Review article

Effects of electromagnetic fields on bone regeneration in experimental and clinical studies: a review of the literature

ZHONG Cheng, ZHAO Teng-fei, XU Zheng-jian and HE Rong-xin

Keywords: electromagnetic fields; fracture; non-union; regeneration

Objective To assess the experimental and clinical data regarding the effects of electromagnetic fields (EMFs) on fracture non-union.

Data sources The English language literature regarding EMFs on fracture non-union were searched using MEDLINE, Web of Science and Embase, for the period January 2006 to June 2011. The search terms were electromagnetic fields and non-union/ bone marrow stem cells (BMSCs)/bone.

Study selection Articles were included in the review if they were related to the use of EMFs on BMSCs or bone tissue. Papers without full manuscripts available were excluded.

Results The basic and clinical research in this field, while somewhat limited, supports the insightful application of EMFs to ameliorate disability due to fracture non-union.

Conclusions Further basic and clinical research to validate the use of EMFs in facilitating function and bone reparative processes in fracture non-union is required.

Many factors contribute to the pathogenesis of bone non-union. Important characteristics of the fracture include fracture displacement, the severity of the injury to the soft tissue envelope, energy transfer at the time of injury, infection at the fracture site and the speed and success of initial management. Non-union is a problem in more than 20% of fractures, especially in specific areas of the body such as the tibia. Many techniques are currently in use for the treatment of delays in consolidation and non-unions, including several types of internal fixation, bone grafts, bone substitutes such as demineralized bone matrix, protein fractions such as platelet extract or morphogenetic protein, and biophysical therapy systems, including mechanical stimulation, ultrasound and electric and electromagnetic stimulation. Autologous bone grafting, in which damaged or missing bone tissue is replaced with tissue from the patient’s own healthy nonessential bones, is widely regarded as the “gold standard” for alternative therapeutic approaches and has been practiced for decades. Currently, many conditions are treated with grafts (allogeneic or autologous), but grafts are successful only with relatively small bone defects such as cleft palates. The limited availability of the patient’s own bone tissue and donor site morbidity such as bleeding, infection and chronic pain are common drawbacks of grafts. Approximately 25% of patients suffer donor site pain up to 2 years after the operation. Additionally, the transplantation of bone parts from allogeneic or xenogeneic origins bears the risks of immunological rejection and transmission of diseases. Other cases require the replacement of large bone fragments.

Appreciable attention has been paid to the practical medical effects of physical therapies on bone injury. Electromagnetic fields (EMFs) have a significant potential as a non-invasive physical therapy for delayed bone fracture healing and non-union. Several decades of clinical application of various EMFs have clearly demonstrated the potential benefit. Extremely low-frequency EMFs can stimulate bone tissue to remodel itself. This feature has been widely applied in the treatment of skeletal diseases such as osteoporosis, tendonitis, osteonecrosis, fracture and non-union. The success of treatment with EMFs depends on accurate diagnosis and selection of physical parameters of the applied fields. The complex picture of the processes that take place in bone marrow stem cells (BMSCs) as well as in the bone tissue was supplemented by recent studies which show a correlation between the presence of EMFs gradients and cellular reactions. Thus, EMFs studies in experimental biology and currently applied clinical therapies may now have the chance to explain the link between the clear-cut causal explanations of physics and the observed cellular and organic changes. Many hypotheses and postulates have been developed in an attempt to explain the therapeutic or biological principle of EMFs on musculoskeletal tissues, particularly bone tissues.

EMFs have a number of well documented physiological...
effects on cells and tissues, including the up-regulation of gene expression of collagen type II, the preservation of extracellular matrix (ECM) integrity of cultured explants, and the increase in prostaglandin E2 vascular endothelial growth factor (VEGF) and tumor growth factor-β (TGF-β), cytokine levels in an experimental model of decalcified bone matrix-induced stem cell ossification. In addition, investigators also measured the effects of cell exposure to EMFs on mRNA expression of the bone morphogenetic protein (BMP) family by reverse transcription polymerase chain reaction. An anti-inflammatory action has also been shown due to a direct effect on adenosine receptors on cell membranes. These experiments demonstrated that fields similar to the ones applied clinically for a variety of orthopedic conditions including non-union fractures have a reproducible osteogenic effect in vitro. Therefore, there is a strong rationale supporting the in vivo use of biophysical therapy stimulation with EMFs for treatment.

In the present review, experimental (in vitro and in vivo) and clinical studies on the effect of EMFs on osteogenesis and bone regeneration will be summarized. We searched the English language literature of the MEDLINE database, Web of Science and Embase from January 2006 to June 2011 (keywords or title words: electromagnetic fields and BMSCs/bone). Articles were included in the review if they were related to the use of EMFs on BMSCs or bone tissue. We excluded reviews and papers for which full manuscripts were not available. Finally, we excluded papers published before 2005 in an attempt to examine the most up-to-date methodology and outcome measures. We included a total of 51 papers (38 in vitro, 12 in vivo and 1 clinical).

EMFS EFFECTS ON BONE TISSUE RELATED CELLS, CYTOLOGY AND MICROENVIRONMENT IN IN VITRO STUDIES

We summarized studies from the last 5 years on the in vitro effect of EMFs on BMSCs, osteoclast-like cells and osteoblast-like cells. In these studies, EMFs were tested in human and animal monolayer cell cultures and tissue explants and their effects were investigated by various methodologies. Most authors investigated: (1) the mRNA expression of multiple genes, and if some of these regulators can be modulated by EMFs; (2) the contemporaneous administration of anabolic BMP-2, VEGF and TGF-β3 cytokines with EMFs stimulation; (3) the EMFs mechanism of action and the therapeutic effect in conditions that simulate Staphylococcus aureus in vitro; and (4) if EMFs accelerate apoptosis in osteoclasts. Several relevant findings were reported. Expression of RANK mRNA with EMFs application was significantly higher than that in the sham group and mRNA levels of alkaline phosphatase, α(I) procollagen, and osteocalcin (OC) increased. EMFs enhanced osteogenesis of mesenchymal stem cells (MSCs) in the presence of an inductive stimulus and increased BMP and VEGF expression. The levels of BMP-2 and BMP-4 were elevated with respect to controls and were directly related to the duration of field exposure. A low EMFs of 1 mT field intensity significantly increased VEGF expression. It was concluded that the effect of EMFs treatment on VEGF is regulated by reactive oxygen species (ROS) generation, presumably through NAD(P)H oxidase activity. EMFs in combination with the antibiotic gentamicin improved activity against the growth of Staphylococcus aureus. When exposed to low-frequency EMFs (5 mT, 20 Hz), a reduction in Staphylococcus aureus concentration of about 32% was shown after 24 hours. An application of a sinusoidal alternating EF (470 mV/cm, 20 Hz) demonstrated a reduction of 43% in colony-forming units. The presence of growth factors in the microenvironment and the bone tissue related cells both contribute to the recovery of fractures. Simultaneously, inflammatory and osteoclast-like cells have been retrained. Furthermore, the basic mechanism of action of the EMFs on cells may be the forced vibration of all free ions on the surface of a cell’s plasma membrane, caused by an external oscillating field. It has been shown that this coherent vibration of electric charge is able to irregularly gate electrosensitive channels on the plasma membrane and thus cause disruption of the cell’s electrochemical balance and function.

EMFS THERAPEUTIC EFFICACY ON ANIMALS

Because bone tissue related cells, cytology and microenvironment all contribute to the development of bone regeneration and healing defects of bone tissues, the use of animal models is essential both to understanding the process of repair and to assessing the value of new therapeutic regimens.

Many kinds of experimental animals have been employed by researchers to assess the function of designed devices. The studies summarized in Table 1 on the in vivo effect of EMFs on rat bone tissues have appeared in the literature over the last 5 years. Milena’s experiment involved 12 adult male New Zealand rabbits. Six animals were stimulated with pulsed EMFs (PEMFs) for three consecutive weeks for 6 hours/day, while the remaining animals were sham-treated as a control group. Rabbits were sacrificed.
It is suggested that low-intensity EMFs affect the biomechanical and chemical properties of animal bones, especially cortical bone quality and bone strength. Therefore, EMFs can affect the intrinsic properties of bone structure as a result of stimulation of inactive bone cells responsible for bone remodeling. It is important to assess the effects of magnetic stimulation on different types of bone, at different growth stages and in different health conditions. Further detailed studies should be done to explore the interaction of EMFs and bone cells.

**CLINICAL STUDIES**

Although animal models have characteristics similar to the human, none of them has proven to be a true model of bone regeneration and therefore any treatment has to be tested in human clinical trials. Even when different physical parameters and stimulation exposure times were used, positive results were obtained in clinical studies.²⁹

Dante et al.³⁰ conducted the first randomized, prospective, double blind study to evaluate whether the employment of PEMFs after prosthesis replacement favored bone healing around the prosthesis and reduced the time to functional recovery. Thirty subjects who had undergone hip prosthesis revision were enrolled. Stimulation was started within 7 days of the operation and maintained up to day 90. The subjects were instructed to use the PEMFs devices for at least 6 h/d. The peak amplitude of the magnetic field was (2.0±0.2) mT, with single voltage pulses at 75 Hz, each lasting 1.3 ms. Preoperative Merle D’Aubigné scores were 5.7±0.4 in the stimulated group, with an increase of 2.5 points (+78%), and 4.9±0.6 in the control group, with an increase of 1.5 points (+44%), which was a statistically significant difference (P <0.05). The overall increase in bone mineral density (BMD) was more evident among stimulated subjects but the chi-square analysis only reached a P <0.06 value. In some

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**Table 1. A summary of the literature from 2006–2011 on the in vivo effect of EMFs on rat bone tissues**

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Main results</th>
<th>Reference No.</th>
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<tr>
<td>100 mT and 500 mT-MF, 50 Hz, during 10 months, 2 hours a day, respectively in experimental groups</td>
<td>A significant decrease in EMFs about the values of cross-sectional area of the femoral shaft. Maximum load increased in exposed rats. The cortical thickness of the femurs of EMFs were significantly decreased; length of the femur, displacement, stiffness, energy absorption capacity, elastic modulus, and toughness of bone have no significant differences.</td>
<td>45</td>
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<tr>
<td>(5±0.2) μT, 15 Hz in both experimental and control cages; 6 hours a day (daytime or nighttime), during 12 weeks</td>
<td>Femoral bone mineral density, trabecular area percentage, thickness, number and decreased trabecular separation increased under PEMF; the bone turnover biomarkers and the dynamic histomorphometric parameters in the daytime group decreased to a larger extent compared with the nighttime group.</td>
<td>46</td>
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<tr>
<td>50 kV/m and 400 kV/m EMP, 400 pulses daily for 7 consecutive days at 2 seconds intervals</td>
<td>The ALP activity, serum calcium concentration and osteocalcin level and BV/TV in experimental groups remained unchanged after EMP exposure.</td>
<td>47</td>
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<tr>
<td>A pulse duration of 8 ms and frequency of 15 Hz, the intensity at the middle point of the axial ray was 8 G, 2 hours a day, during 8 weeks</td>
<td>The bone mineral density and serum TGF-β1 concentration in the PEMF group increased significantly after 8 weeks, PEMF group showed significantly lower IL-6 level than the DOP group. On days 45 and 60, a continued influence of the magnetic field on the surgical cavity and on the bone graft was observed in samples from the experimental group, the osteoconductor condition of the graft may be more susceptible to stimulation.</td>
<td>48</td>
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<td>Mean initial intensities on days 0, 15 and 60 were 51.52 × 10⁻⁴ T, 43.83 × 10⁻⁴ T and 25.36 × 10⁻⁴ T, respectively.</td>
<td>Induce a significant thickness increase in cortical and trabecular in vivo stimulated bone tissues.</td>
<td>49</td>
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<tr>
<td>30 minutes magnetic stimulation sessions for 20 consecutive days. pulses of 30 mT at the stimulation point, and repetition frequency of 1 Hz</td>
<td>Breaking force, bending strength, and total fracture energy decreased in the irradiated groups but increased in the treatment groups.</td>
<td>50</td>
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<tr>
<td>Exposed to 900 MHz or 1800 MHz EMF (30 min/d), 5 days a week for 4 weeks.</td>
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Gruen zones corresponding to the medial cortex, 40% responders were observed in both areas in the control group, while in the stimulated group, 93% and 66% responders were observed, respectively \((P < 0.05)\). Additionally, Aaron et al\(^{31}\) observed that EMFs stimulation was safe and aids clinical recovery and bone stock restoration.

At the end of EMFs treatment, pain and hip movements improved significantly with the exception of flexion and extension. Decreased pain and improved function suggest that EMFs are effective in improving symptoms of patients with bone defects. Although the double-blind study was performed on a small, homogeneous group of subjects, it was able to show bone changes after only 90 days and the positive effect of PEMF stimulation on BMD and on pain and consequently, functional recovery of subjects. The treatment was not associated with any negative side effects.\(^{12,30}\)

The limitation of the Dante study is that only short-term results were investigated. Peter et al\(^{32}\) reported that differences between treated and control subjects became evident after 3 months and significant bone loss of up to 14% occurs during the first 3 months after total hip arthroplasty. Long-term follow-up is essential to clarify the effects of EMFs.

**DISCUSSION**

Bassett et al\(^{33}\) first described the use of EMFs to facilitate bone repair, and later these investigators used them in the treatment of ununited fractures. Since then, many reports have documented the beneficial effects of the methods of electromagnetic stimulation.

Non-union pathogenesis is now well accepted as a potential feature of fracture recovery. The data from recent studies conclusively demonstrate that EMFs induced VEGF expression, the mRNA of BMP expression, and growth factor expression. They stimulate angiogenesis, migration, proliferation, and differentiation of stem cells from the surrounding mesenchymal tissues into cartilage- and bone-forming cells in an area of injury.\(^{34,35}\) EMFs are mediated via adenosine receptors and the modulation of the adenosine-receptor-mediated pathway may offer novel methods for treatment of inflammation in the presence of fracture.\(^{15,14,27,36}\) Thus, EMFs therapy resulting in an anabolic effect on osteoblasts, a catabolic effect on cytokines, a stimulatory effect on BMP-family production and an inhibitory effect on the inflammatory process would be extremely useful for fracture non-union treatment. Only a few studies dealing with the enhancement of antibiotic activity by EMFs are available in the literature. Future experimental studies may be aimed at clarifying the cellular and molecular events, which are involved in the response to EMFs in a series of bone tissue related cells. The clinical anti-infection efficacy of EMFs has yet to be proven in well-designed, evidence-based, randomized clinical studies.

The mentioned *in vitro* mechanisms seem to be active *in vivo* as well. At present, mice are the main experimental animal *in vivo*.\(^{27,28}\) Due to the limitations of the species, *in vivo* large mammal experiments will be more persuasive. Few *in vivo* studies are reported and they are all on the same animal model. Therefore, there is the need for other investigations in other animals such as rabbits and sheep. From a clinical point of view, all of the experimental results would need to be confirmed by human clinical trials. Unfortunately, the recent literature on the usefulness of EMFs in humans in cases of consolidation failure is not abundant. In clinical use, the control of physical stimuli is achieved by exposing only the specific region of interest, and a therapeutic effect can be activated by different parameters such as dose, intensity, time and frequency. Thus, the evidence has failed to lead to the establishment of EMFs stimulation as an everyday treatment modality.\(^{39}\)

Importantly, unlike drugs, no side-effects of electromagnetic fields have been reported in the literature, and the effects on bone osteogenesis have been comparable to those produced by normal functional activity.

Major drawbacks of the previous studies include a poor assessment of treatment dose and subject compliance, and inadequate control for the large variations in natural physiology within experimental objects (cells, animals and the human population). Importantly, unlike studies involving medication, EMFs effects may be prolonged. Further studies should focus on EMFs effects in relation to the cellularity of bone, anti-inflammatory effects and in preventing bone loss. In addition, its efficacy when combined with other physiotherapy modalities such as infrared radiation and micro-gravity environment as well as its effect on drug consumption also warrant further investigation.\(^{40}\) Additionally, choosing the experimental parameters (intensity, frequency, impulse amplitude, etc.) likely to have the greatest beneficial effects in physical therapy has been problematic. The differences in experimental conditions may change the regulation of the expression of certain osteogenesis-related genes during BMSC osteogenic differentiation.\(^{41}\) Due to the lack of a standard for equipment and associated treatment conditions, it is difficult to compare clinical and experimental results.

In conclusion, experimental and clinical studies suggest that EMFs would be an ideal therapy for bone regeneration because of the action on bone tissue related cell metabolism that has been demonstrated *in vitro* and *in vivo*.\(^{32,43}\) On the basis of the previously mentioned effects of EMFs on bone tissue related cell culture, it could be hypothesized that stimulation might accelerate and ameliorate both expansion and redifferentiation, but
more experimental and clinical evidence is required.44

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