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Influence of physiotherapy on exercise tolerance in patients after COVID-19

Wpływ fizjoterapii na tolerancję wysiłku u chorych po przebytym COVID-19

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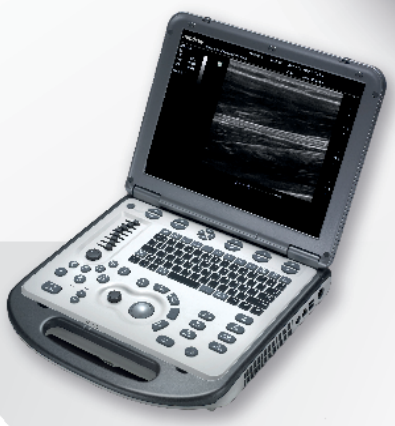
ULTRASONOGRAFIA W FIZJOTERAPII



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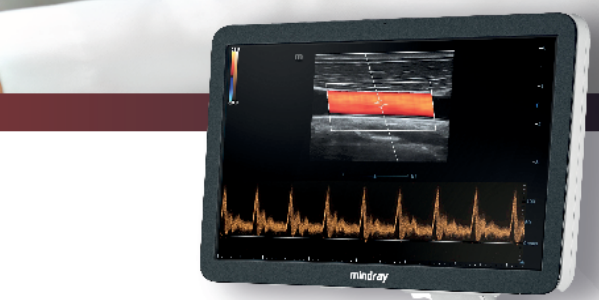

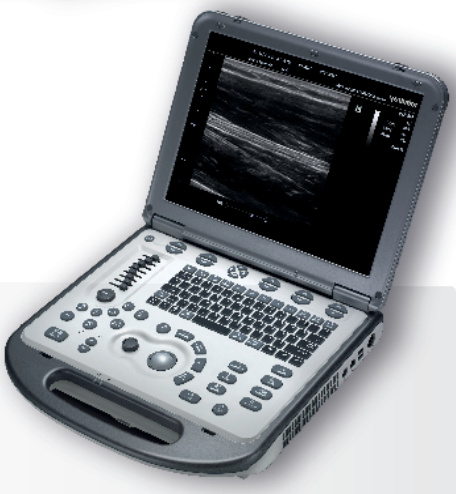

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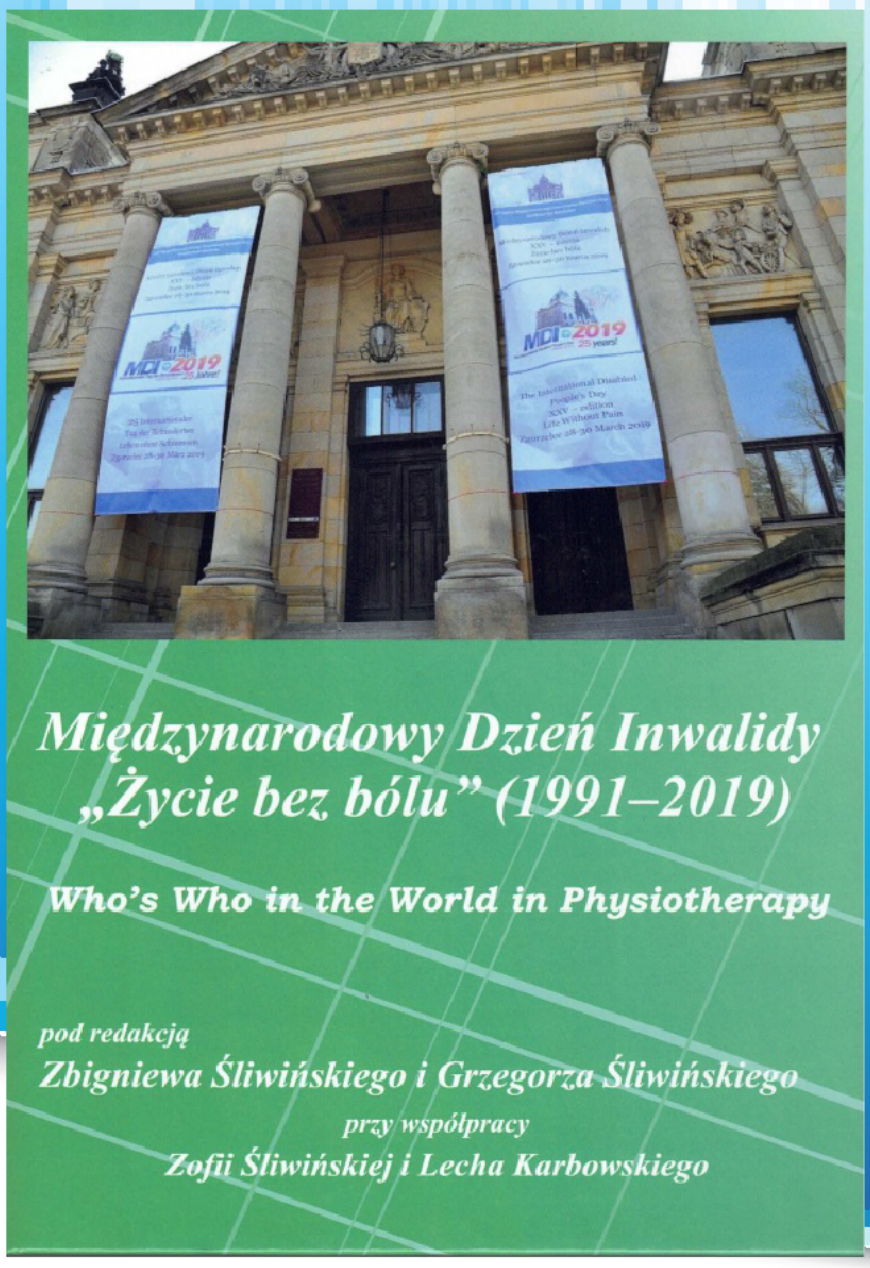

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Impact of aerobic versus resistive training on functional capacity in acute myeloid leukemia survivors: a comparative study

Wpływ treningu aerobowego i treningu oporowego na wydolność funkcjonalną u osób po ostrej białaczce szpikowej: badanie porównawcze

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Abstract

Background. Cancer-related fatigue is a persistent symptom in acute myeloid leukemia survivors, with associated decreased functional capacity, which further deteriorates their quality of life. The current study aimed to compare between the impact of aerobic training and resistive training on functional capacity in acute myeloid leukemia (AML) survivors. Fifty nine patients with AML from both sexes aged between 35 and 45 years,were selected from hematology department in (BLINDED FOR PEER REVIEW), where the study was conducted. Patients were randomly assigned into two groups; Group (A) underwent aerobic training in the form of cycling within 50-60% of maximum heart rate. Group (B) underwent resistive training conducted in the form of a series of exercises using free weights, and dumbbells. Sessions were carried out three times per week, for a total of eight weeks period. Six minute walk test (6MWT), 10 repetitions maximum test (10 RM). Ventilatory functions test, fatigue severity assessment (FAS) and quality of life (QoL) scales were measured in both groups before and after the study period. Results. Significant improvement in 6MWT, maximum oxygen consumption (VO_2 max) and vital capacity in group (A), significant improvement in fatigue and QoL in both groups and significant improvement in 10 RM test in group (B). Conclusion. Both aerobic and resistive training significantly improved functional capacity in acute myeloid leukemia survivors with a more significant improvement due to aerobic training.

Key words:

acute myeloid leukemia, aerobic training, resistive training, functional capacity, quality of life

Streszczenie

Informacje wprowadzające. Zmęczenie związane z rakiem jest uporczywym objawem u osób po ostrej białaczce szpikowej, z towarzyszącą zmniejszoną zdolnością funkcjonalną, co dodatkowo pogarsza jakość ich życia. Niniejsze badanie miało na celu porównanie wpływu treningu aerobowego i treningu oporowego na wydolność funkcjonalną u osób po ostrej białaczce szpikowej (AML). Pięćdziesięciu dziewięciu pacjentów po ostrej białaczce szpikowej obu płci w wieku od 35 do 45 lat zostało wybranych z oddziału hematologii w (ZAŚLEPIONE DLA CELÓW OCENY NAUKOWEJ), w którym przeprowadzono badanie. Pacjenci zostali losowo przydzieleni do dwóch grup; Grupa (A) realizowała trening aerobowy w postaci jazdy na rowerze w zakresie 50-60% tętna maksymalnego. Grupa (B) realizowała trening oporowy prowadzony w formie serii ćwiczeń z wykorzystaniem ciężarów i hantli. Sesje odbywały się trzy razy w tygodniu, łącznie przez osiem tygodni. Wykonano test sześciominutowego marszu (6MWT) oraz 10 powtórzeń testu maksymalnego (10 RM). W obu grupach mierzono funkcję oddechową, oceniano nasilenie zmęczenia (FAS) oraz jakość życia (QoL) przed i po okresie badania. Wyniki. Znacząca poprawa 6MWT, maksymalnego zużycia tlenu (VO2max) i pojemności życiowej w grupie (A), znaczna poprawa w zakresie zmęczenia i jakości życia w obu grupach oraz znaczna poprawa w teście 10 RM w grupie (B). Wniosek. Zarówno trening aerobowy, jak i oporowy znacznie poprawiły wydolność funkcjonalną u osób po ostrej białaczce szpikowej, z bardziej znaczącą poprawą po zastosowaniu treningowi aerobowemu.

Słowa kluczowe

ostra białaczka szpikowa, trening aerobowy, trening oporowy, zdolność funkcjonalna, jakość życia

Introduction

Leukemias are a group of various neoplastic disorders of white blood cells. They can be classified as; myeloid or lymphoid according to their origin, and into two types; acute or chronic, based on their coarse threats [1].

Acute myeloid leukemias (AMLs) are exceptionally dangerous neoplasms, liable for countless malignant growth related deaths [2]. They are typically manifested by bleeding, anemia, infection or organs'infiltration [3]. AML incidence has been close to stable in recent years. It persistently shows two peaks in occurrence in early childhood and later adulthood. With a prevalence of 3.7 per 100,000 people and an age-dependent mortality of 2.7 to almost 18 for every 100,000 people, there is a rising awareness in the Western world of AML's special features ensuing from an increasingly-aging population [4].

The treatment for leukemia entails the utilization of chemotherapy followed by a bone marrow transplant in the majority of cases. However, incapacitating fatigue, nausea, malignancy cachexia, anemia, and depression are among expected side effects generally seen in leukemia patients going through chemotherapy [5].

The positive impact of a moderate exercise program on physical and psychological aspects in cancer patients had been shown in some researches [6]. A directed multimodal exercise intervention including high and low intensity components was doable and could securely be utilized in patients with different malignant growths, who were getting adjuvant chemotherapy or treatment for advanced disease. It has shown decreased fatigue and improved vitality, aerobic capability and muscular power [2].

Acute myeloid leukemia cases represent almost 20% of total cases referred to physical therapy department, a large portion of cases in remission stage after ending their chemotherapy dosages experience low functional capacity and muscle weakness. There were hardly any past studies done to contemplate the effect of various sorts of exercise trainings on functional capacity in AML patients. Hence the significance of this study is to contribute to filling the gap in knowledge about this specific area in rehabilitation of AML patients/survivors.

Methods

Design of the study

This study was designed as a randomized single-blinded parallel study with active treatment groups. Clinical examiner and patient were blinded to treatment. The study was proactively approved by the ethical committee of Faculty of Physical Therapy, Cairo University. Number of approval: P.T.REC/012/001874. It was registered 30/10/2020 retrospectively in ClinicalTrials.gov, ID: NCT04617145.The study was conducted in compliance with the declaration of Helsinki ethical principles for medical research involving human subjects.

Participants

Sixty-eight patients of both sexes diagnosed as AML were screened for eligibility to participate in the study, however six patients were excluded from the beginning; as four patients didn't meet the inclusion criteria of the study, the other two patients refused to participate. Patients were selected from the hematology department, where the study was conducted, after they had fulfilled the inclusion criteria of the study; Acute myeloid leukemia survivors from both sexes were included. Their ages ranged from 35 to 45 years. All Patients were in remission stage with less than 5% blast cells in their bone marrow, absolute neutrophil count (> 1000/µL), platelet count (> 100,000/µL), and independent from red blood cell transfusion. A bone marrow biopsy revealed no clusters or collections of blast cells.

However, patients were excluded from the study if they had; extramedullary leukemia, musculoskeletal deformities, severe anemia (hemoglobin less than 8g/dl) or autoimmune thrombocytopenia (platelets less than 10,000/µL), Leucopenia (leucocytes count less than 3000/µL) and Body Mass Index (BMI) ≥ 35.

Before participation in the study, patients received a full explanation about the nature, purpose, and benefits of the study. All patients signed an informed consent form and it was clearly stated that they have the right to refuse or withdraw from participation in the study at any time, and their personal information is to be kept confidential.

Sixty two patients who fulfilled the inclusion criteria of the study were randomly assigned to either aerobic training group (A) or Resistive training group (B). Aerobic training group (A) included thirty one patients, who received aerobic exercise for 30-40 min at 50-60% of maximum heart rate in the form of cycling using bicycle ergometer, three times per week for eight weeks, in addition to usual daily living activities, medication and nutritional support. While the Resistive training group (B), included thirty one patients who underwent a resistive training in the form of a series of exercises using free weights, and dumbbells three times per week for eight weeks, in addition to usual daily living activities, medication and nutritional support. Randomization was done by an independent research assistant through computer-generated random numbers.

After equal allocation in both groups and before starting any exercise training, two patients had died in the aerobic training group, and so became only twenty nine patients. As well as, the withdrawal of one patient from the resistive training group before being assessed at the end of the study, and so excluded from analysis.

Initial medical screening was performed for every patient by an oncologist and clinical history was recorded for all participants. Study protocol and the objectives of the study were altogether explained to all participants, who were asked to maintain their pharmacologic treatment, general eating routine, and typical daily activities and lifestyle all through the study.

Echocardiography had been done for every patient before the commencement of the study as a part of the follow up routine in the heamatology department to avoid cardiac toxicity as a result of the administration of Anthracyclines, which may lead to dilated cardiomypathy.

Instrumentation and tools

For evaluation

Coulter hematology analyzer

Beckman-Coulter AcT 5 Diff CP Hematology Analyzer (Coulter electronics, Atlanta, USA-6605580) was used to measure hemoglobin, platelets, leucocytes and neutrophils count for all patients, as a regular follow up to monitor any adverse effects.

Weight and height scale
A clinical stadiometer (Wincom Company Ltd., Hunan, made in China) height of each patient, and a digital calibrated precision scale (Thinner MS-7400, Fairlfield NJ, made in China used to measure his weight and then calculate the BMI [weight (kg)/height(m^2)].

Spirometer: (Smart PFT Co transfer, Mee, India, No.EC0812-00010), used to asses Vital Capacity of each patient.

Six minutes walking test (6MWT)
which was used to assess functional capacity; its tools are:
a. *Tape measurement*; to measure the distance covered the patient in six minutes.
b. *Stop watch*: to start and record the time of the test.
Maximum oxygen consumption (VO_2 max): Results of (6MWT) was used to calculate VO_2 max by using Cahalin Equation as follows;
VO_2 max = 0.03x distance in meters +3.98, where distance is obtained from (6MWT) [7].

Ten repetitions maximum test (10RM)
was used to evaluate muscle strength which the maximum weight a person can lift for 10 consecutive exercise repetitions, using Free weights (dumbbells and sand bags of different weights), used also for resistive training.

For training
Electronic bicycle ergometer
(Biodex LBC, made in New York) equipped with electronic break, display screen, adjustable seat, handle bar and foot straps.

Outcome measures
Both groups underwent an identical battery of tests: baseline(before training) and after 8week exercise training program (after training). Firstly, data on the patients' characteristics were collected in the first session including resting heart rate (HR) (beats/min) and resting respiratory rate (cycles/min). In addition, HR and blood pressure were measured during the sessions to exclude any signs or symptoms that may interfere with the progression of the study. Weight (kg) was measured to the closest 0.1 kg using a standard weight scale. Height was measured to the closest 0.1 cm with the patient standing in an erect position against a vertical scale of a portable stadiometer. BMI (kg/m^2) was estimated as weight in kilograms divided by squared height in meters to exclude BMI more than or equal to 35.
Blood samples were taken from all patients in both groups before, during and at the end of the study to measure hemoglobin, platelets, leucocytes and neutrophils counts.

The following measurements were done before starting treatment training sessions and at the end of the whole training sessions (after 8 weeks) for both groups as follows:
- ***Six minutes walking test (6MWT)*** which was used to assess functional capacity by measuring the distance the patient was able to walk over a time of six minutes. According to American thorax society guidelines; patients were instructed to walk as fast as possible as far as possible in six minutes, in a 30 meters obstacle-free corridor marked by turnaround cones and distance was measured [7].
- ***10 repetitions maximum test (10RM)***: was used to evaluate muscle strength which the maximum weight a person can lift for 10 consecutive exercise repetitions [8].
- ***Vital capacity (VC)*** was measured by using electronic spirometry used to assess the volume of exhaled air after maximal inspiration, for both groups, pre and post treatment [9].
- ***Fatigue assessment scale (FAS)*** was used to assess fatigue severity before and after treatment in both groups. FAS is a 10-item scale evaluating symptoms of chronic fatigue [10].
- ***Quality of life questionnaire (QoL)*** was used to evaluate the quality of life before and after treatment training for both groups. The Quality of Life Instrument (Cancer Patient/Cancer Survivor Version) is a forty one-item ordinal scale. The patient is asked to read and then to circle a number indicating the degree to which he/she agrees or disagrees with the statement. The scoring should be based on a scale of 0 = worst outcome to 10 = best outcome [11].

Procedures
Aerobic training
At first; maximum heart rate (HRmax) was calculated for each patient using predicted maximum heart rate equation (220 – age [yrs]) [12]. Aerobic exercise training for patients in Aerobic training group (A) was conducted using bicycle ergometer with moderate intensity (50-60%) of maximum heart rate. Exercise intensity had been prescribed as target heart rate (THR) based on each patient maximum heart rate (HRmax) and resting heart rate (HRrest) and calculated according to (Karnoven formula) as follows:
THR = HR + (HRmax - HRrest) x TF, where TF is the training fraction was found to be 50%-60% in moderate training [12].
All patients had started with warming up exercises, in the form of stretching exercises for 5–10 minutes, marching in place, or cycling until heart rate reaches 30-40% of maximum heart rate to adjust cardiopulmonary system. Warming up phase was followed by active phase of exercise until patient reaches the 50–60% of HR max for 20 minutes. Then the exercise session was ended by cooling down phase by gradual reduction of bicycle speed to allow 5–10 minutes of very slow cycling before totally stopping the bicycle. Sessions were conducted three times / week for eight weeks.

Resistive training
Resistive training for Resistive training group (B) was conducted in the form of a series of exercises using free weights (dumbbells for upper limbs and sand bags for lower limbs) to increase the strength of upper limb, pectoral muscles, abdominal, back muscles and lower limb muscles. Each Patient in this group carried out three sets of 20–30 dynamic repetitions or static isometric exercises for 40-60 seconds for each muscle group and rested 1–2 min between sets. Sessions were conducted three times /week for eight weeks.

Statistical analysis

Statistical analysis was conducted using SPSS for windows, version 25 (SPSS, Inc., Chicago, IL). Prior to final analysis, data were screened for normality assumption and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculations of the analysis of difference. Descriptive analysis using histograms with the normal distribution curve and Normality test of data using Shapiro-Wilk test showed that the data of all numeric tested variables (6MWT, VO_2 max, and FAS) were normally distributed and did not violate the parametric assumption. Dependent sample t-test was used for within group comparison, while independent sample t-test was used for comparison between normally distributed variable among groups before and after treatment. Regarding statistical analysis of non-normally distributed variable (VC, 10 RM, and QoL). Wilcoxon Signed Ranks Test was used for within group comparison, while Mann-Whitney Test was used to compare between both groups before and after treatment, (P value = 0.05).

Results

The final statistical analysis included 59 patients, 29 in Aerobic training group and 30 in Resistive training group.

At baseline as shown in (Table 1), there was non-significant difference between both groups regarding age, height, weight, BMI, hemoglobin (HGB), platelets (PLT),white blood cells (WBCs) count, ($P > 0.05$). Furthermore, there was non-significant difference in sex distribution between both groups, ($P > 0.05$).

The results of this study (Table 2) revealed that there was a significant increase in the mean values of 6MWD, VO_2 max, VC, and a significant decrease in FAS in both groups after the treatment, where P values were as follows; $P < 0.001$, $P < 0.001$, $P < 0.05$, $P < 0.05$ respectively. With a more significant improvement in aerobic group more than resistive training group, $P < 0.001$. While there was also an improvement in 10RM results in Resistive group after treatment, as compared to before treatment value, $P < 0.001$, while non significant improvement was shown in aerobic training group, ($P > 0.05$). However, the results of this study also showed that there was no significant difference in mean values of QoL scale scores before treatment in between both groups, ($P > 0.05$). While there was significant improvement in QoL score in both groups after treatment, ($P < 0.001$), with no significant difference between two groups after treatment, ($P > 0.05$).

Table 1. Patients demographic data in both groups

Qualitative variables	Group A (N = 20) Mean ± SD (Median)	Group B (N = 20) Mean ± SD (Median)	p-value
Age [years]	38.72 ± 3.79	39.29 ± 2.84	0.513
Weight [kg]	74.79 ± 5.18	75.55 ± 5.57	0.589
Height [cm]	172.17 ± 5.06	170.16 ± 4.66	0.115
BMI	25.22 ± 1.27	26.03 ± 1.9	0.061
HGB	9.11 ± 0.39	9.09 ± 0.41	0.874
WBCs	(31.05)	(29.98)	0.812
PLT	(33.29)	(27.89)	0.230
Non Qualitative variables	**Count (percentage)**	**Count (percentage)**	**P-value**
Male	13 (45)	13 (43)	0.823
Female	16 (55)	17 (57)	

Table 2. Comparison between (Mean ± SD or Median) values of outcome measured variables pre- and post-treatment within and between groups

		Aerobic Ex Group (n = 29) Mean ± SD (Median)	Resisted Ex Group (n = 31) Mean ± SD (Median)	(P value)
6MWD	Pre Post (P value)	315.138 ± 10.803 428.69 ± 19.367 −46.304 (0.001)**	311.065 ± 13.89 343.323 ± 20.537 −9.384 (0.001)**	(0.212) (0.001)**
VO2 max	Pre Post (P value)	13.434 ± 0.324 16.841 ± 0.581 (0.001)**	13.307 ± 0.418 14.28 ± 0.616 (0.001)**	(0.196) (0.001)**
FAS	Pre Post (P value)	41.759 ± 2.984 23.621 ± 3.099 29.287 (0.001)**	42.903 ± 2.271 25.032 ± 2.089 34.366 (0.001)**	(0.099) (0.042)*

		Aerobic Ex Group (n = 29) Mean ± SD (Median)	Resisted Ex Group (n = 31) Mean ± SD (Median)	(P value)
	Pre	(2.65)	(2.8)	(0.263)
	Post	(3.15)	(3.1)	(0.011)*
	(P value)	(0.001)**	(0.001)**	
	Pre	(5)	(5)	(0.663)
	Post	(5)	(6)	(0.001)**
	(P value)	(1.00)	(0.001)**	
	Pre	(3.5)	(3.4)	(0.139)
	Post	(4.6)	(4.6)	(0.375)
	(P value)	(0.001)**	(0.001)**	

*6MWD = 6 Minutes Walking Distance; VO_2 max = Maximum Oxygen Consumption, FAS = fatigue assessment scale, VC = vital capacity, 10RM = 10 repetition maximum, QoL = Quality of life, * = significant at P < 0.05; ** = significant at P < 0.01*

Discussion

Curative treatment for acute myeloid leukemia (AML) involves chemotherapy, which is associated with prolonged bed rest and toxicities, leading to worsening of quality of life (QoL), fatigue, and decreased fitness. There is a gap in literature concerning the effect of aerobic exercises versus resistive exercises on functional capacity in AML survivors. Hence, the importance of the current study, that was conducted to clarify the difference between the two types of exercise training. This study showed statistical significant improvement in 6MWD, VO_2 max, VC, reduced fatigue and improvement in QoL in Aerobic training group (A) more than that gained in Resistive training group (B). The significant improvement in 6MWD, VO2 max and VC in patients who received aerobic training resulted from the well established beneficial effects on respiratory function, and the increased stroke volume of the heart. These respiratory adaptations help facilitation of oxygen supply to tissues, leading to the improvement of respiratory fitness as well as, the increase in aerobic capacity [14].

These results came in accordance with Alibhai et al. [15] who concluded that exercise compared to no-exercise has positive effects on cardio-respiratory fitness, muscle strength and functional mobility. These positive effects of aerobic exercise were approved also by many previous studies [16, 17, 18].

This study results revealed improvement in associated fatigue as well, with a resultant improvement in the patients' quality of life following aerobic training. These results were justified by Furzer et al [19] and Van Moll et al [20], who concluded that aerobic exercise rehabilitation program resulted in reduction of fatigue, cardiovascular fitness and muscle strength in hematological cancer patients.

The benefits of aerobic training in patients undergoing high-dose chemotherapy were helpful to counteract a further increase in fatigue, as well as, a further decrease in physical endurance [21, 22, 23], also improving symptoms of distress, anxiety, and depressive status [24].

Broderick et al [25] also concluded that 8 weeks of supervised aerobic exercise training was feasible and may improve aerobic fitness, fatigue and quality of life in de-conditioned cancer survivors. In addition, Courneya et al [26] suggested that supervised aerobic exercises might be associated with improved progression-free survival (PFS) in lymphoma patients.

On the other hand, resistive training results showed more significant improvement in 10 RM, and quality of life. The improvement in the other variables was less significant than in the aerobic training group. That was supported by the results reached by Liang et al [27] who wrapped up, that resistive training had no effect on participants' cardiorespiratory fitness, upper muscle strength, and psychosocial fitness.

However, Wehrle et al [28] concluded that resistance training is a key component when exercising during induction chemotherapy as it not only improved maximum strength, but also influenced endurance capacity even during intensive treatment. Once again, Perondi [29]) stated that A 12-week training program including high-intensity resistance exercises promotes marked strength improvements in patients during the maintenance phase of the treatment for ALL patients without side-effects. Improvement in their quality of life was also encountered.

The favorable outcomes of multimodal exercise training was investigated by Jarden et al [30], where their intervention consisted of cycling for 20-25 minutes, six dynamic resistance exercises using hand weights in 2 sets of 12 repetitions, all integrated into the clinical management of acute leukemia, the results revealed improved physical function and quality of life during consolidation chemotherapy. The measurements were; 6MWD, VO2 max, sit-to-stand test and biceps curls. Improvements in all measures found in the intervention group differed significantly from the usual care group in favor of the intervention group.

From the previous stated findings; it is shown that administration of exercise to acute leukemia patients undergoing treatment is feasible. The exercise protocol used increased cardiovascular endurance, reduced fatigue and maintained quality of life. Both aerobic exercises and resistive exercises can induce muscular contraction, improve oxygenation which may increase strength, improve function and physical performance.

Conclusion

Both aerobic and resistive training significantly improved functional capacity in acute myeloid leukemia survivors with more significant improvement due to aerobic training. Future studies can be designed to investigate the effect of combination between two types of training on such patients.

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