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Whole-body vibration as a modality for the rehabilitation of peripheral neuropathies: implications for cancer survivors suffering from chemotherapy-induced peripheral neuropathy

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Abstract

The objective was to study the effect of whole-body vibration (WBV) on strength, balance and pain in patients with peripheral neuropathies and to consider its significance for the rehabilitation of patients suffering from chemotherapy-induced peripheral neuropathy (CIPN). Using a broad search strategy, PubMed was searched for clinical trials on WBV interventions aimed at improving strength, balance or pain in patients with peripheral neuropathies, which were published in English until 5th June 2014. The search was performed by the first author and generated a total of 505 results, which yielded 5 articles that met the inclusion criteria, being studies: i) published in English; ii) involving adult human subjects' peripheral neuropathies; iii) evaluating the effect of WBV as a therapeutic intervention; and iv) reporting findings for at least one of the following outcomes: strength, bal-

ance or pain. Methodological quality of included studies was assessed independently by first and second author, using the physiotherapy evidence database scale. The overall methodological quality of included studies was low. Two studies found a beneficial effect of WBV on neuropathic pain, but another study failed to find the same effect. One study found significant improvements in both muscle strength and balance, while another study found improvements only in some, but not all, of the applied tests to measure muscle strength and balance. The results of this literature search suggest insufficient evidence to assess the effectiveness for the effects of WBV on neuropathic pain, muscle strength and balance in patients with peripheral neuropathies. More high-quality trials are needed to guide the optimization of rehabilitation programs for cancer survivors with CIPN in particular.

Introduction

A common side effect of cancer treatment with chemotherapy is chemotherapy-induced peripheral neuropathy (CIPN). This neuropathy often occurs in treatment with platinum agents, a number of antimitotic drugs (taxanes, vinca alkaloids and thalidomide) and bortezomib.¹ These neurotoxic agents target the nervous system at different sites, including the dorsal root ganglions, and the microtubules, ion channels and blood vessels of peripheral axons.² Symptoms are dose-dependent, and mostly sensory (e.g. pain, loss of sensibility) but they can also manifest as motor weakness or autonomic dysfunction.^{3,4} The symptoms of the peripheral nervous system are related to the components affected. Damage of small fibers causes pain, hyperesthesia and loss of pain and temperature senses, while injury to large fibers produces loss of vibration sense, loss of proprioception and muscle weakness.⁵ Currently available pharmacological agents to prevent or treat CIPN have not been proven conclusively effective or have shown only minor effects.^{3,6-10} The most recent clinical practice guideline of the American Society of Clinical Oncology states that no agents are recommended for the prevention of CIPN and that best available data only support a moderate recommendation for treatment with duloxetine.¹⁰ Since CIPN symptoms can persist for years after onset, they may have a significantly negative long-term effect on daily activities and quality of life in cancer survivors.¹¹⁻¹³ Furthermore, CIPN is a major dose-limiting factor in cancer therapy and can even be a reason to terminate treatment prematurely, compromising patient survival.⁷

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Finally, due to considerable progress in cancer treatment and survival rates, the population of cancer survivors suffering from CIPN can be anticipated to expand in the foreseeable future, making its management an increasingly important issue.

Rehabilitation may play an important role in the recovery process and in improving daily functioning in patients with CIPN. Rehabilitation training can be offered to cancer patients during, as well as after completion of chemotherapy treatment. The optimal timing and intensity of such programs are currently being investigated in a large randomized clinical trial in the Netherlands.¹⁴ Interest in the role of exercise and physical rehabilitation programs as a symptomatic treatment for patients with CIPN has been increasing.^{1,15-20} Tofthagen *et al.* proposed a conceptual model in which exercise, by increasing mitochondrial energy production and blood flow to the peripheral nervous system, may result in fewer neuropathic symptoms.¹⁵ Wonders *et al.* argued that exercise could be an effective strategy in preserving neurological function following chemotherapy, suggesting a possible analogy in the pathogenesis of diabetic peripheral neuropathy (DPN) and CIPN through SERCA2a expression and ErbB2 activation.²⁰ However, to this date these theories regarding the possible beneficial effects of exercise programs on gait, balance, mobility and muscle strength in cancer survivors with CIPN remain to be investigated in clinical trials in this particular subgroup of cancer patients. This article aims to consider the theoretical role of one particular modality, namely whole-body vibration (WBV), as a beneficial component of rehabilitation programs for CIPN patients.

Nowadays, vibrating platforms for WBV training are practically available to anyone who holds a gym license. Such vibrating platforms are powered by an engine, and can vibrate mechanically with various frequencies and amplitudes.²¹ The mechanical oscillations cause energy to be transferred from the vibrating platform to the lower extremities. Consequently, the human body standing on the vibrating platform acts as a resonator to the mechanical oscillations.²² Partly supported by scientific literature, manufacturers promise health effects, varying from a higher bone-density,^{23,24} improved muscle power,^{24,25} increased joint stability,²⁶ oxygen blood flow,²⁷ and GH hormone production^{25,28} to a more effective glucose uptake.²⁹ The available literature indeed shows some controversial results and some of the study designs can be rightfully criticized. Nevertheless, as also argued in a comprehensive review by Rittweger,²² there seems to be a growing evidence base justifying the interest in the possible advantages of WBV in both the fields of sports and medicine. In addition to vertical vibration platforms, so-called side-alternating vibrating platforms exist. In side-alternating vibration, the left and right side of the platform are raised alternately, as opposed to conventional vertical vibration in which both sides are raised simultaneously. Using side-alternating vibration would supposedly result in more effective training of the back muscles³⁰ and in a smaller vibration-load being transferred to the trunk.²²

As it will be described in more detail further on, from a theoretical point of view WBV seems an appealing training modality in the rehabilitation of CIPN. Additionally, it would be an easily implementable addition to current rehabilitation programs for cancer survivors. Since there have been no studies researching any rehabilitation options for patients with CIPN to this date, this review will focus on the available evidence for effects of WBV on respectively muscle strength, balance and pain in patients with peripheral neuropathies that are not specifically chemotherapy-induced, but of any etiology.

Methods of research

The electronic database PubMed was systematically searched by the first author (AV) for articles describing clinical trials on WBV interven-

tions, aimed at improving strength, balance and pain for patients with peripheral neuropathies, which were published until 5th June 2014. Using a broad search strategy, a variety of search terms for the disorder *peripheral neuropathy* was combined (AND) with a broad selection of search terms for the intervention *whole-body vibration* and subsequently combined with search terms for the outcomes, respectively *strength, balance* and *pain*.

Inclusion criteria were: i) studies published in English; ii) studies involving adult human subjects with a peripheral neuropathy; iii) studies evaluating the effect of WBV as a therapeutic intervention; and iv) studies reporting findings for at least one of the following outcomes: strength, balance or pain.

The titles and abstracts retrieved from the initial database search were screened by the first author, using the inclusion criteria as described. Related citations in PubMed and reference lists of selected articles were searched for additional studies. Methodological quality of included studies was assessed independently by first (AV) and second author (HV), using the physiotherapy evidence database (PEDro) scale for clinical trials. The PEDro scale is an 11-item scale used to rate randomized controlled trials, designed by the Centre of Evidence-Based Physiotherapy. It covers all assessment criteria included in the Jadad scale and Delphi list.³¹ Results were compared and differences were resolved by discussion. Final levels of evidence and grades of recommendations were established using the grading system of the Scottish Intercollegiate Guidelines Network.³²

Results

The search generated 91 results for the outcome *strength*, 63 results for the outcome *balance* and 351 results for the outcome *pain*. These results yielded a total of 5 articles³³⁻³⁷ that met the inclusion criteria. Four studies^{33-35,37} worked with patients suffering from DPN and one study³⁶ with HIV (human immunodeficiency virus) -positive patients suffering from painful distal symmetrical polyneuropathy (DSPN). Two articles^{35,37} described the effect of WBV on both strength and balance, and three articles^{33,34,36} described the effect of WBV on pain. The overall methodological quality was low, with four studies^{33,34,36,37} scoring 0-4 on the PEDro scale and one study³⁵ scoring 7 (Table 1).³³⁻³⁷

Two studies^{33,34} in subjects with DPN found a beneficial effect of WBV on neuropathic pain, but another study³⁶ failed to find the same effect for pain-relief in HIV-associated DSPN. One study³⁵ found significant improvements in both muscle strength and balance, while another study³⁷ found improvements only in some, but not all, of the applied tests to measure muscle strength and balance. The main findings of the included studies are summarized in Table 2.³³⁻³⁷

The final levels of evidence and grades of recommendation for the effects of WBV on pain, balance and muscle strength in patients with peripheral neuropathies are summarized in Table 3, using the grading system of the Scottish Intercollegiate Guidelines Network.³²

Discussion

As indicated before, CIPN still comprise a major challenge as a dose-limiting factor in cancer treatment, for which as of yet no adequate method of prevention or cure has been identified. The results of this literature search suggest a low level of evidence for a positive effect of WBV on muscle strength and balance and for no effect of WBV on neuropathic pain in patients with peripheral neuropathies. However, the body of evidence is small and of low methodological quality. Additionally, none of the studies includes outcome measures such as

Table 1. Methodological quality of included studies.

| Internal validity - Statistical reporting | Hong <i>et al.</i> ³³ | Kessler <i>et al.</i> ³⁴ | Lee <i>et al.</i> ³⁵ | Paice <i>et al.</i> ³⁶ | Yoosefinejad <i>et al.</i> ³⁷ |
|--|----------------------------------|-------------------------------------|---------------------------------|-----------------------------------|--|
| Random allocation | - | - | + | + | - |
| Concealed allocation | - | - | + | - | - |
| Baseline similarity | - | - | + | - | - |
| Subject blinding | - | - | - | + | - |
| Therapist blinding | - | - | - | - | - |
| Assessor blinding | - | - | + | + | - |
| Follow-up >85% | + | - | + | - | + |
| Intention-to-treat analysis | - | - | - | - | - |
| Between-group comparisons | - | - | + | + | - |
| Point measures and measures of variability | - | - | + | - | + |
| PEDro score | 1 | 0 | 7 | 4 | 2 |
| Eligibility criteria | - | + | + | + | + |

PEDro, physiotherapy evidence database.

Table 2. Summary of the main findings of included studies.

| | Study population | Intervention details | Outcome(s) | Main findings | PEDro score |
|--|---------------------|--|-------------------|--|-------------|
| Hong <i>et al.</i> ³³ | DPN | Exercise Standing; knees slightly bent WBV parameters f: 20 Hz; u: ns | Pain | A significant reduction of pain in the VAS was found directly after application of WBV (P=ns) Significant reduction of pain in the long-term was found in both the VAS (P=ns) and in the NPS variables intensity, sharpness, unpleasantness and deep pain (P=ns) | 1 |
| Kessler <i>et al.</i> ³⁴ | DPN | Exercise Standing; knees bent at 20° to the vertical WBV parameters f: 25 Hz; u: 5 mm | Pain | A significant acute reduction of pain was found in the VAS (P=0.018) A significant chronic reduction of pain was observed in both the VAS (P<0.001) and in the NPS variables intense, sharp, hot, sensitive, unpleasant and deep pain (P<0.05) | 0 |
| Lee <i>et al.</i> ³⁵ | DPN | Exercise 110° squatting position WBV parameters f: 15-30 Hz; u: 1-3 mm | Strength, balance | Significant improvements were noted in the static balance, dynamic balance and muscle strength in the WBV + balance exercise group, compared to the balance exercise and control groups (P<0.05) | 7 |
| Paice <i>et al.</i> ³⁶ | HIV-associated DSPN | Exercise None; subjects sitting WBV parameters f: 58.3 Hz; u: ns | Pain | No statistically significant differences were found between the vibration and sham groups with respect to percentage pain relief (P=0.19) or the pre- and post-treatment current-pain difference (P=0.92) | |
| Yoosefinejad <i>et al.</i> ³⁷ | DPN | Exercise Squatting with knees in 30° flexion WBV parameters f: 30 Hz; u: 2 mm | Strength, balance | Pre- and post-intervention difference strength was significant for m. tibialis anterior strength (P=0.014), but not for m. quadriceps and general strength (P>0.05) Pre- and post-intervention difference in balance was significant for TUGT (P=0.004), but not for ULS (P>0.05) | 2 |

PEDro, physiotherapy evidence database; DPN, diabetic peripheral neuropathy; WBV, whole-body vibration f: frequency; u, amplitude; ns, not specified; VAS, visual analogue scale; NPS, neuropathic pain scale; HIV, human immunodeficiency virus; DSPN, distal symmetrical polyneuropathy; TUGT, timed up and go test; UST, unilateral stance test.

Table 3. Final levels of evidence and grades of recommendations for the effects of whole-body vibration on pain, balance and muscle strength in patients with peripheral neuropathies using the grading system of the Scottish Intercollegiate Guidelines Network.

| | Finding | Level of evidence | Grade of recommendation |
|----------------------------------|-----------------|-------------------|-------------------------|
| Effect of WBV on pain | No effect | 2- | D |
| Effect of WBV on balance | Positive effect | 2+ | C |
| Effect of WBV on muscle strength | Positive effect | 2+ | C |

WBV, whole-body vibration.

pinpricks or *tingling*, although these are symptoms which are most relevant in CIPN. Therefore, until more high-quality research on the subject is performed, it seems worthwhile to discuss some of the underlying theories that have led to considering WBV as a potentially interesting modality in the rehabilitation of peripheral neuropathies in general, and in CIPN specifically.

The first consideration concerns the potential effect of WBV on muscle strength. This potential effect is based on the theoretical assumption that vibration training induces chronic adaptive effects at a neuromuscular level.^{22,38} From a physiological point of view, these adaptive effects would derive from the large number of vibration-induced repetitive cycles of eccentric and concentric muscle contraction and from the specific adaptive effects of muscle spindles and mechanoreceptors.²² These specific reflex mechanisms, typically referred to as the tonic vibration reflex (TVR), seem to be involved in influencing muscle activity and motor-unit recruitment strategy during vibration,³⁹ most likely with the aim of stabilizing the joint. In fact, it has been reported that the application of vibration directly to a muscle or a tendon stimulates Ia afferents inducing the TVR.^{37,40} Using vibrating tools during exercise has been suggested to elicit similar responses.⁴¹ TVR was also seen in muscle groups not directly stimulated with vibration.⁴² Furthermore, alterations in spindle sensitivity and gamma-drive have been observed during reinforcement maneuvers such as the Jendrassik maneuver.⁴³ It follows that the elevated muscle activation and neuromuscular response observed with vibration in several studies^{44,45} may be the result not only of motor unit activation strategies, but also of alterations in spindle sensitivity, possibly facilitating muscle neuromuscular conditioning through specific training programs.³⁸

Although less common than sensory symptoms, motor symptoms such as muscle weakness may occur in CIPN. Therefore, a modality intervening at the neuromuscular level may be well worth considering as a rehabilitative tool. High-intensity strength training programs have already been proven to be both safe and effective in cancer survivors, in the short term^{46,47} as well as up to a year after completion of the training program.⁴⁸ Modalities such as WBV, which would potentially contribute to building muscle strength, could be a worthwhile addition to such programs.

The second consideration is the potential beneficial effect of WBV on balance in patients with CIPN, the research has shown that the risk of falling is increased in patients with CIPN.^{19,49,50} Furthermore, it is also likely that cancer- and chemotherapy-related fatigue and consequent inactivity contribute to muscle wasting, further raising the risk of falling.^{15,49} Studies suggested that WBV improves balance in elderly,⁵¹⁻⁵⁴ even though there still seems to exist some ambiguity as to whether the effect of WBV is actually supplemental to traditional training programs.⁵⁴ The effect of WBV on balance, being either direct or through increasing muscle strength, implies that vibration-training may be a worthwhile adjunct to balance training in cancer patients suffering from CIPN.

The third and final consideration is whether WBV could be of use in reducing neurologic pain in patients with CIPN, which is a common symptom and is described by patients as tingling, pinpricks, electrical shocks or stabbing.⁵⁵ The supposed pain-reducing effect of WBV is twofold: both mechanisms, an acute and a chronic pain-reducing effect, have been described.

The acute pain-reducing effect of WBV in diabetic peripheral neuropathy could derive from peripheral mechanisms in agreement to the gate-control theory, in which the vibration-induced axonal signal temporarily inhibits the pain-signaling axons.³⁴ This hypothesis shows some similarity with the spinal pathway possibly involved in the autogenic inhibition of gamma drive, as observed by Fromm *et al.* during muscle vibration.⁴⁰ Another explanation for the acute pain-reducing effect would be that the areas processing respectively vibratory stimuli and pain, lay in close proximity of each other in the somatosensory cor-

tex.^{34,56} The prevailing explanation for the chronic pain-reducing effect of WBV is based on the process of central sensitization.³⁴ In chronic pain, there seems to be a lack of spinal inhibition of pain signaling, resulting in a hyperalgesic state.⁵⁷ WBV may compensate for this hyperalgesic state by generating presynaptic spinal inhibition and consequently reducing spinal excitability.⁵⁸ Although so far the presynaptic inhibitory effect of WBV has been observed only in motor neurones, resulting *e.g.* in suppression of the Hoffmann reflex (H-wave) resulting from transcutaneous electrical stimulation after 40-Hz WBV,⁵⁹ it is plausible that in chronic pain a similar effect occurs for nociceptive stimuli in the spinal ganglia of sensory neurones.³⁴

On a final note, the effect of the most commonly used neurotoxic agents in the treatment of cancer - being platinum-derivates, vinca alkaloids, taxanes and thalidomide - takes place at the level of the dorsal ganglia.² Since the prevailing theory for the chronic pain-reducing effect of WBV is based on the process of presynaptic inhibition at the same level in the peripheral nervous system,³⁴ it may be possible that WBV would have a favorable effect on neurologic pain in cancer patients with CIPN.

Conclusions

The results of this literature search suggest insufficient evidence to assess the effectiveness for the effects of WBV on neuropathic pain, muscle strength and balance in patients with peripheral neuropathies, as there is a clear lack of methodologically high-quality research on the subject. In order to further explore the potential role of WBV in the rehabilitation of CIPN, high-quality trials - based on possible mechanisms - in cancer survivors will need to be performed.

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