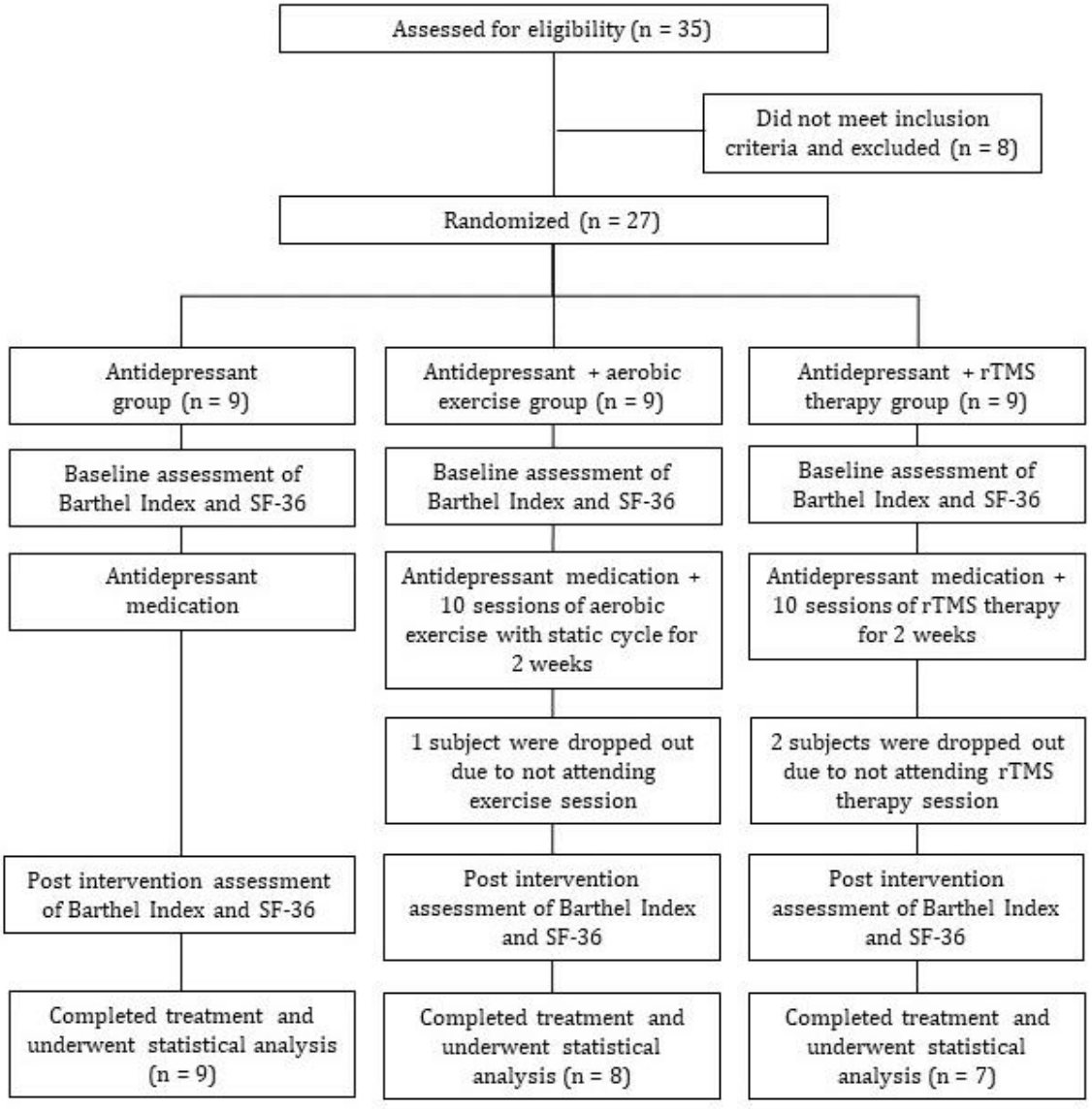

Table 1. Demographic Characteristics of Research Subjects

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					
- 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. Pre and post-intervention comparison of the Barthel Index in each group

Group	Pre (*Mean*±SD)	Post (*Mean*±SD)	p
Antidepressant	98.89±3.333	99.44±1.667	0.317
Antidepressant + aerobic exercise	98.13±3.720	99.38±1.768	0.157
Antidepressant + rTMS therapy	97.86±3.934	99.29±1.890	0.157

Table 3. Between-group comparison of change of Barthel Index (Δ)

	Groups			*P*
	Antidepressant	Antidepressant + aerobic exercise	Antidepressant + rTMS therapy	
The Barthel Index	0.56±1.667	1.25±2.315	1.43±2.440	0.664

Table 4. Pre and post-intervention comparison of SF-36 in each group

Domain		Groups					
		Antidepressant	p	Antidepressant + Aerobic exercise	p	Antidepressant + rTMS therapy	p
Physical function	Pre	73.33±7.071	<0.001*	85.00±4.269	0.015*	66.43±19.730	0.010*
	Post	78.67±6.782		91.25±5.825		76.43±15.469	
Role of physical functioning	Pre	55.56±32.543	0.081	59.38±18.601	0.080	29.29±35.989	0.112
	Post	63.89±25.345		68.75±17.678		42.86±31.339	
Bodily pain	Pre	14.67±17.393	0.102	20.75±24.818	0.102	23.57±16.102	0.102
	Post	29.44±20.063		37.38±21.540		47.57±18.174	
Public health	Pre	35.56±8.457	0.009*	33.75±6.944	0.010*	31.43±19.303	<0.001*
	Post	40.00±9.014		41.88±10.670		47.14±19.117	
Vitality	Pre	29.33±7.746	0.001*	34.50±12.995	0.012*	29.14±21.752	0.026*
	Post	39.11±7.149		49.50±12.817		44.57±19.243	
Social Function	Pre	50.22±8.843	0.034*	64.50±4.243	0.025*	41.43±21.431	0.001*
	Post	57.33±9.179		72.00±5.555		57.29±17.519	
Role of emotional functioning	Pre	48.89±9.740	0.038*	64.50±4.243	0.046*	41.43±21.431	0.001*
	Post	55.89±9.198		70.50±6.211		57.29±17.519	
Mental health	Pre	40.00±6.614	0.016*	49.38±13.999	0.004*	41.43±12.488	0.001*
	Post	46.67±5.000		56.25±11.877		55.71±11.339	

* = $p < 0.05$

Table 5. Between-group comparison of the change in various domains of SF-36 (Δ)

Domain	Groups			P
	Antidepressant	Antidepressant + Aerobic exercise	Antidepressant+ rTMS therapy	
Δ Physical function	5.33±2.693	6.25±3.536	10.00±7.071	0.207
Δ Role of physical functioning	8.33±12.500	9.38±12.939	13.47±19.303	0.932
Δ Bodily pain	11.11±16.669	12.50±17.254	14.29±17.821	0.933
Δ Public health	4.44±3.909	8.13±6.512	15.71±6.075	0.009*
Δ Vitality	9.78±6.037	15.00±8.485	15.43±9.914	0.305
Δ Social Function	7.11±6.754	7.50±6.211	15.86±6.256	0.099
Δ Role of emotional functioning	5.56±5.270	5±5.345	20.29±11.940	0.049*
Δ Mental health	6.67±5.000	6.88±4.581	14.29±6.075	0.041*

* = $p < 0.05$

Discussion

This study showed no significant changes in the Barthel Index after therapy in all three groups. This can be due to participants in each group in this study did not experience disturbances in their daily activities before the intervention. Hence, the improvements achieved by the intervention were not significant. This was different from the research by Wada et al.[16] They compared the level of daily activity ability of participants with and without depression and found a decrease in the group of depression participants.[16]

After the intervention, groups receiving antidepressants (I), antidepressants combined with aerobic exercise (II), and antidepressants combined with rTMS therapy (III) all showed significant gains in their SF-36 scores in the domains of physical function, public health, vitality, social function, emotional role function, and mental health. These domains were associated with the level of depression severity[17], and the significant increase could be the result of reducing in depression produced by antidepressants. Similar results were obtained in the study by Beusterien et al.[17] which the administration of selective serotonin reuptake inhibitor (SSRI) antidepressants can reduce depression and improve the quality of life in the 6th week. The administration of SSRI worked by inhibiting serotonin transport, thereby increasing the number of neurotransmitters that were thought to cause depression.[18] The superiority of antidepressant and rTMS therapy combination is shown in three domains closely related to depression levels: public health, emotional role function and mental health. This is in line with a study by Solvason et al.[19], who found that adding rTMS therapy for four weeks increased SF-36 scores in the public health and mental health domains. There were many studies on rTMS as an adjunct therapy for the depressed patient. Still, because of heterogeneity in the stimulation parameters and site of stimulation making, comparison across different studies is difficult.[3]

A better quality of life improvement mechanism after the combination of antidepressant drugs and rTMS therapy could be associated with a better reduction in depression[20] achieved through increased Brain-Derived Neurotrophic Factor (BDNF) and neurotransmitter activity, which is associated with improved nerve excitability, synapse efficacy, and accelerated transmission of signal transmission in the brain.[21] Other factors influence the outcome of rTMS therapy, including age, gender and menopausal status.[22] The limitation of this study was that all subjects did not have activity daily living disorders, so the effect of rTMS as an adjunct therapy on it was invisible.

The mechanisms of aerobic exercise therapy for depression were related to psychological and physiological mechanisms, including anti-inflammatory effects, neuroplasticity mechanisms, etc. The biochemical factors involved include β-endorphin, vascular endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF).[23]

In this study, after two weeks of aerobic exercise intervention, quality of life evaluation was performed using SF-36. There were some improvements in the domain of physical function, public health, vitality, social function, the role of emotional functioning and mental health.

This was similar to the study of Askari et al. in Iran, which assessed the quality of life of depressed patients with WHOQoL-BREF. The results showed improvements in the domains of psychological health and social relationships.[24] Social interaction seems to inhibit the negative effects of mental disorders, especially depression. It is also assumed that the positive feedback provided by social interaction through participation in exercise and physical activities increases the individual's sense of self-confidence. An effective exercise mechanism helps create and increase social inclusion, decreasing depression.[24] The same results were also shown by the Aydin et al. study (2021) with improved quality of life after eight weeks of aerobic exercise evaluated by WHOQoL in depressed patients due to breast cancer.[25] When compared between the three groups, there was a significant improvement in public health, mental health and emotional functioning in group III (antidepressant and rTMS).

Conclusion

Improvement in quality of life was apparent in all groups. The group with rTMS as an adjunct therapy had better emotional role functioning, public health, and mental health results than the other two groups. This result supports using rTMS therapy as an adjunct treatment to improve the quality of life in patients with first-episode moderate and severe depression. However, no change in the activity of daily living levels after the intervention was found. This study supports further investigation into the potential therapeutic applications of rTMS in a depressed patient with attention to age, gender, menopausal status, and other variables.

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