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Effects of continuous and interval physical training through the intensity of the incremental Shuttle walk test, on functional capacity and quality of life in women with malignant breast cancer during chemotherapy treatment - randomized clinical trial

Efeitos do treinamento físico contínuo e intervalado por meio da intensidade do teste incremental de caminhada Shuttle, na capacidade funcional e qualidade de vida em mulheres com câncer de mama maligno durante o tratamento quimioterápico - ensaio clínico randomizado

Efectos del entrenamiento físico continuo e interválico mediante la intensidad de la prueba incremental de caminata de Shuttle, sobre la capacidad funcional y la calidad de vida en mujeres con cáncer de mama maligno en tratamiento con quimioterapia - ensayo clínico aleatorizado

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Grasiani Breggue Pires
ORCID: https://orcid.org/0000-0002-1683-7054
Universidade Nove de Julho, Brazil
E-mail: gbreggue@gmail.com
Conceição Aparecida Vitoriano Silva
ORCID: https://orcid.org/0000-0001-5291-8735
Universidade Nove de Julho, Brazil
E-mail: convitoriano@gmail.com
Ivan Peres Costa
ORCID: https://orcid.org/0000-0002-8566-7976
Universidade Nove de Julho, Brazil
E-mail: yvanperes@gmail.com
Simone Dal Corso
ORCID: https://orcid.org/0000-0001-9190-6796
Universidade Nove de Julho, Brazil
E-mail: si.dal.corso@gmail.com
Luciana Maria Malosá Sampaio
ORCID: https://orcid.org/0000-0002-0110-7710
Universidade Nove de Julho, Brazil
E-mail: lucianamalosa@gmail.com

Abstract
Objective: To compare the effects of continuous and resistance aerobic training at high intensity and resistance in women with breast cancer during chemotherapry treatment. *Design*: A randomized clinical trial. Forty patient's diagnostics with breast cancer and undergoing chemotherapy. Will be recruited and randomized into two groups: (a) Combined training (continuous aerobic + resistance); (b) Combined training (high-intensity interval (IAI) + resistance). They will follow a protocol for inclusion One-Repetition Max Test (1RM), Grocery Shelving Task Test, Shuttle walk test incremental and the questionaries: Quality of life questionarie (EORTC QLQ-C30), Functional Assessment of Cancer Therapy Breast (FACT-B) e Brief Fatigue Inventory (BFI). The training protocol proposed for the study groups should be carried out for 8 weeks, three times a week on alternate days, totaling 24 training sessions. *Conclusion*: The focus of research in this area has predominantly been over the past two decades, focused on the effectiveness of exercise as an adjuvant strategy after cancer diagnosis. Observational studies indicate that physical exercise is directly linked to a reduction in the risk of cancer recurrence and mortality. We hypothesized that all the training protocols proposed to promote the benefits in health indicators in this study and potential for therapies for patients safely undergoing cancer treatment will present, but which protocol can still pursue the beneficial effect.
Keywords: Exercise; Breast cancer; Quality of life; Fatigue; Functional capacity.

Resumo
Objetivo: Comparar os efeitos do treinamento aeróbio contínuo e resistido de alta intensidade e resistência em mulheres com câncer de mama durante o tratamento quimioterápico. *Desenho*: Um ensaio clínico randomizado.

Quarenta pacientes com diagnóstico de câncer de mama e em tratamento quimioterápico. Serão recrutados e randomizados em dois grupos: (a) Treinamento combinado (contínuo aeróbico + resistido); (b) Treinamento combinado (intervalo de alta intensidade (IAI) + resistência). Eles seguirão um protocolo para inclusão de One-Repetition Max Test (1RM), Grocery Shelving Task Test, Shuttle walk test incremental e os questionários: Questionário de qualidade de vida (EORTC QLQ-C30), Avaliação funcional da terapia do câncer de mama (FACT-B) e Inventário Breve de Fadiga (BFI). O protocolo de treinamento proposto para os grupos de estudo deve ser realizado durante 8 semanas, três vezes por semana em dias alternados, totalizando 24 sessões de treinamento. *Conclusão*: O foco de pesquisa nesta área tem sido predominantemente nas últimas duas décadas, focado na eficácia do exercício como estratégia adjuvante após o diagnóstico de câncer. Estudos observacionais indicam que o exercício físico está diretamente ligado à redução do risco de recorrência e mortalidade por câncer. Hipotetizamos que todos os protocolos de treinamento propostos para promover os benefícios nos indicadores de saúde deste estudo e potencial de terapias para pacientes submetidos a tratamento oncológico com segurança apresentarão, mas cujo protocolo ainda pode buscar o efeito benéfico.
Palavras-chave: Exercício; Câncer de mama; Qualidade de vida; Fadiga; Capacidade funcional.

Resumen
Objetivo: Comparar los efectos del entrenamiento aeróbico continuo y resistido de alta intensidad y resistencia en mujeres con cáncer de mama durante el tratamiento con quimioterapia.*Diseño*: Un ensayo clínico aleatorizado. Cuarenta pacientes diagnosticadas de cáncer de mama y sometidas a quimioterapia. Serán reclutados y aleatorizados en dos grupos: (a) Entrenamiento combinado (aeróbico continuo + resistencia); (b) Entrenamiento combinado (intervalo de alta intensidad (IAI) + resistencia). Seguirán un protocolo para la inclusión del One-Repetition Max Test (1RM), el Grocery Shelving Task Test, el Shuttle walk test incremental y los cuestionarios: Quality of Life Questionnaire (EORTC QLQ-C30), Functional Assessment of Breast Cancer Terapia (FACT-B) e Inventario Breve de Fatiga (BFI). El protocolo de entrenamiento propuesto para los grupos de estudio deberá realizarse durante 8 semanas, tres veces por semana en días alternos, totalizando 24 sesiones de entrenamiento. *Conclusión*: El foco de investigación en esta área ha sido predominantemente en las últimas dos décadas, centrado en la efectividad del ejercicio como estrategia adyuvante después del diagnóstico de cáncer. Los estudios observacionales indican que el ejercicio físico está directamente relacionado con la reducción del riesgo de recurrencia y mortalidad por cáncer. Presumimos que todos los protocolos de capacitación propuestos para promover los beneficios en los indicadores de salud de este estudio y el potencial de las terapias para pacientes en tratamiento contra el cáncer se presentarán de manera segura, pero cuyo protocolo aún puede buscar el efecto beneficioso.
Palabras clave: Ejercicio; Cáncer de mama; Calidad de vida; Fatiga; Capacidad funcional.

1. Introduction

Cancer on the world stage remains a major public health problem, breast cancer is the most common type among women. Despite advances in antineoplastic therapies, breast cancer accounts for about 28% of new cases each year in Brazil (INCA, 2018; Anastasiadi et al.,2017).

The development of new therapies in oncology over the past few decades has been an impressive success and has fundamentally changed the prognosis of cancer patients. Early diagnosis and a growing arsenal of modern therapies allow achieving a higher rate of cancer-free survival. As a result, a significant improvement in survival rates, in this way, science is faced with a greater number of patients who have a history of cancer treatment and are at risk of complications, including related cardiac ones. If expressed in numbers, one can see an increase in overall 5-year survival rates for all cancers, which have risen from about 50% in the late 1970s to 69% in the last decade (Miller et al., 2016).

Women often survive breast cancer and other diseases such as chronic diseases such as diabetes, pulmonary obstruction, heart disease, arthritis, hypertension, among others. Antineoplastic treatment for breast cancer associated with chronic diseases predisposes as advanced diseases with cardiotoxicity increasing the risk of developing heart disease (CVD) and may lead to a decline in quality of life when associated. In cancer patients, pathophysiology of cardiovascular dysfunction can be very different from cancer treatment that has not been differentiated from cardiovascular cancer treatment. This situation is due to the adverse effects that antineoplastic therapy exerts on the cardiovascular system (Cornette et al., 2016; Dieli-Conwright et al., 2018).

According to the American Heart Association and American Cancer Society, physical exercise is one of the strategies adopted to prevent and reduce the effects of antineoplastic therapy, promoting effects on cardiovascular reserve, hypertension, hypercholesterolemia, obesity and global attenuations in mortality in individuals without neoplasia (Dieli-Conwright et al., 2018; Schmitz et al., 2010). Exercise programs for cancer survivors must meet guidelines established by the American Cancer Society and American College of Sports Medicine (ACSM), which advocate 150 minutes of aerobic exercise and 2 to 3 days of strength training per week (Schmitz et al., 2010).

Some recent studies performed continuous and resistance aerobic training in breast cancer survivors, observing improvement in functional capacity, quality of life and strength of these patients, (Scott et al., 2018; Schmidt et al., 2015), however, few investigated women during chemotherapy treatment (Cornette et al., 2016; Courneya et al., 2014; Karlsen et al., 2017) and few evaluated the benefits of IAI training in this group of patients (Thum et al., 2017; Saanijoki et al., 2018).

Evidence-based exercise regimens with identified benefits are highly endorsed by healthcare providers and patients. In healthy individuals and in various pathological conditions, high-intensity interval training (IAI) provides significant and time-efficient improvements in cardiorespiratory fitness, obesity, and associated comorbidities (Tjønna et al., 2008) and pilot studies present the IAI as a safe training strategy in women with cancer (Jaureguizar et al., 2016)

There is growing evidence that highlights the benefits of shorter workouts with high-intensity exercise for clinical populations (Karlsen et al., 2017; Schmitt et al., 2016). Studies not only show improvements in cardiorespiratory fitness compared to moderate-intensity aerobic training, but also added benefits in quality of life (Karlsen et al., 2017), mood state (Tjønna et al., 2008) and cognitive health, increasing endorphin release in areas of the brain associated with controlling blood pressure. emotion and pain (Jaureguizar et al., 2016). Pilot studies have shown that cancer patients can safely perform IA (Thum et al., 2017). One of the main barriers to performing physical exercise is the lack of time and motivation (Saanijoki et al., 2018), the IAI during chemotherapy can be favorable to optimize health outcomes and improve adherence to training. Our hypothesis is that the combination of IAI with resistance exercise provides additional benefits on functional capacity and quality of life, corroborating a recent and unique study comparing IAI exercise combined with resistance and continuous aerobic associated with IAI (Saanijoki et al., 2018).

No studies were found in the literature evaluating functional capacity in patients during chemotherapy comparing IAI training combined with resistance and continuous aerobic training with resistance on cardiometabolic status and quality of life.

In this context, it is justified to carry out the present study with the objective of improving the effects of different types of physical training in antineoplastic women for the treatment of breast cancer. We hypothesized that all the training protocols proposed to promote the benefits in health indicators in this study and potential for therapies for patients safely undergoing cancer treatment will present, but which protocol can still pursue the beneficial effect.

2. Methodology

Study design and population

A randomized clinical trial will be developed in the physiotherapy clinic of a reference center in São Paulo, applying different types of physical training. To carry out this study, volunteers will be recruited from the hospital's chemotherapy sector. All potential participants will be interviewed in person to verify inclusion/exclusion criteria. Volunteers will be selected according to the following criteria. This work was approved by the ethics committee registered number 5.204.615. This work is registered in the Clinical Trail with Identifier: NCT05241925.

Eligibility

Based on the study eligibility criteria, all individuals who agree to participate in the study, and commit to the research terms by signing the Informed Consent Form (ICF)

Inclusion criteria

• Diagnosis of breast cancer confirmed by a doctor; duration of adjuvant chemotherapy treatment; undergoing surgery to treat breast cancer;

Exclusion Criteria

• Diagnosis of another (1) neoplasm prior to breast cancer; (2) heart disease; (3) skeletal muscle; (3) respiratory disease; (4) uncontrolled high blood pressure or (5) factors that limit the performance of any of the estimates and/or training in the study. Not having undergone chemotherapy or treatment prior to the diagnosis of breast cancer;

Randomization and training groups

Subsequently, individuals will be randomly assigned, by means of a draw, to one of the two groups, a group consisting of continuous and resistance aerobic training and a group of high-intensity and resistance interval training.

The allocation of participants will be carried out by a person not involved in the study, selecting an opaque envelope from inside a box. Block randomization will be performed using the website www.randomization.com.

The training protocol proposed for the study groups should be carried out for 8 weeks, three times a week on alternate days, totaling 24 training sessions.

Combined training (continuous aerobic + resistance)

The protocol will consist of supervised exercise lasting 1h10min each session (5 min of warm-up, 30 min of aerobic exercise, 30 min of resistance exercise and 5 min of cool-down/relaxation).

- Aerobic exercise on a treadmill (Athletic Treadmill Extreme). The exercise load will be predetermined by the speed obtained in the incremental Shuttle walk test and will be gradually increased during training sessions (once an individual completes two consecutive sessions at the specified level of exercise intensity).

Combined training (high-intensity interval (IAI) + resistance)

- Supervised exercise lasting 30 min each session (5 min warm-up, 20 min IAI and 5 min cool-down/relaxation).

- Exercise on a treadmill (Athletic Treadmill Extreme). IAI protocol: Intensive intervals 3 x 3 min of maximum effort 85 to 90% FC max interspersed with active rest of 50 to 60% FC max (= 20 min of training).

Intervention

Resistance Training

- Resistance exercise will be performed at 70-80% of one repetition maximum (1-RM); 2 to 3 sets 8 to 12 sets. The main groups will be trained using training equipment with weights and body mass of the participants. Exercises include leg extensions, biceps curls, squats, seated numbness postures, sit-ups, presses, and standing pulldowns19. The workload through tools will be used to work with the training program. As recommended by the American Cancer Society (ACS) and American College of Sports Medicine (ACSM).

Body composition

Body composition will be evaluated initially in a fasted state and after the last training session. the tetrapolar bioimpedance method (Biodynamics® Model 450, TBW).

One-Repetition Max Test (1-RM)

To determine the training protocol loads, the 1-RM test will be applied gradually increasing the load until the volunteer can perform no more than one repetition. as recommended by the American Cancer Society and American College of Sports Medicine .

Shuttle Walk Test Incremental (SWTI)

Before and after the 8 weeks of training, an assessment of the functional capacity of the participants will be carried out through the application of the SWTI. The SWTI will be carried out according to the original description (Singh et al.,

1992). A 10m corridor will be used, where 9m is demarcated by two cones inserted 0.5m from each end. The patient must come and go on this predetermined path according to the rhythm imposed by sound stimuli previously recorded on a CD.

European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire - EORTC QLQ-C30

Before and after the training protocol, an assessment of the participants' quality of life will be carried out through the application of the EORTC QLQ-C30 questionnaire. (Cull A et al., 1998). The Brief Fatigue Inventory (BFI) questionnaire is a one-dimensional tool based on the Brief Pain Inventory that assesses the severity and impact of cancer pain. Functional Assessment of Breast Cancer Therapy (FACT-B) (Matthies et al., 2019).

Grocery Shelving Task Test

The Grocery Shelving Task test there is a need for a bookcase with movable shelves. The patient is positioned in orthostatism in front of a table positioned in front of the shelf. The patient was asked to perform bilateral shoulder forward flexion and the evaluator adjusted the shelf 15 cm above shoulder level. A table 30 cm wide and 90 cm high was to be placed in front of the shelf and 20 cans weighing 420 g were divided equally and placed in two shopping bags on the floor on either side of the chair. A chair was positioned for the patient to sit at a distance of 1 meter from the table. (Breggue, 2019).

The primary outcome will be the distance SWT and the secondary quality of life and GSTT.

Data analysis

Data will be tabulated and submitted to statistical analysis. Measures of central tendency (median, mean, standard deviation) will be used to describe numerical variables and absolute and relative frequencies for categorical variables.

To compare the independent groups in terms of demographic and clinical data, the Kruskal-Wallis test will be used for numerical variables and the chi-square test or Fisher's exact test for categorical variables. To compare the groups regarding the EORTC QLQ-C30, BFI and FACT-B scores, the Kruskal-Wallis test will be used, and the variables of biochemical tests, functional capacity and muscle strength will be used the Anova, intention to treatment.

The SPSS 23 program (Statistical Package for Social Sciences, Inc., Chicago, USA) will be used for the analysis, and the null hypothesis rejection level will be set at 5% ($\alpha \leq 0.05$).

3. Results and Discussion

The focus of research in this area has predominantly been over the past two decades, focused on the effectiveness of exercise as an adjuvant strategy after cancer diagnosis (Cornette et al, 2016). Observational studies indicate that physical exercise is directly linked to a reduction in the risk of cancer recurrence and mortality. Few trials report the effects of exercise during chemotherapy on breast cancer (Dieli-Conwright et al., 2018, Scott et al., 2018). In contexts outside the oncological scenario, resistance exercises have been shown to be fundamental when associated with aerobic exercise (Dieli-Conwright et al., 2018). Furthermore, few studies have compared different types and doses of exercise for breast cancer patients (Tjønna et al., 2008; Jaureguizar et al., 2016) to identify the optimal exercise prescription for a given outcome.

Aerobic exercise can be performed through HIIT, a new exercise strategy that maximizes exercise intensity using short-term high-intensity efforts alternating with recovery periods, which allows patients to perform high-intensity exercise due to the on-off' exercise, and rest (Thum et al., 2017; Saanijoki et al., 2018). We know that high-intensity interval training (HIIT) is more effective than continuous moderate-intensity aerobic exercise, but for adequate prescription, an assessment of physical fitness is necessary to quantify the initial exercise intensity (Saanijoki et al., 2018). The cardiopulmonary exercise test (CPET) is used to determine physical fitness, but it is a test that requires expensive and sophisticated equipment, as well as a test that demands longer execution time and makes it difficult to evaluate patients on large scales. However, the incremental walk test

(ISWT) reached maximal levels of effort with no significant difference in any physiological response in relation to CPET. ISWT can be a simple, effective, and safe alternative to CPET, as it is the only test that provides incremental intensities, which shows a greater physiological response compared to other field tests (Marsico et al., 2021).

4. Conclusion

The focus of research in this area has predominantly been over the past two decades, focused on the effectiveness of exercise as an adjuvant strategy after cancer diagnosis. Observational studies indicate that physical exercise is directly linked to a reduction in the risk of cancer recurrence and mortality. We hypothesized that all the training protocols proposed to promote the benefits in health indicators in this study and potential for therapies for patients safely undergoing cancer treatment will present, but which protocol can still pursue the beneficial effect.

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