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Chemotherapy-induced-peripheral neuropathy, gait and fall risk in older adults following cancer treatment

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ABSTRACT

Background: Cancer patients undergoing chemotherapy often experience chemotherapy-induced peripheral neuropathy (CIPN), which reportedly causes gait disturbances that may increase their risk for falls. The purpose of this study was to investigate whether CIPN is associated with spatial-temporal gait adaptations and fall risk in post-treatment adult cancer survivors.

Method: This study enrolled 16 subjects between 50 and 70 years of age, including 8 subjects with CIPN and 8 subjects with age and morphologically-matched controls. Gait velocity, step length, step time, base of support, swing time, single support time, and double support time as measured by GAITRite. Fall risk was assessed utilizing the Timed Up and Go (TUG) test.

Results: Overall, gait velocity (110.75 cm/s, $SD = 26.79$, $p = 0.006$) was significantly slower, and step length (53.92 cm, $SD = 23.55$, $p = 0.005$) was significantly shorter in those subjects with CIPN. Additionally, CIPN participants had a significantly higher TUG Score (12.33 s, $SD = 6.25$, $p = 0.001$) compared to the controls (6.62 s, $SD = 1.10$).

Conclusion: Our investigation suggested that gait speed and step length are key indicators for fall risk. Compared to controls, cancer patients with CIPN may display slower gait velocities, shorter step length, and are at an increased fall risk as indicated by TUG scores. The presence of CIPN appears to increase fall risk, which may easily be assessed in a clinical setting using the TUG test.

1. Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is generally classified as a series of neuromuscular symptoms, both sensory and motor in nature, that result from nerve damage caused by the neurotoxic effects of chemotherapy drugs for the treatment of cancer.[1,2] It is postulated that chemotherapy agents will often inflict their neurotoxic effects on various parts of the axon, decreasing somatosensory feedback and causing many of the typical CIPN symptoms.[3–7] Symptoms of CIPN may be acute, mild or severe, transient or chronic, depending upon the treatment regime and dose of the agents, and may manifest in a variety of ways, involving sensory and motor symptoms.[2,3,8] Sensory signs and symptoms may include numbness, tingling, burning, pain, ataxia, loss of deep tendon reflex, and reduced sense of touch, vibration, and proprioception. Motor symptoms may include weakness, balance disturbances, and difficulty performing fine motor skills and a diminished or absent deep tendon reflex.[2,3–6]

The exact cause of CIPN remains elusive. It is postulated that chemotherapy agents will often inflict their neurotoxic effects on various parts of the afferent nerve, such as the axon, mitochondria, voltage-gated channels, as well as the cell body, and dorsal root ganglion neurons. The cumulative neurotoxic impact of chemotherapy may cause many of the CIPN symptoms as well as a decrease of somatosensory feedback.[3–7]

Intact somatosensory systems are essential to fluid and stable ambulation. The literature supports the proposition that somatosensory systems contribute to the modulation of spinal pattern

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generators, modulation of motor commands, and the perception and control of movements by providing information about mechanical stimuli, temperature changes, potential damage to the skin, body and limb movement and position, and velocity and muscle activation. Cutaneous sensory receptors provide information about the body's orientation within the immediate environment and provide information necessary for reflexive responses.[9,10] Cumulatively, sensory receptors within the somatosensory aide in the modulation of gait.[11]

Abnormalities in gait parameters such as cadence, stride length, swing, double support, stride length variability, and swing time variability, may increase the risk of falling.[12,13] Falling is a significant event for the elderly population, as falls have been linked to serious injuries and disabilities, loss of independence, and increased mortality.[14] In 2005, 1.8 million individuals over the age of 65 went to the emergency room to be treatment for a fall-related injury. It is estimated that 60% of individuals over the age of 60 will be diagnosed with cancer. As the age of cancer patients treated with chemotherapy increases, with a 10–40% incidence of CIPN in patients treated with neurotoxic agents, there is a growing need to identify individuals at risk of falls in order to prevent subsequent injuries and complications.[15]

Although CIPN is prevalent in cancer patients undergoing chemotherapy, researchers have not explored changes in spatiotemporal gait parameters in cancer patients between 50 and 70 years of age undergoing chemotherapy which may impact their fall risk.[16] Hence, the aim of this study was to investigate the effect that presence of CIPN may have on spatiotemporal gait parameters and fall risk in breast and colon cancer patients who have completed their chemotherapy treatment for cancer.

2. Participants and methods

2.1. Participants

This study included a convenience sample of 8 participants between 50 and 70 years of age with a histologically confirmed stage 2–3 breast or colorectal cancer diagnoses, with a confirmed treatment plan consisting of taxane-based or oxaliplatin-based chemotherapy. Participants also had a confirmed diagnoses of chemotherapy-induced peripheral neuropathy according to the Peripheral Sensory Neuropathy category of the Common Terminology Criteria for Adverse Events (CTCAE), version 4. Using a quasi-experimental design, 8 age-and-morphologically-matched-subjects were recruited to compare to the group of breast and colon cancer patients. They were recruited from the same community to match the recruited cancer patients in order to assess differences in spatiotemporal gait parameters. Hence, the present study contained a total of 16 participants and two groups: a control group, which consisted of 8 healthy, disease-free, age and morphologically matched controls, and an intervention group, which consisted of 8 breast or colon cancer patients diagnosed with CIPN. Individuals voluntarily provided written informed consent and completed the Seton Hall University and Saint Michael's Medical Center's Institutional Review Board-approved research protocol. Individuals meeting any of the following criteria were excluded: a history of peripheral neuropathy (i.e., hereditary peripheral neuropathy associated with nutritional agents and paraneoplastic syndrome-related neuropathy), or diseases that may contribute to peripheral nerve damage such as diabetes, renal insufficiency, alcohol abuse, vitamin B12 deficiency, HIV, and vasculitis, brain or spinal cord metastases, orthopedic problems that affect balance, or vestibular system or visual disease, use of a walking aide, and lastly, participated in 150 min of light-to-moderate intensity exercise per week over the past year.

2.2. Outcomes and statistical analysis

Following the signing of the informed consent forms, demographic and biometric data was collected, including the subject's cancer diagnosis, name of the chemotherapy agent received, age, sex, height, and weight. The patients' right and left leg lengths were measured (from the greater trochanter to the floor) using a standardized, flexible cloth tape, and entered into the GAITRite software for data processing.

Following standard protocol, fall risk was assessed using the valid and reliable Timed Up and Go test (TUG), which is a mobility test used to measure basic mobility skills.[17] The measurement outcome for TUG is the time it takes to rise up out of a chair, walk 3 m away from the chair, walk 3 m back to the chair, and return to the seated position; the time it takes to complete this task is recorded. Previous research indicates that a time of greater than 10.7 s indicates risk for falls.[18] The TUG has been shown to have a sensitivity of 90%, and specificity of 88.5% as well as a high diagnostic accuracy at 88.9% when a modified cutoff score of 10.7s is applied.[18]

After the completion of the TUG test, the GAITRite system was used to compute spatiotemporal gait parameters. The GAITRite system is an electronic pathway which is 8.2 m in length and resembles a carpet runner; the active area is 61 cm wide and 732 cm long, and contains 27,648 sensors placed 1.27 cm apart and are activated by mechanical sensors. Data from the activated sensors are collected by a series of onboard processors and transferred to the computer through a serial port.[17] The GAITRite system has been shown to be a valid and reliable tool for assessing spatiotemporal gait parameters. Walking speed, cadence, step length and step time variables have been shown to have intra-class correlation coefficients (ICCs) between 0.92 and 0.99, and repeatability coefficients (RCs) between 1.0 and 5.9% of mean values. Step length and step time variables have also been shown to have good agreement, with ICCs between 0.91 and 0.99 and RCs between 2.6 and 7.8%).[17]

For each trial, participants were instructed to initiate walking from a non-sliding standing spot marked 2 m before the beginning edge of the GAIT Rite carpet. This allowed walking to be initiated from the same location at every trial, and also permitted a steady state of ambulation to be achieved prior to stepping on the GAITRite walkway. Participants negotiated the entire length of the 5.18-m GAITRite carpet walkway at a steady pace while looking straight ahead. Three trials were performed by each participant without environmental distractions.

The independent variable was the presence of CIPN. There were multiple dependent variables, which included the participants' TUG score and spatiotemporal gait parameters obtained from the GAITRite system. Thus, the research question was answered using a one-way Multiple Analysis of Variance (MANOVA). An alpha level of 0.05 was used.[19] While the sample size may appear to be small, a post-hoc analysis indicated that the present study was powered at 0.87, indicating that the sample size of 16 was sufficient to detect a difference between the two groups if in fact there was an effect to be detected.[19]

3. Results

3.1. Participant characteristics

There were 16 subjects between the ages of 50–70 that participated in the study, and 8 aged and morphologically matched subjects (age, height, weight BMI) served as study controls. Eight of the participants had a histologically confirmed stage 2–3 breast or colorectal cancer diagnosis and were treated with either taxane- or

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