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Effect of pulsed magnetic field therapy on the level of fatigue in patients with multiple sclerosis – a randomized controlled trial

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Twenty-five multiple sclerosis patients, taking part in a rehabilitation program, were randomly assigned to treatment with pulsed magnetic field therapy (PMFT) or to sham therapy in order to study the additional effect of PMFT as part of a multimodal neurological rehabilitation program on fatigue. Patients demographic and disease specific characteristics were recorded. Level of fatigue was measured by fatigue sverity scale (FSS) at entrance and discharge and with a visual analog scale (VAS) immediate before and after a single treatment session. The 'Magnetic Cell Regeneration' system by Santerra was used for PMFT. A single treatment lasted 16 minutes twice daily over 3–4 weeks and consisted of relaxed lying on a PMF mattress. Sham intervention was conducted in an identical manner with the PMF-device off. Patients and statistics were blinded.

Level of fatigue measured by FSS was high at entrance in both treatment group (TG) and control group (CG) (5.6 versus 5.5). Over time of rehabilitation fatigue was reduced by 18% in TG and 7% in CG which was statistically not significant. There was a statistically significant immediate effect of the single treatment session witch 18% reduction of fatigue measured by VAS in TG versus 11% in CG.

Because of a high 'placebo effect' of simple bed rest, a only small and short lasting additional effect of PMFT and high costs of a PMF-device, we cannot recommend PMFT as an additional feature of a multimodal neurological rehabilitation program in order to reduce fatigue level of MS-patients.
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Introduction

Multiple sclerosis, a demyelination disease of the central nervous system presents with a wide spectrum of neurologic symptoms. Amongst visual disturbances, cerebellar symptems, paresis, bowel- and bladder dysfunction, sensory loss and cognitive impairment, excessive fatigue is one of the most disturbing symptoms. 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. 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.[1–3]

Different components of fatigue have been described such as motor and cognitive fatigue and lassitude. Management strategies include medications, exercise, and behavioural therapy. In most cases a combined approach seems to be appropriate.[4,5]

Pulsed magnetic field therapy (PMFT) was applied to promote bone-healing, treat osteoarthritis and inflammatory diseases of the musculoskeletal system, alleviate pain, enhance healing of ulcers and reduce spasticity. There is some evidence for a beneficial effect on bone healing and pain alleviation of electromagnetic fields whereas in the treatment of other disorders the results are contradictory.[6]

Newer studies showed a beneficial effect of pulsed electromagnetic field therapie also on various symptoms of MS, especially on fatigue.[7–10]

Our study was designed to evaluate the immediate and long-term effect of PMFT as an additional feature of a neurological rehabilitation program on the level of fatigue in an inpatient population of MS patients.

Material and methods

Twenty-five patients with clinically defined multiple sclerosis (MS),[11,12] who took part in an inpatient rehabilitation program in Valens, Switzerland, and were randomly assigned to treatment with pulsed magnetic field therapy (PMFT) or to sham therapy twice a day during 3–4 weeks. The patients came from the eastern part of Switzerland, where the prevalence of MS is about 110/100 000 inhabitants.[13]

Patients were examined neurologically at the first day of hospitalisation. The grade of disability was rated according to the Expanded Disability Status Scale (EDSS) by Kurztke.[14]

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Patients' level of fatigue was measured with the Fatigue Severity Scale (FSS) on the first and last day of hospitalisation. This scale consists of nine statements on the possible interference of fatigue with daily activities. According to the degree of acceptance to the statements the patients judged between 1 = 'absolutely not true' and 7 = 'absolutely true'. The scale ranged from 1 (no fatigue) up to 7 (extreme fatigue). Validity and reliability of FSS is known to be high.[15,16]

Patients were enrolled in the study when they (1) had MS as defined by Poser, (2) accepted the informed consent, and (3) had a score in FSS greater or equivalent to 3.5.

Reasons to refuse were (1) previous therapy with pulsed electronic fields, (2) acute relapse of MS within the last month, (3) psychiatric disorders, (4) pacemaker, (5) epilepsy, and (6) acute bacterial infection with feaver.

Randomisation to treatment or control group was done by alternation according to the time of entrance in our center.

Patients and physician/statistician were blinded. For technical reasons the caregiver who manipulated the magnetic mattress could not be blinded.

The 'Magnetic Cell Regeneration' system by Santerra was used for PMFT (50 Hz, 17.5 myT).

A pulsed magnetic field mattress and a PMF-pillow were used. The latter standing two meters beside the mattress upright in a corner of the room, covered by a ferromagnetic metal. Patients layed on the mattress for 16 minutes twice a day, five days a week during three to four weeks. In the treatment group (TG) the mattress was activated whereas in the control group (CG) only the pillow evoked a magnetic field which was blocked by the ferromagnetic metal while the mattress remained off. Only the directly involved caregiver knew whether the mattress was active or not.

The schedule of treatment was randomly assigned to the patients by the schedule organizing service to avoid bias by diurnal peaks of fatigue.

Directly before and after the 16 minutes 'treatment' patients rated their level of fatigue with an visual analog scale (VAS), 0 indicating 'no fatigue at all' and 10 indicating 'extremly fatigue'. Similar to other highly subjective symptoms like pain a VAS seems to be an adequate instrument for measurement.[9]

Beside the PMFT each patient took part in a multimodal neurological rehabilitation program.

The following hypotheses were formulated:

1) A 16 minute rest on a mattress will reduce fatigue as measured by VAS immediately after the rest.
2) PMFT will intensify this reduction.
3) Fatigue as measured by FSS will decrease more markedly in the TG over the whole period of time.

Statistics

Categorial variables were tested with the Chi Square test. The difference of means for VAS were tested with a *t*-test for independent groups and a non-parametrical test (Wilcoxon) was used to detect group differences of FSS.

The correlation between VAS and relative change of VAS was proven by Spearman correlation procedure.

Results

Demographic and disease characteristic data

Between April and August 2003, 35 MS-patients took part in our inpatient rehabilitation program. Twenty-five qualified for our study. Twenty-four data sets were complete at the end of the study because one patient refused to sign the FSS a second time. Mean age was 46.2 years, mean EDSS was 5.43. Six of the patients were male, 18 female. Nine had a relapsing remitting, nine a secondary progressive and six a primary progressive course of the disease. Table 1 shows demographic data for TG and CG. Baseline demographic and disease specific data did not differ statistically significantly.

Fatigue severity scale data

Baseline score of fatigue (FSS) at entrance was 5.58 ± 1.44 (mean $\pm$ SD) in TG and 5.50 ± 1.20 in CG ($P = 0.80$). After the intervention FSS scored 4.50 ± 1.47 in TG and 5.10 ± 1.23 in CG ($P = 0.29$). In relative terms the decrement of FSS in TG was $18.7\% \pm 18.32$ and $7.23\% \pm 10.92$ in CG. The group differences (TG versus CG) for both absolute and relative changes in FSS over time were not significant ($P = 0.18$ and $P = 0.13$).

Time schedule of treatment

Four time zones were defined in which the treatment was carried out: Early morning (8.00–10.00), late morning (10.00–12.00), early afternoon (13.30–15.30) and late afternoon (15.30–17.30).

In both groups the distribution of the number of treatments in every time zone was quite similar with a slight tendency for the TG to have their intervention more often in the early morning and early afternoon sessions. Nevertheless with $P = 0.31$ there was no statistically significant difference.

Baseline values of VAS, change of VAS, endpoint values of VAS

By chance baseline values of VAS before treatment were highly significantly differnt in TG and CG: Before laying

Table 1 Demographic data for TG and CG

Group	*Mean*	*SD*	*Range*	
EDSS	TG	5.33	1.54	3–8
	CG	5.54	1.64	1.5–7.5
Age	TG	48.00	8.81	
	CG	44.42	6.86	
Sex	TG			
	CG			
Disease	TG			
	CG			

SD = standard deviation; rel–rem = relapsing–remitting; sec-prog = secondary progressive; prim-prog = primary progressive course of disease.

down on the mattress VAS in TG scored only 2.89 ± 2.66 but 6.01 ± 2.52 in CG.

Immediately after the treatment VAS decreased to 2.35 ± 2.57 in TG and to 5.30 ± 2.43 in CG. In relative terms VAS was reduced by $17.04\% \pm 43.04$ in TG and $11.67\% \pm 20.48$ in CG.

Endpoint data of VAS were also statistically significantly different from each other for both groups as could be expected by the baseline differences. Absolute decrements of VAS did not differ significantly from each other ($P = 0.08$), whereas relative change did ($P = 0.035$). Since the relative change of VAS was not dependent on baseline VAS ($r = 0.03$, $P = 0.94$) we focussed on this for further discussion.

Discussion

There is growing evidence in the literature for a beneficial effect of PMFT on different MS symptoms such as fatigue, bladder control, spasticity and quality of life.

Nielsen[17] reported a reduction of spasticity by magnetic stimulation over the thoracic myelon while Sandyk[10] reported cases of prompter recovery from fatigue following physical activity by extracranially applied electromagnetic field.

Our study was designed to evaluate if there is an additional therapeutic effect of PMFT on fatigue which adds on the effect of a multidisciplinary inpatient rehabilitation program. The study was focussed on an immediate effect of PMFT measured by VAS score before and after each treatment session and a more long-term effect over the 3–4 week rehabilitation program measured by FSS.

A statistically significant advantage for the verum treatment group concerning an effect on the FSS over a four week period could *not* be demonstrated. Both groups showed a decrement of fatigue over the intervention time. This was more pronounced in the TG (18%) and less so in the CG (7%) but statistically this 11% difference was not significant.

In contrast to our results Lappin[8] demonstrated in 117 MS patients a reduction of 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 four weeks. Expressed in relative terms this was a decrement of fatigue by roughly 20% quite similar to our effect size in the treatment group. The placebo effect of the sham intervention in their study was 0.36 points (about 14%) and thus even larger as in our group. Thus a very small advantage of the active device was shown by the study of Lappin. A preliminary study of the same study group with 30 patients with the same device used 24 hours per day over a two month period also demonstrated a beneficial effect of PMFT on a combined performance scale rating for bladder control, cognitive function, fatigue level, mobility, spasticity and vision.[7]

Different factors may have accounted for the failure to show a significant difference concerning FSS in our study:

Time of treatment: Since our patients took part in a routine inpatient rehabilitation program over three to four weeks the treatment time was limited to 30 up to 40 single sessions with a duration of 16 minutes each. Thus the maximal cumulated time of treatment in our study was 640 minutes whereas Lappin and Richards treated their patients 1440 minutes every day over a time period of at most eight weeks with their portable unit, which was about 70 times more.

Number of patients: Since the number of patients who took part in our study was low the staistical power for a negative result has to be considered in detail: With our small sample size ($n = 12$ per group) only a large difference of 1.8 points in the FSS-score could have been detected with a power of 90% on a 5% significance level. Since the observed difference in FSS after treatment was small (TG 4.5 versus CG $5.1 = 0.6$ points difference), a larger sample size would have been needed to prove its significance ($n = 114$). Thus beta error in our study increased up to 80%, which means the possibility that we failed to detect a small but *real existing* difference between the two treatment groups is very high.[18]

The level of fatigue as measured by FSS was quite high (5.5) and almost exactly the same in both groups. Concerning inclusion criteria and baseline fatigue there were no group differences. Nevertheless the fatigue scores measured immediately before each single treatment session by VAS were highly significantly different from each other with much lower values in the TG (2.9) compared with the CG (6.0). The reason for this baseline difference remained unclear.

The satistical analysis revealed a diurnal course of fatigue with peaks in the late morning and late afternoon. This was true for both groups. By chance there was a statistically insignificant tendency for the TG to be treated with PMF more often early in the morning and early in the afternoon at times when the fatigue level seems to be lower. This could probably count for a part of the observed difference but cannot explain the difference of almost 100%.

Because the baseline values of VAS were so different, clearly the post-treatment values differed in the same manner. Thus for statistical analysis we focused on the relative decrement of fatigue as measured by VAS in relation to the baseline VAS-score. This procedere was justified because the relative change of the VAS-score was independent of the baseline value of VAS, as was shown by a correlation analysis.

Both groups showed an immediate decrease of fatigue as measured by VAS over the single treatment session. Even in the CG some minutes of rest on a mattress could decrease their fatigue by 11%. The PMFT showed an additional effect of about 7%, thus exhibiting a relative decrease of fatigue by 18%. The group difference reached statistical significance, as was pointed out above.

As to our initial hypotheses we can state:

1) A 16 minute rest on a mattress whilst receiving a sham intervention reduces fatigue measured by VAS immediately before and after rest by 11%, exhibiting a large placebo effect.
2) PMFT enhances the effect of a simple rest by additional 7%
3) Because there was no statistical long-term effect (as measured by FSS) of both interventions we conclude that the effect of both verum treatment and sham intervention only was of limited duration. (beta error of this statement 0.80).

Beside the self criticism concerning the small number of patients in our study some points have to be made. On the one hand, the effect of PMFT on fatigue in the work of Richards and Lappin and in our study was very small and the placebo effect quite large. On the other hand, a PMFT device is quite expensive and costs around 3500 SFr (2350 €). Thus it is questionable if the statistically significant results which have been demonstrated by others and in our study really correspond with a clinically relevant improvement and if this is cost effective.

Furthermore the PMFT is an absolutely passive kind of treatment which is given to a patient population which per se is a physically very inactive group.[19]

In a previous study which evaluated the effect of an exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis we demonstrated an improvement of fatigue in the exercise group by 14%,[20] which is almost identical to the effect of simple bed rest of 16 minutes twice daily as was shown above.

Obviously aerobic exercise as an active treatment and rest as passive consumption are two completely different approaches to reduce fatigueIn our opinion the active way yields more advantages because it has further positive implications on cardio-vascular risk factors, depression, osteoporosis etc. and stimulates the patients own initiative.[21]

Surely this is only true for the subgroup of MS patients which has sufficient mobility to practise physical exercise. Thus for the more disabled population with higher EDSS scores the PMFT could be a possible alternative.

Conclusion

Because of the large placebo effect of simple bed rest, the only small additional effect of PMFT on fatigue and the costs of the device, we cannot recommend PMFT as regular part of a multimodal neurorehabilitation.

Instead of a passive method we would rather recommend aerobic fitness training which reduces fatigue in a similar manner but yields many more positive side effects.[18–20]

Only in the subgroub of severely disabled patients, when aerobic exercise is impossible PMFT could be an alternative.

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