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EFFECTS OF A 12-WEEK AEROBIC EXERCISE PROGRAM COMBINED WITH MUSIC THERAPY AND MEMORY EXERCISES ON COGNITIVE AND FUNCTIONAL ABILITY IN PEOPLE WITH MIDDLE TYPE OF ALZHEIMER'S DISEASE

*[1]Christina Kampragkou PT
[1]Paris Iakovidis PT, MSc
[1]Eftychia Kampragkou PT
[2]Eleftherios Kellis PT, PhD

ABSTRACT

Background: The Alzheimer's disease is the most common form of dementia and represents 60% of its cases. The disease is characterized by cognitive, non-cognitive and functional deficits and it's incurable. The main of this study was to examine the effects of the aerobic exercise in combination with the music therapy and memory exercises in functional and cognitive ability on a patient with that have been affected by middle type (Second stage) of Alzheimer's disease.

Methods: Thirty patients from Chronic Diseases Center, with Alzheimer's disease, divided between an intervention and a control group, participated in this randomized controlled study. (Thirty patients with Alzheimer's were chosen from chronic disease center, and are divided into an intervention and a control group). The intervention requires 30 minutes of aerobic exercise, 10 minutes of memory games and music therapy, three times a week, for the duration of 12 weeks. The outcome measures the "Mini Mental State Examination" (MMSE) scale and the "Alzheimer's Disease Assessment Scale cognitive test" (ADAS) for the cognitive ability, "Katz Index Independence in Activities of Daily Living" (ADL), "Get up and Go test" and "One leg standing balance test" (OLST) for the functionality. A three-way analysis of variance designs was applied to compare changes in each outcome measure before and after the intervention between the groups.

Results: The MMSE score decrease significantly for the control group (males: 16.00 ± 4.04 to 15.14 ± 4.01 and for females: 16.00 ± 1.85 to 15.25 ± 1.98 before and after intervention) but not for the intervention group ($p > 0.05$) (males: 16.25 ± 2.71 to 16.12 ± 2.94 and females: 12.85 ± 2.67 to 12.57 ± 2.93). The ADAS score on intervention experimental therapy group was significantly low (males: 39.00 ± 7.98 to 37.50 ± 8.12 and females: 49.85 ± 6.54 to 48.28 ± 6.79). In the Get up and Go test (males: 18.87 ± 5.24 to 17.87 ± 4.15 and females: 19.85 ± 4.94 to 18.57 ± 4.64) and in the OLST (males: 4.57 ± 3.10 to 6.00 ± 2.77 and females: 4.00 ± 3.26 to 5.28 ± 3.40) there was a sign of progress in the results, while in the ADL no difference was observed in any group. (experimental group males: 3.50 ± 1.19 to 3.50 ± 1.19 and females: 2.57 ± 1.13 to 2.57 ± 1.13, control group males: 3.57 ± 1.51 to 3.57 ± 1.51 and females: 3.50 ± 0.75 to 3.50 ± 0.75).

Conclusion: The aerobic exercise combined with the music therapy and the memory tests offer some improvement in cognitive and functional ability and contribute to the deteriorating delay of the symptoms of patients that suffer from Alzheimer and are hospitalized.

Keywords: Alzheimer's disease; aerobic exercise; music therapy; functional ability; cognitive ability; elderly.`

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[1]Department of Physiotherapy, Alexander Technological Institute of Thessaloniki, Greece.
[2]Laboratory of Neuromechanics, Department of Physical Education and Sport Science at Serres, Aristotle University of Thessaloniki, Serres, Greece.

CORRESPONDING AUTHOR

*[1]Christina Kampragkou PT

Department of Physiotherapy, Alexander Technological Institute of Thessaloniki, Greece.
Tel:+30 2310 013859 Fax:+30 2310 791166
e-mail: ckampragkou@yahoo.com

INTRODUCTION

The Alzheimer's Disease is the most common form of dementia [1]. It constitutes of one of the most significant medical and socioeconomic problems, as it affects over 26 million people all over the world [1-3]. It is a progressive degenerative brain disease and it is expressed through neuropathological and neurochemical changes [4]. People with Alzheimer Disease develop brain damage and cognitive deficits which result in the gradual loss of their functional autonomy-independence and in the growth of change-disorders of their natural behavior. The loss of memory, the difficulty in communication, the disorientation in space and time, the discount in the ability of absorbing new knowledge or the reset of the old one, contribute to the loss of personal freedom and the weakness of covering and implementing daily needs and activities (personal hygiene, clothing, feeding, movement) [5].

Physical exercise is required at all stages of the Alzheimer's Disease [6] aiming to maintain motor control and functional status and therefore to the quality of the patients' life. The purpose of exercise interventions is to improve movement problems, coordination problems reflected in balance and walking. Memory problems make communication difficult and in final stages impossible [7]. Exercise programs tend to be personalized depending on the patient's functional deficits and usually they include free energetic exercises combined with breathing and aerobic exercise [8,9].

Aerobic exercise is an integral part of the non-medical treatment of the Alzheimer's Disease [10]. This type of exercise stimulates the release of neurotrophic factors and promotes the angiogenesis, enabling neurogenesis and synaptogenesis, which improve memory and cognitive functions [11]. Furthermore, aerobic exercise increases the tumor of the gray matter in the hippocampus, it improves the blood supply to the brain, it contributes to the neuroplasticity, it increases the production and function of the neurotransmitters while it reduces the pathological b' amyloid thresholds [1,11].

According to the American Collection of Music therapy, this kind of therapy is "the clinical and evidence-based use of music interventions to accomplish individualized goals within a therapeutic relationship". (American Music Association, 2011) [12] Music therapy has a positive influence on people that suffer from dementia [13] and particularly for people with the Alzheimer's Disease [14]. Generally, this type of therapy is used for the maintenance or the increase of physical, mental, social and emotional function levels. (Ziv N et al., 2007) [15] The short improvement of feelings and the reduction of the behavioral disorders after music therapy treatment have been previously reported. (McDermott O et al., 2013) [16] Music therapy is characterized as a safe and effective method of non-medical treatment thanks to which anxiety, aggressiveness, and scrimmage that occur in patients with a moderate and severe form of Alzheimer's Disease is reduced and it minimizes depression in people with a mild or moderate form of the disease [17]. However, the long term effects of music therapy have not been previously examined (McDermott O et al., 2013) [16].

The purpose of this study was to examine the effects of the aerobic exercise combined with the music therapy and the memory exercises ~~in~~ on people (patients) suffering from a middle type of Alzheimer. The main research hypothesis was that the combined aerobic, memory and music therapy exercise intervention would display an improvement in cognitive function, functional ability than controls.

METHODS

Study Design

Individuals with the middle type of Alzheimer were randomly assigned into an experimental therapy group and a control group. Two measurement sessions were conducted one before the start of the intervention and one after the end. The outcome measures the scale "Mini Mental State Examination", "Katz Index of Independence in Activities of Daily Living", the "Alzheimer's Disease Assessment Scale cognitive test", Get up and Go test and the "One leg standing balance test". OR the nurses of the foundation did not take part in both therapies.

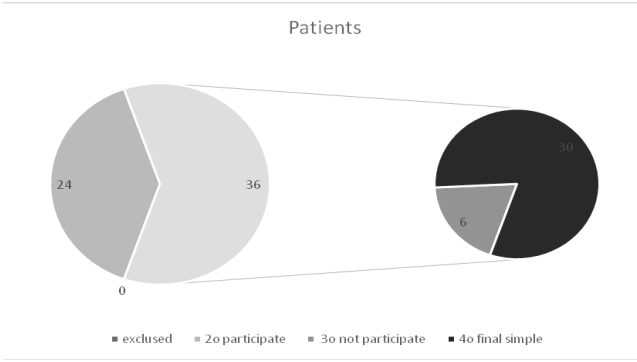
Study Participants

A total of 60 patients who were hospitalized in the geriatric department of the Chronic Diseases Center of Thessaloniki "Saint Panteleimon" were initially recruited during a 12-month period (from September 2014 to September 2015). The criteria for inclusion were as follows:1) they had to stay permanently at CSPCMACDT "Saint Panteleimon", 2) they had to show clinical evidence of the AD according to the criteria NINCDS-ADRDA (Mc Khan et al, 1984) from middle type of the disease, 3) they had to be able to stand and walk by themselves or with someone else's help or some help tool, 4) they had to be 65 years old and over, 5) they should not be independent in at least one of the following: transportation, moving in bed, walking or balance. And the criteria for exclusion from the therapy is stated below 1) patient with any other form of dementia, 2) patient any other damage of the neural system, 3) patients history of psychiatric disorders, 4) patients with mental retardation. The trial was approved by the Physiotherapy Department of the Alexander Technological Institute of Thessaloniki, Greece and the Ethics Committee of the "Saint Panteleimon" Foundation. Written consent of participation was obtained from the responsible legal guardian of the participants.

A total of 24 patients were excluded from the study, as 17 patients did not meet the inclusion criteria, 5 declined to participate and 2 for other reasons (Figure 1). The remaining 36 patients were randomly assigned to a treatment (N = 18 patients) or a control (N = 18) group using a series of random numbers. For this purpose, each patient was given a sealed envelope ensuring concealed randomization. One of the investigators (P.I) was responsible for allocation sequence generation, enrollment of the participants and assignment of the participants to their groups. The therapist who administered the memory game program (common

to both groups) had a 12-year experience in this clinic and she was blinded to group assignment. The therapist who applied the music therapy and aerobic exercise were not blinded to group assignment.

Figure 1: Study Participants



PROCEDURE

The experimental therapy group intervention, include sessions, three times a week each consisting of 40 minutes of aerobic exercise, memory games and music therapy. Specifically, each session consisted of 30 minutes of aerobic exercise, 10 minutes of memory games, attention, speech, and music. The control group only followed a memory game program. The memory-attention-speech exercises that were used came from the guide, "Empowering the disorganized mind" by Eleni Tsantali and Magda Tsolaki 2005 [18]. The choice of music used for each subject depending on their origin and their music past experience (traditional music). The aerobic exercise that was implemented included 20 minutes of walking at 60-70% of the Maximum Heart Rate (MHR) of every patient. The MHR was calculated as 220 minus age. The heart rate was calculated with a telemetered heart frequency meter and 10 minutes of free and dynamic exercises with bars and balls.

Outcome Measures

The Mini Mental State Examination (MMSE) is considered a tool of systematic evaluation and assessment of the mental and cognitive ability in clinical practice.[19] It was selected because it is fast and easy to use. The MMSE scale examines five areas of the cognitive function: the orientation in time and location, the commands executing in 3 stages-submit, the focus-attention-ability of calculation, the recall and the language ability. It includes 30 questions each rated with 0 or 1 if the answer given is wrong or correct, respectively. The highest score is 30 points. Scores between 0 and 10 show serious cognitive damage, scores between 11 to 20 moderate cognitive damage, 21-26 middle cognitive disorders and 27-30 natural cognitive function [20].

The Katz Index of Independence in Activities of Daily Living (ADL) index was developed to study the therapy results and to provide a prognosis for the old people and the chronic sufferers reliably and objectively [21]. The ADL index examines six areas of the functional ability: the possibility of taking a bath, the ability of dressing, toilet use, the transport (movement), the ability to control the bladder and the intestine (existence of incontinence) and feeding. The patients are rated with 0 when they are unable to execute the function and with 1 when they execute it. The highest score is 6, which means full functionality, 4 medium inadequacies and 2 or less serious functional inadequacy [22].

The Alzheimer's Disease Assessment Scale Cognitive Test (ADAS scale) is frequently used to assess cognitive function in clinical trials [23-27]. It is used as an indicator of diagnosing the AD, it defines the disease stage, indicating the level of the mental condition and cognitive ability as well as non-cognitive functions (mood-behavior) in people with or without AD [23-27]. The highest ADAS score is 70 and the lowest one is 0. Wrong answers were rated, which means that the highest score indicates a higher dysfunction, while a person without AD should have a score between 0 and 5.

The Get up and Go a test is a tool of mobility and fall risk assessment [28,29]. Particularly, the patients were asked to get up from the chair, walk three meters, return to the chair and sit down. The time was measured in seconds from the moment they got up until they sat again down. The risk percentage is evaluated in falls (no danger, low, mediocre, high, very high) through observation of balance and stability during sitting, upright, change in direction and walking [30]. In the bibliography, various times of completing the test have been given, depending on the age of the participant, yet views are different [28-30]. Overall, it is considered that times higher than the 30s make people apt to falls whilst time (measurement in seconds) for the age groups of 60-69, 70-79 and 80-89 years are 8.1 (7.1 to 9.0 s), 9.2 (8.2 to 10.2s) and 11.3 (10.0 to 12.7s), respectively.

The One Leg Standing Balance Test (OLST) is an index of balance assessment and it has been used in trials that examine balance [31]. Its use is not only limited to the elderly, but it is also met with musculoskeletal pain, in neural system damages and in any other case of disorder or danger related with balance [32]. For the execution of the OLST, it was asked from the examinees to put their hands on their waist and lift one of their legs so that their hip is in a neutral position and their knee flexed at 90°. The test is performed with open and closed eyes, on each leg. The test is interrupted in case the foot touches the ground, overcomes the 30s or if the examinees open their eyes when they are supposed to be closed. For the open eyes condition, normative values for the age groups 60-69, 70-79 and 80-89 years old are 26.0 s, 14.0 s and 8.0 - 10.0 s respectively [31,32].

Final sample

Three patients did not participate in the initial measurement session. Additionally, three patients discontinued the intervention (two patients because they were transferred to another medical care center and one patient because of unrelated reason). Therefore, a total of 30 patients (15 men and 15 women) completed all measurements. There were 15 patients in the experimental group and 15 for the control group (Table 1).

Statistical Analysis

The statistic Shapiro-Wilk test was implemented which showed that data come through a regular allocation ($p > 0.05$). Consequently, for every dependent variable, a two (group: therapy vs control) X 2 (gender: men vs women) and 2 (time: pre vs post intervention) analysis of variance (ANOVA). In case of a statistically significant interaction, the Tukey test was implemented for the discovery of the statistically important difference between the price couples. The mean and the 95% confidence intervals difference between pre and post intervention measurements were also calculated. The significance level was set at $a = 0.05$.

RESULTS

The results of the MMSE score are displayed in Table 1. The analysis of variance for the MMSE scale showed that there was a statistically non-significant triple interaction (Time X Group X Gender) on the MMSE score ($F_{1.26} = 0.32$, $p > 0.05$). However, there was a statistically significant double interaction of Time X Group on the MMSE score ($F_{1.28} = 6.51$, $p < 0.05$). Analysis with the Tukey tests showed that the MMES score decreased significantly after training only for the control group ($p < 0.05$), while for the experimental therapy group the score remained unaltered ($p > 0.05$). The main effect for the factors Group ($F_{1.26} = 1.14$, $p > 0.05$) and Gender ($F_{1.26} = 2.53$, $p > 0.05$) was not statistically significant.

The Analysis of Variance for the ADAS cog scale (Table 1) showed that there was a statistically non-significant triple interaction (Time X Group X Gender) on ADAS cog scale ($F_{1.26} = 0.29$, $p > 0.05$). There was, though, a statistically significant double interaction of the factor Time X Group in ADAS cog ($F_{1.28} = 52.57$, $p < 0.05$). Analysis with the Tukey test showed that the ADAS cog scale significant decreased after the intervention only for the experimental therapy group ($p < 0.05$), while the score remained unaltered for the control group ($p > 0.05$). Furthermore, the two group scores were significantly different ($p < 0.05$) before the intervention (the experimental therapy group showed a higher score than the control group), while after the end of the intervention the difference between the Groups was not statistically significant ($p > 0.05$). The main effect of the factor Group ($F_{1.26} = 0.15$, $p > 0.05$) was non-statistically significant while there was Gender main effect ($F_{1.26} = 4.32$, $p < 0.05$) as the score was higher for the women in relation to the men.

Table 1: Average (±standard deviation) of Mini Mental State Examination (MMSE) and of Alzheimer's Disease Assessment Scale cognitive test (ADAS cog) for the experimental therapy group and control group before and after the therapeutical intervention

	Group Therapy		P value	Control Group		
	Before	After		Before	After	
MMSE						
Men	16.25 ± 2.71	16.12 ± 2.94		16.00 ± 4.04	15.14 ± 4.01*	
Women	12.85 ± 2.67	12.57 ± 2.93		16.00 ± 1.85	15.25 ± 1.98*	
Total	14,66 ± 3,13	14,46 ± 3,37	>0.05	16,00 ± 2,95	15,20 ± 2,98*	0.017
ADAS cog						
Men	39.00 ± 7.98^	37.50 ± 8.12*		42.14 ± 9.66	42.85 ± 9.28	
Women	49.85 ± 6.54^	48.28 ± 6.79*		42.25 ± 4 .16	43.15 ± 4.13	
Total	44,06 ± 9,03	42,53 ± 9,15	.0001	42,20 ± 6 ,98	43,06 ± 6,74	.0001

* = statistically significant difference in a relation with the measurement before the intervention, ^ statistically significant difference between the two teams, $p < 0.05$.

The results of the ADL, Get up and Go test, and OLST test are displayed in Table 2. The results for the ADL indicator (showed that there were not any changes to the ADL score and thus the statistical analysis was impossible. The analysis of variance for the Get up and Go test showed that there was not a statistically significant triple interaction (Time X Group X Gender) on Get up and Go test score ($F_{1.26} = 0.82$, $p > 0.05$). There was a statistically significant double interaction of the factor Time X Group on this score ($F_{1.26} = 22.09$, $p < 0.05$). The analysis with the Tukey test showed that the score remained unaltered for both Groups ($p > 0.05$). However, the two Groups' scores were not significantly different ($p < 0.05$) before the intervention, while after the end of the intervention the difference between the Groups was statistically significant ($p > 0.05$) (the experimental therapy group showed a lower score than the control group). The main effect for the factors Group ($F_{1.26} = 1.24$, $p > 0.05$) and Gender ($F_{1.26} = 2.72$, $p > 0.05$) was not statistically significant.

Table 2: Average (±standard deviation) of Katz Index of Independence in Activities of Daily Living (ADL), of Get up and of Go test and the One leg standing balance test (OLST) for the experimental therapy group and control group before and after the therapeutical intervention.

	Group Therapy		P value	Control Group		
	Before	After		Before	After	
ADL						
Men	3.50 ± 1.19	3.50 ± 1.19		3.57 ± 1.51	3.57 ± 1.51	
Women	2.57 ± 1.13	2.57 ± 1.13		3.50 ± 0.75	3.50 ± 0.75	
Total	3,06 ± 1,22	3,06 ± 1,22	>0.05	3,53 ± 0,75	3,53 ± 0,75	>0.05
Get up and Go test						
Men	18.87 ± 5.24	17.87 ± 4.15		22.42 ± 4.64^	23.00 ± 4.16	
Women	19.85 ± 4.94	18.57 ± 4.64		17.37 ± 2.44^	19.37 ± 5.01	
Total	19,33 ± 4,95	18,20 ± 4,24	>0.05	19,73 ± 4,36^	21,06 ± 4,84	>0.05
OLST						
Men	4.57 ± 3.10	6.00 ± 2.77*		3.42 ± 1.39^	3.14 ± 1.57	
Women	4.00 ± 3.26	5.28 ± 3.40*		4.50 ± 2.72^	3.75 ± 2.76	
Total	4,40 ± 3,09	5,66 ± 2,99*	.0001	4,00 ± 2,20^	3,46 ± 2,23	>0.05

* = statistically significant difference in a relation with the measurement before the intervention, ^ statistically significant difference between the two teams, $p < 0.05$.

The analysis of variance for the OLST test showed that there was no statistically significant triple interaction (Time X Group X Gender) on OLST score ($F_{1.26} = 0.76$, $p > 0.05$). There was, however, a statistically significant double interaction effect of Time and Group on OLST score ($F_{1.26} = 39.03$, $p < 0.05$). The analysis with the Tukey test showed that OLST score significantly increased only for the experimental therapy group ($p < 0.05$), while for the control group the score remained unaltered ($p > 0.05$). Furthermore, the two Groups' scores were not significantly different ($p < 0.05$) before the intervention, while after the end of the intervention the difference between the Groups was statistically significant ($p > 0.05$) (the experimental therapy group showed a higher score than the control group). The main effect for the factor Group ($F_{1.26} = 0.03$, $p > 0.05$) and Gender ($F_{1.26} = 0.63$, $p > 0.05$) were not statistically significant.

Table 3: P values of significance resulting from pre-post intervention comparisons for each group, for each outcome measure.

	Experimental group	Control group
MMSE	>.05	.017
ADL	>.05	>.05
ADAS	.0001	>.05
Get up and Go test	>.05	>.05
OLST	.0001	>05

DISCUSSION

In this present study, a combination of various non pharmaceutical ways of treating the AD was implemented. The results showed a small improvement of the functional and mental condition of the patients of the experimental therapy group and a deterioration delay of the evolution of the disease (as reflected by the unchanged MMSE score) in those people.

Initially, the MMSE score was not altered for the experimental therapy group, before and after the intervention (Table 1). This indicates that the patients in this group maintained their cognitive ability, contrary to the control group, whose score was decreased which may be indicative due to the deterioration of the disease. Other research studies reported similar results to the present study, utilizing, however, different types of intervention programs [6,33-36]. For example, Venturelli et al., (2011) [36], by using a walking program in a retirement home, Hernandez et al.,(2015) [6], through physical activity, and Requena et al.,(2004) [37], through cognitive treatment, contributed to the cognitive decrease delay. In other research studies, a program of moderate aerobic exercise [33], another one with exercise and walking [34] and a stamina program with walking and cycling [35], showed a MMSE score improvement for the experimental groups.

The ADAS scale scores decreased for the experimental therapy group indicating an improvement in their cognitive ability. The research studies by Requena et al.,(2004)[37], Yang et al.,(2015) [33] and Yu F. et al., (2014) [1] lead to the AD symptoms decrease for the experimental therapy groups, in which a cognitive treatment program or aerobic exercise is used, while the ADAS cog scores maintain similar results with the current research. This indicates that the present program was particularly effective for the cognitive ability of the people suffering from AD.

With respect to the functionality scores, the ADL scale was unaltered for any group of this current project. Rolland Y. et al., (2000) [35] reported similar same results after implementing a stamina program. On the contrary, the results of other research studies are different [34,36], showing that experimental therapy groups of which showed mobility and independence improvement (the ADL scale scores increased). In addition, Rolland Y. et al.,(2007)[9] reported a delay in the disease development with an exercise program in nursing home residents, without changing the ADL score in the experimental therapy group.

The Get up and Go test and OLST scores were altered, enhancing the experimental group's functional ability. Specifically, the Get up and Go test score was not altered after the intervention period for any group. However, the experimental therapy group indicated a lower score after the intervention compared to the control group. The OLST score increased only for the experimental group, whereas for the control group it remained unchangeable. The research study by Rolland et al.,(2007) [9] came to the conclusion that the AD improvement delay is related to the exercise. In addition, Arcoverde et al., (2008) [38] found that a physiotherapy program improves the Get up and Go test scores and decreases the functional reduction which agrees with the present findings. Finally, Ahn et al., (2015) [39] commented that exercise with lenient belts contributes to the enhancement of strength, stamina, heart function and walking speed, by improving the OLST efficiency, while the Get up and Go test scores do not indicate significant changes in dynamic balance. Consequently, any physical program applied in the experimental therapy group, the score of the Get up and Go test and the OLST score is positively affected.

Limitations

The results of this study should be considered within certain limitations. Particularly, a number of patients that participated in the therapy (30 patients) are small and it may not represents of all patients with the disease. Further, the participants were patients who are permanently hospitalized. Third, the intervention time (12 weeks) might have been long enough for general exercise adaptations but not long enough for dementia patients. Although every effort has been made to standardize exercise and music characteristics, exercise program details are personalized for each patient. In addition, only some therapists were

blinded relative to the experimental aims. Finally, no adverse or side effects of both interventions were reported by any patient at any stage of the intervention period.

CONCLUSION

A 12-week intervention combining aerobic exercises with music therapy and memory tests offered some improvement in cognitive and functional ability in hospitalized people that suffer from Alzheimer disease. Further, the results showed that this program might be beneficial to the deteriorating delay of the symptoms of the disease. Combinations of various therapy methods could be beneficial for improving quality of life of these patients, although further research in identifying the precise role of each method is required.

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