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Effects of exercise on cancer patients suffering chemotherapy-induced peripheral neuropathy undergoing treatment: A systematic review

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ABSTRACT

Background: Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological and clinically relevant side effect of many commonly used chemotherapeutic agents. Moreover, little effort has been done to investigate the potentially beneficial effects of specific exercises to counteract the CIPN symptoms.
Objective: This document aims to summarize and analyze systematically the current body of evidence about the effects of specific exercise protocols on CIPN symptoms, balance control, physical function and quality of life in patients with CIPN.
Literature survey: Specific terms were identified for the literature research in MEDLINE, Scopus, Bandolier, PEDro, and Web of Science.
Methodology: Five manuscripts were considered eligible for this review. Quality appraisal distinguished two studies as high quality investigations while three with low quality. Results were summarized in the following domains: "CIPN symptoms", "Static balance control", "Dynamic balance control", "Quality of life and Physical function".
Synthesis: Significant improvements were detected on postural control. Additionally, patients' quality of life and independence were found ameliorated after exercise sessions. Combined exercise protocols including endurance, strength and sensorimotor training showed larger improvements.
Conclusions: This systematic review comes from a highly selected but small source of data. Nevertheless, specific exercise for cancer patients undergoing chemotherapy with CIPN symptoms should be recommended since these interventions appeared as feasible and have been demonstrated as useful tools to counteract some of the limitations due to chemotherapy.

1. Introduction

In the past decades, there was an increase of cancer-survivors and prevalence rates resulting from the development of novel treatments and improved diagnostic methods. Nevertheless, chemotherapeutic treatments are continuing to induce by itself a huge number of long-term side effects, that can be highly detrimental for both physiological and psychological patients' health (Derksen et al., 2017). Besides physical damages, there are specific decreases in the quality of life and patients often encounter limitations in the neuromuscular function (Niederer et al., 2014). Within this clinical framework, in cancer patients Peripheral Neuropathy (PNP) plays a pivotal role since it is the most common neurological and clinically relevant side effect (Streckmann et al., 2014a) of many commonly used chemotherapeutic agents such as taxanes (paclitaxel) (Song et al., 2017), bortezomib, lenalidomide, vinca-alkaloids (vinorelbine) (Wolf et al., 2008), and platinum-based antineoplastic (Kerckhove et al., 2017). The incidence of Chemotherapy-Induced Peripheral Neuropathy (CIPN) can be variable, ranging from 30% to 60% on patients treated with neurotoxic chemotherapy (Seretny et al., 2014), and it can affect both youth and elderly subjects. There are several factors that can influence the incidence, such as the dose intensity, the cumulative dose, the therapy duration, the co-administration of other neurotoxic chemotherapy agents and the potential pre-existing conditions, for example diabetes and alcohol abuse (Kannarkat et al., 2007; Quasthoff and Hartung, 2002; Windebank and Grisold, 2008). Also, patients with CIPN generally suffer from a variety of symptoms including: pain, muscle weakness, reduced balance control, insecure gait, reduced or absent

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reflexes (Streckmann et al., 2014a). They also present an altered sensation (numbness, burning, tingling, etc.) (Streckmann et al., 2014a), with dysesthesias and paresthesias in a stocking and glove pattern (Wampler et al., 2007), commonly located in lower and upper extremities. These symptoms may be resolved but a complete resolution is rare; indeed, in a large number of cases it is not reversible at all, as indicated by Quasthoff and Colleagues (Quasthoff and Hartung, 2002).

For these reasons, motor deficits including balance impairment, lower gait speed and lower limb strength are also recurring, with an increased falling frequency (Niederer et al., 2014). Moreover, the postural control shows clinical meaningful impairments, and as a vicious circle, gait speed is also negatively affected due to a decrease in physical exercise participation with a framework of general physical deconditioning. These deficits, associated with an increased fear of falling, may limit patients' independence (Schwenk et al., 2016). In addition, the neuropathy often interferes with the daily activities leading to severe impairments of the patient's quality of life (QOL) (Izycki et al., 2016). From these perspectives, on the other side, it can be supposed that an improvement of quality of life, due to physical active lifestyle, in turn, could enhance the overall physical function, the postural control, and promotes a reduction in the risk for falls (Bullo et al., 2015). Furthermore, CIPN has become a crucial limiting factor for therapy, causing treatment delays, dose reductions, or even discontinuation of therapy, which can affect the outcome and compromise survival rates (Stubblefield et al., 2009).

Nowadays, research has mainly focused on pharmacological therapies, whereas little effort has been done to investigate the potentially beneficial effects of specific exercises to counteract the described symptoms (Streckmann et al., 2014a). In a summary document of Streckmann et al. (2014a), the effects of exercise were evaluated in different disease conditions; in particular, protocols included type II diabetic patients, one study on cancer patients and six about other diseases. In general line, these trials have shown that exercise can reduce motor deficits induced by Peripheral Neuropathy and can ameliorate coordination, preventing muscle loss with an adequate dose of strength training, also improving related neuromuscular parameters (Streckmann et al., 2014a). More specifically, other several improvements were found in Diabetic Peripheral Neuropathy (DPN), that is a frequent encountered form of PNP (Landowski et al., 2016). About the type of exercise, it has been shown that long-term, supervised aerobic training could prevent the onset or modify the natural history of DPN (Balducci et al., 2006). Also, an intense exercise regimen, designed to enhance distal lower extremity strength, has been able to improve tandem stance, functional reach, and unipedal stance, three important outcome measures of balance control (Richardson et al., 2001).

At the base of these statements, the aim of this systematic review is to summarize and analyze the current body of evidence about the effects of specific exercise protocols on CIPN symptoms, balance control, physical function and quality of life in patients with CIPN.

2. Materials and methods

2.1. Study design

This is a systematic review of the literature with the aim to analyze all studies that investigate the effects of physical exercise protocols on the physical function, balance control, quality of life (QOL), and the reduction of CIPN symptoms, only including investigations with cancer patients undergoing chemotherapy.

2.2. Literature search

The methodological search was carried out in September 2017 and was performed through the online databases: MEDLINE, Scopus, Bandolier, PEDro and Web of Science. Keywords "Chemotherapy", "Induced", "Peripheral", "Neuropathy" were entered in the systematic search, associated with "postural control", "balance control", "physical activity", "physical exercise", "proprioception", "equilibrium" and "stability". In addition, references were examined in each eligible article and further relevant manuscripts were screened when a positive match was observed.

2.3. Inclusion and exclusion criteria

Studies considered for this review had to include a physical exercise intervention with at least a quality of life or a balance evaluation, preferably with a structured exercise protocol tailored for cancer patients undergoing treatment with diagnosed CIPN. Only original manuscripts published in indexed and peer-review journals and written in English language were considered. Further inclusion criteria required pre- and post-intervention comparisons, one or both genders from all races, in all ages, and with whatever diagnosis of cancer. Cross-sectional studies, case reports, published abstracts, dissertation materials, and conference presentations were not included.

2.4. Study quality assessment

The quality of the studies was assessed through the adapted nine criteria checklist provided by the Cochrane Collaboration Back Review Group (van Tulder et al., 1997). As in previous reviews, the checklist had to be marginally adapted to rate the strength of the evidence (Bullo et al., 2015; Bergamin et al., 2012; Gobbo et al., 2014). Each study in the review was scored based on the following nine criteria: (1) 'Was the method of randomization adequate?'; (2) 'Were the groups similar at baseline regarding the outcome measures?'; (3) 'Were inclusion and exclusion criteria adequately specified?'; (4) 'Was the drop-out rate described adequately?'; (5) 'Were all randomized participants analyzed in the group to which they were allocated?'; (6) 'Was the compliance reported for all groups?'; (7) 'Was Intention-to-treat analysis performed?'; (8) 'Was the timing of the outcome assessment similar in all groups?'; (9) 'Was a follow-up performed?'. When the study provided a satisfactory description, a positive value was assigned (+). If the criterion description was considered absent, unclear, or lacked the specified content, a negative value was assigned (−). A study was qualitatively estimated as high quality if it showed a positive score on five to nine of the criteria; otherwise, it was considered a low quality study (van Tulder et al., 1997).

2.5. Data extraction and synthesis

Two researchers independently examined all abstracts of the sourced studies. Full manuscripts were then analyzed in more detail to determine whether they met eligibility criteria. Each researcher performed a final quality check on each study. Afterwards, the individual searches were combined, compared, and reviewed for applicability, and a consensus was made regarding their inclusion in the study. In case of discrepancies, the review process was repeated and a third researcher was consulted. Quality assessment using the modified Cochrane methodological quality criteria was then independently applied and discussed before final appointment of the quality score.

Several domains were identified for the categorization of study outcomes. In particular, results were

classified to "CIPN symptoms", "Static balance control", "Dynamic balance control", "Quality of life and Physical function".

3. Results

3.1. Description of the studies

A total of 2221 studies resulted from the literature search. Firstly duplicates were removed, then 1318 records were screened. Applying inclusion and exclusion criteria, 5 studies (Schwenk et al., 2016;