EFFECTS OF BALANCE STRATEGY TRAINING IN MYASTHENIA GRAVIS: A CASE STUDY SERIES

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ABSTRACT: *Introduction:* Studies of exercise in patients with myasthenia gravis (MG) are sparse. Balance strategy training (BST) multimodal exercise has proven efficacy in adults for enhancing balance and functional mobility. This prospective study aims to determine if BST improves functional ability and balance in people with MG. *Methods:* Seven individuals with MG participated in a 16-session workstation intervention. Repeated measures (pre/post-intervention and 4-week follow-up) consisting of quantitative myasthenia gravis score (QMG), 6-minute walk test (6MWT), timed up and go (TUG) with dual task (TUG_{manual} and $TUG_{cognitive}$), and standing stability on foam with eyes closed (foamEC) were assessed. *Results:* Most measurements showed sustained improvement at follow-up. QMG, $TUG_{cognitive}$, and foam EC achieved clinically significant improvements (>15%). No adverse effects were reported. *Conclusions:* BST was effective in improving balance and QMG scores in subjects with MG. A multimodal BST approach is thus suggested to target different aspects of balance and functional mobility.

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Myasthenia gravis (MG) is an autoimmune disease affecting neuromuscular transmission.[1] As a consequence, patients with MG have variable deficits, such as weakness and fatigue. In early disease stages, 85% of patients have ocular symptoms such as diplopia and ptosis.[2] Subsequently, the majority of patients develop generalized weakness in axial, bulbar, and limb muscles, resulting in reduced balance, strength, and fitness, and an overall decline in functional abilities.[3]

Women commonly develop MG between the ages of 20 and 30 years, whereas men more commonly develop MG between the ages of 50 and 70 years.[4] Initial presenting symptoms of MG are similar between patients, regardless of age of onset, but older MG patients generally have more severe forms of MG.[5] The review by Horak *et al.* indicated that performance in balance and function is influenced largely by the sensorimotor system, which declines with aging.[6] Therefore, it is imperative to consider the combined impact of MG and aging on balance and functional mobility.

Currently, common medication options for MG include anticholinesterase, corticosteroids, and immunosuppressive therapy.[7] Although pharmacological treatments are effective in alleviating MG symptoms, they have many side effects, and patients may be unable to achieve pre-morbid functional abilities.[8] Consequently, exercise therapy has established itself as an adjunct, non-invasive therapy to enhance function in patients with MG. Specifically, recent research has demonstrated some potentially beneficial effects of exercise in patients with MG.[9–12]

To date, few published studies have examined the intensity and effects of different types of exercises to improve functional abilities in patients with MG.[13–16] Davidson *et al.* reported moderate improvement in strength and endurance after 6 weeks of lower limb endurance training and low-impact aerobic exercise in a single-subject case report.[14] Although the exercises were based on existing neuromuscular disease rehabilitation literature, the subject also had alterations in prescribed medications during the study period, which may have confounded the effectiveness of the exercise program. In addition, because it was a case report of a single subject, the results have limited validity and cannot be generalized to the MG population. Another study addressed the effects of resistance training in patients with MG. Although the findings established no negative effects and no significant change in strength after 10 weeks of resistance training,[16] the intervention consisted of repetitive maximal isometric contraction, and the exercises prescribed were single-joint movements of the same muscles assessed. Consequently, the impact of this intervention may not translate to improvement in functional ability. Given the lack of an established and effective exercise program for patients with MG, there is a need to develop an exercise program that would enhance motor function of these patients.

Additional Supporting Information may be found in the online version of this article.

Abbreviations: BST, balance strategy training; COP, center of pressure; EO, eyes open; EC, eyes closed; mCTSIB, modified Clinical Test for Sensory Integration of Balance; MG, myasthenia gravis; MGFS, Myasthenia Gravis Fatigue Scale; QMG, quantitative myasthenia gravis; TUG, Timed Up & Go; VOR, vestibular–ocular reflex; VSR, vestibular–spinal reflex; 6MWT, 6-minute walk test

Key words: balance; exercise; functional mobility; myasthenia gravis; strength

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Balance strategy training (BST) consists of exercises that address the functional needs of patients and targets the sensorimotor system to improve function.[17] BST exercises have been shown to be beneficial for increasing balance, strength, and overall functional ability in various populations such as the elderly,[18] osteopenic adults,[19] and menopausal women.[20] Positive effects have also been established in neurological disorders after BST, and a small number of studies have reported significant improvement in balance, strength, and functional ability in subjects.[13,21–23] To our knowledge, the effects of BST exercises on MG have not been documented. Considering that the impact of MG is more significant in older adults,[4] it is possible that BST exercises can improve balance function and reduce the risk of falls by targeting the sensorimotor system. In addition, research has shown that patients with MG are generally sedentary due to muscle weakness and fatigue[15] and, consequently, they have lower bone density.[24] These are compelling reasons to incorporate balance exercises to help enhance balance and functional mobility of patients with MG.

In this prospective study we investigated the effects of a BST exercise program on balance, strength, and fitness in subjects with MG. We hypothesized that the proposed BST intervention would result in clinically significant improvements in all targeted areas.

METHODS

Subjects. Seven individuals diagnosed with MG volunteered to participate in the study. Inclusion criteria required subjects to have confirmation from their treating doctor that their MG was controlled, their symptoms were stable, and medication would not be changed during the study. The individuals were excluded if they had any cognitive deficits that precluded provision of informed consent and any additional neurological or musculoskeletal condition that affected mobility. All subjects provided written informed consent prior to the study. Ethics clearance was obtained from the human ethics committee of the University of Queensland in accordance with the guidelines of the National Health and Medical Research Council.

Procedures. A single-subject research design was chosen with the subjects acting as their own control. The first 5 subjects recruited attended 4 assessment sessions consisting of 2 pre-intervention baseline sessions conducted 4 weeks apart to determine the stability of baseline measurements, followed by 1 post-intervention session within 1 week of completing the intervention and a last session at the 4-week follow-up to determine any carryover effects. Two subjects had only pre- and post-intervention and follow-up assessments.

Intervention. Subjects undertook a total of 16 sessions of intervention within an exercise group either once or twice a week, depending on their work commitments. Each subject had balance strategy, strengthening, and endurance training exercises tailored individually to their physical ability as determined by initial assessment. Physiotherapy students under the supervision of a physiotherapist delivered the intervention.

The intervention program selected in this study was modeled after a workstation delivery method described by Low Choy and Nitz.[17] Similar workstation exercises, which address the functional needs of subjects, have achieved favorable results when used in various studies.[19,20] Examples of these exercises included heel–toe walking, sit to stand, and ball catching and throwing. Progressive increases in challenge were introduced if the subject was able to cope. This was done by increasing the number of repetitions, altering the speed, introducing dual tasks, or changing the base of support or support surfaces. None of the exercises practiced were used to measure intervention effect.

Measures. A number of measures were used to monitor the efficacy of the intervention program. Demographic details, including years since diagnosis of MG, body parts affected, type and number of medications, and medical history, were recorded. The measurements of balance, strength, and fitness collected by the same researcher at each assessment session were included. When subjects were taking anticholinesterase medication, assessments were undertaken approximately 3 hours after ingestion.

Quantitative Myasthenia Gravis Score. The quantitative myasthenia gravis (QMG) scoring system contains 13 quantifiable items to grade the function, strength, and endurance of a subject's muscles.[25] The performance in each of the 13 items was evaluated in accordance with QMG instructions. The overall score can range from 0 to 39, and higher scores indicate greater disease severity or poorer muscle function. Given its high interrater reliability and longitudinal construct validity,[26] the QMG score has been recommended as an assessment tool for prospective studies of therapy for MG.[27]

Six-Minute Walk Test. The 6-minute walk test (6MWT) was administered according to a standardized protocol.[28,29] The 6MWT was chosen because it has shown good test–retest reliability[30] and is validated as a useful indicator of functional capacity and endurance in numerous populations, including patients with neuromuscular diseases.[31–33]

Table 1. Subject self-reported characteristics during the first assessment.

Patient	Age (years)	Gender	Years since diagnosis	MGFA class[48]	Medical history
1	43	M	20	11a	
2	68	W	12	111	
3	53	W	6	11a	
4	61	M	5	11a	Thymectomy
5	75	M	10	11	
6	24	W	7	111	Thymectomy
7	53	W	8	11	Thymectomy

MGFA, Myasthenia Gravis Foundation of America.

Several studies have also used this test to assess clinical changes after therapy.[34–38]

Timed Up & Go. The Timed Up & Go (TUG) test assesses functional mobility and anticipatory balance. It was conducted in accordance with the validated procedure described by Podsiadlo and Richardson.[39] This test was chosen because it is reliable, easy to administer, and useful for tracking clinical changes over time in the older adult population after intervention.[17,40] The TUG cognitive and manual components were also administered to observe subjects' capacity to share attention during functional activities. Standardized procedures described by Shumway-Cook *et al.*[41] were followed, and the time taken to complete each task was recorded.

Standing Stability on Foam Eyes Closed (foamEC). The Modified Clinical Test for Sensory Interaction of Balance (mCTSIB) enables evaluation of the roles of both visual and somatosensory systems necessary in balance control.[42] The test examines postural sway during static stance tasks under 4 conditions: firm surface and on foam, and with eyes open (EO) and eyes closed (EC).[43] Standard procedures were followed to obtain laboratory measures of postural stability using NeuroCom Balance Master 6.1 software (NeuroCom International, Clackamas, Oregon). Only the foamEC condition mean center of pressure (COP) sway velocity data was used, as this measure has been shown to predict falls and fractures in women.[44] High validity, interrater, and test–retest reliability of this measure have been established in young, middle-aged, and older adults.[44] Individuals with MG with ocular symptoms are at risk of reduced efficiency of their vestibular–ocular reflex (VOR) and vestibular–spinal reflex (VSR). Thus, they are more likely to present with poor postural stability in standing on foamEC.

Data Analysis. Descriptive statistics were used to report baseline demographic characteristics and assessment results for all phases.

Consistent with other single-subject studies, an approach involving assessment of clinical significance was adopted to reflect important change after intervention.[45] Clinical significance was determined by the percentage change from baseline values. To date, no cut-off value for clinical significance in a MG population for the outcome measures used in this study has been established for comparison. A mean improvement of at least 15% was selected to determine clinically significant results, as this criterion had been used in various single-subject studies involving patients with neurological disorders.[46,47]

In this study, the mean values of the data obtained from first and second assessment of the first 5 subjects recruited were regarded as pre-intervention values. The changes between pre- and post-intervention and between pre-intervention and follow-up were expressed in percentages. The median percentage values for all subjects were calculated subsequently for evaluation of effect.

RESULTS

Subjects' Characteristics. Six subjects (3 women) completed the 16-hour BST intervention for the study. One woman (subject 6) dropped out during the intervention phase due to work commitments. One woman (subject 7) became ill and developed a cardiac arrhythmia between the post-intervention and follow-up assessments, so she did not complete the follow-up assessment. No subjects reported or showed adverse effects during the study period. Baseline demographic and clinical characteristics of all subjects are listed in Table 1. Previous treatment for MG was not recorded except where thymectomy had been performed. The mean age of subjects was 53.9 years (range 24–75 years), and mean time from first symptom onset was 7.9 years (range 5–20 years). All subjects reported having ocular symptoms initially, whereas 5 subsequently developed generalized weakness. Results of all subjects are summarized in Table 2.

Quantititive Myasthenia Gravis Score. Table S1 (refer to Supplementary Material available online) shows the change in QMG item scores for baseline pre-intervention, post-intervention, and follow-up for each subject. The median change in QMG

Table 2. Assessment results of the outcome measures at pre- and post-intervention and follow-up for 7 subjects completing intervention.

Variable	Subject	Pre-intervention	Post-intervention	% change	Median % change	Follow-up	% change§	Median % change
QMG score¶ (out of 39)	1†	8.50*	7	−17.65	−28.57††	5	−41.18	−41.18††
	2‡	17.5*	11	−37.14		9	−48.57	
	3‡	10*	8	−20.00		6	−40.00	
	4†	6*	3	−50.00		4	−33.33	
	5‡	8	4	−50.00		4	−50.00	
	6	14.5						
	7‡	6	5	−16.67				
6-minute walk test (meters)	1	407.5	423	3.80	6.33	428	5.15	5.15
	2	156	377.7	142.12		294	88.46	
	3	427.5	479.6	12.19		438	2.46	
	4	437.5	471	7.66		540	23.54	
	5	443.0	430	−3.00		413	−3.84	
	6	359.5						
	7	510	533	4.50				
TUG (seconds)¶	1	7.36	6.16	−16.30	−12.75	6.47	−12.09	−7.57
	2	9.37	7.84	−16.33		6.78	−27.64	
	3	7.13	6.81	−4.42		6.49	−7.57	
	4	6.88	5.81	−17.01		6.12	1.05	
	5	6.88	6.25	−9.2		6.5	5.52	
	6	7.28						
	7	5.9	6.68	12.45				
TUG_{manual} (seconds)¶	1	8.16	6.69	−17.96	11.67	7.68	−5.88	5.88
	2	10.97	8.13	−25.85		8.88	−19.05	
	3	9.94	7.41	−6.68		7.06	−11.08	
	4	6.69	5.81	−13.09		6.38	−4.63	
	5	7.8	7	−10.25		8.41	18.08	
	6	7.14						
	7	5.9	6.68	−13.20				
$TUG_{cognitive}$ (seconds)¶	1	8.47	7.09	−16.24	−18.89††	8.09	−4.48	−13.43
	2	9.89	7.91	−20.02		6.91	−30.13	
	3	8.33	6.82	−18.13		7.03	−15.60	
	4	6.85	5.50	−19.65		5.93	−13.43	
	5	6.6	6.94	−5.00		8.06	−8.06	
	6	8.76						
	7	6.6	7.9					
Sway velocity foam eyes closed (radians/second)¶	1	1.4	1.5	7.14	−28.57††	0.8	−42.86	−45.45††
	2	6	1.4	−76.66		2.2	−63.33	
	3	2.1	1.6	−23.81		1.5	−28.57	
	4	1.65	1.3	−21.21		0.9	−45.45	
	5	2.7	1.3	−51.85		1.1	59.26	
	6	0.96						
	7	0.9	0.6	−33.33				

*Mean results from assessments 1 and 2.

†Subjects 1 and 4 undertook the intervention once a week.

‡Subjects 2, 3, 5, and 7 undertook the intervention twice a week.

§Percent change from pre-intervention.

††Clinically significant results, above 15% improvement.

¶Negative change indicates improved performance.

score between pre-intervention and post-intervention was 28.6%. This is above the 15% change considered for clinical significance. The clinically significant improvement was maintained at follow-up, with a median percentage change of 41.2% from baseline, reflecting continual improvement (Table 2).

Six-Minute Walk Test. The median change from pre- to the post-intervention and follow-up assessments was 6.1% and 5.2%, respectively, as listed in Table 2. Little change was found for most subjects in this measure; 1 subject had an improvement of 142.1% in distance covered in the post-intervention assessment and continued to improve at the follow-up assessment.

Timed Up & Go. A clinically significant change exceeding 15% was achieved for $TUG_{cognitive}$ (17.2%), and measures for TUG and TUG_{manual} approached this level (13% and 12%, respectively). At follow-up all had maintained gains over pre-intervention levels with improvement scores ranging from 6% to 13%.

FoamEC. A clinically significant change of 28.6% representing a reduction in COP sway velocity was observed. At follow-up this had continued to improve to a 45.5% change from pre-intervention indicating greater postural stability (Table 2).

DISCUSSION

The results of this study support the hypothesis that a BST exercise program results in overall improvement in balance and QMG score in subjects with MG. This is consistent with previous research studies that evaluated different exercise approaches, which have shown that exercise is not detrimental in MG.[9,11,14]

The QMG scores reflect clinically significant improvement by >15% in subjects at post-intervention and additional improvement at follow-up. Because QMG is a composite measure of myasthenia symptoms, this indicates continual improvement in function, strength, and endurance. One proposed explanation for the observed improvement is that the exercises may have led to various physiological effects such as increased quantity of mitochondria, skeletal muscle mass, and improved lactate degradation.[49] These effects may translate to improved efficiency of neuromuscular transmission, increased ability of muscles to cope with fatigue, and improved strength and endurance.[14] Future research can consider a closer examination of specific changes at the neuromuscular junction to investigate this proposal and monitor the effects of exercise on the muscle system.

No clinically significant difference was observed in the 6MWT, as the median percentage improvement was 6.1% after intervention. Although clinical significance was not attained, the distance mobilized increased across all except the oldest subject. This suggests a possible improvement in performance, which may translate to the subjects attaining improved community mobility and participation after BST exercises. In a systematic review by Dourado,[50] 6MWT performance was influenced by various demographic, anthropometric, and physiological factors, such as gender, age, weight, height, and medication. In addition, as the 6MWT is a self-paced test, the distance mobilized varies depending on the individual's motivation.[51] Therefore, these factors can limit the extent of improvement for individual subjects and may suggest why the results were not clinically significant.

Improvements in dynamic balance and functional mobility were demonstrated by reduced time to perform the TUG. We propose that the sensory component addressed in the BST during the intervention may have led to these improvements, as similar findings have been reported in previous studies in healthy and neurological populations after balance training.[18,20,21,23] In addition, the time needed to complete the TUG during additional cognitive task was improved significantly from baseline. This implies that the ability to perform dual tasks improved after intervention, which may be translated to improved ability to respond to functional demands. These results are consistent with findings by Low Choy and Nitz where older adult subjects who received BST showed significant improvements in all TUG components.[17] Cognitive fatigue is a recognized feature of MG.[52] It is possible the clinically significant improvement in the $TUG_{cognitive}$ performance post-intervention achieved in our subjects was related to some amelioration of cognitive fatigue, but this was not investigated here and certainly could be measured in future studies.

The test of foamEC demonstrated a clinically significant improvement. The reduction in COP sway velocity is considered to indicate an improvement in static balance. As the BST is proposed to target the sensorimotor system, it can be argued that improvements in multiple aspects within this system led to the improved balance function we observed.[53,54] Regarding the improvement under conditions of foamEC, it is also proposed that improvement in vestibular integration would translate to improvement in balance function.[44] This is because, under this condition, integration of vestibular input is suggested to play a key role in balance control, as the visual and somatosensory systems are either reduced or confounded.[6] Because the majority of patients with MG experience ocular symptoms and truncal weakness affecting the efficiency of VOR and VSR, BST exercises incorporating reaching to limits of stability on different surfaces and walking while moving the head and tracking an object, will provide additional vestibular stimulation and challenge to VOR and VSR. This approach is also utilized widely in studies involving hippotherapy and whole body vibration to increase vestibular stimulation to gain balance control.[46,47] Given that balance control and function are dependent on efficiency of the sensorimotor system, which deteriorates with generalized aging,[54] the concept of targeting these systems in balance training has face validity, as MG generally affects older adults. Future research might also seek to justify the need to incorporate further vestibular components in the exercise program to improve balance function.

Because dynamic activities require resolution of sensory conflict resulting from numerous input signals, effective integration of the sensory system is necessary for such functional demands. The workstation intervention utilized in this study corresponds with this theory, as the BST exercises can be modified and progressed as the individual improves to optimize challenge. Thus, incorporating the sensory component into the training program will lead to positive changes, which was reflected in the improvement in TUG and foamEC.

Although other studies on MG focused on specific strength or endurance training,[13,16,55,56] we adopted a functional strengthening approach to improve strength and endurance. This was to mimic functional demands in daily activities and to encompass a multisystem approach. This is essential, as the majority of patients with MG experience weakness and fatigue related to abnormal neuromuscular transmission.[5,57] Consequently, patients are likely to be less active and have lower bone density, increasing the risk of fractures from a fall.[57] Therefore, increasing strength and endurance of muscles through appropriate exercises can reduce weakness and fatigue[16,49] and subsequently may increase participation. The results from our study, specifically QMG scores, have reflected improvements in strength and endurance, which has been related to better balance control.[6] Incorporation of functional strengthening in the exercise program seems to be appropriate to achieve these gains.

Because this is a pilot study of the effects of the BST exercise program, comparison of methodology and results were limited to previous studies involving healthy and neurological populations.[19,21,23,58] Because MG is a variable condition, selecting individuals in a stable stage of disease also helped to distinguish between treatment effects and extraneous variables. In addition, when comparing across the phases of assessment, the pre-intervention finding was derived from mean values obtained from the first and second assessment session to account for some fluctuation of symptoms that may have caused variability in the results and to demonstrate stability of response. Possible variability resulting from learning effects was minimized, and medication management was unchanged over the period of study. Thus, with all conditions kept as stable as possible, any change detected between the assessments could be taken to represent the effects of the BST exercise program.

When comparing between subjects, we noted variability in the extent of improvements. This may be related to comorbidities, duration of MG, and age, which suggests large numbers would be needed in controlled clinical trials. Given that this was a prospective, single-subject research design, there were some limitations, including limited external validity, a lack of a control group, and absence of blinding of subjects and assessors.[59] However, there are also strengths within this research design. The same assessor was also present to conduct the assessment and to ensure consistency in instructed commands to optimize the reliability of the results. The diversity in symptoms among these patients should also be considered, as balance exercises must be tailored specifically for different presenting symptoms, requiring a pragmatic approach.[3] Thus, the design of this study was most suitable despite its inherent limitations. Another limitation was the small sample size. Analysis of the data using usual statistical methods and calculation of effect size was not appropriate and may limit the confidence of the reported results. Further research on a larger population using a randomized, controlled design is desirable to validate these findings.

Overall, the BST exercise program appears to be a promising intervention strategy to improve balance and strength in patients with MG. These results are similar to previous findings in both healthy and neurological populations. As this was a pilot study, future research should involve repeated assessments over a longer period of time on a greater number of subjects with a randomized, control group design to investigate the sustained effects of the program.

REFERENCES

1. Drachman DB. Myasthenia gravis. N Engl J Med 1994;330:1797–810.
2. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37:141–149.
3. Allen JA, Scala S, Jones HR. Ocular myasthenia gravis in a senior population: diagnosis, therapy, and prognosis. Muscle Nerve 2010;41:379–384.
4. Angelini C. Diagnosis and management of autoimmune myasthenia gravis. Clin Drug Investig 2011;31:1–14.
5. Donaldson DH, Ansher M, Horan S, Rutherford RB, Ringel SP. The relationship of age to outcome in myasthenia gravis. Neurology 1990;40:786–790.
6. Horak FB, Shupert CL, Mirka A. Components of postural dyscontrol in the elderly: a review. Neurobiol Aging 1989;10:727–738.
7. Keesey JC. Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004;29:484–505.
8. Paul RH, Nash JM, Cohen RA, Gilchrist JM, Goldstein JM. Quality of life and well-being of patients with myasthenia gravis. Muscle Nerve 2001;24:512–516.
9. Fregonezi GA, Resqueti VR, Guell R, Pradas J, Casan P. Effects of 8-week, interval-based inspiratory muscle training and breathing retraining in patients with generalized myasthenia gravis. Chest 2005;128:1524–1530.
10. Rassler B, Hallebach G, Kalischewski P, Baumann I, Schauer J, Spengler CM. The effect of respiratory muscle endurance training in patients with myasthenia gravis. Neuromuscul Disord 2007;17:385–391.
11. Rassler B, Marx G, Hallebach S, Kalischewski P, Baumann I. Long-term respiratory muscle endurance training in patients with myasthenia gravis: first results after four months of training. autoimmune diseases. Autoimmune Dis 2011:808607, 2011.
12. Weiner P, Gross D, Meiner Z, Ganem R, Weiner M, Zamir D, et al. Respiratory muscle training in patients with moderate to severe myasthenia gravis. Can J Neurol Sci 1998;25:236–241.
13. Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, Munneke M, van Engelen BG, Hendricks HT, et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. Arch Phys Med Rehabil 2007;88:1452–1464.

14. Davidson L, Hale L, Mulligan H. Exercise prescription in the physiotherapeutic management of myasthenia gravis: a case report. NZ J Physiother 2005;33:13–18.
15. Grohar-Murray ME, Becker A, Reilly S, Ricci M. Self-care actions to manage fatigue among myasthenia gravis patients. J Neurosci Nurs 1998;30:191–199.
16. Lohi EL, Lindberg C, Andersen O. Physical training effects in myasthenia gravis. Arch Phys Med Rehabil 1993;74:1178–1180.
17. Nitz JC, Choy NL. The efficacy of a specific balance-strategy training programme for preventing falls among older people: a pilot randomised controlled trial. Age Ageing 2004;33:52–58.
18. Shumway-Cook A, Gruber W, Baldwin M, Liao S. The effect of multidimensional exercises on balance, mobility, and fall risk in community-dwelling older adults. Phys Ther 1997;77:46–57.
19. Hourigan SR, Nitz JC, Brauer SG, O'Neill S, Wong J, Richardson CA. Positive effects of exercise on falls and fracture risk in osteopenic women. Osteoporos Int 2008;19:1077–1786.
20. Fu S, Choy NL, Nitz J. Controlling balance decline across the menopause using a balance-strategy training program: a randomized, controlled trial. Climacteric 2009;12:165–176.
21. Cattaneo D, Jonsdottir J, Zocchi M, Regola A. Effects of balance exercises on people with multiple sclerosis: a pilot study. Clin Rehabil 2007;21:771–781.
22. Krivickas LS. Exercise in neuromuscular disease. J Clin Neuromuscul Dis 2003;5:29–39.
23. Learmonth YC, Paul L, Miller L, Mattison P, McFadyen AK. The effects of a 12-week leisure centre-based, group exercise intervention for people moderately affected with multiple sclerosis: a randomized controlled pilot study. Clin Rehabil 2012;26:579–593.
24. Stel VS, Smit JH, Pluijm SMF, Lips P. Consequences of falling in older men and women and risk factors for health service use and functional decline. Age Ageing 2004;33:58–65.
25. Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: assessment of responsiveness and longitudinal validity. Neurology 2005;64:1968–1970.
26. Barohn R, McIntire D, Herbelin L, Wolfe G, Nations S, Bryan W. Reliability testing of the quantitative myasthenia gravis score. Ann NY Acad Sci 1998;841:769–772.
27. Jaretzki A III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards.Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg 2000;70: 327–334.
28. ATS Committee. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–117.
29. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985;132:919–923.
30. Steffen TM, Hacker TA, Mollinger L. Age- and gender-related test performance in community-dwelling elderly people: Six-Minute Walk Test, Berg Balance Scale, Timed Up & Go Test, and gait speeds. Phys Ther 2002;82:128–137.
31. Kierkegaard M, Tollback A. Reliability and feasibility of the six minute walk test in subjects with myotonic dystrophy. Neuromuscul Disord 2007;17:943–949.
32. Laforet P, Clemens PR, Corzo D, Escolar D, Florence J, van der Ploeg A, et al. Safety and efficacy results from a randomized, double-blind, placebo-controlled study of alglucosidase alfa for the treatment of Pompe disease in juveniles and adults. Neuromuscul Disord 2008; 18:832–833.
33. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 2001;119:256–270.
34. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: validity, reliability and responsiveness—a systematic review. Physiotherapy 2012;98:277–286.
35. Demers C, McKelvie R, Negassa A, Yusuf S. Reliability, validity, and responsiveness of the six-minute walk test in patients with heart failure. Am Heart J 2001;142:698–703.
36. King MB, Judge JO, Whipple R, Wolfson L. Reliability and responsiveness of two physical performance measures examined in the context of a functional training intervention. Phys Ther 2000;80:8–16.
37. Kovar PA, Allegrante JP, MacKenzie CR, Peterson MGE, Gutin B, Charlson ME. Supervised fitness walking in patients with osteoarthritis of the knee. Ann Intern Med 1992;116:529–524.
38. Leach RM, Davidson AC, Chinn S, Twort CH, Cameron IR, Bateman NT. Portable liquid oxygen and exercise ability in severe respiratory disability. Thorax 1992;47:781–789.
39. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991; 39:142–148.
40. Hakim R, DiCicco J, Burke J, Hoy T, Ardolino E. Differences in balance related measures among older adults participating in Tai Chi, structured exercise, or no exercise. J Geriatr Phys Ther 2004;27:13–17.
41. Shumway-Cook A, Brauer S, Woollacott M. Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther 2000;80:896–903.
42. Shumway-Cook A, Horak FB. Assessing the influence of sensory interaction of balance. Suggestion from the field. Phys Ther 1986;66: 1548–1550.
43. Boulgarides LK, McGinty SM, Willett JA, Barnes CW. Use of clinical and impairment-based tests to predict falls by community-dwelling older adults. Phys Ther 2003;83:328–339.
44. Nitz JC, Stock L, Khan A. Health-related predictors of falls and fractures in women over 40. Osteoporos Int 2013;24:613–621.
45. Franklin RD, Allison DB, Gorman BS. Design and analysis of single-case research. Hillsdale, NJ: Lawrence Erlbaum Associates; 1996. p 391.
46. Hammer A, Nilsagard Y, Forsberg A, Pepa H, Skargren E, Oberg B. Evaluation of therapeutic riding (Sweden)/hippotherapy (United States). A single-subject experimental design study replicated in eleven patients with multiple sclerosis. Physiother Theory Pract 2005; 21:51–77.
47. Wunderer K, Schabrun S, Chipchase L. Effects of whole body vibration on strength and functional mobility in multiple sclerosis. Physiother Theory Pract 2010;26:374–384.
48. Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Neurology 2000;55:16–23.
49. McDonald CM. Physical activity, health impairments, and disability in neuromuscular disease. Am J Phys Med Rehabil 2002;81:108–120.
50. Dourado VZ. Reference equations for the 6-minute walk test in healthy individuals [in Portuguese]. Arq Bras Cardiol 2011;96:e128–e138.
51. Enright PL. The six-minute walk test. Respir Care 2003;48:783–785.
52. Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenia gravis. Muscle Nerve 2000;23: 1401–1406.
53. King MB, Judge JO, Wolfson L. Functional base of support decreases with age. J Gerontol 1994;49:258–263.
54. Woollacott M, Shumway-Cook A. Changes in posture control across the life span—a systems approach. Phys Ther 1990;70:799–807.
55. Stout JR, Eckerson JM, May E, Coulter C, Bradley-Popovich GE. Effects of resistance exercise and creatine supplementation on myasthenia gravis: a case study. Med Sci Sports Exerc 2001;33:869–872.
56. Wolfsegger T, Stieglbauer K, Topakian R, Weiss E, Aichner F. Endurance and strength exercise intensity in patients with myasthenia gravis. Deutsche Zeitschrift Sportmedizin 2011;62:125–129.
57. Kittiwatanapaisan W, Gauthier DK, Williams AM, Oh SJ. Fatigue in myasthenia gravis patients. J Neurosci Nurs 2003;35:87–93.
58. Low Choy N, Isles R, Barker R, Nitz J. The efficacy of a work-station intervention programme to improve functional ability and flexibility in ageing clients with cerebral palsy: a pilot study. Disabil Rehabil 2003;25:1201–1207.
59. Backman C, Harris SR. Case studies, single-subject research, and N of 1 randomized trials: comparisons and contrasts. Am J Phys Med Rehabil 1999;78:170–176.