BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, August 2014. Vol. **11**(2), 611-620

A Review of Electromagnetic Field Based Treatments for Different Bone Fractures

Ali Yadollahpour* and Samaneh Rashidi

[1]Department of Medical Physics, School of Medicine,
Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

doi: http://dx.doi.org/10.13005/bbra/1313

(Received: 05 July 2014; accepted: 08 August 2014)

Bone fractures are among the common disorders worldwide. The healing process of a fracture is a relatively long period. Furthermore, a significant portion of fractures become nonunions or delayed that increase the long healing process of fractures even more. These characteristics have provoked the researchers to develop new techniques for reducing the healing process of fresh bone fracture as well as alternative treatments for nonunions and delayed fractures. Electromagnetic fields (EMFs) have shown a promising potential for this purpose. Different techniques have been proposed as alternative or adjunctive treatments for bone fractures the most important of them are direct current, capacitive coupling, inductive coupling (pulsed EMF), static and combined magnetic fields. For each technique, different protocols have been proposed and the studies are under investigation to optimize the treatment protocol for each method. Characteristics of a bone fracture are important factors for choosing the appropriate EMF based technique and its protocols. The characteristics include bone fracture type including closed or open fracture, union or nonunions, delayed and fresh fractures as well as the fracture site and volume. There are few comprehensive comparative studies on different modalities to determine the appropriate technique for each bone fracture type. This study reviews and compares the current EMF based treatments for different bone fractures to propose appropriate treatment for each type of fracture. In addition, despite the wide range of EMF based treatments and devices for bone fractures, the mechanisms of action of each technique are not yet completely understood. The present study reviews the mechanisms of action of different EMF techniques for bone fracture.

Key words: Bone Fracture, Electromagnetic Fields, Non-drug Treatment, Mechanism of Action.

Bone fractures are among the common disorders worldwide. The healing process of a fracture is a relatively long period. Furthermore, a significant portion of fractures become nonunions or delayed that increase the long healing process of fractures even more. These characteristics have provoked the researchers to develop new techniques for reducing the healing process of fresh bone fracture as well as alternative treatments for nonunions and delayed fractures.Electromagnetic fields (FEMs) have shown promising therapeutic potentials for a wide variety of diseases including musculoskeletal diseases (MSDs)[1], cancer treatment[2], neurological disorders[2-4], wounds[5-7]. Selective control of cell function by applying specifically configured, weak, time varying magnetic fields has added a new exciting dimension to biology and medicine. Field

* To whom all correspondence should be addressed.
Tel.: +(98) 9125144130;
E-mail: yadollahpour-a@ajums.ac.ir

parameters for therapeutic pulsed EMF (PEMFs) were designed to induce voltages similar to those produced, normally, during dynamic mechanical deformation of connective tissues. A mutual link between physical forces and bone biology has been recognized since the early 1800s. Mechanical forces (compression, distraction, and shear), electrical forces, magnetic forces, and ultrasonic waves have been shown to affect bone growth and healing. As a result, various MSDs have been treated successfully over the past two decades by EMFs[1]. Bone fractures as one of the main MSDs have also benefited from EMF based treatments. Electromagnetic stimulations of bone have been appreciated as effective and noninvasive methods for enhancing bone healing, and treating different types of bone fracture.

Brief historical overview

Kratzenstein first described electricity for the treatment of rheumatism and the plague based on the theory of replacing ''good electricity'' with ''bad electricity'' in 1744[8]. Boyer described the effect of electricity on the healing of a tibial fracture in 1816[9]. During the following years different researchers had investigated several techniques[10-13] for non-union fracture treatments. Wolff (1892) claimed that the architecture of living bone continuously adapts to surrounding operational stresses resulting in different efficient techniques[14]. This theory, known as Wolff's Law, states that the structure of bone conforms to changes in its stress environment. The studies on bioelectricity and therapeutic applications of EMFs have dramatically increased during the first decades of the 20th century. Fukada and Yasuda (1954) demonstrated the piezoelectric properties in a dry bone where deformity and electrical potentials have a mutual relation. They experimentally demonstrated that in the compression areas the bone is electronegative and causes bone resorption, whereas areas under tension are electropositive and produce bone[15]. In 1962, Becker *et al.,*[16] and Bassett *et al*.,[17] described the electrical properties of hydrated bone[16]. Their findings were confirmed by Friedenberg and Brighton[18] in 1966. In line with these findings, Shamos and Lavine (1967) evaluated the piezoelectric properties of biological tissues[19]. These findings have drawn research interests of scientists to seek the potential therapeutic applications of EMFs in different bone fractures. Therefore, different technologies have been tested for the biophysical stimulation of bone formation, including extracorporeal shock-waves, electrical and electromagnetic, laser, mechanical, and ultrasound[20].

Bone fractures

Bone fractures are divided into two main groups including osteoporotic fractures and stress fractures based on their origin causes[21]. Bone fractures are among the most common orthopedic problems worldwide[22]. The prevalence of bone fracture varies in different countries or regions[23]. In general, any person in developed country experiences two fractures in their lifetime[24]. The combined lifetime risk for hip, forearm and vertebral fractures coming to clinical attention is around 40%, equivalent to the risk for cardiovascular disease[25]. Osteoporosis causes more than 8.9 million fractures each year worldwide, resulting in an osteoporotic fracture every 3 seconds[23]. The distribution of stress fractures differs according to activity and lifestyle of the person[26]. Tibia is the most common stress fractures, followed by the fibula, metatarsal, and pelvis[26]. The traditional treatments of bone fractures include orthopedic surgery, grafting, casting and medications depending on the type of fractures. The average period of bone fracture healing process is 3 to 5 months. Furthermore, a significant percent of bone fractures become delayed or nonunion that their healing period can be very long[22, 25, 26]. On the other hand, the medications used for bone fractures especially osteoporotic fractures have low treatment outcomes. Therefore, non-drug treatments have been developed as alternative or adjunctive treatments for bone fractures[27-32].

The speed and intensity of fracture healing process dependon the interaction of various factors such as activating and using of reparative cells and genes[33,34]. If these factors are inadequate or interrupted, fracture healing is delayed or impaired, resulting in a nonunion bone fracture. Approximately 10% of the annual fracture patients in the world experience nonunion and/or delayed unions that impose significant economic burden and also decrease the quality of life of patients[35].

Bone Healing Process

When a bone is damaged, it begins certain processes to build a new bone and rebuild itself. The stages of bone formation include biochemical and biological processes[33,34,36,37].

The usual bone healing process in a tubular bone fracture consists of five phases which are sometimes overlapped: 1. fracture and inflammatory phase, 2. granulation tissue formation, 3. cartilage callus formation, 4. lamellar bone deposition and 5. remodeling to original bone contour[38,39]. In a brief description, the five stages cycle as follows:

When the bone is broken, blood vessels are tearing in and around it and the blood accumulates around the fracture site. This collection of blood is called hematoma.The loss of blood vessels results in the death of major bone cells that are called osteocyte. The next stage is subperiosteal and endosteal cellular proliferation. In this stage, cells of internal surface of periosteum proliferate and then convert into osteoblast. On the other side, the cells of bone marrow within the medullary canal begin to proliferate. There are two bone masses begin to grow up to join together in each side that result in the binding broken pieces. The next step is callus formation. The primary cells are converted into osteoblast and chondroblast cells. The osteoblast cells begin to produce a specific protein scaffold called collagen and calcium deposits on the scaffold. Therefore, a primary bone grows in fracture site that is called woven bone or callus. If the process of union fails, the entire callus becomes fibro tissues. The final phase of bone healing is the consolidation stage[38-40]. The continuous activities of osteoblast and osteoclast cells streng then the callus cells that gradually acquire properties of original bone. The interactions of physical forces like EMFs in any stages of bone healing process can improve the process provided the appropriate conditions. EMFs can influence all of these stages and modulate the activities and release of several growth factors such as platelet derived growth factor (PDGF), insulin-like growth factor (IGF), bone morphogenetic protein (BMP), and transforming growth factor beta (TGF β), which play an important role in bone formation and remodeling[41-44].

Electromagnetic Fields in Bone Fractures

The underpinning idea of EMFs applications in MSDs has its root in the piezoelectric effect, converting electromagnetic oscillations to mechanical vibrations and vice versa. In the early 1950s, Fukada and Yasudademonstrated that imposing stress to a bone to cause deformity will generate electrical potentials: In the compression areas the bone is electronegative and causes bone resorption, whereas areas under tension are electropositive and produce bone[15]. Therefore,

Table 1. Therapeutic applications of each EMF technique for different bone fractures along with the proposed mechanisms of action

Technique	Bone Fracture type	Mechanisms of action
DC	Spinal fusion Osteonecrosis of the femoral head	Electrochemical reaction at the cathode, Increasing pH; decreasing oxygen; increasing osteoblast; decreasing osteoclast; increasing vascular endothelial growth factor
CC	Spinal fusion; Delayed union fractures; Nonunion fractures	Activation of intracellular calcium stores; Increasing osteoblast; altering BMPs; calcium translocation via voltage-gated calcium channels; Enhancing activated calmodulin
IC (PEMF)	Bone healing; Spinal fusion; Osteotomy; Fresh fracture; Delayed union fractures; Nonunion fractures	Increasing the calcium uptake of bone; activation of intracellular calcium stores; enhancing activated calmodulin; altering BMPs, TGF-β1, and gene expression
SMG	chronic pain; osteonecrosis; back pain	Cytoprotection of cells; stimulation of growth factor synthesis; anti-inflammatory; analgesic effects
CMF	Spine fusion; osteoarthritis; osteoporosis; Nonunion fractures	Increasing osteoblast; decreasing Osteoclast; altering BMPs and gene expression;

DC: direct current, CC: capacitive coupling, IC: Inductive coupling, PEMF: pulsed electromagnetic field, SMF: static magnetic field, CMF: Combined magnetic field. BMPs: bone morphogenetic proteins, TGF-β1: transforming growth factor-beta 1.

one can conclude that stimulating the endogenous electric fields of the bone using an electrical stimulation would enhance bone healing. There are five clinical methods of administering electrical current to bone or damaged site including direct current (DC)[45], capacitive coupling (CC), inductive coupling (IC) or pulsed EMFs, static magnetic field (SMF) and combined magnetic field (CMF)[46]. In the following sections we introduce each technique, its physical principles and applications in treatment of bone fractures[46].

Direct Current

DC is an invasive method where implanted electrodesare surgically placed directly at the fracture or fusion site[47]. DC techniques are commonly used during initial spinal fusion procedures, these stimulators also are implanted during fixation and bone grafting of nonunions. A cathode is placed at the site of the bone defect with an anode in the soft adjacent tissue[47]. Osteogenesis is reportedly to be stimulated at the cathodal electrode site using currents ranging 5 to 100 µA and varying the number of electrodes between 2 and 4[47]. Constant uniform current at the target site and the patient compliance to the therapy are the advantages of this technique[48], while the disadvantages are short battery life of approximately 6-8 months, difficult hardware placement, short circuits from leads touching other lead wires, tissue reaction, soft tissue discomfort, risk of infection, and a second procedure for hardware removal[49].

Capacitive Current

CC is a non-invasive method applied by an external power source connected to two cutaneous electrodes that are applied on the opposite sides of the target region[47,50,51]. The external power source (1 to 10 V) produces EMFs (20–200 kHz) that induce electric fields ranging 1 to 100 mV/cm[51]. The induced electric fields are sufficient enough for bone stimulation and initiating physiological processes in tissues[52].

The disadvantages of CC include short lifespan of battery for instance when using the unit for 24 hours, patients must change batteries daily. In addition, despite the small and lightweight of electrodes, they may cause irritation of the skin in the contact sites[53]. One of the proposed mechanisms of action in CC is that the electro-stimulation regulates gated ion channels to increase the flux of calcium within the cells[54].

Inductive Current

IC, otherwise known as pulsed EMFs (PEMFs), is noninvasive and enhances bone and joint healing by PEMF stimulation. IC is performed by placing 1 or 2 current-carrying coils on the skin over the fracture or damaged site[49]. EMF sranging 0.1 to 20 G are usually used to induce an electrical field of 1 to 100 mV/cm at the target site. IC techniques are painless and surgery free[49]. Furthermore, they can be easily and conveniently used by patients at home[49]. The power unit for IC techniques can be used through or placed under casting material, with the patient wearing an external battery for up to 10 hours of daily application[51, 53].

Magnetic Field in Bone Fracture

The important therapeutic point in the application of magnetic fields in bone fractures is that South and North Pole has different physiological and biological effects on living organizations[55-61]. In this regard, North Pole, South Pole, or concurrent application of both poles can result different and even opposite physiological effects. Some of biological effects of North Pole include pain relieving, anti-inflammation, alkaline effect, inhibiting infection. However, for the South Pole the effects are increasing inflammation, excitatory effects on bio-systems, decreasing tissue oxygen, acidic effects and promoting microorganisms[55, 62]. The magnetic fields based treatments can be divided into two groups: SMF and CMF.

Static Magnetic Field

SMFs have shown different therapeutic effects in humans and animal models including anti-inflammatory, pain relieving, antibacterial and inhibition /excitation effects. The SMFs have therapeutic effects in different organisms and systems including cardiovascular, skeleton, endocrine and reproductive systems[58, 61-63].

Combined Magnetic Field

CMF is a combination of a static DC electric field and a sinusoidal waveform[46] produced by external coils placed on the targeted site or worn by patient. The use of CMF is based on theoretic calculations that predicted coupling to calcium-dependent cellular signaling processes in tissues[64, 65]. CMFs have been shown to stimulate bone formation and fracture healing in animal model systems[66, 67]. Previous studies have shown that theses therapeutic methods may act by stimulating endogenous production of growth factors that regulate the healing process[68]. The first clinical application of combined magnetic fields was on long bone nonunion healing and received FDA approval in 1994[69].

The ease of use and short daily application are some advantages of CMFs that can improve patient compliance to the technique. One of the possible mechanisms of action of CMFs in influencing cell signaling is presumably through intracellular stores of calcium to increase[54,70] levels and result in bone cell proliferation.

Which Technique for Which Bone Fracture?

The previous studies have shown higher therapeutic outcomes of some techniques for specific bone fractures. This might be due to the mechanisms of actions of the method in one hand and the different characteristics and electrical properties of different bone fractures. Table 1 shows the therapeutic applications of each EMF based treatment for different bone fractures along with the proposed mechanisms of action.

DCs have been used to enhance bone healing in spinal fusion, nonunions, delayed unions, and as an adjunct for promotion of bone healing in ankle surgery (Table 1). The therapeutic efficacy of DC as an adjunctive therapy in hind-foot fusion and revision ankle arthrosis and also in osteonecrosis of the femoral head has been shown by different studies[45, 71, 72]. However, findings of previous studies have not shown effective outcomes from the use of DC in nonunion and delayed union fractures.

CCs have been used to enhance bone healing in nonunions, delayed unions, and spinal fusion (Table 1)[50, 52, 69, 73]. In the nonunion fractures especially long bone nonunions and spinal fusion, CC showed the best therapeutic outcome[69,73].

The use of ICs or PEMFs for bone healing, spinal fusion, femoral and tibial osteotomies, fresh fracture, congenital pseudarthrosis, osteoporosis, osteoarthritis, and delayed union and nonunion fractures showed significant therapeutic outcomes[27, 29-31, 74-80] (Table 1).

SMFs show low therapeutic outcomes for bone fractures, but high performance for rheumatoid arthritis, osteoarthritis, chronic pain, osteonecrosis and back pain[55-58, 60-63, 81-83]. The main point in the SMF applications is that different magnetic poles, North Pole or South Pole, have different and sometimes opposite effects on biological tissue which should be considered in therapeutic applications. SMFs can be used for pain relieving of bone fracture during the healing process and considering the ease of use of different magnetic devices by patients in home, they can be a good candidate for this purpose.

CMFs have shown higher treatment efficiency for spine fusion, osteoarthritis, osteoporosis and nonunion fractures. In conclusion, among the current therapeutic methods of EMFs, PEMF and CMF have higher therapeutic potential and flexibility to be developed for different bone fractures.

Clinical Outcomes of EMFs in Bone Fracture

Fresh Fracture

Experimental studies have shown some evidence that EMF stimulation results in enhanced bone regeneration during fracture healing[84, 85]. EMF treatment has been shown to accelerate and stimulate fracture healing and callus maturation.

Abdelrahimet al (2011) evaluated the effect of a PEMF on the healing of mandibular fractures[86]. They used 2 h daily stimulation for 12 days. The treatment group showed higher changes of bone density at the thirtieth postoperative day compared with the control group. Furthermore, the pain intensity was significantly decreased in the patients from severe to mild at the 7th day postoperative day. They suggested PEMF stimulation might have beneficial effects on the healing of mandibular fractures. Ottaniet al (2002) studied the effect of electromagnetic stimulation on the bone growth in the rabbit model. The PEMF group was exposed to EMFs immediately after surgery. The protocol of stimulation was 50 Hz frequency, 8 mT peak intensity and 30 min per 12 h for 2-4 weeks. They evaluated bone growth and the healing process two and four weeks after surgery using a backscatter electron detector. Their results showed that PEMF treatment has beneficial effects in accelerating bone formation at early time periods[87].

Delayed Fracture

Numerous studies have confirmed significant reduction in the healing time of delayed fractures by PEMFs and efficacy of PEMF in stimulating osteogenesis treating delayed healing of fractures[70, 88, 89].

In a double-blind trial, Sharrard investigated the effects of PEMF stimulation on delayed union of tibial fractures for 12 weeks. The radiological analysis of the treatment group showed radiological union in five fractures, progress to union in five but no progress to union in 10. In the control group there was union in one fracture and progress towards union in one but no progress in 23. According to the statistical analysis and orthopedic surgeon's assessment,he showed that PEMF significantly influence healing in tibial fractures with delayed union (90). Nozomuet al (2002) studied the effects of PEMFs on late bone healing phases in a canine tibial model. Animals in the treatment group were exposed to PEMF with 1.5 Hz frequency, 1-h daily stimulation, starting 4 weeks after surgery for a total of 8 weeks. They evaluated the treatment outcomes with radiographic analysis, biomechanical testing, histological and histomorphometric analyses and statistical analysis. They observed that PEMF stimulation speed up the recovery process, a significant increase in new bone formation and a higher mechanical strength of a healing mid-tibial osteotomy. Their study showed the useful effects of PEMF stimulation on the late-phase of osteotomy healing[91].

Nonunion Fracture

EMFs enhance bone formation in nonunion bone fractures. PEMFs reduce osteotomy gap widening and bone volume loss (88, 92, 93). Michael et al (2003) studied the effects of EMFs in 15 adult male rats that achieved a nonunion status within 3-4 weeks post-surgery. The protocol of radiation was 15 Hz frequency with 3.8 KHz burst frequency, 3 hours daily for 10 weeks. They investigated the healing process with μCT imaging, histological assessments and biostatistical analysis. Their result showed that PEMF reduces further osteotomy gap widening and bone volume loss[94]. Sharrardet al studied the treatment of fibrous non-unions of fractures by pulsing electromagnetic stimulation. They investigated treating fifty-three nonunion fractures of the tibia by electrical stimulation using pulsing EMFs. Union was achieved in 38 cases in six months and the success rate was higher 86.7 percents[95]. Barker et al in a double-blind study investigated the effects of PEMF therapy on tibial non-union fracture. In this study patient with tibial nonunion fracture exposed to PEMF stimulation with 15 Hz frequency, 5 mT, 12-16 h daily stimulation for 24 weeks. They showed higher success rate of treatment of +33% to -61% compared with the placebo stimulation[96].

Physical Interactions of EMFs in Bone Formation

EMF stimulations have therapeutic benefits for different bone fractures such as bone aiding internal and external fixation, enhancing delayed restoration and osteotomies, increasing bone mineral density, reducing chronic pain, treating fresh fractures, and aiding femoral osteonecrosis.

Despite the various studies conducted on the therapeutic effects of EMFs fields on the bone fractures, the mechanisms of actions of the techniques are not completely understood. There have been several in vitro and in vivo studies conducted to shed light on the mechanisms of actions of each EMF based treatment modality. Different techniques of EMF based techniques have distinct interactions to impose therapeutic actions on bone fractures. We can distinguish the mechanisms of action of DC, CC, IC and magnetic fields: DC works by an electrochemical reaction at the cathode. CC modulates molecular pathways and growth factors to enhance proliferation and differentiation of the osteoblast. IC enhances osteoblast differentiation and proliferation through alteration of growth factors, gene expression, and trans-membrane signaling. For magnetic field each pole has distinctive effects and usually opposed to each other. SMFs can be used for pain reduction during the bone fracture healing process. Furthermore, modification of intracellular calcium is one of the important mechanisms by which IC and CC influence on the bone healing process. The exact mechanism by which EMF stimulation improves the bone healing processis not fully understood and further quantitative assessments should be conducted to fulfill the gap.

CONCLUSION

There are five different techniques of EMFs for the treatments of bone fractures: direct current, inductive coupling or PEMF, capacitive coupling, static magnetic field and combined magnetic field. Of these techniques, PEMFs and CMFs show higher efficacy in the treatment of different bone fractures. The electrical characteristics of the bone and adjacent tissues along with the physical parameters of stimulating fields are important factors in exerting the therapeutic effects of EMFs on each bone fracture. The exact mechanisms by which EMFs improve bone healingare not fully understood and further quantitative assessments should be conducted to fulfill the current gap. The important point in bone fracture healing by EMFs is that for different bone fractures different techniques should be selected based on the type of the fractures and other physical parameters of the stimulating technique.

ACKNOWLEDGEMENTS

This Research Project has been financially supported by Ahvaz Jundishapur University of Medical Sciences (Grant no. U-93073).

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