Original Article

Effect of Light-Intensity Cycle Ergometer Aerobic Exercise on 2-Min Walking Test Distance and Maximum Oxygen Uptake in Myasthenia Gravis Patients: A Randomized Controlled Trial

Yunita Dwi Anggarini[1], Dewi Poerwandari[1], Inggar Narasinta[1], Paulus Sugianto[2], Mazlina Mazlan[1,3], Soenarnatalina Melaniani[4], Lisa Kartika[1], Muhammad Suhail Bin Satri[5]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [2]Department of Neurology, Faculty of Medicine, Universitas Airlangga - Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [3]Department of Rehabilitation Medicine, Malaya University, Kuala Lumpur, Malaysia, [4]Department of Epidemiology, Biostatistics, Population Studies, and Health Promotion, Faculty of Public Health, Airlangga University, Surabaya, Indonesia, [5]Malaysian Armed Forces Veteran Doctor, Malaysia

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ABSTRACT

Introduction: Fatigue and impaired functional capacity are more likely to be observed with myasthenia gravis (MG). MG prevalence in the Indonesian population is still limited. MG can benefit from participating in aerobic exercise without causing a decline in function, but relatively few exercise training studies have been conducted in this group of patients. This study analyzed how light-intensity cycle ergometer aerobic exercise influences functional and aerobic capacity in MG. **Methods:** An 8-week randomized controlled trial using a light-intensity cycle ergometer for aerobic exercise three times a week was carried out on adult patients with MG Foundation of America Class I-IIa, and adult patients. Eighteen MG patients were randomly assigned to the intervention or control group (standard exercise training). Two-min walking tests (2MWTs) distance and maximum oxygen uptake (VO_{2Max}) were measured before and after the 8-week intervention. VO_{2Max} was calculated from the 2MWT formula. A *t*-test was used to compare 2MWT distance and VO_{2Max} within and between groups with a significance level of $P < 0.05$. **Results:** Light intensity cycle ergometer aerobic exercise significantly improved the functional and aerobic capacity in the intervention group at 8 weeks (2MWT distance $P = 0.001$ and VO_{2Max} $P = 0.001$) but not in the control group ($P = 0.523$ and $P = 0.575$, respectively). Substantial changes were also found between groups in both 2MWT distances ($P = 0.002$; effect size = 1.75) and VO_{2Max} ($P = 0.001$; effect size = 1.81) pre- and post-test. **Conclusion:** Eight weeks of light-intensity cycle ergometer aerobic exercise improves the functional and aerobic capacity of adult MG patients.

KEYWORDS: *Cycle ergometer aerobic exercise, myasthenia gravis, two-min walking test, VO_{2Max}*

INTRODUCTION

The combination of higher incidence, increased prevalence, and lower mortality rates renders myasthenia gravis (MG) a condition with significant morbidity.[1] The peak incidence and prevalence of MG are frequently observed in adults, whereas MG in children is quite uncommon, accounting for only 10%–15% of MG cases.[2,3] There is limited research investigating severe morbidity in MG, which is characterized by a decline in functional capacity.[4] Prior studies have shown that MG patients exhibit lower functional capacity and VO_{2Max} compared to healthy individuals.[5] Muscle weakness and fatigue are the contributing factors to the limited functional capacity[6] and exercise intolerance.[7,8]

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Address for correspondence: Dr. Dewi Poerwandari, Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo General Academic Hospital, Jl. Mayjend Prof. Dr. Moestopo. No. 6–8, Airlangga, Gubeng, Surabaya 60286, East Java, Indonesia.
E-mail: nastitisoemarno@gmail.com

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Medications used to treat MG can potentially worsen the condition and have wide-ranging metabolic effects.[6,8] As a result, it is challenging for individuals with MG to engage in exercise, as it is often believed that exercise can exacerbate the condition.[8]

Physical exercise increases VO_{2Max}, which can benefit MG patients.[7,9] However, the optimal exercise intensity for MG patients remains unknown.[6,10] Due to the limitation of the small sample size in previous research, there is a lack of agreement on the ideal physical activity regimen to achieve positive effects without risking the development of side effects.[6,10,11] Many MG studies use moderate-high-intensity aerobic exercise, but light-intensity aerobic exercise research is scarce, so little information is known about its effects on functional capacity.[7,9]

In addition, the standard assessment method of using a 6 minute walking test may not be suitable for evaluating the functional capabilities of MG patients.[12,13] Most patients have difficulties completing the 6MWT; however, the distance covered can improve with aerobic exercise.[7,9,13] The two-min walking tests (2MWT) may be more appropriate for MG patients who have muscle weakness, exercise intolerance, low endurance, and fatigue.[13] It was found that both 2MWT and 6MWT were reliable and valid measures for MG functional capacity measurement.[14]

Since there is no consensus guideline on the type and intensity of physical exercise in MG to improve functional capacity, especially since this is the first study to evaluate quantitatively the cardiorespiratory function in the Indonesian population, this study investigates whether the light-intensity cycle ergometer affects 2MWT distance and VO_{2Max} in adult MG patients.

Methods

Study design

This 8-week randomized control study was conducted in the Physical Medicine and Rehabilitation Outpatient Clinic, Dr. Soetomo Academic General Hospital, Surabaya, Indonesia, from January to February 2023, based on the Consolidated Standards of Reporting Trials 2010 guidelines.[15,16] This study followed the principles of the Helsinki Declaration and was approved by the Hospital Ethics Committee (0441/KEPK/VII/2022).

Sample size calculation

The sample size was calculated based on a previous pilot study.[9] With a test power of 0.95, a level of significance of 0.05, a population standard deviation of 3.65, $\mu1 = 7.16$, $\mu2 = 5.5$, and a 20% dropout rate, the sample size is 20 patients, comprising 10 in each group. The formula used was:

$$n = \frac{2\sigma^2 (Z_{1-\alpha/2} + Z_{1-\beta})^2}{(\mu1 - \mu2)}$$

Participants

Twenty-three patients from the neurology outpatient clinic were recruited consecutively. Clinical examination and repetitive nerve stimulation (RNS) tests were used to confirm MG patients. The positive RNS result for MG is defined as a 10% manual decrement or a 5% computer decrement. Other inclusion criteria were MG Foundation of America Class I and IIa,[17] aged 18–59, cooperative, and normal cognition.

Exclusion criteria: myasthenia crisis; undergoing routine aerobic exercise 2 until 3 days a week in the past 1 month; and condition that may affect independent ambulation or exercise capacity such as cardiorespiratory disorders; systemic disease; pregnancy; body mass index (BMI) ≥30; balance and vision disturbance; using walking aid; other neurological disorder such as stroke; erythema, sores, ulcers, or gangrene on one or both feet; restricted knee flexion >45°, extension >10°, hip flexion >45°; and lower limb vascular neuromusculoskeletal illness that impairs ambulation.

Randomization and allocation

Twenty-seven patients were initially screened, and four patients were excluded. The details of the remaining 23 patients were number-coded to ensure anonymity. All consecutive patients were randomly assigned to either the intervention or the control group with a 1:1 allocation ratio using the lottery method of randomization. Participants and investigators were not blinded since the intervention could not be blinded. All patients provided written informed consent after receiving information about the study purpose and study design.

Twenty-three MG patients participated in this study, with 11 in the intervention group and 12 in the control group. Two patients drop out of the intervention group (sinusitis and muscle discomfort) and three from the control group (noncompliance in the 1st week). Hip muscle discomfort improved about 30 min to 1 h following exercise. The patient complained of dyspnea 10 days after the last exercise, which was categorized as no exercise adverse effect. This patient was admitted to the hospital and passed away a month later. Another patient was dropped from the research because he had sinusitis 2 days after exercise that was unrelated to and required routine control at the ear, nose, and throat outpatient clinic. These two incidents were reported to the hospital ethics committee within 24 h. Hence, only

18 patients (intervention group n = 9 and control group n = 9) completed the study. All processes are shown in Figure 1.

Study procedure

The intervention group received low-intensity (30% heart rate reserve (HRR) or Borg scale 11–12) cycle ergometer (BTL stress test, Massachusetts, USA) aerobic exercise. Preintervention familiarity sessions were conducted to teach patients how to do the exercises. Thirty min of aerobic exercise, consisting of 5 min of warming up, 20 min of main exercise, and 5 min of cooling down, were prescribed three times a week for 8 weeks.

Pyridostigmine is taken 1.5–2 h before aerobic exercise to reduce fatigue and muscle weakness, which might compromise respiratory muscles and cause a myasthenic crisis. Pyridostigmine has a 4-h half-life; therefore, the exercise intervention and outcome measurement should include peak dosage exercise. This would allow the patient to exercise safely after 1.5–2 h of taking pyridostigmine.[17]

The exercise intensity was gradually raised until it reached 30% HRR, or Borg scale 11–12. The increment rate was based on the patient's condition. Exercise is ceased, and the patient is asked to rest if fatigue, muscle pain, shortness of breath, or dizziness occur. Exercise may begin again after rest. Exercise and rest can be done at a maximum 1:1 ratio. Exercise for 3 min, rest for 3 min, etc., until 30 min are achieved. The exercise is halted after 5 min if the subject cannot continue. If the patient can continue exercising before 60 min and the predicted completion time is 2 h following the peak dose of pyridostigmine, then exercise starts from the beginning.

Two health staff accompanied the patient during the exercise and waited for another 30–60 min. The patients can leave the clinic after 30–60 min if there is no complaint. In addition, emergency kits are prepared and located nearby. If there are emergency indications during or 30–60 min following the completion of aerobic exercise, the subject is given emergency protocol and referred to the emergency room.

The MG composite (MGC) score, vital signs, complaints, and Borg scale score were recorded before, during, and after (until 1 h) exercise. During the exercise,

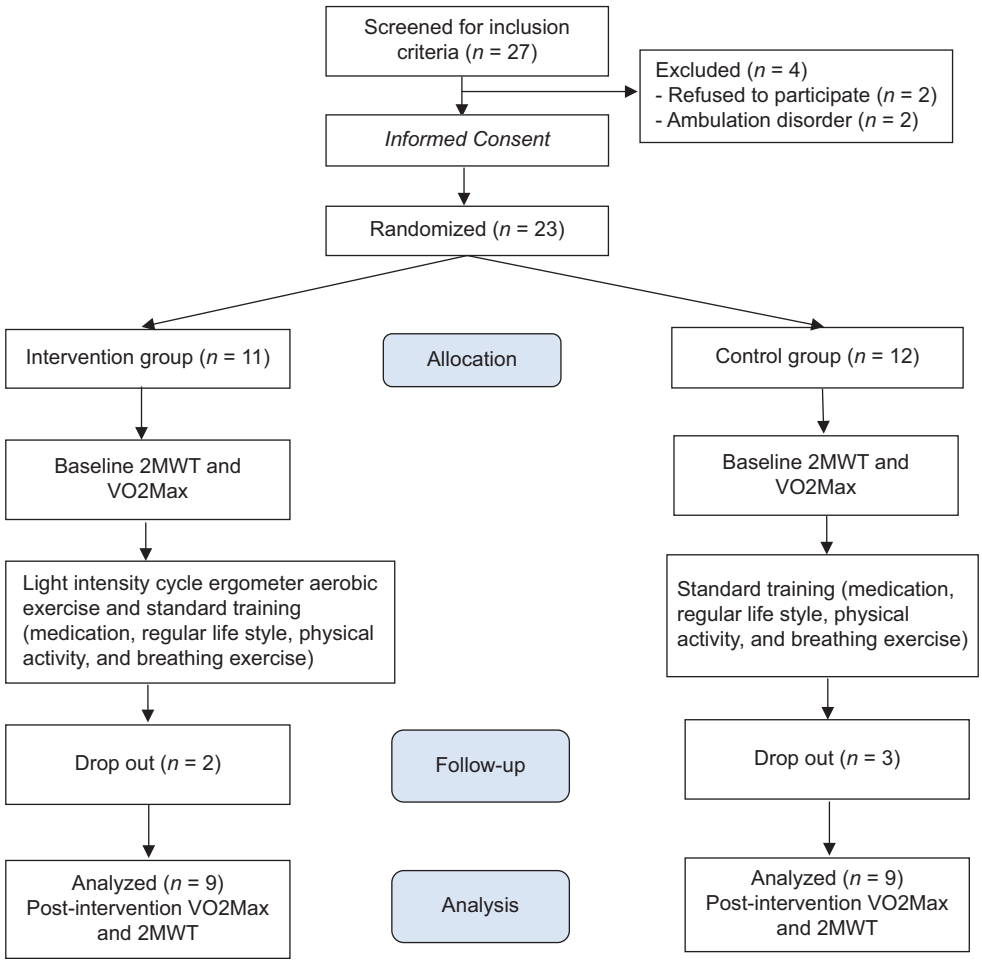

Figure 1: Flowchart of the study design

lead electrodes are placed on the subject's chest and connected to a computer, which is monitored through a computer monitor screen to monitor heart conditions. Male patients should remove their chest hair to ease lead electrode placement. Subjects were asked to wear comfortable clothing and shoes/footwear when doing the exercise. No heavy work before exercise.

The control group did not receive light-intensity cycle ergometer aerobic exercise. Throughout the study, both groups were asked to continue their neurology follow-up, continue taking all medications, including pyridostigmine, methylprednisolone, and/or azathioprine, and maintain their regular lifestyle, physical activity, and breathing exercises.

A specialized exercise programs

Deep breathing

One hand was put over the umbilicus during this procedure. The hand will rise when the patient breathes in through the nose and descend when he breathes out through the mouth. This procedure takes 3 min, at least twice a day. Breathing exercises can be done while lying, sitting, standing, walking, climbing stairs, and conducting daily tasks.[18]

Pursed-lip breathing

This exercise requires inhaling deeply through the nose and gently exhaling through the mouth with a 1:2 or greater inspiration–exhalation ratio. Pursed-lip breathing involves blowing candles, ping-pong balls, and suction pipe bubbles into drinking water.[18]

Outcome measurement

Before and after 8 weeks of intervention, the patients' functional and aerobic capacity was measured using the 2MWT distance and VO_{2Max}, respectively. Then, researchers taught patients how to perform the tests.

Two-min walking test distance

The patient walks 30 m on a straight track for 2 min. Each 5-m track distance is marked. Preparation for the walk test includes enough sleep, no activity or strenuous work, comfortable clothes, and proper footwear. The vital signs of patients were taken before and after the 2MWT. Patients walked as fast as possible for 2 min without running or stopping. A stopwatch starts when the patient starts walking. If patients feel short of breath or fatigued, especially on their legs, they can sit on a chair, but the stopwatch will continue for 2 min. The patients can resume walking as long as the 2 min are not over. Finger pulse oximeters were used during the 2MWT to measure oxygen saturation and heart rate. The researcher records the total distance walked on the worksheet.[19,20]

Maximum oxygen uptake

VO_{2Max} is the maximum oxygen intake, delivery, and usage by the pulmonary, cardiovascular, and muscular systems. VO_{2Max}, evaluated with a treadmill or ergometer, is a clinical and physiological fitness indicator.[21] A low VO_{2Max} increases the risk of premature death and chronic diseases.[22] Safe and simple submaximum tests such as walking, running, and cycling are the most common VO_{2Max} tests. A specified time for walking and running distances determines VO_{2Max}.[23] To compute VO_{2Max} from 2MWT, Pratiwi *et al*. suggest the formula below:[19]

$$VO_{2Max}\ (mL/KgBW/min) = 2.809 + (0.868 \times A) - (0.412 \times BW) - (0.0382 \times BH) - (0.474 \times WS)$$

Note: mL = milliliter, KgBW = kilogram body weight, min = minute, A = age (years), BW = body weight (kilogram), BH = body height (centimeter), WS = walking speed (meter/minute).

Criteria for discontinuation

The patients would be dropped from the study if they missed more than 2 days of training or 20% of attendance, refused to continue the study, or could not finish the protocol-compliant training.

Statistical analysis

All statistics were computed with SPSS 27 (IBM Corp., Armonk, NY, USA). The mean standard deviation indicated quantitative data, while frequency and percentage showed qualitative data. Shapiro–Wilk tested data normality (significant level $P > 0.05$). An independent *t*-test or Mann–Whitney test evaluated changes in 2MWT distance and VO_{2Max} pre- and posttest between intervention and control groups. In the intervention and control groups, a paired *t*-test or Wilcoxon test was used to compare 2MWT distance and VO_{2Max} pre-and posttest. The significant level of the *t*-test or nonparametric test is $P < 0.05$.

Results

Patient's characteristic

There was no significant difference in characteristics between the groups (including adults aged 18–59) except gender, MG type, body weight, BMI pretest, comorbidity in the control group, Δ2MWT, and ΔVO_{2Max} [Table 1]. In both groups, female patients outnumber male patients; the majority are diagnosed with general MG type, and more than half have comorbidities.

Effect of treatment on both groups

There was a significant increase in 2MWT distance and VO_{2Max} value after 8 weeks of exercise in the intervention group, with Cohen's d effect size of 1.12 (large) and 0.78 (moderate), respectively [Table 2].

Table 1: Baseline characteristics of patients

Characteristic	Intervention (*n*=9), mean±SD/*n* (%)	Control (*n*=9), mean±SD/*n* (%)
Age (years)	47.78±5.36	43.78±6.63
Age since onset (years)	38.22±11.10	36.78±4.89
Gender		
Male	2 (22.2)**	3 (33.3)**
Female	7 (77.8)**	6 (66.7)**
Duration of treatment (years)	9.56±7.55	7.00±4.41
Myasthenia gravis type		
General	8 (88.9)**	9 (100.0)**
Ocular	1 (11.1)**	0**
BW pretest (kg)	57.22±12.60	62.51±14.45**
BMI pretest (kg/m^2)	21.72±3.77	25.50±5.73**
Underweight	2 (22.2)	0
Normal	2 (22.2)	4 (44.4)
Overweight	3 (33.3)	2 (22.2)
Obese grade I	2 (22.2)	1 (11.1)
Obese grade II	0	2 (22.2)
Comorbid		
Dyslipidemia	1 (11.1)	2 (22.2)**
Hypertension	2 (22.2)	1 (11.1)**
Dermatitis atopic	1 (11.1)	1 (11.1)**
Postpolio lower limb	1 (11.1)	0**
Hyperuricemia	1 (11.1)	0**
None	3 (33.3)	5 (55.6)**
2MWT distance pretest (m)	145.34±26.40	131.56±30.25
2MWT distance posttest (m)	174.52±25.52	127.10±21.55
VO_{2Max} pretest (mL/kgBW/min)	19.94±9.03	23.18±12.79
VO_{2Max} postest (mL/kgBW/min)	26.84±8.68	22.35±12.13
Δ2MWT (m)	29.18±18.30**	−4.46±20.03**
ΔVO_{2Max} (mL/kgBW/min)	6.90±4.29**	−0.83±4.25**

**Normality test using Shapiro–Wilk, P<0.05. BW: Body weight, BMI: Body mass index, 2MWT: 2-min walking test, VO_{2Max}: Maximum oxygen uptake, SD: Standard deviation, Δ2MWT: 2MWT pre- and posttest changes, ΔVO_{2Max}: VO_{2Max} pre- and posttest changes

There was a significant increase in the 2MWT posttest between intervention and control groups compared with pretest (P < 0.05), with an effect size of 2.01 (very large). The VO_{2Max} of the post–pre-test between the intervention and control groups showed no significant difference (P > 0.05), with both effect sizes being 0.29 and 0.43 (small). Δ2MWT and $\Delta VO_{2Max,}$ which were the reductions between the posttest and pretest in the intervention and control groups, showed a significant increase (P < 0.05), with both effect sizes (1.753–1.811) being very large [Table 3].

Discussion

This study found that an 8-week program of light-intensity cycle ergometer aerobic exercise can benefit MG patients. Aerobic cycle ergometer training increases MG's functional capacity. To determine functional capacity, 2MWT was used in this study while VO_{2max} to measure the aerobic capacity. There was a significant increase in the 2MWT distance among the intervention group, which indicates improvement in functional capacity. Functional capacity measures an individual's ability to perform daily activities that require an adequate aerobic metabolism and efforts to maintain cardiovascular, pulmonary, and musculoskeletal health.[24] The trend of functional capacity improvement was also observed in previous studies by Westerbeg *et al*. and Chang *et al*., although their studies used 6MWT instead of 2MWT.[6,9]

Patient characteristics show that number of female subjects was higher than male, with an average onset age of 38 years old. Andersen[1] and Bubuioc *et al*.[25] reported that MG mostly affected young women (20-39 years) and older men (50-70 years) of all races. The women's incidence ratio was 3:1 before 50, which started around 20–39 in women and 50–70 in men.[1,25] The majority of patients had a generalized MG (GMG) type with an average treatment duration of 8 years, multiple comorbidities, and an overweight/obese condition. 23.3%–80% of ocular MG becomes GMG after 2 years of treatment.[2,26] Muscle weakness and body composition change due to neuromuscular junction dysfunction in MG, which will increase comorbidities. In addition, MG patients are afraid of doing additional activities that enhance adipocyte accumulation and obesity.[6,8,27,28]

This study was advantageous since it had more mild-type MG patients with a slightly younger age, a lighter exercise intensity, and no additional physical activity. This improves functional ability without aggravating fatigue, shortness of breath, or myasthenia crises. This study also demonstrates that VO_{2Max} increases considerably after ergometer exercise, but the number of studies examining the relationship between aerobic exercise and VO_{2Max} outcomes remains limited.

The mean 2MWT distance after the exercise program was 174.5 m. This value is within the higher normal range of 2MWT in healthy adults. Previous study has reported that the 2MWT value for 1137 healthy adults ranges from 64.6 to 300.8 m.[29] It is believed that this value and the distance achieved after the 8-week exercise program are also clinically meaningful.

Increased functional capacity following the cycle of ergometer aerobic training can be due to the physiological effects on the muscle, blood, circulatory, and lung systems.[30] Acute and extended aerobic exercise naturally adapts to normal and chronic adaptation.[31]

Table 2: Predicted 2-min walking test distance and maximum oxygen uptake before and after (after 8 weeks) the light-intensity cycle ergometer aerobic and standard exercise

Outcome measure	Group	Mean±SD	*P*	Effect size
2MWT distance (meter)	Intervention			
	Pretest	145.34±26.40	0.001*	1.12
	Posttest	174.52±25.52		
	Control			
	Pretest	131.56±30.25	0.523	0.17
	Posttest	127.10±21.55		
VO_{2Max} (mL/kgBW/min)	Intervention			
	Pretest	19.94±9.03	0.001*	0.78
	Posttest	26.84±8.68		
	Control			
	Pretest	23.18±12.79	0.575	0.07
	Posttest	22.35±12.13		

*P<0.05. Test using paired *t*-test. 2MWT: 2-min walking test, VO_{2Max}: Maximum oxygen uptake, SD: Standard deviation

Table 3: Predicted and differences of 2-min walking test distance and maximum oxygen uptake between groups

Outcome measure	Group	Mean±SD	*P*	Effect size
2MWT	Pretest			
	Intervention	145.34±26.40	0.318	0.49
	Control	131.56±30.25		
	Posttest			
	Intervention	174.52±25.52	0.001*	2.01
	Control	127.10±21.55		
Δ2MWT distance (m)		12.36±25.41	0.002*	1.75
VO_{2Max}	Pretest			
	Intervention	19.94±9.03	0.543	0.29
	Control	23.18±12.79		
	Posttest			
	Intervention	26.84±8.68	0.380	0.43
	Control	22.35±12.13		
ΔVO_{2Max} (mL/kgBW/min)		3.04±5.74	0.001*	1.81

*P<0.05. Test using independent *t*-test. 2MWT: 2-min walking test, VO_{2Max}: Maximum oxygen uptake, SD: Standard deviation, ΔVO_{2Max}: VO_{2Max} pre- and posttest changes

Muscular, enhanced capillarization, and cardiovascular adaptation responses result in vein O2 inhibition. Lung and blood adaptation reactions increase arterial O2 content.[32] Higher arterial oxygen concentrations and lower vein oxygen concentrations increase the artery–vein oxygen differential. Increasing cardiac output and arteria–vein oxygen difference prevents VO_{2Max} reduction in MG patients.[31] Previous three studies utilizing aerobic cycle ergometer exercise used a protocol of more than 8 weeks, while only one study used an 8-week protocol. The 8-week aerobic cycle ergometer training study did not increase functional capacity, but the aerobic exercise study that lasted more than 8 weeks did.[6,9,33,34]

This study of low-intensity aerobic exercise revealed no adverse events, allowing MG patients to gain the benefits of increased functional capacity, whereas the study of high-intensity cycle ergometer aerobic exercise revealed adverse events.[17] The positive outcomes of this research suggest that this protocol can be used by health-care professionals for safe aerobic exercise without significant adverse events for MG patients. A 2MWT can be used as a measure of cardiorespiratory fitness in MG patients who are unable to complete a 6MWT.

The limitations of this study are the lack of blinding of the investigator and patient, the small number of patients in each group, and the fairly short duration of the assessment without follow-up. It was difficult to recruit many patients as MG is considered a rare autoimmune disease, but we managed to achieve the estimated sample size. The lack of blinding was unavoidable due to the different exercise regimes used, but the 2MWT distance and VO_{2Max} measured were objective assessments and were reliable and valid.

Conclusion

An 8-week program of light-intensity aerobic exercise on a cycle ergometer increases the functional and cardiopulmonary endurance of patients with MG. It can be safely applied to well-regulated MG.

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Conflicts of interest

There are no conflicts of interest.

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