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

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Short Running Title: Walking Ability After Cycle Ergometer in MG

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ABSTRACT

Background and objectives. MG is associated with muscle weakness which induced 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 symptom, optimal dosage of rehabilitation program is still debatable due to lack of high quality evidence. The aim of this study was to analyzed 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 exercising. Paired t-test is used to analyze within group variables, and independent t test to evaluate between-group analysis.

Results. 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

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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].

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 shown that there is still lack of high quality evidence for all strategies, and neither optimal dosage adjustment for endurance nor strengthening was known [5]. Furthermore, there is no research beforehand that study 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 accessor 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 drop out in control group, and 1 sample drop 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, normal cognitive function using Montreal Cognitive Assessment - Indonesian version, willing to participate, and to sign a consent form. The exclusion criteria were myasthenia crisis, had cardiorespiratory diseases such as myocardial infarction, chronic obstructive pulmonary disease, interstitial lung disease, pregnant, had new stroke, and had musculoskeletal and vascular diseases on 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, also 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 (β = 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 participant in the control group received only had breathing education using diaphragmatic breathing, thoracic expansion and energy conservation technique. The allocation ratio was equal in either group.

All data obtained in this study was analysed 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. 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 $p \leq 0.05$ 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 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 described other 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, while the control group showed no improvement (Table 2). There is 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 more MG in men occurred more in the 6th decade of age [6]. This epidemiology is probably caused by estrogen hormone that is expected to be the mediator of autoimmune [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 until three years of onset [8].

Obesity is considered as one of the most frequent complication of MG due to decrease of physical activity or long term steroid usage. However in this study, majority of the patient has a normal weight. Different life style, types of food consumed and several external factors can be the cause of such difference [7]. Previous study state that patient 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 subject doesn't have any comorbid, 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 control and intervention group after 24 sessions. Aerobic exercise has been proven in increasing VO2max by several mechanism such as increase cardiac output, improvement of lung function, induce an increase in skeletal muscle mitochondrial density up to 40% which corelates with an increase in slow-twitch muscle fiber, also increases 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 low correlation of VO2 peak and walking speed [13]. Several other studies proof that by increasing physical fitness will improve cardiorespiratory endurance and also walking speed [14].

Despite improvement of cardiorespiratory endurance, improvement in muscular endurance also occur in response to aerobic exercise. Previous study 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 resistance to fatigue [15]. This finding corelates with other study by Bogdanis in which exercising will increase type I muscle fiber [16].

Cycling exercise has a positive effect on excitability over motor area of lower limbs and improve lower extremity muscle strength especially quadriceps and hamstring muscle [15,17]. Increase in muscle strength correspond well with increased stride length, speed and push off. Strengthening exercise provides also feedback from the entire lower extremity and increase the stimulation of the mechanoreceptor around the joints and firing of muscle spindle. Adequate sensory input from vestibular system, feet, and neck may stimulate the spinal locomotory circuitry leading to a regular walking pattern [17].

Even though walking and cycling is two different kind of activities, the patterns of muscle activation during cycling and walking is similar to each other. Both of them requires 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 lead 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 and result in positive mood [20].

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

CONCLUSION

This study confirm 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 reduce complications caused by sedentary behavior.

Conflict of interest

The author reports no conflicts of interest in this work.

Author's contributions

Conceptualization, L.K., I.P.A.P., L.A.; methodology, L.K.; software, I.P.A.P.; validation, L.K., I.P.A.P., L.A.; formal analysis, L.A.; investigation, P.S.; resources, P.S.; data curation, L.A.; writing—original draft preparation, L.K.; writing—review and editing, I.P.A.P.; P.S.; visualization, P.S.; supervision, I.P.A.P., L.A., P.S.; project administration, L.K. All authors have read and agreed to the published version of the manuscript.

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TABLES

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)	7.25 ± 5.18	9.78 ± 7.36	0.421
Mean ± SD	1 - 15	2 - 25	
Min – Max			
Type			
General	8 (100%)	9 (100%)	-
Ocular	0 (0%)	0 (0%)	
Comorbid factors			
Hypertension	2 (25%)	3 (33.3%)	0.134
Hypercholesterolemia	1 (12.5%)	1 (11.1%)	
Polio	0 (0%)	1 (11.1%)	
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%)	0.818
Normal	5 (62.5%)	5 (55.6%)	
Overweight	2 (25%)	2 (22.2%)	
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%)	0.916
1	1 (12.5%)	1 (11.1%)	
2	1 (12.5%)	0 (0%)	
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

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

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FIGURES

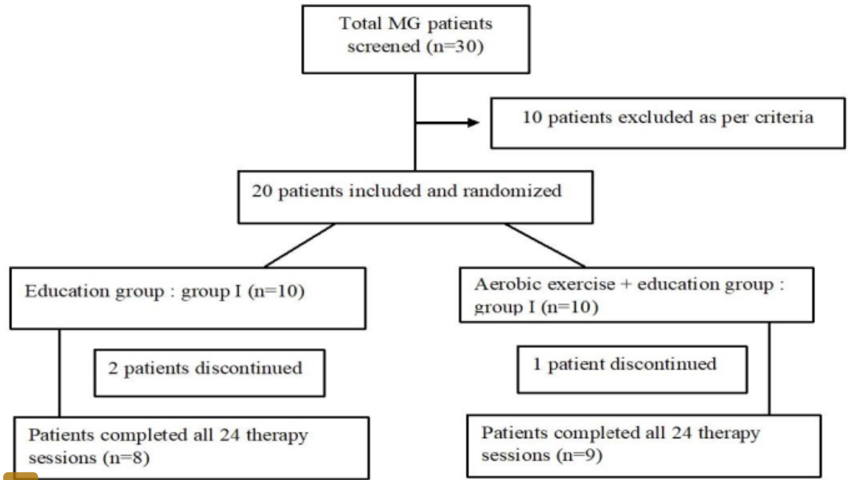

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Figure 1. Flow diagram for randomized subject assignment in this study.