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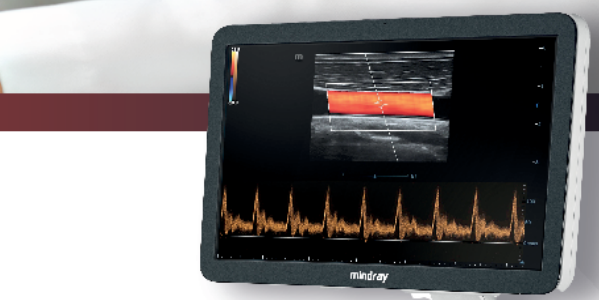

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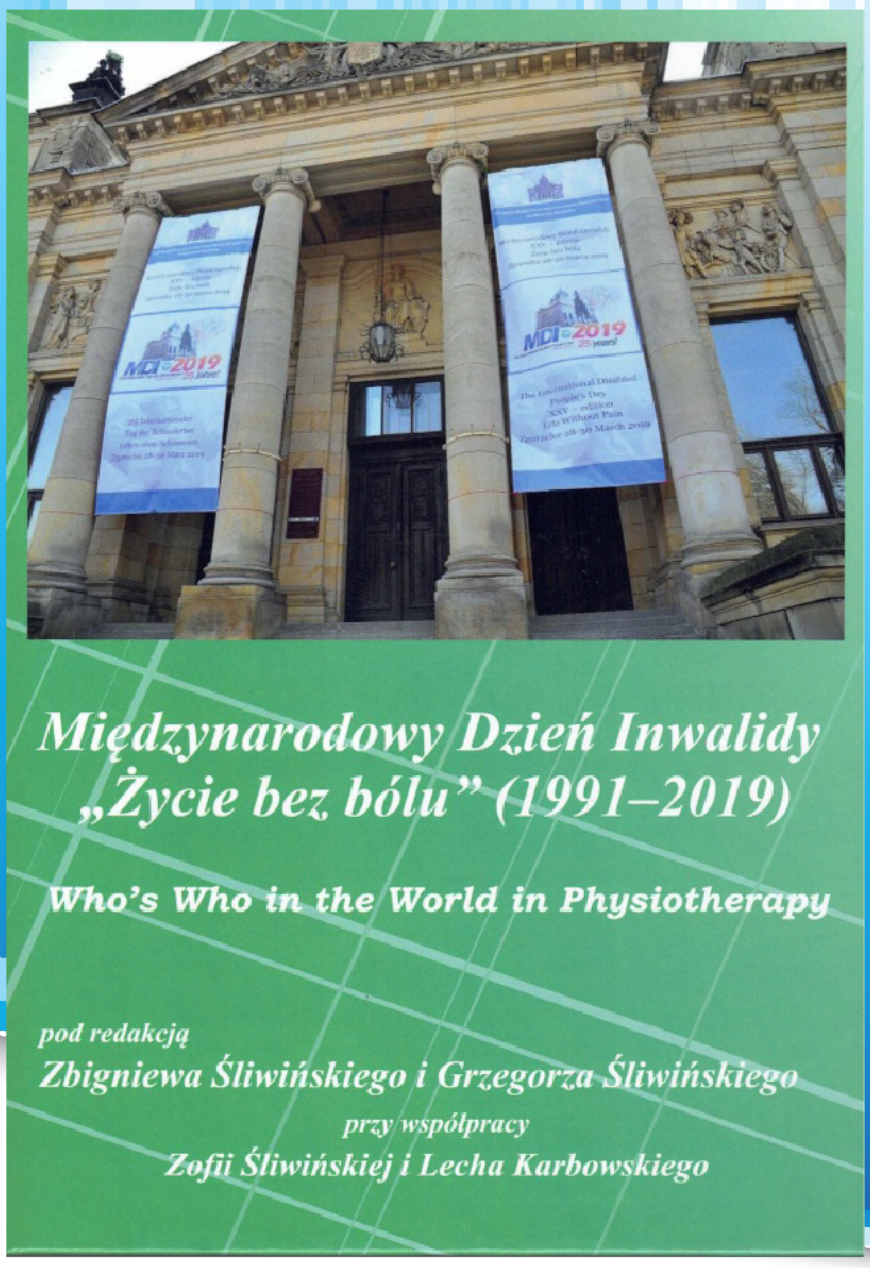

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Resistance versus aerobic exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy: A randomized controlled study

Wpływ ćwiczeń oporowych oraz aerobowych na zmęczenie związane z rakiem i odporność u pacjentek z rakiem piersi poddawanych chemioterapii uzupełniającej: randomizowane badanie kontrolowane

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Abstract

Purpose. To compare the effects of resistance and aerobic exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy.

Methods. sixty female patients with ages ranged from 30 to 60 years, diagnosed as breast cancer undergoing adjuvant chemotherapy, complaining of cancer related fatigue and decreased immunity, were recruited from oncology department at Medical Research Institute in Alexandria and divided randomly into two equal groups in number; Group (A), received resistance exercises for 3 months, Group (B), received aerobic exercises for 3 months. Pretreatment, after 6 weeks and after 3 months of treatment assessment was done using Fatigue assessment scale (FAS), Hemoglobin (Hb) level test for fatigue and White blood cells count (WBCS)for immunity were done for all patients.

Results. The comparison between both groups post-treatment revealed statistically significant reductions in FAS, as well as improvement in Hb and WBCS count (p = 0.0001) in favor of group (B).

Conclusion. Aerobic exercise is more effective than resistance exercises in cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy.

Key words:

cancer-related fatigue, immunity, aerobic exercise, resistance exercises, adjuvant chemotherapy

Streszczenie

Cel. Porównanie wpływu ćwiczeń oporowych i aerobowych na zmęczenie związane z rakiem i odporność u pacjentek z rakiem piersi poddawanych chemioterapii uzupełniającej.

Metody. 60 pacjentek w wieku od 30 do 60 lat, u których zdiagnozowano raka piersi poddawanych chemioterapii uzupełniającej, skarżących się na zmęczenie związane z rakiem i obniżoną odporność, zostało wybranych z oddziału onkologii w Instytucie Badań Medycznych w Aleksandrii i podzielonych losowo na dwie równe liczebnie grupy; Grupa (A) wykonywała ćwiczenia oporowe przez 3 miesiące, Grupa (B) wykonywała ćwiczenia aerobowe przez 3 miesiące. Przed leczeniem, po 6 tygodniach i po 3 miesiącach leczenia dokonano oceny za pomocą skali oceny zmęczenia (FAS), u wszystkich pacjentów wykonano test poziomu hemoglobiny (Hb) pod kątem zmęczenia oraz badanie białych krwinek (WBCS) pod kątem odporności.

Wyniki. Porównanie obu grup po leczeniu wykazało statystycznie istotne zmniejszenie FAS oraz poprawę Hb i WBCS (p = 0,0001) na korzyść grupy (B).

Wniosek. Ćwiczenia aerobowe są skuteczniejsze niż ćwiczenia oporowe w przypadku zmęczenia związanego z rakiem i odporności u pacjentek z rakiem piersi poddawanych chemioterapii uzupełniającej.

Słowa kluczowe

zmęczenie związane z rakiem, odporność, ćwiczenia aerobowe, ćwiczenia oporowe, chemioterapia uzupełniająca

Introduction

Chemotherapy (chemo) is a type of treatment that includes a medication or combination of medications to treat breast cancer. The goal of chemo is to stop or slow the growth of cancer cells. Chemo is considered a systemic therapy that may affect the entire body. Chemo medications attack rapidly growing cancer cells, but they can also affect healthy cells that grow rapidly. The effect of these medications on normal cells often causes chemo side effects [1].

White blood cells protect the body from infection. A low white blood cell count is known as neutropenia. If white blood cell count gets too low, infection may occur [2].

Red blood cells carry oxygen throughout the body. A low red blood cell count is known as anemia. Anemia can lead to fatigue, chest pain, and more serious complications [3].

Cancer related fatigue (CRF) is now recognized as one of the most common and distressing side effects of cancer and its treatment. Fatigue may be elevated before treatment onset and typically increases during cancer treatment, including treatment with radiation, chemotherapy, hormonal, and/or biological therapies [4]. Prevalence estimates of fatigue during treatment range from 25% to 99% depending on the patient population, type of treatment received, and method of assessment. In the majority of studies, 30% to 60% of patients report moderate to severe fatigue during treatment, which in some cases may lead to treatment discontinuation [4].

Adjuvant chemotherapy is part of the standard treatment in a large subset of patients, 58–94% of breast cancer patients experience fatigue during treatment with adjuvant chemotherapy. Fatigue incidence was 90% in breast cancer patients receiving six cycles of chemotherapy and severity remained stable throughout the treatment cycles [5]

It is proved that fatigue has a negative impact on work, social relationships, mood, and daily activities as well it causes significant impairment in overall quality of life during and after treatment [6]. One of the barriers to the assessment and management of fatigue may be a lack of information about mechanisms underlying this symptom, risk factors, and effective treatments [7].

Treatment modalities for CRF include non-pharmacologic interventions, such as psychosocial interventions, exercises, sleep therapy, and acupuncture. Pharmacologic interventions include stimulants, namely modafinil and methylphenidate. In some patients antidepressants may be beneficial [8].

Chemotherapy also causes long-term immune system damage(neutropenia), reducing levels of key immune cells in breast cancer patients for at least nine months after treatment, leaving them vulnerable to potentially life-threatening viral and bacterial infections. Levels of all the major types of lymphocytes dropped significantly after chemotherapy. This included T and B cells and natural killer cells [9].

Resistance exercise (also known as strength exercise) is any physical activity that causes the muscles to work against an additional force or weight. It is resulted in less decline in cardiorespiratory fitness, greater muscle strength and less physical fatigue directly after chemotherapy, less need for chemotherapy dose adjustment, and higher return to work rates in the working population, as compared to usual care [10].

Influence of resistance exercise on the immune system of breast cancer patients described the effect on the cells of the immune system and changes in cytotoxins, the natural killer cells populations increase or their function improves in addition a change in the lymphocyte population. Both the natural killer cells and also the lymphocytes play an important role in the immune system and the immune reaction [11].

Aerobic exercise (also known as cardio) is physical exercise of low to high intensity that depends primarily on the aerobic energy-generating process. Generally, light-to-moderate intensity activities that are sufficiently supported by aerobic metabolism can be performed for extended periods of time. The intensity should be between 60 and 85% of maximum heart rate [12].

Benefits of aerobic exercise on CRF in patients with solid tumor after chemotherapy and/or radiotherapy have been carried out [13]. Aerobic exercises are not limited to better cardiovascular or muscular function. Indeed, the improvement of physical performance can increase the feeling of control, independence, and self-esteem of patients; this improved self-confidence can result in better social interaction and a reduction in anxiety and fear. Therefore, aerobic exercises also can result in secondary benefits, such as an improved mood state [14]. There is also evidence suggesting that aerobic exercises can have an effect on the immune system [15]. Therefore, this study aimed to evaluate which is more effective resistance or aerobic exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy.

Subjects and methods

Design

A randomized controlled trail was conducted to compare the effects of resistance and aerobic exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy. Data were collected pre treatment, after 6 weeks and after 3months post treatment from December 2020 to March 2021. This study was approved by the Research Ethical Committee of the Faculty of Physical Therapy, Cairo University. [No. P.T.REC/012/002968].

Participants

Sixty female patients with age ranged from 30 to 60 years diagnosed as breast cancer undergoing adjuvant chemotherapy and they had cancer related fatigue and decreased immunity were recruited from oncology department of the Medical Research Institute in Alexandria. Patients were excluded if they met one of the following criteria; concurrent malignant disease suffering from any condition for which resistance or aerobic exercises were contraindicated as metastasis, sever osteoporosis and cardiac diseases.

Randomization

The recruited patients were randomly assigned, after signing their consent form, into two equal groups in number. A single blind randomization was carried out by assigning the odd numbers to group (A) and the even numbers were assigned to group (B). Following randomization, there was no dropping out of subjects from the study, Figure 1.

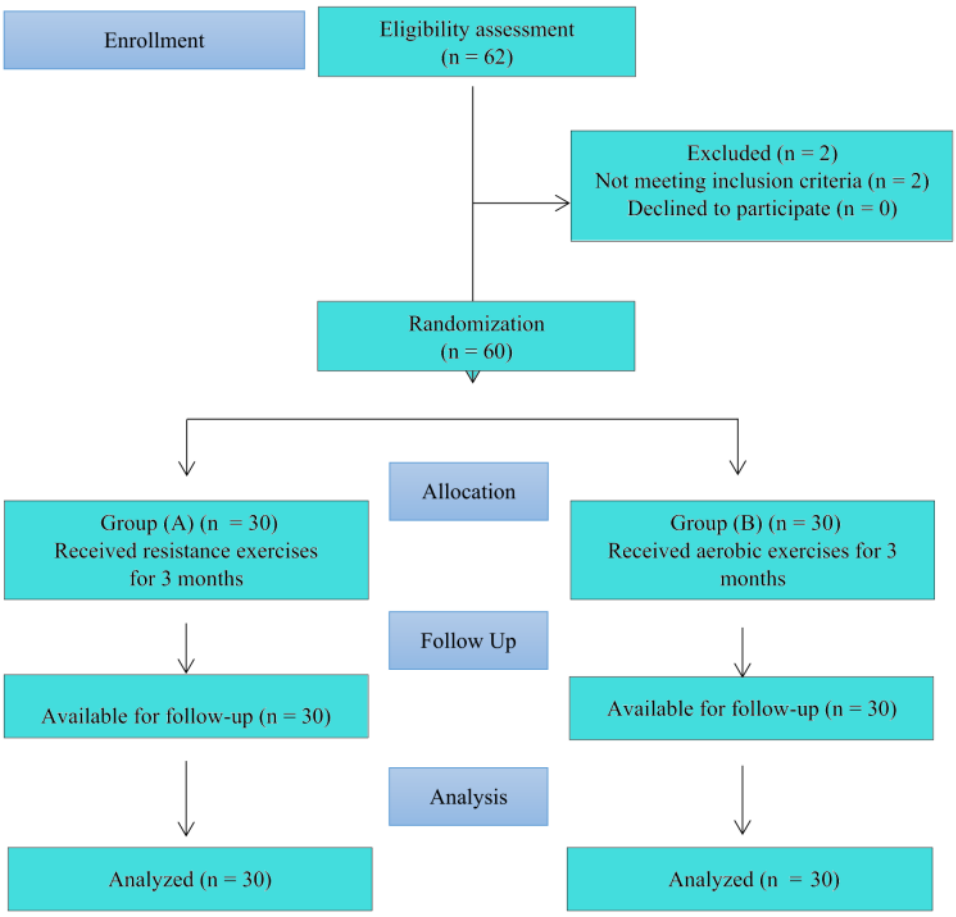

Figure 1. Flow chart of the study

Interventions

Group (A) (resistance exercises group) included 30 participants who received resistance exercises for 3 months, whereas Group (B) (aerobic exercises group) included 30 participants who received aerobic exercises for 3months.

Resistance exercises

Achieved by using hand-held dumbbells, bottles of water, sand bags and body weight (3 times daily and five times per week) for shoulder flexion, abduction and horizontal adduction, elbow extension and flexion, calf raise, leg extension and squatting) time of exercise equal time of rest. The 1 repetition maximum (1RM) was measured at baseline and following the intervention. Initially, participants did two circuits using 50% of their 1RM and repeated them 10 times for the first and second weeks, progressing to two circuits, using 60% of their 1RM and repeat 10 times for the third and fourth weeks. In fifth and sixth weeks, participants did three circuits using 60% of their 1RM and repeated 10 times. In the last 6 weeks, patients did three circuits using 70% of their 1RM and repeated 10 times. Time of exercise was equal to the time of rest [16].

Aerobic exercises

This type of exercises was achieved using treadmill (45 min five times per week). Treadmill is not used to harness power, but as exercise machines for running or walking in one place. Rather than the user powering the mill, the machine provides a moving platform with a wide conveyor belt driven by an electric motor or a flywheel. The belt moves to the rear, requiring the user to walk or run at a speed matching that of the belt. The rate at which the belt moves was the rate of walking or running. Thus, the speed of running might be controlled and measured. Treadmill would be used is Hangzhou Fu Tai Fitness Co., Ltd. (2.3uF 400V), Input voltage: AC 220V, Frequency 50Hz and Input Power: 100W+10 [17].

Aerobic training (AT) program of submaximal intensity included a 45-minute session five times per week under the supervision of the researcher. Aerobic exercise consisted of three phases: warm-up, training and cool down. At the beginning of exercise session, subjects had a ten-minute warm-up. The warm up protocol was slowly running on treadmill. Then, the warm-up phase was followed by the training phase. At baseline, the training phase was commenced with two 30-minute running on treadmill at 50% of their maximal heart rate (MHR) in the first week and increased to 70% MHR by the final week of training. By the end of exercise session, subjects had a five-minute cool down. The cool down protocol was slowly running on treadmill. The vital measures such as HR and blood pressure were monitored before patient left the department [17], maximum heart rate was calculated using the formula: (HR Max = 220 − age) [19].

Outcome measures

Fatigue assessment scale

It was used to evaluate fatigue and find out how patient experience his complaints pre, one and half month and 3 months post treatment for both groups (A & B). The Fatigue Assessment Scale (FAS) is quick and easy to complete for patients, and not time consuming so it is valid and reliable in clinical practice for fatigue assessment. It is also helpful in the follow-up of the patients [19]. The patient was asked ten questions about possible complaints, circled the answer to each question from 1 to 5 grades (1 = Never, 2 = Sometimes; 3 = Regularly; 4 = Often and 5 = Always, Total score 50, higher score was the worst and lower score was the best. There were no correct or incorrect answers [21].

Hemoglobin level test

It was used to evaluate fatigue pre, one and half month and 3 months post treatment for both groups (A & B). It is valid measurement tool that can provide wide-acceptance, validity, and reliability estimation of hemoglobin level. Hemoglobin, or Hb, is usually expressed in grams per deciliter (g/dL) of blood. A low level of hemoglobin in the blood relates directly to a low level of oxygen [22]. Normal range for women 12-15.5 gm/dl [23].

White blood cells count test

It was used to evaluate immunity pre, one and half month and 3months post treatment for both groups (A & B). It is valid measurement tool that can provide wide-acceptance, validity, and reliability estimation of WBCS level. WBCs are the cells of the immune system that are involved in protecting the body against both infectious disease and foreign invaders. All white blood cells are produced and derived from multipotent cells in the bone marrow known as hematopoietic stem cells. Leukocytes are found throughout the body, including the blood and lymphatic system [24]. Normal range is usually between 4,000 and 11,000 per microliter of blood [23].

Statistical analysis

Descriptive statistics and unpaired t-test were conducted for comparison of age between groups. ANOVA with repeated measures was conducted for comparison of Hb, WBCs count and FAS between pretreatment, 6 weeks and 12 weeks in each group and unpaired t test was carried out for comparison between groups. The level of significance for all statistical tests were set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA).

Results

Subject characteristics

Regarding the ages of patients, mean ± SD of the group A and B were 44.46 ± 9.8 and 43.96 ± 9.22 years respectively, while there was no significant difference between both groups ($p > 0.05$).

Within group comparison

Within-group comparison revealed a significant increase in Hb and WBCs in both groups at 6 weeks compared with pretreatment ($p < 0.001$) and a significant increase at 12 weeks compared with pretreatment ($p < 0.001$) and 6 weeks ($p < 0.001$). Also, a significant decrease in FAS in both groups at 6 weeks compared with pretreatment ($p < 0.001$) and a significant decrease at 12 weeks compared with pretreatment ($p < 0.001$) and 6 weeks ($p < 0.001$) (table 1).

Between group comparison

There was no significant difference between groups pretreatment ($p > 0.05$). There was a significant increase in Hb and WBCs and a significant decrease in FAS of the group B at 6 weeks ($p < 0.01$) and 12 weeks ($p < 0.001$) compared with that of the group B. (table 1).

Table 1. Mean Hb, WBCs count and FAS at pretreatment, 6 weeks and 12 weeks post treatment of group A and B

		Pre-treatment Mean ± SD	6 weeks Mean ± SD	12 weeks Mean ± SD	p-value Pre vs 6 weeks	p-value Pre vs 12 weeks	p-value 6 months vs 12 weeks
Hb [gm/dl]	Group A	9.39 ± 0.77	10.05 ± 0.81	10.9 ± 0.88	0.001	0.001	0.001
	Group B	9.62 ± 0.82	10.74 ± 0.8	12.62 ± 0.87	0.001	0.001	0.001
	p-value	**p = 0.27**	**p = 0.002**	**p = 0.001**			
WBCs count [x109/L]	Group A	3217.03 ± 303.2	4002.16 ± 383.67	5144.33 ± 377.56	0.001	0.001	0.001
	Group B	3114.4 ± 162.9	4564.2 ± 279.79	6176.16 ± 300.1	0.001	0.001	0.005
	p-value	**p = 0.1**	**p = 0.001**	**p = 0.001**			
FSS	Group A	41.23 ± 2.28	36.13 ± 2.83	28.76 ± 2.99	0.001	0.001	0.001
	Group B	41.16 ± 2.27	32.46 ± 2.34	21.93 ± 2.87	0.001	0.001	0.001
	p-value	**p = 0.91**	**p = 0.001**	**p = 0.001**			

SD: Standard deviation; p-value: Level of significance

Discussion

The finding of this study indicates that exercise interventions such as aerobic and resistance exercises improve fatigue, pain, immune system, and insomnia in cancer patients, as observed in earlier studies [25]. Exercises help in alleviating cancer-related adverse effects, have a beneficial effect on the whole body and cardiovascular health, and seem to slow cancer progression through probably direct action on tumor-intrinsic factors and by possibly improving the efficacy of the anti-cancer treatment [26]. Aerobic exercises are more effective than resistance exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy. I think this may be due to aerobic exercises pump blood around body to deliver oxygen to organs, tissues and cells, trains cardiovascular system heart, lungs and blood vessels and body as all to work more efficiently, so reduce fatigue, improve immune system, improve psychological state and quality of life.

Adjuvant chemotherapy is part of the standard treatment in a large subset of patients, 58–94% of breast cancer patients experience fatigue during treatment with adjuvant chemotherapy. Fatigue and decrease immune function incidence were 90% in breast cancer patients receiving six cycles of chemotherapy and severity remained stable throughout the treatment cycles [4] which is concomitant with our study.

The results of the current study showed that the significant difference in Hb level with the percent of change 7.03% between pretreatment and 6 weeks, 16.08% between pretreatment and 12 weeks and 8.46% between 6 and 12 weeks post treatment. There was a significant increase in Hb at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group A. The percent of change was 11.64% between pretreatment and 6 weeks, 31.19% between pretreatment and 12 weeks and 17.5% between 6 and 12 weeks post treatment. There was a significant increase in Hb at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group B. There was a significant increase in Hb of group B compared with that of group A at 6 weeks post treatment ($p = 0.002$) and there was a significant increase in Hb of group B compared with that of group A at 12 weeks post treatment ($p = 0.0001$) between both groups.

The results of the current study showed that the significant difference in FAS score with the percent of change 12.37% between pretreatment and 6 weeks, 30.24% between pretreatment and 12 weeks and 20.4% between 6 and 12 weeks. There was a significant decrease in FAS at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group A. The percent of change was 21.14% between pretreatment and 6 weeks, 46.72% between pretreatment and 12 weeks and 32.44% between 6 and 12 weeks. There was a significant decrease in FAS at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group B. There was a significant decrease in FAS of group B compared with that of group A at 6weeks and 12 weeks post treatment ($p = 0.0001$) between both groups.

The results of the current study showed that the significant difference in WBCS count with percent of change 24.41% between pretreatment and 6 weeks, 59.91% between pretreatment and 12 weeks and 28.54% between 6 and 12 weeks. There was a significant increase in WBCs count at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group A. The percent of change was 46.55% between pretreatment and 6 weeks, 98.31% between pretreatment and 12 weeks and 35.32% between 6 and 12 weeks. There was a significant increase in WBCs count at 12 weeks compared with that at 6 weeks and pretreatment ($p = 0.0001$) in group B. There was a significant increase in WBCs count of group B compared with that of group A at 6 weeks and 12 weeks post treatment ($p = 0.0001$) between both groups.

The improvement in Hb level, FAS score and WBCS count in group B as compared to group A, could be attributed to more improvement in cancer related fatigue and immunity during breast cancer patients undergoing adjuvant chemotherapy and improve quality of their life.

The mechanism of improvement that aerobic exercises induce improved metabolic efficiency This could be explained by the fact that there is increased recruitment of the oxidative fibers and decrease in the glycolytic fibers. The oxidative fibers produce less lactate, metabolize the lactate, and oxidize them for fuel generation. Furthermore, oxidative fibers are more resilient to stress as compared to glycolytic fibers. Aerobic training improves oxygen uptake by the exercising muscles, improve the cardiorespiratory function, blood oxygen transport, and muscle aerobic capacities (mitochondrial density or capillarization of muscle fibers). Exercise can attenuate cardiac and skeletal toxicities of certain chemotherapies. It triggers erythropoeisis and attenuates skeletal atrophy by suppressing the inflammatory response, enhancing the rate of protein synthesis, and antioxidant enzyme activities [27]. Aerobic exercises promote protection against infections caused by intracellular microorganisms, since it guides the immune response to a predominance T1 helper cells which stimulate inflammation and other changes in the body as a first defense against infection. They are followed by T2 helper cells that produce an anti-inflammatory response. A recent study at the University of Illinois demonstrated that moderate exercise in mice appears to accelerate the change from a T1 to T2 response enough to help combat infection with the flu [11]. Aerobic exercises may help flush bacteria out of the lungs and airways. This may reduce your chance of getting a cold, flu, or other illness, it causes change in antibodies and white blood cells (WBC). WBCs are the body's immune system cells that fight disease. These antibodies or WBCs circulate more rapidly, so they could detect illnesses earlier than they might have before. However, no one knows whether these changes help prevent infections, the brief rise in body temperature during and right after exercise may prevent bacteria from growing. This temperature rise may help the body fight infection better (This is similar to what happens when you have a fever) and it slows down the release of stress hormones. Some stress increases the chance of illness. Lower stress hormones may protect against illness [28].

Mengyao et al [29] approved that Aerobic and resistance exercise can be regarded as beneficial to CRF in breast cancer patients via increasing oxygen supply to the body, improve cardiopulmonary fitness, rushing insulin-like growth factor, growth hormone, protein, and other nutrients as cytokine to the muscles and helping repair them to make them stronger.

Thorsten et al [30] approved that physical activity such as aerobic and resistance exercises -induced effects on the immune system in terms of cell number changes and cytotoxic activity in breast cancer patients. The studies suggest an improved immunological status of breast cancer patients after physical activity, increased

number and effector function of monocytes, macrophages, NK cells and the increasing release of cytokines.

Our findings are in agreement with the study of Cataldi et al [31] which was concluded that how exercise was used during the last decade and which is the best exercise program in the cancer patient. The results recommend that aerobic exercise improves CRF better than other treatments, but it also provides good outcomes combined with resistance training. To get the best results, the better way is doing exercises at least two days/week, for eight or more weeks. The studies in which are reported best improvements followed a low to moderate intensity of exercises. Thus, according to the American College of Sports Medicine (2018), physical activity makes better the quality of life in cancer patients and improves psychological and physiological fitness.

Based on the findings in a study of Thorsten et al [30] was concluded that aerobic and resistance exercises-induced effects on the immune system in terms of cell number changes and cytotoxic activity in breast cancer patients. The studies suggest an improved immunological status of breast cancer patients after physical activity, however the statements of the included studies about the impact of physical activity are different. More studies concluded that aerobic exercises are more effective than resistance exercises and only few scientific results are available regarding the dosage and appropriate method of exercise intervention. It is still unknown whether endurance training or strength training is more meaningful for immune stimulation. The intensity and duration of exercise have an important influence on the immune system. A more intense and prolonged exposure leads to an enhanced activation of different parts of the immune system. In contrast, a too hard and too long period of physical exertion can have negative effects on the immune system. Exercise in the middle range of intensities seems to have a stimulating and activating effect.

Study limitations

The study was limited by extraneous factors that might have interfered with the results of this study, these factors were related to variations in life style between patients as activity level and nutrition in addition to the psychological variations between subjects during the application of the treatments protocols.

Conclusion

It was concluded that, Aerobic exercise is more effective than resistance exercises on cancer related fatigue and immunity in breast cancer patients undergoing adjuvant chemotherapy.

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