AMERICAN SOCIETY FOR LASER MEDICINE AND SURGERY

LATE-BREAKING ABSTRACTS

ABSTRACTS

CUTANEOUS LASER SURGERY

#LB1

HIGH POWERED BLUE LIGHT PROPERTIES IN SKIN, BONE, MUSCLE, CARTILAGE AND FAT

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Background: A high-power blue semiconductor laser system was developed and utilized in order to ascertain potential clinical indications using a variety of animal tissues. This highly efficient, handheld device was constructed using new laser technology, and may be of significant interest in both the medical and industrial worlds.

Study: This study utilized a high intensity 446 nm semiconductor laser system in two modes to ascertain the laser tissue interaction in skin, muscle, fat, cartilage and bone. Using multi beam and single beam configurations, continuous wave (CW) power was delivered with intensities between 10 and 1000 W/mm2. Tissues were exposed with pulse durations from 100 msec to multiple seconds. Direct visual observation of laser tissue interaction was observed and analyzed histologically.

Results: Both modalities induced striking vaporization of skin, the multibeam module being more efficient at debulking tissue, and the single module providing efficient drilling and tissue incision. Muscle similarly could be drilled or vaporized, but fat simply melted. Cartilage had a unique response in that, at low powers, this device could be used for cartilage shaping, and at high powers, creating clean and discrete holes of up to one centimeter. Histologically, full thickness skin vaporization was confirmed with a high degree of coagulation and few or no red blood cells in tissue specimens.

Conclusion: Blue wavelengths have not previously been described in this capacity. We have demonstrated that high power CW blue laser light can efficiently vaporize skin, muscle and cartilage with little or no bleeding. This could hold significant implications for the future in cutaneous laser surgery, and also robotic endoscopic surgeries, in particular for otolaryngology, orthopedic, urological, pulmonary, and potentially neurological surgery.

#LB2

EFFECTS OF POWER DENSITY AND PULSE MODULATION ON ABLATIVE FRACTIONAL LESION GEOMETRY

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Background: Ablative fractional laser treatments have become widely used. They are typically characterized by wavelength, pulse energy and spot size. While effects of power density have been investigated for large-spot, standard ablative techniques, there is very limited data available related to the effects of power density for ablative fractional lesions. It is also a challenge to vary in a controlled manner the power density of ablative CO_2 laser pulses, as they have typically a very irregular pulse profile. We used a custom-built, high-frequency pulse-width-modulated CO_2 laser to investigate the effects of variation in power density on fractional lesion geometry.

Study: Full thickness human skin samples, procured as discarded tissue from abdominal surgery, were used for the tissue exposures. An UltraPulse CO_2 laser (Lumenis, Yokneam, Israel) was modified to allow for a high-frequency pulse-width-modulation of the laser. This allowed the generation of quasi-CW mode pulses over a wide range (1–0 W) of output power in a controlled manner. The energy per pulse was kept at a constant level of 100 mJ per pulse with a constant spot size of 120 μm. The resulting fractional lesion geometry was assessed and quantified by histology.

Results: Reduction of power density resulted in a reduction of ablation depth in particular for power densities of 20 W and lower. Ablation and coagulation zone diameters were relatively independent over a wide power range. For power levels of less than 5 W, the ablation zone diameter was decreased and the coagulation zone increased.

Conclusion: Power level has a significant effect on the ablation depth and coagulation zone. This should be taken into consideration when characterizing ablative fractional lesions.

#LB3

FRACTIONAL CO_2 LASER IN THE TREATMENT OF PRIMARY CUTANEOUS AMYLOIDOSIS: THE POSSIBLE MECHANISMS OF ACTION

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Background: Current available treatments for primary cutaneous amyloidosis are quite disappointing. This study aims at assessing the efficacy of different modes of fractional CO_2 laser in the treatment primary cutaneous amyloidosis.
Study: Twenty five patients, 16 with macular amyloidosis and 6 with lichen amyloidosis were treated by 3–4 sessions of fractional CO_2 laser using two modes, superficial ablative mode [short pulse duration, 500 msec and lower fluences, 10–15 J] and a rejuvination mode [longer pulse durations, 800 msec and higher fluences, 25 J]. Skin biopsies were obtained prior to treatment, and one month after the end of the last sessions. Results were evaluated clinically, histologically [hematoxylin and eosin and Congo red staining] and by image analysis. In order to study the mechanism of action, 3 patients were subjected to additional biopsies on the second, fourth, and sixth day after the first treatment session.
Results: At the end of the treatment sessions, there was a significant improvement in color, texture as well as pruritus in both macular and lichen amyloidosis. Histologically, a significant reduction in the amount of amyloid was demonstrated in hematoxylin and eosin as well as Congo red stained sections. Image analysis showed a decrease in the amount of melanin deposits that did not reach statistical significance. A significant decrease in epidermal thickness was also obtained. Biopsies, taken during the first week, failed to demonstrate any amyloid material in the created microthermal treatment zones. Clinical and histopathological results of the two treatment parameters showed no significant differences. Transient post-inflammatory hyperpigmentation was observed only in two patients in the areas treated by the rejuvenating mode.
Conclusion: Fractional CO_2 is a safe and effective method for treatment of primary cutaneous amyloidosis. The superficial ablative mode is recommended for both clinical subtypes. Although induction of transepidermal elimination is suggested, the exact mechanism of action cannot be determined.

#LB4

COMPARING THE EFFECTIVENESS OF LOW FLUENCE QUALITY SWITCHED Nd:YAG LASER AND LOW FLUENCE QUALITY SWITCHED ALEXANDRITE LASER FOR MANAGEMENT OF MELASMA IN ASIANS: PRELIMINARY STUDY OF A DOUBLE-BLINDED, SIDE-BY-SIDE COMPARISON

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Background: Low fluence quality switched Nd:YAG laser (QSYL) has been used to treat melasma in recent years. Many published articles showed its efficacy and safety while using appropriate parameters. However, there is no report using other wavelengths for the same purpose. This study's objective is to compare the efficacy and safety for melasma using QSYL and quality switched alexandrite laser (QSAL) by side-by-side comparison.
Study: In a prospective double-blinded study, twenty-two Japanese females with melasma on their cheeks, age 49.5 ± 6.2, skin photo type III or IV were enrolled. All cases received QSYL at 1064 nm, 2.13 ± 0.19 J/cm2 on one cheek and QSAL at 755 nm, 0.77 ± 0.12 J/cm2 on the other cheek; both treated 3 passes with 6 mm spot size by randomized manner at 2-weeks apart without any anesthesia or combination therapy. Efficacy was evaluated by two blinded assessors using modified Melasma Area and Severity Index (mMASI), measured data by spectrophotometer and multi-LED reflectance device at 2 to 8 weeks after the last treatment. Patients' preference also recorded.
Results: Number of treatments was 5.2 ± 2.0. mMASI and melanin index on QSYL and QSAL treated side were decreased from 24.6 ± 8.0 to 8.9 ± 5.6 (63.8% improvement), 25.2 ± 7.3 to 8.9 ± 6.8 (64.8%) and 202.8 ± 49.2 to 160.0 ± 35.0 (23.1%), 204.3 ± 50.8 to 157.0 ± 36.5 (23.2%), respectively. Data from multi-LED reflectance device showed similar improvement. All data, including patient preferences showed no statistical differences. All cases responded to treatment and no case showed severe adverse effect including worsening of melasma.
Conclusion: To our knowledge, this is the first study to use a direct side-by-side comparison of QSYL and QSAL to treat melasma using low fluence, multiple passes and treatments. Our data showed both lasers successfully managed melasma in Asians at early weeks of evaluation.

#LB5

RADIOFREQUENCY AND MAGNETIC PULSE FOR BODY CONTOURING: BRAZILIAN MULTI-CENTER EXPERIENCE

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Background: Body Sculpting has been the objective of several procedures. In Brazil, the desire for body contouring improvements is more frequent than ever in everyday practice. In Brazil the combination of Multipolar Radiofrequency and Magnetic Pulse technology has become a common modality in the aesthetic market for non-invasive body contouring.
Study: A multicenter study in Brasil: Belo Horizonte, Campo Grande and Sete Lagoas with 260 subjects, 234 females, 26 males, 20–65 years old (avg 43), body mass index 23–29 (avg 26,4). Treated areas: Abdomen, Flanks, Arms and lipodystrophy areas in legs. 1 or 2 areas of 20 cm × 20 cm during the same session. Subjects were submitted to 6 sessions, spaced 1 week apart. Treatment protocol use Magnetic Pulse and MultiPolar Radiofrequency applied for 60 second over the area treated so that the surface temperature reached 40–42 Celsius. After reaching this temperature kept applying for another 15 minutes, always with the temperature maintained between 40–42 Celsius.
Results: Photographs and circumference measurements were made at fixed reference points (Example: Abdomen Area - Upper, Middle and Lower Abdomen) before treatment and 2 weeks after the final session. Improvement in body contouring was noticed on all subjects. No adverse side effects were recorded during or after the treatment.
Conclusion: In the Brazilian experience the combination of MultiPolar Radiofrequency and Magnetic Pulse has proven to be safe and effective for the purpose of body contouring and with a high subject satisfaction.

#LB6

RESOLUTION OF POST SURGICAL AND FILLER BRUISING USING OPTIMIZED PULSED LIGHT

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EVALUATION OF SAFETY AND EFFICACY OF USING VENUS FREEZE™ SYSTEM FOR THE TREATMENT OF STRIAE (STRETCH MARKS)

a Post Marketing Study

Jeffrey Dover MD, Dermatology & Kenneth Rothaus M.D., Plastic Surgeon

INTRODUCTION

PatStriae or stretch marks are a common skin condition, occurring in both genders but are more prevalent among women. These are linear dermal scars accompanied by epidermal atrophy. They usually occur frequently in numerous physiological and pathological conditions such as adolescent growth spurts, pregnancy, obesity, Cushing's and Marfan syndromes, and long-term systemic or topical steroid use. Decreased expression of collagen and fibronectin genes has also been associated with striae[5].

Although they do not cause any significant medical problems, aesthetically they can be a cause of great concern or psychological stress for many women. Patient demand for non-surgical, non-invasive, and no-downtime skin rejuvenation procedures has grown dramatically over the past decade as new treatments and technologies have been introduced. During this period there has been a substantial increase in the utilization of medical prescriptive skin care. The effects of dermal heating are well recognized to include the modification of collagen structure and stimulation of neocollagenesis (by induction of inflammation that will end in new collagen production by fibroblasts recruited to the heated area). These changes can help improve the appearance of striae due to the increased collagen and elastin. Electrical energy can be advantageous for deep dermal heating as the movement of electrons is not impeded by tissue proteins.

Radiofrequency (RF) energy heats tissue by creating electric fields between two electrodes causing molecules to vibrate. Optical medical devices have been developed in the last 2 decades to treat signs of skin aging. While ablative lasers are used for full or partial skin ablation, intense pulsed light devices are helpful for non ablative elimination of dyschromias but provide minimal value for collagen remodelling. In addition, use of optical energy devices is limited by skin color – restricting its effective use mostly to fair skinned patients.

Venus Freeze is a non-invasive Multi Polar Magnetic Pulses (MP)[2] radiofrequency (RF) energy generating system with 2 applicators; DiamondPolar™ (4 RF electrodes) for treatment of small areas and OctiPolar™ for treatment of large areas. The treatment applicators transmit Bi-Polar RF energy in a method that creates an organized bi-polar RF energy matrix which produces homogeneous heating in the entire treatment area for maximum safety and efficacy, eliminating the need for pre/post cooling mechanisms.

The RF energy transmitted by Venus Freeze mediates thermal stimulation of the extracellular matrix (ECM) in the dermis. This results in an immediate and temporary shrinkage of the collagen triple helix[1,2,3] and subsequently, micro-inflammatory stimulation of the fibroblast which in response produces new collagen (neocollagenesis), new elastin (neoelastogenesis) and ground substances[2,3]. This treatment enhances the tensile strength and elasticity of the dermis with the aid of the newly produced proteins and protoglycans[1,2,4.]

OBJECTIVES

The objective of this study was to evaluate the safety and effectiveness of using Venus Freeze system for the treatment of striae. The safety of the Venus Freeze system for striae treatment was established by physician's assessment/observation of adverse events or side effects such as signs of pain, edema, burn, localized infection, skin pigmentation and texture alterations.

Efficacy of using Venus Freeze system for striae treatment was established by the level of improvement seen visually and by macro photography.

MATERIALS AND METHODS

Sixteen (16) female subjects between the ages of 30 and 72 (mean age = 46.06 years, SD = 10.247) with varying degree of striae participated in this 2 –centre, single-arm pilot study. The subjects were enrolled into the study after meeting all the inclusion/exclusion criteria and providing signed informed consent.

Each subject had a screening assessment and pre-treatment photograph (baseline), six (6) treatment visits which included 5 measurements of striae bands and pre-treatment photographs and 2 post-treatment visits (1 week and 1 month post treatments). The treated areas were photographed using high-resolution macro photography. The pre and post treatment photographs were compared by two independent physicians. A sterile 6" skin ruler was used to measure the length and width of each striae band on the first appointment, prior to each treatment and at the follow up appointments of one week and one month post treatment series.

Each subject received 6 treatments using the Venus Freeze system. Prior to treatment, the treated areas were assessed visually in order to determine skin relevant parameters. The treated areas were photographed and measured in order to allow comparison and assessment of striae improvement following treatment. The treatment area was cleaned thoroughly with soap and water. The skin surface was dried prior to the treatment.

The treatment parameters such as time (10 minutes for an area approximately 4x5 inches) and output energy (60 – 80% with goal is to reach therapeutic in the first minute of treatment) was determined by the physician depending on patient skin type and area of treatment.

For treatment safety evaluation, treated areas were visually assessed for side effects such as edema, erythema, burn, localized infection and skin pigmentation immediately after the treatment. Subjects were also asked questions to assess their willingness to continue with the treatment as well as their rating on observed improvements.

The pre-treatment, during treatment and post treatment measurement of length and width of each striae bands in the treatment area were recorded per subject. The pre-treatment and post treatment photographs were assessed and graded by 2 physicians.

RESULTS

All 16 subjects enrolled in the study completed the treatment and the following results were recorded:

No side effects or undesirable safety events were recorded for any subjects throughout the study.

Fourteen (14) out of the 16 subjects agreed that they noticed visible improvement, one was not sure while one did not see any improvement.

All subjects (100%) agreed that the treatment was comfortable. Figure 1 below shows the graphical analysis of the outcome of the patient survey conducted during the study.

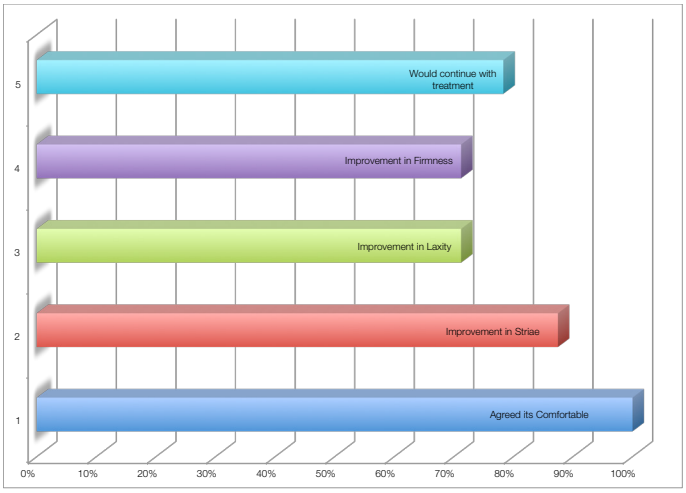
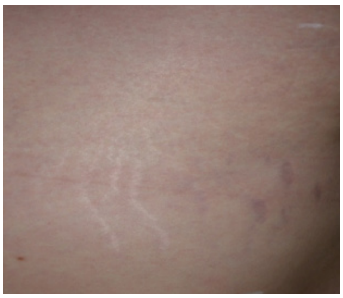
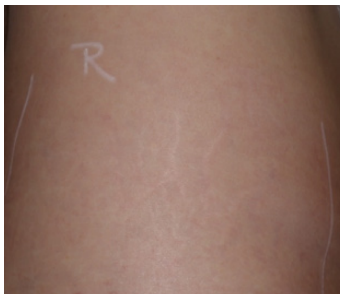


Figure 1

Visual evaluation of pre-treatment (baseline) and post-treatment photographs by the 2 physicians agreed that there was reduction in the visibility of striae after treatment in some of the pairs of photographs reviewed. The Kappa statistical method was used to establish almost perfect agreement on decisions of the 2 physicians at 95% confidence interval (Kappa value of 0.88, SE(κ) = 0.083, 95% CI = 0.71 to 1.04). The following photographs show reduction in the visibility of striae after 6 treatments with Venus Freeze system (Figure 2).



Pre-treatment Photo



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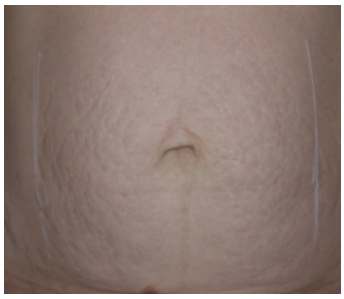

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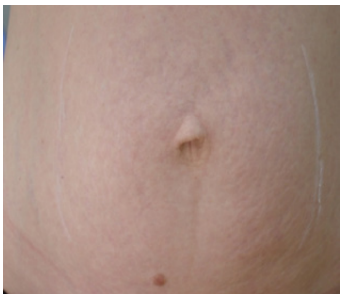

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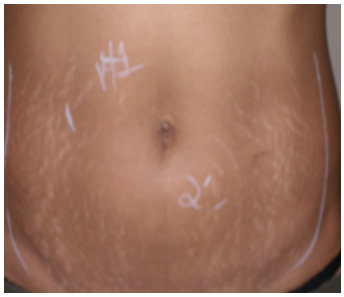
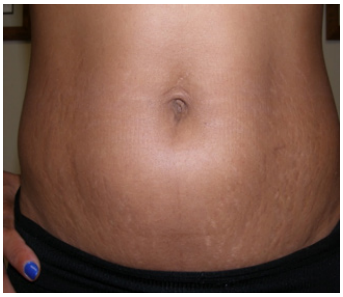


Pre-treatment Photo



Post-treatment Photo

Measurements of length and width of striae bands were statistically analysed to determine the efficacy of Venus Freeze in the treatment of striae (Figure 3). The mean reduction in length of striae bands measured in the 16 subjects after the treatment was 1.031, standard deviation (SD) 0.853. The mean reduction in width of striae bands measured in the 16 subjects after the treatment was 0.160, SD 0.171. Using paired t-test, the reduction in both length and width of striae bands measured at one month post treatment visit compared to baseline measurements were found to be statistically significant at 95% ($p<0.001$).

DISCUSSION AND CONCLUSION

All 16 subjects that participated in this study agreed that the treatment was comfortable and no side effects or undesirable safety events were recorded throughout the 6 weeks treatment. These results support the safety of Venus Freeze.

Fourteen (87.5%) out of the 16 subjects agreed that they noticed visible changes. Further, there were statistically significant reductions in both length and width of striae bands measured at one month post treatment visit compared to baseline measurements in these subjects.

Subjects	Reduction in Length (cm)	Reduction in Width (cm)
1	3.180	0.239
2	0.804	0.159
3	0.638	0.318
4	1.744	0.636
5	2.065	0.000
6	0.635	0.239
7	1.133	0.083
8	-0.067	-0.067
9	1.950	0.125
10	1.533	0.133
11	0.100	0.100
12	0.650	0.200
13	0.700	0.267
14	0.500	0.200
15	0.533	-0.033
16	0.400	-0.033
n (# of subjects)	16.000	16.000
μΔ (mean of Reduction)	1.031	0.160
SD (Standard Deviation)	0.853	0.171
SE (Standard Error)	0.213	0.043
Upper 95% Confidence Interval	1.236	0.201
Lower 95% Confidence Interval	0.826	0.119

Figure 3

In conclusion, the data generated in this study support the safe and effective use of the Venus Freeze system in the treatment of striae.

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RF and Pulsed Magnetic Fields; Achieving and Maintaining Consistent Temperature In-Vivo

James Lacey, MD, Ottawa, Canada

Since the first uses of cosmetic radio frequency (RF), devices have proven the efficacy of this energy when treating rhytides, laxity, focal fat and cellulite. Inconsistencies in temperature and maintaining goal therapeutic temperatures have proven to be the main challenge with traditional radio frequency devices. Pulsed Magnetic Fields (PMF) have proven to accelerate angiogenesis, heal cutaneous wounds, decrease post-surgical pain, reduce edema, negatively influence bacterial and tumour cell growth and repair both bone and nerves, but little has been known of its application in cosmetic medicine until now. . The blending of these two energies has produced a synergistic thermal and non-thermal action inducing long term collagen remodelling and adipose tissue reshaping. Venus Freeze is the first device to deliver a unique algorithm of multi pole RF, allowing the maximum amount of energy to be released while the patient experiences no discomfort due to this deep heating matrix. Each electrode has the potential to be both positive and negative and the rotational system allowing this change to occur one million times per second allows for the treatment to be comfortable and tolerable for patients. The non-thermal PMF energy is emitted simultaneously and continuously throughout the treatment.

Therapeutic threshold is defined as 39 to 41 degrees centigrade on the face or neck and 42 to 45 degrees centigrade on the body. When the tissue is heated to the proposed therapeutic temperature this increases fat cell metabolism and accelerated triglycerides egress from the cell. Increased tissue temperature increases vascular perfusion, which further enhances lipid turnover.[1] Reduction of the convex distension is also partly due to shrinkage of the tissue. Immediate collagen contraction is achieved by the denaturisation of the collagen fibril which subsequently leads to neocollagenesis. The new collagen produces tighter tissue leading to more appreciable measurements.

With the Venus Freeze we have reached the ideal external (epidermal) temperature of 41-43°C, and a sub dermal temperature of 45 - 47°C required for optimal skin tightening. It is possible that the non invasive Venus Freeze can externally achieve the same temperatures as its predeceasing and more invasive energy assisted counterparts.[2]

METHOD

Three patients were selected to participate (women between the ages of 30 – 50 with skin type II

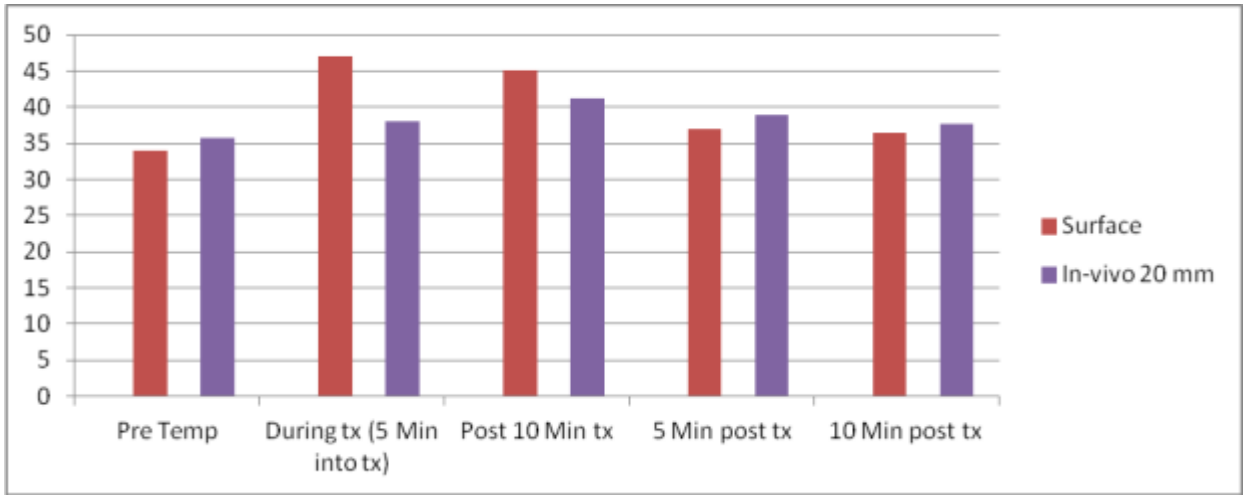
would undergo a Venus Freeze 10 minutes treatment to the abdomen prior to their abdomenoplasty or liposuction surgery. Internal and external temperature was monitored throughout and recorded at set intervals; before the treatment, after 5 minutes during treatment, 5 minutes post treatment and 10 minutes post treatment. The depth of internal monitoring was 20mm. Once the patient is under general anesthetic the abdomen program was selected with the preset values being 80% RF, continuous PEMF and the Octipolar hand piece. The treatment area was cleansed and glycerine was applied. The Octipolar applicator was applied to the skin and treatment commenced using irregular movement s on the skin to cover the area homogenously with heat. After 1 minute the device was placed on pause and the temperature on the surface of the skin was taken using a Fluke 62 mini IR thermometer and the information is recorded. The treatment is then resumed for 4 more minutes. After 4 more minutes the device is placed on pause and the external temperate and the internal temperature were measured using the Fluke Digital Thermometer for the external temperature and the Thermalert TH-8 monitoring thermometer with an MT-23/3 hypodermic needle microprobe at 20 mm depth. The treatment would resume for another 5 minutes. Once the last 5 minutes was complete the temperature was taken again in the same fashion with the same devices at the same depth. After 5 minutes and 10 minutes post treatment, the same temperatures were taken and recorded using the same devices and same depth.

RESULTS

The patients had consistent heating on the surface with no negative responses such as burns, blisters or bruises. All patients reached therapeutic temperature in the first minute of treatment. All patients were able to achieve and maintain higher internal temperatures for the duration of the study which was 10 minutes post treatment. Each of the participants was able to maintain higher therapeutic internal temperatures in comparison to the external temperatures at 5 and 10 minutes post treatment. (see charts)

SUMMARY

While RF and PEMF are both energies which have a achieved success in the area of focal fat, collagen regeneration and tissue tightening, it has been challenging to deliver them with consistency and without pain. The Venus Freeze multipolar system delivers consistent and homogenous heating. This extensive heating effect will aid in achieving reliable and predictable results.



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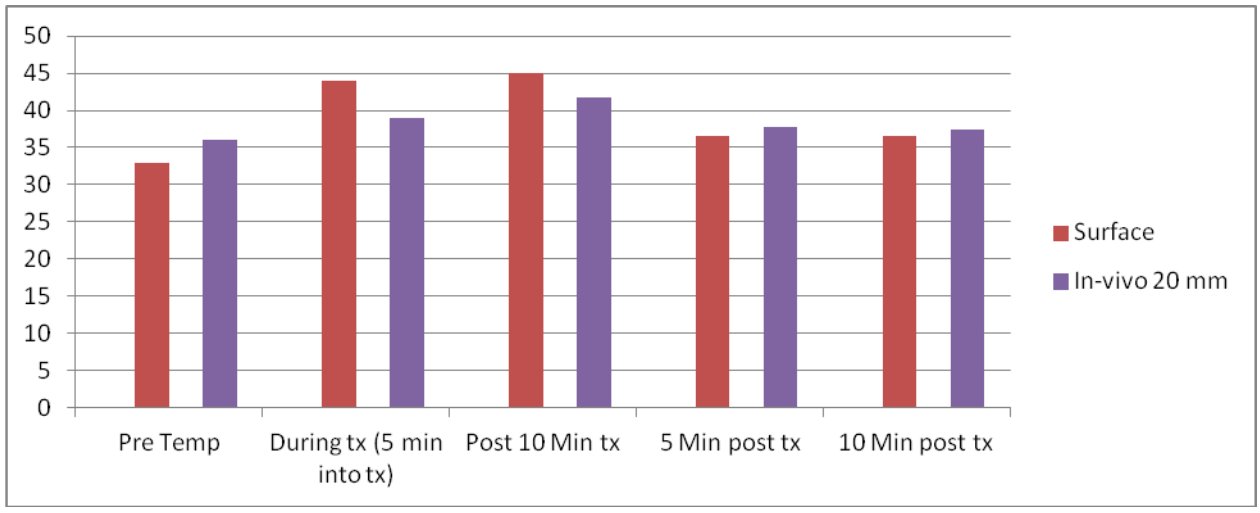

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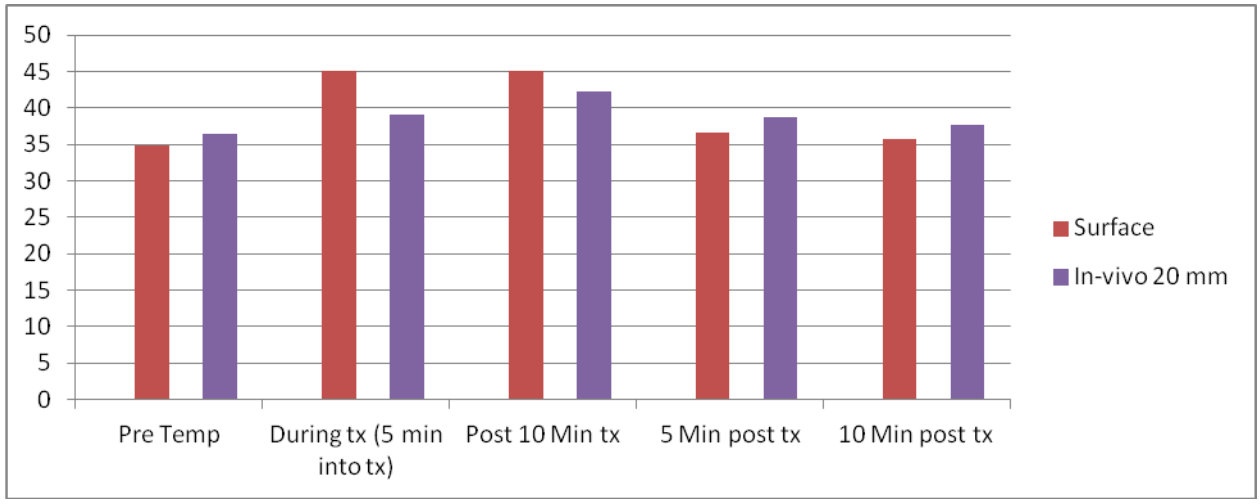

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RF AND PULSED MAGNETIC FIELD COMBINATION: AN INNOVATIVE APPROACH TO EFFECTIVELY ADDRESS SKIN LAXITY, BODY RESHAPING AND CELLULITE.

Leonardo Marini, MD, Trieste, Italy

Many different RF devices have claimed clinical efficacy in rejuvenating the skin through controlled dermal and subcutaneous fat bulk heating. Multipolar RF has shown to be superior to monopolar and bi-polar RF in effectively inducing a sequential electro-thermal tissue stratification effect improving patient comfort and decreasing side effects. Pulsed Magnetic Fields (PMF) have proven to accelerate angiogenesis, cutaneous wound healing, bone and nerve repair. PMF also decrease post-surgical pain and edema as well as negatively influence bacterial and tumoral cell growth.

The association of these two technologies seems to produce a synergistically effective dermal-hypodermal tissue functional improvement inducing long term collagen remodelling, adipose tissue reshaping and cellulite regression. Venus Freeze is the first technical example where these two innovative bio-medical strategies are intimately associated.

Temperature-induced intracellular synthesis of stress proteins could theoretically stand as the very base of the tissue bio-stimulation leading to optimization of cellular function. PMF-induced cellular and around-cell positive micro-environmental changes ideally contribute to speed up and consolidate tissue functional improvements. Long term results are very promising and can be progressively visible 2-4 months after one series of 6-10 treatments.

Patient satisfaction is very high (85% of treated patients); fair-to-acceptable (10%); minimal (5%). Minimal transient side effects were reported and were considered absolutely acceptable by both patients and physicians. More studies are nevertheless required to further understand the full potential of this extremely innovative technique.

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Electromagnetic fields for treating osteoarthritis

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Abstract

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Background

This is an update of a Cochrane review first published in 2002. Osteoarthritis is a disease that affects the synovial joints, causing degeneration and destruction of hyaline cartilage and subchondral bone. Electromagnetic field therapy is currently used by physiotherapists and may promote growth and repair of bone and cartilage. It is based on principles of physics which include Wolff's law, the piezoelectric effect and the concept of streaming potentials.

Objectives

To assess the benefits and harms of electromagnetic fields for the treatment of osteoarthritis as compared to placebo or sham.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 9), PreMEDLINE for trials published before 1966, MEDLINE from 1966 to October 2013, CINAHL and PEDro up to and including October 2013. Electronic searches were complemented by handsearches.

Selection criteria

Randomised controlled trials of electromagnetic fields in osteoarthritis, with four or more weeks treatment duration. We included papers in any language.

Data collection and analysis

Two review authors independently assessed studies for inclusion in the review and resolved differences by consensus with a third review author. We extracted data using pre-developed data extraction forms. The same review authors assessed the risk of bias of the trials independently using the Cochrane 'Risk of bias' tool. We extracted outcomes for osteoarthritis from the publications according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) guidelines. We expressed results for continuous outcome measures as mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval (CI). We pooled dichotomous outcome measures using risk ratio (RR) and calculated the number needed to treat (NNT).

Main results

Nine studies with a total of 636 participants with osteoarthritis were included, six of which were added in this update of the review. Selective outcome reporting was unclear in all nine included studies due to inadequate reporting of study design and conduct, and there was high risk of bias for incomplete outcome data in three studies. The overall risk of bias across the nine studies was low for the other domains.

Participants who were randomised to electromagnetic field treatment rated their pain relief 15.10 points more on a scale of 0 to 100 (MD 15.10, 95% CI 9.08 to 21.13; absolute improvement 15%) after 4 to 26 weeks' treatment compared with placebo. Electromagnetic field treatment had no statistically significant effect on physical function (MD 4.55, 95% CI -2.23 to 11.32; absolute improvement 4.55%) based on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale from 0 to 100 after 12 to 26 weeks' treatment. We also found no statistically significant difference in quality of life on a scale from 0 to 100 (SMD 0.09, 95% CI -0.36 to 0.54; absolute improvement 0.09%) after four to six weeks' treatment, based on the SF-36. No data were available for analysis of radiographic changes. Safety was evaluated in four trials including up to 288 participants: there was no difference in the experience of any adverse event after 4 to 12 weeks of treatment compared with placebo (RR 1.17, 95% CI 0.72 to 1.92). There was no difference in participants who withdrew because of adverse events (measured in one trial) after four weeks of treatment (RR 0.90, 95% CI 0.06 to 13.92). No participants experienced any serious adverse events.

Authors' conclusions

Current evidence suggests that electromagnetic field treatment may provide moderate benefit for osteoarthritis sufferers in terms of pain relief. Further studies are required to confirm whether this treatment confers clinically important benefits in terms of physical function and quality of life. Our conclusions are unchanged from the previous review conducted in 2002.

Plain language summary

Available in **English** | Español | Hrvatski | 日本語 | 한국어 | தமிழ்

Electromagnetic fields for the treatment of osteoarthritis

Review question

We conducted a review of the effect of electromagnetic fields on osteoarthritis. We found nine studies with 636 people.

Background: what is osteoarthritis and what are electromagnetic fields?

Osteoarthritis is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In osteoarthritis, the cartilage that protects the ends of the bones breaks down and causes pain and swelling.

An electromagnetic field is the invisible force that attracts things to magnets. This invisible attraction can be created using an electrical current that may affect the cartilage around the joints. In osteoarthritis, electromagnetic fields are a kind of therapy using electrical currents applied to the skin around the joints. Small machines or mats can be used to deliver electromagnetic fields to the whole body or to certain joints. A doctor or physiotherapist can perform the therapy and some machines can be used at home.

Study characteristics

After searching for all relevant studies up to October 2013, we found nine studies that reviewed the effect of electromagnetic field treatment compared to a sham or fake treatment in 636 adults with osteoarthritis for a duration of 4 to 26 weeks.

Key results

Pain (on a 0 to 100 scale; higher scores mean worse or more severe pain)

- Electromagnetic fields probably relieve pain in osteoarthritis.

- People who received electromagnetic field treatment experienced pain relief of 15 points more compared with people who received fake treatment (15% improvement).

- People who received electromagnetic field treatment rated their pain to be 26 points lower on a scale of 0 to 100.

- People who received fake treatment rated their pain to be 11 points lower on a scale of 0 to 100.

Physical function

- Electromagnetic fields may improve physical function but this may have happened by chance.

Overall health and well-being

- Electromagnetic fields probably make no difference to overall health and well-being.

Side effects

- Electromagnetic fields probably make no difference to whether people have side effects or stop taking the treatment because of side effects, but this may have happened by chance.

We do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects could include skin rash and aggravated pain.

X-ray changes

There was no information available on whether electromagnetic fields show any improvement to a joint with osteoarthritis on an X-ray.

Quality of the evidence

- Electromagnetic fields probably improve pain and make no difference to overall health and well-being and side effects. This may change with further research.

- Electromagnetic fields may improve physical function. This is very likely to change with further research.

Authors' conclusions

Implications for practice

The current, limited evidence shows a moderate clinically important benefit of electromagnetic field treatment for the relief of pain in the treatment of knee or cervical osteoarthritis.

Implications for research

More trials are needed in this field. New trials should compare different treatments and provide an accurate description of the length of treatment, dosage and the frequency of the applications. Larger trials are needed to confirm whether the statistically significant results shown in the trials included in this review confer clinically important benefits.

Summary of findings

Open in table viewer

Summary of findings for the main comparison. Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis

Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis

Patient or population: patients with osteoarthritis
Settings: out-patients recruited from healthcare facilities in Australia, Denmark, UK and the US
Intervention: electromagnetic field treatment
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Electromagnetic field treatment				
Pain 100 mm VAS Scale from: 0 to 100 (Higher scores mean worse pain) Follow-up: mean 6 weeks	The mean change in pain in the control groups was 10.7	The mean change in pain in the intervention groups was 15.10**lower** (9.08 to 21.13 lower)		434 (6 studies)	⊕⊕⊕⊖ **moderate**[1]	MD 15.10 (95% CI 9.08 to 21.13) Absolute risk difference: 15% (95% CI 9.08% to 21.13%) Relative per cent change: 21.03% (95% CI 12.65% to 29.43%) NNT: 2 (95% CI 1 to 6)
Physical function WOMAC function Scale from: 0 to 100 (Higher scores mean more severe limitation) Follow-up: mean 3 months	The mean change in physical function in the control groups was **1.7**	The mean change in physical function in the intervention groups was 4.55**lower** (2.23 lower to 11.32 higher)		197 (3 studies)	⊕⊕⊖⊖ **low**[2]	MD 4.55 (95% CI -2.23 to 11.32) Absolute risk difference: 4.55% (95% CI -2.23% to 11.32%) Relative per cent change: 268% (95% CI -131% to 666%) NNT: not statistically significant

Quality of life SF-36 item Scale from: 0 to 100 (Lower scores mean worse quality) Follow-up: mean 16 weeks	The mean change in quality of life in the control groups was 2.4	The mean change in quality of life in the intervention groups was 0.09 **lower** (0.36 lower to 0.54 higher)		145 (2 studies)	⊕⊕⊕⊖ **moderate**[3]	SMD 0.09 (95% CI -0.36 to 0.54) Absolute risk difference: 1% (95% CI -2.92% to 4.37%) Relative per cent change: 30.38% (95% CI -121.5% to 182.25%) NNT: not statistically significant
Radiographic progression Bone scintigraphic examinations Follow-up: mean 2.5 months	See comment	See comment	Not estimable	78 (1 study)	See comment	No related data were available
Number of patients experiencing any adverse event Follow-up: mean 1 month	**167 per 1000**	**195 per 1000** (120 to 320)	**RR 1.17** (0.72 to 1.92)	288 (4 studies)	⊕⊕⊕⊖ **moderate**[4]	Absolute risk difference: 3% (95% CI -6% to 12%) Relative per cent change: 17% (95% CI -28% to 92%) NNT: not statistically significant

Number of patients who withdrew because of adverse events Follow-up: mean 6 months	**27 per 1000**	**24 per 1000** (2 to 376)	**RR 0.90** (0.06 to 13.92)	78 (1 study)	⊕⊕⊖⊖ **low**[5]	Only 1 study: 1 participant withdrew from each group because of adverse skin reactions unrelated to the therapy

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **NNT:** number needed to treat; **RR:** risk ratio; **VAS:** visual analogue scale;**WOMAC:** Western Ontario and McMaster Universities osteoarthritis index

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded for moderate heterogeneity (I^2 = 55%); unclear risk for random sequence generation (Zizic 1995), allocation concealment (Zizic 1995), blinding of outcome assessors (Fary 2011; Nelson 2013; Zizic 1995), selective reporting (all six studies) and high risk for incomplete outcome data (Zizic 1995).
[2]Downgraded for considerable heterogeneity (I^2 = 84%); Zizic 1995: unclear risk for random sequence generation, allocation concealment, blinding of outcome assessors, selective reporting and high risk for incomplete outcome data. Fary 2011: unclear risk for blinding of outcome assessors and selective reporting. Garland 2007: unclear risk for selective reporting.
[3]Fary 2011: unclear risk for blinding of outcome assessors and selective reporting. Pipitone 2001: high risk for incomplete outcome data.
[4]Unclear risk for random sequence generation (Thamsborg 2005; Zizic 1995), allocation concealment (Zizic 1995), blinding of outcome assessors (Thamsborg 2005; Zizic 1995), selective reporting (all four studies) and high risk for incomplete outcome data (Garland 2007; Thamsborg 2005; Zizic 1995).
[5]Only Zizic 1995 reported this outcome. Downgraded for imprecision (wide confidence interval and few events); unclear risk for random sequence generation, allocation concealment, blinding of outcome assessors and selective reporting and high risk for incomplete outcome data.

Background

Description of the condition

Osteoarthritis is a progressive rheumatic disease which occurs most commonly in older populations. It is becoming increasingly common due to the ageing population in many societies. The degeneration and eventual loss of articular cartilage causes changes in periarticular bone, synovial tissue and other periarticular soft tissue structures such as ligaments and muscles. This causes the pain, swelling, tenderness and stiffness that characterise osteoarthritis, especially in the weight-bearing joints of the lower extremities.

Description of the intervention

Current osteoarthritis treatment options include pharmacological and non-pharmacological procedures to decrease progression and treat the pain associated with this condition. They include:

1. oral pharmacological medications: analgesics such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs); symptomatic slow-acting drugs for osteoarthritis (SYSADOA) such as glucosamine sulphate (Towheed 2005), diacerein (Fidelix 2006) and the non-saponifiable oils of avocado and soya; and the newer disease-modifying osteoarthritis drugs (DMOAD);
2. topical therapies (applied as gels or creams), including NSAIDs and capsaicin;
3. intra-articular therapies, including corticosteroid and hyaluronic acid injections (Bellamy 2006a; Bellamy 2006b);
4. non-pharmacological therapies, including aquatic exercise therapy (Bartels 2007), balneotherapy (Verhagen 2007), physical therapy (Rutjes 2010), occupational therapy, strengthening exercises (Fransen 2008; Fransen 2009), wedged insoles and braces and orthoses (Brouwer 2005); and
5. surgical treatment: joint replacement (Singh 2013a; Singh 2013b) and arthroscopic debridement (Laupattarakasem 2008) of the affected joint.

Management of osteoarthritis of the knee aims to relieve pain, maintain or improve mobility, and minimise disability. However, these goals are seldom achieved through drug therapy alone, as many treatments are ineffective or lead to serious adverse effects, including the potentially lethal complications encountered with selective NSAIDS (Blower 1996). Different modalities in physiotherapy have been shown to help improve clinical symptoms and function in knee osteoarthritis, generally with fewer adverse effects than medical treatment (Brosseau 2003; Rutjes 2010). Electromagnetic fields are among these non-invasive therapies, already considered a proven adjunct therapy for delayed union fractures (Bassett 1974). Interest in electromagnetic field stimulation began after observing that physical stress on bone causes the appearance of tiny electric currents called piezoelectric potentials that are thought to act as the transduction signals to promote bone formation. In vitro studies showed that chondrocyte proliferation and

matrix synthesis are significantly enhanced by pulsed electromagnetic field stimulation (De Mattei 2001; De Mattei 2003; De Mattei 2004; Fioravanti 2002; Pezzetti 1999). A number of multicentric randomised and double-blind clinical trials have been carried out with promising results (Fini 2005).

Electromagnetic fields can be delivered to biological systems by the direct placement of an electrode or non-invasively by two means:

- capacitive coupling, in which opposing electrodes are placed within a conducting medium, that is, in contact with the skin surface overlying a target tissue (e.g. bone, joint, wound);
- inductive coupling, in which a time-varying pulsed electromagnetic field induces an electrical current in the target tissue. This technique does not require direct contact with the skin or biological system.

Although the former relies on direct application of an electrical field rather than creating induced current through magnetic impulses, they act by the same mechanism. Thus both pulsed electromagnetic fields and pulsed electrical stimulation are considered electromagnetic field interventions in this update.

How the intervention might work

Three basic principles of physics are proposed to explain how electromagnetic fields may promote the growth and repair of bone and cartilage: Wolff's Law, the piezoelectric effect and the concept of streaming potentials (Shupak 2003).

Electromagnetic field stimulation first garnered interest as treatment for osteoarthritis following the discovery of evidence that stimulation of chondrocytes increased the synthesis of the major component of the cartilage matrix, known as proteoglycans (Aaron 1993). Experimental studies suggest that electromagnetic fields may interact with ligands on the chondrocyte cell surface membrane, potentially leading to changes in internal calcium concentrations which trigger proteoglycan synthesis (Graziana 1990; Lee 1993).

Electromagnetic field treatments might also help to preserve extracellular matrix integrity in the early stages of osteoarthritis by down-regulating proteoglycan production and degradation (Ciombor 2001; Liu 1997) and by increasing chondrocyte DNA replication and cell proliferation (Pezzetti 1999; Rodan 1978).

Through these improvements in bone and cartilage maintenance and repair, pulsed electromagnetic field stimulation could influence the osteoarthritic disease process by decreasing inflammation and providing temporary relief from pain (Darendeliler 1997; Lee 1997; Trock 2000).

Why it is important to do this review

Electromagnetic field therapy is already being widely used for the management of joint pain associated with osteoarthritis and has a promising theoretical basis for clinical application. Clinical trials evaluating its therapeutic effectiveness have been conducted recently, but with inconsistent results. A 2002 Cochrane

review suggested that pulsed electromagnetic field therapy led to improvements in all measurements for knee osteoarthritis, but concluded that further studies were required to confirm whether the statistically significant results shown in these trials conferred important benefits to patients (Hulme 2002). The optimal frequency, duration and intensity of electromagnetic fields for osteoarthritis were also yet to be determined. This update of the 2002 review will include new clinical studies which have since been published.

Objectives

To assess the benefits and harms of electromagnetic fields for the treatment of osteoarthritis as compared to placebo or sham.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials or quasi-randomised trials which examined the effects of electromagnetic fields for treating osteoarthritis, with four or more weeks treatment duration.

Types of participants

Participants over 18 years of age, with clinical or radiological confirmation of the diagnosis (or both) were considered. The diagnosis of osteoarthritis was defined using the American College of Rheumatology (ACR) criteria for classification of osteoarthritis (Altman 1986; Altman 1997). We excluded trials where participants had received any previous surgical intervention for the treatment of osteoarthritis.

Types of interventions

All types of pulsed electromagnetic fields and pulsed electrical stimulation were included. Trials that compared the intervention group using electromagnetic fields to usual care were included, as well as placebo-controlled studies.

Types of outcome measures

The primary measure of effectiveness was pain relief, as suggested by the third Outcome Measures in Rheumatology (OMERACT) conference (Bellamy 1997). We included the other outcomes from this conference for analysis. According to OMERACT 3 (Bellamy 1997) (last reviewed in OMERACT 6) (Pham 2003) standardised, validated instruments, such as visual analogue scales (VAS) (Carlsson 1983) and the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale for pain (Bellamy 1988) and the Lequesne Functional Severity Index (Lequesne 1987), should be used to evaluate these outcomes.

Major outcomes

1. Pain
2. Physical function
3. Health-related quality of life measure
4. Radiographic joint structure changes
5. Number of patients experiencing any adverse event
6. Patients who withdrew because of adverse events
7. Patients experiencing any serious adverse event

Search methods for identification of studies

Electronic searches

We identified relevant studies by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 9), PreMEDLINE for trials published before 1966, MEDLINE from 1966 to October 2013, CINAHL and PEDro up to and including October 2013. We used the search strategies recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Details of the search strategy can be found in the following appendices: MEDLINE (Appendix 1), CINAHL (Appendix 2), EMBASE (Appendix 3), CENTRAL (Appendix 4) and PEDro (Appendix 5).

Searching other resources

We complemented the electronic searches with handsearching:

- bibliographic references; and
- abstracts published in special issues of specialised journals or in conference proceedings (American Orthopaedic Physicians Annual Meeting; Asia-Pacific Orthopedic Society for Sports Medicine Meeting).

We contacted the Trial Search Co-ordinators of the Cochrane Rehabilitation and Related Therapies Field and the Cochrane Musculoskeletal Group.

We manually searched conference proceedings, used the Science Citation Index to retrieve reports citing relevant articles, contacted content experts and trialists, and screened the references of all articles obtained, including related reviews. We did not use abstracts if additional data could not be obtained.

Finally, we searched several clinical trial registries (www.clinicaltrials.gov, http://www.controlled-trials.com, http://www.anzctr.org.au/, www.umin.ac.jp/ctr) to identify ongoing trials.

The last update of the manual search was conducted on 3 October 2013.

Data collection and analysis

Selection of studies

Two review authors (SL and BY) independently screened the abstract, keywords and publication type of all publications obtained from the searches described. We obtained all studies which might be eligible RCTs, or quasi-RCTs, in full and independently assessed these. The two review authors independently selected trials according to the selection criteria.

When necessary, we sought information from the authors of the primary studies.

Data extraction and management

Two review authors (SL, BY) extracted data using a standard, pre-developed form that we pilot-tested. We extracted details of trial design, patient characteristics, treatment duration and the mechanics of the electromagnetic field device used, and established baseline and end of study outcomes. We resolved differences in data extraction by referring back to the original article and by establishing consensus. A third review author (CH or JH) was consulted to help resolve differences. Where the method of randomisation or allocation concealment was not clearly described, or where data were missing, we contacted the authors of the study to clarify the issues.

Assessment of risk of bias in included studies

The review authors assessed the risk of bias in the included studies using The Cochrane Collaboration 'Risk of bias' tool (Higgins 2011). We considered six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, selective outcome reporting and incomplete outcome reporting. We expressed the judgements simply as 'low risk', 'high risk' or 'unclear risk' of bias.

We assessed two components of randomisation: generation of allocation sequence and concealment of allocation. We considered the generation of sequence adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate included random number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards and drawing lots. We considered trials using an

unpredictable allocation sequence to be randomised. We considered trials using potentially predictable allocation mechanisms, such as alternation or the allocation of patients according to date of birth, to be quasi-randomised.

We considered concealment of allocation adequate if both the patients and the investigators responsible for patient selection were unable to predict allocation to treatment or placebo groups. Adequate concealment included central randomisation and sequentially numbered, sealed, opaque envelopes.

Since the primary measure of effectiveness was patient-reported pain relief, we considered blinding of patients adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used.

We considered analyses adequate if all randomised patients were included in the analysis according to the intention-to-treat principle. We further assessed the reporting of major outcomes.

Measures of treatment effect

For continuous data, we presented results as a mean difference (MD). However, where different scales were used to measure the same concept or outcome, we used standardised mean difference (SMD). For dichotomous data, we used risk ratio (RR) (Hennekens 1987; Petitti 2000). Only if a comparison resulted in a statistically significant difference and baseline values were reported did we calculate the clinical relevance, i.e. the number need to treat to benefit (NNTB) or harm (NNTH).

Unit of analysis issues

If we identified cross-over trials presenting continuous outcome data which precluded paired analysis, we did not plan to include these data in a meta-analysis to avoid unit of analysis error. Where carry-over effects were thought to exist, and sufficient data existed, we planned to include only data from the first period in the analysis (Higgins 2011).

Dealing with missing data

We contacted the study investigators for missing data via email. Where possible, the analyses were based on intention-to-treat data from individual clinical trials.

Assessment of heterogeneity

We assessed statistical heterogeneity by examining the I^2 statistic (Higgins 2011), a quantity that describes approximately the proportion of variation in point estimates due to heterogeneity rather than sampling error. If considerable between-group statistical heterogeneity was detected (i.e. an I^2 value of more than

75%), we explored the causes of heterogeneity (Higgins 2011). In addition, we employed the Chi^2 test of homogeneity to determine the strength of evidence that the heterogeneity is genuine. We considered heterogeneity significant when the probability (P value) was < 0.10.

Assessment of reporting biases

We planned to assess reporting bias by screening the clinical trials register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch/) (De Angelis 2004) to determine whether the protocol for each RCT was published before recruitment of patients for the study was started. Furthermore, we planned a comparison between the fixed-effect estimate and the random-effects estimate, as well as a funnel plot if data were available, in order to assess for the possible presence of small sample bias and reporting bias, respectively.

Data synthesis

We planned to pool clinically homogeneous studies using the fixed-effect model for meta-analysis. When there was important heterogeneity (I^2 > 25%), we pooled studies using the random-effects model for meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis to examine the efficacy of electromagnetic fields with different application methods and modalities, including frequency, length of treatment and different techniques, if data were available.

Sensitivity analysis

We conducted a sensitivity analysis based on the methodological quality of each trial. We undertook sensitivity analyses to explore the impact of studies with poor ratings for domains described in the 'Risk of bias' table. We planned a priori sensitivity analyses for:

1. concealment of allocation;
2. blinding of outcome assessors;
3. extent of drop-outs (we considered 20% as a cut-point).

'Summary of findings' table

We presented key findings in a 'Summary of findings' table. These included the magnitude of effect of the interventions examined, the sum of available data on the main outcomes and the quality of the evidence.

For dichotomous outcomes, we calculated the absolute risk difference using the risk difference (RD) statistic in RevMan (RevMan 2012) (RR - 1 calculated the weighted relative per cent change). We calculated the number needed to treat to benefit (NNTB) or to harm (NNTH) from the control group event rate (unless the population event rate was known) and the risk ratio using the Visual Rx NNT calculator (Cates 2004).

For continuous outcomes, we calculated the absolute benefit as the improvement in the treatment group (follow-up mean minus baseline mean) less the improvement in the control group (follow-up mean minus baseline mean). We calculated the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group. We calculated NNTB or NNTH using the Wells calculator software available at the CMSG editorial office. We determined the minimal clinically important difference (MCID) for each outcome for input into the calculator.

We used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2011), defined as the extent of confidence in the estimates of treatment benefits and harms. The GRADE approach specifies four levels of quality (high, moderate, low and very low).

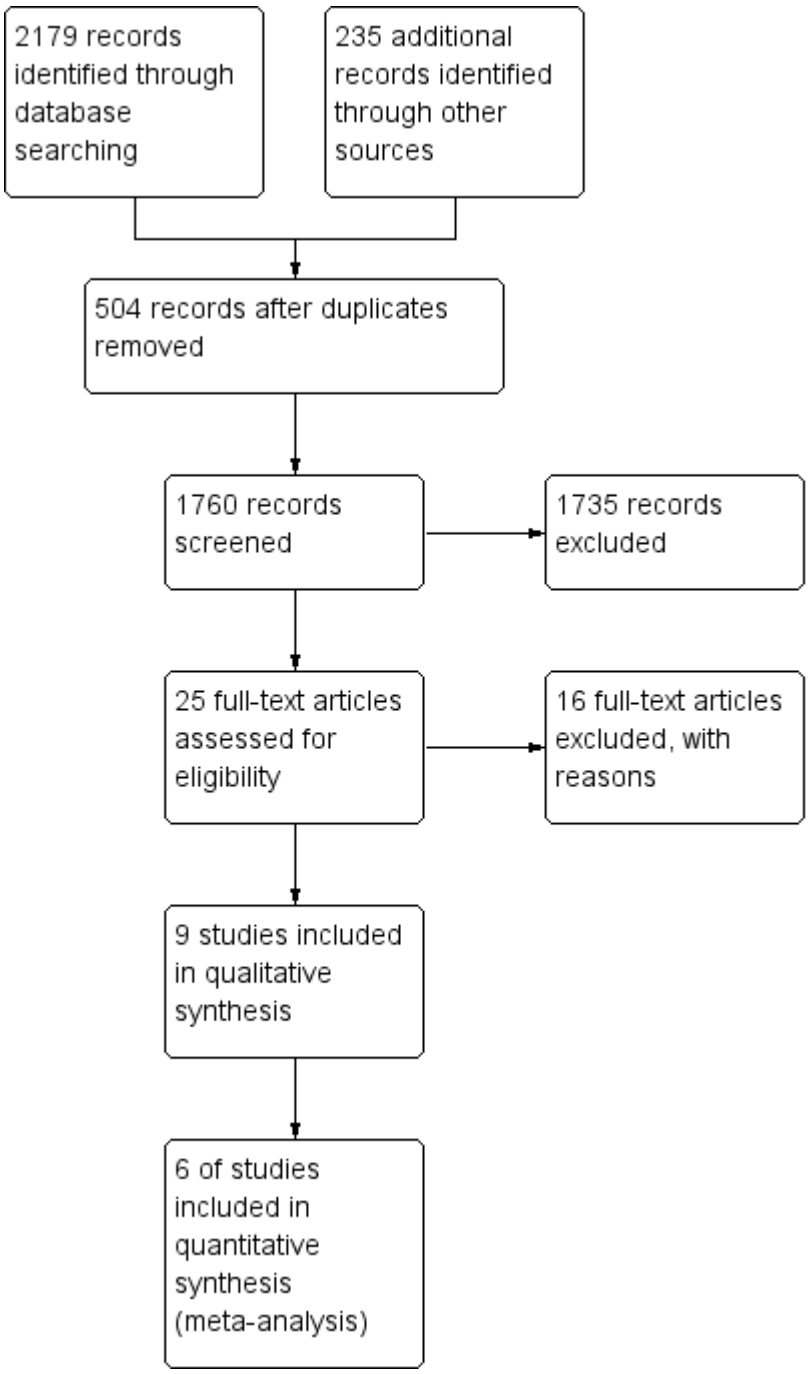
Results

Description of studies

Results of the search

The search strategies retrieved 2037 articles (Figure 1). The literature search identified 25 potentially relevant articles. Of these, only nine studies met the inclusion criteria (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995) (see Characteristics of included studies table). Sixteen studies were excluded for the reasons given in the Characteristics of excluded studies table (Alcidi 2007; Ay 2009; Battisti 2004; Danao-Camara 2001; Fischer 2005; Fischer 2006; Hinman 2002; Jack 2006; Jacobson 2001; Kulcu 2009; Liu 2004; Ozgüçlü 2010; Pavlović 2012; Rigato 2002; Sutbeyaz 2006; Tomruk 2007).

Figure 1 **Open in figure viewer** | **Download as PowerPoint**



Study flow diagram.

Included studies

The eligible RCTs collectively involved 327 participants in active electromagnetic field treatment groups and 309 participants in placebo groups.

Six trials used pulsed electromagnetic fields (Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994) while three studies (Fary 2011; Garland 2007; Zizic 1995) used pulsed electrical stimulation.

One study used a pulsed electromagnetic field signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at one burst/s and delivering a peak induced electrical field of 34 ± 8 V/m in the knee from a portable battery-operated device (Palermo, Ivivi Health Sciences, LLC, San Francisco, CA). Patients were treated for 15 minutes twice daily for 42 days (Nelson 2013).

Another study reviewed a pulsed electromagnetic field device (Medicur) that generates pulses of magnetic energy via a soft iron core treated with 62 trace elements. Pulses are selected at base frequencies of 3 Hz, 7.8 Hz and 20 Hz and have a rise time of 1 μs, a low magnetic output (< 0.5 gauss) and a range of activity of up to 30 cm around the unit. The Medicur device runs on batteries, requires no wires or electrodes, and only needs to be held close to the area to be treated. Patients were treated for 30 minutes per session three times a day for six weeks (Pipitone 2001).

In one study a pulsed electromagnetic field was administered to the whole body using a mat which produced a field from 1 Hz to 3000 Hz with a mean intensity of 40 μT (wave ranger professional, program 12, Mediscan GmbH, Bad Haller Straße34, 4500 Kremsmünster, Austria). The frequency of the pulsed electromagnetic field ranged from 1 Hz to 3000 Hz. Patients lay on the mat for 30 minutes per session twice a day for six weeks (Nicolakis 2002).

A fourth study measured the effect of a pulse generator that yields G50V in 50 Hz pulses, changing voltage at 3 ms intervals. This results in a maximal electrical gradient of 1 to 100 mV/cm as sensed by charged particles in the tissue, depending on the distance from the coils. As a result of this current, the coils become slightly warmer than the surroundings after 30 minutes (28 to 35 °C). Treatment was given for two hours daily, five days per week for six weeks (Thamsborg 2005).

Two other trials used a non-contact device that delivered three signals in a stepwise fashion, ranging from 5 Hz to 12 Hz frequency at 10 G to 25 G of magnetic energy (Trock 1993; Trock 1994). These studies exposed the affected knee to nine hours of stimulation over a one-month period.

In one study a commercially available TENS stimulator (Metron Digi-10s) was modified by a biomedical engineer to deliver pulsed electrical stimulation current parameters as follows: pulsed, asymmetrically biphasic, exponentially decreasing waveform with a frequency of 100 Hz and pulse width of 4 ms. Current was delivered via 120 mm x 80 mm multiple-use conductive silicone electrodes inserted into larger calico pockets. The participants were asked to wear the device seven hours daily, preferably overnight, for 26 weeks (Fary 2011).

Two other pulsed electrical stimulation studies used a pulsed electrical device to deliver a 100 Hz low-amplitude signal to the knee joint via skin surface electrodes. The patients were exposed for 6 to 14 hours a day for three months and 6 to 10 hours a day for four weeks, respectively (Garland 2007; Zizic 1995).

All studies reported on patients with knee osteoarthritis and Trock 1994 also included patients with cervical osteoarthritis, with their results reported separately. The main outcome measures related to pain (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995). The major outcomes were assessed using the WOMAC osteoarthritis index: severity of joint pain, stiffness and limitation of physical function (Garland 2007; Nicolakis 2002; Pipitone 2001; Thamsborg 2005), ability to conduct activities of daily living (ADL) in terms of pain or difficulty (Trock 1993; Trock 1994), joint pain on motion (Trock 1993; Trock 1994), patient's overall assessment (Garland 2007; Trock 1994), patient evaluation of function (Zizic 1995) and physician's global assessment (Trock 1993; Trock 1994; Zizic 1995). The UK 36-item short form of the Medical Outcomes Study (SF-36) and the EuroQol (Euro-Quality of Life, EQ-5D) were also considered (Pipitone 2001).

Excluded studies

We excluded nine RCTs with a shorter duration than four weeks since this time frame may be too short to assess harms and benefits based on biological plausibility (Alcidi 2007; Ay 2009; Battisti 2004; Jacobson 2001; Kulcu 2009; Liu 2004; Ozgüçlü 2010; Pavlović 2012; Sutbeyaz 2006;Tomruk 2007). We excluded one RCT because it included patients with cervical spondylosis and shoulder periarthritis without separately reporting results and we could not extract data on cervical osteoarthritis (Rigato 2002). We excluded four other studies because they were not RCTs (Danao-Camara 2001; Fischer 2005; Fischer 2006; Jack 2006). We excluded one study because the aim of the study was to assess the effect of static magnetic fields for chronic knee pain but not specifically for osteoarthritis (Hinman 2002). We excluded one study because the treatment period was only 10 days (Pavlović 2012).

Risk of bias in included studies

Two review authors (SL, BY) assessed risk of bias independently. Differences were resolved by consensus with a third review author (DZ).

The overall assessment of the methodological quality of the trials in this review was as follows: we judged seven studies (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Trock 1993; Trock 1994) to be at a low risk of bias for random sequence generation, and two studies omitted a description of the randomisation process (Thamsborg 2005; Zizic 1995).

Nine of the included studies met the allocation concealment criterion (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994).

Seven trials (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Trock 1993; Zizic 1995) had appropriate, well-described placebo treatments and we assessed them as low risk of bias for blinding.

We assessed seven studies (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Thamsborg 2005; Trock 1994; Zizic 1995) as low risk of bias for incomplete outcome data; six trials reported loss to follow-up ranging from 5% to 20% (Garland 2007; Nicolakis 2002; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995), balanced across compared groups, while one trial did not report the loss to follow-up (Pipitone 2001).

No information on selective outcome reporting was found in any study.

See the 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

Figure 2

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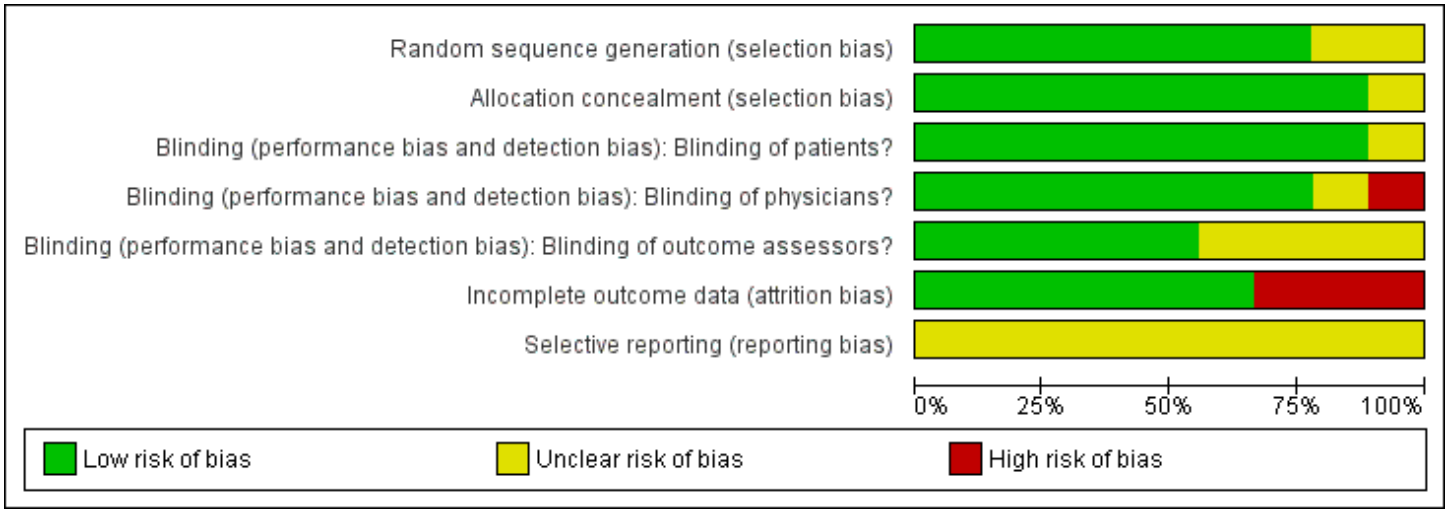

'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3

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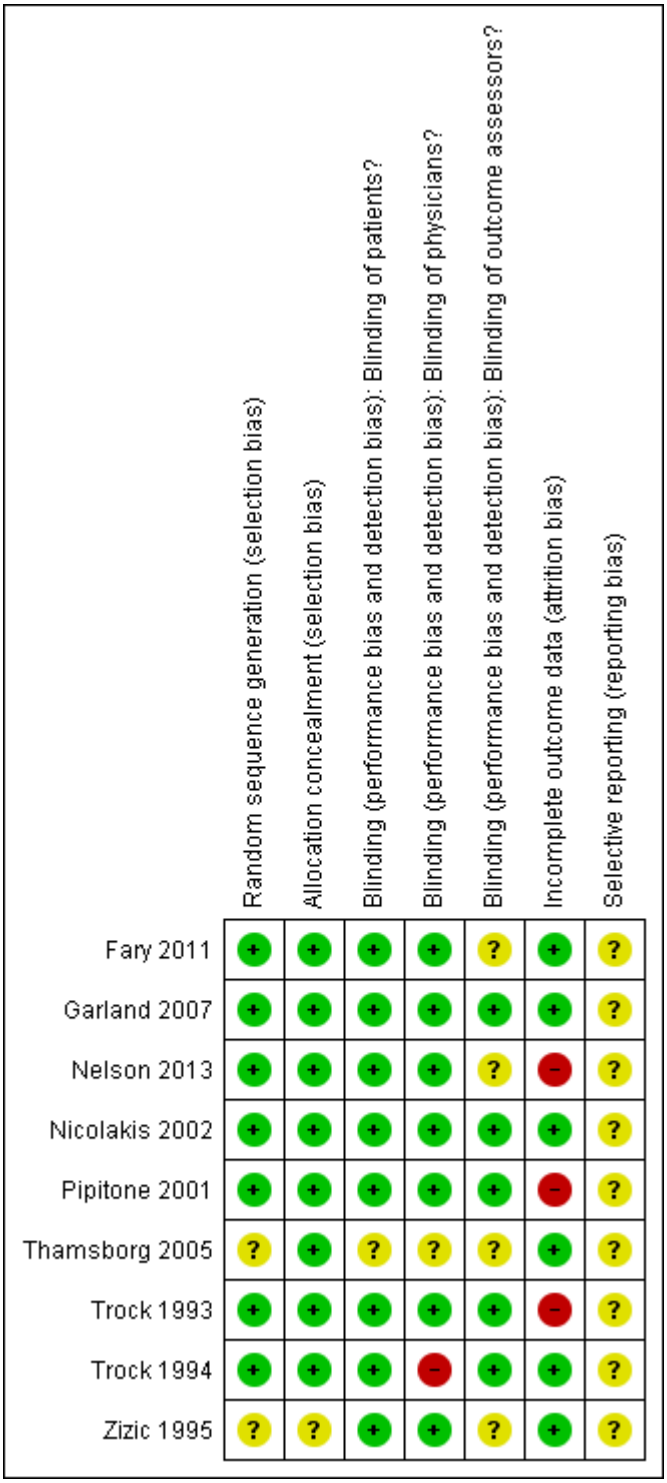

'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Effects of interventions

See: **Summary of findings for the main comparison** Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis

In the nine controlled trials included in the analysis, a total of 636 participants were randomised: 327 participants to electromagnetic field treatment and 309 to a placebo device. The pulsed electromagnetic field treatment trials lasted approximately four to six weeks, with treatment duration ranging from 27 hours to 60 hours (Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994). The treatments in three other pulsed electrical stimulation trials were more intensive, involving 26 weeks of seven hours treatment daily (Fary 2011), four weeks of six hours per day treatment (Zizic 1995) and three months of 6 to 14 hours per day, respectively (Garland 2007). These trials did not provide the statistical details required for inclusion in meta-analysis, therefore the analysis of the relative effects of treatment times, frequencies and modes of treatment delivery was limited (see summary of findings Table for the main comparison).

Electromagnetic field treatment versus placebo for osteoarthritis

Pain

The combined results from the six included studies of electromagnetic field treatment which measured pain as an outcome (Fary 2011; Garland 2007; Nelson 2013; Trock 1993; Trock 1994; Zizic 1995) showed a statistically significant beneficial effect for patient pain relief (mean difference (MD) 15.10, 95% confidence interval (CI) 9.08 to 21.13). People who received electromagnetic field treatment rated their pain to be 15.10 points lower on a scale of 0 to 100 (15.10% absolute improvement and 21.03% relative improvement) (Analysis 1.1).

Physical function

Three studies including 107 patients in the electromagnetic field treatment group and 90 patients in the placebo group measured function as an outcome (Fary 2011; Garland 2007; Pipitone 2001). Improvement of function was not statistically significant in electromagnetic field-treated patients compared to control group patients (MD 4.55, 95% CI -2.33 to 11.32; 4.55% absolute effect and 10.13% relative effect) (Analysis 1.2).

Health-related quality of life measure

Two studies including 68 patients in the electromagnetic field treatment group and 71 patients in the placebo group measured quality of life as an outcome (Fary 2011). Improvement in quality of life was not statistically significant in electromagnetic field-treated patients compared to control group patients (SMD 0.09, 95% CI -0.36 to 0.54; 9% absolute effect and 100.8% relative effect) (Analysis 1.3).

Radiographic joint structure changes

Only two studies (Thamsborg 2005; Trock 1993) mentioned radiographic joint structure change but no data were available.

Number of patients experiencing any adverse event

Adverse events were presented in four studies with 156 participants in the intervention group and 132 participants in the control group (Garland 2007; Pipitone 2001; Thamsborg 2005; Zizic 1995), although specific definitions of adverse events were not provided in any study. The total number of adverse events was not statistically significantly increased in electromagnetic field-treated patients (19.9%) compared to 16.7% of placebo-treated patients, after six weeks (RR 1.17, 95% CI 0.72 to 1.92) (Analysis 1.4).

Patients who withdrew because of adverse events

Specific reasons for withdrawals were unrelated to the therapy except in the case of adverse skin reactions which were encountered in Zizic 1995 and occurred in patients receiving both placebo and active electrical stimulation treatment. There was no significant difference between groups (RR 0.90, 95% CI 0.06 to 13.92) (Analysis 1.5), suggesting that there is no difference between the active treatment and placebo in terms of adverse effects.

Patients experiencing any serious adverse event

No study reported any serious adverse events.

Subgroup analyses

We did not conduct the pre-planned subgroup analyses of the most effective means of delivering therapy due to the small number of trials and insufficient data.

Sensitivity analyses

We undertook sensitivity analyses to explore the impact of studies with poor ratings for concealment of allocation, blinding of outcome asessors and extent of drop-out and there was no change in the direction and significance of the effect sizes (results not shown).

Discussion

Summary of main results

Osteoarthritis is the most common of the rheumatic diseases. With an estimated 40,000 new cases of osteoarthritis diagnosed each year, it is the third leading cause of life-years lost due to disability and is associated with high morbidity and healthcare utilisation (March 2004; Towheed 2004). The range of treatments for osteoarthritis is continually increasing as conventional therapies, such as pharmaceutical management, physiotherapy and joint replacement surgery, are coupled with emerging and established complementary therapies.

Osteoarthritis results from a failure of chondrocytes within the joint to synthesise a good-quality matrix and to maintain a balance between synthesis and degradation of the extracellular matrix. The change in the quality of the matrix is mainly the result of dedifferentiation of chondrocytes, whereas the imbalance between synthesis and degradation of the extracellular matrix is caused by increased synthesis of proteinases and decreased anabolic effects of growth factors, mainly from chondrocytes but also from synovial tissue and subchondral bone. The biochemical reasoning behind the electrical stimulation of cartilage has been clearly demonstrated in vitro; its value in the treatment of delayed union fracture has been proven over two decades of use and it has been established as a standard of care (Aaron 1989; Baker 1974; Bassett 1974). The question remains as to whether it provides a financially accessible, clinically significant alternative to current therapies for osteoarthritis. The purpose of this systematic review was to evaluate the effectiveness of electrical stimulation treatment. However, its major limitation is the small number of contributing studies that could be included; this also prevented the planned subgroup analysis of variations in treatment.

All of the studies' participants had osteoarthritis of one or both knees, or cervical osteoarthritis, diagnosed by clinical symptoms and radiographic evidence, and the osteoarthritis was painful despite medical treatment.

The protocols for pulsed electrical stimulation or pulsed electromagnetic field device setting and application varied widely between studies, as did the outcome measures. Some pulsed electrical stimulation devices delivered a low-frequency (100 Hz), low-amplitude, voltage sourced (mean = 6.2 peak volts), monophasic, spiked signal to the knee via skin surface electrodes (Fary 2011; Garland 2007; Zizic 1995). In Nelson 2013 a pulsed electromagnetic field signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at one burst/s delivered a peak induced electrical field of 34 ± 8 V/m to the knee from a portable battery-operated device. Other devices used in the included trials generated a pulsating electromagnetic field with a mean intensity of 40 μT (the frequency of the pulsed magnetic field ranged: 1 Hz to 3000 Hz) (Nicolakis 2002); or generated pulses of magnetic energy via a soft iron core with base frequencies (3 Hz, 7.8 Hz and 20 Hz) (Pipitone 2001), G50V in 50 Hz pulses changing voltage in 3 ms intervals (Thamsborg 2005) and extremely low-frequency pulsed waves at 5 Hz, 10 to 15 gauss for 10 minutes, 10 Hz 15 to 25 gauss for 10 minutes and 12 Hz 15 to 25 gauss for 10 minutes (Trock 1993; Trock 1994). Characteristics of the devices, such as electromagnetic field modes, and application characteristics, such as duration, could not be evaluated in this systematic review due to the small number of trials.

Pain relief was measured using visual analogue scales (VAS). We pooled this outcome from six trials and found a significant difference between the electromagnetic field and placebo-treated groups (Fary 2011; Garland 2007; Nelson 2013; Trock 1993; Trock 1994; Zizic 1995). All were randomised controlled trials with appropriate blinding and they had appropriate, well-described placebo treatments (see Characteristics of included studies). There was moderate heterogeneity in the results. The intervention and its duration also differed between the studies.

The improvement in physical function in patients with knee osteoarthritis treated with pulsed electromagnetic fields was not statistically significant (Fary 2011; Garland 2007; Pipitone 2001). There was high heterogeneity in the results. This might be due to the different measurement tools used in the included studies. Two studies (Fary 2011; Garland 2007) used WOMAC physical function (on a 100 mm VAS) to measure the efficacy variable, while one study (Pipitone 2001) used the WOMAC disability score on a 20 cm VAS of the EuroQol. The intervention duration also differed among these studies.

Quality of life was not statistically significantly different between the treatment and placebo groups (Fary 2011; Pipitone 2001). This might be explained by the small sample sizes of the included studies measuring these outcomes, the wide variation in electromagnetic field devices and application protocols, or the inadequate intervention periods.

There were no life-threatening events reported among participants exposed to electromagnetic fields.

Overall completeness and applicability of evidence

A comprehensive search of the literature revealed a number of studies of electromagnetic field interventions for osteoarthritis. Although the studies presented differences between placebo and active treatment for osteoarthritis for some outcomes, these effects did not meet the generally accepted criteria for clinical importance. There are currently insufficient data to draw conclusions about the efficacy of electromagnetic field interventions in the management of osteoarthritis, thus highlighting the need for larger independent studies that focus on the OMERACT core outcomes with complete documentation of results.

In summary, electromagnetic field treatment has a moderate benefit for patients' pain relief. There is inconclusive evidence that electromagnetic field treatment improves physical function, quality of life or radiographic joint structure. No serious adverse effects of electromagnetic field treatment were reported in the included trials. This might be because of the relative safety of electromagnetic fields compared to physiotherapy, which could be an advantage. This meta-analysis did not reveal clinically important results overall and the analysis was limited by the paucity of literature on electromagnetic fields for osteoarthritis. However, the statistically significant benefits seen here do support the undertaking of further large-scale studies to allow definite conclusions to be drawn.

Quality of the evidence

The quality of the evidence of all included trials was moderate or low. Six trials described generation of allocation sequence or concealment of allocation, or reported whether primary outcomes were specified a priori. All trials described double-blinding of patients and physicians or assessors. Four of the trials were analysed according to the intention-to-treat principle. We also downgraded for heterogeneity and imprecision.

Potential biases in the review process

We believe that we identified all relevant studies. We devised a thorough search strategy and searched all major databases for relevant studies, and we applied no language restrictions. Two review authors independently assessed the trials for inclusion in the review and for risk of bias, with a third review author adjudicating if there was any discrepancy. The biggest limitation of the review process was the heterogeneity between the trials and the lack of data in a form that could be extracted for meta-analysis.

Agreements and disagreements with other studies or reviews

A systematic review has assessed the effectiveness of pulsed electromagnetic fields compared with placebo in the management of osteoarthritis of the knee (Vavken 2009). Nine studies, including 483 patients, were pooled. They reported that pulsed electromagnetic field treatment improved clinical scores and function in patients with osteoarthritis of the knee and that it should be considered as an adjuvant therapy in the management of these patients. However, there is still equipoise regarding the evidence in the literature for an effect on pain.

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Review article

Pulsed electromagnetic field therapy effectiveness in low back pain: A systematic review of randomized controlled trials

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ABSTRACT

Background: Low back pain is a worldwide prevalent musculoskeletal condition in the general population. In this sense, the pulsed electromagnetic fields (PEMF) therapy has shown significant clinical benefits in several musculoskeletal conditions.
Objective: To assess the effectiveness of the PEMF therapy in reducing pain and clinical symptomatology in patients with low back pathological conditions.
Methods: It was performed a comprehensive database search using Pubmed, Scopus, Cochrane Library and PEDro databases to assess the effectiveness of the PEMF therapy in reducing pain and clinical symptomatology in patients with low back pathological conditions. The search was performed from January 2005 to August 2015 and conducted by two independent investigators, which scrutinize the reference list of most relevant studies. The methodological quality was assessed by the PEDro scale and the level of evidence was set according Oxford Center for Evidence-Based Medicine scale.
Results: Six studies were eligible inclusion on the qualitative analysis and five into the quantitative analysis, scoring an overall 6.8 points according the PEDro scale. The studies showed heterogeneity concerning the intervention protocols. Nevertheless, the effect sizes' indicated a clear tendency to reduction of the pain intensity favoring the PEMF groups, reaching a minimal clinically important difference.
Conclusion: PEMF therapy seems to be able to relieve the pain intensity and improve functionality in individuals with low back pain conditions. Further research is needed regarding PEMF effects on the different conditions of low back pain, with standardized protocols, larger samples and adjustment for low back pain confounders in order to achieve stronger conclusions.

Abbreviations: PEMF, pulsed electromagnetic field; NSAIDs, non-steroidal anti-inflammatory drugs; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PEDro, Physiotherapy Evidence Database; CI, confidence intervals; CEBM, Center for Evidence-Based Medicine; MCID, minimal clinically important difference.

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Introduction

Low back pain is a very common health problem in general population and one of the major reasons for medical treatment seeking. It is expected that between 60 and 80% of the world population will experience low back pain during lifetime,[1] with 65% being recurrent and longstanding episodes. Low back pain can be caused by different etiologies, such as muscle or ligament strains, herniated discs, arthritis, alteration in the curvature of the spine or osteoporosis related fractures but, the majority of the patients do not have a clinically identified problem.[2] Despite the variety of treatments available, no modality or therapeutic approach has stand out as a definitive solution.[3] Thus, there is still a demand for new approaches, less invasive and free of side effects.

The risk/benefit ratio in pharmacotherapy for low back pain conditions often does not have strength enough to persist with the drugs usage. Moreover, the risk of pharmacologic addition, potential side-effects and adverse events, as well as long-term toxicity may weaken the potential benefit of the pharmacotherapy approach.[4,5] In this sense, the pulsed electromagnetic fields (PEMF) therapy can play an important role in the pain relief since is a drug-free, non-thermal, with low risk that works to enhance cellular activity healing and repair.[3] Therefore, it could be an option to the non-steroidal anti-inflammatory drugs (NSAIDs) medication, avoiding several potential side-effects from chronic NSAIDs usage.

The PEMF therapy is based in low frequency signal, with a wide range of frequencies, which will produce membrane disturbances and activation of multiple intracellular pathways.[6,7]

It has been reported that PEMF therapy yields several benefits into the bone unification, acute pain relief, wound healing, edema and inflammation control, as well as, chronic pain associated with connective tissue (cartilage, tendon, ligaments and bone) injury and joint-associated soft tissue injury, osteoarthritis, fibromyalgia, osteoporosis, skin ulcers and further potential applications.[8–11] Along this line, many reviews have been performed to assess the PEMF effectiveness in several conditions. In this sense, the PEMF showed moderate[7] or no benefits in knee osteoarthritis,[12] a beneficial tendency on the bone growth stimulation in acute fractures[13] and efficient in relieving pain and enhancing bone formation in osteoporosis.[14]

Although the use of PEMF therapy in low back pain is growing and there is substantial investigation on this topic, a systematization of its effects on the low back pain is still lacking. Therefore, this study aims to search for randomized controlled trials that assessed the effectiveness of the PEMF therapy in reducing pain symptomatology in patients with low back pathological conditions.

Methods

Search strategy

The systematic review was conducted according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which aims to improve the standard of reporting of systematic reviews and meta-analyses.[15] Additionally, the protocol for this review was à *priori* registered in the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/prospero/; ID: CRD42015025308).

It was conducted a comprehensive database search using Pubmed, Scopus, Cochrane Library and PEDro, searching for relevant studies that assessed the efficacy of the PEMF therapy on reducing pain on individuals with low back pain. The search was performed according the following key-words: pulsed electromagnetic field therapy; back; spine; spinal; lumbar; and further combined with the Boolean operators (AND; OR). An example of the search can be seen in Table 1. The reference list of most relevant studies was scanned for additional studies in order to achieve the greatest number of available studies on the scientific literature. All searches were comprised to the period of January 2005 to August 2015 and were conducted by two independent investigators (R.A., H.D.), which confronted both results to check for overlapping; any disagreements were discussed by until consensus was reached.

Table 1
Example of search strategy for Pubmed database.

Search	Search term(s)	Results
#1	Search **pulsed electromagnetic field therapy**	342
#2	Search **back**	86,722
#3	Search **spine**	82,093
#4	Search **spinal**	120,484
#5	Search **lumbar**	43,342
#6	Search **(#2 OR #3 OR #4 OR #5)**	237,516
#7	Search **(#1 AND #6)**	32

Study selection

All titles and abstracts from the selected databases were screened. After, the potential relevant studies were selected and retrieved, full texts were read in order to apply the eligibility according the following inclusion criteria: (1) assessment of pain outcome; (2) use of pulsed electromagnetic field therapy; (3) prospective design; (4) randomized controlled trials; (5) English language studies. For exclusion criteria it was determined: (i) other reviews or meta-analyses; (ii) clinical commentaries or expert opinions; (iii) case series; (iv) non-randomized controlled trials; (v) animal studies; (vi) skeletally immature population.

Data collection and extraction

Two independent investigators (R.A., H.D.) retrieved all the information and matched for consensus. The main outcome of interest was the quantification of intensity of pain overtime. Thus, after the application of the eligibility criteria and the included studies were determined, the studies were analyzed based on sample demographics, study's aim, statement of conflict of interest, study duration and follow-up (period of time and percentage), PEMF devices used, treatment window, intervention protocol, parameters assessed (clinical and functional) and most significant results.

In addition, the figures of pain intensity and the Oswestry Disability Index were assessed based on their means and standard deviation values and calculated their mean differences, i.e., difference between the study's end-point and baseline values. Additionally, the Cohen's effect size, within the 95% confidence intervals (CI) was calculated. The effect sizes were computed by subtracting the experimental group mean to the control group mean and further divided by the pooled standard deviations of both groups.[16,17] Thus, a positive effect reflects a greater decrease on the pain intensity toward the experimental group. The 95% CI provides information concerning the variability of the observed effect size, its precision, as well as the accuracy with which the interval contains the population parameter (i.e., the true value). The standardized Cohen effect sizes were interpreted according to the guidelines established by Cohen[17] in which values <0.20 are trivial or not substantial, 0.20 and 0.49 are small but substantial, 0.50 and 0.79 are moderate, and ≥0.80 are large. In case of missing values (means and/or standard deviations), the authors from the respective studies were contacted in order to obtain them.

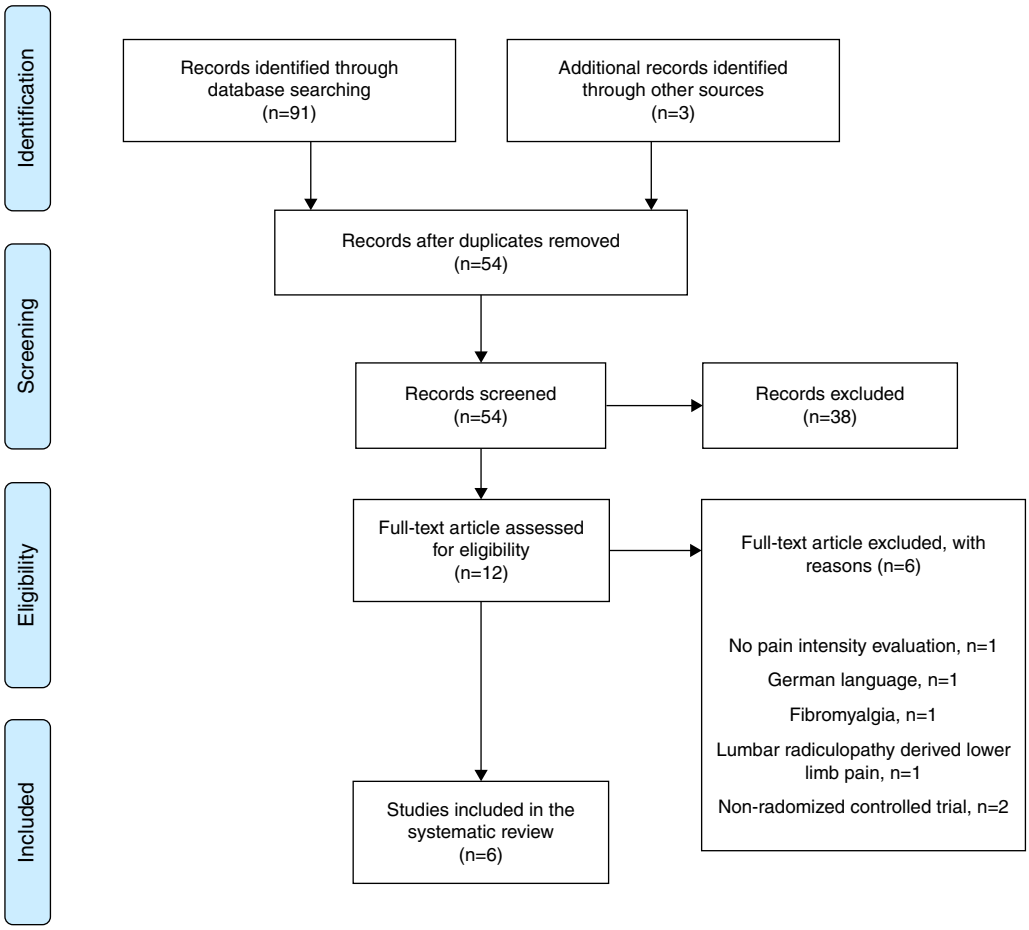

Fig. 1. PRISMA flow diagram of the eligibility process.

Methodologic quality assessment

The PEDro scale in order to assess the methodological quality (external validity, internal validity and statistical reporting) and the level of evidence was set according the Oxford Center for Evidence-Based Medicine (CEBM) scale.[18] PEDro scale has been reported to be a valid and reliable tool to measure the methodological quality of interventional clinical trials.[19,20] These parameters were independently assessed by two authors (R.A., H.D.) and all disagreement were resolved until consensus was reached.

Results

Study selection

The database and hand search yielded 91 titles, which were reduced after duplicates removal and title/abstract reading to 12 full-text articles that were screened for eligibility. After screening, 6 studies were excluded[21–26] which the reasons for exclusion are highlighted in the PRISMA flow chart (Fig. 1). The remaining 6 studies were eligible inclusion on the qualitative analysis and 5 into the quantitative analysis.

Description of studies

In Table 2 are presented the characteristics of the 6 included original studies. Overall, the studies included a total of 210 participants (90 men and 120 women), with an overall mean age of 43.3 years old. All the included participants reported complains of low back pain, however with different etiologies: generalized low back pain[27]; acute non-specific low back pain[3]; discogenic lumbar radiculopathy[28]; failed back surgery syndrome pain[26]; chronic low back pain.[4,29]

The inclusion criteria varied across the studies. Nonetheless, across the included studies some similarities were found. All of the studies were performed in adult populations with clinically evaluated low back pain. A visual analogue scale above 5 points and a numeric rating scale above 4 points were also considered in Park, Sun, Lee, Kang, Lee, Hwang and Cha[30] and Lee, Kim, Lim, Lee, Choi, Park, Lee and Lee[29] studies, respectively. The presence of a cardiac pacemaker or other electronic implants were the only exclusion criteria enclosed in all studies. Other exclusion criteria were study-specific related comorbidities.

Generally, the studies enrolled the use of different devices, however with the same objectives and principles of PEMF therapy application. Their description can be seen in Table 3. The PEMF therapy was often compared with placebo interventions (comprising sham devices) or analgesic medication. Moreover, the studies showed heterogeneity concerning the PEMF therapy protocols, where the duration of the application ranged from 5 days to 3 weeks, and the frequency of the application from 4 times a day to just twice a week. The follow-up period also showed heterogeneity, ranging from 3 to 7 weeks,[3,4,29,30] or in some cases it was not reported.[27,28] The follow-up percentage was very satisfactory, being above the 85%, excepting Oke and Umebese[27] study which did not report the follow-up.

Table 2
Characteristics and main results of the included studies.

References	Demographics	Aim	Duration/ follow-up	Intervention protocol	Treatment window	Parameters assessed	Results	Follow-up (%)
Krammer et al.[3]	$n = 40$ 20M/20F 33 y.o.	Explore the additional benefits of PEME used as an adjunct to physiotherapy in treatment of acute non-specific low back pain	1 weeks 4 weeks	Experimental group: physiotherapy and PEME Control group: physiotherapy and placebo 7 days of PEME and physiotherapy 2×/week for 4 weeks	During 7 days	ODI; NPRS; Patient Specific Functional Scale; Level of Function	Both groups showed improvements on ODI, Patient Specific Functional Scale and NPRS scores over both follow-up periods ($p < 0.05$); however, without any significant differences between them ($p > 0.05$)	100
Park et al.[30]	$n = 38$ 11M/27F 32 y.o.	Investigate the efficacy of PEMF on the lumbar myalgia	2 weeks 3 weeks	Experimental group: PEMF Control: sham device 6 times, 3×/week for 2 weeks	10 min day, 3 days a week, during 2 weeks	VASB; VASP; Korean version of: ODI; SF-36; EQ-5D; BDI; RMDQ	Significant decrease of VASB ($p < 0.007$), VASP ($p < 0.015$) and RMDQ in PEMF group in comparison to the control group	100
Oke et al.[27]	$n = 16$ 9M/7F 42.8 y.o.	Assess the therapeutic efficacy of PEMF in treatment of back pain	5–9 days N.R.	Experimental group: analgesics + NSAIDs and PEMF Control group: analgesics Both groups received soft tissue manipulation with an analgesic gel 4×/day (2 h)	4 times a day during 2 h (Min 5 days and Max 9 days of treatment)	NPRS; Modified version of Functional Activity Scale	Significant differences on experimental group on pain rating scores ($p > 0.061$) and functional activity score ($p > 0.000$)	N.R.
Omar et al.[28]	$n = 40$ 11M/29F 38.8 y.o.	Evaluate the effect of PEMF in patients with discogenic lumbar radiculopathy	3 weeks N.R.	Experimental group: PEMF every day for 3 weeks Control group: standard medical treatment and placebo	20 min day, during 3 weeks	VAS; ODI; Radiological evaluation; Somatosensory evoked potentials	Significant reduction in pain severity ($p < 0.024$) Significant improvement in modified OSW ($p < 0.001$) Improvement of SSEPs ($p < 0.05$)	100
Harden et al.[4]	$n = 40$ 20M/20F 40.3 y.o.	Evaluate the TEMF on chronic low back pain	2 weeks 6 weeks	Experimental group: TEMF Control: sham device	40 min session, 10 sessions in 3 weeks	VAS; MPQ-SF; BDI; STAI; QPDI; Physical performance tests	Although both groups improved over time ($p < 0.05$), the experimental group improved significantly over sham treatment during the 2-week follow-up period (20.5% reduction in pain, $p = 0.003$)	100
Lee et al.[29]	$n = 36$ 19M/17F 75 y.o.	Study the effect of PEMT in patients with chronic low back pain	3 weeks 7 weeks	Experimental group: active PEMT Control group: placebo 3×/week for 3 weeks	The 15-min treatment 3 times a week for 3 weeks	NPRS; Revised ODI	PEMT reduced pain and disability in patients with chronic low back pain ($p < 0.05$)	100

PEME – Pulsed Electromagnetic Energy; PEMF – pulsed electromagnetic fields; TEMF – Therapeutic Electromagnetic Fields; ODI – Oswestry Disability Index; NPRS – Numeric Pain Rating Scale; M – Male; F – Female; y.o. – years old; N.R. – not reported; VAS – visual analogue scale; VASB – visual analogue scale for discomfort for low back pain; VASP – visual analogue scale for pain intensity; SF-36 – Short-Form 36; EQ-5D – EuroQol-5 Dimension (Korean adapted); BDI – Beck's Depression Inventory (Korean adapted); RMDQ – Roland-Morris Disability Questionnaire (Korean adapted); NSAIDs – nonsteroidal anti-inflammatory drugs; IL-4/IL-6 – interleukins 4 and 6; MPQ-SF – McGill Pain Questionnaire – Short Form; BDI – Beck Depression Inventory; STAI – State-Trait Anxiety Inventory; QPDI – Quebec Pain and Disability Index.

Table 3
PEMF devices used across the included original studies and its reported characteristics.

References	Devices	Additional reported information
Krammer et al.[3]	RecoveryRx (BioElectronics Corp)	Carrier frequency of this device is 27.12 MHz. Pulse rate of 1000 pulses p/s and a 100 μs burst width. Magnetic flux density or field strength of the device is 0.03 mT
Harper et al.[26]	Provant Therapy System Model 4201 (Regenesis Biomedical Inc., Scottsdale, AZ, USA)	Carrier frequency of this device is 27.12 MHz. Pulse durations are 42 ± 4 μs repeated every 1000 ± 25 μs
Park et al.[30]	NUGA MRT-II (NUGA MEDICAL, Wonju, Korea)	The maximum strength of PEMF was 820 mT with pulse frequency of 8.56 kHz
Oke et al.[27]	EMpulse, Model 301 (EM-Probe Technologies, USA)	Non reported
Omar et al.[28]	NR	Field strengths ranged from 5 to 15 Gauss (G) and the frequency ranged from 7 Hz to 4 kHz
Saggini et al.[24]	NR	Electromagnetic fields of low intensity with inferior frequencies at 100 kHz
Lee et al.[29]	CR-3000 system (CR Technology Co., Kyungki-do, Korea)	Carrier frequency of this device range from 1 to 50 MHz. The magnetic pulse produced is biphasic and has a pulse width of 270 μs. Maximum output amplitude of 2 T

Table 4
Quantification of pain intensity and effect sizes by group.

Reference	Control		Experimental		Effect size (95% CI)
	Mean ± SD	Mean difference	Mean ± SD	Mean difference	
Krammer et al.[3 b]	0.77 ± 1.19	−4.14	0.91 ± 0.81	−4.09	−0.14 (−0.76, 0.49)
Park et al.[30 a]	6.29 ± 1.33	−0.53	4.53 ± 2.29	−2.1	0.94 (0.25, 1.59)
Oke et al.[27 b]	1.63 ± 0.74	−6.62	1.38 ± 1.51	−6.37	0.21 (−0.78, 1.18)
Omar et al.[28 a]	5.8 ± 2.7	−1.2	3.6 ± 1.5	−3.5	1.01 (0.33, 1.64)
Lee et al.[29 c]	5.4 ± 1.2	−1.1	4.5 ± 1.2	−2.2	0.48 (−0.19, 1.14)

[a] Visual analogue scale.
[b] Numeric Pain Rating Scale.
[c] 11-Point numerical rating scale.

Outcomes of interest

The main outcome of interest was the quantification of the intensity of low back pain. All studies reported reduction on the pain intensity, at least, on the experimental group. When assessing the mean difference on pain intensity from baseline to the end-point, it was found a reduction on the pain intensity from 2.1 to 6.4 points out of 10 on the visual analogue scale or on the numerical rating pain scale (Table 4); however, when analyzing the effect sizes, two studies showed a small effect size[27,29] and two studies showed a large effect size.[28,30]

Regarding the functionality assessment, several scales and indexes were used to quantify the participant's function: Oswestry Disability Index[3,28–30]; Patient Specific Functional Scale[3]; Korean version of Roland-Morris Disability Questionnaire[30]; Modified version of Functional Activity Scale[27]; Quebec Pain and Disability Index.[4] When focusing the Oswestry Disability Index alone, which was the most commonly reported scale for measuring the functionality, despite its large mean differences from baseline to end-points (Table 5), the effect sizes were small (<0.20). The study of Omar, Awadalla and El-Latif[28] was an exception, achieving a large effect size (>0.80), however using an adapted Oswestry Disability Index.

Methodological quality

The mean score of methodological quality of the included studies was 6.8 ± 1.9 (range 4–9) out of 10 points according PEDro scale and the level of evidence was 1b in all studies (Table 6).

The most common methodological limitation across the studies was the lack of "intention-to-treat" analysis, which was only performed by Park, Sun, Lee, Kang, Lee, Hwang and Cha.[30] Another major methodological issue was the concealment of the randomization, which also only performed in two studies.[3,30] Lack of subjects and the assessors blinding was also a methodological limitation across the studies, especially when concerning the therapist, once only two studies blinded the therapists.[3,29]

Discussion

The main finding of this systematic review is that PEMF therapy seems to reduce the pain intensity and enhance better functionality in individuals with low back pain.

When used alone, the PEMF seem to have great effect in reducing the pain intensity in low back patients, independently of the low back pain condition.[28–30] However, when added to other standard

Table 5
Oswestry Disability Index and effect sizes by group.

Reference	Control		Experimental		Effect size (95% CI)
	Mean ± SD	Mean difference	Mean ± SD	Mean difference	
Krammer et al.[3]	6.5 ± 9.08	−28.7	5.7 ± 6.03	−29.9	0.10 (−0.52, 0.72)
Park et al.[30 a]	16.06 ± 8.79	−13.83	14.47 ± 12.39	−13.37	0.15 (−0.49,0.78)
Omar et al.[28 b]	48.2 ± 10.09	−25.60	33.4 ± 9.04	−42	1.54 (0.81, 2.21)

[a] Used Korean version of Oswestry Disability Index.
[b] Used Modified Oswestry Low Back Pain Disability Questionnaire and presented the results in percentages.

Table 6
Methodological quality of the included studies.

References	Study design	PEDro											Oxford CEBM	Conflict of interest
		E	2	3	4	5	6	7	8	9	10	11	Total	Level of evidence	
Krammer et al.[3]	Randomized, double-blind, placebo-controlled trial	+	+	+	+	+	+	+	+	–	+	–	8	1b	None
Park et al.[30]	Randomized, double-blind, placebo-controlled trial	+	+	+	+	+	–	+	+	+	+	+	9	1b	Corporations funding
Oke et al.[27]	Randomized controlled trial	+	+	–	+	–	–	–	–	–	+	+	4	1b	Missing
Omar et al.[28]	Randomized controlled trial	+	+	–	+	–	–	–	+	–	+	+	5	1b	None
Harden et al.[4]	Randomized, single-blind, placebo-controlled trial	+	+	–	+	+	–	+	+	–	+	+	7	1b	Missing
Lee et al.[29]	Randomized, double-blind, placebo-controlled trial	+	+	–	+	+	+	+	+	–	+	+	8	1b	None

E: eligibility criteria (this item is not used to calculate the total score); 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: participant blinding; 6: therapist blinding; 7: assessor blinding; 8: <15% dropout; 9: intention-to-treat analysis; 10: between-group statistical comparisons; 11: point estimate and variability statistical measures.

therapies (such as, standard physiotherapy[3] or analgesic therapy[27]) seems to do not add additional effect to the standard therapy.

Measuring the intensity of pain related to the different low back conditions plays a key role in following up the patient's recovery. However, because of the subjective nature of pain, clinical importance is not always easy to determine.[31] In an effort to overcome this variability, measures of improvement usually adjust for the individual's baseline by calculating raw change or percent change.[32]

The PEMF therapy has been pointed out as an effective and relatively safe tool for conservatively treat the low back pain.[4,27–30] Furthermore, it has a high potential of compliance due to its low risk of side-effects and high tolerance.[29] In fact, when analyzing the pain intensity alone, the included studies effect sizes indicate a tendency to a greater reduction on pain intensity for the PEMF groups. Nevertheless, when compared to standard therapies (such as, physiotherapy[3] or analgesic therapy[27]) seemed to produce a low effect or no effect at all. Considering the minimal clinically important difference (MCID) – minimal change in an outcome score that is clinical meaningful for the patients – all studies showed that the PEMF was able to produce a clinical meaningful pain reduction since the mean differences were higher than the minimum 2-point suggested by Childs, Piva and Fritz.[33]

Several scoring systems are frequently used in the clinical environment in order to measure the disability related to the low back conditions, which should be reliable, valid and sensitive to clinically relevant changes, taken into account both patients' and physicians' perspective and is short and practical to use.[34–37] Although, impairments such as decreased range of movement or reduced straight leg raise can be clinically observed by physiotherapists, the direct observation of activity restriction is not sufficient. Therefore, the physiotherapists have the need to rely on the patient's self-report assessment to measure the impact of low back pain on daily activities.[34]

Several studies have been demonstrating the PEMF effectiveness in reducing the disability related to the low back pain.[27–30] Regarding the studies included in this systematic review, the disability assessment was mostly made by the Oswestry Disability Index,[38] showing improvements after application of PEMF therapy, however with small effect sizes. Nevertheless, the MCID's were above the minimum recommended by Ostelo, Deyo, Stratford, Waddell, Croft, Von Korff, Bouter and de Vet[39] – between 6–10 points or 12–20 percent – indicating a meaningful improvement on the patient's functionality. On the other hand, Omar, Awadalla and El-Latif[28] showed a large effect size toward the PEMF group ($d = 1.54$, 95% CI: 0.81, 2.21) using the Modified Oswestry Low Back Pain Disability Questionnaire, obtaining a 42% mean reduction after daily applications of PEMF therapy for 3 weeks. Still, some caution should be taken when considered this study since they used an adapted score.

Other usual subjective scores – generic and disease-specific – to evaluate the low back functionality have already been explored during the last decades and are currently available for orthopedic clinical and research practice.[35] In this sense, beneficial results were reported in the included studies using different scores: Patient Specific Functional Scale[3]; Korean version of Roland-Morris Disability Questionnaire[30]; Modified version of Functional Activity Scale[27]; Quebec Pain and Disability Index.[4] Although the studies showed improvements from the baseline to the study's end-point, two studies did not achieved significant improvements toward the PEMF group when compared to the control group.[3,4]

Due to the comprehensiveness and complexity within the low back pain umbrella and allied to its associated multiple etiologies, specific attention should be directed to the characteristics of subgroups of responders.[4] In this line, the studies included in our systematic review explored the PEMF therapy effectiveness in different conditions of low back pain: generalized low back pain[27]; acute non-specific low back pain[3]; discogenic lumbar radiculopathy[28]; lumbar myalgia[30]; chronic low back pain.[4,29] Due to the high heterogeneity of the different low back pain conditions of the original studies included in this systematic review, and the small sample sizes (ranging from $n = 16$ to $n = 40$), no strong recommendations can be drawn regarding the non-specific low back pain or its several conditions.

Moreover, it was found high heterogeneity between the protocols of PEMF therapy of the different studies, differing in the devices used and its parameters (frequency, pulse rate and width, magnetic flux density, among others), duration and frequency of application (4 times a day until 3 times a week) and type of application. Hence, considerable caution should be taken when comparing the results from the different studies, highlighting the importance in achieve the most effective dosage and standardized protocol parameters. In this line, future studies should shift their focus on analyzing the different mechanisms of action (e.g., myofascial, radiculopathic, among others) and subgrouping (acute or chronic, specific or generalized, mechanical or idiopathic) the individuals with low back pain in order to evaluate the effects of PEMF therapy in these different groups of low back pain and identify the responsiveness of each specific group. Thus, it will be possible to achieve the most effective PEMF protocol to the most suitable subgroup of patients.

Generally, the studies showed a good methodological quality according the PEDro scale, with a mean of 6.3 points out of 10 possible, which is above the recommended by.[40] The studies showed a good methodological quality, i.e., good external and internal validity, providing sound interpretation of the data. However, precisely in the internal validity, some limitations were found across the

studies that could provide additional bias to the results: lack of "intention-to-treat" analysis; lack of randomization concealment; lack of blinding of subjects, therapists and assessors. Moreover, another important limitation was the statement of conflict of interest, where only three studies stated that had no conflict of interest at all. Two other studies did not make any statement about conflict of interest whatsoever and two studies reported funding upon the study's conduction.

Study limitations

To the best of our knowledge, no other systematic review has investigated the therapeutic effects of PEMF specifically on low back pain. Moreover, it was used 2 independent reviewers for screening and critical appraisal and registered our protocol which could have reduced the bias within the systematic review. Still, there are some limitations that are needed to be pointed out. Firstly, the low number of studies available on the scientific literature that investigates the effectiveness of PEMF on low back pain is scarce, and even fewer if we consider de low back pain subgroups. Another limitation is the small size of the studies samples, which should be larger in order to provide power to the conclusion taken from the results. Also, the lack of data (means and standard deviation values) was a limitation in some studies, and the wide range of devices and low back pain conditions, precluded the systematization of the quantitative data. The search was restricted to English language studies; however, previous work demonstrated that the restriction to English language studies on systematic reviews does not provide additional bias.[41–44] Furthermore, the studies did not made an adjustment for confounders (e.g., volume of analgesic medication consumption or psychosocial variables), which could lead to further biased results. These confounders may mix with the primary exposure or outcome and bias the true relationship of interest.[45]

Conclusion

In conclusion, the evidence within this systematic review demonstrates that the PEMF therapy seems to be able to relieve the pain and improve functionality in individuals with different low back pain conditions. However, when added to a standard therapy, it seems to do not add any beneficial effect. Nonetheless, due to the low risk associated, it can be a potential alternative to the conventional pharmacological therapy. The lack of studies in this theme warrants further research on PEMF effects on the different conditions of low back pain, with standardized protocols, larger samples and adjustment for low back pain confounders in order to achieve stronger conclusions.

Disclosure

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE Open Access

Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study

Hong-fei Shi, Jin Xiong*, Yi-xin Chen*, Jun-fei Wang, Xu-sheng Qiu, Yin-he Wang and Yong Qiu

Abstract

Background: Pulsed electromagnetic field (PEMF) is reported to be an effective adjunct for the management of nonunion long-bone fractures. Most studies implement PEMF treatment after 6 months or longer of delayed union or nonunion following fracture treatment. Despite these variations in treatment, the early application of PEMF following a diagnosis of a postoperative delayed union has not been specifically analyzed. In this study, the outcomes of postoperative delayed union of long-bone fractures treated with an early application of PEMF were evaluated as compared with a sham-treated control group.

Methods: In this prospective, randomized controlled study, a total of 58 long-bone fracture patients, who presented with delayed union of between 16 weeks and 6 months, were randomly split into two groups and subjected to an early application of PEMF or sham treatment. Clinical and radiological assessments were performed to evaluate the healing status. Treatment efficacy was assessed at three month intervals.

Results: Patients in the PEMF group showed a higher rate of union than those in the control group after the first three months of treatment, but this difference failed to achieve statistical significance. At the end of the study, PEMF treatment conducted for an average of 4.8 months led to a success rate of 77.4%. This was significantly higher than the control, which had an average duration of 4.4 months and a success rate of 48.1%. The total time from operation to the end of the study was a mean of 9.6 months for patients in the PEMF group.

Conclusions: Fracture patients treated with an early application of PEMF achieved a significantly increased rate of union and an overall reduced suffering time compared with patients that receive PEMF after the 6 months or more of delayed union, as described by others.

Keywords: Electromagnetic field, Delayed union, Fracture healing, Long-bone fracture

Background

Despite recent improvements in fracture management, delayed union and nonunion remain as intractable complications following surgical reduction and fixation of long-bone fractures. It is estimated that 5–10% of all fractures show impaired healing [1]. Surgical management is usually preferred in the treatment of an established nonunion, especially in those fractures that are accompanied by infection, deformity, shortening or bony defect. Otherwise, nonsurgical methods are considered for delayed union to facilitate osteogenesis, osteoinduction, as well as osteoconduction and thus stimulate the healing process [2,3]. Among the reported therapeutic methods, the use of biophysical interventions, such as pulsed electromagnetic field (PEMF) therapy, has attracted the attention of clinicians in the past decades, because of their noninvasive characteristics [4,5].

PEMF was introduced in the mid-1970s as a beneficial tool for fracture healing [6]. Although the mechanism remains poorly understood, PEMF provides an effective

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adjunct for the management of un-united long-bone fractures [7-10]. However, the indication and treatment strategies for the use of PEMF vary within the literature. The majority of investigators do not start PEMF treatment until an established nonunion is diagnosed [11-14], and others consider a late stage of delayed union (over 6 months after fracture) as the indication for its use [15-17]. Very few studies have addressed the early application of PEMF immediately after diagnosis of a delayed union (at about 16 weeks after fracture) [18], and no reports have specifically investigated the efficacy of the early application of PEMF.

Long-bone fracture healing has been recognized as an orchestration of prompt hematoma formation, inflammatory response, cell proliferation and differentiation, followed by a long-term process of ossification and remodeling [19]. Since the healing process is not considered to be accomplished in the case of a delayed union in orthopaedic terms, the early intervention of PEMF possesses the theoretical advantage of reactivating the biological process of bone repair, thereby facilitating fracture healing and possibly shortening the treatment duration. In the present study, the authors aimed to evaluate the efficacy of early-applied PEMF on postoperative delayed union of long-bone fractures. We hypothesized that the early application of PEMF in patients with delayed union might lead to an increased rate of fracture union compared with sham-treated patients. The outcomes of postoperative delayed union of long-bone fractures in patients treated with an early application of PEMF after the delayed union diagnosis were evaluated and compared with the placebo-treated controls.

Methods

Patients

This prospective study was approved by the Medical Ethics Committee of Nanjing Drum Tower Hospital (Ref. No. 070321). A flowchart of the study is presented in Figure 1. Between April 2007 and September 2010, patients with postoperative delayed union of long-bone fracture were recruited from the outpatient clinic. During the baseline assessment, anteroposterior and lateral radiographs were taken to address the fracture healing status and the fixation method. Data on the demographic characteristics, comorbidity, medication history, lifestyle habits, fracture type, soft tissue condition were collected, as was information on the surgery and postoperative rehabilitation. Delayed union was defined as a failure to heal after at least 16 weeks and not more than 9 months following surgical reduction and fixation of the fracture [12,18]. Radiographically, healing failure was identified when callus bridging was not observed in more than three cortices on biplane radiographs. The exclusion criteria consisted of implant loosening or failure, infection, established nonunion (healing failure after more than 9 months, without any clinical or radiographic sign of progression to union within the last 3 months) [20], a fracture gap greater than 5 mm, and the presence of the implant within the fracture gap [11]. Patients with metabolic disorders were excluded as were those patients who received medications that could affect fracture healing [18,20].

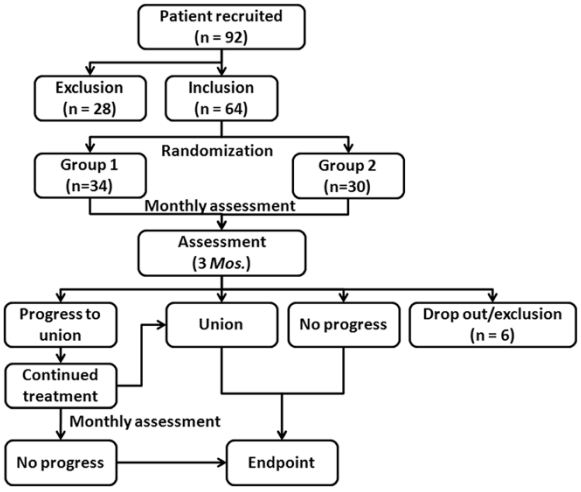

Figure 1 Flowchart of the study.

The authors had intended to initiate intervention 16 weeks after fracture for each patient, but not all patients were referred to the clinic in time. Therefore, patients were included in the study if they were enrolled between 16 weeks and 6 months postoperatively. A power analysis was conducted to estimate the sample size, with reference to a previously reported randomized controlled trial that achieved a union rate of 89% in PEMF-treated tibial nonunion cases compared with a 50% union rate in the sham-treated controls [13]. To detect the similar change in union rate with 80% power in our study, we required more than 48 patients.

Interventions

Once included in the study, the patient was blindly assigned into the PEMF treatment group (Group 1) or the control group (Group 2) according to randomly generated numbers. In Group 1, PEMF treatment commenced immediately after enrollment. An electromagnetic field was delivered through a coil (Orthopulse® II, OSSATEC, Uden, The Netherlands) centered over the fracture site for 8 h/day (Figure 2), with the signal specification adjusted according to Punt's study [14]. In Group 2, the coil was applied for 8 h/day with a sham signal generator from the same manufacturer. Therefore, patients were blinded to the treatment. Protected weight

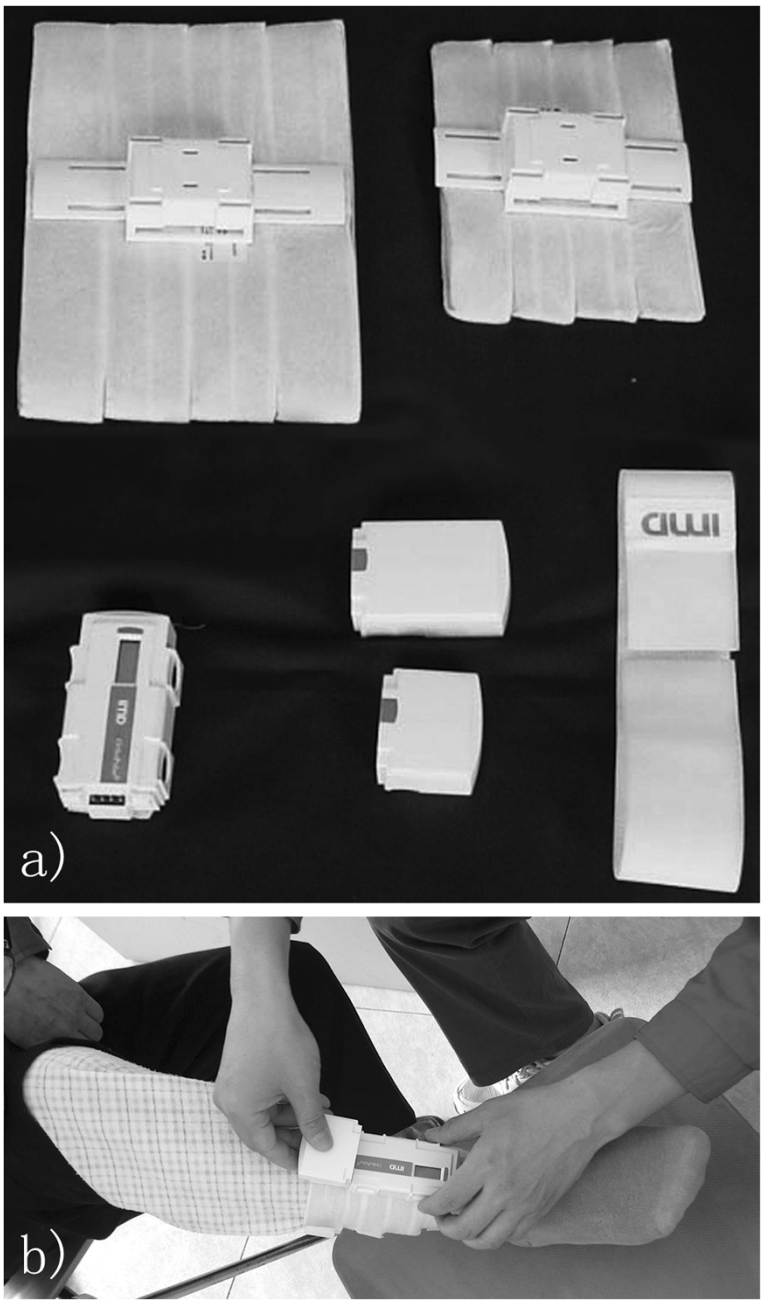

Figure 2 The portable treatment equipments used in the study. (**a**) A set of Orthopulse® II stimulator consisted of different sizes of coils, signal generator, batteries, and removable fixation band; (**b**) Patient in Group 1 received pulsed electromagnetic field treatment with the coil centered over the fracture site.

bearing was encouraged unless it compromised the stability of the fractured area. All patients were requested to record their potential discomfort and the duration of the treatment. They were also asked to refrain from smoking, alcohol abuse, or additional forms of therapy during the study period. Biweekly contact through phone calls was performed by two research assistants to exclude patients with poor compliance.

Outcomes

Clinical and radiological assessments were performed monthly following commencement of the treatment. Clinical evaluations of pain when stressed and motion at the fracture site were carried out by two senior surgeons (JFW and XSQ) independently, who were blinded to the grouping information. The consensus was derived from further discussion if necessary. Another two blinded

surgeons (JX and YXC) reviewed the anteroposterior and lateral radiographs of the fracture to assess cortical bridging. Union was considered positive when there was no pain during joint stressing or during motion at the fracture site, and callus bridging was present for three out of four cortices on orthogonal radiographs [21]. Treatment was ceased in all patients when union was achieved or no radiographic progress to union was observed for a continuous three-month period (Figure 1).

Statistical methods

Group demographics were compared using independent *t*-test or Fisher's exact test. The successful rate of fracture union was calculated after three months of treatment and at the end of the study in each group, with the difference between groups compared with Fisher's exact test. SPSS version 15.0 software (SPSS Inc, Chicago, IL) was used and the level of significance was set as 0.05.

Results

During the study period, 92 patients with delayed union were recruited, with 64 patients meeting our inclusion criteria for early PEMF or sham treatment initiated 16 weeks and not more than 6 months postoperatively (Figure 1). Four patients dropped out after a short period of treatment, and another two patients, who received herbal supplements during the study, were excluded. The remaining 58 patients were included for statistical analysis. Patient demographics (Table 1) were comparable between the two groups, with no significant differences determined for patient age ($P = 0.450$), fracture site ($P = 0.439$), or method of fixation ($P = 0.430$). The original fracture sites included the humerus (5 cases), the ulna and/or radius (4 cases), the femur (24 cases), and the tibia (25 cases).

A total of 31 patients received PEMF treatment, whilst the remaining 27 cases were assigned to the control group (Table 1). Before treatment, the average elapsed time since fracture operation were 4.8 months and 5.1 months in the two groups, respectively ($P = 0.238$). Following three months of treatment, 12 cases achieved union with a success rate of 38.7% (95% confidence interval (CI), 0.21 to 0.57) in Group 1 (Figure 3). Meanwhile, the fracture union success rate was 22.2% (6 out of 27, 95% CI, 0.08 to 0.42) for Group 2, which was slightly lower than that for Group 1 ($P = 0.256$), but not statistically significant. The relative risk of fracture union was 1.74 (95% CI, 0.76 to 4.01). Radiographic progress to union was observed in 17 patients in each of the groups, who subsequently received extended PEMF or sham treatment. At the end of the study, the average lengths of treatment were 4.8 months and 4.4 months in the two groups ($P = 0.489$), with a union rate of 77.4% (24 out of 31, 95% CI, 0.58 to 0.90) in Group 1 (Figure 4) compared with a union rate of 48.1% (13 out of 27, 95% CI, 0.28 to 0.68) in Group 2 ($P = 0.029$, Table 1). The relative risk of fracture union was 1.61 (95% CI, 1.04 to 2.48). The total times from operation to the end of the study were averaged at 9.6 months and 9.5 months in Group 1 and Group 2 respectively ($P = 0.849$). No discomfort was reported by the patients in either group during treatment.

Table 1 Patient demographics and results

	Treatment group	Control group	P Value
No. of patients	31	27	
Age (*Yr.*)*	41.1 ± 14.5 (range 19 to 68)	38.4 ± 11.6 (range 20 to 62)	0.450
Fracture Site (No. of patients)			0..439
Femur	10	14	
Tibia	16	9	
Humerus	3	2	
Radius and/or Ulna	2	2	
Methods of Fixation			0.430
Plate	18	12	
Intramedullary Nail	13	15	
Elapsed Time before Treatment (*Mo.*)*	4.8 ± 0.9 (range 4 to 6)	5.1 ± 0.8 (range 4 to 6)	0.238
Duration of Treatment (*Mo.*)*	4.8 ± 2.3 (range 2 to 12)	4.4 ± 1.6 (range 2 to 7)	0.489
Rate of fracture union (3 *Mo.*)	38.7%	22.2%	0.256
Rate of fracture union (Endpoint)	77.4%	48.1%	0.029
Total Time from Operation to Endpoint (*Mo.*)*	9.6 ± 2.3 (range 7 to 17)	9.5 ± 1.5 (range 7 to 12)	0.849

* presented as mean ± SD.

Discussion

In this randomized controlled study, we investigated, for the first time, the clinical efficacy of the early application of PEMF treatment in postoperative delayed union of long-bone fractures. Following three months of PEMF treatment, patients showed a higher rate of union (38.7%) than the sham-treated patients (22.2%), but this difference failed to achieve statistical significance. At the end of the study, PEMF treatment, conducted for an average duration of 4.8 months, led to a success rate of 77.4%, which is significantly higher than that in the control group (48.1%).

Clinically, the concepts and techniques surrounding the surgical management of long-bone fractures have evolved rapidly in recent decades. By comparison, the ensuing individual progress of fracture healing, in terms

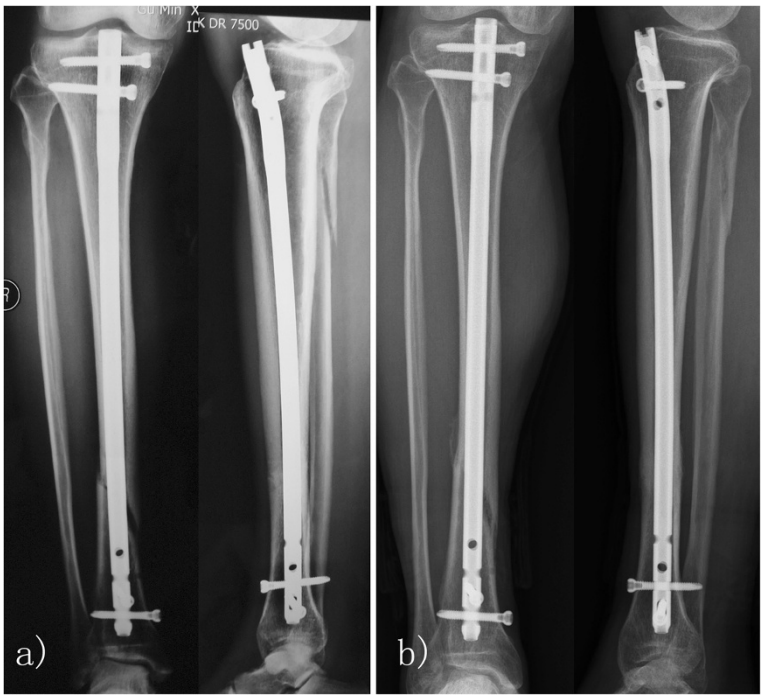

Figure 3 Delayed union of tibia fracture treated with PEMF. (**a**) A delayed union of tibia fracture was observed in a 65-year-old male patient following close reduction and intramedullary fixation 16 weeks ago. PEMF treatment was initiated; (**b**) Fracture union was observed after 3 months of treatment.

of biological and mechanical changes after surgery, has been poorly examined, despite the impaired healing rate of 5-10% in long-bone fracture patients. Among the multidisciplinary approaches explored to treat delayed union and nonunion fractures, the majority of studies employ the use of invasive procedures, such as surgical debridement, bone grafting and harvesting, or local injections [22,23], and hence, these procedures have been primarily examined in established nonunions. For delayed unions, noninvasive interventions, such as PEMF, are preferred before further invasive procedures are considered [4,24].

The original aim for this study was to instigate PEMF treatment immediately after the diagnosis of a post-operative delayed union (at 16 weeks after fracture). In our opinion, an earlier intervention is likely to be more effective because of the potentially deteriorated state of the biological environment after 16 weeks of delayed union or nonunion [25,26]. However in most published trials, PEMF stimulation was deferred until 6 months or

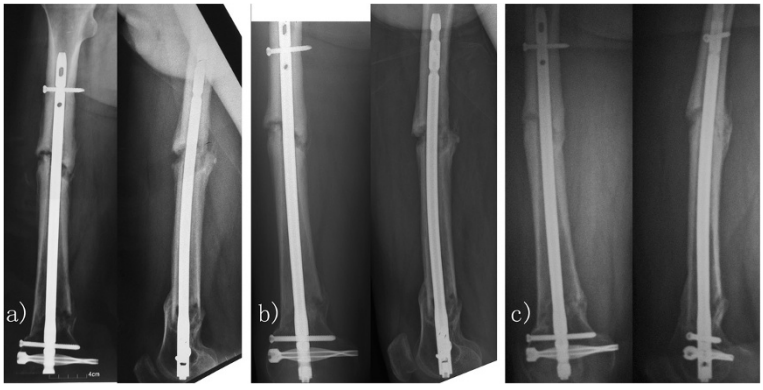

Figure 4 Delayed union of femoral fracture treated with PEMF. (**a**) PEMF treatment was started in a 59-year-old male patient who received reduction and intramedullary fixation 5 months ago; (**b**) Radiographies showed progress to union following 3 months of treatment; (**c**) Fracture united after 8 months of treatment.

later after fracture, with very few studies addressing the early application of PEMF in patients with delayed union. Sharrard conducted a randomized controlled trial with PEMF treatment initiated on patients with tibial delayed unions at 16 to 32 weeks after fracture [18]. Although the results revealed a significantly higher rate of union than the control, the authors did not specify the information and outcomes pertaining to the patients who received earlier intervention. A case series by Bassett addressed the effect of PEMF on 125 cases of delayed union and nonunion [27], with the earliest intervention started at four months after fracture. However, here again, the author only presented the overall success rate of the patients treated with PEMF within the nine month study period, without clarifying the impact of an early application of PEMF treatment. Similarly, in a report by Colson, there was a lack of consideration of the early effects of PEMF amongst 33 cases of long-bone delayed union or nonunion with treatment commenced from 2 to 120 months after fracture [28]. As such, our study provides pertinent evidence for the early application of PEMF on the delayed union of long-bone fractures.

The success rate following PEMF treatment in delayed union or nonunion varies dramatically (15.4–93.9%) across published studies due to different parametric settings and treatment strategies [28,29]. Considering studies with more than 30 subjects enrolled for PEMF treatment (a total of 12 studies, as summarized by Griffin), the average success rate was 80.1% (ranging from 67.6% to 93.9%) [10]. Using the same instrument as that used in our study, Punt examined a case series on established nonunions and achieved a success rate of 76–79% [14]. These results are comparable with the final success rate in our study (77.4%), demonstrating the similar stimulative effect of PEMF on delayed union, despite its earlier application in the present study. Therefore, our "sooner rather than later" hypothesis did not necessarily prevail for the clinical efficacy of PEMF. A recent report by Adie on the negative effect of PEMF on acute tibial shaft fractures further supports this [30].

Considering the treatment duration, no significant difference was observed between the groups in our study. However, the total time from fracture surgery to the end of PEMF treatment was obviously shortened in our study (9.6 months on average) compared with that in other studies who initiated PEMF stimulation after a postoperative window of 6 months, or longer in some cases (over 17.1 months in Heckman's study, and 11.6 months in de Haas's study) [15,16], not to mention the studies wherein PEMF treatment was applied in established nonunions. The early application of PEMF treatment, therefore, benefitted the patients by reducing the fracture suffering time. In clinical practice, PEMF treatment for delayed unions should be considered and initiated as early as possible, making patients fully aware of the success rate but also the increased cost.

At present, a definitive reason for the occurrence of a delayed union remains far from conclusive [31]. Both systemic and local factors are believed to be involved [23,32]. In our study, strict inclusion and exclusion criteria were set with reference to previously published clinical trials to rule out the interference of confounding variables such as metabolic disease, medication, smoking, alcohol abuse, infection, and unfavorable reduction or fixation from previous operations [11,18,20]. However, there were several factors constrained by practicality that may have influenced the outcome. For instance, the degree and extent of local damage caused by the accident or previous operation was difficult to trace. Further, patient activity levels, as a subject-related factor, could not be standardized during the study period, despite our recommendations for protected weight bearing. Another limitation of the present study was the relatively small numbers of patient for each fracture site or fixation method. We therefore could only draw an overall conclusion. Besides, serum biochemical markers were not measured in this study, which may potentially shed light on the biological mechanism of the early application of PEMF treatment.

Conclusions

In conclusion, within the limitations discussed above, the early application of PEMF treatment promotes fracture healing and leads to a significantly increased rate of union compared with the sham treatment. Even though the final success rate in this study was not superior to that measured in other PEMF trials, we show that our patients benefitted from a reduced overall suffering time between fracture and repair.

Competing interests

There's no competing interests. No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

Authors' contributions

All authors read and agreed with the contents of the manuscript. JX and YXC participated in the study design and the radiographic outcome assessment. JFW and XSQ carried out the clinical outcome analysis. HFS was in charge of interpreting the data analysis and drafting the manuscript. YHW and YQ assisted in revising the manuscript. All authors read and approved the final manuscript.

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