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Effect of low intensity aerobic cycle ergometer on maximal walking speed and cadence of myasthenia gravis patients

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ABSTRACT

Background and objectives. *MG is associated with muscle weakness which induces fatigue. This condition interferes with patients' ability to pursue activities of daily living and could cause many complications such as decrement in walking and depression. Though rehabilitation has been proved to reduce symptoms, the optimal dosage of the rehabilitation program is still debatable due to lack of high-quality evidence. The aim of this study was to analyze the effect of aerobic cycle ergometer on maximal walking speed, cadence and fatigue of MG patients.*

Materials and methods. *This randomized control group study was conducted to 20 Myasthenia Gravis patients with MGFA classification I until IIb. 10 meter walking test was used to assess maximal walking speed, 1 minute walking test was used to assess cadence, while Fatigue Severity Scale was used to measure fatigue. Measurement was done before and after 8 weeks of exercise. Paired t-test is used to analyze within group variables, and independent t test to evaluate between-group analysis.*

Results. *There was improvement on maximal walking speed, cadence and fatigue at intervention group with large effect size (CI 95%, p = 0,05), even though the results didn't differ statistically between groups.*

Conclusion. *There is improvement of maximal walking speed, cadence and fatigue of Myasthenia Gravis patients after exercising using low intensity aerobic cycle ergometer.*

Keywords: aerobic exercise, cadence, fatigue, myasthenia gravis, walking speed

Abbreviations:
MG – Myasthenia Gravis;
MGFA – Myasthenia Gravis Foundation of America

INTRODUCTION

Myasthenia Gravis is an autoimmune disorder of neuromuscular junctions that induce fatigue and muscle weakness [1]. The prevalence of MG is estimated about 150-250 per 1 million population per year, with incidence about 8-10 cases per year [2]. Neuromuscular disorder in MG may cause reduction of aerobic power, thus subsequently resulted in decrease of physical activity which could increase the risk of having chronic diseases, depression, and also difficulty in performing activities of daily living [3-4].

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Multidisciplinary rehabilitation approach may consist of physical, respiratory and balance training in order to improve functional outcomes, reduce fatigue, and improve quality of life. However, previous research has shown that there is still a lack of high-quality evidence for all strategies, and neither optimal dosage adjustment for endurance nor strengthening was known to work [5]. Furthermore, there is no research beforehand that studies the effect of exercise on MG patients in Indonesia. In order to promote safety in deconditioned MG patients, this study decided to give low intensity aerobic exercise with the aim to improve walking ability and fatigue in patients with MG.

MATERIALS AND METHODS

The study was conducted in compliance with the Helsinki's Declaration to experiment with humans. This study protocol was approved by the ethical Committee of "Dr. Soetomo" General Academic Hospital Surabaya, Indonesia (date: 30.11.2022, no: 0532/KEPK/XI/2022) and written informed consent was obtained from each participant. This study was randomized controlled trial with no assessor blinding.

The participants of the study were MG patients recruited from the Rehabilitation Outpatient Clinic "Dr. Soetomo" General Hospital and simple random allocation was used to randomize participants into control group (n=10) and interventional group (n=10). There were 2 samples dropped out in control group, and 1 sample dropped out in interventional group due to lack of motivation. A consecutive sampling method was used until the required sample size was obtained (Figure 1).

The inclusion criteria were: age between 18 and 59 years, diagnosed with MG with classification I until IIb based on MGFA, cooperative, with normal cognitive function using Montreal Cognitive Assessment - Indonesian version, willing to participate and to sign a consent form. The exclusion criteria were myasthenia crisis, cardiorespiratory diseases (such as myocardial infarction, chronic obstructive pulmonary disease, interstitial lung disease), pregnancy, new strokes, musculoskeletal and vascular diseases on the lower extremity that limit ambulation.

Prior to the intervention, baseline characteristics, including demographics (age, sex), onset age, duration of treatment, type of MG, comorbid factors, BMI and dosage of pyridostigmine were collected. Maximal walking speed (MWS) and cadence were evaluated at baseline and 8 weeks (Post-intervention). MWS was measured using 10 meter walking test (10-mwt). It requires 2 meter for acceleration, 6 meter for steady state walking, and 2 meter for deceleration. Time was counted only in the 6 meter-walk timed section. Cadence was collected by counting steps in a minute. On the other hand, fatigue was measured using Fatigue Severity Scale (FSS).

The sample size was estimated using the pilot data's pooled estimate of within group standard deviations (4.7). The power calculations revealed that 16 individuals were required to provide an 80 percent (ß = 0.20) chance of identifying a 20 percent (α = 0.05) difference between the groups.

Participants in the experimental group received a treatment program that consist of 24 sessions of low-intensity aerobic cycle ergometer and breathing education that lasted 30 minutes, 3 days a week for 8 weeks, while participants in the control group received only breathing education using diaphragmatic breathing,

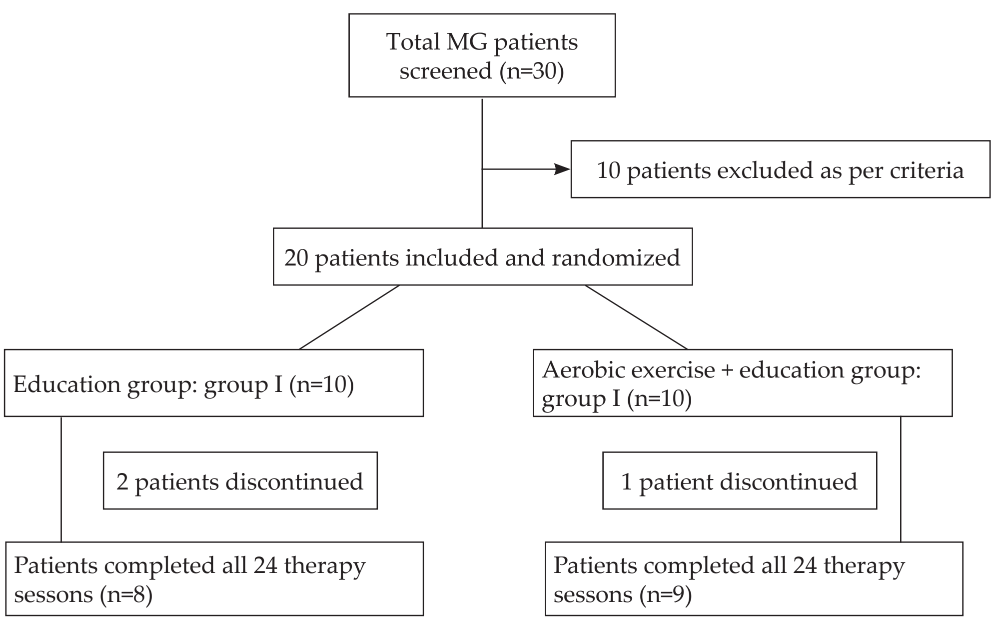

FIGURE 1. *Flow diagram for randomized subject assignment in this study.*

thoracic expansion and energy conservation technique. The allocation ratio was equal in each group.

All data obtained in this study was analyzed using SPSS statistics 26 (IBM, USA). Statistical analysis was performed for 17 participants (8 in control group and 9 in interventional group) who completed the study. The test for normality of data distribution is performed using the Shapiro-Wilk.

Within-group analysis of the variables was performed using the paired t-test, while an independent sample t-test was performed to evaluate between-group analysis among the post-intervention score for mean walking score and cadence score. Statistical significance was set at p ≤ 0.05 with a 95% confidence interval.

RESULTS

Twenty eligible participants were recruited in this study from December 2022 until March 2023. Two participants from control group and one participant from interventional group dropped out from the interventional group due to difficulty in following the schedule. Statistical analysis was performed on 17 participants. None of them showed any signs of clinical deterioration (according to vital signs and MGC) or any uneasiness regarding the training regimen.

The demographic profile at baseline measurement of the two groups showed no significant differences. (Table 1) The intervention group showed improvement on MWS, cadence and FSS (P <0.05) after 24 sessions,

TABLE 1. *Demographic profile of the control and intervention group*

Profile	Control group (n=8)	Intervention group (n=9)	Normality (statistic, P) Shapiro-Wilk test
Age (years)			
Mean ± SD	45.63 ± 6.35	47.78 ± 5.36	0.616
Min – Max	35-55	37-55	
Sex			
Male	3 (37.5%)	2 (22.2%)	0.521
Female	5 (62.5%)	7 (77.8%)	
Onset age			
0-49 years old (EOMG)	8 (100%)	8 (88,9%)	0.362
≥ 50 years old (LOMG)	0 (0%)	1 (11.1%)	
Duration of medication (years)			
Mean ± SD	7.25 ± 5.18	9.78 ± 7.36	0.421
Min – Max	1-15	2-25	
Type			
General	8 (100%)	9 (100%)	–
Ocular	0 (0%)	0 (0%)	
Comorbid factors			
Hypertension	2 (25%)	3 (33.3%)	
Hypercholesterolemia	1 (12.5%)	1 (11.1%)	
Polio	0 (0%)	1 (11.1%)	0.134
Lipoma	1 (12.5%)	0 (0%)	
Nephrolithiasis	0 (0%)	1 (11.1%)	
None	4 (50%)	3 (33.3%)	
BMI			
Underweight	0 (0%)	1 (11.1%)	
Normal	5 (62.5%)	5 (55.6%)	
Overweight	2 (25%)	2 (22.2%)	0.818
Obese grade I	1 (12.5%)	1 (11.1%)	
Obese grade II	0 (0%)	0 (0%)	
Height (cm)			
Mean ± SD	159.3 ± 5.31	160.4 ± 7.19	0.539
Min – Max	157-165	156-167	
Pyridostigmin dosage (60 mg/day)			
0	1 (12.5%)	0 (0%)	
1	1 (12.5%)	1 (11.1%)	
2	1 (12.5%)	0 (0%)	0.916
3	2 (25%)	4 (44.4%)	
4	2 (25%)	0 (0%)	
5	1 (12.5%)	4 (44.4%)	

EOMG: Early Onset of Myasthenia Gravis; LOMG: Late Onset of Myasthenia Gravis while the control group showed no improvement (Table 2). There are also differences after 24 sessions between groups, except cadence (Table 3).

DISCUSSION

To our knowledge, no studies have been conducted to evaluate the effect of low intensity aerobic cycle ergometer on maximal walking speed and cadence and MG. Majority of the subjects included in this study are women, with a mean age of 45-47 years old, and classified as EOMG. This finding is supported by several previous study showing that cases of MG in women were higher in the first five decades of age, while MG in men occurred more in the 6th decade of age [6]. This epidemiology is probably caused by estrogen hormone [7]. All of the subjects have general MG type. Early symptoms of MG usually manifest as an ocular type, however 90% of patients with ocular MG will develop into general type MG within two to three years of onset [8].

Obesity is considered as one of the most frequent complications of MG due to decrease of physical activity or long-term steroid usage. However, in this study, the majority of the patients have normal weight. Different life styles, types of food consumed and several external factors can be the cause of such difference [7]. Previous studies state that patients with EOMG have high probability of autoimmune comorbidities, while LOMG probably have non autoimmune comorbidities. Frequent comorbidities are dyslipidemia, hypertension, diabetes mellitus and thyroid disease [9]. Findings of this study reveal that most of the subjects doesn't have any comorbidity, but this can be caused by lack of general check up by them.

Results of statistical analysis in this study show that low intensity aerobic cycle ergometer exercise improves maximal walking speed, cadence and fatigue in MG patients, though there is no difference in cadence between the control and intervention group after 24 sessions. Aerobic exercise has been proven to increase VO2max by several mechanisms such as increase cardiac output, improvement of lung function, increase in skeletal muscle mitochondrial density up to 40%, which corelates with an increase in slow-twitch muscle fiber, and also an increase in blood flow in the skeletal muscle. Thus, exercising is able to enhance better improvement of cardiopulmonary function that may lack on MG patients who suffer from deconditioning [10-11].

The effect size after exercise in the intervention group after 24 sessions is considered large on maximal walking speed, cadence and fatigue in MG. This result is consistent with those reported by Wu and Zhao that demonstrate a moderate correlation between functional fitness that is shown by aerobic endurance and walking speed [12]. Another systematic review study also reported that there is a low correlation of VO2 peak and walking speed [13]. Several other studies prove that by increasing physical fitness, cardiorespiratory endurance and walking speed will improve as well [14].

Despite improvement of cardiorespiratory endurance, improvement in muscular endurance also occurs in response to aerobic exercise. Previous studies reveal that a year of aerobic training will result in increase in type I and II A muscle fiber area, capillary density, citrate synthase activity and percentage of type II A fiber which gives resistance to fatigue [15]. This finding corelates with another study by Bogdanis in which exercising increases type I muscle fiber [16].

Cycling exercise has a positive effect on excitability over motor area of lower limbs and improves lower extremity muscle strength especially quadriceps and hamstring muscle [15,17]. Increase in muscle strength corresponds well with increased stride length, speed and push off. Strengthening exercise also provides feedback from the entire lower extremity and increases the

TABLE 2. *Differences in outcome variable change scores within groups*

	Control Group			Interventional Group		
	Δ	***P***	**Effect size**	**Δ**	***P***	**Effect size**
Maximal walking speed	-0.081 ± 0.045	0.115‡	0.132	0.083 ± 0.015	0.001‡	0.64
Cadence	1.25 ± 1.52	0.438‡	0.35	6.1 ± 1.93	0.013‡	0.8
FSS	-1.04 ± 0.306	0.054‡	0.006	-0.017 ± 0.275	0.019‡	0.68

‡ t test paired samples

TABLE 3. *Differences in post-test analysis (after 24 sessions) between groups*

	After 24 sessions			
	Δ Control group	**Δ Interventional group**	***P***	**Effect size**
Maximal walking speed	-0.081 ± 0.045	0.083 ± 0.015	0.008§	4.89
Cadence	1.25 ± 1.52	6.1 ± 1.93	0.067§	2.8
FSS	-1.04 ± 0.306	-0.017 ± 0.275	0.025§	3.53

§t test independent samples

stimulation of the mechanoreceptor around the joints and firing of muscle spindle. Adequate sensory input from the vestibular system, feet, and neck may stimulate the spinal locomotory circuitry leading to a regular walking pattern [17].

Even though walking and cycling are two different kinds of activities, the patterns of muscle activation during cycling and walking are similar to each other. Both of them require rhythmic reciprocal flexion and extension movement, and need a well-alternated use of agonist and antagonist muscle. Peripheral sensory inputs such as muscles and skin afferents, vision, audition and vestibular dynamically regulate central pattern generator (CPG) in central nervous system. CPG produce stereotyped and reproducible pattern of rhythmic output during locomotion. CPG responds to the feedback during cycling training and stimulates descending pathways that may affect gait pattern in particular phases of step cycle [17-18].

Engagement in exercise training leads to a moderate reduction in fatigue levels by anti inflammatory mechanisms. Each exercise will benefit in increasing white blood cells, granulocyte-related proteins, and several plasma cytokines to maintain balance between pro and anti-inflammatory [19]. Exercise also induces release of endorphin in the hypothalamus which results in positive mood [20].

Limitations in this study include no blinding during procedure and the evaluation being performed by the same examiner. The study had limited population as Myasthenia Gravis is rare. Participants were MG patients with mild symptoms that might haved no decrease in walking ability. The study was performed in eight weeks and didn't evaluate long term follow up. Measurement of maximal walking ability wasn't performed using a standardized method, but automatic timing.

CONCLUSION

This study confirms that low intensity aerobic cycle ergometer exercise for 24 sessions can improve maximal walking speed, cadence and fatigue in MG patients. Exercise is proven beneficial and feasible for MG, especially with mild symptoms. Nevertheless, providing physical activity programs for MG based on their abilities is necessary. More physical activity is better for optimal health outcomes and it reduces complications caused by sedentary behavior.

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