High tone therapy for chemotherapy induced neuropathy: Clinical study protocol

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Background

Neuropathy means the damage of peripheral nerves due to various conditions like chronic diseases, injury or as a side effect of specific medications. In particular, chemotherapy-induced peripheral neuropathy (CIPN), a side effect of antineoplastic medication, was reported to occur in about 68% of the patients receiving chemotherapy (Seretny et al., 2014). CIPN does not only limit quality of life due to neuropathic symptoms but also may lead to dose reductions or premature interruption of therapy and thus to suboptimal cancer treatment.

Patients with neuropathy suffer from sensory disturbances as tingling, numbness, burning pain or sleep disturbances and even though numerous drugs are available, it is still difficult to sufficiently control these symptoms (Javed et al., 2018).

High tone therapy / high tone external muscle stimulation (HTEMS) seems to be an effective treatment for neuropathic symptoms. Previous studies observed promising results in diabetics (Hidmark et al., 2017; Humpert et al., 2009; Kempf & Martin, 2010; Reichstein et al., 2005) and chronic kidney disease (CKD) patients (Klassen et al., 2012; Strempska et al., 2013).

To date, there is no investigation on HTEMS in patients with chemotherapy induced neuropathy.

Therefore, this aim of this project is to test if HTEMS would bring about a stronger decrease in neuropathic symptoms in this specific patient group, compared to a placebo treatment.

The primary objective is the alleviation of paresthesias. The secondary objective focuses on detailed symptoms of neuropathiy as well as on health-related quality of life.

Methods

Design

This two-center study will be conducted at the Departments of Physical and Rehabilitation Medicine of the Danube Hospital and the Wilhelminen Hospital, Vienna, Austria. This study will be randomized, double-blind and placebo-controlled.

Subjects

Female and male patients of the oncologic clinics of the Danube Hospital and Wilhelminen Hospital will be screened for elegibility and invited to participate in the study. The inclusion- and exclusion criteria will be checked ad the Departments of Physical and Rehabilitation Medicine. Before any study-related procedure, written informed consent will be obtained and subjects will be randomized consecutively. The allocation to group A or B will be performed according to a randomization protocol designed by the Directorate General, Board Division of Health Care Management. This protocol will be based on online randomization.

Inclusion criteria will be:

- Patients with histologically verified colorectal cancer and adjuvant treatment with a platin derivate (e.g., cisplatin, oxaliplatin): This group was chosen due to relatively high risk of neuropathy due to this special therapeutic agent (Park et al., 2013; Seretny et al., 2014).
- Cumulative dose of at least 3 cycles
- Interval of 2 weeks since the last chemotherapeutic cycle in order to prevent false worsenings due to delayed neurotoxic effects
- Life expectancy of at least 3 months
- Stable medication (no changes of especially pain medication during the study)
- Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0-2 (that is, the capability to walk and to spend less than 50% of waking hours sitting or lying)
- Ability to walk (with or without aids)
- European Organisation for Research and Treatment of Cancer (EORTC) common toxicity criteria (CTC) peripheral sensory neuropathy grade 1 or 2
- Intensity of paresthesias of 3/10 or higher on the Numeric Rating Scale (NRS)

Exclusion criteria will be:

- Prevalent neuropathy of different etiology
- Serious central-neurological or psychiatric disorder that would interfer with a proper order of the study, according to the judgement of the investigators
- Epilepsy
- Minors or persons unable to give informed consent
- Current neurotoxic medication
- Implanted pacemakers or defibrillators
- Pregnancy
- Wounds in the area to be treated, acute local or systemic infection
- Peripheral arterial occlusive disease > grade 2

Treatment

The HiTop® 191 (GBO Medizintechnik AG, Rimbach, Germany) is a CE-certified and patented (European Patent 1322379B1) medical product.

It delivers medium frequency alternating current and to date, no undesirable side effects have been reported. In detail, the carrier frequency lies between 4-33kHz and is modulated at a defined frequency of 20Hz. This procedure is called SimulFAM® (simultaneous frequency amplitude modulation).

The electrodes will be placed onto the calfs and soles, respectively.

The HiTop treatment does not involve a typical “electricity sensation” but rather only a feeling of muscular contraction in some but not all persons. In other words, according to personal communications with several rehabilitation units, some persons are do not feel anything during the *verum* treatment. Therefore, a placebo-controlled study seems to be feasible.

The mechanisms of action have not been clarified yet. However, two major possible ways have been discussed: 1. spinal stimulation, thereby decreasing the excitability of small fibers (Humpert et al., 2009) and 2. promotion of attachment and differentiation of hematopoietic stem cells (Hidmark et al., 2017). Concerning stem cells, there is only a single study on diabetics reporting a higher number of molecules mediating attachment and differentiation of hematopoietic stem cells. However, in this study there was no

control group. Therefore, the possible effect via stem cells should be called a hypothesis rather than a verified mechanism.

Nevertheless, due to accumulation of platin in the dorsal root ganglia chemotherapy-induced neuropathy seems to result from ganglionopathy with subsequent axonal hyperexcitability (Beijers et al., 2014). Therefore, we rather think that the effect of high tone therapy seems to result from sensory afferent actions.

In the placebo group, a placebo device of the same design will be used with no current output.

To ensure a double-blind procedure, the participants will be supervised by two physicians per center. Physician one will perform the assessments and physician two will manage the randomization and instruction in the handling of the device. All subjects will be informed that they may feel tingling or muscle contraction during the treatment but also about the possibility of not feeling any senzations. Subjects will be required not to tell physician one if they felt tingling or contractions.

Previous studies observed alleviation of neuropathic symptoms after a relatively short treatment period (Hidmark et al., 2017; Humpert et al., 2009; Kempf & Martin, 2010; Reichstein et al., 2005). However, most of these studies had no control group and therefore, the data on the effect of high tone therapy is weak.

Therefore, the treatment phase in our study will last three weeks. One treatment session will take about 60min. The minimum number of treatment sessions to be completed will be 5 out of 7 days. The device saves minutes of treatment and therefore offers the clinician to monitor the participants´ compliance. Therefore, the treatment will be home-based.

Assessments

Assessments will be carried out at the following points of time: Baseline, after the first treatment week, at the end of the treatment phase and follow up after two weeks.

After completing the follow-up assessment, the participants will be unblinded and subjects of the placebo group will be offered to join the treatment group (opt in).

The baseline assessment includes a test of vibration sensation by using a clanging tuning fork (Panosyan et al., 2016). In this examination, certain anatomical localizations will be touched with the tuning fork (i.e., the dorsum of the interphalangeal joint of the hallux and the medial malleolus). Several studies reported that this test not only detects peripheral neuropathy accurately but also that it is superior to the monofilament test (Meijer et al., 2005; Oyer et al., 2007). Moreover, normative values for several age groups have been published (Martina et al., 1998).

In addition, full medical and social history will be collected, including:

- demographic data (date of birth, height, weight)
- previous conditions and operations
- course and treatment of the current cancer, duration of neuropathy
- (pain) medication (patients will be required not to change their medication during the study)
- Walking aids
- Need for social / nurse support (type of support and hours per week)
- Social history (profession, level of education, family status)

The following outcome parameters will be determined and quantified as part of all assessments:

Pain and sensory disturbances

- Numeric rating scale (NRS, 0-10): Paresthesia intensity, mental stress due to paraesthesia, pain intensity, mental stress due to pain, tightness/pressure intensity and mental stress due to tightness/pressure
- European Organisation for Research and Treatment of Cancer Chemotherapy-Induced Peripheral Neuropathy 20 questionnaire (EORTC CIPN 20): This is an international questionnaire to assess chemotherapy induced neuropathy with a

sensory scale, motor scale as well as an autonomic scale (Postma et al., 2005). The CIPN 20 questionnaire has been used in recent studies (Coyne et al., 2013; Gewandter et al., 2018).

- Neuropathy Symptom Score (NSS): This validated questionnaire assesses and quantifies neuropathic symptoms and has been used in recent studies (Hidmark et al., 2017; Jende et al., 2018; Mao et al., 2018).

Quality of life

- EORTC Core 30 (EORTC C30) questionnaire: This questionnaire is designed to assess health-related quality of life specifically in cancer patients and has been used recently (Elfeki et al., 2018).

Objectives

The primary objective is to compare the changes in intensity of paresthesias between the two patient groups. This will be performed via standardized questionnaires with numeric rating scales (NRS) in the baseline assessment, after the first treatment week, at the end of the treatment phase and follow up after two weeks.

The secondary objective is to evaluate neuropathic symptoms further in detail and to assess quality of life via standardized questionnaires with NRS as well as via internationally accepted questionnaires.

Hypothesis

We hypothesize that high tone therapy will bring about a significantly stronger reduction in neuropathic symptoms, compared to the placebo treatment.

Statistical analysis

To show that the primary objective, changes in intensity of paresthesias measured with the numeric rating scale, will bring about a significantly stronger reduction in the intervention group, a repeated measures analysis of variance will be conducted. A mean value out of 8 questions will be calculated wich will be compared between the intervention group and the placebo group (between-subject-factor) and between 4 measurements (within-subject-factor). A 4*2 within-between-interaction can point out differences in intensity of paresthesias between all times of measurements and between both groups. In a two-sided test the alpha level will be set at 0.05 to show significant effects.

Also, the secondary objectives, measured with standardized questionnaires, will be analysed in a repeated measures analysis of variance model, since all questionnaires will be tested at 4 times of measurement. With the EORTC QLQ-C30 (3rd version) a global health status, functional scales and symptom scales are calculated. With the EORTC QLQ-CIPN20 moreover a sensory scale, a motor scale and an autonomic scale are calculated. Since all subscales of both questionnaires are metric, a multivariate model can be calculated via repeated measures analysis of variance (alpha 0.05, two-sided)

In addition, a neuropatic-symptom-score (NSS) with 5 more questions is calculated. At a range of 0-10 points patients can be classified in 4 groups (<3 points, 3-5 points, 6-8 points, 9-10 points) and a Chi-square analysis can show differences in frequencies

at 4 times of measurement (alpha 0.05). Under the assumption of a normal distribution of the residuals and homoscedasticity the 4 classified groups of the NSS questionnaire could be used to build an additional factor and show differences in a repeated measures ANOVA between the 4 groups (additional between-subject-factor) in the primary objectice and the secondary objective model (alpha 0.05, two-sided)

Logistic-Regression models could show combined effects of primary and secondary objectives, if the quality of data is sufficient (alpha 0.05). If the quality of data is insufficient simple effects between primary and secondary objectives, and all subscales of the secondary objectives questionnaires, could be shown with Pearson correlations (alpha 0.05, two-sided).

Descriptive statistics and frequencies will be calculated for sampling variables.

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