Received: 5 March 2020 | Revised: 31 May 2020 | Accepted: 15 June 2020

DOI: 10.1111/ane.13300

ORIGINAL ARTICLE

Acta Neurologica Scandinavica WILEY

Transcranial low-frequency pulsating electromagnetic fields (T-PEMF) as post-concussion syndrome treatment

Claire Prener Miller[1] | Martin Prener[1,2] | Steen Dissing[3] | Olaf B. Paulson[1,2]

[1]Neurobiology Research Unit, Department of Neurology, Rigshospitalet, Copenhagen, Denmark

[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[3]Department of Cellular and Molecular Medicine, Panum Institute, University of Copenhagen, Copenhagen, Denmark

Correspondence
Olaf B. Paulson, Neurobiology Research Unit, N- 6931, Department of Neurology, Neuroscience Centre, Rigshospitalet, University of Copenhagen, 9 Blegdamsvej, DK-2100 Copenhagen, Denmark.
Email: olaf.paulson@nru.dk

Funding information
This work was supported with a grant from Hørslev Fonden.

Background: Treatment options for the subgroup of people who develop long-lasting symptoms following mild traumatic brain injury are limited. Transcranial pulsating low-frequency electromagnetic stimulation (T-PEMF) in other patient groups has shown promising results in several studies with proposed neuroprotective and anti-inflammatory effects.

Objective: The present pilot study was conducted to access feasibility and tolerability of T-PEMF in treating post-concussion syndrome.

Methods: Seven patients with post-concussion syndrome received 5 weeks of daily 30 minutes T-PEMF treatment with evaluation after 2 and 5 weeks and 3 months after ending treatment.

Results: Compliance was high as all subject completed the full treatment. Two patients however experienced a worsening of their concussion symptoms during the course of treatment. The remaining patients had some discomfort in relation to treatment, mainly headache, but passing and less for each treatment. The majority (n = 5) had a reduction in symptoms overall, up to 61% (2%-61%) based on the Rivermead Post-Concussion Symptoms Questionnaire.

Conclusion: Further studies on T-PEMF as a treatment option for post-concussion syndrome are warranted.

KEYWORDS

concussion, electromagnetic stimulation, mTBI, PCS, post-concussion syndrome, T-PEMF

1 | INTRODUCTION

A small but significant number of mild traumatic brain injuries (mTBI) result in development of persistent prolonged symptoms, including cognitive deficits, headaches, and mental fatigue.[1] Such symptoms are called post-concussion syndrome (PCS), usually diagnosed according to the International Classification of Disease (ICD)-10 or the Diagnostic and Statistical Manual of Mental Disorder (DSM)-IV. However, the concept of PCS as one unique syndrome is debated, and it remains unclear clear why and who develops PCS.[2] The majority of studies use the term PCS to describe persistent concussion symptoms over 3 months following a non-penetrating direct or indirect blow to the head accompanied by loss of consciousness or alterations in mental state for <30 minutes.[1]

Current management of PCS consists of a multidisciplinary approach of pharmaceutical treatment, vestibular and vision rehabilitation, cognitive behavioral therapy and physical therapy. A meta-analysis from 2018 of PCS intervention, however, found evidence of concussion treatment limited.[2]

Treatment with low-frequency pulsating electromagnetic fields (PEMF) is a non-invasive, self-administered method best known from treatment of non-union long bone fractures where accelerated bone

healing process has been well-established.[3] Low-frequency electromagnetic field therapy has since evolved to include transcranial application based on in vitro and experimental in vivo findings of neuroprotective effects including cell proliferation and differentiation,[4,5] enhanced neurite outgrowth,[6] reduced apoptosis,[5] increased angiogenesis,[7] and increased microvascular perfusion and tissue oxygenation.[8]

The effects of transcranial pulsed electromagnetic field stimulation (T-PEMF) have been demonstrated on otherwise treatment-resistant patients with depression in several studies.[9-11] Furthermore, a recent study in patients with Parkinson's disease indicates a positive effect after 8 weeks of daily T-PEMF treatment on motor function, though only significant in patients treated early in disease progression.[12] To our knowledge, no studies have to date looked at T-PEMF as a treatment option for post-concussion syndrome.

The purpose of the present pilot study was to assess the feasibility and tolerability of T-PEMF treatment in patients with post-concussion syndrome. The primary hypothesis is that this patient group will tolerate treatment as observed in studies of depressed patients where no significant side effects were reported.[10] Furthermore, we hypothesized that short-term daily T-PEMF treatment can have a cerebral effect that translate to a lasting reduction in chronic symptoms from concussion.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was set up as an eight-person pilot study to determine proof-of-concept prior to a potential larger randomized controlled trial. Recruitment was done through the Danish Concussion Patient Union (Hjernerystelsesforeningen) by postings on their website, their social media platforms, flyers at their classes and seminars and through their newsletter. Patients were screened with a questionnaire over e-mail and follow-up questions on the phone and/or in person prior to inclusion. Patient assessments occurred at the Neurology Department of Rigshospitalet, Copenhagen, Denmark.

The patients received 5 weeks of daily 30 minutes T-PEMF treatment as described below. Primary outcome was tolerability. Patients were given a diary to fill daily. They were instructed to note time and duration of treatment along with any new symptom or change in excising symptoms. The diary was explored together with the patient at 2 and 5 weeks of treatment.

Secondary outcome was tendency of effects using Rivermead Post-concussion Symptoms Questionnaire (RPQ) measured at baseline, after 2 and 5 weeks of treatment, and 3 months after ending treatment.

The study was approved by The Ethics committee of the capital region of Denmark (H-16029349S-2017031884) and The Danish Medicines Agency (2017031884) and was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

2.2 | Participants

Eight patients were recruited. One was however excluded after inclusion, but prior to treatment, due to questionnaire inconsistencies (Figure 1).

Inclusion criteria were as follows: (a) Post-concussion syndrome defined by The International Classification of Diseases (ICD-10) or/and Diagnostic and Statistical Manual of Mental Disorder, edition 5 (DSM-V) from a mild traumatic brain injury (mTBI) defined by Head Injury Severity Scale (HISS) and symptoms within 7 days post-trauma; (b) Time from concussion to study inclusion between three and 18 months; (c) Age 18-50; (d) Ability to transport themselves or arrange for transportation to and from study inclusion and follow-up appointments; (e) Danish speaking; (f) Rivermead Post-Concussion Symptoms Questionnaire (RPQ) score at inclusion of 21 or more.

Patients were excluded based on (a) Prior mTBI; (b) History of chronic headache and/or substance abuse; (c) Prior or ongoing psychiatric illness including moderate/severe depression defined as HAM-D17 score ≥ 18; (d) Overuse of over-the-counter analgesics defined by more than 14 days a month of paracetamol, aspirin, codeine and/or NSAID; (e) Overuse of migraine medication defined by more than 9 days a month of sumatriptan and/or rizatriptan; (f) Change in medication 1 month prior to inclusion; (g) Any contraindication to magnetic stimulation including pregnancy, medicine pump implants, cochlea implants, nerve stimulators; pacemaker and cerebral stents; (h) Previous or ongoing diagnosis of malignancy.

At inclusion, patient questionnaires were re-assessed to assure they fulfilled inclusion criteria. Baseline data furthermore included years of education; social status; current medication and dosage including over-the-counter supplements; Hamilton Depression Rating Scale score (HAM-D17); CT or MRI scans as part of concussion work-up; Current concussion treatment, for example, physiotherapy, vision and vestibular rehabilitation, osteopathy, craniosacral therapy, chiropractor, cognitive behavioral therapy, and public service concussion programs. Plans on upcoming pregnancy were assessed in female subjects and a urinary pregnancy test required as was ongoing use of contraception.

Data at 2- and 5-week follow-ups were mainly focused on the Rivermead Post-Concussion Symptoms Questionnaire (RPQ) and Symptom Diary, but also included any practical problems with use of T-PEMF device; change in medication and/or supplements; change in concussion treatment and "Free conversation" were patients were asked about any current stressors such as remodeling of house, new baby, problems with receiving government sick leave payments, and changes in activity levels both professionally (changes in hours of work per week) and at home (eg, change in duration of time able to participate in social events or gain/loss of function such as able to drive car, screen time) Relevant comments from "Free Conversation" are included as personal statements (Table S1).

Data at 3 months following end of treatment included RPSQ; HAM-D17 score; current medication and dosage including supplements and "Free conversation".

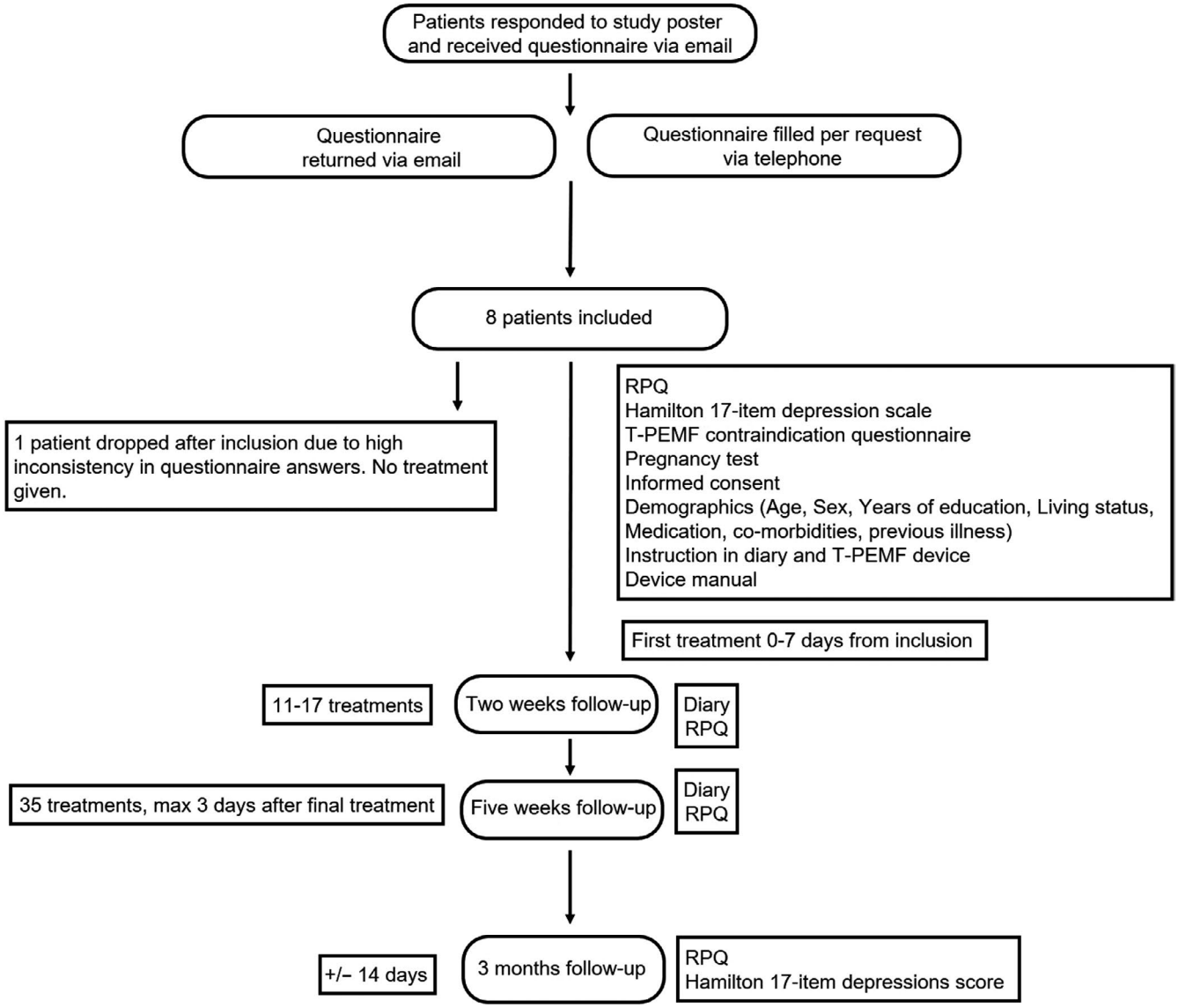

FIGURE 1 Study flowchart

FIGURE 2 The helmet in use. A, Dorsal view (B) Posterior view (C) Side view

2.3 | T-PEMF treatment

The participants received 30 minutes self-administered T-PEMF at home once daily for five consecutive weeks (35 treatments in total). A personal chip card was inserted into the pulse generator recording all T-PEMF device use.

The T-PEMF device used (Re5 NTS Post-concussion Syndrome Treatment System, Re5, Frederiksberg, Denmark) consisted of a

pulse generator and head applicator with seven coils located centro-occipital (one), fronto-parietal (two), anterio-temporal (two), and posterior temporal region (two) (Figure 2).

The principle behind T-PEMF is stimulation with pulsating electromagnetic fields with the same form and frequency as the spontaneous electrical potentials (E-field), surrounding a single neuron.[13] (Figure 3). As described in the figure the principle for treatment is to mimic the naturally occurring E-Fields outside excitable tissue.

2.4 | The Rivermead Post-concussion Symptoms Questionnaire

The Rivermead Post-Concussion Symptoms Questionnaire (RPQ) is a 16-item survey that assesses the severity of the most common post-concussion symptoms on a scale of 0 to 4, with a total score range from 0 to 64 (least to greatest symptom severity).

3 | RESULTS

All 7 patients investigated completed the full 5 weeks of daily 30 minutes of T-PEMF treatment, verified by the T-PEMF recording device. Patient 3 had problems with device turning off at 20 minutes instead of the scheduled 30 minutes but completed treatment by turning device back on and timing 10 minutes himself.

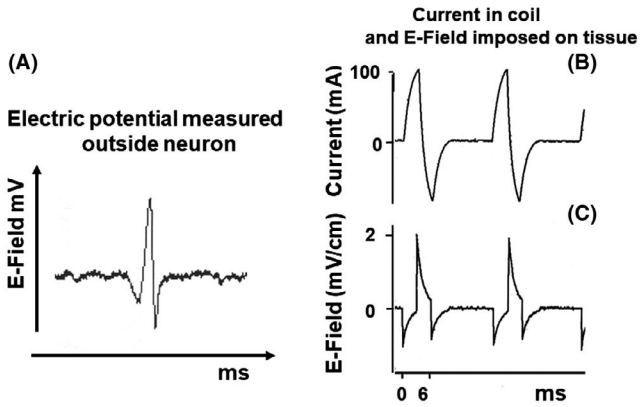

FIGURE 3 Shape of electric fields imposed on the brain tissue. The pulses are composed such that they in shape, frequency, and amplitude mimic pulses recorded from neurons seen with an externally placed electrode recording action potential propagation (A). B, is the current in the T-PEMF coils with 50 Hz pulses applied by alternating ± 50 Volts. C, is a measurement of the electric field in a sense coil adjacent to the coil. It can also be calculated as: E-field = dB/dt · k where B is the magnetic field, t is time, and k is a constant. C, is thus the electric fields imposed on brain tissue at 50 Hz. Note that, they are similar to the field in (A) measured outside a neuron. The E-field is considered to be active up to 8 cm from the coild. The 7 coils will thus affect the brain globally

3.1 | Demographics

Mean age at inclusion was 34 years, mixed female and male subjects with a mean of 17 years education and no or few subscribed medications or other illnesses (Table 1).

3.2 | Discomfort and headache

At week two, all but one reported a transient worsening of pretreatment headache (n = 4) and/or de novo headache type (n = 2) during treatment and a few hours after treatment. De novo headaches were described as "jabs from neck and up" and "warm sensation of forehead." Three patients had accompanying nausea with their headache, which subsided after treatment. Pretreatment photo- and phono-sensitivity was worsened in two patients, but mainly during and a few hours after treatment. Two patients experienced respectively "redness of eyes" and "vibrating sensation of fingers," which was described as a passing symptom only occurring on treatment days one to three.

At week five, the same six patients still experienced headaches when using the device, though less pronounced and for shorter durations. Two patients continued to experience worsening of nausea during and a few hours after treatment, but less over time (Table 2).

3.3 | General outcome of PCS

Five of the seven included patients (Pt.1, Pt.3, Pt.4, Pt.5, Pt.6) felt subjective improvements during the course of the treatment, corresponding to a decrease in RPQ score, ranging from 2% to 61% (Table 3). Patient 4 had improved at the 2-week follow-up but had a bad cold on her 5-week follow-up which due to the nature of RPQ scoring could explain the change in score of her otherwise subjective improvement in PCS symptoms. She had an eye and sinus infection and her RPQ scores were increased in the categories: blurred vision, photosensitivity; dizziness; headache, fatigue, and nausea. Two patients (Pt.2, Pt.7) however worsened during and after treatment and had an increase in RPQ scores. (Tables 3 and S2).

Patient 2 and 7 got worse during and in Pt.7's case also after ending T-PEMF treatment. Pt.2 began vision therapy 4 days after inclusion. Somatic symptoms that worsened included blurred vision, photosensitivity, and sleep disturbances. Despite the increase in RPQ score over the course of treatment with T-PEMF, Pt.2 stated a reduction in over-the-counter pain medication during the study and a "head lightness" at week five that persisted at 3-month follow-up. Pt.7 experienced an overall worsening during the T-PEMF treatment which continued following treatment. Thus, during the treatment (up to week 5) RPQ scores increased from 32 to 40, and noticeably the RPQ scores increased further from 40 to 45 during the 3 months following T-PEMF treatment. Especially, headache, nausea, sensitivity to light, and sleep disturbances were affected. The patient was asked at 2-week follow-up if he wished to discontinue treatment but

TABLE 1 Demographics

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7	Mean
Age at inclusion (years)	29	28	34	42	33	41	30	34
Gender	M	F	F	F	M	F	M	N/A
Years of education	17	14	16	18	18	18	18	17
Medication including supplements	Tabl. Gabapentin 750 mg daily Tabl. Multivitamin daily	Tabl. Panadul 1 g 1-2 times per month Tabl. Vitamin D 10 mcg daily	Tabl. Pamol 1 g, 6 times monthly	Tabl. Pamol 1 g twice monthly	Tabl. Panodil 1 g, 1-2 times per week Tabl. Ipren 400 mg 1-2 times per week	Tabl. Panodil 1 g and Tabl. Ipren 200 mg 9 times monthly Magnesium 350 mg daily Fish oil	Tabl. Panodul 1 g 2-3 times monthly	N/A
Co-morbidities	Backpain Restless leg syndrome	No	No	No	No	Pollen allergy	Colon irritable	N/A
Time since mTBI to study enrollment (months)	5	11	14	4	15	10	16	11 mo
Imaging (normal/abnormal)	No	No	No	MRI (normal)	MRI (normal)	No	MRI and CT (both normal)	N/A

declined. The month after ending T-PEMF intervention (last treatment 28th of November), the patient describes concussion symptoms returning to the same level as prior to study enrollment. In January, the patient started a public service concussion intervention program (BOMI) consisting of occupational-, cognitive-, physio-, and vision therapy and rehabilitation. During January and February up to the 3-month follow-up (27th of February), the patient describes a relapse in symptoms.

For patients 2, 5, and 6, there was feedback of decrease in over-the-counter (OTC) pain medication, and one patient (Pt.1) was able to reduce tablet gabapentin from 750 to 250 mg during and after treatment (Table S1). Patient 7 had an increase in OTC pain medication.

4 | DISCUSSION

The present pilot study was important in order to record tolerably and compliance prior to a potential larger randomized clinical trial. All patients completed full treatment according to the protocol. Two (Pt.2 and Pt.7) of the seven patients enrolled experienced a worsening of PCS symptoms during the study. Patient 2's commencement of vision therapy at the same time as starting T-PEMF treatment made it difficult to properly assess whether her decline was due to negative effects of T-PEMF treatment or vision therapy. As to patient 7, we struggled to explain his worsening in symptoms, especially since they continued to worsen 3 months after ending treatment. The remaining five patients experienced up to 61% reduction (2%-61%) in symptoms during the 5 weeks of T-PEMF treatment that persisted 3 months following treatment.

Previous studies have not found any statistically significant treatment-related side effects using T-PEMF including a sham-controlled double-blind study with 50 patients that compared 5 weeks of active or sham T-PEMF in patients with treatment-resistant major depression.[10]

The proposed effect of T-PEMF on post-concussion syndrome is based on the theory of persistent low-grade neuroinflammation as a driving force of ongoing cognitive deficits following mTBI and on T-PEMF's potential in exerting several neuroprotective effects. Thus, rodent studies have repeatedly demonstrated an inflammatory response following mTBI with acute and delayed activation of microglia and astrocytes and an increased cytokine production both systemically and within the brain.[14] Recently, the first study in humans using molecular imaging demonstrated neuroinflammation after mTBI was published, with findings indicating neuroinflammation of deeper brain regions 3-4 months after mTBI, and with correlation to presence of post-concussion symptoms.[15]

T-PEMF is the newest in a long line of non-invasive brain stimulation (NIBS) devices, including repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). NIBS is found to affect neural excitability, but with great variability in terms of spatial distribution, strength, and variation of the produced electromagnetic field. T-PEMF differs in its diffuse multifocal stimulation of several cortical regions.

The signaling pathways underlying T-PEMFs effect on neuronal tissue are complex and not fully understood. The pulses have shown to active the Src kinase[13] leading to its phosphorylation on the activation site and dephosphorylation on its inactivation site. This in turn causes an upregulation of mRNA for, that is, brain-derived

TABLE 2 Reported side effects from T-PEMF treatment at two and 5 wks

	Two-week follow-up	Five-week follow-up
Pt.1	None	None
Pt.2	Transient nausea and tension type headache during and a few hours after treatment. Less each week. Headache type familiar to patient.	No specific symptoms during treatment
Pt.3	Worsening of headache and other concussion symptoms especially sound- and light sensitivity during and 1-2 h after treatment. Headache type familiar to patient.	Same side effects as at 2 wks, however less severe and faster to resolve.
Pt.4	During the first few treatments reports of a "feeling of vibration" in fingers. One treatment session gave the patient a "warm sensation of forehead" followed by temple pain (de novo headache type)	Worsening of symptoms in general (headache, dizziness, abdominal pain, eye infection, nausea, fatigue) the last 1-2 wks. No symptoms are specifically changed during or immediately after treatment.
Pt.5	Nausea and headache during and hours after treatment (especially on day two). Headache type familiar to patient.	Gradual improvement in severity and time to resolution of nausea and headache during treatment
Pt.6	Redness of eyes after first treatment and fogginess similar to after alcohol intake. ne episode of stabbing pain in the head on day 12 that only lasted a few minutes ("jabs from the neck and up")	Prickling sensation in head during and 30-60 min after treatment. Headache type new to patient.
Pt.7	Increase in headache, dizziness, fatigue, photo- and phono-sensitivity. Onset of nausea not previously known to the patient. The other symptoms similar to symptoms the patients regularly experienced after concussion. Symptoms occurring during and hours after treatment but improving with each treatment.	Unchanged from 2-week follow-up.

TABLE 3 RPQ scores at baseline, during and following treatment

	Pt.1	Pt.2	Pt.3	Pt.4	Pt.5	Pt.6	Pt.7
Time from mTBI to inclusion (months)	5	11	14	4	15	10	16
RPQ scores\Patient							
1. Baseline	48	21	41	53	31	28	32
2. At 2 wks of treatment	30	27	34	34	24	15	40
3. At end of treatment after 5 wks	25	39	32	52	19	11	36
4. At tree months follow-up	22	37	37	33	17	11	45
Change from 1 to 3	−48%	+86%	−22%	−2%	−39%	−61%	+13%
Change from 3 to 4	−12%	−5%	+14%	−37%	−11%	0%	+25%

Note: Green = percentage of reduction in symptom scores. Red = percentage of increase in symptom scores.

neurotrophic factor (BDNF) and fibroblast growth factor receptor 1 (FGFR1) in neurons.[13,16,17] The authors of a study on depression and T-PEMF proposed this effect as one of the main reasons behind the effects of treatment.[11] BNDF is involved in memory, learning, and higher thinking and is clinically known to significantly increase with exercise.[18] Exercise is currently one of the most effective treatment options available to post-concussion syndrome[19]; the effects hereof might be caused by the increased BDNF. However, exercise does prove difficult for several PCS patient's due to autonomic disturbances leading to difficulties regulating cerebral blood flow properly causing exacerbation of symptoms,[20] and other options of increasing BNDP are therefore desirable. PEMFs anti-inflammatory properties

are proposed to be partly due to its effect in significantly reducing IL-1β, a possible biomarker for cerebral inflammation and seen as an important contributing factor in neuroinflammatory response to head trauma.[16]

Arguably the effects of T-PEMF could be more pronounced in the acute phases following mTBI. Though we did not see a correlation between improvement and time from mTBI in this small selection of patients, a study treating PCS using repetitive transcranial magnetic stimulation (rTMS), a different non-invasive brain stimulation device, found that patients that were within a year of their head trauma had a significant effect of treatment compared to those receiving sham treatment and those over 12 months post-trauma.[21]

4.1 | Study limitations and strengths

Strengths included consistency in scoring of all patients by one of the authors (MP) and ability to confirm compliance of treatment, due to the personalized chip card in the device.

There were several limitations of this study. Recruitment of patients was done mainly through the Concussion Patient Union (Hjernerystelsesforeningen). This could have led to a selection bias in patients. It is possible patients that use the Concussion Patient Union's services are younger and have had post-concussion syndrome for longer time.

Interference from other treatments during the specific treatment window was problematic. We did however not find it ethical to deny the patients seeking alternative non-medical treatments such as visual and physical rehabilitation during the intervention.

The study solely relayed on self-reported measures (eg, RPQ scoring, Symptom Diary) and though three patients had received imaging as part of their concussion work-up (Table 1) expanding future studies to include objective measures such a neurocognitive testing would provide a better insight into the effects of T-PEMF treatment, positive and negative.

5 | CONCLUSIONS

Due to the nature of the study, it cannot form the basis for justifying an effectiveness of T-PEMF treatment for post-concussion syndrome, nor does it include enough patients to determine safety. However, the treatment shows promise and feasibility criteria for compliance and tolerability were meet. Therefore, further studies are justified to confirm effectiveness. Modifications in a potential future study should include expansion of eligibility criteria, change in methods of recruitment, and addition of objective testing. Objective testing could help better capture the subjective changes in life quality described by the majority of the patients and provide understanding to the reasons behind the patients that worsened under treatment.

The data that support the findings of this study are available from the corresponding author upon request.

CONFLICT OF INTEREST

While the study was conducted Steen Dissing (SD) had a 0.6% ownership of the Re5 Company producing the T-PEMF device. The other authors, Claire Prener Miller (CPM), Martin Prener (MP) and Olaf B. Paulson (OBP), have nothing to declare.

AUTHORS CONTRIBUTIONS

CPM took the initiative to the study, participated in planning the study and subject recruitment, had main responsibility for the data analysis and drafting the manuscript. MP was responsible for acquisition of data, revising of article and final approval. SD participated in conception of study design, revising of the manuscript and final approval. OBP supervised all parts of the study and participated in planning, writing the manuscript, and final approval.

ACKNOWLEDGEMENT

We are grateful to Hørslev Fonden, Copenhagen, Denmark for financial support.

ORCID

Claire Prener Miller https://orcid.org/0000-0001-6719-9219
Martin Prener https://orcid.org/0000-0003-1680-8090
Steen Dissing https://orcid.org/0000-0002-0741-907X
Olaf B. Paulson https://orcid.org/0000-0001-7712-8596

REFERENCES

1. Dwyer B, Katz D. Chapter 17- Postconcussion syndrome. *Handbook of Clinical Neurology*. Cambridge, MA: Elsevier; 2018;158:163-178.
2. CovicA, Gorbunova A, Voormolen DC, Master CL, Haagsma JA, Diaz-Arrastia R, von Steinbuechel N. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. *Frontiers in Neurology*. 2018;9:1113. http://dx.doi.org/10.3389/fneur.2018.01113
3. Daish C, Blanchard R, Fox K, Pivonka P, Pirogova E. The application of pulsed electromagnetic fields (PEMFs) for bone fracture repair: past and perspective findings. *Ann Biomed Eng*. 2018;46(4):525-542.
4. Hei WH, Byun SH, Kim JS, et al. Effects of electromagnetic field (PEMF) exposure at different frequency and duration on the peripheral nerve regeneration: in vitro and in vivo study. *Int J Neurosci*. 2016;126(8):739-748.
5. Urnukhsaikhan E, Cho H, Mishig-Ochir T, Seo YK, Park JK. Pulsed electromagnetic fields promote survival and neuronal differentiation of human BM-MSCs. *Life Sci*. 2016;151:130-138.
6. Zhang Y, Ding J, Duan W. A study of the effects of flux density and frequency of pulsed electromagnetic field on neurite outgrowth in PC12 cells. *J Biol Phys*. 2006;32(1):1-9.
7. Tepper OM, Callaghan MJ, Chang EI, et al. Electromagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2. *FASEB J*. 2004;18(11):1231-1233.
8. Bragin DE, Statom GL, Hagberg S, Nemoto EM. Increases in microvascular perfusion and tissue oxygenation via pulsed electromagnetic fields in the healthy rat brain. *Journal of Neurosurgery*. 2015;122(5):1239–1247.
9. Bech P, Lindberg L, Straaso B, Larsen ER. A 2-year follow-up study of patients participating in our transcranial pulsating electromagnetic fields augmentation in treatment-resistant depression. *Acta Neuropsychiatr*. 2015;27(2):119-125.

10. Martiny K, Lunde M, Bech P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol. Psychiatry*. 2010;68(2):163-169.
11. Straaso B, Lauritzen L, Lunde M, et al. Dose-remission of pulsating electromagnetic fields as augmentation in therapy-resistant depression: a randomized, double-blind controlled study. *Acta Neuropsychiatr*. 2014;26(5):272-279.
12. Malling ASB, Morberg BM, Wermuth L, Gredal O, Bech P, Jensen BR. Effect of transcranial pulsed electromagnetic fields (T-PEMF) on functional rate of force development and movement speed in persons with Parkinson's disease: a randomized clinical trial. *PLoS One*. 2018;13(9):e0204478.
13. Rahbek UL, Tritsaris K, Dissing S. Interactions of low-frequency, pulsed electromagnetic fields with living tissue: biochemical responses and clinical results. *Oral Biosci Med*. 2005;2(1):29-40.
14. Collins-Praino LE, Arulsamy A, Katharesan V, Corrigan F. The effect of an acute systemic inflammatory insult on the chronic effects of a single mild traumatic brain injury. *Behav Brain Res*. 2018;336:22-31.
15. Ebert SE, Jensen P, Ozenne B, et al. Molecular imaging of neuroinflammation in patients after mild traumatic brain injury: a longitudinal 123 I-CLINDE single photon emission computed tomography study. *Eur J Neurol*. 2019;26(12):1426-1432.
16. Clausen F. Exploring a new approach to treating brain injury: anti-inflammatory effect of pulsed electromagnetic fields. *Neurosci Lett*. 2012;519(1):1-3.
17. Gessi S, Merighi S, Bencivenni S, et al. Pulsed electromagnetic field and relief of hypoxia-induced neuronal cell death: the signaling pathway. *J Cell Physiol*. 2019;234(9):15089-15097.
18. Ploughman M. Exercise is brain food: the effects of physical activity on cognitive function. *Developmental Neurorehabilitation*. 2008;11(3):236-240.
19. Leddy JJ, Wilber CG, Willer BS. Active recovery from concussion. *Curr Opin Neurol*. 2018;31(6):681-686.
20. Miranda NA, Boris JR, Kouvel KM, Stiles L. Activity and exercise intolerance after concussion: Identification and management of postural orthostatic tachycardia syndrome. *J Neurol Phys Ther*. 2018;42(3):163-171.
21. Moussavi Z, Suleiman A, Rutherford G, et al. A Pilot Randomised Double-Blind Study of the Tolerability and efficacy of repetitive Transcranial Magnetic Stimulation on Persistent Post-Concussion Syndrome. *Scientific Reports*. 2019;9(1). http://dx.doi.org/10.1038/s41598-019-41923-6

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Miller CP, Prener M, Dissing S, Paulson OB. Transcranial low-frequency pulsating electromagnetic fields (T-PEMF) as post-concussion syndrome treatment. *Acta Neurol Scand*. 2020;142:597–604. https://doi.org/10.1111/ane.13300