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High-Intensity Pulsed Magnetotherapy in the Rehabilitation Programme of Patients with Chemotherapy-Induced Peripheral Polyneuropathy: a Prospective Randomized Clinical Study

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ABSTRACT

INTRODUCTION. Chemotherapy-induced peripheral polyneuropathy (CIPN) is one of the most frequent side effects caused by anticancer drugs, with a prevalence ranging from 19 % to 85 %. For effective multicomponent rehabilitation of patients with CIPN at different stages, a number of non-medicinal methods are recommended to improve the tolerance of chemotherapy and reduce the side effects of the antitumor treatment performed.

AIM. Study of the effect of high-intensity pulsed magnetotherapy on clinical manifestations and microcirculation state in patients with CIPN.

DESIGN. This is a randomized controlled study.

SETTING. Randomization, organization of the study and data analysis were performed on the premises of the Department of Medical Rehabilitation in National Medical Research Centre for Rehabilitation and Balneology, Moscow, Russia.

POPULATION. Sixty patients with CIPN were included in this study and were randomized by a simple random distribution method in a ratio of 1:1 into 2 groups of 30 people.

METHODS. Sixty patients with CIPN four weeks after completion of chemotherapy were examined. The first group, the main group, included patients who received high-intensity pulsed magnetotherapy (HIPMT) in combination with drug therapy. In the second group (control group), the patients received only drug therapy. The EORTC-QLQ-C30 questionnaire (version 3) was used to assess the quality of life. The HADS scale was used to assess the severity of anxiety and depression symptoms. The state of microcirculation was assessed using laser Doppler flowmetry (LDF). The severity of CIPN was assessed according to the CTS-NCIC scale, version 3.0.

RESULTS. According to the results of this study, there is a statistically significant difference in the scores on the EORTC-QLQ-C30 questionnaire (version 3), HADS scale and LDF data between the groups in favour of the group receiving HIPMT in combination with drug therapy.

CONCLUSION. Based on the LDF study, significant disturbances at the microcirculatory level were detected for the first time in patients with CIPN. The obtained results convincingly demonstrate that the use of HIPMT in patients with CIPN leads not only to improvement of microcirculation in the extremities due to normalisation of arterial vessel tone, elimination of venous stasis and increase in the nutritive blood flow, but also has an analgesic effect, improves initially impaired sensitivity, and improves the quality of life of these patients.

CLINICAL REHABILITATION IMPACT. The use of HIPMT in combination with drug therapy in patients with CIPN was more effective than drug therapy alone.

KEYWORDS: CIPN, cancer rehabilitation, chemotherapy, magnetic field therapy, polyneuropathy.

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Высокоинтенсивная импульсная магнитотерапия в реабилитационной программе пациентов с периферической полинейропатией, индуцированной химиотерапией: проспективное рандомизированное клиническое исследование

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РЕЗЮМЕ

ВВЕДЕНИЕ. Периферическая полинейропатия, индуцированная химиотерапией (ПНПИХ), является одним из наиболее частых побочных эффектов, вызываемых противоопухолевыми препаратами, с распространенностью от 19 % до 85 %. Для эффективной многокомпонентной реабилитации пациентов с ПНПИХ на различных этапах рекомендован ряд немедикаментозных методов с целью улучшения переносимости химиотерапии и снижения побочных эффектов проводимого противоопухолевого лечения.

ЦЕЛЬ. Изучение влияния высокоинтенсивной импульсной магнитотерапии (ВИМТ) на клинические проявления и состояние микроциркуляции у пациентов с ПНПИХ.

ДИЗАЙН. Это рандомизированное контролируемое исследование.

МЕСТО ПРОВЕДЕНИЯ ИССЛЕДОВАНИЯ: Рандомизация, организация исследования и анализ данных были выполнены на базе отделения медицинской реабилитации ФГБУ «НМИЦ РК» Минздрава России, Москва, Россия.

НАСЕЛЕНИЕ. В это исследование были включены 60 пациентов с ПНПИХ, которые были рандомизированы в соотношении 1:1 на 2 группы по 30 человек.

МЕТОДЫ. Были обследованы 60 пациентов с ПНПИХ спустя четыре недели после завершения химиотерапии. Первая группа — основная включала пациентов, которые получали ВИМТ в сочетании с медикаментозной терапией. Во второй группе (контрольной) пациенты получали только медикаментозную терапию. Для оценки качества жизни использовали опросник EORTC-QLQ-C30 (версия 3). Для оценки выраженности симптомов тревожности и депрессии применяли шкалу HADS. Состояние микроциркуляции оценивали, применяя лазерную доплеровскую флоуметрию (LDF). Степень тяжести ПНПИХ оценивали согласно шкале CTC-NCIC, версия 3.0.

РЕЗУЛЬТАТЫ. Согласно результатам этого исследования, существует статистически значимая разница в оценках по опроснику EORTC-QLQ-C30 (версия 3), шкале HADS и по данным лазерной допплеровской флоуметрии (ЛДФ) между группами в пользу группы получавших ВИМТ в сочетании с медикаментозной терапией.

ЗАКЛЮЧЕНИЕ. На основании проведенного исследования с помощью ЛДФ впервые у пациентов с ПНПИХ были выявлены существенные нарушения на микроциркуляторном уровне. Полученные результаты убедительно демонстрируют, что применение ВИМТ у пациентов с ПНПИХ приводит не только к улучшению микроциркуляции в конечностях за счет нормализации тонуса артериальных сосудов, устранения венозного застоя и увеличения нутритивного кровотока, но и оказывает обезболивающее действие, улучшает исходно нарушенную чувствительность, а также улучшает качество жизни данных пациентов.

ВЛИЯНИЕ РЕАБИЛИТАЦИИ. Применения ВИМТ в сочетании с медикаментозной терапией у пациентов с ПНПИХ было более эффективно чем применение только медикаментозной терапии.

КЛЮЧЕВЫЕ СЛОВА: полинейропатия, индуцированная химиотерапией, реабилитация при раке, химиотерапия, терапия магнитным полем, полинейропатия.

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INTRODUCTION

One of the urgent problems of modern medicine is the development of effective methods of rehabilitation of cancer patients after radical surgery against the background of specific antitumour therapy, including the use of a number of physical factors. Chemotherapy-induced peripheral polyneuropathy (CIPN) is one of the most frequent side effects caused by antitumour drugs, with a prevalence ranging between 19 % and 85 % [1]. In the pathogenesis of CIPN, great importance is attached to direct diffusion of cytostatics into nerve fibres from the surrounding interstitial fluid, disturbances of microtubular architectonics of axons through increased tubulin polymerisation, which causes impaired axonal transport, diffuse or segmental demyelination of neurons, degeneration of neuronal bodies, and induction of neuronal apoptosis. At the moment, there is no single effective method of prevention of CIPN, moreover, the treatment options for this syndrome are very limited [2].

For effective multicomponent rehabilitation of patients with CIPN at various stages, a number of non-medicamentous methods are recommended to improve tolerance to chemotherapy and

reduce side effects of the antineoplastic therapy. Among the non-medicinal methods, acupuncture, manual therapy, massage, and therapeutic exercises are used [3–14]. A number of studies evaluated the effectiveness of low-frequency magnetotherapy, percutaneous electroneurostimulation, low-intensity laser therapy. However, the results of studies on the effectiveness of these methods are not convincing enough [15–25].

In this connection, the development of new physiotherapeutic methods for rehabilitation of patients with CIPN is an important medical and social problem. The method of HIPMT based on the induction of eddy electric currents of significant density affecting excitable structures of deep tissues seems promising in this respect. HIPMT has a significant analgesic effect due to the blockade of pain impulse transmission in the central nervous system, as well as a pronounced trophic, anti-edematous and anti-inflammatory effect [26].

AIM

Study of the effect of HIPMT on clinical manifestations and microcirculatory state in patients with chemotherapy-induced peripheral polyneuropathy.

MATERIALS AND METHODS

Participants

Starting from March 2021 until January 2023, 60 patients (51 women and 9 men) with CIPN four weeks after completion of chemotherapy were sent to the departments of medical rehabilitation of the National Medical Research Centre for Rehabilitation and Balneology Moscow, Russia for examination and treatment.

Recruitment for this randomized trial approved by the local ethics committee, was carried out in the local community. This trial was followed by the recommendations of the CONSORT statement [27].

Prior to their inclusion in the study, all the patients had received potentially neurotoxic chemotherapy (oxaliplatin or periwinkle alkaloids) as part of their cancer treatment. The mean number of cycles of chemotherapy received by the patients was 11 [6;15] in both groups, and the mean period between the last chemotherapy and the start of rehabilitation was 65 [49;186] days in both groups. All patients were provided with information about the planned rehabilitation and gave their written consent.

Participants were informed about the possibility of being randomly assigned to one group or another. Participants were randomized in one of two treatment groups — main group and control group. The randomization schedule was generated using the random.org website. The allocation schedule was printed on cards. These cards were sequentially numbered in opaque and sealed envelopes, each containing the name of one of the groups. The envelopes were selected by an external person who was not enrolled in the trial (Figure 1).

Inclusion Criteria

Age of patients — 56.5 ± 5.7 years; presence of peripheral polyneuropathy induced by chemotherapy, I–II degree of severity according to STS-NCIC scale version 3.0; four weeks after completion of chemotherapy.

All patients received information about the planned rehabilitation. They gave their written consent. Materials of the planned clinical study were submitted to the Local ethics committee at the National Medical Research Centre for Rehabilitation and Balneology Moscow, Russia and approved by it (Protocol No. 2 of 14 January 2021).

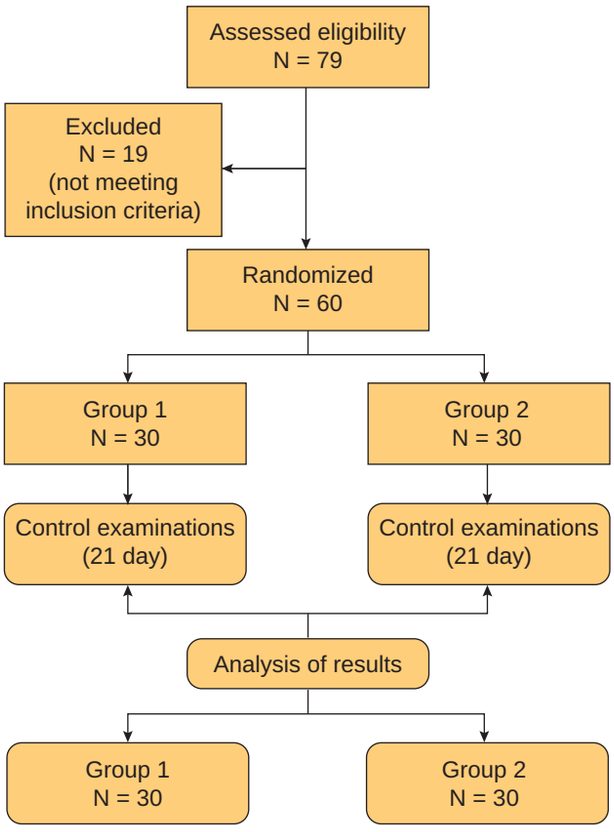

Fig. 1. CONSORT diagram illustrating the process from recruitment to data collection (21day follow-up)

Exclusion Criteria

Under 18 years of age and over 75 years of age; women during pregnancy, childbirth; diabetes mellitus; history of polyneuropathy prior to chemotherapy; acute cardiovascular disease, thrombosis or arterial occlusive disease in the limb to be treated; cognitive impairment; presence of metal implants in the area of exposure; presence of pacemaker, acute infection, and lack of written informed consent from the patient.

Exclusion Criteria for Patients

Development of serious adverse events during the study, patient's refusal to participate in the study.

The patients of the 1st and 2nd groups were comparable by the main clinical and demographic indicators: sex (p = 0.75), age (p = 0.69), average duration of the main disease (p = 0.092), average duration of polyneuropathy (p = 0.38), as well as the studied clinical manifestations of polyneuropathy.

Study Design

A prospective randomized clinical study was conducted. The study complied with the Declaration of Helsinki and the guidelines of good clinical practice and was approved at the meeting of the Local Ethical Committee of National Medical Research Centre for Rehabilitation and Balneology, Moscow, Russia (Protocol No. 2 of 14.01.2021). The patients with CIPN were included in this study and were randomized by a simple random distribution method in a ratio of 1:1 into 2 groups of 30 people.

The first group (main group) included patients who received HIPMT in combination with drug therapy. The patients in the second group (control group) received only drug therapy.

An online calculator (https://www.sealedenvelope.com) was used to calculate the necessary sample sufficient to determine the planned impact (the clinical benefit response effect was 89 % in the main group and 65 % in the control group). When calculating the required sample size based on the outcome of the frequency of achieving a clinical response, the hypothesis of the superiority of binary outcomes was used. The sample size was calculated with a given statistical power of 90 % and a level of "error of the first kind" of 5 %.

Randomization, organization of the study and data analysis were performed in the Department of Medical Rehabilitation, National Medical Research Centre for Rehabilitation and Balneology, Moscow, Russia. The authors developed the study protocol and all the authors had access to the original data after the completion of the study. All the authors attest to the accuracy of these results.

Data were collected and analyzed only by the principal investigator. Decisions regarding the content of this article were made by the principal investigator and other authors.

All data about the patients were stored using standard documentation. The data collected in such manner were computerized for further evaluation and analyzed using a statistical program.

Clinical intervention: Depending on the degree of manifestation of clinical symptoms, the upper limbs (hands) or lower limbs (feet) were treated. High-intensity pulsed magnetotherapy (HIPMT) procedures were performed using a high-intensity magnetotherapy device — Super Inductive System (SIS) BTL-6000 (United Kingdom), using 6 modes, which were changed stepwise one after another. Consecutively for 30 seconds a frequency of 5Hz, pulse/pause ratio 1:1 was applied, for the next 30 seconds a frequency of 1Hz, pulse/pause ratio 1:1 was applied, for 2 minutes a frequency of 10Hz pulse/pause ratio 12: 6 was applied, for 1 minute a 1Hz frequency, pulse/pause ratio 1:1 was applied, for 2 minutes a 10Hz frequency pulse/pause ratio 12:6 was applied and, finally, a 1Hz frequency was applied, for 1 minute a pulse/pause ratio 1:1 was applied. The intensity value on the surface of the inductor coil was changed in the following mode: during the first procedure the magnetic induction intensity was 200 mTl, the second — 300 mTl, the third — 400 mTl, the fourth — 500 mTl, from the fifth to the tenth — 600 mTl. Total exposure time per procedure was 14 minutes, 7 minutes per limb. For a course of 10 procedures, performed every second day.

The EORTC-QLQ-C30 questionnaire (version 3) was used to evaluate the quality of life. The current version 3 includes 30 questions and consists of 5 functional scales: physical function (PF), role function (RF), cognitive function (CF), emotional function (EF), and social function (SF); symptoms scale: fatigue (F), nausea/vomiting (N/V), and pain (P); general health status (GHS) scales; 6 single items — insomnia (I), loss of appetite (LA), constipation (C), diarrhoea (D), dyspnoea (D), financial difficulties (FD). For the functional and general health status scales, the patient's best condition corresponds to 100 % (or points), and the worst condition corresponds to 0. For all symptoms scales, the best condition corresponds to 0 and the worst condition corresponds to a score of 100 points.

To assess the severity of CIPN, the disease-specific EORTC QLO-CIPN20 questionnaire was used, which is an add-on module to the main EORTC-QLQ-C30 questionnaire with 20 items assessing sensory, motor and autonomic symptoms experienced by patients during the past week. Each item can be scored from 1 (no symptoms at all) to 4 (very many), with higher scores indicating worse symptom severity.

To assess the severity of symptoms of anxiety and depression we used the HADS (Hospital Anxiety and Depression Scale), which consists of two parts: the HADS-A subscale (A — anxiety) and the HADS-D subscale (D — depression) and includes 14 items, each of which corresponds to 4 response options, reflecting the degree of symptom progression. The patient should choose the answer that most closely matches how he or she has been feeling over the past week. The total score for each subscale determines the result: 0–7 points «norm» — absence of reliably expressed symptoms of anxiety and depression; 8–10 points «subclinically expressed anxiety/depression»; 11 points and above "clinically expressed anxiety/depression".

Spectral analysis based on wavelet transformation of periodic oscillations of the laser Doppler flowmetry (LDF) signal was used to analyse skin blood flow. LDF grams were recorded on the anterior surface of the forearm and in the foot area — volar (plantar) surface of the big toe.

Periodic oscillations were registered with frequencies of about 0.005–0.0095 Hz and 0.0095–0.02 Hz, reflecting the regulation of the vascular tone due to endothelial activity; with frequencies of 0.05–0.15 Hz, characterizing myogenic mechanisms of the vascular tone regulation; with frequencies of 0.02–0.05 Hz, reflecting neurogenic sympathetic vasomotor activity, as well as with frequencies of 0.45–1.6 Hz and 0.2–0.45 Hz, which carry information about the influence of cardiac contractions and chest movements on the peripheral blood flow.

The severity of CIPN was assessed according to the CTS-NCIC scale, version 3.0:

- 1st degree (mild) — impairments not affecting quality of life (e.g., loss of tendon reflexes);
- 2nd degree (moderate) — objective neurological disorders that impair limb function but do not affect the patient's daily activity;
- 3rd degree (severe) — severe objective disorders impairing limb function and daily activity of the patient.
- 4th degree (extremely severe) — complete loss of limb function.

The subjective and objective status of the patient was assessed before and after the course of medical interventions (on the 21st day of the study).

In all patients (n = 60), subjective and objective status was assessed before and after the course of medical interventions (on day 21 of the study).

Statistical Analysis

The results of the studies were analysed using IBM SPSS Statistics 23 application software package and Microsoft Office Excel 2016. The Mann-Whitney U-criterion, Wilcoxon test were used to compare two independent samples.

RESULTS

The patients were admitted for outpatient treatment to the medical rehabilitation department after a course of special anti-tumour therapy. Most of them (75.0 %) received chemotherapy for breast cancer. Characteristics of the patients by cancer localisation, age and severity of polyneuropathy are presented in Table 1.

Table 1. Participant baseline characteristics

Parameters under study	Group 1 (main), *n* = 30		Group2 (control), *n* = 30	
Age (years), mean (SD)	56.5 [49.1; 61.7]		56.9 [48.2; 62.2]	
Cancer primary, *n* (%)				
Cervical cancer	3	10	3	10
Bladder cancer	2	6.7	2	6.7
Breast cancer	22	73.3	23	76.6
Lung cancer	3	10	2	6.7
Neuropathy grade (%)^				
1	12	40	11	36.6
2	18	60	19	63.4

Note: *The data are presented in the form of median (Me) and quartile [Q1, Q3]. All differences were not statistically significant with p > 0.05.*

The 1st degree of CIPN severity was detected in 40 % of patients, which was characterized by complaints of numbness and tingling in the fingers of both hands and feet, while objective examination revealed decreased tendon reflexes. The 2nd degree of CIPN severity was observed in 60 % of patients, in which numbness, weakness in hands and feet were noted. Objective examination revealed swelling of hands, shins, pain sensitivity hypoesthesia of »gloves» and «socks» type. Using the EORTC QLQ-CIPN 20 questionnaire, baseline scores in all observed patients were: 18 [15; 20] for sensory symptoms, 15.8 [13;21] for motor symptoms, and 3.36 [2;5] for autonomic symptoms. Signs of polyneuropathy predominated in 75 % of the subjects predominantly in the distal upper extremities, and in 25 % in the lower extremities.

According to pre-intervention LDF data, 57 % of patients with predominantly upper extremity lesions had an increased contribution of myogenic and neurogenic oscillations to the total vasomotions level. The presence of endothelial dysfunction was observed. An increase in the contribution of cardiac oscillations was revealed, indicating an increased inflow of arterial blood into the microcirculatory bed. The predominance of oscillations in the range of 0.01 Hz (of endothelial origin), combined with high-amplitude cardiac oscillations confirms the presence of dilatation of small arteries and large arterioles. Disturbances in the venular section of the microcirculatory channel in the form of obstruction of blood outflow were also detected. Most frequently, this type of microcirculatory disorders was observed in patients with upper limbs lesions and the 1st degree of CIPN severity.

In 43 % of patients with predominant lower limb lesions there was a reduced contribution of myogenic, neurogenic and endothelial vasomotions, suggesting spasticity in arterioles and low perfusion. These microcirculatory disorders were predominant in the patients with the 2nd degree of CIPN severity.

According to the HADS scale, the level of anxiety and depression was high with 9.05 [8.8; 9.4] and 8.84 [8.5; 9.3] points in the main and control groups respectively.

In assessing quality of life, the observed patients had high scores on the role and physical function scales of 84.3 [71.6; 913] and 81.5 [68.6; 89.3], respectively. Emotional function had the lowest score among the functional scales at 71.7 [56.1; 84.2]. The median general health status scale score was only 54.1 [50.6; 67.3] points. Regarding the symptoms, fatigue, pain, and insomnia were the most bothersome for the patients: 25.0 [12.2; 36.1], 11.9 [10.2; 16.1], 24.9 [11.2; 35.1], respectively.

All patients tolerated the treatment well. No serious adverse events developed during the study and no patients withdrew from the study. All 60 subjects completed treatment.

After the clinical intervention, improvement in the subjective and objective parameters was observed. The patients noted a decrease in numbness and weakness in the extremities. Using the EORTC QLQ — CIPN20 questionnaire, it was found in the subjects of the first group: 12 [10; 13] points for sensory symptoms, 8.0 [6; 9] points for motor symptoms, and 2.0 [1; 3] points for autonomic symptoms. The data compared by groups are presented in Table 2.

Table 2. Treatment outcomes of patients with CIPN according to the EORTC QLQ — CIPN20 questionnaire (Me [Q1; Q3])

Observation period	Group 1 (main), *n* = 30	Group2 (control), *n* = 30
EORTC QLQ — CIPN20 Sensory scale		
Before treatment	18.0 [15; 19]	18.3 [15; 20]
After treatment	12.5 [10.2; 13.4]*#	14.8 [13.9; 25.1]
EORTC QLQ — CIPN20 Motor scale		
Before treatment	15.29 [13.4; 20.5]	15.87 [13.6; 21.1]
After treatment	8.51 [6.2; 9.1]*#	13.3 [12.2; 18.7]
EORTC QLQ — CIPN20 Vegetative scale		
Before treatment	2.1 [2.2; 5.4]	3.39 [2.1; 5.51]
After treatment	2.4 [1.2; 3.4]*#	3.1 [2.1; 4.9]

Note: ** p < 0.05 — significance of differences compared to the pre-treatment values (Wilcoxon test); # p < 0.05 — compared to the values in the control group (Mann-Whitney test).*

The patients of the main group showed a significant decrease in the level of anxiety and depression. The data compared by groups are presented in Table 3.

After the clinical intervention, the patients of the first group with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities showed positive dynamics of LDF parameters. Significant improvement of the contribution of myogenic, neurogenic and endothelial oscillations was found, which contributed to the improvement of the blood flow in the capillaries and arterioles. The control group showed no significant changes in the above-mentioned parameters (Figures 2–6).

The subjects of the first group with spasticity in the microcirculation system with predominant lesions of the lower extremities also showed positive dynamics of LDF parameters, which was expressed in the improvement of

Table 3. Dynamics of indicators of anxiety and depression in patients with CIPN according to HADS before/after treatment Me [Q1; Q3]

Observation period	Group 1 (main), *n* = 30	Group2 (control), *n* = 30
HADS / Anxiety scale		
Before treatment	9.14 [8.61; 9.51]	9.27 [8.82; 9.44]
After treatment	7.7 [7.1; 8.52]*#	9.3 [8.34; 9.2]
HADS / Depression scale		
Before treatment	8.84 [8.39; 9.15]	8.7 [8.45; 8.95]
After treatment	7.18 [6.82; 14.2]*#	9.31 [8.1; 12.4]

Note: ** p < 0.05 — reliability of differences compared to the pre-treatment values (Wilcoxon test); # p < 0.05 — compared to the control group values (Mann-Whitney test).*

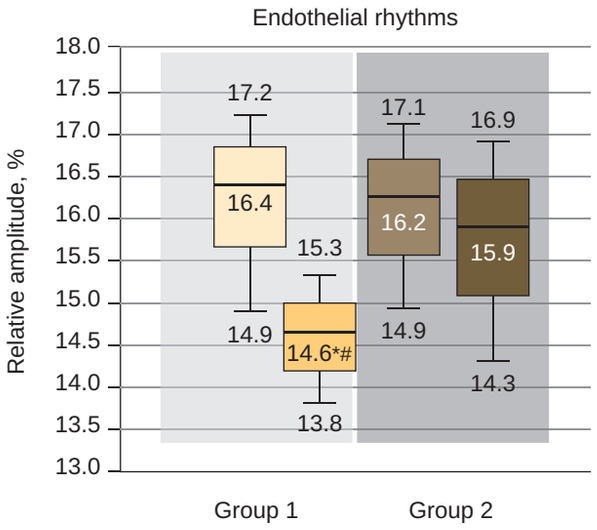

Fig. 2. Dynamics of endothelial rhythms in patients with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities

Note: *The data are represented by the Median (Me), 1 and 3 quartiles [Q1; Q3]. * p < 0.05 compared to the baseline (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

endothelial function, increase of initially reduced oscillations of myogenic range, indicating the elimination of precapillary constriction and increase of nutritive blood flow. No significant changes in LDF parameters were found in the second group of subjects (Table 4).

After a course of HIPMT application, the patients in the main group, in contrast to the control group, demonstrated an improvement in the role and physical function scales. The emotional function, which had the lowest score among the functional scales, also improved. The median of the general health status scale increased. Symptoms such as fatigue, pain and insomnia significantly decreased (Figures 7, 8).

DISCUSSION

The period of development of new physiotherapy methods of rehabilitation of oncological patients after radical operations against the background of specific antitumor therapy had been preceded by a long stage of experimental and clinical studies to investigate the effectiveness and safety of a particular physical factor for oncological patients. The major areas of application of physiotherapy methods in the rehabilitation of cancer patients are prevention and therapy of complications of specific antitumor treatment and compensation of disturbed functions by restoring and increasing the body's own defense and adaptive mechanisms.

There is now convincing scientific evidence for the advisability of using alternating, pulsed and rotating magnetic fields in oncological patients [28]. It is assumed that the therapeutic effects of magnetic fields are based

Table 4. Dynamics of LDF parameters in patients with spasticity in the microcirculatory system and predominant lesions of the lower extremities (Me [Q1; Q3])

The studied indicator Amax/3 σ × 100 %	Group 1 (main), *n* = 30		Group2 (control), *n* = 30	
	Before treatment	After treatment	Before treatment	After Treatment
E Endothelial rhythms	9.1 [8.8; 10.0]	14.4 [13.8; 15.3]*#	9.2 [8.9; 10.1]	9.9 [9; 10.3]
N Neurogenic rhythms	9.9 [9.6; 11.0]	16.9 [15.9; 17.2]*#	9.68 [9.5; 11]	10.1 [9.7; 11]
M Myogenic rhythms	10.2 [9.8; 11.0]	14.7 [13.8; 16.5]*#	10.78 [9.9; 11]	11.1 [10.2; 12]
R Respiratory rhythms	9.2 [8.9; 10.0]	8.15 [7.9; 9.0]*#	9.08 [8.8; 10.0]	8.65 [7.9; 9.6]
H Heart rhythms	7 [6.7; 8]	6 [5.2; 6.4]*#	7.58 [6.9; 8]	7.25 [6.8; 8]

Note: ** p < 0.05 compared to the baseline level (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

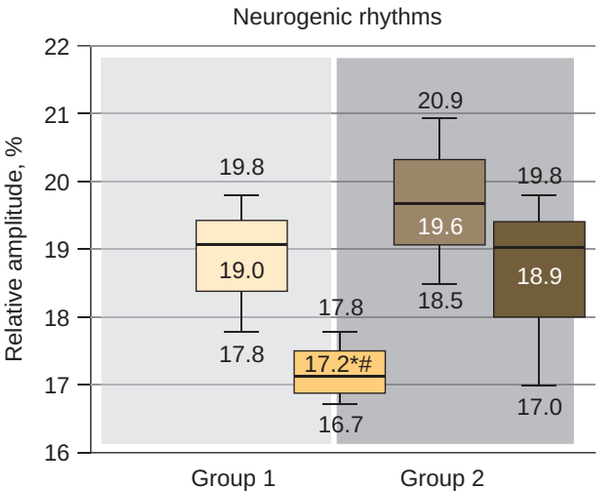

Fig. 3. Dynamics of neurogenic rhythms in patients with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities

Note: *The data are represented by the Median (Me), 1 and 3 quartiles [Q1; Q3]. * p < 0.05 compared to the baseline (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

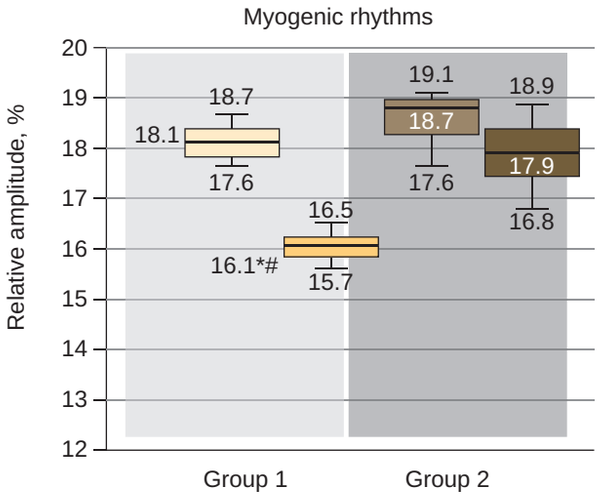

Fig. 5. Dynamics of respiratory rhythms in patients with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities

Note: *The data are represented by the Median (Me), 1 and 3 quartiles [Q1; Q3]. * p < 0.05 compared to the baseline (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

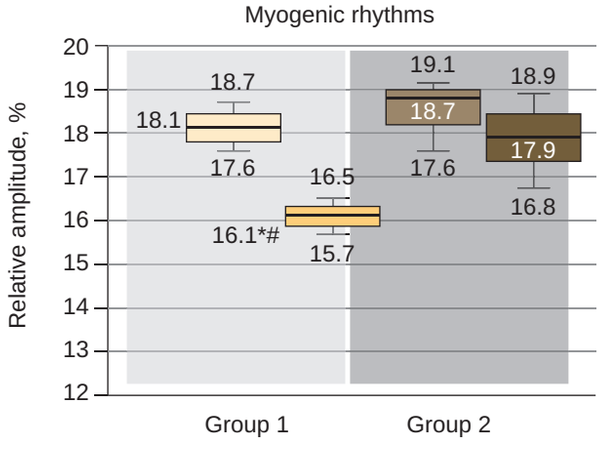

Fig. 4. Dynamics of myogenic rhythms in patients with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities

Note: *The data are represented by the Median (Me), 1 and 3 quartiles [Q1; Q3]. * p < 0.05 compared to the baseline (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

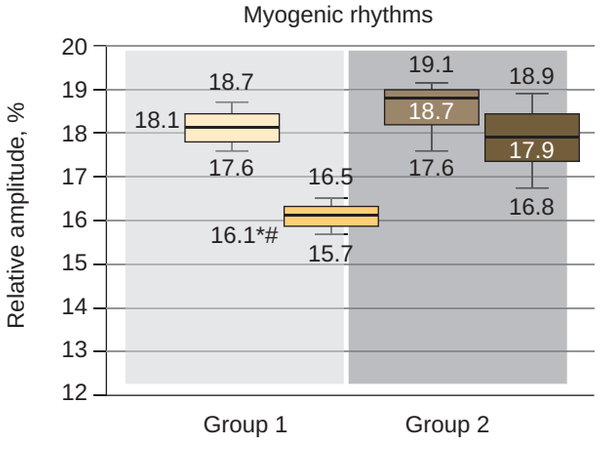

Fig. 6. Dynamics of heart rhythms in patients with disorders in the microcirculation system in the form of vasodilatation of arterioles and with predominant lesions of the upper extremities

Note: *The data are represented by the Median (Me), 1 and 3 quartiles [Q1; Q3]. * p < 0.05 compared to the baseline (Wilcoxon test), # p < 0.05 compared to the control group (Mann-Whitney test).*

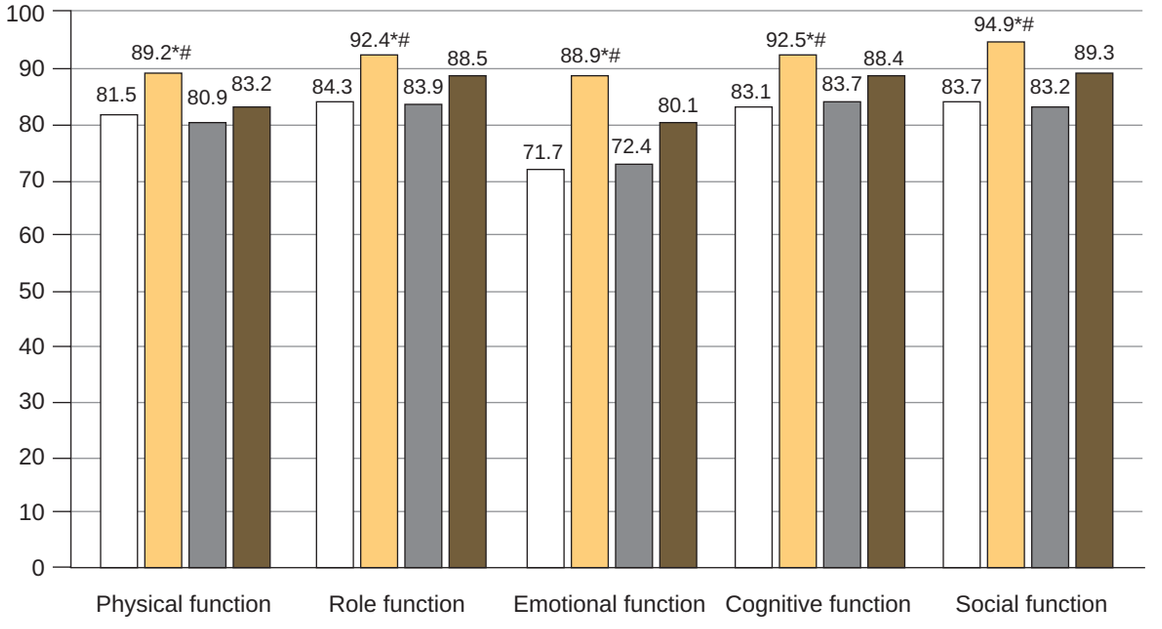

Fig. 7. Dynamics of the quality of life indicators according to the EORTC-QLQ-C30 questionnaire (according to functional scales)

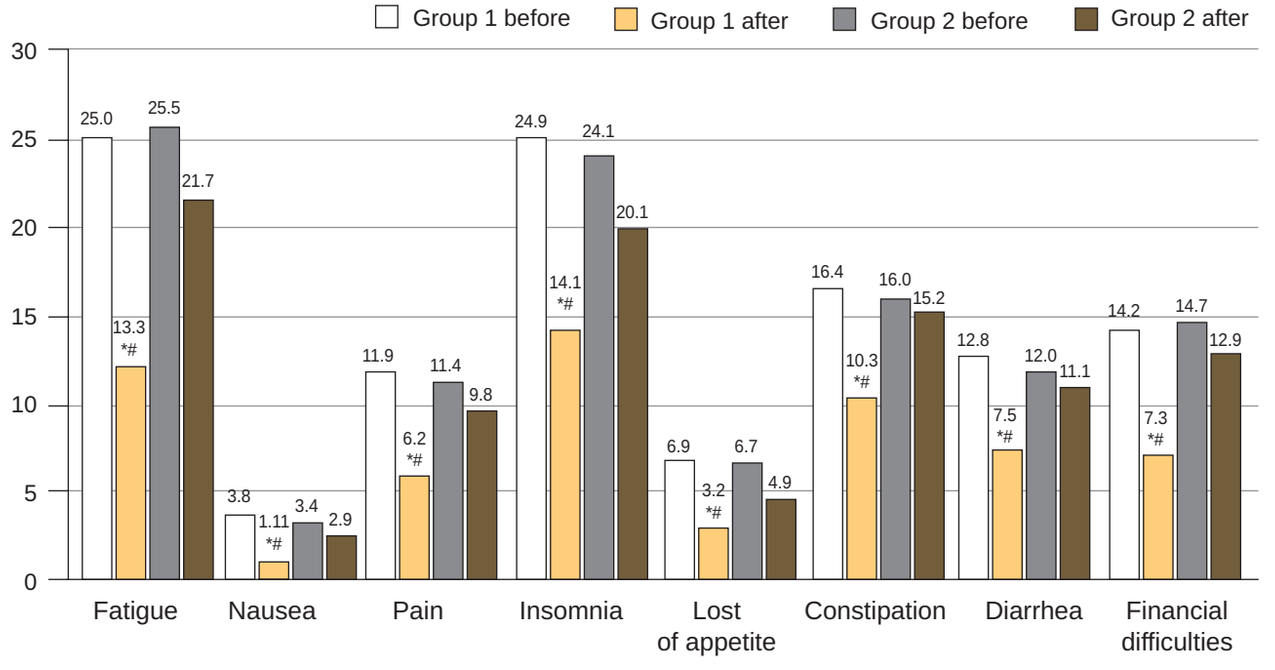

Fig. 8. Dynamics of the quality of life indicators according to the EORTC-QLQ-C30 questionnaire (based on the symptoms scales)

on the increase in the rate of metabolic processes, improvement of microcirculation and enhancement of resorption of decay products in the focus of inflammation, changes in the dispersibility of colloids and permeability of cell membranes, which contributes to the reduction of oedema, decrease in inflammation and pain management. Randomized clinical trials have reported positive effects of magnetotherapy in patients with chemotherapy-induced polyneuropathy in terms of the main clinical symptoms of CIPN and most neurophysiological parameters [29].

In recent years, there have been isolated publications on the successful use of HIPMT in patients with CIPN [26]. The authors used a portable magnetotherapy device consisting of four 45-degree segments made of special magnetic material mounted symmetrically on a 6-cm-diameter, 28-cm2 rotating disc with a magnetic flux density of 420 mTl. The treatments were performed for 5 minutes on each affected limb, daily, 2 times a day, for 3 weeks. At the end of the course, the researchers found a statistically significant difference with the placebo group in terms of sensory neurotoxicity of the ulnar and peroneal nerves (nerve conduction velocity increased ($p = 0.015$) and subjectively perceived neurotoxicity by the patients ($p = 0.04$).

HIPMT is superior to low-frequency magnetotherapy in terms of myostimulating, analgesic and anti-inflammatory effects. The advantages of pulsed magnetotherapy are the possibility of wider variation of dosimetric parameters, availability of impact on more deeply located organs and tissues, more pronounced specificity and physiological effect of exposure [31].

Analysis of the available data in the literature allowed us to propose a hypothesis about the therapeutic effect of HIPMT on clinical manifestations and the state of microcirculation in patients with peripheral polyneuropathy induced by chemotherapy.

According to the results of the randomized study, it was found that under the influence of HIPMT, in contrast to the control group, there was an improvement in the quality of life, which was confirmed by the positive dynamics of indicators of the scales of role, physical and emotional functions (EORTC-QLQ-C30).

One of the important objectives of the present study was to investigate the state of microcirculation in patients with CIPN and to evaluate the effect of HIPMT on the cutaneous blood flow in this category of patients, since to date there are only few studies on the state of microcirculation in patients with CIPN. Using laser Doppler flowmetry we evaluated skin microcirculation in 60 subjects. Based on the data obtained by LDF, 43 % of patients with predominant lesions of the lower extremities initially showed spasticity in the arterioles and low perfusion, whereas 57 % of patients with predominant lesions of the upper extremities showed dilatation of the small arteries and large arterioles. After 10 HIPMT procedures, the patients with spasticity showed an increase in the initially reduced cutaneous microhemodynamics. One can make a hypothesis that this increase was caused by the registered strengthening of oscillations of endothelial genesis in comparison with the initial values, as well as by the direct effect of HIPMT on the vascular wall. The latter is confirmed by the established improvement of intrinsic myogenic vasomotions 0.07–0.145 Hz, which indicates the state of the oscillatory component of the precapillary muscle tone regulating the blood flow in the nutrient channel. Our data correlated with the results of experimental studies by Smith et al. on rats [30]. The authors found that when pulsed electromagnetic fields were used, a 9 % increase in the diameter of the arteriolar microvessels was observed, which, according to the Hagen-Poiseuille law, implies an increase in the blood flow by about 40 %. Tepper et al. showed a positive effect of pulsed electromagnetic fields (PEMF) on angiogenesis. In vivo the exposure to PEMF increased angiogenesis by more than two times [31]. The above findings are supported by the study of Diniz et al., who found that PEMF results in increased synthesis of nitric oxide (NO), which has an effect on the vascular wall in addition to its vasodilatory effect [32]. Klopp RC et.al. in their work investigated the effect of low-frequency pulsed electromagnetic field (< 35 μTl) on the state of microcirculation in patients with diabetic polyneuropathy and trophic lesions of the foot [33]. Their series of placebo-controlled studies on a random sample of patients with the above pathology resulted in the improvement of microcirculation by restoring physiological vasomotion of the small arterioles and venules.

After 10 HIPMT procedures, a decrease in the initially increased cutaneous blood perfusion was found in patients, who initially had had predominant vasodilatation of the arterioles. It can be assumed that the decrease was due to the reported decline of initially increased oscillations of the endothelial genesis. Before the course application of HIPMT in these patients, these slow nitric oxide (NO)-related oscillations had dominated the overall level of vasomotion, causing vasodilation and increased blood perfusion. However, the use of HIPMT resulted in the elimination of microcirculatory disturbances. A decrease in the contribution of the heart and respiratory oscillations was observed, indicating unloading of the venular link.

Based on the LDF study, significant disturbances at the microcirculatory level were detected for the first time in patients with CIPN. Our results convincingly demonstrate that the use of HIPMT in patients with CIPN has a corrective and regulating effect on the microcirculatory system.

The main limitations of our proposed clinical intervention are acute infections, blood diseases and haemorrhagic syndromes, and the presence of a pacemaker in the patient. This technique is used in cancer patients who have undergone radical anti-tumour treatment in the absence of metastases and relapses.

CONCLUSION

Thus, we can conclude that the developed HIPMT technique is effective and safe in patients with CIPN. We have obtained reliable positive changes in the main efficacy criteria characterizing the state of microcirculation. It was found that HIPMT leads not only to the improvement of microcirculation in the extremities due to the normalization of the arterial vessel tone, elimination of venous stasis and increase of the nutritive blood flow, but also has an analgesic effect, improves the initial impaired sensitivity and generally improves the quality of life in patients with CIPN. The data obtained give grounds to continue scientific research with the use of HIPMT in rehabilitation programmes for patients with CIPN in other medical institutions in compliance with treatment protocols.

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Ethics Approval. The authors declare that all procedures used in this article are in accordance with the ethical standards of the institutions that conducted the study and are consistent with the 2013 Declaration of Helsinki. The study was approved by the Local Ethical Committee of National Medical Research Centre for Rehabilitation and Balneology, Moscow, Russia (Protocol No. 2 of 14.01.2021).

Data Access Statement. The data that support the findings of this study are available on reasonable request from the corresponding author.

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