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The Effect of Supervised Exercise Training on Symptoms of Chemotherapy-Induced Peripheral Neuropathy

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Abstract

Chemotherapy-Induced Peripheral Neuropathy is a common, dose-limiting effect of chemotherapy treatment. Pharmacological therapies are largely uneffective, making the investigation of other interventions warranted. Home-based exercise programs have produced promising improvements in quality of life and pain symptoms, yet compliance to programs is low. Thus, the purpose of this investigation was to examine the outcomes of a structured, supervised exercise program in reducing symptoms of CIPN and improving physical fitness and overall QOL. A total of 38 individuals actively in chemotherapy treatment participated in this investigation. The McGill QOL and Leeds Assessment of Neuropathic Symptoms and Signs questionnaires, followed by a comprehensive fitness evaluation was administered both before and after the 12-week supervised exercise program. Results revealed that 12-weeks of supervised exercise training helped attenuate symptoms of CIPN. Overall QOL was significantly improved, and troublesome symptoms related to CIPN significantly decreased ($p<0.05$). Thus, we assert that exercise is an effective tool in managing symptoms of CIPN.

Keywords: Neuropathy; Chemotherapy; Exercise programs; Neuropathic symptoms

Introduction

The most common neurological side effect of chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN), which occurs when the peripheral nervous system is damaged [1]. This effect appears to be dose and duration dependent, and is most often caused by the chemotherapy agents Docetaxel, Paclitaxel, or Vinorelbine. Damage to the peripheral nervous system pathways results in neuropathic pain [2], producing symptoms described as stabbing, burning, or electric shock-like sensations, leading to impairments in daily activities, including walking, sleep, and work [3,4].

Because the exact mechanism of CIPN is not fully understood, pharmacological treatments are largely ineffective [5]. Some therapies provide modest improvements in neurological function. However, in most instances, these agents are associated with additional negative side effects for cancer patients, such as cardiac conduction defects and increased chemotherapy resistance [6-8]. Thus, other interventions that address the symptoms of CIPN should be investigated.

One intervention that has produced promising results in populations with diabetic peripheral neuropathy is exercise rehabilitation [9-11]. Exercise appears to support nerve health, producing both acute and long term benefits. Short-term exercise stimulates endothelium-dependent vasodilatation and endoneurial blood flow [12]. Likewise, the shear stress that results from long term increased blood flow increases vasodilation [12]. In a previous investigation, our lab surveyed the current exercise behaviors of individuals experiencing symptoms of CIPN. Only 15% of patients surveyed were currently meeting the recommended levels of physical activity. Yet, these physically active patients reported a significantly higher quality of life (QOL) and experienced less pain than their sedentary counterparts [13], lending some credibility to the hypothesis that an exercise intervention would be beneficial in attenuating symptoms of CIPN and improving the overall QOL of cancer patients. However, it was unknown if the sedentary patients refrained from exercise because of the symptoms of CIPN or some other factor. Therefore, a follow-up study conducted by our lab involving a 10-week home-based exercise study produced promising results, in that pain symptoms significantly decreased following exercise training. In this home-based study, exercise adherence was an issue, and it was speculated that subjects may not have exercised at a high enough intensity to produce more significant results [14]. Thus, the purpose of this investigation was to examine the outcomes of a structured, supervised exercise program in reducing symptoms of CIPN and improving physical fitness and overall QOL.

Methods

Subjects

A total of 40 patients currently undergoing treatment for cancer were selected for participation in this study. Eligibility criteria included patients who i) had been diagnosed with CIPN by their oncologist, OR ii) were currently taking the chemotherapy agents Docetaxel, Paclitaxel, or Vinorelbine, iii) were previously sedentary, iv) were able to read and write English. All forms and procedures were approved by the Wright State University Institutional Review Board prior to the onset of data collection.

Data collection

Data collection took place over three phases. The first phase was the pre-participation screening and paperwork phase. Initially, each

participant was asked to complete an informed consent and two questionnaires designed to assess their current level of neurological health and quality of life (McGill QOL, and Leeds Assessment of Neuropathic Symptoms and Signs). A comprehensive fitness evaluation was then administered to each participant, and included assessments for VO_{2max}, muscular strength and endurance, flexibility, and body composition, as well as height, weight, and resting blood pressure measurements. A submaximal VO_{2max} (75% max) was measured via the Bruce Treadmill test. Muscular strength was measured with a hand grip dynamometer (Camry Electronic Hand Dynamometer). Flexibility was measured via modified sit and reach (Lafayette Flexibility Tester). Body composition was assessed using the 7-site skinfold assessment (Lange). Finally, muscular endurance was measured via the partial curl up test.

The second phase involved supervised, individualized exercise programming. Based on the fitness assessment results, a personalized exercise program was developed, and individualized to each participant. Subjects underwent twice weekly personal training sessions with a certified cancer exercise specialist for a period of 12-weeks. Each exercise session included mild stretching, a cardiovascular component of approximately 20-30 minutes in length at 40-60% VO_{2max}, and strength-training that involved a full-body workout focused on muscular endurance improvements. Subjects completed 2-3 sets of 10-12 repetitions of exercises targeting major muscle groups.

At the conclusion of this 12-week period, the third phase of data collection began. In this phase, both of the questionnaires were again administered, and subjects completed a follow-up comprehensive fitness evaluation.

Statistical analyses

Data was analyzed using descriptive statistics. Pre-post test data was analyzed via student t-tests at the 0.05 level of significance.

Results

Subjects

A total of 40 people met the eligibility criteria and were recruited for this study. Of those, 38 completed the 12-week program of supervised exercise; 14 men and 28 women. One individual withdrew from the study because they were too sick to continue exercising, and the second patient withdrew because they needed to have a surgery. Of these patients, 24 were being treated for breast cancer, 16 were receiving treatment for colon cancer, 2 for lung cancer, and 6 for prostate cancer. Table 1 presents the subject characteristics of these participants.

	Gender (n)	Age (yrs)
Male	14	62.3 ± 2.5
Female	24	57.4 ± 4.2

Table 1: Subject Characteristics. Values are Means ± SE.

Fitness data

Each subject underwent a comprehensive fitness assessment at the start and at the conclusion of the 12-week exercise program. The fitness components measured included body composition, muscular strength, muscular endurance, flexibility, and VO_{2max}. Tables 2 and 3 present the mean scores on each assessment for the subjects. Table 2 illustrates the mean scores measured pre-supervised exercise (Pre-SuEx), and Table 3 presents mean scores measured post-supervised exercise (Post-SuEx). Figure 1 presents the changes in each fitness parameter from pre- to post-test. Subjects significantly improved in VO_{2max} and muscular endurance following 12-weeks of supervised exercise training.

Body Composition (%)	VO_{2max} (mL/kg/min)	Muscular Endurance (Number)	Flexibility (cm)	Muscular Strength (Kg)
35.7 ± 0.07	19.8 ± 3.2	20.2 ± 3.7	11.8 ± 2.2	65.25 ± 5.4

Table 2: Pre-SuEx Fitness Assessment results. Values are means ± SE.

Body Composition (%)	VO_{2max} (mL/kg/min	Muscular Endurance (Number)	Flexibility (cm)	Muscular Strength (Kg)
34.3 ± 1.2	34.5 ± 4.8*	51 ± 4.2*	12.5 ± 1.3*	66 ± 3.3

Table 3: Post-SuEx Fitness Assessment results. Values are means ± SE.

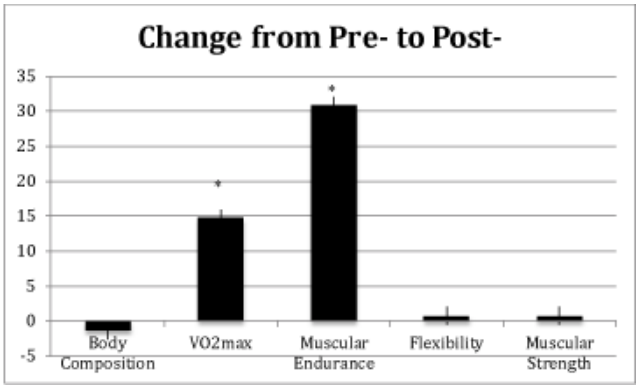

Figure 1: Fitness Assessment Data. Values are the changes in scores on each assessment from Pre- to Post- 12 weeks of supervised exercise. * indicates a significant improvement from Pre- to Post- 12 weeks of supervised exercise ($p<0.05$).

Pain questionnaire

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire was administered to each subject at the start of the 12-week supervised exercise program, and again at the conclusion of the 12-weeks. This is a validated, 7-item pain scale consisting of grouped sensory description and examination. Participants were asked to classify the neuropathic pain they experience by indicating either "Yes" or "No" to different descriptions of pain. Raw data to these questions are found in Tables 4 (Pre-SuEx) and 5 (Post-SuEx). Initially, the majority of respondents indicated that their pain produced unpleasant sensations in their skin, their skin was abnormally sensitive to touch, and came on suddenly and in bursts for no apparent reason. At the conclusion of 12-weeks of supervised

exercise, a significantly lower number of participants reported experiencing these symptoms for each of these questions ($p<0.05$).

Question #	Question with description	Responses (n)
1	Does your pain feel like strange, unpleasant sensations in your skin?	Y - 35
	i.e. pricking, tingling, pins and needles	N - 3
2	Does your pain make the skin in the painful area look different from normal?	Y - 9
	i.e. mottled; red or pink in appearance	N - 29
3	Does your pain make the affected skin abnormally sensitive to touch?	Y - 27
	i.e. unpleasant sensations when lightly touched	N - 11
4	Does your pain come on suddenly and in bursts for no apparent reason?	Y - 23
	i.e. electric shocks, jumping/bursting sensations	N - 15
5	Does your pain feel as if the skin temperature in the painful area has changed?	Y - 12
	i.e. hot and burning	N - 26

Table 4: LANSS Questions and response data, prior to 12-weeks of supervised exercise. Values indicate raw data scores.

Question #	Question with description	Responses (n)
1	Does your pain feel like strange, unpleasant sensations in your skin?	Y -21*
	i.e. pricking, tingling, pins and needles	N - 17
2	Does your pain make the skin in the painful area look different from normal?	Y - 11
	i.e. mottled; red or pink in appearance	N - 27
3	Does your pain make the affected skin abnormally sensitive to touch?	Y - 14*
	i.e. unpleasant sensations when lightly touched	N - 24
4	Does your pain come on suddenly and in bursts for no apparent reason?	Y -11*
	i.e. electric shocks, jumping/bursting sensations	N - 27
5	Does your pain feel as if the skin temperature in the painful area has changed?	Y - 8
	i.e. hot and burning	N - 30

Table 5. LANSS Questions and response data, after the 12-weeks of supervised exercise. Values indicate raw data scores. *indicates a significant decrease from Pre-SuEx ($p<0.05$).

Psychological questionnaires

The McGill QOL questionnaire was administered initially, and at the conclusion of the 12-week supervised exercise program. We analyzed the responses to two questions on the questionnaire. The first question we analyzed asked patients to rate on a scale of 1-10 their overall QOL for the last 2 days. An answer of 10 would indicate that all parts of the individual's life (physical, emotional, social, spiritual, and financial) over the last two days was *excellent*. An answer of 0 would indicate that all parts of the individual's life was *very bad*. The second question analyzed asked patients to indicate on a scale of 1-10 the level of troublesome symptoms they have experienced related to their CIPN over the last two days. A rating of 0 would indicate that the troublesome symptom (CIPN) was *no problem*. A rating of 10 indicated that the troublesome symptom was a *tremendous problem*.

Results revealed that 12-weeks of supervised exercise are beneficial in improving both overall quality of life and troublesome symptoms related to CIPN. Initially, prior to the supervised exercise program (Pre-SuEx), overall quality of life was rated 6.25 ± 1.3. At the conclusion of the supervised exercise program (Post-SuEx), overall QOL was rated 9 ± 0.7 ($p<0.05$, Figure 2). Similarly, the troublesome symptoms related to CIPN was rated 8.31 ± 0.6 before 12-weeks of supervised exercise, and a 4.22 ± 1.2 after the exercise program ($p<0.05$, Figure 3).

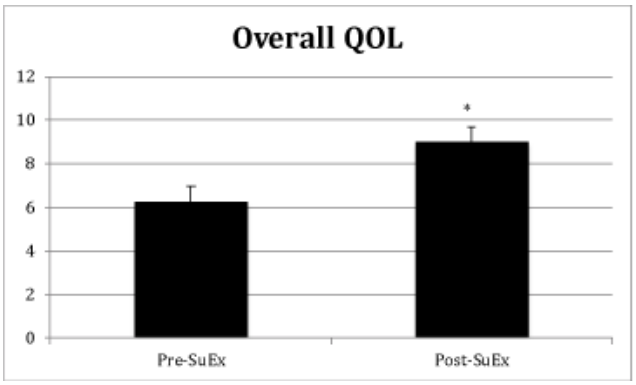

Figure 2: Overall QOL. Values are means ± SE. *$p<0.05$.

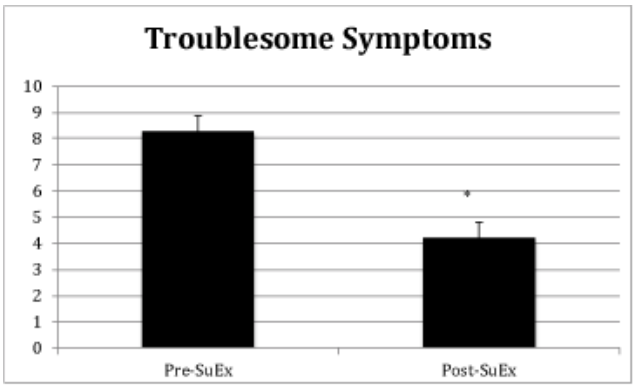

Figure 3: Troublesome Symptoms. Values are means ± SE. *$p<0.05$.

Discussion

The purpose of this investigation was to determine if 12-weeks of supervised exercise training would help alleviate symptoms of CIPN. The onset, severity, characteristics, and duration of clinical manifestations of CIPN are highly variable, but are typically characterized by a glove-and-stocking distribution in the hands and feet with sensory loss or hypersensitivity, and in some cases motor and autonomic dysfunction. These symptoms are difficult to treat, and often significantly impact QOL and functional ability in patents. Thus, the primary finding of this investigation, that exercise training may positively impact neurological function, is clinically significant.

Our finding that unpleasant skin sensations and sensitivity related to neuropathic pain were attenuated following chronic exercise training is consistent with a previous investigation examining the role of exercise on sciatic nerve pain, which found reduced abnormal responses to temperature and pressure following exercise [15]. While the mechanisms underlying the role of exercise in neuroprotection are unclear, several theories have been circulated. Plausible explanations center around the exercise-induced increase in endoneurial blood flow and nitric oxide synthesis, as well as improved Na^+/K^+-ATPase activity [11]. In addition, exercise helps to alleviate pain related to nerve damage and neuropathic pain by reducing levels of certain inflammation-promoting factors, specifically, tumor necrosis factor-alpha and interleukin-1-beta [15]. Previous studies suggest that inflammation and pro-inflammatory cytokines play a role in the development of neuropathic pain in response to nerve injury [16]. Yet, exercise has been shown to reduce the expression of inflammation-promoting cytokines in damaged nerve tissue [15], and heat shock protein-27, which may have contributed to the reductions in cytokine expression [16]. A direction for future research would be to measure inflammation-promoting factors following exercise training in patients with CIPN.

Also noteworthy is the improvement in fitness parameters found in the present investigation. While all measured variables showed some improvement from pre-post test, significant improvements in both aerobic capacity and muscular endurance were measured. This is important, as loss of muscle strength and flexibility are commonly experienced by individuals with peripheral neuropathy [16]. Being able to maintain, or even improve fitness levels while undergoing chemotherapy is remarkable, and could be one explanation for the improved QOL scores measured in this investigation.

Previously, in a home-based exercise program conducted by our lab, modest improvements were measured in neuropathic pain [17]. It was speculated that had the subjects exercised at a higher intensity, these findings would have been more substantial. The hypoalgesic effect was attributed to a phenomen called Exercise Induced Hypoalgesia (EIH), which has been observed in healthy subjects following acute bouts of exercise. With EIH, pain threshold and tolerance levels increase following exercise intensities of 60-75% VO_{2max} [18,19]. The triggering mechanism for the hypoalgesic effects appears to be the related to the release of endogenous opioids in response to increases in blood pressure observed during exercise. In the present investigation, subjects gradually worked up to an intensity of 40-60% VO_{2max} for each exercise session. This was higher than the "moderate" intensity level that subjects in the home-based study were instructed to exercise at (30-50% VO_{2max}) [14], and may be a plausible mechanism behind the decrease in pain measured in the present study.

Summary

Twelve weeks of supervised exercise training attenuated symptoms of CIPN, significantly improved overall QOL, and decreased troublesome symptoms related to CIPN ($p<0.05$). While the underlying mechanism is unknown, theories center around the expression of cytokines and EIH, and should be further explored. Since neuropathic pain associated with CIPN is one of the more difficult types of pain to treat, and in light of the findings that pharmalogical treatments often bring about many unwanted side effects, we assert that exercise is an effective tool in managing symptoms of CIPN.

Directions for Future Research

An estimated 30-40 percent of cancer patients experience symptoms related to CIPN, and is one of the most common reasons chemotherapy treatment is stopped. The underlying etiology of CIPN is not fully understood, making it difficult to treat. Therefore, more research in this field is warranted. Because this and other investigations 14 have shown exercise to be beneficial in alleviating some of the troublesome symptoms related to CIPN, future research should examine whether this change is acute or chronic. In addition, the expression of cytokines should be directly measured in an exercising population with CIPN. Lastly, more investigation into how CIPN impacts an individual's ability to exercise would be useful in designing training studies.

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