

ORIGINAL ARTICLE

Impact of moderate intensity aerobic exercise on chemotherapy-induced anemia in elderly women with breast cancer: A randomized controlled clinical trial



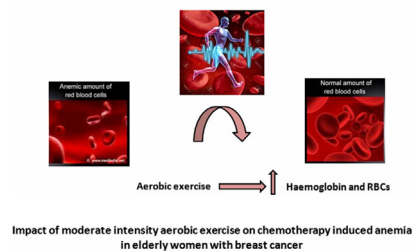
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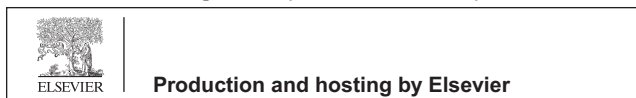
GRAPHICAL ABSTRACT



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ABSTRACT

Exercises are often recommended for patients suffering from anemia to improve physical conditioning and hematologic parameters. Hence, the present study aimed to investigate the impact of moderate intensity aerobic exercise on chemotherapy-induced anemia. Thirty elderly women with breast cancer underwent chemotherapy and were randomly assigned into two equal groups; Group A received aerobic exercise for 25–40 min at 50–70% of the maximum heart rate, 3 times/week for 12 weeks in addition to usual daily living activities, medication and nutritional support. Group B who did not train served as controls. Hemoglobin (Hb), and red blood cell count (RBCs) were evaluated pre-treatment and after 12 weeks of training. There were significant declines of both Hb ($t = 16.30$; $P < 0.001$) and RBCs ($t = 10.38$; $P < 0.001$) in group B relative to group A. Regarding group A, Hb increased from 11.52 ± 0.62 to 12.10 ± 0.59 g/dL with a 5.03% change, while RBCs increased from 4.24 ± 0.37 to 4.49 ± 0.42 million cells/ μ L with a 5.89% change. Between-group differences were noteworthy regarding Hb ($t = -5.34$; $P < 0.001$) and RBCs ($t = -5.314$; $P < 0.001$). The results indicate that regular participation in moderate intensity aerobic exercise can enhance chemotherapy-induced anemia.

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Introduction

Chemotherapy-induced anemia (CIA) is a common complication in patients receiving myelosuppressive chemotherapy [1]. Blood hemoglobin (Hb) level of less than 12 g/dL is frequently defined as anemia, but many individuals may not feel much difference until the hemoglobin level falls below 11 g/dL [2]. Anemia is associated with fatigue and dyspnea on exertion, which can affect a patient's capacity to perform normal daily living activities [1,3].

Current treatment choices for CIA incorporate red blood cell (RBC) transfusions and erythropoiesis-stimulating agents (ESAs); however, both treatments are associated with an increased risk of thrombotic events [4]. Also, ESAs might be connected with conceivable diminished survival and shortened time to tumor progression in patients with cancer, and RBC transfusions carry a risk of infection, transfusion-related reactions, and possible decreased survival [4–6]. Given these safety concerns, other treatment alternatives for CIA that are efficacious and safe are required.

The overall goal of treatment in individuals with CIA is reduction in transfusion requirements and maximization of quality of life [7]. Exercise could be an appropriate non-pharmacologic intervention to counteract the decline in erythrocyte observed in many breast cancer patients undergoing chemotherapy. Aerobic exercise training (AET) is associated with improved hemorheology [8,9] and can increase blood volume through an increase in plasma volume and RBC mass [10]. Few studies have evaluated the effect of exercise training on erythrocyte in breast cancer patients undergoing adjuvant chemotherapy. Previous studies have reported positive changes in erythrocyte with exercise in cancer patients, but the samples were clinically heterogeneous, with inefficient training intensity or brief interventions of 6–7 weeks, which occurred after chemotherapy [11,12]. So the purpose of this study was to examine whether moderate-intensity aerobic exercise would have an effect on erythrocyte in elderly women with breast cancer compared with non-training ones also undergoing chemotherapy.

Patients and method

Thirty women patients with breast cancer (aged 60–70 years), who underwent chemotherapy, were screened and randomly assigned to either Control or Intervention group to participate in this 12-week randomized-controlled trial. They were recruited from National Cancer Institute, Cairo University, to participate in this study.

Patients were selected to be enrolled into this study after they had fulfilled the inclusion criteria of the study; female patients with breast cancer undergoing chemotherapy, they were medically stable and not receiving Erythropoietin therapy, their BMI ranged from 30 to 35, and they had an inactive lifestyle for at least the previous 6 months. *Patients had provided informed consent for participation in the study and for publication of the results. This study was approved by University Ethics Committee for scientific research [No: P.T.REC/012/001353].*

Exclusion criteria were BMI more than 35, age older than 70 or younger than 60 years. Patients who received Erythropoietin treatments, suffered uncorrected visual problems, had scars under their feet, and had a history of serious cerebrovascular or cardiovascular diseases, or severe musculoskeletal problems restricting physical activity.

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.

Design of the study

Patients who fulfilled the inclusion criteria of the study were randomly assigned to either group A, the study group, who received aerobic exercise for 25–40 min at 50–70% of the maximum heart rate, 3 times/week for 12 weeks in addition to usual daily living activities, medication and nutritional sup-

port, or group B, the control group, who performed the usual daily living activities in addition to administration of their medication and nutritional support.

Randomization was done by opening an opaque envelope prepared by an independent individual using random number generation.

Instrumentation

For evaluation

Coulter hematology analyzer. Beckman-Coulter AcT 5 Diff CP Hematology Analyzer (Coulter electronics, Atlanta, USA-6605580) was used to measure Hb % and RBCs for all patients in both groups before and after treatment [13].

Weight and height scale. ZT-120 (Wincom Company Ltd., Hunan, China) was used to measure the weight and height of each participant and then calculate the BMI [weight (kg)/height (m²)].

For training

Electronic treadmill. Electronic treadmill Manufactured by Bonte BV - JK Hedel – Holland, 02-328 was used for exercise training. The apparatus is equipped with a display screen showing time in minutes and speed in kilometers per hour.

Outcome measures

Both groups underwent an identical battery of tests: baseline (before training) and after 12-week exercise training program (after training). The evaluated parameters included Hb and RBCs measurement.

Firstly, data on the subjects' 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 subject standing in an erect position against a vertical scale of a portable stadiometer. BMI (kg/m²) was estimated as weight in kilograms divided by squared height in meters to exclude BMI more than or equal to 35.

Laboratory investigations

Complete blood count measurements

Five milliliters of blood were drained under an aseptic condition from the ante-cubital fossa on the side of the untreated breast by guaranteed technicians with the subject in a seated position. Blood draws were performed principally in the morning and approximately 90 min before the treadmill exercise evaluations, with participants in a postprandial state. Normal values used for women were 12.1–15.1 g/dL for Hb, and 4.2–5.4 million cells/ μ L for RBCs.

Training procedures

After warm-ups, participants of this group performed walking on a treadmill three times per week (on nonconsecutive days).

Aerobic exercise intensity was determined using the Karvonen formula in which Target Heart Rate = [(max HR – resting HR) \times % intensity] + resting HR, where maximum heart rate = 220-age [14].

Parameters of exercise program

Mode:	Walking on a treadmill
Duration:	25–40 min
Intensity:	50–70% of maximum heart rate (MHR). (Karvonen formula)
Frequency:	3 times per week [15]
Treatment duration:	12 weeks

Each exercise session consisted of

Warming up:	Light walking for 5 min
Active phase:	Walking on a treadmill at moderate speed with no inclination for 15–30 min
Cooling down:	Light walking for 5 min [16]

Progression of exercise program

Duration:	Increased by 5 min every 2 weeks until 40 min were attained and then maintained
Intensity:	By the 4th week, patient was exercised at 70% of measured maximum heart rate [16]

After the end of the session, patients were asked to step off the treadmill and were observed carefully for any signs of fatigue i.e. fainting or loss of consciousness (syncope), near-syncope, rapid heartbeat (palpitation), or dizziness.

Data collection

For each group, both demographic and clinical characteristics [hemoglobin (Hb), and red blood cell count (RBCs)] of patients were collected pre and post training.

Statistical analysis

Descriptive statistics for all parameters in the form of

Mean and standard deviation of [Demographic and clinical characteristics; Hb and RBCs] and percentage of change in Hb and RBCs post training were evaluated.

Inferential statistics in the form of

Paired *t*-test to examine the changes in Hb and RBCs pre and post training in each group and Independent *t*-test to compare between the two groups regarding the Hb and RBCs pre and post training. The level of significance was set at $P \leq 0.05$ [17].

Results

Demographic and clinical characteristics of patients in both groups

In the baseline (pre-training) evaluation, results revealed that there were non-significant differences between the two groups with regard to demographic characteristics and clinical parameters where ($P > 0.05$), are shown in Table 1.

Table 1 Demographic and clinical characteristics of patients in both groups (Mean \pm SD).

Variables	Group A (N = 15)	Group B (N = 15)	t-value	P-value
Age (year)	54.6 \pm 4.23	58.25 \pm 2.65	0.61	0.540
Height (m)	162.07 \pm 4.89	162.33 \pm 5.70	0.137	0.892
Weight (kg)	91.27 \pm 9.40	93.33 \pm 14.21	0.470	0.642
Body Mass Index (kg/m ²)	34.81 \pm 3.44	35.25 \pm 3.36	0.354	0.726
Hb (g/dL)	11.52 \pm 0.62	11.70 \pm 0.96	0.60	0.548
RBCs (10 ⁶ / μ L)	4.24 \pm 0.37	4.30 \pm 0.317	0.43	0.668

SD = Standard Deviation. Level of significance at $P \leq 0.05$.

Table 2 Hemoglobin (Hb) in the two groups pre and post-treatment.

Variable	Groups Hb (g/dL)			
	Group (A) (N = 15)		Group (B) (N = 15)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Mean \pm SD	11.52 \pm 0.62	12.10 \pm 0.59	11.70 \pm .96	10.32 \pm 1.04
Percentage of Change	5.03%		-11.79%	
t-value	-8.52		16.30	
P-value	0.001*		0.001*	

SD = Standard Deviation. Level of significance at $P \leq 0.05$.

* $P \leq 0.05$.

Hemoglobin and red blood cell count in the two groups pre and post-treatment

Hemoglobin in the two groups pre and post-treatment

Table 2 shows the statistical analysis of the mean difference of Hb pre-treatment and 12-week after treatment (post-treatment) with significant differences found in Hb measures between Group A and Group B following training. Group A experienced significant increases ($t = -8.52$; $P < 0.001$) in Hb from 11.52 \pm 0.62 g/dL to 12.10 \pm 0.59 g/dL, with a 5.03% change. However Group B experienced significant declines ($t = 16.30$; $P < 0.001$) in Hb from 11.70 \pm .96 g/dL to 10.32 \pm 1.04 g/dL with a -11.79% change. Results are illustrated in Fig. 1.

Red blood cell count in the two groups pre and post-treatment

Table 3 shows the statistical analysis of the mean difference of RBCs count pre-treatment and 12-week after treatment (post-treatment) with significant differences found in RBCs measures between Group A and Group B following training. Group A experienced significant increases ($t = -8.35$; $P < 0.001$) in RBCs from 4.24 \pm 0.379 to 4.49 \pm 0.42 million cells/ μ L, with a 5.89% change. However Group B experienced significant declines ($t = 10.38$; $P < 0.001$) in RBCs from 4.30 \pm 0.317 to 3.74 \pm 0.33 million cells/ μ L with a -13.02% change. Results are illustrated in Fig. 2.

Post-treatment hemoglobin and red blood cell count in the two groups (A and B)

Table 4 shows that, after 12-week of moderate-intensity aerobic exercise, there was a significant statistical difference between the two groups post-treatment in the measured vari-

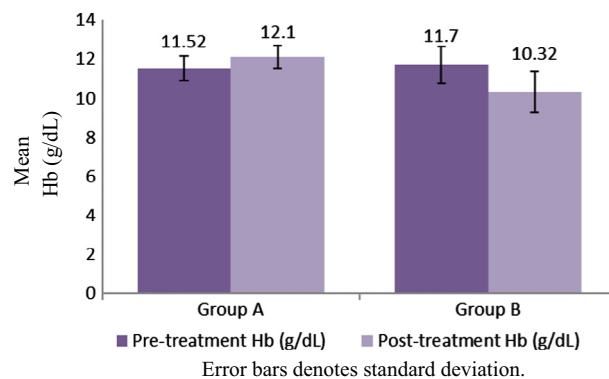


Fig. 1 Hemoglobin (Hb) in the two groups pre and post-treatment.

ables, Hb and RBCs; where t -values were [(-5.34) and (-5.314)] and P -values were [(0.001) and (0.001), respectively].

Discussion

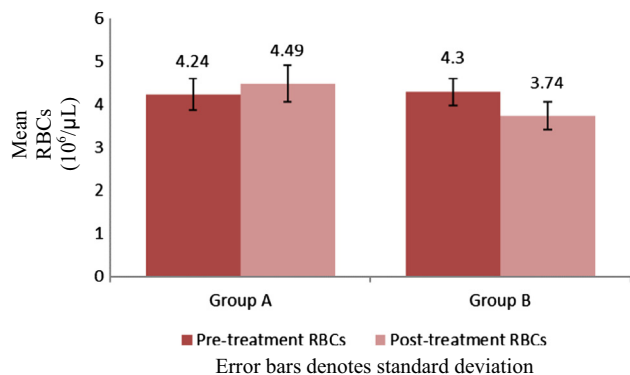
The present study investigated the impact of moderate-intensity aerobic exercise on chemotherapy-induced anemia in breast cancer patients undergoing chemotherapy. Women undergoing chemotherapy for breast cancer ordinarily encounter declines in erythrocyte levels that may last several months after treatment [18]. Declines in erythrocyte levels may be associated with chemotherapy complications that incorporate fatigue, anemia, depression, and diminished physical capacity [19,20]. Lessened erythrocyte levels have also been associated with increased local and regional failure and diminished survival rates in some cancers [21,22].

Table 3 Red blood cell count (RBCs) in the two groups pre and post-treatment.

Variable	Groups RBCs ($10^6/\mu\text{L}$)			
	Group (A) ($N = 15$)		Group (B) ($N = 15$)	
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Mean \pm SD	4.24 \pm 0.37	4.49 \pm 0.42	4.30 \pm 0.31	3.74 \pm 0.33
Percentage of Change	5.89%		-13.02%	
<i>t</i> -value	-8.35		10.38	
<i>P</i> -value	0.001*		0.001*	

SD = Standard Deviation. Level of significance at $P \leq 0.05$.

* $P \leq 0.05$.

**Fig. 2** Red blood cell count (RBCs) in the two groups pre and post-treatment.

The current study found that women who performed moderate intensity aerobic exercise during chemotherapy of breast cancer could keep the declines in erythrocyte levels that were experienced by their non-training peers, where there were statistically significant differences in the two groups with noteworthy decline of both Hb and RBCs in group B relative to group A.

Few studies have assessed the impact of exercise on Hb in breast cancer patients undergoing chemotherapy. Dimeo et al. [11] examined the effects of 6 weeks of treadmill walking after the completion of high-dose chemotherapy and autologous peripheral stem cell transplantation. After training, walking speed and hemoglobin increased significantly in the training subjects, whereas non-training subjects' values remained statistically unchanged.

They have proposed that aerobic exercise can induce correction of anemia in cancer patients after myelotoxic chemotherapy, decrease fatigue, and enhance emotional and mood state in these patients and thus physical rehabilitation is strongly recommended.

Drouin et al. [12] assessed the effects of 7 weeks of aerobic exercise training on erythrocyte levels during radiation therapy for breast cancer. After training, erythrocyte levels increased significantly in the training subjects in contrast to the non-training ones.

Lianne et al. [23] stated that enhancement of oxygen transport and tissue oxidative capacity after Low- to moderate-intensity aerobic exercise caused by increased blood volume through an increase in plasma volume and (RBCs) mass, improved red cell deformability and decreased blood viscosity that may have allowed patients to maintain their aerobic capacity during chemotherapy.

Walking is a weight-bearing activity that has its effect on bone and bone marrow. Bone is able to detect and adapt to mechanical stimulation by modulating its mass, geometry and structure as it is a dynamic tissue. These changes might be because of the mechanical stimulation applied on the bone tissues in the form of walking. This mechanical stimulation had an impact on the process of blood formation occurring mainly in the bone marrow. From this, one can see that there is a close relation between bone tissues and hematopoietic processes [24,25].

Dimeo et al. [26] have found that endurance exercises 'in the form of walking on a treadmill' at an intensity of 80% of the maximal heart rate enhances the process of hematopoiesis as a result of increased production of growth hormone in anemic patients. They have found that intense or prolonged exercise has been shown to affect the concentration of several cytokines and hormones that regulate the self-renewal, proliferation and maturation of blood stem cells.

However, few studies on this topic did not find significant differences in erythrocyte levels between training and non-training subjects. Schwartz et al. [27] examined the treatment with endurance training during either conventional or high-dose chemotherapy with stem cell rescue. Although participants walked daily on a treadmill for 30 days, physical performance and erythrocyte measures stayed unchanged proposing

Table 4 Post-treatment hemoglobin (Hb) and red blood cell count (RBCs) in the two groups (A and B).

Variable	Hb (g/dL)		RBCs ($10^6/\mu\text{L}$)	
	Group (A) ($N = 15$)	Group (B) ($N = 15$)	Group (A) ($N = 15$)	Group (B) ($N = 15$)
Mean \pm SD	12.10 \pm 0.59	10.32 \pm 1.04	4.49 \pm 0.42	3.74 \pm 0.33
<i>t</i> -value	-5.722		-5.314	
<i>P</i> -value	0.001*		0.001*	

SD = Standard Deviation Level of significance at $P \leq 0.05$.

* $P \leq 0.05$.

that the training intensity or duration might not have been adequate for training effect to occur.

Also, Fetscher et al. [28] examined the effect of aerobic exercise in cancer patients during high-dose chemotherapy. Training intensity was 50% of the maximum heart rate and training duration was 13–15 days. They did not find significant differences in erythrocyte levels between trained and untrained subjects. This may also be attributed to inefficient training intensity or duration to cause changes in erythrocyte measures.

The limitation of the current study is that changes in erythrocyte levels were not assessed aerobically, so it would be beneficial that subsequent studies determine its association with changes in aerobic capacity ($VO_{2\text{peak}}$).

Conclusions

Moderate intensity aerobic exercise has valuable effects on chemotherapy-induced anemia in elderly women with breast cancer as evidenced by the significant increase in mean values of Hb and RBCs in the study group compared with the control group. In turn, these results could provide healthcare professionals with an appropriate non-pharmacologic intervention to counteract the decline in erythrocyte observed in many breast cancer patients undergoing chemotherapy.

Conflict of Interest

The authors have declared no conflict of interest.

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