Radio Frequency PEMF Therapy Produces Rapid and Substantial Pain Reduction in Early Knee Osteoarthritis: A Randomized Double-Blind Pilot Study.

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Non-Thermal Radio Frequency PEMF Therapy Produces Rapid and Substantial Pain Reduction in Early Knee Osteoarthritis: A Randomized Double-Blind Pilot Study.

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Ivivi Health Sciences, LLC, San Francisco, CA manufactured the PEMF devices utilized in this study and provided partial financial support. AAP received compensation as Chair of the Scientific Advisory Board of Ivivi Health Sciences, and had no contact with patients in this study,

ABSTRACT

Objective: To determine if a non-thermal, non-invasive, pulsed electromagnetic field (PEMF), known to target the calmodulin (CaM)-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling pathway, could reduce pain in early knee OA.

Methods: This was a randomized, placebo-controlled, double-blind pilot clinical study which enrolled 34 patients. The primary outcome measure was mean VAS pain score vs baseline. Patient selection required initial VAS ≥ 4, two hours of standing activity per day, and no recent interventions such as cortisone injections or surgery. The active PEMF device automatically delivered a 15 min treatment. Sham devices were identical, but emitted no signal. PEMF was a 7 msec burst of 6.8 MHz radio frequency repeating at 2 bursts/sec. Peak induced electric field averaged 34 V/m in tissue. Patients self-treated twice daily for 42 days.

Results: The PEMF cohort had a nearly 2-fold decrease in VAS pain score vs baseline by the end of day 1, which persisted to day 42 ($P < 0.001$). There was no significant decrease in VAS vs baseline at any time point to day 42 in the sham cohort ($P = 0.227$). The overall decrease in mean VAS score for the active cohort was nearly 3-fold that of sham cohort.

Conclusions; The results demonstrate that the non-thermal, non-invasive PEMF utilized in this randomized, double-blind, placebo-controlled clinical study has a significant and rapid impact on pain from knee OA.

In an effort to avoid pharmacological approaches to the conservative treatment of knee OA, non-thermal electromagnetic fields (EMF) have been employed with varied success. Capacitively coupled electric fields are used clinically in end stage knee OA and require the use of two electrodes in skin contact across the knee for 10 hours each day. The time required to notice a clinically significant difference may be as long as 75 days. This treatment appears to delay the time to total joint replacement in some individuals[1]. A recent meta-analysis concluded pulsed electromagnetic fields (PEMF), which are inductively coupled using a wire coil, improve clinical scores and function in patients with osteoarthritis of the knee and should be considered as adjuvant therapies in their management[2]. That study further concluded the evidence is still equivocal for an effect of PEMF on knee OA pain. The studies compared a wide variety of PEMF signals, from pulsed radio frequency (PRF) to very low frequency (ELF), none of which supplied adequate information concerning PEMF dosimetry. Proper accounting of PEMF dosimetry for knee OA requires that *in situ* electromagnetic field parameters be well defined[3,4].

It is relevant to review the state of knowledge of the mechanism of non-thermal PEMF bioeffects. Bone growth stimulator (BGS) signals, that are now part of the standard armamentarium of orthopedic practice worldwide for the treatment of recalcitrant bone fractures[5-7], were configured to modulate ion binding and/or transmembrane transport in second messenger pathways by ascribing a signaling function to the induced electric field[3]. Separately, radio frequency signals, originally developed for deep tissue heating (diathermy), were shown to produce biological effects when applied at non-thermal levels using pulse-modulation techniques to produce pulsed radio frequency (PRF) signals[8]. At the cellular level, numerous studies report that BGS, PRF and other EMF signals modulate the release of growth factors and cytokines[9-14]. At the molecular level EMF has been shown to modulate calmodulin (CaM)-dependent enzyme

activity[15,16].

This abundance of data led to the suggestion that a non-thermal EMF signal could be configured to modulate the physiologically meaningful CaM-dependent signaling pathways that orchestrate the release of cytokines and growth factors in cellular responses to injury[3,17-20]. One such pathway is the CaM-dependent nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling pathway, a rapid response cascade[21] which can modulate peripheral and cardiac blood flow, as well as lymph flow, in response to normal and inflammatory physiologic demands[22]. This same pathway also modulates the release of inflammatory cytokines, such as interleukin-1beta (IL-1β)[23] and growth factors such as basic fibroblast growth factor (FGF-2) and vascular endothelial growth factor (VEGF)[24] which have pleiotropic effects on cells involved in tissue repair and maintenance.

PRF signals specifically configured, *a priori*, to be effective in the NO/cGMP pathway, have been shown to modulate these early signaling cascades in articular chondrocytes, and endothelial and neuronal cells using CaM antagonists, and NO and sGC inhibitors[13,19]. Such PRF signals have also been shown to accelerate cutaneous wound repair by 59% and Achilles' tendon repair by 69% at 21 days in rat models[25,26], and angiogenesis as quickly as 7 days in a thermal myocardial necrosis rat model[8], as well as to 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 study[14]. This study was, thus, designed to determine if a non-invasive, non-pharmacological pulsed electromagnetic field (PEMF) configured to modulate the CaM/NO/cGMP signaling pathway would reduce pain in early knee osteoarthritis.

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[27], 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 hours 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 PRF signal, configured, *a priori*, to accelerate Ca^{2+} binding to CaM in the NO/cGMP signaling pathway, consisting of a 7 msec burst of 6.8 MHz sinusoidal waves repeating at 1burst/sec delivering a peak induced electric field amplitude of 34 ± 8 V/m in the knee from the portable battery operated device shown in Figure 1 (Palermo, Ivivi Health Sciences, San Francisco, CA), was used for 15 minutes twice daily, and as needed for pain relief. Each device had an inaccessible counter which recorded the total number of treatments for each patient (see Fig 1). The PRF 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 PRF signal from these devices is non-thermal, i.e., it does not produce heat or cause any other sensation in tissue related to nerve membrane depolarization. The average *in situ* magnetic field induced by the non-thermal radio frequency PEMF signal employed in this study is at least 1000-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. Thus, physicians, practitioners and patients could not know whether a device was active or sham throughout the study. General un-blinding occurred after all data was collected.

PRF signal parameters were verified for each device by a third party, who had no contact with patients, at the beginning and end of PEMF 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). Measurement of the PEMF signal distribution in a tissue phantom and in air provides an accurate map of induced electric field in tissue[28]. Such plots revealed that the mean peak amplitude of the electromagnetic field in the treated knee from active devices was 34 ± 8 V/m.

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. Each daily VAS score was placed in a sealed envelope. The two week gap in VAS data collection was designed to assess for possible accommodation to PEMF therapy, which could result in loss of effect. By not reporting VAS scores for two weeks, patients would be more likely not to remember their last score. Results were analyzed using Mann-Whitney, one-way ANOVA or repeated measures ANOVA, as appropriate. Significance was accepted at $P \leq 0.05$. Data is displayed ± SEM.

RESULTS

The portable PRF 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 PRF 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 to 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 I.

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. The results for all enrolled patients show the PEMF signal caused a significant initial decrease in mean maximum VAS of approximately 2-fold, i.e., about 45% of mean baseline VAS for the treated group by the end of day 1, which persisted to day 42 ($P < 0.001$). In contrast, there was no significant decrease in mean maximum VAS compared to mean start VAS at any time point to day 42 in the sham group ($P = 0.227$). The overall decrease in VAS scores was 2.7 ± 0.47 ($P < 0.001$) for the active group vs 1.0 ± 0.31 ($P = 0.168$) for the sham group, a nearly 3-fold difference. 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 VAS scores from baseline to day 42 for all patients is shown in Figure 2. Inter-cohort comparisons to day 42 showed mean VAS scores for the sham cohort were consistently about 1.5-fold higher from day 1 to day 42, as shown in Table II. There were no significant differences between mean VAS scores on day 29 compared to day 14, for either active ($P = 0.959$), or sham ($P = 0.713$) cohorts.

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 knee OA. This is in contrast to the many PEMF studies with equivocal results on knee OA, none of which employed signals specifically configured to target anti-inflammatory biochemical cascades[2]. 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 two hours 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 vs 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[29]. Effusion (edema) is one manifestation of the inflammatory response to bone injury attributable to knee OA. Others have proposed that CaM-dependent NO production can relieve OA pain by increasing circulation, decreasing nerve irritation, and decreasing inflammation[30]. Injury, e.g., of mechanical origin, causes cytosolic Ca^{2+} to increase above its homeostatic levels, immediately activating CaM, which, equally immediately, activates endothelial and/or neuronal nitric oxide synthase, eNOS and nNOS, respectively (both are also known as constitutive, cNOS)[31]. Once cNOS is activated by CaM it converts L-arginine to citrulline, releasing one molecule of NO[32], which activates sGC, which catalyzes the synthesis of cGMP[21], which is the body's natural anti-inflammatory signaling cascade. This pathway is sensitive to PEMF via its effect on Ca/CaM binding. The result is that both transient NO production and cGMP release can be increased significantly by PEMF[19].

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 hours post-op[14]. That study also showed IL-1β, a master inflammatory cytokine, was concomitantly reduced by approximately 2.5-fold in the wound bed. Although there is no directly supporting data from this study, it is reasonable to speculate that the effect of PEMF on knee OA pain reported here also involved the down-regulation of IL-1β, with its consequent rapid effect on inflammation (effusion), in this patient population. Thus, in contrast to other PEMF signals which have produced equivocal results for knee OA pain, the

new signal used in this study was configured based on the vast cited biological, animal and clinical evidence that this signal modulates CaM-dependent signaling pathways by modulating CaM-dependent NO release.. For an injury such as knee OA, this can produce immediate vaso and lymph dilatation, which would result in rapid reduction of edema (effusion) with the concomitant rapid reduction of pain observed here.

The persistence of pain reduction in active patients to day 42 suggests daily use of PEMF produced a sustained anti-inflammatory effect, 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 the evidence that PEMF can 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[33]. Similar studies showed the decreased production of proteoglycans caused by exogenous IL-1β was reversed by PEMF in human chondrocyte cultures[34] and in bovine articular cartilage explants[35]. There are also reports that PEMF can increase proliferation in chondrocyte cultures[36-39], including one which recently showed PEMF increased DNA synthesis in articular chondrocyte cultures via CaM/NO/cGMP signaling[13]. Finally, there are reports which suggest that PEMF can affect cartilage homeostasis[40], the progression of OA[41], and heal cartilage defects in animal models[42,43].

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 treatment of OA.

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TABLE 1

Baseline Patient Demographics

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

TABLE 2

Mean VAS Pain Scores: Inter-Cohort Comparison

Day	Mean VAS Active	Mean VAS Sham	P value
Baseline	6.85 ± 0.33	7.18 ± 0.31	P = 0.481
1	4.30 ± 0.67	6.43 ± 0.50	P = 0.017*
7	3.94 ± 0.68	6.15 ± 0.45	P = 0.002*
14	3.98 ± 0.55	6.16 ± 0.49	P < 0.001*
29	3.64 ± 0.64	5.84 ± 0.50	P = 0.015*
36	3.63 ± 0.65	5.59 ± 0.51	P = 0.003*
42	3.76 ± 0.75	5.64 ± 0.68	P = 0.023*

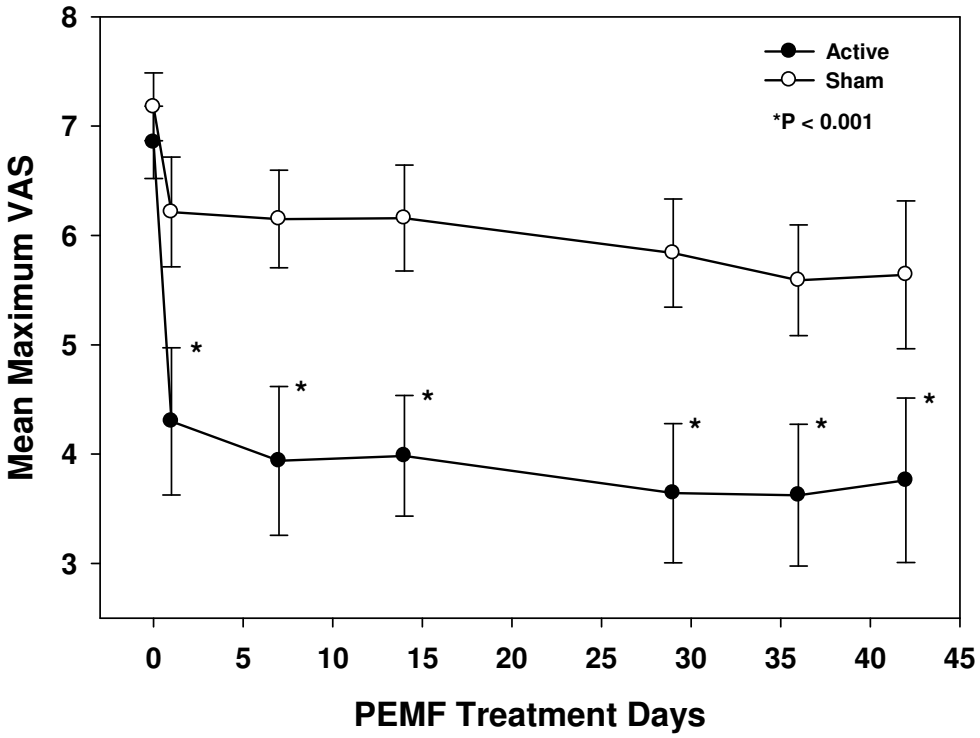
* significantly different

Figure Legends

Figure 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) which delivers a PRF signal configured to modulate the CaM/NO/cGMP signaling pathway, which consisted of a 7 msec burst of a 6.8 MHz sinusoidal carrier repeating at 2 bursts/sec, 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.

Figure 2: 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 signal caused a nearly 2-fold reduction in mean VAS pain scores within the first 24 hours 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**.**

Nelson et al., Figure 1



Nelson et al., Figure 2