The efficiency of pulsed electromagnetic field in refractory migraine headaches: a randomized, single-blinded…

7 authors, including:

Boshra Hatef
Baqiyatallah University of Medical Sciences
41 PUBLICATIONS   93 CITATIONS

SEE PROFILE

Leila Simorgh
(SBMU) Shahid Beheshti University of Medica…
8 PUBLICATIONS   5 CITATIONS

SEE PROFILE

Forough Rahimi
Shahid Beheshti University of Medical Sciences
17 PUBLICATIONS   14 CITATIONS

SEE PROFILE

Mansoureh Togha
Tehran University of Medical Sciences
92 PUBLICATIONS   674 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:

Project   Selective Stimulation of Excitable tissue: BioElectromagnetic Phenomena Simulation and Electrophysiological Experiments View project

Project   Psychometry of the Persian version of the inventory for quality of life in adult patients with epilepsy View project

Research Article

The efficiency of pulsed electromagnetic field in refractory migraine headaches: a randomized, single-blinded, placebo-controlled, parallel group

Boshra Hatef[1], Fahime Hashemirad[2], Gholam Hossein Meftahi[1], Leila Simorgh[3], Soodeh Razeghi Jahromi[4], Forough Rahimi[5], Mansoureh Togha[4]*

[1]Neuroscience Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2]Monash University, Melbourne, Victoria, Australia
[3]Department of Rehabilitation Sciences, Shahid Beheshti University of Medical Science, Tehran, Iran
[4]Department of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[5]School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Correspondence:
Dr. Mansoureh Togha,
E-mail: toghae@sina.tums.ac.ir

ABSTRACT

Background: The study attempts to investigate the effect of PEMF therapy on Refractory Migraines (RM), both those which were related and those which were not related to menstrual cycle, in a randomized, single blind, placebo-controlled study.
Methods: The study attempts to investigate the effect of PEMF therapy on Refractory Migraines (RM), both those which were related and those which were not related to menstrual cycle, in a randomized, single blind, placebo-controlled study.
Results: There was a significant improvement for the active group in terms of their headache days, durations and work-loss hours due to headache compared to the placebo group after 2 weeks. The added results of the assessment of the active group indicated a significant improvement in the days and duration of headaches, work-loss hours and number of medications even after a following 4-8-month period. Headache intensity and the amount of medication used for headache were reduced only in RM patients that had headaches which were not related to their menstrual cycles.
Conclusions: PEMF (10 Hz, 4-5mT) can be considered as a beneficial and persistent prophylactic treatment option for refractory migraine.

Keywords: Refractory migraine, Pulsed electromagnetic field therapy, Randomized clinical trial

INTRODUCTION

Migraine is a serious illness with a spontaneous clinical evolution that has a tendency to become chronic.[1,2] The International Headache Society introduced refractory migraine (RM) into the International Classification of Headache Disorders 3 (ICHD-3 beta and 2 (ICHD-2) with a prevalence of 5%.[3-5] RM characteristics include chronic migraines or migraines without an aura, that significantly interfere with the quality of life in spite of preventive medications.[3,4]

Many studies suggest that there are various causes behind migraines such as dysfunction within certain voltage channels in the CNS, neural regulation of the brain stem and cerebral circulation.[6,7,10] Furthermore electro-

physiological and imaging studies have shown that changes appear in the brain before headache (in the pre-ictal phase). However, they return to the normal state after the migraine attack.[10-13] Evidence indicates that non-pharmacologic treatments can play an important role in controlling RM.[14] Pulsed electromagnetic field (PEMF) has shown promising results in the prophylactic treatment of migraine. Patients achieved over 70 percent improvement in their activity after using PEME.[15-17]

Extremely low-frequency electromagnetic fields may have a beneficial effect in controlling migraines through several mechanisms. The exposure of neural and vascular cells to electromagnetic fields that resonate at 10 Hz can induce intracellular calcium oscillations and change the signaling cascades such as calcium-calmodulin-NO.[18,19] Electromagnetic fields also enhance vascular tonicity and velocity.[20,21] They stimulate ATP, mitochondrial enzymes synthesis as well as the anti-inflammatory process.[21,22] They also increase the rate of synthesis (turnover) of dopamine and serotonin, eventually reducing the alpha band of EEG.[23-25] It seems that there is a correlation between the etiology of migraines and the effects of an electromagnetic field on the human brain.[9] Nevertheless, there is no strong evidence to support efficiency of this treatment in migraine sufferers.[17] Therefore, the aim of this study was to investigate the effects of applying the PEMF to patients experiencing RM headache.

METHODS

Subjects

Thirty patients from the out-patient department of the Clinic of Neurology participated in this study. They had been diagnosed as sufferers of migraine or medication-overuse headaches by the corresponding author, who is an expert in headaches. The study was approved by the Ethics Committee of Tehran University of Medical Sciences and recorded in the www.clinicaltrials.gov website with the tracking number NCT01670214. The subjects were informed about the procedures involved in the study and gave written informed consent according to the Helsinki convention.

Inclusion criteria required patients in an age range of 18 to 60 years, either male or female, and to have been diagnosed with migraine or chronic migraine for at least 12 months based on ICH-II with a low quality-of-life score (MIDAS>11). Exclusion criteria were pregnancy or lactation, psychiatric, systemic diseases, epilepsy, and malignancy within the past year. Patients were also excluded if they had the criteria of concomitant non-migraine headaches more than three times per month within the last 3 months, or alcohol or drug addiction according to the Diagnostic and Statistical Manual of Mental Disorders-IV. They were also excluded. If they had received oral contraceptive during or within 3 months before the study.[26,27]

The design of the study

This research was a randomized single-blind placebo-controlled study performed in three phases (Figure 1). Characteristics of headaches of patient who met the inclusion and exclusion criteria were recorded in two weeks before starting the treatment. After this two-week headache-assessment, patients were randomly assigned into two groups: active or placebo. In female patients, menstrual-related migraine was also assessed according to ICHDIII-beta. They were categorized as menstruation-related RM, if their symptoms were associated with menstrual period.[28]

All patients had an experience of taking of a combination of propranolol- nortriptyline +/- sodium valproate or topiramate, as prophylactic drugs. However, the mentioned medications had not been adequately effective for the patients. One month before beginning the study, the patients were asked to stop taking preventive medicines, alone or in combination. During this period, they were allowed to take minor pain relief medications such as Sumatriptan, Ibuprofen or Acetaminophen for their acute attacks.

The first phase of the study consisted of six sessions (three sessions per week) of PEMF treatment for both groups. The electromagnetic instrument was turned on for both groups, but electromagnetic current was not employed for the placebo group.[8] None of the patients knew to which group they belonged. In the second phase, patients in the active PEMF group continued the treatment for six more sessions (two additional weeks), and were then followed up for four months in the third phase. For the subsequent 8 months, participants were telephoned twice a month and asked about headache frequency. No other variables were included during this phase. In the placebo group no further follow up or additional exposure to the magnetic field were perfpormed001.
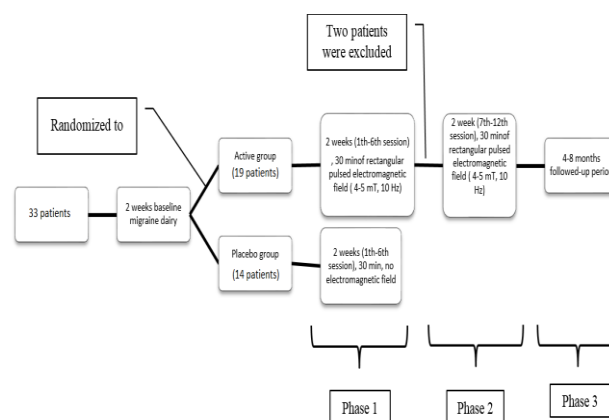

Figure 1: The schematic view of the procedure.

The pulsed electromagnetic field therapy

Parameters of the pulsed electromagnetic field (generated by: BTL 5000, made in UK) were rectangular electromagnetic pulses with 10 Hz frequency (pulse for 3ms, pause for 97 ms) and 4-5 mT intensity. The patients were exposed to the electromagnetic field for 30 minutes per session. The solenoid (diameter was 70 cm) was placed around the patients' head while they lay supine on the treatment bed. The lines of electromagnetic field were paralleled to body. PEMF has been approved by FDA for fracture treatment.[29] The treatment dosage used in this study was in the safety range of PEMF without any hazardous effect.[11,21,30,31]

Outcome measures

All the participants were asked to record their symptoms in a migraine diary form. This recording began two weeks prior to the study (baseline measurement) and continued during the first phase in both groups. Patients in the active group continued logging their symptoms in the diary for the second and third phases. The MIDAS score (Persian version) was employed both at baseline and at the end of three months of treatment.[32]

The following parameters were assessed in the diary for each phase: 1) Frequency of migraine attacks, number of days per two weeks with migraine or headache, 2) Intensity of headache rated using Visual Analog Scale (VAS), 3) Duration of migraine attack, 4) The hours of impairment in everyday activities or work missed, and 5) The type and dosage of medications taken.

The patients were allowed to take only simple analgesics, no triptans or ergot derivatives during the migraine attacks. Frequency of headache was considered as the primary outcome measure and was followed for eight months. Other outcomes were considered as secondary outcomes.

Statistics

Chi-square and independent sample t-tests were used to compare the demographic and clinical characteristics in both active and placebo groups. A two-way mixed model ANOVA was conducted to evaluate two main factors, group (active and placebo) and menstrual relationship of migraine (menstrual RM and non-menstrual RM), and pre vs. post treatment. A simple mixed-model ANOVA was used to assess the changes in the outcome measures from the beginning of the study until the end of the follow-up period in the active treatment group that was divided to sub-groups. One group with RM is related to menstrual cycle and the other one is not related to menstrual cycle. The MIDAS scores before and after three months of treatment were evaluated in the active treatment group by paired sample t-test. The significance level was set at 0.05. All analyses were performed using the IBM SPSS statistics 21.

RESULTS

A total number of 33 patients were enrolled to participate in the study. Nineteen patients were randomly assigned to the active treatment group while the remaining 14 patients were placed in the placebo group. Table 1 presents the demographic and clinical characteristics of both groups. No significant difference was found between the groups in terms of gender, age, years and type of migraine, MIDAS score and menstrual relationship of migraine and migraine symptoms such as nausea, vomiting or aura.

Table 1: Demographic and clinical characteristics of groups.

	Active group (n=19)	Placebo group (n=14)	P-value
Gender	89.4% female	78.5% female	0.38
Age (years)*	35.5 (8)	37.7 (9)	0.52
History of migraine (years)*	12.7 (6)	16.5 (8)	0.18
RCM / RM	12 / 7	8/ 6	0.72
Nausea or vomiting	68.4 % yes	71.4 % yes	0.85
Aura	26.3 % yes	28.5 % yes	0.88
Menstrual related	47.3% yes	50% yes	0.88
MIDAS score*	77.76 (42)	72.33 (39)	0.76

*: the data are mean (standard deviation)

Table 2 represents the means, lower and upper band of 95% CI of headache activity, and relation to menstrual cycle in both groups before and after two weeks of treatment.

Table 3 reports the means of outcome measures from both groups before and after two weeks of treatment. Results of the two-way mixed model ANOVA test demonstrated that there is a significant interactional effect between time and group in three variables of frequency, duration of headache and work loss due to headache. Following up the interaction between group and time in these variables indicated a significant decrease over time in the active group. However, there was no change from pre to post treatment in the placebo group. The findings show that there are significant interactions between time and menstrual relationship with respect to the intensity of headache and amount of medication used. The bonferroni pairwise comparison evaluated this interaction and showed that these variables significantly diminished in patients who had migraine not related to menstrual cycle, after two weeks regardless of the type of treatment (Table 3).

Table 2: The means (standard deviation) of number of days, intensity and duration of headache, work-loss and number of medications because of headache for active and placebo groups.

Outcome measurements	Pre/post treatment	Relation to menstrual cycle	Mean (lower and upper of 95% CI) Active group (n=19)	Mean (lower and upper of 95% CI) Placebo group (n=14)
Day	Pre	Yes	9.78 (7.2-12.4)	11.4 (8.6-13.6)
		No	7.6 (4.8-10.6)	7.5 (3.6-11.8)
	Post	Yes	3 (2-4)	11.2 (8.3-14)
		No	3.9 (3.1-4.8)	7.1 (3.2-11.8)
Intensity (VAS)	Pre	Yes	6.6 (4.9-8.3)	7.7 (6.4-9)
		No	8.1 (7.2-9)	8 (6.5-9.3)
	Post	Yes	6.5 (4.7-8)	8.2 (7.3-9.2)
		No	5 (3.5-6.6)	5.8 (4-8)
Duration (hours)	Pre	Yes	177.11 (99.7-261.5)	210 (144-290)
		No	135.2 (69.4-216.6)	108.3 (41.5-220.4)
	Post	Yes	41.6 (25.7-60.4)	201 (130-280)
		No	34.3 (16.1-54.9)	101.5 (18.3-221.5)
Work-Loss (hours)	Pre	Yes	28.11 (13.6-43.8)	48.4 (22.5-74)
		No	40.8 (21.2-62.1)	39.8 (11-73)
	Post	Yes	9.6 (3-19.5)	42.8 (15.4-69.7)
		No	7.4 (2-13.3)	28.5 (1-69.2)
Medication (number)	Pre	Yes	5.3 (2.6-8)	8.1 (3.2-15)
		No	12.8 (5.6-19.5)	14.8 (5-26.6)
	Post	Yes	4.4 (1.7-8.1)	10.5 (4-18.3)
		No	1.9 (0.7-3)	11.6 (1.3-24.6)

The 95% CI excludes the value zero. Time frame for baseline and post-intervention is two weeks. Day: the number of days that patient had headache.

Table 3: Results of two-way mixed ANOVA comparing active and placebo groups in relation to menstruation cycle, pre and post treatment.

	Time	Group	RTM	Time × Group	Time × RTM	Group× RTM	Time × Group× RTM
Days*	0.0001	.0.016	.0.04	0.0001	0.32	0.121	0.12
Intensity*	0.002	0.14	0.55	0.21	0.0001	0.51	0.77
Duration*	0.0001	0.075	00.029	0.002	0.615	0.159	0.552
Work-Loss*	0.0001	0.071	0.75	0.037	0.20	0.40	0.56
Medications*	0.0007	0.067	0.237	0.151	0.002	0.726	0.811

*: Time frame for each variable is two weeks. Significances are bolded. Pre-post: comparison before and after 6 sessions of treatment, Group: comparison the placebo and active group, RTM: comparison the patients who had migraine related and not related to menstrual cycle

The results of the remaining active group participants (19 patients) were analyzed using mixed design ANOVA. The assumption of sphericity was violated so the Greenhousee Geisser correction was employed for the F-ratio computations. There was a significant interaction between times and menstrual relationship. The number of days with headache (F (3.2, 49.1) =22.4, P <0.0001) was decreased after the 8 month follow ups (Figure 2). The durations of headache (F (1.6, 26.1) =18.6, P<0.0001) and work loss hours (F (1.6, 26) =18.6, P<0.0001) considerably decreased after 4 months follow up. The mean intensity of headache (F (10, 160) =1.9, P=0.048), and the number of medications (F (2.3, 35.8) = 4, P= 0.02) that interacted with the menstrual relationship decreased after 4 months follow up. This means that the effect of treatment persisted in the RM without menstrual relationship in intensity and medications used for headache. The bonferroni test showed that there was a significant difference in intensity between groups with and without menstrual relationship at the 6th, 8th and 10th week follows ups (Figure 3). A similar result was seen only in the last time frame for the number of medications used for headache. The days of headache and work-loss hours in RM patients that had headaches related to their

menstrual cycles were significantly higher than that of patients who reported that their headaches were not related to menstrual cycle.
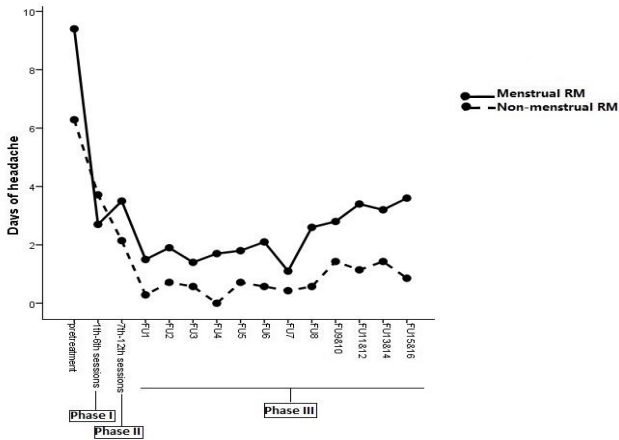

Figure 2: The mean number of days with headache in menstrual RM and non-menstrual RM. Each time frame is two weeks of pre-treatment, 1st-6th session (phase I), 7th-12th sessions (phase II) of treatment, as well as the 1st-16th frames of follow up (FU) in the active PEMF group. The days of FU11&12 until FU15 & 16 was normalized to two weeks (phase III). Results showed that the number of headache days significantly decreased in the active group after treatment and this improvement persisted after eight-months.
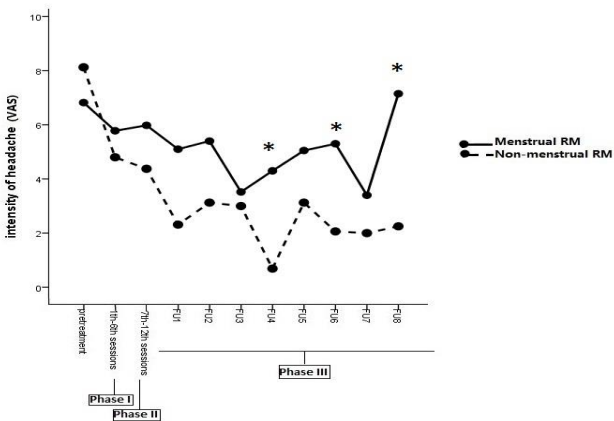
Figure 3: The mean intensity of a migraine episode in the menstrual RM and non-menstrual RM. Each time frame is two weeks of pretreatment, 1ts-6th sessions (phase I), 7th-12th sessions of treatment(phase II), as well as 1st-8th frames of follow up (FU) after treatment(phase III) in the active group.

MIDAS scores were obtained three months after active PEMF treatment which were then compared to the MIDAS scores prior to treatment initiation. A significant decrease was obtained (t=7.5, sig<0.0001) (Figure 4).
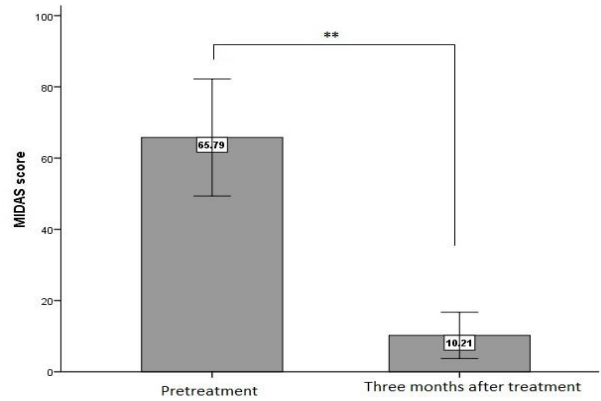
Figure 4: The bar plots represent the MIDAS score before and three months after the treatment in the active group. **: P value <0.0002.

DISCUSSION

Results showed significant beneficial effects of active PEMF therapy in headache activity for RM patients. Days and durations of headache and work-loss hours due to headache were reduced in comparison with the placebo group. This improvement was consistent in the active group, even after the 10-week follow up period. Menstrual relationship with headache had an interactional effect on both intensity and amount of medication used for headache. However, the results showed that PEMF did not have any therapeutic effect on headache linked with women's hormone fluctuations. The current study has several strengths in comparison with the previous studies that were collected by Vincent et al in.[17] For example, the existence of the parallel placebo group in a randomized clinical trial, assessment of PEMF in RM patients for whom the routine treatment did not work, and consideration of menstrual relation to migraine as factors in a mixed model analysis have not been previously included in published work.

EEG studies have shown that electromagnetic field has a dose-dependent effect, being well demonstrated in pain and EEG studies.[25,33,34] Many of the studies from 1985 to 2005, gathered in a review article, illustrated the effect of the use of large spread spectrum of PEMF doses on decreasing headache activity.[17] Although most of these research studies had no control or comparison group, or had very brief follow-up periods and uncompleted reports of dosimeter. Sherman et al in 1998 revealed a therapeutic effect of PEMF at 27.12 MHz in their pilot study of six migraine patients exposed to a PEMF machine, showing a change in headache activity from 3.32 to 0.58 per week compared to the controls.[35] They also showed that 75% of 42 participants had significant improvement in their migraine headaches after exposure for two weeks (10 sessions).[16] In another study, 76% of participants indicated that they were "clear" or "very clear" of their complaints about headaches, with no side effects from the treatment (4 weeks PEMF: 16 Hz, 5

microT), while no improvement was observed in the control group.[15]

The effect of menstrual relationship on the intensity of migraine attacks and medication used for headache, may demonstrate that PEMF has little effect on the women's hormonal fluctuations that trigger the headaches in this group.

There are currently no studies that actually demonstrate how electromagnetic fields reduce migraines. However, several explanations can be considered for the therapeutic effects of PEMFs on headache. These rationales include electrophysiological, neurochemical, and vascular phenomena.[17] Some animal and human studies support neurochemical effects of weak electromagnetic fields that may act on neurotransmitters such as melatonin, cortisol, serotonergic and dopaminergic systems implicated in the pathophysiology of migraine.[3,23,36] Many electro-physiological studies in migraines often showed high power and asymmetry in the low EEG frequency band due to the reduction of the cholinergic activity of the brainstem that induces dysrhythmia in the thalamo-cortical pathway.[11,37] On the other hand, an electromagnetic field with a frequency of 10 Hz reduced the alpha band of the EEG.[25,38,39] There are some controversies regarding the effect of PEMF due to the intensity and frequency of exposure on EEG.[24,38,39] Then the electrophysiological rationale of effect of electromagnetic field on migraine may be supported. Exposure to PEMF at 10 Hz also stimulates the calcium oscillation in the cell.[19] It causes minimum calcium leakage from the cell membrane synthesis of ATP and mitochondrial enzymes, and anti-inflammatory process.[21,22,40,41] Therefore, use of an electromagnetic field at 10 Hz also increases the rate of synthesis (turnover) of dopamine and serotonin.[23] The cellular effect of PEMF on calcium oscillation for modulating Calcium-Calmodulin-NO signaling is a basis for any response from vascular and neural cells to PEMF.[18,19,21,31,42] Many studies have revealed that electromagnetic fields at a wide range of frequencies, activate certain cellular mechanisms, increase blood flow, and produce vasodilation of the vascular tone.[20,43] These mechanisms may be related to cellular survival activity, the vascular system, as well as inflammation process following the use of PEMF. On the other hand, an abnormal rhythmic activity between thalamus and cortex, along with a decrease in the velocity of blood flow through cerebral arteries (especially the middle cerebral artery), were observed on the affected hemisphere in migraine.[9,13,44] Almost 50% of migraine sufferers have inter-hemispherical asymmetries in regional cerebral blood flow (rCBF).[9,45] The blood flow in several parts of the brain, including the anterior cingulate cortex, auditory and visual association cortices, brainstem (locus coeruleus and dorsal raphe nuclei), bilateral insula, bilateral cerebellar hemispheres, prefrontal cortex, putamen, and rostral medulla, are all increased during a migraine attack.[7] There is also a correlation between autonomic system dysfunction and migraines, as well as an increased risk of cardiac ischemia.[46,47] Olesen in 2009 revealed that disturbance of the para-sympathetic input to the cerebrovascular system (especially pial arteries) initiates migraines without an aura.[48] This study also showed that PEMF is effective in migraine prevention.

One limitation of the current study was the combination of both episodic and chronic forms of migraine among participants. Moreover, there was a lack of adequate control on the use of abortive medications because each patient was used to taking certain drugs. The short time frame of baseline and post intervention (two weeks) to compare placebo and active groups in the first phase was another limitation of the study. Although the pilot study and power of analysis showed that the number of subjects was sufficient, an increased number of subjects would increase the reliability of the results.

CONCLUSION

In future studies, PEMF can be compared to traditional migraine therapies to establish comparative efficacy and safety. Furthermore, longer follow-up periods will be needed in order to determine whether any therapeutic benefits, resulting from the use of PEMFs, endure over time. More clinical trials are suggested to find a dose of PEMF therapy with the best therapeutic result and the least amount of side effects.

This randomized single-blinded parallel-placebo controlled study showed significant improvement of headache activity in the PEMF active group, while no changes of headache parameters were seen in the placebo group in the first phase. The second and third part of the study showed that improvements in the active group persisted even after an 8 month follow-up period. The study also showed that menstrual dependency of headache diminished the effect of PEMF treatment.

REFERENCES

1. Negro A, D'Alonzo L, Martelletti P. Chronic migraine: comorbidities, risk factors, and rehabilitation. Intern Emerg Med. 2010;5(1):S13-9.
2. Valade D. Chronic migraine. Rev Neurol (Paris). 2013;169(5):419-26.

3. Lewczuk B, Redlarski G, Ak Zi A. Influence of Electric, Magnetic, and Electromagnetic Fields on the Circadian System: Current Stage of Knowledge. BioMed Research International. 2014;2014:13.

4. Peterlin BL, Calhoun AH, Siegel S, Mathew NT. Rational Combination Therapy in Refractory Migraine. Headache: The Journal of Head and Face Pain. 2008;48(6):805-19.

5. Irimia P, Palma JA, Fernandez-Torron R, Martinez-Vila E. Refractory migraine in a headache clinic population. BMC Neurol. 2011;11:94.

6. Ferrari MD. Migraine genetics: a fascinating journey towards improved migraine therapy. Headache. 2008;48(5):697-700.

7. Aurora SK, Barrodale PM, Tipton RL, Khodavirdi A. Brainstem dysfunction in chronic migraine as evidenced by neurophysiological and positron emission tomography studies. Headache. 2007;47(7):996-1003.

8. May A. The window into headache research: what have we learned from functional and structural neuroimaging. Schmerz. 2010;24(2):130-6.

9. Denuelle M, Fabre N, Payoux P, Chollet F, Geraud G. Posterior cerebral hypoperfusion in migraine without aura. Cephalalgia. 2008;28(8):856-62.

10. Leone M, Proietti CA, Mea E, Curone M, Tullo V, Casucci G. Functional neuroimaging and headache pathophysiology: new findings and new prospects. Neurol Sci. 2007;28(2):S108-13.

11. Sand T. Electroencephalography in migraine: a review with focus on quantitative electroencephalography and the migraine vs. epilepsy relationship. Cephalalgia. 2003;23(1):5-11.

12. Olesen J, Friberg L, Olsen TS, Iversen HK, Lassen NA, Andersen AR. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Annals of Neurology. 1990;28(6):791-8.

13. Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. J Headache Pain. 2013;14(1):65.

14. Bronfort G, Nilsson N, Haas M, Evans R, Goldsmith CH, Assendelft WJ. Non-invasive physical treatments for chronic/recurrent headache. Cochrane Database Syst Rev. 2004(3):CD001878.

15. Pelka RB, Jaenicke C, Gruenwald J. Impulse magnetic-field therapy for migraine and other headaches: a double-blind, placebo-controlled study. Adv Ther. 2001;18(3):101-9.

16. Sherman RA, Acosta NM, Robson L. Treatment of migraine with pulsing electromagnetic fields: a double-blind, placebo-controlled study. Headache. 1999;39(8):567-75.

17. Vincent W, Andrasik F, Sherman R. Headache treatment with pulsing electromagnetic fields: a literature review. Appl Psychophysiol Biofeedback. 2007;32(3-4):191-207.

18. Pilla A, Fitzsimmons R, Muehsam D, Wu J, Rohde C, Casper D. Electromagnetic fields as first messenger in biological signalling: Application to calmodulin-dependent signaling in tissue repair. Biochim Biophys Acta. 2011;1810(12):1236-45.

19. Yu-Hong Z, Yong Z, Tong-Jun Z, Ya-Fei C, Chang-Qing Y. Model for Influences of Magnetic Fields on Intracellular Calcium Oscillations. Communications in Theoretical Physics. 2009;52(1):168.

20. McKay JC, Prato FS, Thomas AW. A literature review: the effects of magnetic field exposure on blood flow and blood vessels in the micro-vasculature. Bioelectromagnetics. 2007;28(2):81-98.

21. Habash. Bio Effects and Therapeutic Applications of Electromagnetic Energy. New York: Hardcover. 2008.

22. Tong JJ. Mitochondrial delivery is essential for synaptic potentiation. Biol Bull. 2007;212(2):169-75.

23. Sieron A, Labus L, Nowak P, Cieslar G, Brus H, Durczok A. Alternating extremely low frequency magnetic field increases turnover of dopamine and serotonin in rat frontal cortex. Bioelectromagnetics. 2004;25(6):426-30.

24. Shafiei S, Firoozabadi S, Rasoulzadeh Tabatabaie K, Ghabaee M. EEG changes during exposure to extremely low frequency magnetic field on a small area of brain. Koomesh. 2011;12(2):167-74.

25. Cvetkovic D, Cosic I. Alterations of human electroencephalographic activity caused by multiple extremely low frequency magnetic field exposures. Med Biol Eng Comput. 2009;47(10):1063-73.

26. Silberstein S, Tfelt-Hansen P, Dodick DW, Limmroth V, Lipton RB, Pascual J. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008;28(5):484-95.

27. Pryse-Phillips WE, Dodick DW, Edmeads JG, Gawel MJ, Nelson RF, Purdy RA. Guidelines for the nonpharmacologic management of migraine in clinical practice. Canadian Headache Society. CMAJ. 1998;159(1):47-54.

28. Silberstein SD, Hutchinson SL. Diagnosis and treatment of the menstrual migraine patient. Headache. 2008;48(3):S115-23.

29. Markov MS. Expanding Use of Pulsed Electromagnetic Field Therapies. Electromagnetic Biology and Medicine. 2007;26(3):257-74.

30. Yamaguchi-Sekino S, Sekino M, Ueno S. Biological effects of electromagnetic fields and recently updated safety guidelines for strong static magnetic fields. Magn Reson Med Sci. 2011;10(1):1-10.

31. Funk RH, Monsees T, Ozkucur N. Electromagnetic effects - From cell biology to medicine. Prog Histochem Cytochem. 2009;43(4):177-264.

32. Ghorbani A, Chitsaz A. Comparison of validity and reliability of the Migraine disability assessment (MIDAS) versus headache impact test (HIT) in an Iranian population. Iran J Neurol. 2011;10(3-4):39-42.

33. Cook CM, Saucier DM, Thomas AW, Prato FS. Changes in human EEG alpha activity following exposure to two different pulsed magnetic field sequences. Bioelectromagnetics. 2009;30(1):9-20.

34. Robertson JA, Juen N, Theberge J, Weller J, Drost DJ, Prato FS. Evidence for a dose-dependent effect of pulsed magnetic fields on pain processing. Neurosci Lett. 2010;482(2):160-2.

35. Sherman RA, Robson L, Marden LA. Initial exploration of pulsing electromagnetic fields for treatment of migraine. Headache. 1998;38(3):208-13.

36. Touitou Y, Selmaoui B. The effects of extremely low-frequency magnetic fields on melatonin and cortisol, two marker rhythms of the circadian system. Dialogues Clin Neurosci. 2012;14(4):381-99.

37. Bjork M, Sand T. Quantitative EEG power and asymmetry increase 36 h before a migraine attack. Cephalalgia. 2008;28(9):960-8.

38. Shafiei SA, Firoozabadi SM, Rasoulzadeh Tabatabaie K, Ghabaee M. Study of the frequency parameters of EEG influenced by zone-dependent local ELF-MF exposure on the human head. Electromagn Biol Med. 2012;31(2):112-21.

39. Bell GB, Marino AA, Chesson AL. Frequency-specific responses in the human brain caused by electromagnetic fields. J Neurol Sci. 1994;123(1-2):26-32.

40. Bauréus Koch CLM, Sommarin M, Persson BRR, Salford LG, Eberhardt JL. Interaction between weak low frequency magnetic fields and cell membranes. Bioelectromagnetics. 2003;24(6):395-402.

41. Blackman CF, Kinney LS, House DE, Joines WT. Multiple power-density windows and their possible origin. Bioelectromagnetics. 1989;10(2):115-28.

42. Wade B. A Review of Pulsed Electromagnetic Field (PEMF) Mechanisms at a Cellular Level: A Rationale for Clinical Use. American Journal of Health Research. 2013;1(3):51-5.

43. Ding GR, Li KC, Wang XW, Zhou YC, Qiu LB, Tan J. Effect of electromagnetic pulse exposure on brain micro vascular permeability in rats. Biomed Environ Sci. 2009;22(3):265-8.

44. Chiapparini L, Ferraro S, Grazzi L, Bussone G. Neuroimaging in chronic migraine. Neurol Sci. 2010;31(1):S19-22.

45. May A. A review of diagnostic and functional imaging in headache. J Headache Pain. 2006;7(4):174-84.

46. De Marinis M. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology. 2003;61(3):424-5.

47. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ. 2009;339:b3914.

48. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. Lancet Neurol. 2009;8(7):679-90.