Anxiety, Depression, Pain and Fatigue in Patients with Breast Cancer who Submitted to Combined Training

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Ansiedade, Depressão, Dor e Fadiga em Pacientes com Câncer de Mama que Realizaram Treinamento Combinado

Ansiedad, Depresión, Dolor y Fatiga en Pacientes con Cáncer de Mama con Entrenamiento Combinado

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ABSTRACT

Introduction: Despite the increase of the survival of patients with breast cancer, many persist with anxiety, depression, fatigue, and pain even after anticancer treatment, factors associated with a worse quality-of-life. **Objective:** Evaluate the influence of combined training on anxiety, depression, pain and fatigue in breast cancer patients. **Method:** Randomized controlled trial with 26 patients undergoing chemotherapy, radiotherapy, or clinical follow-up at a referral centre for cancer treatment, aged 30 to 59 years, not practicing physical training in the last three months. The intervention group (IG) (n=13) was submitted to 3 sessions per week of aerobic and resistance training, for 12 weeks, lasting 60 minutes, and 2 sessions per week of flexibility training lasting 20 seconds in 3 sets. The control group (CG) (n=13) submitted only to conventional hospital treatment. All assessments were performed at baseline and after 12 weeks. **Results:** IG patients showed a significant reduction in anxiety (p=0.0242), pain intensity (p=0.0290) and the behavioral dimension of fatigue (0.0033). No differences were observed in depression (p=0.0803), interference of pain in usual activities (p=0.0933) and affective (p=0.0583) and sensory/cognitive/emotional (p=0.5525) dimensions of fatigue. The CG remained unchanged in all variables. **Conclusion:** Combined training involving aerobic, resistance and flexibility exercises for 12 weeks has beneficial effects on anxiety, fatigue and pain in breast cancer patients.

Key words: breast neoplasms; exercise; pain management.

RESUMO

Introdução: Apesar do aumento na sobrevida de pacientes com neoplasias de mama, muitas persistem com ansiedade, depressão, fadiga e dor mesmo após o tratamento anticancerígeno, fatores associados a uma pior qualidade de vida. **Objetivo:** Avaliar a influência do treinamento combinado na ansiedade, depressão, dor e fadiga em pacientes com câncer de mama. **Método:** Ensaio controlado randomizado com 26 pacientes em quimioterapia, radioterapia ou acompanhamento clínico em um centro de referência em tratamento de câncer, com idade 30 a 59 anos, não praticantes de treinamento físico nos últimos três meses. O grupo experimental (GE) (n=13) foi submetido a três sessões por semana de treinamento aeróbico e resistido em 12 semanas, com duração de 60 minutos, e duas sessões de treinamento de flexibilidade por semana com duração de 20 segundos em três séries. O grupo controle (GC) (n=13) realizou somente o tratamento hospitalar convencional. Todas as avaliações foram realizadas no tempo basal e após 12 semanas. **Resultados:** As pacientes do GE apresentaram redução significativa da ansiedade (p=0,0242), intensidade da dor (p=0,0290) e dimensão comportamental da fadiga (0,0033). Não foram observadas diferenças na depressão (p=0,0803), interferência da dor nas atividades habituais (p=0,0933) e dimensões afetiva (p=0,0583) e sensorial/cognitiva/emocional (p=0,5525) da fadiga. O GC permaneceu inalterado em todas as variáveis. **Conclusão:** O treinamento combinado, envolvendo exercícios aeróbios, de resistência e de flexibilidade durante 12 semanas, apresenta efeitos benéficos na ansiedade, fadiga e dor em pacientes com câncer de mama.

Palavras-chave: neoplasias da mama; exercício físico; manejo da dor.

RESUMEN

Introducción: A pesar del aumento de la supervivencia de las pacientes con cáncer de mama, muchas persisten con ansiedad, depresión, fatiga y dolor incluso después del tratamiento anticanceroso, factores asociados a una peor calidad de vida. **Objetivo:** evaluar la influencia del entrenamiento combinado sobre la ansiedad, la depresión, el dolor y la fatiga en pacientes con cáncer de mama. **Método:** Ensayo controlado aleatorio con 26 pacientes bajo quimioterapia, radioterapia o seguimiento clínico en un centro de referencia para el tratamiento del cáncer, con edades comprendidas entre los 30 y los 59 años, que no han practicado entrenamiento físico en los últimos tres meses. El grupo experimental (GE) (n=13) fue sometido a tres sesiones semanales de entrenamiento aeróbico y de resistencia en 12 semanas, de 60 minutos de duración, y a dos sesiones semanales de entrenamiento de flexibilidad de 20 segundos en tres series. El grupo de control (GC) (n=13) sólo realizó el tratamiento hospitalario convencional. Todas las evaluaciones se realizaron al inicio y después de 12 semanas. **Resultados:** Los pacientes del GE mostraron una reducción significativa de la ansiedad (p=0,0242), la intensidad del dolor (p=0,0290) y la dimensión conductual de la fatiga (0,0033). No se observaron diferencias en la depresión (p=0,0803), la interferencia del dolor en las actividades habituales (p=0,0933) y las dimensiones afectivas (p=0,0583) y sensoriales/cognitivas/emocionales (p=0,5525) de la fatiga. El GC se mantuvo sin cambios en todas las variables. **Conclusión:** El entrenamiento combinado de ejercicios aeróbicos, de resistencia y de flexibilidad durante 12 semanas presenta efectos beneficiosos sobre la ansiedad, la fatiga y el dolor en pacientes con cáncer de mama.

Palabras clave: neoplasias de la mama; ejercicio físico; manejo del dolor.

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INTRODUCTION

Breast cancer is a public health problem most frequent in women. In addition to high global incidence of nearly 2.1 million new cases, 66,280 new cases were estimated for Brazil and 840 for the State of Maranhão for each year of the triennium 2020-2022[1].

Oncological treatments improved the survival of patients with cancer[2], approximately 3.9 million women are survivors in the United States (USA) alone[3], but many of them continue to face adverse events as fatigue, depression and anxiety from months to years after the diagnosis associated with worst quality-of-life[2].

The prevalence of depression and anxiety disorders in patients with cancer is 20.7% and 10.3%, respectively, two-fold higher than the population in general[4]. Further to these symptoms, acute or chronic pain[5] is frequent in nearly 50% of the patients who undergo breast surgeries, including conserving ones.

Physical activity was identified as a relief therapy for depression[6], anxiety[7,8], fatigue[8] and pain[6] as an alternative to manage the adverse effects and treatments because it can improve the systemic inflammatory response, hormone profile, reduction of pro-inflammatory cytokines and body composition, cardiorespiratory resistance and autonomy of this population[2,9].

However, the volume, intensity, duration and types of exercises are the main factors to be considered for patients with cancer[10]. The objective of this study is to evaluate the effect of combined training – aerobic, resistance and flexibility exercises for 12 weeks − over breast cancer treatment related anxiety, depression, pain and fatigue and analyze the impact on the outcomes.

METHOD

Randomized clinical trial with women invited by telephone, consultations and referred by physicians, physiotherapists and psychologists from a list of 300 names in oncological treatment offered by "*Hospital do Câncer Aldenora Bello (HCAB)*". The women who accepted to participate signed the Informed Consent Form (ICF).

The study was conducted in São Luís do Maranhão, Brazil from March 2014 to September 2015 whose inclusion criteria were: women diagnosed and in treatment of breast cancer (chemotherapy or radiotherapy and/or hormone therapy) or in follow-up, at HCAB, aged 30-59 years who had not submitted to physical training in the last three months.

The exclusion criteria were: patients unable to communicate verbally or move around and pregnant women or in breastfeeding. Patients who did not attend three consecutive visits, who failed to complete the evaluation, died, got pregnant, withdrew or discontinued by the physicians were considered missed.

The sample by convenience consisted of 31 randomized patients assigned to two groups (1:1): control group (CG) with one additional patient submitted to conventional hospital treatment (CHT) alone and intervention group (IG) with patients submitted to 12-weeks combined treatment (CT) simultaneous with conventional hospital treatment (CHT) as chemotherapy, radiotherapy and hormone therapy according to medical conduct.

The Institutional Review Board of "*Universidade Federal do Maranhão (UFMA")* approved the study, CAAE (Submission for Ethical Review) 20665713.2.0000.5087 in compliance with Directive 466/12[11] of the National Health Council (CNS), number NCT03061773 of Clinical Trials.

The study was initiated upon the IRB approval and the patients were later evaluated by physical training, psychology, nutrition and physicians professionals. The evaluations (primary and secondary outcomes) were completed prior to physical training (basal) and 12 weeks later. Anamneses and sample characterization variables were obtained only at basal period.

The main outcomes of the study were anxiety and depression evaluated by the Hospital Anxiety and Depression Scale (HADS) validated to Brazil's Portuguese[12].

It is an easy to apply questionnaire utilized for the initial diagnosis and to evaluate the evolution of anxiety and depression[13]. The main characteristics of the scale are: non-inclusion of vegetative symptoms which may occur in physical diseases, separation of concepts of anxiety and depression with interspersed questions, detection of affective disorders in non-psychiatric environments and simple to complete[12]. Questions 1, 3, 5, 7, 9, 11, 13 at the final evaluations address anxiety and questions 2, 4, 6, 8, 10, 12, depression; the score of each question is added and results equal or lower than 7 of each variable indicate uncertain diagnosis, from 8 to 11, possible diagnosis and higher than 12, acceptable[14].

Secondary outcomes were pain and fatigue. Pain was evaluated by the Brief Pain Inventory (BPI) validated to Brazil's Portuguese, it evaluates the intensity and location of the pain, its impact on patients' life and effectiveness of pain therapies[15]. The scores ranged from 1 to 4, mild, from 5 to 7, moderate and from 8 to 10, severe[15].

Fatigue was evaluated by the 22-items Piper Fatigue-Revised Scale (PFS-R)[16,17] divided in three dimensions: behavioral (global, work, social, individual and sex questions), affective (self-image and self-perception) and sensorial/cognitive/emotional or sensorial-psychological

(psychological, cognitive and emotional status), analyzed by the mean of the respective items. Questions from 2 to 7 address behavioral dimension, from 8 to 12, affective dimension and from 13 to 23, sensorial/cognitive/emotional dimension at the final evaluation; the rating of each response is utilized as mean and the score ranges from 1 to 3 = mild fatigue, 4 to 6 = moderate fatigue and 7 to 10, severe fatigue[17].

The data from anamnesis and variables of sample characterization were weight (kg), height (cm) and age (years)[18], marital status, education, labor, family income (minimum wage of R$ 788.00 for 2014 and 2015). Type of neoplasm, breast cancer staging and phase of the treatment were evaluated by hospital registry and anamnesis.

The hemodynamic variables as heart rate (HR) at rest were measured by the Polar® FT2, systolic blood pressure (SBP) and diastolic blood pressure (DBP) with conventional mercury thermometer BD®, after five minutes at rest in comfortable position[18].

The level of physical activity was evaluated with the questionnaire International Physical Activity Questionnaire (IPAQ), short form[20,21]. The period without physical training (from 3 to 12 months and >1 year and never practiced) were included in the anamnesis.

The participants were submitted to mock training prior to the combined training. The adaptation to resistance and aerobic training occurred during three sessions in one week, with 15-watts cycle ergometer for aerobic, mild band (Theraband) and own body weight for resistance from eight to 12 repetitions and 1-minute interval for each exercise. Mock flexibility training was developed during three sessions per week during two weeks.

Physical education professionals conducted the 12-weeks combined training at the hospital with aerobic, resistance and flexibility exercises, five sessions a week, three for aerobic and resistance training in the same session (supervised by skilled instructors) and two for flexibility (with instructions to stretch at home) interspersed in-between aerobic and resistance training. The protocol followed the order: 60-minutes aerobic and resistance training at each session, with 30 minutes in cycle ergometer, followed by five resistance exercises. Flexibility training session (interspersed in-between aerobic and training days) for nearly 15 minutes with ten exercises.

Aerobic training was controlled by frequency of heart training (FHT)[22], measured by frequency meter Polar® FT2. Cardiorespiratory capacity test was performed to control the intensity of the training by the cycle ergometer ramp protocol[23] (brand ERGOFIT, model ERGO 167-FITC CYCLE) with initial load of 15 watts for five minutes of warm up followed by increment stages of 60 seconds, with additional 15 watts. After the maximal stage was reached, a 3-minute active recovery with the initial load was performed and stages of 70 to 90 rotations per minute (RPM). During aerobic training, blood pressure (BP), heart rate (HR) and subjective perception of effort were measured by Borg-scale (InforFisic) for patient's safety.

The intensity of aerobic and resistance training followed load increases at every four weeks: 1st phase – from the 1st to 4th week with 50 to 60% of FHT for aerobics and body weight or 1 kg (dumbbells and shin guards), moderate Theraband for resistance training; 2nd phase – from 5th to 8th week with 70% to 80% of FHT for aerobic and increase of 1 kg and strong Theraband for resistance training; 3rd phase – from 9th to 12th week for aerobic training and continued intensity from the 5th to 8th week for resistance training. The prescription respected the biological individuality of the cardiorespiratory test and maximal repetitions for initial load[24].

The load of resistance training was checked by the test of maximal repetitions with 12 repetitions and 72-hour for mock training[25]. Patients who exceeded 12 repetitions had 5-minute interval to increase the load and more 12 repetitions. The protocol of resistance training consisted in 3 sets for each exercise with 12 repetitions and 1-minute interval among sets and repetitions. The speed of the exertion of each movement was three seconds at the concentric phase and three seconds for the eccentric phase[26]. The exercises changed per segment with priority to great muscle groups. The loads were determined by sheen guards, dumbbells, Therabands and own body weight. Resistance training exercises were: 1) flexion and extension of the hip; 2) shoulder development; 3) squatting with Swiss ball; 4) French triceps; 5) bent-over row. All the resistance exercises were performed standing, except the French triceps in supine.

Flexibility training was active (great range of movement in one articulation by contracting the agonists and relaxation of the antagonists), painless for 20 seconds in three sets[24]: 1) bilateral adduction of the shoulder with extension of the elbow; 2) bilateral flexion of the shoulder and elbow with the palm of the hand at the back; 3) wrist flexion; 4) wrist extension; 5) abduction of the hip with bent knees; 6) flexion of the hip with adduction of shoulder and flexion of the elbow, seated; 7) legs extended, seated, touching the feet; 8) bilateral, extended and crossed legs, seated, touching the feet; 9) flexion and adduction of the shoulder with hands in front of the thorax; 10) flexion of the back with foot touching the wall.

Descriptive statistics were expressed by mean and standard deviation, the dichotomic and categorial variables with absolute and relative frequencies. The

Shapiro-Wilk test was utilized to check the normality of the variables: age, height, weight, HR, SBP and DBP at rest for both groups, dimension intensity of the pain and depression for IG and dimension intensity of pain, anxiety and depression for CG. The other variables presented non-parametric results.

The paired Student *t* test was applied to the dependent and parametric variables; the paired Wilcoxon test was applied to non-parametric dependent variables. The chi-square test was applied to paired and dichotomic variables. The unpaired Student *t* test was applied to parametric and independent variables. The Mann Whitney test was applied to independent, non-parametric and ordinal variables and the chi-square for independent and dichotomic variables.

Pearson's correlation test was applied to the normal secondary outcomes and Spearman's test for non-normal outcomes classified as negligible correlation (r=<0.2), weak (r=0.2-0.4), moderate (r=0.4-0.6), strong (r=0.6-0.8) and very strong (r=>0.80).

The software Stata 10.0 with α=5% was utilized and p<0.05 was considered statistically significant.

RESULTS

Thirty-one patients who met the inclusion criteria were enrolled, however, two of the IG were excluded for failing to complete the final evaluation and one patient of the CG died and two did not complete the final evaluation. Eventually, the sample consisted of 26 patients (Figure 1).

No significant differences were found for anthropometric, social, hemodynamic, type of neoplasm, cancer staging, phase of the treatment, level of physical activity and period without physical activity both for IG and CG, which reveals homogeneity (Table 1).

The descriptive data related to anxiety, depression, intensity and interference of pain in daily activities and fatigue dimensions are presented in Table 2. The patients of the IG improved all the scores.

The patients of IG had significant reduction of anxiety (p=0.0242), intensity of the pain (p=0.0290) and behavioral dimension of fatigue (p=0.0033), while for the CG, these variables remained unchanged. There was significant difference among the groups for the variable anxiety after 12 weeks (p=0.0231) (Table 3).

However, no differences in depression (p=0.0803), interference of pain in daily activities (p=0.0933) and affective (p=0.0583) and sensorial/cognitive/emotional (p=0.5525) dimensions of fatigue were found. CG remained unchanged for all variables (Table 3).

For the IG, anxiety was strongly and significantly correlated with intensity of the pain, interference of the pain in daily activities and behavioral and affective dimensions of fatigue after 12 weeks. The intensity of the

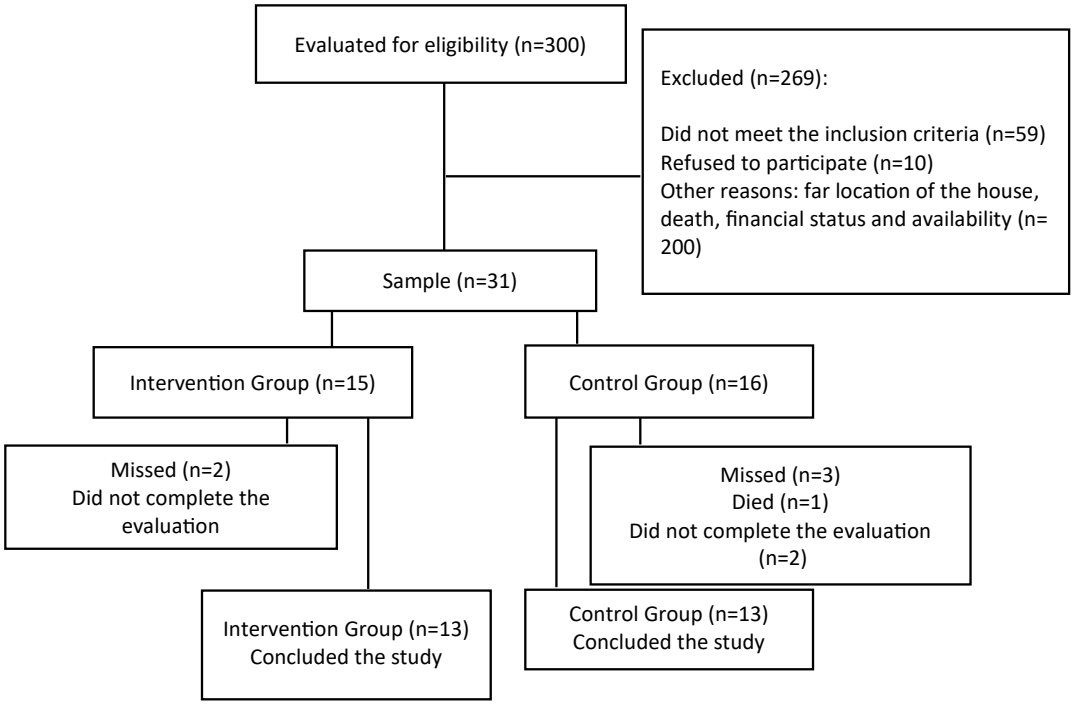

Figure 1. Flowchart

Table 1. Anthropometric, social, hemodynamic characteristics, level of physical activity and period without physical activity of patients with breast cancer (n=26)

Variables	IG (n=13)	CG (n=13)	Value of p
Anthropometric[a]			
Age (years)	46.92±7.40	46.85±7.40	0.9791
Height (cm)	153.91±4.77	154.85±6.11	0.6663
Weight (kg)	58.21±9.66	65.27±15.61	0.1782
Marital Status[b]			
Married	6 (46.15%)	7 (53.85%)	0.695
Single	7 (53.85%)	6 (46.15%)	
Education[b]			
High-school	11 (84.62%)	12 (92.31%)	0.539
University	2 (15.38%)	1 (7.69%)	
Employment[b]			
No	9 (69.23%)	12 (92.31%)	0.135
Yes	4 (30.77%)	1 (7.69%)	
Family Income[b]			
Up to 2 minimum wages	8 (61.54%)	10 (76.92%)	0.395
>2 minimum wages	5 (38.46%)	3 (23.08%)	
Hemodynamic[a]			
HR at rest (bpm)	79.61±7.80	74.85±14.44	0.3051
SBP at rest (mmHg)	117.31±13.60	110.38±12.04	0.1820
DBP at rest (mmHg)	74.07±10.36	70.77±9.36	0.4016
Type of neoplasm[c]			
Ductal carcinoma	13 (100%)	10 (76.92%)	0.0714
Epithelioid and fusocellular neoplasm	0	2 (15.38%)	
Mixed tumor of the breast	0	1 (7.69%)	
Staging[c]			
0	1 (7.69%)	0	0.6152
2	6 (46.15%)	9 (69.23%)	
3	6 (46.15%)	4 (30.77%)	
4	0	0	
Phase of treatment and follow-up[c]			
Follow-up	6 (46.15%)	4 (30.77%)	0.4231
Chemotherapy	5 (38.46%)	6 (46.15%)	
Radiotherapy	2 (15.38%)	3 (23.08%)	
Level of physical activity[c]			
Active	7 (53.85%)	8 (61.54%)	0.7254
Irregularly active	5 (38.46%)	4 (30.77%)	
Very active	1 (7.69%)	1 (7.69%)	
Time without physical activity[b]			
3 to 12 months	1 (7.69%)	1 (7.69%)	1.000
>1 year and never practiced	12 (92.31%)	12 (92.31)	

Captions: IG = intervention group; CG = control group; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.
(a) Unpaired Student t test.
(b) Chi-square test.
(c) Mann-Whitney test; values expressed as mean ± standard deviation, absolute frequency (relative frequency).

Table 2. Evaluation of anxiety, depression, intensity of the pain, interference of pain in daily activities and behavioral, affective and psychological dimensions of fatigue in patients with breast cancer (n=26) submitted to physical training

	IG (n=13)		CG (n=13)	
	Basal	12 weeks	Basal	12 weeks
Anxiety				
Unlikely	7 (53.85%)	11 (84.61%)	9 (69.23%)	8 (61.54%)
Possible	4 (30.77%)	1 (7.69%)	2 (15.38%)	4 (30.77%)
Probable	2 (15.38%)	1 (7.69%)	2 (15.38%)	1 (7.69%)
Depression				
Unlikely	8 (61.54%)	11 (84.61%)	9 (69.23%)	8 (61.54%)
Possible	3 (23.07%)	2 (15.38%)	3 (23.07%)	4 (30.77%)
Probable	2 (15.38%)	0 (0%)	1 (7.69%)	1 (7.69%)
Intensity of the pain				
Mild	10 (76.92%)	11 (84.61%)	9 (69.23%)	8 (61.54%)
Moderate	1 (7.69%)	1 (7.69%)	2 (15.38%)	4 (30.77%)
Severe	2 (15.38%)	1 (7.69%)	2 (15.38%)	1 (7.69%)
Interference on Daily Activities				
Mild	8 (61.54%)	10 (76.92%)	6 (46.15%)	9 (69.23%)
Moderate	4 (30.77%)	2 (15.38%)	4 (30.77%)	2 (15.38%)
Severe	1 (7.69%)	1 (7.69%)	3 (23.07%)	2 (15.38%)
Behavioral dimensions of fatigue				
Mild	7 (53.85%)	10 (76.92%)	7 (53.85%)	8 (61.54%)
Moderate	3 (23.07%)	3 (23.07%)	2 (15.38%)	1 (7.69%)
Severe	3 (23.07%)	0 (0%)	4 (30.77%)	4 (30.77%)
Affective				
Mild	7 (53.85%)	11 (84.61%)	6 (46.15%)	7 (53.85%)
Moderate	2 (15.38%)	1(7.69%)	3 (23.07%)	4 (30.77%)
Severe	4 (30.77%)	1(7.69%)	4 (30.77%)	2 (15.38%)
Sensorial/cognitive/emotional				
Mild	10 (76.92%)	11 (84.61%)	6 (46.15%)	6 (46.15%)
Moderate	1 (7.69%)	1 (7.69%)	4 (30.77%)	6 (46.15%)
Severe	2 (15.38%)	1 (7.69%)	3 (23.07%)	1 (7.69%)

Captions: IG = intervention group; CG = control group.
Note: Absolute frequency (relative frequency).

pain, interference of the pain in daily activities, depression and behavioral dimension of fatigue had moderate and significant correlation with anxiety at basal for the CG, similar to intensity of the pain, depression and affective dimension of fatigue after 12 weeks (Table 4).

DISCUSSION

Anxiety and depression are associated with lower therapeutic adherence and increase of medical and emergency care for patients with cancer[13]. Notwithstanding, there are innumerous barriers to diagnose mental disorders of this population as the fear of psychiatric diagnosis interfering with oncologic treatment, in addition to lack of time for a proper mental health evaluation, limited availability of experts and fragmented psychosocial services[13].

According to the American Society of Clinical Oncology Guideline[27], all the patients with cancer should be evaluated for symptoms of anxiety and depression during the course of care and failure to identify and treat these pathologies are associated with poor quality-of-life and increase of morbimortality[27]. Anxiety can still cause other side effects as fatigue, sleep disorders, digestive problems, tachycardia, agitation, muscle tension, sweating, tremor, weight and energy loss further to pathological

Table 3. Evaluation of the outcomes in patients with breast cancer (n=26) submitted to physical activities

Variables	IG (n=13)			CG (n=13)			IG versus CG	
	Basal	12 weeks	Value of p	Basal	12 weeks	Value of p	Basal	12 weeks
Anxiety and depression								
Anxiety	7±4.69	4.54±3.26	0.0242*[b]	7.46±5.16	7.15±3.65	0.7407[a]	0.8134[c]	0.0231*[d]
Depression	5.85±5.30	3.46±2.57	0.0803[a]	5.46±4.27	6±4.71	0.4069[a]	0.8404[c]	0.1008[c]
Pain								
Intensity	3.65±2.55	2.61±2.53	0.0290*[a]	3.63±3.15	3.69±2.99	0.9253[a]	0.9865[c]	0.3316[c]
Interference in daily activities	3.58±2.87	2.47±3.11	0.0933[b]	4.43±3.42	3.31±3.70	0.1296[b]	0.5016[c]	0.6002[d]
Fatigue								
Behavioral Dimension	4.37±3.10	1.93±2.50	0.0033**[b]	4.05±3.70	3.79±3.81	0.2938[b]	0.8123[c]	0.1398[d]
Affective Dimension	3.90±3.92	2.03±2.49	0.0583[b]	4.34±4.13	3.57±3.46	0.3782[b]	0.8339[d]	0.2310[d]
Sensorial/cognitive/emotional Dimension	2.75±3.28	2.31±2.45	0.5525[b]	3.94±3.56	3.53±2.97	0.4631[b]	0.7581[d]	0.2631[c]

Captions: IG = intervention group; CG = control group.
Note: Values expressed as mean ± standard deviation.
([a]) Paired Student t test.
([b]) Wilcoxon test.
([c]) Unpaired Student t test.
([d]) Mann-Whitney test.
(*) p<0.05.
(**) p<0.01.

Table 4. Correlation of anxiety with secondary outcomes in patients with breast cancer (n=26) submitted to physical activities

Variables	IG (n=13)				CG (n=13)			
	Basal		12 weeks		Basal		12 weeks	
	r	Value of p	r	Value of p	r	Value of p	r	Value of p
Pain								
Dimension intensity	0.5145	0.0720[a]	0.6105	0.0267*[b]	0.6896	0.0091**[a]	0.6446	0.0174*[a]
Dimension interference	0.5138	0.0725[a]	0.8283	0.0005**[b]	0.6227	0.0230*[a]	0.5450	0.0541[b]
Depression	0.7603	0.0026**[a]	0.7561	0.0028**[b]	0.8022	0.0010**[a]	0.6841	0.0099**[a]
Fatigue								
Behavioral Dimension	0.5006	0.0815[a]	0.5781	0.0385*[b]	0.7905	0.0013**[a]	0.4709	0.1043[b]
Affective Dimension	0.5127	0.0732[b]	0.6860	0.0096**[b]	0.5165	0.0707[b]	0.5977	0.0310*[a]
Sensorial/cognitive/emotional Dimension	0.5393	0.0572[b]	0.5256	0.0650[b]	0.4721	0.1033[b]	0.5312	0.0617[a]

Captions: IG = intervention group; CG = control group.
([a]) Pearson's test.
([b]) Spearman's test.
(*) p<0.05.
(**) p<0.01; negligible correlation (r=<0.2), weak (r=0.2-0.4), moderate (r=0.4-0.6), strong (r=0.6-0.8) and very strong (r=>0.80).

concerns, low immunity, feeling of powerlessness and pessimism[28].

Even after many years of investigation, the prevalence of anxiety and depression symptoms in patients with cancer is still arguable, in part because of different types of scales utilized and heterogeneity of the population, cancer stages and type of treatment received[13]. In addition, studies demonstrate that oncologists may have difficulties to identify psychiatric morbidities because the diagnosis of anxiety, in general, is made by primary attention doctors (45%) and mental health practitioners (27%) and only 1% by oncologists[13].

One of the main outcomes was anxiety with a significant reduction in the intervention group and in both groups after 12 weeks. A meta-analysis involving 17 randomized controlled trials raised the hypothesis that the prescription of resistance exercises plus two sessions of moderate intensity aerobic activity for 20 weeks are able to reduce the anxiety in this population[4]. Another meta-analysis with 33 randomized clinical trials has also found

a significant reduction of this variable[29]. A clinical trial with combined training (aerobic and resistance) detected reduction of anxiety in patients in adjuvant treatment for breast cancer[7].

Clinical improvement but non-statistically significant of depressive symptoms in IG was found, although several studies concluded that depression improved with physical exercises[2,4,29]. These results can be explained partially by low basal scores and sample size, making the conclusion about the impact of physical exercises on depression difficult.

Some authors have hypothesized that the antidepressant and anxiolytic symptoms result from physiological changes arising from hippocampal neurogenesis explained by several mechanisms as increase of beta-endorphins, endothelial growth factor, and serotonin and brain-derived neurotrophic factor[6]. Other mechanisms include increase of noradrenaline levels and alteration of the hypothalamic-pituitary-adrenal axis because the increased secretion of the corticotropin-releasing hormone was associated with depression and the exercises delay the axis' response to the physical and mental stress. In addition, aerobic and resistance exercises result in improvement of self-esteem, body image and perception of domain all of them related to lessening of depressive symptoms[6].

Decrease of pain intensity of the CG with the protocol of combined training was detected but no significant improvement of pain on daily life occurred, which is possibly explained by the small sample size. Less intense pain can be the result of combined training because aerobic exercises raise the peripheral levels of beta endorphins which reduce the sympathetic activity, increase sleeping hours and create psychological stability, in addition to improving the serotoninergic system and the relation between the terminal area of the nerves and the length of the muscle fibers. The resistance exercise produces better synchronization of motor units, better efficacy of neural recruitment, activation of the central nervous system and excitability of motoneurons, in addition to depressing the neural inhibitory reflex and create inhibition of Golgi tendon organs[30,31].

Significant difference was found in the behavioral dimension of fatigue of the CG alone, despite the declining scores of the affective and sensorial/cognitive/emotional dimensions. Fatigue can be caused by physical deconditioning (diminishing of physical strength and physical fitness), comorbidities, increase of pro-inflammatory cytokines, psychosocial factors (anxiety and depression), deregulation of neurotransmitters, alteration of the hypothalamic-pituitary-adrenal axis and sleep dysfunction[32].

Some authors[33] differentiate peripheral from central fatigue, the first caused by neuromuscular abnormalities (for instance, excitation-contraction coupling and reduction of calcium recapture) and the second by abnormalities of the central nervous system (lack of motivation influenced by psychosocial factors as depression). Although additional studies are necessary, central fatigue has been reported as main cause of fatigue in cancer survivors. It is expected that exercises without psychosocial support improve peripheral fatigue more than central fatigue, which may have contributed to the study results[33].

The results of the correlations show that oncologic patients with anxiety have more depression, pain and fatigue both in the IG and CG which can be explained by the impact of the disease and on the patient's life. However, stronger correlations were found in the IG, being possible to conclude that physical exercises for patients with breast cancer with symptoms of anxiety are beneficial to improve pain, depression and fatigue.

The evidences support the concept that interventions with physical exercises are beneficial and safe for breast cancer survivors[34,35], some prospective longitudinal studies[36] demonstrated that physical activity reduces during anticancer treatment. The intervention with exercises should be prescribed to breast cancer survivors, encouraging them to continue their regular physical activities or adjust to their needs[28].

The investigation during different moments of anticancer therapy and the small sample are some of the study limitations, but difficulties for patients with cancer exist because of side effects and economic conditions to access venues where physical training is administered[37] which is an obstacle to generalize the results, as some studies have also concluded. The positive aspect is that only one type of cancer was investigated with significant results during a small period of intervention.

CONCLUSION

The combined intervention involving aerobic, resistance and flexibility exercises for 12 weeks is safe and viable with beneficial effects on anxiety, fatigue and pain with patients with breast cancer. Based in this initial study, new investigations can be done more effectively to test the results achieved for further generalization.

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CONTRIBUTIONS

Marília de Oliveira Bringel, Andréa Dias Reis and Letícia Campos Aguiar contributed to the study design, acquisition, analysis and interpretation of the data, wording and critical review. João Batista Santos Garcia contributed to the wording and critical review. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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