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Effect of Exercise Training on Exercise Tolerance and Level of Oxidative Stress for Head and Neck Cancer Patients Following Chemotherapy

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Background: Chemotherapy decreases fitness performance via repression of cardiopulmonary function and oxidative stress. This study was designed to investigate whether exercise intervention could improve exercises capacity and reduce systemic oxidative stress in patients with head and neck (H&N) cancer receiving chemotherapy.

Methods: This is a single-center study. Forty-two H&N cancer patients who were undergoing chemotherapy were recruited in this study. An 8-week exercise intervention was performed by conducting the combination of aerobic and resistance exercise 3 days a week. The exercise training was conducted by a physiotherapist. The exercise capacity and exercise responses were measured from blood pressure (BP) and heart rate (HR). Oxidative stress markers from human plasma, such as total antioxidant capacity, 8-hydroxy-2′-deoxyguanosine, malondialdehyde, and carbonyl content, were tested by activity kits.

Results: We provide compelling evidence that exercise training ameliorated exercise responses and increased exercise capacity by repressing resting BP and increasing 1- and 3-min BP recovery. We also found the resting HR was reduced, and the 1- and 3-min HR recovery was increased after exercise training. In addition, the rating of perceived exertion after the peak exercise was reduced after exercise intervention. We also found that exercise training repressed oxidative stress markers by elevation of total antioxidant capacity and suppression of 8-OHd and carbonyl content in plasma.

Discussion: We clearly demonstrate that exercise can promote exercise capacity and reduce oxidative stress in H&N cancer patients receiving chemotherapy, which might guide new therapeutic approaches for cancer patients, especially those undergoing chemotherapy.

Keywords: head and neck cancer, exercise, exercise capacity, oxidative stress, chemotherapy

INTRODUCTION

Head and neck (H&N) cancers are gaged to be one of the most prevalent cancer types in this world (1). During the past decades, chemotherapy of H&N cancer has undergone extensive testing in clinical trials, and important milestones have been achieved in several fields (2). Several chemotherapy drugs have been used in patients with H&N cancer such as cisplatin or carboplatin. Cisplatin given at a concentration of 80–120 mg/m^2 per month causes an overall treatment response rate of 28% (3). Although chemotherapy has improved survival markedly in H&N cancer patients, a large percentage of cases with H&N severely suffered from side effects such as decreased quality of life (QoL) and physical function, neuropathy, and fatigue during treatment (4). A previous study suggested that chemotherapy not only attacks cancer cells but also influences normal tissue to cause systemic organ injury. One of the most critical problems is reduced fitness performance caused by the cardiopulmonary function during chemotherapy, which leads to low QoL (5).

Persuasive studies have concluded that cancer patients receiving chemotherapy have significant impairments in cardiorespiratory fitness and exercise capacity. The reduced physical activity suppresses cardiorespiratory fitness (6). Chemotherapy has been shown to cause muscle weakness and muscle atrophy, which reduces the diffusion transport of blood in skeletal muscle and thus results in decreased cardiorespiratory fitness (7). Moreover, deterioration of cardiac function is another important cause of reduced cardiorespiratory fitness. Chemotherapy can induce significant dysfunction in left ventricle, eventually leading to a reduction of cardiac contractility and cardiac output (8). In addition, the increased apoptosis and oxidative stress in cardiomyocytes are critical mechanisms in chemotherapy-induced cardiotoxicity (9).

A previous study reported increased formation of serum oxidative markers in patients with H&N cancer (10). In addition, chemotherapy has been reported to increase oxidative stress in cancer patients. This is obviously due to increased lipid peroxidation products that reduce free radical–scavenging capacity and antioxidant activity during chemotherapy (11). Oxidative stress has been suggested to modulate cellular signals that are required for chemotherapy to effectively destroy cancer cells (12). The systemic antioxidant capacity is suppressed, and the protein oxidation is elevated in cancer patients undergoing chemotherapy; therefore, it may be probable that oxidative stress contributes to cardiorespiratory fitness reduction in cancer subjects after cancer management (13). Antioxidants supplements can reduce or prevent side effects caused by chemotherapy, but they may diminish the clinical effectiveness of chemotherapeutic treatments (14). Thus, to find effective interventions rather than antioxidants supplements for cancer patients is important.

Exercise is very helpful for the recovery from cancer treatments. Moderate-intensity exercise training can improve cancer patients' mental health as compared to non-exercise subjects (15). In addition, a previous study has also suggested that appropriate exercise can improve the discomforts caused by chemotherapy in cancer patients. Mohamady et al. (16) reported that 12 weeks of moderate-intensity aerobic exercise enriched hemoglobin and erythrocytes in the circulatory system, thereby improving the clinical symptoms of anemia. However, whether exercise training can reduce oxidative stress in H&N cancer patients receiving chemotherapy is still unclear. The primary aim of this present study was to investigate the effect of 8 weeks' combinative exercise training on cardiorespiratory fitness in patients receiving chemotherapy. We hypothesized that exercise intervention ameliorates exercise responses and exercise capacity in cancer subjects undergoing chemotherapy. The secondary aim was to examine changes in oxidative stress marker in patient plasma. The hypothesis was that exercise training reduces oxidative stress markers in cancer subjects undergoing chemotherapy.

MATERIALS AND METHODS

This single-center study was conducted between September 2016 and December 2017 as a single-arm study. The National Cheng Kung University and National Cheng Kung University Hospital were responsible for the integrity and conduct of this study. This study was approved by the ethical committee of National Cheng Kung University Hospital Institutional Review Board, Tainan, Taiwan (B-ER-105-102), and this trial was registered in Thai Clinical Trials Registry (TCTR20171211001). After explaining all the experimental procedures in detail, each case provided written consent to join in the study.

Subjects

Head and neck cancer patients were recruited from the Department of Hematology and Oncology at the National Cheng Kung University Hospital, Tainan, Taiwan. The patient sample size was referred by previous cancer exercise reports (17, 18). The characteristics of the studied population are presented in **Table 1**. The inclusion criteria included (1) age 20 years or older with H&N cancer; (2) H&N cancer

TABLE 1 | Basic characteristics of subjects.

Basic characteristics	Exercise group (*N* = 30)
Gender	
Female	7
Male	23
Risk factor	
Smoke	15
Drink	20
Chew the betel nuts	13
Age (years)	56 ± 12.3
Height (m)	1.6 ± 0.7
Body weight (kg)	64.6 ± 11.2
Chemotherapy drugs	
Cisplatin	22
Gemcitabine	1
Medroxyprogesterone	7

diagnosed by pathology, cytology, or imaging; (3) no serious complications; (4) no brain tumor metastasis; and (5) no history of mental illness. The exclusion criteria included (1) those who could not sign the consent, (2) neurological disorders (e.g., stroke), (3) pregnant or lactating women, (4) severe psychiatric disorders (e.g., bipolar disorder and schizophrenia), (5) musculoskeletal disorders that limited mobility (e.g., myopathy, amputation), (6) severe organ failure, and (7) clinically determined to have a survival rate of less than 3 months.

Exercise Intervention

The subjects undergoing chemotherapy were arranged to receive 8 weeks of exercise training. Aerobic exercise and resistance exercise were included in the exercise program for patients. The participants were asked to perform exercise training 3 days per week in the gym in the National Cheng Kung University supervised by a physiotherapist. The training intensity was based on the American College of Sports Medicine's cancer patient guidelines: using moderate-intensity exercise training, with the intensity of the maximum heart rate (HR) ranging between 60 and 70%, where the maximum HR calculation formula is usually 220 − age (19). Forty to fifty minutes of training time included a 5-min warm-up, aerobic exercise training for 30 min, and a 5-min cool-down. In addition, the TheraBand resistance band was used for resistance exercise in this study. Resistance exercise was performed by TheraBand at the intensity of the rating of perceived exertion (RPE) scale from "somewhat heavy" to "heavy." Each exercise consists of 10 to 12 repetitions for one set, three sets per training. Both upper and lower extremities were trained.

Primary Outcome Measure–Exercise Responses

The cardiovascular physiological parameters, including blood pressure (BP), HR, SpO_2, and RPE, were measured in this study. Before and after exercise training, subjects were asked to perform an exercise to test the maximal exercise capacity and exercise responses. From the first day of recruitment to the last day of exercise training, the parameters in 1 and 3 min of recovery time were recorded after exercise testing.

Secondary Outcome Measures–Measurement of Oxidative Stress

Human plasma was isolated from total blood collected from the first day of recruitment to the last day of exercise training. Total antioxidant capacity, 8-hydroxy-2′-deoxyguanosine (8-OHdG), and carbonyl levels were measured using commercial kits (ab65329, ab201734, and ab126287; Abcam) according to the manufacturer's instructions. The malondialdehyde (MDA) level was determined by a commercial kit (MAK085, Sigma) according to the manufacturer's instructions.

Statistics

Data were expressed as mean ± standard deviations for all variables. No adjustment was made for analysis. The paired *t*-test was used to measure the differences in the mean values of the parameters between preintervention and postintervention. Statistical significance was set at $p < 0.05$. All analyses were done using SPSS version 22.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Participant Flow and Recruitment

A total of 42 patients were screened in this study, 30 subjects were enrolled, and 12 subjects were excluded including 5 subjects who withdrew from participation, 2 subjects with changed treatment plan, 2 subjects with severe metastasis, and 3 subjects lost to follow-up (**Figure 1**). All participants completed 8 weeks' exercise training and data collection.

Demographic Data

Participant demographics are shown in **Table 1**. A total of 23 of 30 participants were male; a total of 7 of 30 participants were female. The mean ± SD age of the total subjects was 56 ± 12.3 years. The mean ± SD height of the total subjects was 1.6 ± 0.7 m, and the mean body weight of the total subjects was 64.4 ± 11.2 kg. All participants had undergone chemotherapy (22 subjects were treated with cisplatin, 1 case was treated with gemcitabine, 7 subjects were treated with medroxyprogesterone).

Outcomes

Blood Pressure

As shown in **Table 2**, the results from BP revealed that resting systolic BP (SBP) and dystolic BP (DBP) are lower after exercise training (SBP pretraining 111 ± 18.7, SBP posttraining 106.8 ± 12.1; DBP pretraining 69.6 ± 12.6, SBP posttraining 64 ± 10.6; all $p < 0.05$). There was no significant difference in both SBP and DBP in peak exercise before and after exercise training. In addition, exercise training increased 1- and 3-min BP recovery in DBP ($p < 0.05$) and increased 3-min BP recovery in SBP ($p < 0.05$) (**Table 2**).

Heart Rate

The results from HR indicated that resting HR is lower after exercise training (rest HR pretraining 85.2 ± 12.1, rest HR posttraining 76.4 ± 10.2; $p < 0.05$). There was no significant difference in HR in peak exercise before and after exercise training. Moreover, exercise training reduced 1- and 3-min HR after peak exercise (1-min HR pretraining 99.3 ± 13.3, 1-min HR posttraining 93.6 ± 12.1; 3-min HR pretraining 94.8 ± 12.1, 3-min HR posttraining 85 ± 13.2; all $p < 0.05$). A similar result had been found in HR recovery (HRR) data (all $p < 0.05$).

Oxygen Saturation

There was no significant difference in oxygen saturation in resting or peak exercise before and after exercise training.