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The Effectiveness of an Aerobic Exercise Program as Measured by the Six Minute Walk Test and Subjective Fatigue Scales in Patients with Multiple Sclerosis with a Primary Complaint of Decreased Walking Ability Secondary to Fatigue

Shandrea Hubbs
Pacific University

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The Effectiveness of an Aerobic Exercise Program as Measured by the Six Minute Walk Test and Subjective Fatigue Scales in Patients with Multiple Sclerosis with a Primary Complaint of Decreased Walking Ability Secondary to Fatigue

Disciplines

Physical Therapy

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Title: The Effectiveness of an Aerobic Exercise Program as Measured by the Six Minute Walk Test and Subjective Fatigue Scales in Patients with Multiple Sclerosis with a Primary Complaint of Decreased Walking Ability Secondary to Fatigue

Clinical Scenario: The patient who led me to pursue this question is a 45 year old male with a diagnosis of multiple sclerosis whose primary complaint was decreased walking ability secondary to fatigue. Medical treatment for this diagnosis to date has included aerobic exercise, resistance training (Gutierrez et al, 2005), and neurorehabilitation training (Rampello et al, 2007) for increasing walking ability and decreasing fatigue. Problems identified with multiple sclerosis include a decrease in sensory and motor functions such as balance, coordination, postural control, and gait (Gutierrez et al, 2005). According to Rampello et al (2007), poor exercise tolerance and exertion fatigue are common complaints of patients with multiple sclerosis.

Brief Introduction: For the purposes of my clinical question, I want to know what the research says about the intervention of aerobic exercise on patients with multiple sclerosis in increasing walking ability and decreasing fatigue. I saw that patients in a neurorehabilitation facility often have complaints of fatigue, high fall risk, gait abnormalities, and inability to perform activities of daily living (ADLs) independently. According to Smith (2012), many patients with multiple sclerosis find exercise daunting in regards to their fatigue and fear of disease progression.

My Clinical Question: Does aerobic exercise significantly increase walking ability and decrease fatigue for patients with multiple sclerosis?

Clinical Question PICO:

- Population:** The patients of interest were 35-50 years old with a diagnosis of multiple sclerosis for greater than 1 year. Patients had a main complaint of decreased walking ability secondary to fatigue, but were still able to walk independently with or without an aid. Patients were medically cleared for exercise, but were not regularly participating in an exercise program. Patients did not have cognitive or other musculoskeletal impairments.
- Intervention:** The intervention consisted of a lower extremity endurance based aerobic exercise program including a warm-up period, aerobic exercise for at least 30 minutes, and a cool-down period for three days a week for eight weeks.
- Comparison:** The comparison treatment consisted of patients refraining from regular exercise for eight weeks.
- Outcome:** Gait improvements were assessed with the six minute walk test, and the timed-up-and go test. Fatigue improvements were measured with the fatigue severity scale (FSS) and the modified fatigue impact scale (MFIS).

Overall Clinical Bottom Line: Based on the results of the outcomes from Costello et al (2009) and Sabapathy and Minahan (2011), aerobic exercise may significantly improve walking ability and decrease fatigue in patients diagnosed with multiple sclerosis. The studies included participants who were similar to the patient of interest. Also, the studies were similar between populations, interventions, comparisons, and outcomes measured (Table 1). Treatment included an aerobic home walking program and aerobic circuit training. Controls included either not participating in regular exercise or performing resistance exercises. Outcome measures focused

on gait and fatigue and included the six minute walk test (6MWT), timed up and go test (TUG), physiological cost index (PCI), FSS, and MFIS. In both of the studies, the aerobic treatment group demonstrated significant improvements in gait as compared to within-group pre-treatment scores; however effect sizes were small (Sabapathy and Minahan, 2011) and medium (Costello et al, 2009) resulting in a variable clinical value. The 95% confidence intervals (CI) also varied among experiments: positive, negative, and large CI's. All experiments included randomization, acceptable external validity, had fair to good internal validity, and feasible parameters. The primary cost of aerobic treatment was the expense of the equipment for the circuit training and time commitments for the home walking program. The primary benefits of treatment were improved gait and fatigue (Sabapathy and Minahan, 2011) in the participants which correlates to increased community participation. From a clinical perspective, the benefits of treatment outweigh the cost.

Search Terms: Multiple Sclerosis, aerobic, fatigue

Appraised By: Shandrea Hubbs, SPT
School of Physical Therapy
College of Health Professions
Pacific University
Hillsboro, OR 97123
Hubb9616@pacificu.edu

Chosen Articles:

Costello E, Raivel K, and Wilson R. The effects of a twelve-week home walking program on cardiovascular parameters and fatigue perception of individuals with multiple sclerosis: a pilot study. *Cardiopulmonary Physical Therapy Journal*. 2009; 20:5-12.

Rampello A, Franceschini M, Piepoli M, Antenucci R, Lenti G, Olivieri D, and Chetta A. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. *Physical Therapy*. 2007; 87:545.

Sabapathy NM and Minahan CL. Comparing endurance and resistance exercise training in people with multiple sclerosis: a randomized pilot study. *Clinical Rehabilitation* 2011; 25: 14-24.

Rationale for Chosen Articles: I chose articles that would closely match the population, interventions, comparison, and outcome measures with those of my patient of interest with multiple sclerosis. From the list of articles, which I got from the search terms, I selected the abstracts that appeared to have the best research design while focusing on outcome measures and interventions related to the primary complaints of fatigue and walking ability.

As Table 1 presents, the final three articles chosen had populations similar to the patient of interest, interventions focused on aerobic training, comparisons that were focused on within group changes, and outcomes related to ambulation and fatigue.

Table 1: Comparison of article PICOs

| | Costello et al | Rampello et al | Sabapathy and Minaham |
|---|---|--|--|
| Population | <ul style="list-style-type: none"> • 18-65 y/o • Dx of MS > 1 year • EDSS ≤ 6 • No Hx of exacerbation within 6 months • No regular participation in aerobic exercise within 6 months • No cardiovascular, pulmonary, or orthopedic conditions preventing aerobic exercise • Walk Independently 100m | <ul style="list-style-type: none"> • 20-55 y/o • Dx of MS • EDSS < 6 • No Hx of exacerbation within 4 weeks • No Hx of steroid therapy within 2 months • No regular physical activity within 2 months • No cardiovascular, pulmonary, or orthopedic conditions preventing aerobic exercise | <ul style="list-style-type: none"> • 47-66 y/o • Dx of MS • Given consent to participate by their physicians • Able to walk independently with or without an aid |
| Intervention | <ul style="list-style-type: none"> • Home walking program based on 6MWT and staying within prescribed HR zone • 20-30 min of walking exercise • 3 d/w for 12 weeks | <ul style="list-style-type: none"> • Aerobic training within target HR zone • 60 min of exercise • 3 d/w for 8 weeks | <ul style="list-style-type: none"> • Endurance circuit training with eight stations • 48 min of circuit intervention • 2 d/w for 8 weeks |
| Comparison | <ul style="list-style-type: none"> • Refraining from regular exercise • 12 weeks | <ul style="list-style-type: none"> • Neurorehabilitation training • 60 min of Neuro Training • 3 d/w for 8 weeks | <ul style="list-style-type: none"> • Resistance exercise training • 8 exercises, 2-3 sets, 6-10 reps, 30-60 secs rest between sets • 2 d/w for 8 weeks |
| Outcome Measures | <ul style="list-style-type: none"> • FSS • 6MWT • PCI • RPE • HRR • Polar Fitwatch HR Monitors | <ul style="list-style-type: none"> • EDSS • MFIS • MSQOL-54 • 6MWT | <ul style="list-style-type: none"> • Grip Strength • Functional Reach • 4-Step Square • TUG • 6MWT • MSIS • MFIS • SF-36 |
| <p>6MWT: 6 minute walk test d/w: days per week Dx: Diagnosis EDSS: Expanded Disability Status Score FSS: Fatigue Severity Scale HR: Heart rate HRR: Heart rate reserve Hx: history</p> <p>MFIS: Modified Fatigue Impact Scale MS: Multiple Sclerosis MSIS: Multiple Sclerosis Impact Scale PCI: Physiological Cost Index RPE: Rating Perceived Exertion SF-36: Health Status Questionnaire Short Form 36 TUG: Timed 'Up and Go' Test y/o: years old</p> | | | |

Table 2 presents the final three articles PEDro scores which are measures of the quality and integrity of each experiment including randomization and blinding.

Table 2: Comparison of PEDro Scores

| | Costello et al | Rampello et al | Sabapathy & Minahan |
|-------------------------------|----------------|----------------|---------------------|
| Random | 1 | 1 | 1 |
| Concealed allocation | 0 | 0 | 0 |
| Baseline comparability | 1 | 1 | 1 |
| Blind Subjects | 0 | 0 | 0 |
| Blind Therapists | 0 | 0 | 0 |
| Blind Assessors | 0 | 0 | 0 |
| Adequate Follow-up | 0 | 0 | 1 |
| Intention-to-treat | 0 | 0 | 0 |
| Between Groups | 1 | 1 | 1 |
| Point Estimates & Variability | 1 | 0 | 1 |
| Total Score | 4/10 | 3/10 | 5/10 |

Based on the above comparisons, I have chosen to write this critically appraised paper on the articles by Costello et al (2009) and Sabapathy and Minahan (2011). These articles fit my population of interest, closely match the intervention of lower extremity aerobic training, have comparisons that can focus on within-group changes, and include outcome measures that assess the quality of subject walking ability as well as the amount of fatigue perceived by the patient.

Costello E, Raivel K, and Wilson R. (2009). The Effects of a Twelve-Week Home Walking Program on Cardiovascular Parameters and Fatigue Perception of Individuals with Multiple Sclerosis: A Pilot Study. *Cardiopulmonary Physical Therapy Journal*. 20(1): 5-12.

Clinical Bottom Line: The evidence from this article suggests that therapy incorporating a home walking program for aerobic exercise does significantly improve gait, but does not significantly decrease fatigue levels in patients with a diagnosis of multiple sclerosis. The treatment group participated in twelve weeks of a home walking program while the control group was asked to refrain from regular exercise for twelve weeks. Performance was measured via the 6MWT, PCI, and FSS. The evidence presents with a medium effect size for the 6MWT and PCI, and a small effect size for the FSS. This study was flawed with multiple threats to internal validity including a lack of examiner and patient blinding, lack of appropriate statistical tests, not following a strict protocol, inadequate statistical power, lack of power analysis, and study design. External validity of this study is fair and does not compromise the ability to generalize results to the patient of interest.

Article PICO

Population: The subjects included participants between the ages of 18-65 years old with a diagnosis of multiple sclerosis greater than one year. The participants had no history of exacerbations within six months and did not participate in a regular aerobic exercise program within six months of the study. Participants were able to walk independently 100 meters with or without resting and had an

Expanded Disability Status Score (EDSS) of less than or equal to six. Participants were medically cleared to participate in an aerobic exercise program and did not have cardiovascular, pulmonary, or orthopedic conditions preventing aerobic exercise.

Intervention: The intervention consisted of 30-40 minutes of a home walking program based on the 6MWT and staying within their prescribed heart rate zone. Aerobic training sessions were three days a week for twelve weeks.

Comparison: The comparison treatment included the participants refraining from regular exercise for six months prior to the study and refraining from regular exercise during the twelve week study.

Outcomes: Gait was assessed via 6MWT and PCI. Fatigue was assessed via the FSS. Exercise intensity was measured and monitored via the rating of perceived exertion (RPE), heart rate reserve (HRR), and the Polar Fitwatch heart rate monitors.

Blinding: Blinding did not occur in this study: the participants, researchers, and analysts were aware of group allocation and the type of task being performed. Complete lack of blinding is a threat as a Hawthorne effect, Rosenthal effect, or rater bias may occur; a participant's recorded performance may be influenced by their knowledge or other's knowledge of their group allocation. Although the outcome measures for gait were objective and less likely to be affected by the lack of blinding, the outcome measures for fatigue were subjective and more likely to be affected by the lack of blinding. Blinding either participants or clinicians would be difficult in this study. These threats are also minimized by within-group comparisons that would control for lack of blinding as each person is compared to their own group's performance.

Controls: All participants had a history of multiple sclerosis, participated in a pretest session in which baseline data for resting heart rate, blood pressure, and fatigue was recorded, and completed a 6MWT. The control group was asked to refrain from regular exercise during the twelve week study. The treatment group participated in an individualized home walking program, utilizing the Polar Fitwatch heart rate monitor, three times per week for twelve weeks. The control group may not have been an appropriate comparison group because the difference between the groups could be attributed to factors other than the intervention. However, this threat may be minimized by within-group comparisons in which differences in baseline performance and post-intervention data could be accredited to the intervention.

Randomization: Subjects were randomly assigned, by a coin toss, to either the control group or to the home walking program after they met the inclusion criteria. Randomization did seem to be successful since both groups had similar initial test scores in clinical and demographic characteristics as well as in the 6MWT and PCI. The authors did not state the pre-test scores for the FSS for either group.

Study: This study was a randomized control trial which recruited fifteen subjects with a diagnosis of multiple sclerosis (MS). Subjects were recruited using the National Multiple Sclerosis Chapter Website and using flyers that were distributed over a two year period at a MS Walkathon. All subjects participated in a pre-test session which involved the collection of demographic and baseline data. The treatment group (n = 9) received a home walking program

in which subjects were given a five minute warm-up, 20-30 minutes of walking within their prescribed heart rate zone, and then a five minute cool-down; the total time for the treatment session was 30-40 minutes of a home walking program. The treatment group was instructed to walk three times a week for twelve weeks. The control group (n = 6) was asked to refrain from regular exercise for six months prior to the study and also during the twelve week study.

Inclusion criteria included subjects being between the ages of 18 and 65 with a diagnosis of MS greater than one year, no history of exacerbations within six months prior to the study, no regular participation in aerobic exercise within six months prior to the study, having the ability to walk independently 100 meters with or without resting, and an EDSS score of less than or equal to six. Exclusion criteria included having cardiovascular, pulmonary, or orthopedic conditions preventing aerobic exercise.

Outcome Measures: I am interested in the 6MWT and the PCI scores because these tests assess the quality of subject walking ability. I am interested in the FSS score because this test assesses the amount of fatigue perceived by the patient. Tests were performed prior to testing and performed again twelve weeks following the interventions. I am interested in within-group changes for the 6MWT and the PCI, as the between-group comparison may be attributed to factors other than the intervention. The authors provided pre-treatment and post-treatment data for the 6MWT and the PCI, and provided mean change in variables between groups for the FSS. The authors did not provide pre-treatment and post-treatment data for the FSS. Therefore, within-group comparisons will be made for the home walking program for the 6MWT and the PCI, but a between-group comparison will be made for the FSS. The authors noted that these tests were reliable and valid (per other studies), but the authors did not validate the outcome measures with a second independent sample. The authors did not state a minimally clinically important difference (MCID). However, they did state a minimal detectable difference (MDD) of 0.15 beats/meter for the PCI. Steffen and Seney (2008) found the MCID for the 6MWT to be 106 meters for patients with MS. Pouchot et al (2008) found an MCID for the FSS to be 20.2 for patients with Parkinson's disease.

Study Losses: All subjects completed the training. However, in the treatment group, one subject (11%) was excluded from data analysis. In the control group, two subjects (33%) were excluded from data analysis. Reasons for study losses were due to poor compliance and failure to show for posttest assessment.

Summary of internal validity: This study had fair internal validity: randomized allocation to groups, a control group, and reliable instruments. Four significant threats to internal validity were identified: lack of examiner and patient blinding, lack of appropriate statistical tests, not following a strict protocol, and inadequate statistical power. Study design was a minor internal threat. A lack of examiner and patient blinding may cause a Hawthorne effect, Rosenthal effect, or rater bias to occur. However, blinding either participants or clinicians would have been difficult in this study. The authors chose to use the Mann-Whitney U test to compare the results of their between group score data. An appropriate statistical test, to show within-group results, would be the Paired T-test which was analyzed, by me, using Microsoft Excel software. The authors did not follow a strict protocol as demonstrated by having the patients receive a self-administered aerobic walking program in their homes. Also, the authors asked the control group to refrain from any regular exercise during the twelve week study, but they did not clearly define

‘regular exercise’ criteria to ensure control group compliance. Although the study had twelve subjects participate, the study did not include a power analysis to determine the minimum number of subjects needed to detect a statistical relationship within the home walking program group and control group. A pre-test and post-test study design can sensitize subjects to a treatment and cause an increase or decrease in scores. This study did not use an independent reference standard.

Evidence: I am interested in the within-group comparisons of the before and after treatments for the 6MWT and for the PCI, and a between-group comparison for the FSS. Table 3 presents each group’s mean changes and standard deviations from each test. Within-group data for the 6MWT and PCI was calculated by me using the pre-test and post-test data provided by the authors and between-group data for the FSS was provided by the authors. All data from Table 3 will be used for further analysis in Table 4 and Table 5.

Table 3: Mean Changes and Standard Deviation (SD) from Pre-Treatment to Post-Treatment Collected from the 6MWT, PCI, and FSS

| | Control Group (No regular exercise) | | Treatment Group (Home Walking Program) | |
|-------------------|--|-------|---|-------|
| | Mean | SD | Mean | SD |
| 6MWT (m) | 46.75 | 37.25 | 65.75 | 24.35 |
| PCI (beats/meter) | -0.02 | 0.044 | -0.088 | 0.043 |
| FSS (points) | -0.17 | 0.49 | -0.24 | 0.72 |

The FSS questionnaire has nine statements measuring subjective fatigue symptoms on a seven point scale (the higher the score, the more fatigue is being experienced). Patients with MS typically score greater than or equal to 45 points out of 63 possible points, whereas people who do not experience fatigue typically score less than or equal to 25 points out of 63 points (Tarver, 2010). The PCI estimates oxygen consumption during exercise (a lower PCI score shows improved aerobic metabolism). According to Fredrickson, Ruff, and Daly (2007), an increase in exercise results in an increase of oxygen demand in the muscle which then leads to an increase of cardiac output. Cardiac output is the result of heart rate multiplied by stroke volume, and can therefore be measured with a heart rate monitor. PCI can be calculated with the following formula: (heart beats per minute during exercise minus heart beats per minute at rest) divided by meters per minute (Fredrickson, Ruff, and Daly, 2007).

Table 3 indicates that those who received the home walking program performed better than those who did not, as demonstrated by the home walking program group having higher mean scores on the tests. The treatment group had the highest values for the 6MWT showing that the treatment group had the greater improvements in gait for distance ambulated. The treatment group had the greatest decrease in PCI and FSS scores showing that the treatment group had the greatest improvement in gait efficiency, energy expenditure, and subjective fatigue scores.

Table 4: Mean Difference, P-Value, Effect Size, and 95% Confidence Intervals (CI) for Within-Treatment Group Data Changes Collected from the 6MWT and PCI and Between-Group Data Changes for the FSS

| | Mean Difference | Mean Difference 95% CI | P-Value | Effect Size | Effect Size 95% CI |
|-------------------|-----------------|------------------------|---------|-------------|--------------------|
| 6MWT (m) | 65.75 | 8.16 to 123.33 | 0.015 | 0.44 | NA |
| PCI (beats/meter) | -0.08 | -0.19 to 0.02 | 0.042 | 0.45 | NA |
| FSS (points) | 0.07 | -0.74 to 0.88 | 0.61 | 0.11 | -1.09 to 1.31 |

A paired t-test for the 6MWT and the PCI was performed by me using the pre-treatment and post-treatment data supplied by the authors to determine if the home walking program was effective. Mean difference refers to the difference in scores between the pre-treatment and post-treatment for the home walking program group. Mean difference and the 95% CI were calculated by me based from the paired t-test data. Effect size refers to the significance of the mean difference and is used to discuss if the difference is remarkable. Effect size was calculated by me based from the data presented in the paired t-test.

Table 4 indicates that within treatment group differences are significant and not due to random chance as evidenced by p-values of less than 0.05, providing evidence that the home walking program was effective in increasing gait. The FSS shows a p-value of greater than 0.05 indicating that there was no significant difference between groups in decreasing fatigue. A 95% CI about the mean distance ambulated was 8.16 to 123.33 meters. The MCID for the 6MWT was found to be 106 meters for patients with MS (Steffen and Seney, 2008), showing that the home walking program was clinically beneficial for 22% of the patients. The positive values of the mean difference 95% CI for the PCI indicate that gait efficiency and energy expenditure may increase for the treatment group, if the experiment were repeated 100 times. The authors stated a MDD of 0.15 beats/meter for the PCI, showing that the home walking program was clinically important for 25% of the patients. The positive values of the mean difference 95% CI for the FSS indicate that the treatment group might experience more fatigue than the control group, if the experiment were repeated 100 times. According to Table 4, there was a medium effect size for the 6MWT and the PCI, and a small effect size for the FSS.

Applicability of Study Results:

Similarity to my patients: The subjects in this study were similar to the patient of interest. The home walking program group mean age was 51.4 ± 3.7 with two men and six women. The control group mean age was 34.8 ± 5.8 with one man and three women. The participants and my patient of interest were all diagnosed with multiple sclerosis for greater than one year, lacked a history of regular aerobic exercise for greater than six months, were able to walk independently greater than 100 meters, and were cleared by their physician for participation in an aerobic exercise program.

Benefits vs. Costs: The home walking program group significantly improved in their 6MWT and PCI scores, but did not significantly improve their FSS scores. As walking was a functional and familiar task, the patients did not require significant time for practice sessions or

to be oriented to this task. The primary expenses of the home walking program was the financial cost of a heart rate monitor and the time commitment of 40 minutes of aerobic training at home three days a week. Walking programs were covered by insurances (as therapeutic activities) and were utilized in typical treatment sessions for MS. PT education on the equipment usage was most likely not a significant amount of time. The home walking program had an 89% compliance rate as compared to the 67% compliance rate of the non-exercising group (Costello et al, 2009), thus it may be assumed that the home exercise program was more enjoyable or feasible as refraining from regular exercise. The authors did not elaborate on the causes of non-compliance for the control group. In general, the treatment did not harm the patient and potential adverse effects such as delayed onset muscle soreness (DOMS) following treatment could be avoided by adhering to the standard PT guidelines for exercise prescription. The benefit of improved gait was associated with increased functional abilities, increased community participation, and decreased likelihood of falls. The treatment frequency and duration was also reasonable. A home walking program could be used for a variety of conditions and by other disciplines (occupational therapy and speech therapy)—however the cost and benefits were being considered in relation to the patient of interest, exclusively.

Feasibility of treatment: The home walking program can be readily applied to the clinical setting. The frequency and duration of treatments were typical of a home exercise plan for patients with a diagnosis of multiple sclerosis and would be covered by insurances. Study procedures for the treatment group were described well and could be easily reproduced. The treatment was feasible as PT commonly uses gait training for multiple sclerosis rehabilitation. The higher compliance rate for the home walking program group suggests that the treatment is neither painful nor unreasonable for patients to endure. The treatment did not require additional education, however treatment did require an additional time commitment for at home exercise.

Summary of external validity: The study had fair external validity: overall the study was very similar to my clinical scenario and PICO. The participants were of similar characteristics as the patient of interest and received a similar prescription of treatment (frequency and duration of treatment). The exclusion criteria reasonably excluded those who had the cardiovascular, pulmonary, or orthopedic conditions that would contraindicate an aerobic exercise program.

Sabapathy NM and Minahan CL. Comparing endurance and resistance exercise training in people with multiple sclerosis: a randomized pilot study. *Clinical Rehabilitation* 2011; 25: 14-24.

Clinical Bottom Line: The evidence from this article suggests that therapy incorporating aerobic circuit training does significantly improve gait and fatigue in patients with MS. Participants in this study were similar to my patient of interest in age, diagnosis, and ambulation. The aerobic circuit training group participated in eight weeks of aerobic circuit training while the control group participated in resistance exercises for eight weeks. Performance was measured via the 6MWT, TUG, and MFIS. The evidence presents with a small effect size for the 6MWT, TUG, and the MFIS. This study was flawed with multiple threats to internal validity including lack of examiner and patient blinding, inadequate statistical power, and study design. External validity of this study is fair and does not compromise the ability to generalize results to the patient of interest.

Article PICO

- Population:** The subjects included participants between the ages of 47-66 years old with a diagnosis of multiple sclerosis. The participants were able to walk independently with or without an aid and were given consent to participate in the study by their physicians. Participants had a Disease Steps Score of less than or equal to three.
- Intervention:** The intervention consisted of a 5 minute warm-up, 48 minutes of aerobic circuit training, and 15-20 minutes of stretching. Aerobic circuit training sessions were two days a week for eight weeks.
- Comparison:** The comparison treatment consisted of a 5 minute warm-up, 2-3 sets of 6-10 repetitions of 8 resistance exercises, and 15-20 minutes of stretching. Resistance training sessions were two days a week for eight weeks.
- Outcomes:** Grip strength was assessed via a hand-held dynamometer. Balance was assessed via functional reach and the four step square test. Gait was assessed via the 6MWT and the TUG. Fatigue was assessed via MFIS. Disease impact was assessed via the Multiple Sclerosis Impact Scale (MSIS). Depression was assessed via the Beck Depression Inventory. Quality of life was assessed via the Health Status Questionnaire Short Form-36 (SF-36).

Blinding: Blinding did not occur in this study. Although two of the four assessors were blinded to the program training order, the participants, researchers, and analysts were aware of group allocation and the type of task being performed. Complete lack of blinding was a threat as a Hawthorne effect, Rosenthal effect, or rater bias may occur; a participant's recorded performance may be influenced by their knowledge or other's knowledge of their group allocation. Although the outcome measures for gait was objective and less likely to be affected by the lack of blinding, the outcome measures for fatigue and quality of life was subjective and more likely to be affected by the lack of blinding. Blinding either participants or clinicians would be difficult in this study. These threats were also minimized by within-group comparisons that would control for lack of blinding as each person was compared to their own group's performance.

Controls: All participants had a history of multiple sclerosis and participated in a pre-test session in which outcome measures were recorded. The control group participated in resistance exercise training which consisted of 2-3 sets of 6-10 repetitions of eight exercises two days a week for eight weeks. The treatment group participated in forty-eight minutes of aerobic circuit training two days a week for eight weeks. The control group may not have been an appropriate comparison group because it could be unclear if the difference between the groups was attributed to aerobic circuit training or attributed to resistance exercises. However, this threat may be minimized by within-group comparisons in which differences in baseline performance and post-intervention data could be accredited to the intervention.

Randomization: Subjects were randomly assigned, by a coin toss, to either participating in the aerobic circuit training or resistance exercise training program first after they met the inclusion criteria. The authors used a mixed factor analysis of variance (ANOVA) using Bonferroni adjustments to determine baseline differences. Randomization did seem to be successful since the authors found no significant difference in baseline measures between training modes and training program order. Both groups had similar initial test scores for the 6MWT, grip strength,

functional reach test, four step square test, TUG, MFIS, MSIS, the Beck Depression Inventory, and the SF-36.

Study: This study was a randomized cross-over study in which subjects with multiple sclerosis completed eight weeks of aerobic circuit training and eight weeks of resistance exercises with an eight week interval between training programs. Twenty-one subjects were recruited using a flyer displayed at local community health centers. Although sixteen subjects participated in both treatment groups, program order was randomly selected. The aerobic circuit training group had six subjects in the first eight weeks and eleven subjects in the second eight weeks, while the resistance training group had fifteen subjects in the first eight weeks and five subjects in the second eight weeks. All subjects participated in a pre-test session which involved the collection of baseline data. All subjects underwent two sessions a week for eight weeks of one treatment type, participated in an eight week resting interval, and then underwent two sessions a week for eight weeks of the other treatment type. The aerobic training group received a 5 minute warm-up, 48 minutes of aerobic circuit training, and 15-20 minutes of stretching; the total treatment time was 73 minutes. The resistance exercise group received a 5 minute warm-up, 2-3 sets of 6-10 repetitions of 8 resistance exercises, and 15-20 minutes of stretching.

Although the authors did not specifically state exclusion criteria, the following inclusion criteria was enforced: subjects being able to ambulate independently either with or without a walking aid, subjects having a diagnosis of multiple sclerosis, and subjects obtaining approval for participation from their general practitioner.

Outcome Measures: I am interested in the 6MWT and the TUG scores because these tests assess the quality of subject walking ability. I am interested in the MFIS because this test assesses the effects of fatigue as perceived by the patient. Tests were performed prior to testing and again following the interventions. I am interested in within-group changes for aerobic circuit training group for the 6MWT, TUG, and the MFIS group because it could be unclear if the difference between the groups was attributed to aerobic circuit training or attributed to resistance exercises. The authors did not note if these tests were reliable and valid and they did not validate the outcome measures with a second independent standard. However, Paltamaa et al (2006) has found that the test-retest reliability of the 6MWT, for patients with MS, was excellent with an intra-class correlation coefficient (ICC) value of 0.96. According to Nilsagard et al (2009) the reliability of the TUG was excellent with an ICC of 0.98. Amtmann et al (2012) found that the internal consistency for the MFIS was 0.96. The authors did not state an MCID. However, Steffen and Seney (2008) found the MCID for the 6MWT to be 106 meters for patients with MS. Reitberg et al (2010) found that the minimal detectable change (MDC) for the MFIS for patients with MS was 19.23%. According to Ries et al (2009), the MDD for the TUG was 4.09 seconds for patients with Alzheimer's disease.

Study Losses: In the treatment group, 81% of the subjects completed the training. In the control group, 90% of the subjects completed the training. Reasons for study losses were due to difficulties with time commitments, moving to a new house, and ill dependents.

Summary of internal validity: This study had good internal validity: randomized allocation of program order, a control group, proper statistical tests, reliable instruments, and subjects followed a strict protocol. Two significant threats to internal validity were identified: lack of examiner and patient blinding and inadequate statistical power. Study design was one minor internal threat. A lack of examiner and patient blinding may cause a Hawthorne effect, Rosenthal effect, or rater bias to occur. However, blinding either participants or clinicians would have been difficult in this study. Although the study had twenty-one subjects participate, the study did not include a power analysis to determine the minimum number of subjects needed to detect a statistical relationship between the aerobic circuit training group and resistance exercises group. A pre-test and post-test study design could sensitize subjects to a treatment and cause an increase or decrease in scores. This study did not use an independent reference standard.

Evidence: I am interested in the within-group comparisons of the before and after treatments for the 6MWT, TUG, and MFIS. Table 5 presents each group’s mean changes and standard deviations from each test. Within-group data was calculated by the authors using a repeated measure ANOVA with Bonferroni adjustments. All data from Table 5 will be used for further analysis in Table 6.

Table 5: Mean Changes and Standard Deviation (SD) for Pre-Treatment and Post-Treatment Data Collected from the 6MWT, TUG, and the MFIS

| | Control Group (Resistance Exercise) | | Treatment Group (Aerobic Circuit Training) | |
|-----------------------------------|--|------|---|------|
| | Mean | SD | Mean | SD |
| 6MWT (m) | 38.1 | 70.0 | 18.6 | 40.1 |
| TUG (secs) | -0.7 | 0.8 | -0.5 | 0.7 |
| MFIS: Physical Scale (Points) | -1.6 | 3.3 | -2.7 | 5.3 |
| MFIS: Psychosocial Scale (Points) | -1.6 | 11.6 | -0.8 | 1.4 |
| MFIS: Cognitive Scale (Points) | -3.3 | 7.8 | -2.3 | 6.0 |

Table 5 indicates that those who received resistance exercises (the control group) performed better than those who received aerobic circuit training, as demonstrated by the resistance exercise group having greater mean changes on the 6MWT, TUG, MFIS: Psychosocial Scale, and the MFIS: Cognitive Scale. The aerobic circuit training group performed better than the control group only in the MFIS: Physical Scale, as demonstrated by a greater mean change.

Table 6: Mean Difference, P-value, Effect Size, and 95% Confidence Intervals (CI) for Within-Aerobic Circuit Training Group Data Changes collected from the 6MWT, TUG, and MFIS

| | Mean Difference | Mean Difference 95% CI | Mean Difference % Change | P-Value | Effect Size |
|------------|-----------------|------------------------|--------------------------|-----------|-------------|
| 6MWT (m) | 19 | -52.32 to 90.32 | NA | < 0.01 | 0.19 |
| TUG (secs) | 0.5 | -0.63 to 1.63 | NA | < 0.01 | 0.29 |
| MFIS: Phy | 2.7 | -2.13 to 7.53 | 14% | < 0.05 | 0.36 |
| MFIS: Psy | 0.7 | -0.39 to 1.79 | 26% | < 0.01 | 0.47 |
| MFIS: Cog | 2.3 | -5.05 to 9.65 | 15% | Not Given | 0.23 |

Table 6 indicates that the within treatment group differences are significant and not due to random chance as evidenced by p-values of less than 0.05, providing evidence that the aerobic circuit training was effective in increasing gait and decreasing fatigue. Mean difference refers to the difference in scores between the pre-treatment and post-treatment for the aerobic circuit training group. Mean difference and the 95% CI were calculate by me using Microsoft Excel software and were based from the data provided by the authors. Mean difference percent change scores shows the percentage of change between the MFIS post-training scores and the pre-training scores. Effect size quantifies the size of the difference between two groups and is used to discuss if the difference is remarkable. Effect sizes greater than 0.60 are considered to be large, effect sizes greater than 0.30 are considered to be medium, and effect sizes greater than 0.00 are considered to be small. Effect size was calculated by me based from the data presented by the authors.

The negative values of the 95% CIs indicate that the treatment group may perform worse, if the experiment were repeated 100 times. The MCID for the 6MWT was found to be 106 meters for patients with MS (Steffen and Seney, 2008), showing that the aerobic circuit training was not clinically beneficial in increasing gait. The MDC for the TUG was 4.09 seconds for patients with Alzheimer’s disease (Ries et al, 2009), also showing that the aerobic training did not produce clinically important changes in gait. The MDC for the MFIS was found to be 19.23% (Reitberg et al, 2010), showing that the aerobic circuit training group had clinically important changes in fatigue as measured by the psychosocial scale. According to Table 6, there was a small effect size for the 6MWT, TUG, and MFIS.

Applicability of Study Results:

Similarity to my patients: The subjects in this study were similar to the patient of interest. The subject mean age was 55 ± 7 years with four men and twelve women. The participants and the patient of interest were all diagnosed with multiple sclerosis, could ambulate independently with or without the use of a walking aid, and were given approval to participate in an aerobic exercise program by their general practitioners. An important difference between the patient of interest and the participants in this study was that the patient of interest did not previously

participate in a regular exercise program. Whereas the subjects in this study were recruited from flyers placed at local community health centers.

Benefits vs. Costs: The aerobic circuit training group significantly improved in their 6MWT, TUG, and MFIS. Patients would require a training session to be oriented towards the eight circuit training stations, but would not otherwise require significant time for practice. Aerobic circuit training did not produce consistent or remarkable benefits as seen by the negative 95% CI values in Table 6. The equipment – which includes steps, an arm cranking bike, an upright stationary cycle, a recumbent stationary cycle, a cross-trainer, and a treadmill – were expensive. However, these were also common types of exercise equipment found at a health center. Although the aerobic circuit training group had an average compliance rate of 81%, there was a higher rate of compliance with the resistance exercise group. Therefore, it could be assumed that the aerobic circuit training was less enjoyable or harder to accomplish than the resistance exercises. In general, the treatment did not harm the patient and potential adverse effects such as DOMS following treatment could be avoided by adhering to the standard PT guidelines for exercise prescription. The benefit of improved gait was associated with increased functional abilities, increased community participation, and decreased likelihood of falls. This treatment would be covered by insurances (as therapeutic activities) and utilized in typical treatment sessions for patients with multiple sclerosis.

Feasibility of treatment: Aside from the expense, the aerobic circuit training could be readily applied to the clinical setting. The frequency and duration of treatments were typical of treatments for patients with a diagnosis of multiple sclerosis and would be covered by insurances. Study procedures for the treatment group were described well and could be easily reproduced. The treatment was feasible as PT commonly uses aerobic training for multiple sclerosis rehabilitation. The treatment did not require additional time or education; however the equipment was very expensive. The average compliance rate (81%) for the aerobic circuit training suggested that the treatment was neither painful nor unreasonable for patients to endure.

Summary of external validity: The study had fair external validity: overall the study was similar to the patient of interest and PICO. The participants were of similar characteristics as the patient of interest and received a similar prescription of treatment (frequency and duration of treatment). This study lacked exclusion criteria that would exclude those who had visual, cognitive, or musculoskeletal deficits that would impact the results of this study.

Synthesis/Discussion: Per the evidence, my clinical experience, and the patient's response to aerobic exercise, this therapy may be an effective treatment option for improving gait, but may not be effective for improving fatigue for patients with MS. Costello et al (2009) and Sabapathy and Minahan (2011) found that aerobic exercise significantly increased gait in participants who were similar to my patient of interest. From my clinical experience, I have seen aerobic exercise provide activities to improve motor functions, strengthening, and endurance. However, taking into account the small and medium effect sizes, a low percentage of patients that found a clinically important difference gait, and the concern of spasticity, aerobic exercise may not be my first choice as a treatment option for patients with MS whose primary complaint was a decrease in gait. As a therapist, I may utilize aerobic exercise as one treatment option for a patient with MS whose primary complaint was decreased gait.

MS is an autoimmune inflammatory disorder characterized by multiple areas of CNS white matter demyelination. According to White and Dressendorf (2004), MS patients are challenged by their disability to maintain an active lifestyle due to fatigue, motor weakness, spasticity, balance, heat sensitivity, and mental depression. Aerobic exercise has also been found to be safe for all patients with MS; for patients with severe disability, aerobic exercise may be used as a means to maintain cardiovascular fitness (Brown and Kraft, 2005). From my clinical experience, I have seen aerobic exercise provide activities to improve motor functions, strengthening, and endurance.

Aerobic exercise presents activities in a way that promotes motor functions. Salem et al (2011) found that a community-based aerobic aquatic exercise program significantly improved motor functions in patients with MS. Aerobic exercise is commonly defined as low-intensity, high duration exercise in which oxygen is utilized via aerobic metabolism. Many familiar and functional tasks, such as walking, can be incorporated as an aerobic exercise. Aerobic exercises may be measured in increments of time rather than repetitions; therefore, a patient may complete many repetitions without realizing how many he or she has performed. Intensity levels can be easily monitored through either the use of a heart rate monitor or through the manual palpation method of counting the heart beats in the carotid or radial arteries.

Aerobic exercise presents activities in a way that promote muscle strengthening. According to White and Dressendorf (2004), patients with MS often complain of decreased muscle strength due to decreased rate of motor unit recruitment and firing and due to increased central motor conduction time. Howe and Gomperts (2006) conducted a review of four studies focusing on the effects of aerobic exercise for patients with MS and found that aerobic exercise resulted in strength gains for the primary muscle groups involved in the training activity. Howe and Gomperts (2006) also found that subjects with MS who participated in an aerobic aquatic program made improvements with their muscle strength, power, work and fatigability.

Aerobic exercise presents activities in a way that promote endurance. According to White and Dressendorf (2004), regular exercise for patients with MS provides benefits such as increased cardiorespiratory fitness, muscle strength and endurance, reduced systemic fatigue, improved daily mood, and enhanced quality of life. White and Dressendorf (2004) found that exercise prescriptions for patients with mild to moderate MS provides benefits that outweigh potential adverse effects, thereby improving quality of life while reducing the risks of secondary disorders.

Although the compliance rates in the two studies was above average (> 80%), they were below 100% which may suggest that patients participating in aerobic exercise found the treatment to be daunting. Howe and Gomperts (2006) stated that patients with MS find initiating and maintaining regular exercise to be an obstacle when they are already experiencing fatigue. Effect sizes for the two studies were both small and medium for gait and fatigue. Also, according to Steffen and Seney (2008), only 22% of the subjects found aerobic exercise to increase gait greater than an MCID of 106 meters. The cost of aerobic circuit training equipment would be expensive if purchased solely for the treatment of a patient. However, many PT facilities have access to aerobic exercise equipment. At the very least, aerobic exercises can be adapted to functional tasks such as community walking, which would not require the purchasing of any equipment. Muscle spasticity is also a concern. According to White and Dressendorf (2004), patients with MS often complain of spasticity (a velocity dependent upper motor neuron impairment that is associated with increased tendon reflexes, increased resistance to passive

stretch, and muscle weakness) due to extremes in temperature, humidity or infections. Aerobic exercise may cause a change in body temperature, thus aggravating spasticity.

The use of aerobic exercise is supported by evidence-based practice. The aforementioned research, my clinical experiences, and the patients' responses support aerobic exercise as one treatment option for improving gait in patients with multiple sclerosis. Aerobic exercise is presented in a way that promotes motor function, strengthening, and endurance. However, taking into account the small and medium effect sizes, a low percentage of patients that found a clinically important difference gait, and the concern of spasticity, aerobic exercise may not be my first choice as a treatment option for patients with MS whose primary complaint is a decrease in gait. Further research regarding other treatment options that could be used in conjunction with aerobic exercises for this patient population would be beneficial. As a therapist I may utilize aerobic exercises as one treatment option for improving gait for patients with multiple sclerosis.

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