Magnetic Field Therapy in Patients With Cytostatics-Induced Polyneuropathy: A Prospective Randomized Placebo-Controlled Phase-III Study

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No causal treatment for chemotherapy-induced peripheral neuropathy (CIPN) is known. Therefore, there is an urgent need to develop a therapy for CIPN. Only scarce clinical data are available concerning magnetic field therapy (MFT) in this context. We conducted a unicentric, randomized, double-blind, placebo-controlled phase-III trial of an MFT device versus placebo. In this study, we randomized 44 patients with CIPN to two treatment groups, where 21 patients were treated with MFT (Group 1) and 23 patients received placebo (Group 2). We evaluated the efficacy of MFT at baseline (T_1), after 3 weeks of study treatment (T_2), and after 3 months of study treatment (T_3). The primary endpoint was nerve conduction velocity (NCV), while secondary endpoints were the Common Toxicity Criteria (CTCAE) score and the Pain Detect End Score at T_3. Seventeen of the patients in Group 1 and 14 patients in Group 2 completed the respective study treatment. The primary endpoint, significant improvement of NCV at T_3, was achieved by MFT ($P = 0.015$), particularly for sensory neurotoxicity of the peroneal nerve. Also, in respect to the secondary endpoints, significant improvement ($P = 0.04$) was achieved in terms of the patients' subjectively perceived neurotoxicity (CTCAE score), but not of neuropathic pain ($P = 0.11$). From data in the randomized study presented here, a positive effect on the reduction of neurotoxicity can be assumed for the MFT device. Patients with sensory neurotoxicity in the lower limbs, especially, should therefore be offered this therapy. Bioelectromagnetics. 38:85–94, 2017.

Keywords: cancer rehabilitation; CIPN; polyneuropathy; chemotherapy; magnetic field therapy

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) has gradually emerged as a significant long-term toxicity in cancer patients [Hausheer et al., 2008; Wolf et al., 2008]. In this context, it particularly affects patients with colon, bronchial, breast, and ovarian carcinoma, as well as non-Hodgkin lymphomata, head and neck tumors, and germ cell cancers, because these tumors are primarily treated with platinum compounds, taxanes, or vinca alkaloids [Grisold et al., 2012]. While vinca alkaloids result in axonal degeneration, platinum compounds cause demyelination of peripheral nerves [Sahenk et al., 1987; Shemesh and Spira, 2010]. In contrast, data from an electrophysiological study demonstrated that only the sensory compound was affected by CIPN, with a decrease in nerve conduction velocity (NCV), suggesting significant reduction in the number of fast fibers and a corresponding increase in the number of

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slow-conducting ones, although the total amount of active myelinated fibers was thought to be unchanged [Leandri et al., 2012].

Since CIPN is not only painful for patients, impairing their quality of life, and can even result in disability with all the respective socio-economic consequences, effective treatment is needed. Neither preventive measures nor supportive measures and drug therapies have addressed this necessity so far [Hershman et al., 2014; Loprinzi et al., 2014]. For this reason, establishing a biophysical treatment also seems advisable. Initial positive results were achieved by our own study group using low-frequency (50–100 Hz) alternating current therapy. The number of patients suffering from II° and III° sensory CIPN was reduced by 20% during 3–4 weeks of treatment [Geiger and Rick, 2007]. Additionally, Geiger et al. [2015] were the first to demonstrate the possible efficiency of using low-frequency magnetic field therapy (MFT) in patients with CIPN. A considerably larger body of data on MFT is available for the treatment of diabetic neuropathy. Particularly positive influences were found for neuropathic pain in diabetic patients using MFT [Weintraub et al., 2003; Mert et al., 2010].

The objective of this prospective, randomized, placebo-controlled phase-III study was to measure the changes of CIPN during MFT in terms of quantifiable neurophysiological qualities.

PATIENTS AND METHODS

Patients

Eligible patients were aged $\geq$18 years, with histologically confirmed carcinoma and a history of potentially neurotoxic chemotherapy. The inclusion criteria of the study were: CIPN I°–IV°, good patient compliance, life expectancy of more than 6 months. All patients were provided with information regarding the planned treatment and gave their written consent. The exclusion criteria were defined as: acute infection, diabetes mellitus, pernicious anemia, spinal canal stenosis, insufficiently controlled arterial hypertension, metal implants in close proximity to the area to be treated, pacemakers, acute cardiovascular illnesses, thromboses or arterial occlusive diseases in the area of the extremity to be treated, newly implemented or modified pain management due to CIPN within 1 week before study enrollment or during the study, and absence of written informed consent from the patient.

Study Design

The study was a unicentric, randomized, double-blind, placebo-controlled, phase-III trial of an MFT device versus placebo. The trial conformed to the Declaration of Helsinki and the Good Clinical Practice guidelines, and it was approved by the independent Ethics Commission of the German Medical Association. Patients were randomly assigned at a 1:1 ratio to receive MFT or the placebo. Randomization, study management, and data analysis were performed by the Clinical Trials Office at the Medical Center of Cancer Rehabilitation (Klinik Reinhardshöhe, Bad Wildungen, Germany). The authors and the sponsor co-developed the trial protocol, and all had access to the primary data after study completion. 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. Furthermore, all authors vouch for the accuracy of the data.

MAGCELL Device

For patient treatment, the magnetic cell stimulator MAGCELL MICROCIRC (PHYSIOMED ELEKTROMEDIZIN, Schnaittach, Germany) was used, which is a hand-held and battery-powered device. No coils were used for field generation. Instead, four 45° segments of a special magnetic material were mounted symmetrically on a pivoting disc (diameter: 6 cm, area: 28 cm^2). The magnetically active disc area was fully available for treatment. Disc rotation was regulated in increments of 2 Hz to produce frequencies in the range from 4 to 12 Hz. At the end of the therapeutic cycle (5 min), the device stopped automatically. Neither cycle length nor frequency could be changed manually. However, the device could be switched off at any time, if necessary.

Rotation of the magnetic disc was provided by a microprocessor-controlled DC motor. Quasi-sinusoidal magnetic fields were obtained in this way. On the device surface, a magnetic flux density of 420 mT (peak-to-peak) was measured by means of the MP-U device; at a tissue depth of 1 cm, the flux density was still 105 mT. Reduction of the flux density with increasing depth was of no concern, since the therapeutic target in this study were nerves located close to the surface (no more than 1 mm below the surface).

Relevant parameters for the biomedical activity of magnetic fields varying over time are the electric field strength and, in particular, the electric current density induced in the therapeutically relevant target tissue. Computational examples based on the law of induction are given, for example, by Bassen et al. [1992] or Schimmelpfeng and Dertinger [1997]. Using the diameter of the magnetically active area (6 cm), the flux density on the device surface (420 mT), and the average frequency of the therapeutic cycle (8 Hz), an induced field strength of 320 mV/m can be

calculated. This quantity is of advantage for modeling effects in electrically non-conducting tissues. Multiplication of the field strength with specific electric conductivity of the target tissue (nerve) yields the electric current density. Electric conductivity can be computed from electric resistance data measured in various tissues [Rush et al., 1963; Geddes and Baker, 1967]. A value of 0.17 S/m for nerve tissue results in a current density of 55 mA/m^2. Internationally, responses to current densities exceeding 10 mA/m^2 are qualified as well established. Since the MAGCELL produces more than the quintuple of this density, the apparatus can be considered therapeutically effective. Biophysical mechanisms of action with special reference to this study are dealt with in the discussion.

Finally, from current density and exposure time per session (300 s), the energy dose can be calculated. Assuming that only the dose induced in a small volume (1 cm^3) around the target nerve is relevant for our study, the effective figure is calculated to amount to 54 $\mu J/cm^3$. This figure is several orders of magnitude lower than the level of "natural" (e.g., thermal) energies present in biological matter. An explanation as to why such extremely low electromagnetic energies are effective at all is offered by the so-called "Stochastic Resonance" effect published earlier in this journal [Kruglikov and Dertinger, 1994].

MAGCELL placebo devices were identical to the therapy instruments, except that the magnetic sectors were replaced by non-magnetic elements. Neither the patient nor the doctor in attendance could distinguish between the two types.

Study Endpoints, Treatment, and Assessments

The working hypothesis was that MAGCELL is superior to placebo in the improvement of NCV. Therefore, the primary endpoint was the NCV at the end of the study (T_3). Secondary endpoints included the Common Toxicity Criteria (CTCAE) score and Pain Detect End Score, also at T_3.

Each patient received MFT twice daily, in the morning and in the evening, with temporally varying intensity (4–12 Hz, 420 mT) for 5 min separately for each affected extremity. The patient was asked to lightly rest each affected palm and/or sole, one at a time, on the device. In addition, all patients were given one occupational therapy treatment in the area of the affected extremity three times a week.

At the beginning and at the end of the therapy, an assessment was made in terms of the study endpoints, and a thorough physical examination was performed, including the neurological status and a detailed survey, to prevent treatment side effects. According to the neurological examination, the severity of CIPN was recorded, based on the CTCAE form from the National Cancer Institute (NCI) prior to and after treatment. Moreover, at the beginning and at the end of the therapy, NCV (Neurowerk, Sigma Medizin-Technik, Gelenau, Germany) was measured as previously described [Wiederholt, 1969; Bock and Liesegang, 1972]. The neuropathic pain was evaluated using the painDETECT questionnaire (German Research Network on Neuropathic Pain).

Statistical Analysis and Data Handling

All patient data were recorded using standardized documentation. Data collected in this way were computerized for further evaluation, and assessed using a commercially available statistics program (Statistika, StatSoft, Hamburg, Germany). The working hypotheses were statistically significant improvements in NCV and reduction of CIPN as measured by the CTCAE and painDETECT questionnaires after 3 months of study treatment. A two-sided test was performed, and a P-value <0.05 was considered statistically significant. The level was set at $\alpha = 5\%$, power $1–\beta = 80\%$. For the study, 22 patients per group were taken as the random sample size for the primary outcome. The expected dropout rate ($5\% = 2.2$ participants) was based on a pilot trial and general experience with short intervention periods [Geiger et al., 2015]. The total random sample size was thus $n = 44$ patients. Differences recorded between the two groups were represented as box and whisker plots based on mean value and standard deviation, minimum and maximum, and checked for normal distribution by the Shapiro Wilk test. With regard to the CTCAE scale, the painDETECT questionnaire, and the NCV, the two groups were compared using the Mann and Whitney test, while the Wilcoxon test for paired differences was used for comparison of the values from the initial examinations with those from the final examinations.

The study was devised in compliance with the "intent-to-treat" principle, that is, all protocol-compliant patients included in the study were included in the final analysis.

RESULTS

Study Population

From May 2010 to March 2012, 44 patients, of which 31 were women (70%) and 13 men (30%), suffering from CIPN were randomized, with 21 patients being assigned to Group 1 (MFT) and 23 patients to Group 2 (placebo). Three weeks after study enrollment (T_2), 20 and 21 patients were evaluable in Group 1 and

Group 2, respectively. By the end of the study (T_3), a further 10 patients, 3 in Group 1 and 7 patients in Group 2, had quit the study. Thus, only 17 patients with MFT and 14 patients with the placebo completed the study treatment (Fig. 1). The median age of the groups was 58 years (range: 28–73 years in Group 1 and 43–73 years in Group 2). Before study enrollment, all patients had received potentially neurotoxic chemotherapy as part of their cancer treatment. More patients in Group 1 had been treated with platinum-based chemotherapy than had been in Group 2. The median number of chemotherapy cycles received by the patients was six in both groups (range: 2–12 cycles in Group 1, and 6–16 cycles in Group 2), and the median period between the last chemotherapy and the beginning of the study treatment was 91 days (range: 14–774 days) in Group 1, and 85 days (range: 13–1380 days) in Group 2. The median study therapy duration per patient was 103 days (range: 19–186 days) in Group 1, and 123 days (range: 11–276 days) in Group 2. Cancer diagnoses were not balanced well, either. Nearly half of the patients in Group 2 suffered from breast cancer, as opposed to one-third of the patients in Group 1. All differences were statistically insignificant (Table 1).

Neurological Outcomes

Both in Group 1 (MFT arm) and Group 2 (placebo arm), neuropathic complaints abated during

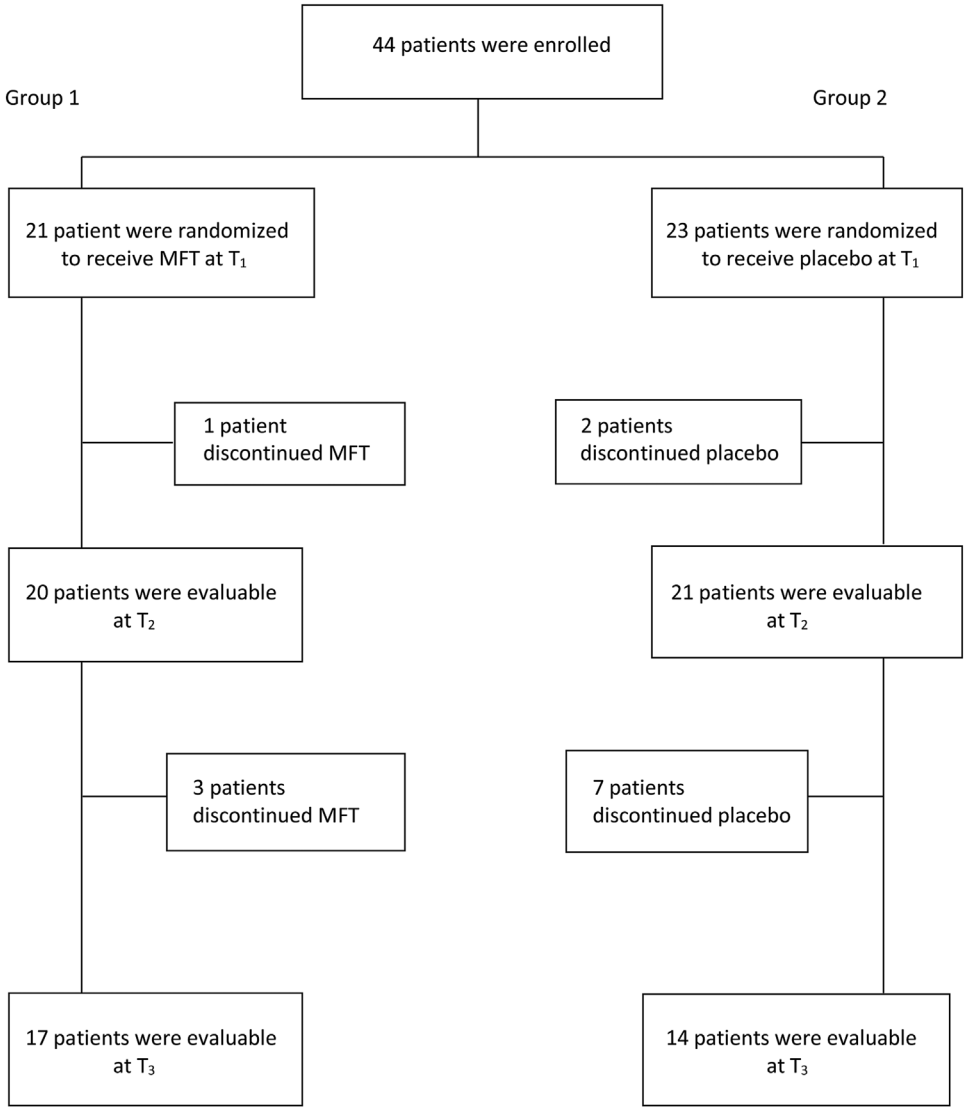


Fig. 1. Study populations. MFT, magnetic field therapy; T_1, study entry; T_2, 3 weeks of study treatment; T_3, 3 months of study treatment.

TABLE 1. Patient Characteristics

	MFT ($n=21$)	Placebo ($n=23$)
	n (%)	*n* (%)
Age (years)		
Median	58	58
Range	28–73	43–73
Gender, *n* (%)		
Male	6 (29)	7 (30)
Female	15 (71)	16 (70)
Diagnosis		
Lymphoma	4 (19)	2 (9)
Breast	7 (33)	11 (48)
Ovarian	4 (19)	2 (9)
Colorectal	5 (24)	5 (22)
Other	1 (5)	3 (12)
Chemotherapy cycles (quantity)		
Median	6	6
Range	2–12	6–16
Cytostatics, *n* (%)		
Platinum	10 (48)	6 (26)
Taxane	10 (48)	11 (48)
Vinca alkaloids	3 (14)	3 (13)
Other	9 (43)	8 (35)
Time from chemotherapy until randomization (days)		
Median	91	85
Range	14–774	13–1380
Duration of study treatment (days)		
Median	103	123
Range	19–186	11–276

MFT, magnetic field therapy; *n*, number.
All differences were not statistically significant with $P > 0.05$.

the study, in terms of subjective perception documented in the CTCAE questionnaire. This effect is particularly noticeable for all neurological qualities in the context of III° toxicities. Consequently, reduction occurred from III° to I° or II° toxicities and even to complete disappearance of neural injury (Table 2). The total CTCAE score was also significantly reduced in both groups. However, these differences were not significant in a comparison of the two groups. Nevertheless, a statistically significant difference at T_2 (4 points in Group 1 and 7.5 points in Group 2; $P = 0.042$) and T_3 (2 points in Group 1 and 3 points in Group 2; $P = 0.04$) measurements between the MFT and placebo groups was established (Fig. 2).

In the measurement of sensory neuropathy of the ulnar nerve at T_1–T_2, a statistically significant improvement of the mean NCV from 49 m/s (range: 26–64 m/s) to 55 m/s (range: 32–72 m/s) was found. In comparison to the placebo group, this effect was also statistically significant ($P = 0.021$). While in the MFT group there was no significant difference between times T_2 and T_3, in the placebo group a significant improvement from 50 m/s (range: 45–56 m/s) at T_2 to 58 m/s (range: 48–68 m/s) at T_3 was measured ($P = 0.013$). However, compared to the MFT group this difference was not significant. Neither was there any significant difference between individual times in a comparison of the two groups (Fig. 3a).

The NCV of the peroneal nerve displayed pathological values for both groups at all three measuring times. The sensory neuropathy of the peroneal nerve also displayed significant improvement in the mean NCV of the patients in Group 1. While at T_1 a mean value of only 18 m/s (range: 10–25 m/s) was measured, at T_2 a mean NCV of 28 m/s (range: 12–51 m/s) was recorded. This difference just fell short of being significant ($P = 0.084$). At the end of the study (T_3), further significant improvement ($P = 0.039$) in the NCV to 40 m/s (range: 18–53 m/s) compared to T_2 was recorded. There were no significant differences between measuring times in the placebo group. In a comparison of the two study groups, there were no significant differences between the measuring times, either. There was only one significant difference between the two groups at time T_3 in favor of the MFT patients ($P = 0.015$) (Fig. 3b).

Based on the Pain Detect End Scores, during the study period significant abatement in neuropathic pain occurred in Group 1 between T_1 and T_2, amounting to a decrease from 16 points (range: 7–28 points) to 11 points (range: 2–21 points) ($P = 0.001$) and between T_1 and T_3 to just 6 points (range: 0–18 points) ($P = 0.001$). However, in the placebo group similarly significant abatement in neuropathic pain occurred between T_1 or T_2 and T_3, from 13 points (range: 9–14 points) and 12 points (range: 4–25 points) down to 3 points (range: 1–14 points) ($P = 0.001$ or 0.002). Neither these differences within the groups nor the score for the individual measuring times differed significantly between the study arms (Fig. 4).

DISCUSSION

This study is the first to subject MFT to double-blind testing in a randomized placebo-controlled manner in patients with CIPN. Furthermore, it is the first trial to show a significant benefit of a therapeutic intervention for CIPN compared to the placebo. The novel finding is that MFT is the only non-pharmacological intervention offering a significant benefit in the treatment of patients with CIPN. The primary study endpoint, significant improvement of NCV, was achieved by MFT at the end of the study (T_3). Also, in respect to the secondary endpoint, a significant improvement in the patients' subjectively perceived neurotoxicity (CTCAE score)

TABLE 2. Neurotoxicity in Accordance With CTCAE in Group 1 and Group 2 at T_1–T_3

	None		I°		II°		III°	
	Group 1 (*n*/%)	Group 2 (*n*/%)	Group 1 (*n*/%)	Group 2 (*n*/%)	Group 1 (*n*/%)	Group 2 (*n*/%)	Group 1 (*n*/%)	Group 2 (*n*/%)
Ataxia								
T_1	0	0	3/14	2/9	7/33	10/44	11/52	11/48
T_2	2/10	2/10	7/35	5/24	8/40	10/48	3/15	4/19
T_3	10/60	1/7	5/29	11/79	2/11	1/7	0	1/7
Peripheral motor neuropathy								
T_1	2/9	0	3/14	5/22	10/48	8/35	6/29	10/44
T_2	13/65	6/29	2/10	7/33	5/25	7/33	0	1/5
T_3	11/65	2/14	6/35	10/71	0	2/14	0	0
Peripheral sensory neuropathy								
T_1	2/10	1/4	3/14	1/4	8/38	8/34	8/38	13/56
T_2	1/5	2/9	9/45	7/33	8/40	8/38	2/10	4/19
T_3	4/23	3/21	12/71	10/71	1/6	1/7	0	0
Myopathy								
T_1	6/28	3/13	6/28	5/22	6/28	9/39	3/14	6/26
T_2	16/80	6/29	1/5	8/38	3/15	7/33	0	0
T_3	14/82	10/71	3/17	3/21	0	1/7	0	0
Myalgia								
T_1	7/33	8/35	10/47	3/13	4/19	7/30	0	5/22
T_2	17/85	13/62	2/10	5/24	1/5	3/14	0	0
T_3	17/100	14/100	0	0	0	0	0	0
Neuropathic pain								
T_1	1/5	3/13	6/28	0	8/38	11/48	6/28	9/39
T_2	3/15	2/10	13/65	5/24	4/20	12/57	0	2/9
T_3	11/65	8/57	5/29	4/28	1/6	2/14	0	0

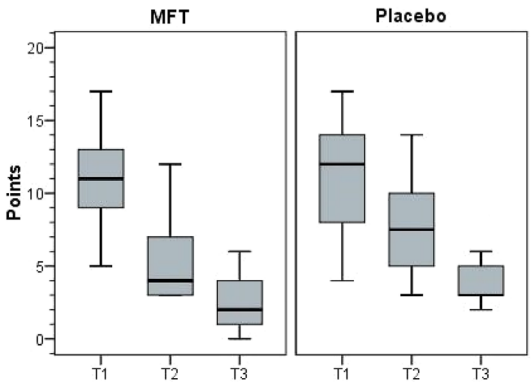
CTCAE, common terminology criteria for adverse events; pts, patients.
T_1: Group 1 = 21 pts., Group 2 = 23 pts.; T_2: Group 1 = 20 pts., Group 2 = 21 pts.; T_3: Group 1 = 17 pts., Group 2 = 14 pts.

was achieved by MFT. The second secondary endpoint, improvement of neuropathic pain (Pain Detect End Score), was not achieved.

Benefits of the study can be found in the largely well-balanced patient characteristics, whereby patients in the MFT arm had received more platinum-based therapy and were treated more briefly with MFT. The positive effect of MFT might have been more pronounced if the patient characteristics had been distributed more evenly. Moreover, pathological values were found for NCV, particularly for the peroneal nerve, which proves that the measuring method selected in this case produced reliable values. In this connection, it was established that MFT has a particularly positive impact when CIPN is more strongly manifested. This effect might be an explanation for the perceptible decline in III° toxicities, as illustrated in Table 2.

However, reduction in neurotoxicity occurs not only in the MFT arm, but also in the placebo arm. The most plausible explanation for this is that during the study, both arms were subject to spontaneous regeneration. In addition, particularly in respect to the patients' subjective assessment of neurotoxicity and neuropathic pain, a psychogenic effect of the therapy as well as of the placebo device cannot be excluded. However, a possible psychogenic effect cannot have influenced the NCV, which is regarded as a strong objective parameter. The improvement at this point must most likely be interpreted as a result of regeneration of nerve fibers by MFT. The particularly strong manifestation of this effect in areas of the peripheral nerves of the lower limbs may be attributable to the fact that in our study population, the crural nerves were affected particularly strongly by neurotoxicity, and at the beginning of the study very low mean values for NCV were recorded. In this situation, MFT seems to have a particularly positive effect and to be more effective than for only minor NCV reductions.

To further support these results, reference is made to the previous pilot study conducted by our study group, which formed the basis for planning the randomized study presented here. Results of the pilot study indicate a trend to positive effect on CIPN in terms of most neurophysiological qualities, although the therapy was conducted for only 3–4 weeks.



Group		CTCAE T_2 vs T_1	CTCAE T_3 vs T_1	CTCAE T_3 vs T_2
MFT	Z	-3.744	-3.625	-3.34
	Significance (two-tailed)	**<.001**	**<.001**	**.001**
Placebo	Z	-3.54	-3.047	-2.772
	Significance (two-tailed)	**<.001**	**.002**	**.006**
MFT vs Placebo	Z	-.793	-.818	-.281
	Significance (two-tailed)	.428	.413	.779
		T_1	T_2	T_3
MFT vs Placebo	Z	-1.699	-2.032	-2.054
	Significance (two-tailed)		**.042**	**.04**

Fig. 2. CTCAE scores in Group 1 and Group 2. In both groups, there are significant differences between T_1 and T_2, between T_1 and T_3, and between T_2 and T_3. Within the groups, these differences are not significant in a comparison of the two arms. Furthermore, significant differences between the MFT and placebo groups at T_2 and T_3, but not at T_1, were established. CTCAE, common terminology criteria for adverse events; MFT, magnetic field therapy; T_1, baseline (at study enrollment), T_2, after 3 weeks of study treatment; T_3, after 3 months of study treatment; Z, standard deviation.

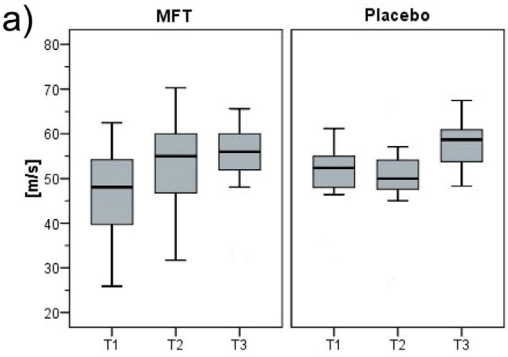
Components of sensory ataxia and neuropathy showed particular improvement, as CIPN predominantly consists of sensory, rather than motor, symptoms. Evaluation of neuropathic pain, which was documented using a visual analogue scale and the painDETECT questionnaire, demonstrated low and non-significant alleviation of symptoms. When comparing the situation before and after therapy, the sensory neurography showed a statistically significant increase of the NCV on the sural nerve, which could represent an objectifiable effect of MFT [Geiger et al., 2015]. Ultimately, data of the pilot study match those of the randomized study and can thus be regarded as confirmed. In the pilot study, a therapeutic effect could also be documented within just 3 weeks, which in the randomized study proved to be significant for the NCV of the ulnar nerve and a trend for the peroneal nerve (Fig. 3a and b).

The clinical practice guideline of the American Society of Clinical Oncology published in June 2014 describes limited evidence presented by recent studies [Hershman et al., 2014]. Only a pilot study of 16 patients with refractory CIPN had, when testing a cutaneous electrostimulation device, shown a statistically significant improvement in pain scores (59% reduction at 10 days, $P < 0.001$) [Smith et al., 2010]. However, another very small, randomized study, not published as a full paper until now, comprising 14 patients, failed to demonstrate a benefit of electrostimulation therapy [Campbell et al., 2013].

Biophysical Mechanisms of Action

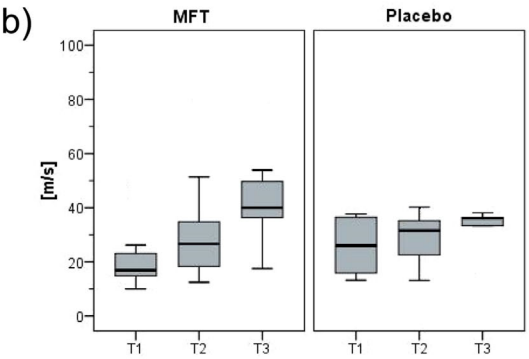
As outlined in Patients and Methods (see description of the MAGCELL device above), the electric current density induced in the target tissue by the magnetic field is accepted to be the relevant parameter to correlate with biologic response. However, since the device uses rotating permanent magnets to generate a temporally varying magnetic field, the magnetic vector itself could possibly contribute to the therapeutic effect. This question was addressed in a study

a)



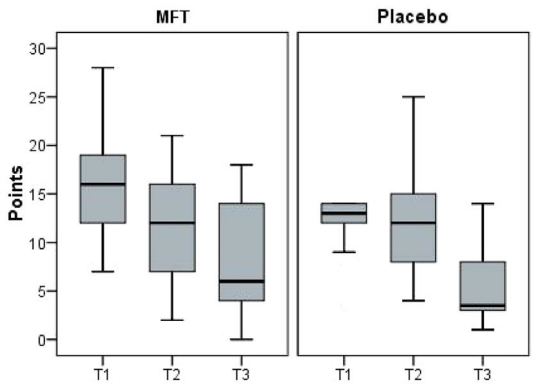
Group		Sensory neurography T2 vs T1	Sensory neurography T3 vs T1	Sensory neurography T3 vs T2
MFT	Z	-2.415	-3.337	-.710
	Significance (two-tailed)	**.016**	**.001**	.478
Placebo	Z	-.610	-2.761	-2.480
	Significance (two-tailed)	.542	**.006**	**.013**
MFT vs Placebo	Z	-2.291	-.298	-1.787
	Significance (two-tailed)	**.021**	.769	.077
		T1	T2	T3
MFT vs Placebo	Z	-.911	-1.476	-1.094
	Significance (two-tailed)		.141	.279

b)



Group		Sensory neurography T2 vs T1	Sensory neurography T3 vs T1	Sensory neurography T3 vs T2
MFT	Z	-1.73	-2.769	-2.068
	Significance (two-tailed)	.084	**.006**	**.039**
Placebo	Z	-.675	-1.601	-1.22
	Significance (two-tailed)	.5	.109	.221
MFT vs Placebo	Z	-1.241	-1.628	-.536
	Significance (two-tailed)	.223	.109	.597
		T1	T2	T3
MFT vs Placebo	Z	-.101	-.088	-2.411
	Significance (two-tailed)		.931	**.015**

Fig. 3. **a**: Sensory neurography on ulnar nerve. In the MFT group, a significant difference was established between T_1 and T_2, and between T_1 and T_3. There were also significant differences between T_1 and T_3, and between T_2 and T_3 in the placebo group. In the comparison between the two groups, there was a significant difference only between T_1 and T_2. **b**: Sensory neurography on peroneal nerve. A significant difference was established between T_1 and T_3, and between T_2 and T_3, only in the MFT group, but not in the placebo group. In the intergroup comparison, a significant difference was established only at T_3. MFT, magnetic field therapy; T1, baseline (at study enrollment), T2, after 3 weeks of study treatment; T3, after 3 months of study treatment; Z, standard deviation.



Statistics for Figure 4

Group		Pain-Detect Score T_2 vs T_1	Pain-Detect Score T_3 vs T_1	Pain-Detect Score T_3 vs T_2
MFT	Z	-3.286	-3.359	-1.709
	Significance (two-tailed)	**.001**	**.001**	.087
Placebo	Z	-1.817	-3.181	-3.048
	Significance (two-tailed)	.069	**.001**	**.002**
MFT vs Placebo	Z	-2.544	-.222	3.533
	Significance (two-tailed)	.085	.924	.109
		T_1	T_2	T_3
MFT vs Placebo	Z	-.224	-1.17	-1.614
	Significance (two-tailed)		.247	.116

Fig. 4. Pain detect end score. A significant difference in the reduction of neuropathic pain was established between T_1 and T_3 in both study groups. In addition, there is a significant difference between T_1 and T_2 in the MFT group, and between T_2 and T_3 in the placebo group. The differences between the two groups were not statistically significant. MFT, magnetic field therapy; T_1, baseline (at study enrollment), T_2, after 3 weeks of study treatment; T_3, after 3 months of study treatment; Z, standard deviation.

conducted at the Institute of Anatomy, Technical University of Dresden [Funk et al., 2014], where stimulation of blood flow in fingers of volunteers by the MAGCELL was investigated. A strong effect was observed after a single local treatment, leading to 37% increase in blood flow above the control figures ($P < 0.001$). When the device was shut off (only the permanent magnetic field remaining active), an increase by only 14% was achieved. Although this effect, which is due to the Lorentzian force acting on ions in the flowing blood, was not statistically significant, its contribution to blood flow stimulation still cannot be fully ruled out. Clarification of this question would require analogous investigations using low-frequency currents applied via electrodes, which were beyond the scope of our study. However, a study in healthy volunteers aiming at investigating electrode-based stimulation of microcirculation in skin by TENS (Trancutaneous Electrical Nerve Stimulation) resulted in 40% increase of microcirculation [Wikström et al., 1999], which is almost identical to the figure of 37% achieved with the MAGCELL device. This result argues against a significant contribution of the magnetic vector. In addition to increased blood flow, Funk et al. [2014] observed rapid onset and significant enhancement of NO radical release (43%, $P < 0.001$) when cultured HUVEC cells were treated with the MAGCELL. This can explain the increase in blood flow in terms of mediator-induced dilatation of micro-vessels.

Among the biological mechanisms promoting the clinical effects presented in this study, nerve regeneration is of particular significance. Neurite outgrowth, elongation, and other parameters have been investigated in several systems under exposure to electrical DC fields and various pulsating electromagnetic fields [Macias et al., 2000]. However, it is questionable whether these results also apply to nerve fibers damaged by cytostatic agents. On the other hand, potent stimulation of microcirculation by the

MAGCELL [Funk et al., 2014] may effectively support regeneration of the damaged nerve fibers, since it improves the physiological and nutritional status of the embedding tissue.The high magnetic flux density provided by the MAGCELL enables even treatment of targets located at a depth of up to 1 cm. A recent clinical study on patients with knee joint osteoarthritis showed benefits from this [Wuschech et al., 2015]. Pain, stiffness, and disability in daily activities improved over the placebo group to a statistically highly significant extent.

In summary, the MAGCELL combines several outstanding features such as: electromagnetic properties superior to other devices, despite hand-held design; battery-powered and microprocessor-controlled operation; and action unhampered by clothes and bandages. Statistically significant effects and the therapeutic benefit from using this device are well documented in studies by Funk et al. [2014] and Wuschech et al. [2015]. Based on significant therapeutic effects observed in the present study, patients with sensory neuro-toxicities should be offered this therapy.

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