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SHORT COMMUNICATION

Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study

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Abstract This study examined whether a non-thermal, non-invasive, pulsed electromagnetic field (PEMF), known to modulate the calmodulin (CaM)-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling pathway, could reduce pain in early knee OA. This randomized, placebo-controlled, double-blind pilot clinical study enrolled 34 patients. Patient selection required initial VAS ≥4, 2 h of standing activity per day, and no recent interventions such as cortisone injections or surgery. Results showed VAS pain score decreased in the active cohort by 50 ± 11 % versus baseline starting at day 1 and persisting to day 42 ($P < 0.001$). There was no significant decrease in VAS versus baseline at any time point in the sham cohort ($P = 0.227$). The overall decrease in mean VAS score for the active cohort was nearly threefold that of the sham cohort ($P < 0.001$). The results suggest that non-thermal, non-invasive PEMF therapy can have a significant and rapid impact on pain from early knee OA and that larger clinical trials are warranted.

Keywords Knee OA · PEMF · Calmodulin · NO signaling

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Introduction

PEMF have been employed for the conservative treatment of knee OA with varied success [1]. A recent meta-analysis concluded PEMF improved clinical scores and function in patients with osteoarthritis of the knee and should be considered as adjuvant therapies in their management [2]. It has recently been suggested that PEMF signals can act as first messengers in the CaM-dependent signaling pathways that orchestrate the release of cytokines and growth factors in cellular responses to injury [3]. This has enabled PEMF signals to be successfully configured a priori to modulate such tissue repair pathways [4–13]. A therapeutic target for the relief of knee OA pain is the CaM-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) cascade [14], which can modulate blood, as well as lymph flow [15]. This same pathway also modulates the release of inflammatory cytokines, such as interleukin-1beta (IL-1β) [16] and growth factors such as basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF) [17].

PEMF signals have been shown to modulate the CaM-dependent NO signaling cascades in articular chondrocytes [9] and other cells [3] using CaM antagonists, and NO and downstream inhibitors. These signals have also been reported to accelerate cutaneous wound repair by 59 % and Achilles' tendon repair by 69 % at 21 days in rat models; angiogenesis as quickly as 7 days in a thermal myocardial necrosis rat model, wherein L-NAME, a nitric oxide synthase inhibitor, blocked the PEMF effect [5]; and rapidly decrease post-operative pain concomitant with an equally rapid reduction of IL-1β in the wound bed in a double-blind, randomized, human clinical trial [10]. This study was, thus, designed to determine whether PEMF, configured to modulate the CaM/NO/cGMP signaling pathway, would reduce pain in early knee osteoarthritis.

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Materials and methods

This double-blind, placebo-controlled, randomized pilot study was approved by the Institutional Review Board at Henry Ford Hospital and all enrolled patients gave informed consent. The primary outcome measure was VAS pain score on a 0–10 cm scale with respect to baseline in each cohort. Although consensus guidelines suggest a 20 % decrease in VAS as the minimum clinically relevant difference in knee OA pain [18], a 40 % difference was chosen as the clinically desirable outcome. Thus, prior to the start of this study, a sample size analysis, assuming a 40 % (±35 % SD) decrease in pain scores from PEMF treatment, suggested a minimum of 14 patients per group were needed. Patient selection required that subjects have knee pain for at least 3 months with an imaging study that confirmed articular cartilage loss, an initial VAS score ≥4, and at least 2 h of daily standing activity in a physical occupation. Patients with rheumatoid arthritis, gout, and pregnancy were excluded. Patients with cortisone injections, surgery, or an effective viscosupplementation series within the past 6 months were excluded. Patients with implanted electronic devices were excluded. Patients on disability or with third party claims were excluded. Since all patients were actively employed, NSAID use was unrestricted. PEMF therapy was the only addition to the current standard of care.

A PEMF signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at 1 burst/s delivering a peak induced electric field of 34 ± 8 V/m in the knee from the portable battery operated device shown in Fig. 1 (Palermo, Ivivi Health Sciences, LLC, San Francisco, CA), was used for 15 min twice daily. Each device had an inaccessible counter which recorded the total number of treatments for each patient. The device was light weight and patients could easily position the coil directly over the knee, even over clothing. Once manually activated, treatment was automatically applied for 15 min. Manual activation was required for each treatment.

Randomization was performed by the blinded assignment of devices according to their serial numbers. Device randomization was performed by the manufacturer (Ivivi Health Sciences, LLC) and all devices with the randomization code were sent to the Epidemiology Dept at Henry Ford Hospital, from which assignment to patients was controlled. Sham devices were activated with a switch, just as active devices, and both sham and active units had blinking indicator lights. The PEMF signal from these devices does not produce heat or cause any other sensation in tissue. The average in situ magnetic field induced by the PEMF signal employed in this study is at least 1,000-fold below the ambient magnetic field and cannot be detected using standard Gauss meters. Therefore, only measurements with specialized laboratory equipment, not readily available to the patient or health care practitioner, could determine whether a device was active. General unblinding occurred after all data were collected.

Fig. 1 The non-thermal pulsed radio frequency PEMF device used in this randomized, double-blind clinical study on knee OA pain. The device consists of a single loop wire coil with integrated amplifier (Palermo, Ivivi Health Sciences, San Francisco, CA) that delivers a PRF signal configured to modulate the CaM/NO/cGMP signaling pathway, which consisted of a 7-ms burst of a 6.8 MHz sinusoidal carrier repeating at 2 bursts/s, delivering a peak induced electric field amplitude of 34 ± 8 V/m in the knee. The device is portable and easily positioned by the patient over the knee with the Velcro™ strap. The *number* displayed is the number of PEMF treatments

PEMF signal parameters were verified for each device by a third party, who had no contact with patients, at the beginning and end of treatment, with a calibrated field probe (model FCC-301-1-MR1, Fischer Custom Communications, Torrance, CA) connected to a calibrated 100-MHz oscilloscope (model 2358, Tektronix, Beaverton, OR).

Patients were required to self-report maximum daily VAS pain scores on an unmarked horizontal 10 cm line (0 is no pain and 10 is worst possible pain) at baseline (day 0), daily for the first 14 days, then daily from day 29 to day 42. The 2-week gap in VAS data collection was designed to assess for possible accommodation to PEMF therapy. By not reporting VAS scores for 2 weeks, patients would be more likely not to remember their last score. Results were analyzed using the Student's *t* test or one-way repeated measures ANOVA with Holm–Sidek post hoc analysis, as appropriate (Sigmastat 3.0, SPSS). Intent-to-treat analysis using last data carried forward [19] was employed for patients who did not complete the study. Significance was accepted at $P \leq 0.05$. Data are displayed ± SEM.

Results

The portable PEMF devices were well tolerated. No adverse events were reported. Device verification for each patient at the end of treatment revealed all devices to be functioning as randomized. No signal variations or deteriorations were noted in the active devices. The mean ± SD of the total number of treatments delivered by all devices in this study was 80 ± 9 compared with the expected 84, suggesting that devices were used as prescribed by all patients. There were no significant baseline differences in mean age, body mass index (BMI), or Kellgren–Lawrence (K-L) radiographic scores, between active and sham cohorts, as shown in Table 1.

Thirty four patients started treatment. Of these, 19 (14F, 5M) were shams, and 15 (10F, 5M) were actives. The imbalance in treatment groups was due to initial drop outs (entered patients not starting treatment), the total number of available randomized devices, and the sequential distribution of devices over time. Given there were no significant differences in baseline parameters between the cohorts, the imbalance was not a factor. All enrolled patients received PEMF treatment to day 14. Thereafter, 3 active and 7 sham patients dropped out of the study by day 42, citing lack of perceived benefit as the reason, confirmed by VAS scores. Patient flow is outlined in Fig. 2.

Table 1 Baseline patient demographics

Index	Active	Sham	*P* value
Age	55.5 ± 2.5	58.4 ± 2.5	0.434
BMI	33.5 ± 1.9	34.7 ± 1.7	0.644
K-L	2.7 ± 0.33	2.9 ± 0.25	0.532

The results for all enrolled patients show the PEMF signal caused 50 ± 11 % decrease in mean maximum VAS versus mean baseline VAS for the treated group starting on day 1, persisting to day 42 ($P < 0.001$). There was no significant decrease in mean maximum VAS compared with mean start VAS at any time point in the sham group ($P = 0.227$). The overall decrease in VAS scores from baseline was 2.7 ± 0.57 ($P < 0.001$) for the active group versus 1.5 ± 0.41 ($P = 0.168$) for the sham group. There was no significant difference in mean start VAS between the active and sham groups (Active = 6.8 ± 0.31, Sham = 7.1 ± 0.34, $P = 0.430$). A summary of mean intra-cohort VAS scores from baseline to day 42 for all patients is shown in Fig. 3. Inter-cohort VAS scores are compared in Table 2. As may be seen, the overall pain decrease in the active cohort was approximately 60 % by

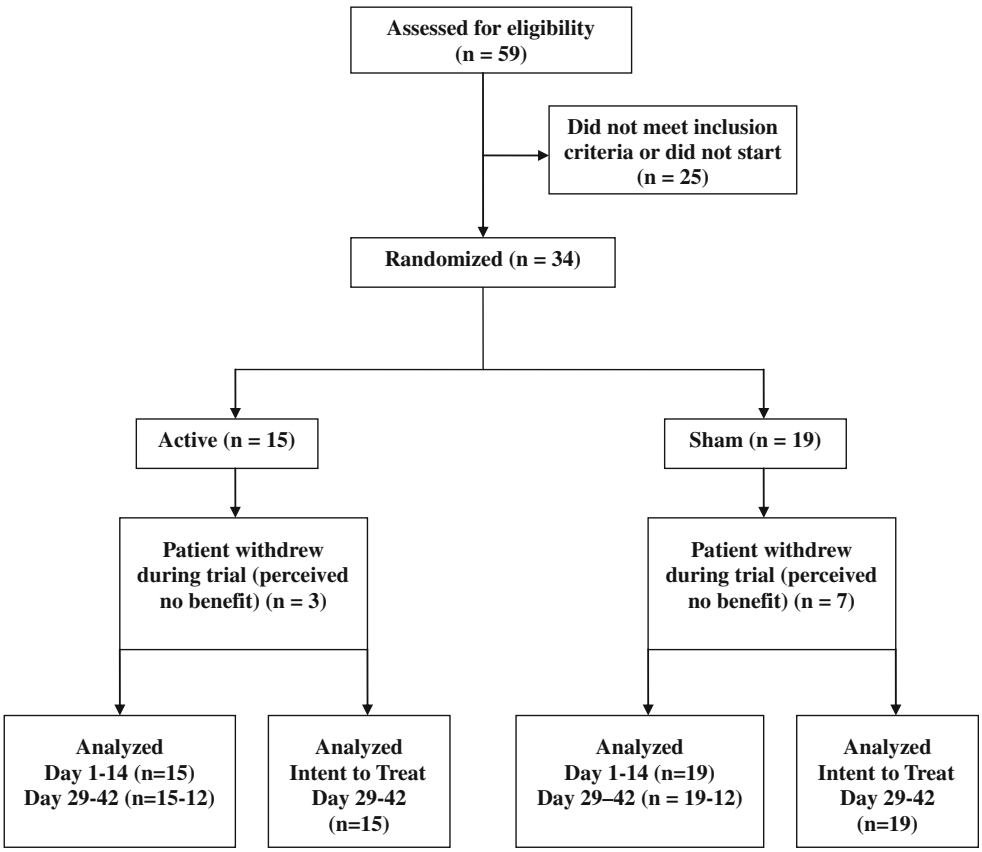

Fig. 2 Randomized pilot clinical trial on PEMF effect on knee OA pain: patient flow chart

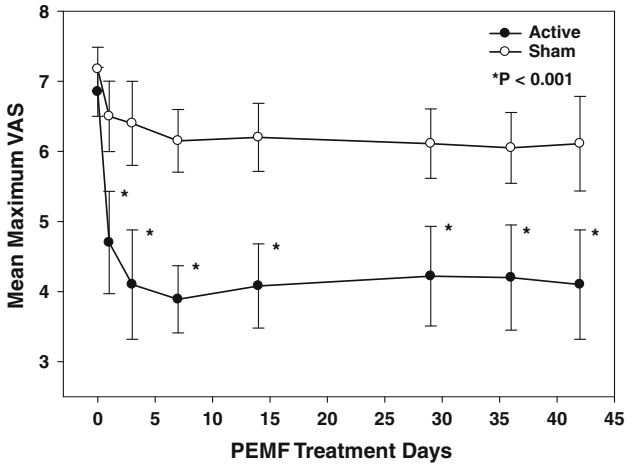

Fig. 3 Effect of a radio frequency PEMF signal, configured, a priori, to target the CaM/NO/cGMP signaling pathway, on pain from early stage knee OA. This is a repeated measures intra-cohort comparison which shows this signal caused a nearly 60 % reduction in mean VAS pain scores within the first 3 days for the active cohort, which persisted to day 42 for all enrolled active patients. There was no significant difference in mean VAS scores for the sham cohort at any time point, or in mean baseline VAS scores for the active and sham cohorts

Table 2 Mean VAS pain scores: inter-cohort comparisons

Day	Mean VAS active	Mean VAS sham	*P* value
Baseline	6.85 ± 0.33	7.18 ± 0.31	0.481
3	4.13 ± 0.48	6.84 ± 0.43	0.008*
14	4.08 ± 0.60	6.21 ± 0.50	0.011*
29	4.22 ± 0.66	6.11 ± 0.52	0.041*,[a]
42	4.19 ± 0.71	6.11 ± 0.54	0.036*,[a]

* Significantly different

[a] Intent-to-treat

day 42 ($P < 0.001$), whereas in the sham cohort pain decrease was only 18 % ($P = 0.206$). Thus, even assuming a placebo effect, pain decrease was approximately three-fold greater in the active cohort, within the first 3 days of PEMF treatment.

Discussion

The results from this randomized, double-blind, placebo-controlled study demonstrate that non-thermal, non-invasive PEMF, when configured to dose CaM-dependent NO/cGMP signaling, has a significant and rapid impact on pain from early knee OA. The intervention is novel since the patient population treated did not have end stage disease and were required to be on their feet at least 2 h a day. The PEMF treatment time is short (15 min), and use of the device did not interfere with work or off-work activities. Review of patient notes reveals that the majority of patients in the active group were convinced the PEMF treatment had a functionally significant impact on their pain. It is noted that more than twice as many sham versus active patients opted out of the study after the initial 14-day phase.

In persons with knee OA, bone attrition, bone marrow lesions, synovitis/effusion, and meniscal tears are all causes of knee pain [20]. Effusion (edema) is one manifestation of the inflammatory response to bone injury attributable to knee OA. The rapid onset response in the active group is remarkably similar to that reported for a similarly configured PEMF signal, which produced approximately 2.5-fold reduction in pain from breast reduction surgery within 5 h post-op [10]. That study also showed IL-1β, a master inflammatory cytokine, was concomitantly reduced by approximately 2.5-fold in the wound bed. Certainly, there are no data from this study, which directly support a PEMF effect on CaM-dependent NO signaling. However, it is reasonable to speculate that the effect of PEMF on knee OA pain reported here could involve modulation of CaM-dependent NO signaling which is known to rapidly reduce edema (effusion) [15]. This is consistent with the rapid effects of similar PEMF signals reported on edema from ankle sprains in randomized studies [21, 22] and could explain the rapidity of the PEMF effect in this patient population.

The persistence of pain reduction in active patients to day 42 suggests daily use of PEMF produced a sustained anti-inflammatory effect, perhaps via down-regulation of IL-1β, which may slow the progression of knee OA. Obviously, this pilot study was not designed to assess the effect of this PEMF treatment on OA per se in this patient population. However, it is useful to consider evidence suggesting that PEMF could attenuate the effects of the prolonged inflammation caused by IL-1β. Thus, weak electric fields partially reversed the decrease in the production of extracellular matrix caused by exogenous IL-1β in full-thickness articular cartilage explants from osteoarthritic adult human knee joints [23]. Similar studies showed the decreased production of proteoglycans caused by exogenous IL-1β was reversed by PEMF in bovine articular cartilage explants [24]. There are also reports that PEMF can increase proliferation in chondrocyte cultures [9, 25]. Finally, there are reports which suggest that PEMF can affect the progression of OA [26] and heal cartilage defects in animal models [27, 28].

The rapid and substantial effect of non-thermal, non-invasive PEMF therapy on knee OA pain in this double-blind, randomized, placebo-controlled pilot clinical study are promising enough to warrant further larger studies designed to confirm the PEMF effect on pain, in which

standard clinical measures of function, as well as effusion and inflammatory markers are included. Once confirmed, use of this PEMF therapy may provide an important simple and economical adjunct for the non-invasive, non-pharmacological treatment of OA.

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Conflict of interest FN and RZ have no association with Ivivi Health Sciences. AAP is a basic science consultant to Ivivi Health Sciences and had no contact with patients in this study.

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