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Effect of BEMER Magnetic Field Therapy on the Level of Fatigue in Patients with Multiple Sclerosis: A Randomized, Double-Blind Controlled Trial

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Abstract

Objectives: Electromagnetic field therapy has been reported to be beneficial in patients with multiple sclerosis (MS) with significant fatigue. This study was designed to evaluate the long-term effects of Bio-Electro-Magnetic-Energy-Regulation (BEMER) on MS-related fatigue.
Design: This was a monocenter, patient- and rater-blinded, placebo-controlled trial.
Patients: There were 37 relapsing-remitting patients with MS with significant fatigue in the study.
Intervention: The intervention consisted of BEMER magnetic field treatment for 8 minutes twice daily in comparison to placebo for 12 weeks.
Outcome measures: The primary outcome criterion was change in the Modified Fatigue Impact Scale (MFIS) between baseline and 12 weeks. The secondary outcome criteria were changes of the Fatigue Severity Scale (FSS), a general depression scale–long version (ADS-L), Multiple Sclerosis Functional Scale (MSFC), and the Expanded Disability Status Scale (EDSS).
Results: There was evidence of a significant difference of MFIS value (primary outcome criterion) after 12 weeks in favor of the verum group (26.84 versus 36.67; $p = 0.024$). In addition, FSS values were significantly lower in the verum group after 12 weeks (3.5 versus 4.7; $p = 0.016$). After 6 weeks' follow-up, verum and placebo groups did not differ in experienced fatigue (MFIS, FSS). Regarding the subscales of the MFIS, there was a significant decrease in physical ($p = 0.018$) and cognitive ($p = 0.041$), but not in psychologic subscales only in the verum group regarding the timepoints baseline and 12 weeks. BEMER therapy was well tolerated.
Discussion: In this pilot study, we were able to demonstrate a beneficial effect of BEMER intervention on MS fatigue. As this was only a pilot study, trials with more patients and longer duration are mandatory to describe long-term effects.

Introduction

Fatigue is among the most common symptoms of multiple sclerosis (MS), affecting at least 75% of patients,[1] for many of whom it constitutes one of the worst and most distressing features.[2] Fatigue is reported in all clinical phenotypes of MS and affects patients of all ages.[3] This symptom is an integral part of the disease process that is usually present at the time of diagnosis and in some cases represents one of the reasons for which patients originally consult a neurologist. Fatigue is not closely related to physical signs of disability or with magnetic resonance imaging markers of disease activity, although it does seem to increase when the patient experiences relapses.[2,4] Fatigue is a major cause of unemployment in patients with MS.[5–7] The etiology and pathophysiology of MS-related fatigue remain unknown. Studies have failed to demonstrate an association between MS-related fatigue and the level of disability, clinical disease subtype, or gender.[8] Imaging studies using positron emission tomography suggest that fatigue in MS is related to hypometabolism of specific brain areas, including the frontal and subcortical circuits.[9] Different components of fatigue have been described such as

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motor and cognitive fatigue and lassitude. Management strategies include medications, exercise, and behavioral therapy.[10] There have been reports on positive effects of immunomodulatory drugs on fatigue.[11] However, the efficacy of treatment remains quite disappointing.[10]

In addition to pharmacological interventions, non-pharmacological treatments including yoga, aerobic exercises, cooling therapy, and energy conservation techniques have been used sucessfully. A recent meta-analysis summarized promising data on electromagnetic field devices[12]: Richards et al. and Lappin et al. demonstrated a positive effect of low-level pulsed, electromagnetic field devices worn by the patients.[13,14] Unfortunately, there were no long-term data available. Although Mostert and Kesselring showed disappointing data on pulsed magnetic field therapy as an additional effect of a multimodal neurological rehabilitation program on fatigue,[15] Sandyk documented improved physical and cognitive fatigue in case studies of patients with MS after a course of treatment.[16,17] It is only hypothetical why there is a positive impact of magnetic field therapy on MS fatigue. Factors such as energy metabolism, oxygen supply, and microcirculation are discussed.[12] The tendency for positive results warrants further investigation using a double-blinded, controlled protocol. There are different patterns of pulsed magnetic field therapies available. Bio-Electro-Magnetic-Energy-Regulation (BEMER, Innomed International AG, Lichtenstein) therapy uses broadband, extremely weak, low frequent pulsed electromagnetic fields induced by flexible, flat electric coils.[18] Although there have been several anecdotal positive reports with this device, no placebo-controlled, double-blinded study is currently available in the literature.

Our study was designed to evaluate the long-term effect of BEMER therapy in patients with MS with significant fatigue in a typical outpatient setting: Patients with relapsing-remitting MS and significant fatigue were randomized to BEMER or placebo treatment and were evaluated after 6 and 12 weeks using different fatigue scales. We hypothesize that patients with relapsing-remitting MS who use the BEMER for 8 minutes twice a day for 12 weeks, will experience improvement in fatigue, compared to patients who use a placebo device.

Methods

The present study was a randomized, patient- and rater-blinded, placebo-controlled trial conducted in a neurological outpatient center in Dresden. The study lasted 3 months and was performed between 2006 and 2007. The study protocol was approved by the international ethical committee Freiburg, Germany (EC 02/TS/06). It was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and pertinent national legal and regulatory requirements. Prior to study entry, each patient provided written, informed consent and was free to withdraw from the study at any time for any reason without consequences on the care provided.

Forty-one (41) ambulatory patients with clinically definite, relapsing-remitting MS were randomly assigned to treatment with BEMER or to sham therapy twice a day over 3 months. The sample size was calculated before using the software nQuery Advisor 6.0 (Statistical Solutions, Cork, Ireland) with a power of 97% (two-sided test, $\alpha = 0.05$). A total of 4 patients were lost to follow-up (2 verum, 2 placebo); all 4 had no time left for the two applications per day. Data analysis was therefore restricted to the remaining 37 patients with complete data sets because for the lost 4 patients, no follow-up data were available. Female and male patients between 18 and 65 years were enrolled in the study when they (1) had relapsing-remitting MS as defined by Poser et al.,[19] (2) accepted the informed consent, and (3) had significant fatigue as reported by the patient. Reasons to refuse were (1) previous therapy with pulsed electromagnetic fields, (2) acute relapse of MS within the last month as we were interested in the effect of magnetic field therapy on chronic fatigue that can be interfered with by an acute relapse, (3) psychiatric or neurological disorders other than multiple sclerosis, (4) actual treatment with amantadine, aminopyridine, or modafinil as drug therapy for fatigue to avoid interference of anti-fatigue effects of drugs and magnetic field therapy or (5) pregnancy. Randomization to verum and placebo group was performed by block randomization. Patients and physician/statistician were blinded. All patients were told in the informed consent document that there was a 50% chance to receive placebo and verum treatment. All devices looked identical and were numbered. The placebo-verum coding was only used for the final analysis. The success of blinding was not evaluated, and patients were unblinded after the end of the study.

The BEMER therapy was used to stimulate by extremely weak, low-frequency pulsed electromagnetic fields (with mean of 14 μT) induced by flexible, flat electric coils. The BEMER signal consists of a series of half-wave-shaped sinusoidal intensity variations. Starting out with low values, the intensity initially increases slowly and then drops again to a value that, however, is located at a higher level within the impulse than the initial value. This sequence keeps repeating itself, while the intensity variations gets denser and the drift from the zero line gradually increases. Correspondingly, the ups and downs keep getting steeper. The intensity process repeats itself 33.3 times per second. After 2 minutes, the magnetic field changes its polarity. The duration of the signal sequences was set empirically via a control device to a period of 8 minutes. In this way, the magnetic field of the BEMER 3000 systems is, in the first approximation, a typical pulsing constant electromagnetic direct current field that is asymmetrical to the zero line. The BEMER device includes a control device that produces the patented BEMER signal and that could be turned on/off by the patient. It is connected with an all-metal mat that is hooked up to the control device via a connecting cable and rolled out.

For this study, patients with MS were asked to lie down on the mattress for 8 minutes twice every day at their private home. Compliance of the patient was controlled by a special diary. In the treatment group (verum), the BEMER mattress was activated whereas in the control group (placebo), no magnetic field was generated although there was the typical BEMER sound.

Patients were evaluated at inclusion and after 6 and 12 weeks of treatment at the same time of day (10 AM). At each visit, patients underwent a full neurologic assessment, any relapses occurring since the previous visit were ascertained, and disability was assessed with the Expanded Disability Status Scale (EDSS).[20] Multiple Sclerosis Functional Composite (MSFC) was performed each time. Fatigue was assessed by the patient using the fatigue severity scale (FSS), a

Table 1. Demographic Characteristics of the Multiple Sclerosis Patients in the Verum and Placebo Group

	Verum	*Placebo*
N	19	18
Age	44 ± 8.3	47.5 ± 8.6
% Female	89.5%	72%
Duration of disease (years)	10.5 ± 9.8	6.8 ± 5.8
EDSS	3.7 ± 2.2	3.1 ± 1.3
MSFC	-0.7 ± 1.8	-0.4 ± 0.8
% Patients on immunomodulation	53%	89%
% Patients on GA	16%	33%
% Patients on IFN	37%	56%

Data are presented as mean ± standard deviation. EDSS, expanded disability status scale; MSFC, Multiple Sclerosis Functional Scale; GA, glatiramer acetate; IFN, interferon-β.

visual analogue scale scored from 0 (no fatigue) to 10 (maximum possible fatigue), and with the Modified Fatigue Impact Scale (MFIS)[21] in its validated German translation. This is a 21-item questionnaire that yields a total score ranging from 0 (no impact of fatigue) to 84 points (maximum impact of fatigue), as well as three subscales representing the physical (score range 0–36), cognitive (score range 0–40), and psychosocial (score range 0–8) dimensions of fatigue. Depression was evaluated by the long German version of the Center for Epidemiologic Studies Depression Scale (CES-D) general depression scale–long version (ADS-L).[22]

Group differences in MFIS, FSS, MSFC, EDSS, and ADS-L scores between verum and placebo groups at the different timepoints were evaluated by Student's *t*-test for independent samples. Changes in fatigue scores over time were statistically assessed by paired *t*-tests for the placebo and the verum group, respectively. Differences in gender group composition were assessed with a χ^2 test. All comparisons were two-tailed and a p value of <0.05 was taken as being statistically significant.

The BEMER devices were kindly supplied by Innomed International AG, Lichtenstein. No additional support was provided.

Results

Study population and baseline characteristics

Baseline demographic characteristics are presented in Table 1. Verum and placebo groups did not statistically differ in terms of age or gender group composition.

At baseline, both groups did not differ in terms of EDSS (Student's test: $t = 1.21$; not significant (n.s.)), MSFC (Student's *t*-test: $t = 0.7$; n.s.), duration of disease (Student's *t*-test: $t = 1.10$; n.s.) and ADS-L (Student's *t*-test: $t = -1.23$; n.s.). Fatigue scores (MFIS, FSS) were slightly higher in the placebo group compared to the verum group, but this effect did not reach statistical significance (Student's *t*-test: MFIS: $t = -1.36$; n.s.; FSS: $t = -1.15$; n.s.) (Table 2).

Primary outcome criterion: MFIS baseline versus 12 weeks' treatment

Regarding the primary endpoint of our study, there was evidence of a significant difference of MFIS value after 12 weeks in favor of the verum group (26.84 versus 36.67; Student's *t*-test for independent samples: $MFIS_{12weeks}$: $t = -2.36$; $p = 0.024$).

Secondary outcome criteria: Baseline versus 6 weeks' treatment

After 6 weeks' treatment, verum and placebo groups did not differ in experiencing fatigue (Student's *t*-test for independent samples; $MFIS_{6weeks}$: $t = -1.38$; n.s.; FSS_{6weeks}: $t = -2.03$; n.s.) (Table 2). However, looking at changes in fatigue over time, there was a decrease in fatigue measured by the FSS in the verum but not the placebo group after 6 weeks compared to baseline (paired *t*-test: $FSS_{6weeks/verum}$: $t = 2.68$; $p = 0.015$; $FSS_{6weeks/placebo}$: $t = 0.98$; n.s.) (Table 3). No differences for the MFIS or MFIS subscales (physical, cognitive, psychologic) over time were observed for either group (paired *t*-test: $MFIS_{6weeks/verum}$: $t = 1.14$; n.s.; $MFIS_{6weeks/placebo}$: $t = 0.98$; n.s.).

Self-rated depressive symptoms by the CES-D did not differ between groups after 6 weeks' treatment (Student's *t*-test for independent samples: $ADS\text{-}L_{6weeks}$: $t = -0.76$; n.s.). There was also no change in depressive symptoms expression over time in either group (paired *t*-test: $ADS\text{-}L_{6weeks/verum}$: $t = 0.33$; n.s. / $ADS\text{-}L_{6weeks/placebo}$: $t = 0.45$; n.s.).

Secondary outcome criteria: Baseline versus 12 weeks' treatment

In addition to significant different fatigue ratings by MFIS between the verum and placebo groups, there was evidence for a significant difference of FSS value after 12 weeks' treatment in favor of the verum group (Student's *t*-test for independent samples: $FSS_{12weeks}$: $t = -2.53$; $p = 0.016$). In the verum group but not in the placebo group, there was a

Table 2. Changes of Modified Fatigue Impact Scale (MFIS) Overall Score and as well as Physical, Cognitive, and Psychologic Subscores in Verum and Placebo Group at Baseline, 6 Weeks, and 12 Weeks

	Baseline				*6 Weeks*				*12 Weeks*			
	Verum		*Placebo*		*Verum*		*Placebo*		*Verum*		*Placebo*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
MFIS	31.68	13.24	37.83	14.26	29.21	14.85	36.06	15.25	26.84	12.061	36.67	13.253
Physical	17.21	6.78	17.72	7.84	14.58	6.70	17,5	7.91	14.11	5.801	17,72	6.47
Cognitive	12.26	7.15	16.33	6.23	11.95	8.84	15.06	6.86	10.37	6.825	15,83	6.373
Psychologic	2.74	2.38	3.78	2.42	2.68	1.64	3.50	2.07	2	1.563	3.11	1.568

Changes of MFIS overall score. Data are presented as mean ± standard deviation (SD).

Table 3. Changes of MSFC, EDSS, MFIS, FSS, and ADS-L in Verum and Placebo Group at Baseline, 6 Weeks and 12 Weeks

	Baseline				*6 Weeks*				*12 Weeks*			
	Verum		*Placebo*		*Verum*		*Placebo*		*Verum*		*Placebo*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
MSFC	−0.7	1.8	−0.4	0.8	−0.5	1.9	−0.2	0.8	−0.3	1.8	0.0	−0.8
EDSS	3.8	2.1	3.1	1.3	3.8	2.1	3.1	1.3	3.8	2.1	3.1	1.3
FSS	4.5	1.2	5.0	1.4	3.8	1.4	4.8	1.6	3.5	1.3	4.7	1.6
ADS-L	13.7	7.5	16.8	8.05	13.2	11.3	15.8	9.6	11.1	8.1	14.8	8.7

Data are presented as mean ± standard deviation (SD).
MSFC, Multiple Sclerosis Functional Scale; EDSS, Expanded Disability Status Scale; MFIS, Modified Fatigue Impact Scale; FSS, Fatigue Severity Scale; ADS-L, general depression scale–long version.

significant decrease in perceived fatigue over this 12-week period (paired *t*-test; $FSS_{12weeks/verum}$: 3.87; $p = 0.001$; $MFIS_{12weeks/verum}$: $t = 3.12$; $p = 0.006$; $FSS_{12weeks/placebo}$: 1.50; $p =$ n.s.; $MFIS_{12weeks/placebo}$: $t = 0.53$; p = n.s.). Regarding the subscales of the MFIS, there was a significant decrease in physical (paired *t*-test: $MFIS_{/phys12weeks/verum}$: $t = 2.6$; $p = 0.018$; $MFIS_{/phys12weeks/placebo}$: $t = 0$; n.s.) and cognitive (paired *t*-test: $MFIS_{/cog12weeks/verum}$: $t = 2.2$; $p = 0.041$; $MFIS_{/cog12weeks/placebo}$: $t = 0.43$; $p =$ n.s.) but not in psychologic subscales (paired t-test: $MFIS_{/psy12weeks/verum}$: t = 1.83; n.s.; $MFIS_{/psy12weeks/placebo}$: t = 1.44; n.s.) only in the verum group regarding the timepoints baseline and 12 weeks' treatment.

Self-rated depressive symptoms by CES-D did not differ between groups after 12 weeks' treatment (Student's *t*-test for independent samples: $ADS\text{-}L_{12weeks}$: $t = 1.35$; n.s.). There was a tendency for decreased depressive symptoms compared to baseline in the verum group, but this effect did not reach statistical significance (paired *t*-test: $ADS\text{-}L_{12weeks/verum}$: $t = 2.03$; (0.058/n.s.)/$ADS\text{-}L_{12weeks/placebo}$: $t = 0.89$; n.s.).

There were no significant side-effects during verum and placebo application.

Discussion

Our study was focused on effects of a new type of pulsed low-frequency electromagnetic fields of the BEMER 3000 device on MS fatigue after 6 weeks and 12 weeks. The patients were evaluated by a panel of different questionnaires (MFIS, FSS, ADS-L) in addition to MSFC and EDSS testing. Using a randomized placebo-controlled protocol, we were able to demonstrate a modest, but statistically significant advantage for the verum treatment group concerning an effect on the MFIS and FSS over a 3-month period. Although both groups showed a decrease of fatigue over the intervention time, MFIS score was significantly lower in the verum than in the placebo group 3 months later, which reflects a statistical advantage of the BEMER treatment according the predefined primary outcome criteria.

There is growing evidence in the literature of a beneficial effect of magnetic field therapy on different MS symptoms such as fatigue, bladder control, spasticity, and quality of life. Nielsen and Sinkjaer reported a reduction of spasticity by magnetic stimulation over the thoracic myelon,[23] while Sandyk reported cases of prompter recovery from fatigue following physical activity by extracranially applied electromagnetic field.[17,24]

A recent meta-analysis summarized beneficial effects of electromagnetic fields on MS fatigue, but recommended long-term studies.[12]

Other experiments have already investigated the effect of electromagnetic fields on MS fatigue so far. Lappin et al. demonstrated a reduction of MS fatigue by 0.5 points on a modified five-item scale out of the MS Quality of Life Inventory by wearing a small portable pulsing electromagnetic device next to the skin over the brachial plexus 24 hours a day for 4 weeks.[14] Expressed in relative terms, this was a decrement of fatigue by roughly 20%. The placebo effect of the sham intervention in their study was 0.36 points (about 14%). A preliminary study of the same study group with 30 patients with the same device used 24 hours per day over a 2-month period also demonstrated a beneficial effect of pulsed magnetic field therapy on a combined performance scale rating for bladder control, cognitive function, fatigue level, mobility, spasticity, and vision.[13]

In contrast, Mostert and Kesselring used a device (magnetic cell regeneration system by Santerra) that was comparable to the BEMER system as it was applied for 16 minutes twice daily. They were not able to demonstrate a beneficial effect of pulse electromagnetic field therapy as an additional component to a multimodal neurologic rehabilitation program on fatigue.[15] In comparison to our study, the level of fatigue was slightly higher as measured by the FSS (5.5). Unfortunately, other studies could not be compared regarding the baseline fatigue level because they used other scales. Because Mostert and Kesselring described a wide variability of measurements using the visual analogue scale, we decided to focus our evaluation of MS fatigue only on FSS and MFIS scales. In contrast to this study, we measured fatigue level not directly after the application of electromagnetic field therapy, but in the study center always at 10 AM. Our patients were not enrolled in a specific rehabilitation program, which may have additional positive effects on MS fatigue that may be confounded in their study. Mostert and Kesselring have already described that a special rehabilitation program with short-time exercise treatment was able to reduce MS fatigue in a significant way.[25]

Of course, there are statistical limitations of this study. Although this study was a randomized, placebo-controlled trial, the number of participants was limited, with only 19/18

patients in each treatment arm. Other studies investigated comparable numbers of patients[13,15]; only Lappin et al. investigated more than 55 patients per group, but only for 4 weeks.[14] Larger trials on this issue are needed in order to confirm the findings from this pilot study. Again, it is not possible to compare the different devices, as the physiology of magnetic field therapy is not well known. Magnetic field therapy is used in a lot of clinical settings. Unfortunately, scientific data on mechanism and so on are still missing. We are beginning to investigate physiologic changes induced by magnetic field therapy.

Conclusions

In this pilot study, we were able to demonstrate a beneficial effect of BEMER therapy on MS fatigue. Although we recognized a placebo effect, there was a statistically significant benefit for treated patients after 12 weeks. From our personal experience, MS patients suffering from MS fatigue can benefit from electromagnetic field therapy. Because devices for pulsed electromagnetic therapy like BEMER are quite expensive, we recommend individual tests for several weeks to see whether there is an individual benefit for the MS patient with significant fatigue.

Disclosure Statement

No competing financial interests exist.

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