Electromagnetic Fields for Bone Healing

Article in The International Journal of Lower Extremity Wounds · October 2002

DOI: 10.1177/153473460200100302 · Source: PubMed

Brigitte E Scammell
University of Nottingham

Electromagnetic Fields for Bone Healing

S.A.W. Pickering, FRCS, and B. E. Scammell, DM, FRCS
Department of Orthopaedic and Accident Surgery, University Hospital, Queen's Medical Centre, Nottingham, UK

Electrical stimulation has been applied in a number of different ways to influence tissue healing. Most of the early work was carried out by orthopedic surgeons looking for new ways of enhancing fracture healing, particularly those fractures that had developed into nonunions. Electrical energy can be supplied to a fracture by direct application of electrodes or inducing current by use of pulsed electromagnetic field or capacitive coupling. Many of these techniques have not been standardized, so interpretation of the literature can be difficult and misleading. Despite this, there have been a few good laboratory and clinical studies to investigate the effect of electrical stimulation on fracture healing, which are reviewed. These do not permit recommendation or rejection of the technique per se; however, there is some room for optimism. The authors present some of the guidelines for using this treatment modality but suggest that all treatment should be carried out as part of a clinical trial in order to generate reliable data.

Key words: fracture healing, electromagnetic, nonunion, electrical stimulation

In most circumstances, tissue healing occurs in a well-controlled and entirely appropriate manner. However, there are many situations in which the efficiency and speed of this process can have an impact on the success of a medical or surgical condition, whether it be healing of a venous ulcer, surgical wound healing, or fracture union. In fracture management, a patient is unable to return to full functionality until the fracture has consolidated, although the full healing process may continue for many months. If this process fails, then there may be a delayed union, where final healing takes longer than expected, or nonunion, where bone healing never occurs.

Much work has been carried out examining possible ways to enhance tissue healing. An expanding area has been the use of various types of electrical stimulation to treat delayed healing of skin wounds—venous and diabetic ulcers. These applications are different, as they concern skin and subcutaneous tissues. The impaired healing of bone is a common and chronic wound-healing problem however. This review examines the mechanisms of electrical stimulation and relevant studies, both laboratory and clinical, applying an electric field to fractures exhibiting delayed healing.

One of the basic principles of orthopedics is to restore and maintain bone morphology and allow a degree of function following trauma until natural bone healing has occurred. This can be achieved by traction, casting, or operative intervention using metallic fixation devices. In the large majority of cases, traumatically acquired fractures can be expected to heal.

In those patients who have recalcitrant fractures, there are a number of possible causes. In certain cases, it is the vascular anatomy of the broken bone implicated such as the scaphoid or talus. In other cases, it is the injury severity that dictates the outcome, where bone fragments are stripped of their periosteal covering and the surrounding soft tissues are seriously traumatized. The mechanism in all cases is poor blood supply to the fracture fragments.

The impact on patients and the economy can be huge. Accurate information on the actual cost of fracture nonunion is difficult to obtain, with most work published focusing on tibial fractures and proximal femoral fractures. Downing et al[1] estimated the cost of treating a standard tibial shaft fracture to be around £6000 when time of work and outpatient visits were taken into consideration. Heckman et al[2] examined the

Correspondence should be sent to: S.A.W. Pickering, FRCS, Department of Orthopaedic and Accident Surgery, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK; e-mail: simonpickering@tiscali.co.uk

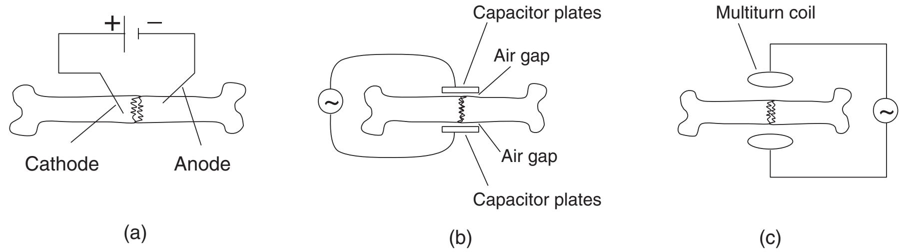

Fig. 1. Schematic showing an electric field interacting with a fractured bone. The direct current stimulation method is shown in (a). In (b), 2 identical electrically conducting parallel plates are used as shown and connected to an alternating current source. Bone is a dielectric material. (c) This figure shows a method of application of paired coils to generate an inductively coupled electromagnetic field in a fractured bone. The coils are identical and separated by a distance equivalent to the diameter of an individual coil.

costs of treating tibial nonunions and found them to be several times higher than for a fracture that healed well. In elderly patients, failure of fracture fixation will often mean further surgery with the attendant risk from repeated general anesthetics, not to mention their loss of mobility and independence.

The electrical stimulation of bone healing in fracture nonunion has been the subject of much work over the past 30 years.

HISTORICAL ASPECTS

Pliny made reference, in the first century AD, to an invisible "attractive" force in rocks now known to be rich in magnetite (Fe_3O_4). However, it was not until the 18th and 19th centuries that Benjamin Franklin, Michael Faraday, and James Clerk Maxwell laid down the basis of our understanding of electricity, magnetism, and the interrelationships between them. There were still misleading references to the magical healing properties of magnets and electric current.[3]

In 1956, Noguchi[4] performed basic experiments that showed increased bone growth in the presence of direct electrical current. Further in vivo work was carried out by Bassett et al[5] using canine femora and a 1.4 V mercury cell battery. Perhaps the most spectacular result was the almost total occupation of the medullary cavity by new bone growth around the cathode, where the current flowing was 100 μA.

The science underlying this effect was not fully understood, although the bioelectric potential of bone tissue had been identified by Friedenberg and Brighton,[6] who demonstrated differing electric potentials in live rabbit tibia and found a significant profile change after a fracture of the tibia, which resolved with fracture healing. Further work identified altered potential in bone segments related to mechanical stress, and it was postulated that this might underlie the control mechanism for new bone formation in fracture healing. Friedenberg and Kohanim[7] went on to repeat studies similar to the work of Bassett et al,[5] by implanting live electrodes into rabbit tibia. With exposure times greater than 20 days and electric current flow of 5 μA, there was very subtle bone formation around the cathode, but, more important, bone absorption around the anode.

The subsequent developments were based on the broad understanding that bone physiologically generated charge that varied with load as well as when it was fractured. These developments were aimed at generating electric fields at the fracture sites. If it were possible to enhance physiological electric charge at the site of a fracture nonunion, it might be possible to stimulate bone healing by turning up the natural response to injury.

GENERATING AN ELECTRIC FIELD

There are 3 ways of administering the effects of electric fields to the fracture site.[8] These are application of direct current via implanted electrodes, generation of transient alternating microcurrents at the fracture site noninvasively by capacitive induction, and generation of transient microcurrents by electromagnetic induction. Figure 1 is a schematic diagram that demonstrates the 3 methods.

Direct application of an electric current is the most reliable and measurable way of delivering electrical energy, with current flow through the bone transmitted ionically such that one electrode will behave as the cathode and the other the anode. A relatively large amount of energy can be delivered in this fashion, the only limit being that of safety.

Capacitive and inductive coupling of electromagnetic fields are noninvasive. If a conductor is placed between negatively and positively charged electrodes, yet insulated from them, there will be a small degree of polarization as positive charges are attracted in one direction and negative charges in the other. If the charge is reversed, then the polarity of the conductor will change. This causes a small shift in charge, and an alternating electric current is generated. If alternating current frequencies in the kHz range are supplied to the electrodes or capacitor plates, even small voltages may produce a very weak electric current at the fracture site.

Alternating current flow through a coil of wire or solenoid will provide a time-varying magnetic field in the axis of the coil and a similarly varying electric field along the same axis but perpendicular to the magnetic field. It is important to realize that, in contrast to direct application of electrodes, there is no actual current flow in a conductor within the coil and there must be a very rapid change in the magnetic field to generate any meaningful electric field component. There are practical limitations.[9] To achieve a rapid rate of change in a magnetic field, it is necessary to drive electric current into the coil very quickly as pulses. Unfortunately, this becomes more difficult due to self-inductance whereby the magnetic field produced in the coil will induce electric current flow in the direction opposite to that supplied, which acts to dampen the rise in current in the coil. There is a limit, therefore, to the magnitude of electric field that can be transiently created.

Calculation and indirect measurement using electromagnetic search coils have shown it possible to produce electric field density up to 20 to 30 mV/cm with pulsed electromagnetic fields (PEMFs). This would be of sufficient density to have an effect at the cell membrane level, bearing in mind that the resting potential in an average cell is between 50 and 80 mV. With capacitance plates, it is possible to generate an electric field of quite high density over a short distance in air. However, as the distance between the plates becomes larger, which may be necessary to sandwich a healing limb fracture, the generated electric field is progressively smaller in magnitude. A point will occur when the background electrical interference outweighs any meaningful biological effect. It is particularly important to bear this in mind when extrapolating results from in vitro studies, where plates will be very close together, and from studies carried out in animals or patients, where much weaker currents will be produced.

Direct Current

The very early work has already been referred to in this article. Because of the necessity to implant electrodes and the complications that can occur, direct current stimulation has remained a specialist technique in a few centers. It has particular relevance in spinal fusion surgery and will be referred to later.

One of the early studies used a rabbit fibula osteotomy as an experimental fracture.[10] Insulated wires were inserted around the osteotomy site and connected to a battery producing currents in the 10 to 20 μA range. In those animals where the fracture site was negatively connected, there was a 200% to 300% increase in bending and torsional strength.

Brighton's group was the first to use this technology in a case of long-standing medial malleolar nonunion following fracture.[11] They went on to treat a series of patients[12] with a range of fracture nonunions with implanted electrodes connected to 20 μA power packs. In 57 patients, there was a 68% healing rate. Becker et al[13] described 13 patients with a variety of nonunions treated with an implanted cathode and surface electrodes to allow 0.1 to 0.2 μA current flow. They also reported a high success rate, but as with Brighton's work, there were no clinical controls or independent observers to assess the patients.

Many explanations have been proferred to explain this effect on bone healing. Following the very early work where there was deposition at the cathode and resorption at the anode, the most obvious explanation seemed to be simple electrolysis. However, as recognizable bone was being formed, this suggested a more subtle mechanism. Brighton et al[14] identified significant oxygen production at the cathode with this form of bone stimulation. They proposed that this high oxygen concentration at the fracture site could be significant.

Capacitive Electric Field

Brighton et al[15] were among the first to investigate the use of capacitive electric field induction to treat fractures. Reports were first published showing healing of osteotomized rabbit fibulae when exposed to capacitance plates supplied with alternating voltage.

In 1 of 2 more recent laboratory studies,[16] rat calvarial cells grown in cell culture were exposed to a 60-kHz capacitively coupled electric field with field strengths ranging from 1×10^{-4} mV/cm to 20 mV/cm. ^{3}H-thymidine incorporation into DNA and alkaline phosphatase activity, both indicators of cell growth, were significantly increased, at field strengths of 0.1 mV/cm, 1 mV/cm, and 20 mV/cm. In the second study,[17] cells derived from bovine periosteum were grown in culture and exposed to saw-tooth pulses of 100 V supplied to capacitance plates at 16 Hz. Computer simulation calculated the field across cell membranes to be 6 kV/m. There appeared to be acceleration of cell culture development, enhancement of alkaline phosphatase activity, and increased secretion of extracellular matrix-related proteins. However, studies have yet to show the mechanism by which these changes occur, although a common hypothesis is by action at voltage-gated calcium channels.[18]

Pulsed Electromagnetic Fields (PEMFs)

The bulk of developmental activity has focused on the use of PEMFs and bone stimulation. Researchers using electromagnetic bone stimulators have used a number of coil arrangements and designs, making direct comparisons of results difficult. There are no dosage regimens to compare studies, though for clinical use some regimens have FDA approval.

Bassett et al[19] are acknowledged to be the first to examine the effect of PEMFs on bone healing. In 1974, they verified a method of electromagnetically inducing a tissue voltage. It was possible to produce a parallel magnetic field between 2 narrow electromagnetic coils separated by a diameter, the application based on the Helmholtz effect on mutual induction. The coils were applied to the site of fibula osteotomy in the hind legs of 41 beagles. Current pulses of 0.15 ms duration were supplied at 65 Hz, inducing a maximum tissue voltage of 20 mV/cm measured indirectly using a search coil. There was a significant difference in mechanical strength at 28 days compared to the control limb; subjective assessments were that histological and radiological appearances of the callus were improved.

Another group led by De Haas[20] developed a similar animal model of fracture healing with radial osteotomies made in the forelimb of rabbits. The osteotomy site was exposed to a PEMF produced by an electromagnet comprising a C-shaped iron core with each limb wound with 1500 turns of copper wire. This electromagnet was then supplied with pulses of current at 0.1 Hz, 1 Hz, and 4 Hz. Exposure was for 5 hours, 5 days a week, for up to 4 weeks. Although increased radiological healing was documented with PEMFs, the only statistically significant result was increased healing in the nonstimulated limb at 2 weeks.

There are 2 important criticisms of the DeHaas et al study,[20] which has become one of the frequently quoted articles in this area of research. First, it is important to clarify the type of electromagnetic field used. In the work of Bassett et al,[19] a high rate of change of magnetic field and electric field of 20 mV/cm was achieved at the osteotomy site. In the study by De Haas et al,[20] no attempt was made to measure or calculate the electric field produced. At 0.1 Hz and 1.0 Hz, the magnetic field reached was 250 G. At 4.0 Hz, it only reached 150 G. The rate of change of the magnetic field is unknown. With so many turns of wire, the coil would have a very high inductance, making the rate of change of magnetic field very slow. It would be safe to assume that the induced tissue electric field would be much less. Second, the observations were not performed by investigators blinded to the treatment used. With a subjective scoring system, bias must always be considered a possibility. Finally, no attempt was made to isolate the control limb from the effect of the PEMF, making any result almost meaningless.

Both research groups moved quickly from these early experiments to using the technology in patients. For their first clinical study, Bassett et al[21] chose patients with either congenital or acquired pseudarthrosis. In their first group, there were 12 patients with congenital pseudarthrosis at a range of sites, but most commonly the tibia. The majority had been operated on several times (the average length of time with a pseudarthrosis was 4.9 years). All patients were exposed to a PEMF via a coil affixed to the plaster. As the study developed, changes were made in the specific type and frequency of pulses. In most cases, there was a rapidly rising leading edge of $< 10^{-6}$ seconds. The total pulse width was 300 μs, with a repetition frequency of 75 Hz. The peak current density induced at the pseudarthrosis was calculated to be 10 μA/cm. In the second group, Bassett et al recruited 14 patients with either traumatically or operatively acquired nonunions at a variety of sites, the average length of time with pseudarthrosis being 2.5 years. In the congenital pseudarthrosis group, 9 of 12 patients went on to achieve functional union. In the acquired group, 6 patients had functional union, 4 had union, 1 was making slow progress, and 3 had failed to make any progress.

De Haas et al[22] also published the results of their series of 17 patients with established nonunion of the tibia. The time from fracture to treatment with electromagnetic stimulation ranged from 9 months to 5 years, the average time being 22 months. Patients were treated with an iron core magnet, similar to that used in the earlier work by this group, for 20 hours a day and from 4 to 8 weeks duration, throughout which time they were confined to bed or a chair. At the end of this time period, the limb was then splinted in a long leg cast until union was judged to be sound. This took from 4 to 6 months. The magnetic field ranged from 150 to 300 G and was pulsed at 1 Hz. All but 2 of the fractures united by 10 months.

There are significant errors in these studies, not the least of which are the absence of a control group, small sample sizes, and considerable variability in patient inclusion criteria. There is little attempt to measure the electric field produced, and it could be argued that the reason the fractures heal is that they have been properly immobilized for a significant period of time.

These 4 articles represent the basis of much of the subsequent research. It is, therefore, difficult to make a clear decision as to the importance of this technology. Anecdotally, the clinical studies suggest an important effect of PEMFs on bone healing. However, due to lack of controls, potential observer bias, and poorly defined test populations, it is difficult to draw firm conclusions. An editorial in the *Lancet*[23] summed up concerns, calling for a proper double-blind, randomized controlled trial.

A number of articles have been written that include fundamental criticisms consistent with the discussion in the preceding paragraph. A selection of clinical work describing benefits of treating long bone fracture nonunion[24-30] and pseudarthroses[31-33] with PEMF have been published. Others have investigated the usefulness of PEMFs in the treatment of nonunions by external fixation,[34] in the treatment of scaphoid fractures,[35] in the treatment metatarsal fractures,[36] in the treatment of lumbar spinal fusion,[37] and in attempting to achieve arthrodesis of the knee following failed total knee arthroplasty.[38] Poor study design makes it difficult to draw any firm conclusions, as the link between treatment and outcome has not been rigorously demonstrated.

In Vivo Studies

There is no evidence in the literature from randomized controlled studies of the clinical efficacy of PEMF.

Animal Studies

Pienkowski et al[39] carried out a randomized controlled study to assess the effect of a PEMF, 5-millisecond pulse bursts at 15 Hz, on the stiffness of experimental fracture site healing in a rabbit fibular osteotomy model. Three hundred ninety-nine rabbits had an experimental fibular osteotomy. Seventeen experiments were carried out with varied electromagnetic coil voltages, but in each experiment there was a control group in which rabbits wore a dummy coil. Importantly, the stimulated group was magnetically shielded from the control group so that there would be no effect of stray electromagnetic field. Rabbits were sacrificed on the 16th postoperative day and the stiffness of the osteotomy measured. There was a significant increase in stiffness after exposure to a variety of PEMF pulse amplitudes. Similarly, Fredericks et al[40] found that torsional strength of healing rabbit tibial osteotomies increased by a factor of 2 with 1 hour of daily treatment using a PEMF pulse burst repeated at 1.5 Hz.

Although not strictly fracture healing, the use of bone stimulators in spinal surgery to augment lumbar spinal fusions has received much attention. Glazer et al[41] performed a prospective randomized trial examining the effect of a PEMF on a rabbit posterolateral fusion model. Rabbits were exposed for 4 hours a day for up to 6 weeks. There was a statistically significant increase of 35% in fusion stiffness. However, there were only 10 rabbits in the study.

A similar model was used by Kahanovitz et al.[42] Bilateral posterior facet fusions were performed in 24 adult dogs. Eight dogs were stimulated for 30 minutes each day with a PEMF, a 30-millisecond pulse burst repeated at 1.5 Hz. The individual pulses were similar in magnitude to those of other experiments, although the pulse burst was much longer and was repeated far less frequently. Eight dogs were stimulated daily for 60 minutes, and 8 dogs were controls. The fusions were assessed radiologically and histologically. At 12 weeks, there was no statistically significant difference. The sample size was small, a limitation common to studies in this topic area.

Grace et al[43] examined the effect of a 72-Hz PEMF with single pulses. Eighteen rats had a small defect drilled into the center of the femoral groove. Nine were exposed to a PEMF for 2 hours a day, 7 days a week. Rats were sacrificed at 1, 2, 4, and 8 weeks to allow a blinded observer to grade healing and perform a histological examination. Grace et al reported a beneficial effect of PEMFs. However, despite the small sample size, the results are interesting and suggest the need for further definitive work.

Collier et al[44] performed radial osteotomies in 12 horses. Six horses received capacitively coupled electrical signals for 60 days, administered by stainless steel electrodes placed on the skin attached to a small portable power unit capable of producing a current of 17 mA between the plates, and 6 horses were controls. No treatment effects were observed either radiologically or histologically.

Clinical Trials

Two studies have examined the use of PEMFs in the treatment of tibial nonunion. Barker[9] selected 17 adults with tibial shaft fracture nonunion confirmed on examination and x-ray appearance by 2 independent observers. Importantly, patients with sepsis, bone disease, a fracture gap greater than 0.5 cm, internal or external fixation, or any operative procedure 6 months preceding the trial were excluded. Each patient was randomly allocated a real stimulator, capable of delivering 5-millisecond pulse bursts 200 microseconds long at 15 Hz, or a dummy stimulator. Fracture site stimulation was carried out for 12 to 16 hours a day for 24 weeks. If healing had not occurred as judged by the independent observers, then electrical stimulation was continued or the dummy stimulators changed for real ones. Limbs were immobilized until healing occurred. Patient compliance was checked by use of internal clocks on the devices to check that they had been switched on. Only 16 patients completed the treatment. There was no significant difference between the groups.

In a second study of tibial shaft fractures, Sharrard[45] identified 51 tibial shaft fractures with radiological signs of nonunion following at least 16 weeks immobilization in a long leg plaster. Patients were again randomized to receive an active or dummy coil as above, with the active unit delivering similar pulses of PEMFs. Both the patients and the surgeon were blinded to the treatment, which was carried out for 12 hours a day for 12 weeks. Of the 45 who completed the trial, 20 received active units. Radiologically, 50% of the active group healed compared to 8% of the control group. Clinically, 45% were considered united compared to 12% of the control group. These were very significant results suggesting a marked effect of PEMFs on fracture healing. However, the mean age in the active group was 34.7 and in the control group 45.4, a potentially important confounding variable.

Borsalino et al[46] examined a group of 32 patients (< 70 years old) with osteoarthritis of the hip considered amenable to treatment by intertrochanteric osteotomy. Patients were randomized to 1 of 2 groups. Age, weight, and sex distributions were very similar. Osteotomy was performed in both groups according to standard procedure, and all osteotomies were fixed with the same type of plate. Patients were discharged at 10 to 14 days and kept non–weight bearing until day 40, partial weight bearing from day 40 to 90, and full weight bearing after that. On the third day, all patients were given either a control or active unit, which was randomly allocated, with both patient and treating surgeon blinded to whether the unit was active. The stimulator delivered a single pulse that was 1.3 milliseconds wide and generated a peak magnetic field of 18 G at 75 Hz. Measurement with a Hall probe showed a peak electric field in air of 2.5 mV. All patients used the stimulators for 3 months. Patients were seen regularly in the interim to check coil attachment. Anteroposterior radiographs were taken at 40 and 90 days. The presence of new periosteal bone and trabecular bridging at the callus was scored by 3 blinded, independent observers. A comparison was made between the patients' iliac crest density and callus density using a digital camera connected to a computer with a special software package. This was an attempt to quantify calcification and callus maturity.

One patient with an active unit dropped out of the study at 15 days. Therefore, 16 patients completed the study as the control group and 15 as the stimulated group. Analysis of the technical quality of osteotomy showed no difference between the groups. At 40 days, there was more pronounced bone callus and greater trabecular bridging in the stimulated group, both being significant at $p < .02$. Although bone callus relative density was higher in the stimulated group, this was not statistically significant. At 90 days, all measurements were significantly better in the stimulated group at $p < .001$ for the trabecular bridging measurements.

The study by Borsalino et al[46] was conducted well. A criticism of this work is the accuracy of the scoring system used for callus formation and trabecular bridging, which is important when the differences are analyzed. The authors were circumspect with their findings by suggesting that the biological effect of the technology was measurable.

Some of the animal studies investigating spinal fusion in the presence of PEMFs have been reviewed; clearly, there are some analogies to fracture healing. Jenis et al[47] carried out a randomized prospective trial comparing standard instrumented posterolateral lumbar fusion and fusion carried out in the presence of either direct current electrical stimulation (DCES) or PEMF. There were 22 controls and there were 22 and 17 samples in the PEMF and DCES groups, respectively. Stimulation was carried out for at least 2 hours a day for a period of 150 days postoperation. Review was carried out at 3 months and 1 year. There was no significantly enhanced fusion rate. Although a number of in-depth reviews in this area suggest good results,[48,49] the referenced studies have limitations similar to the early fracture healing work.

In contrast, Goodwin et al[50] performed a multicenter randomized, double-blind prospective trial comparing capacitively coupled bone stimulation and lumbar fusion, with lumbar fusion alone. Patients were instructed to wear the stimulator 24 hours a day, with treatment continuing up to 9 months unless fusion had occurred. Of 337 patients recruited who underwent a variety of spinal fusions, 179 completed the final review and radiographic evaluation. Seventy-two of the

85 patients in the active stimulator group had a successful fusion compared to 61 of the 94 patients in the dummy unit group. This result was highly significant.

MECHANISM OF ACTION

It is intuitive to expect electromagnetic fields to influence healing at cellular and molecular levels or to act on mediators of inflammation. It might equally be that the milieu is influenced by the electric fields.

Many critics have argued that the inductive methods of inducing an electric field fail to produce a field of magnitude significant to have any effect. By definition, there is a background level of electrical activity with neuromuscular function. All cells have a charged membrane with a resting potential of 50 to 80 mV on average. If electric fields are weaker than the background fields in the body, then it is difficult to see a convincing mechanism of action on the target cells. This is a significant criticism of the capacitive bone stimulators, which can only generate very small currents at high frequency, although less so with PEMFs, which can generate electric potentials in the same order as cell membranes.

A number of effects of PEMFs have been shown on cultured chondrocytes. Hiraki et al[51] exposed cultured rabbit chondrocytes to 15-Hz, 5-millisecond pulse bursts for up to 96 hours. Cyclic adenosine monophosphate (cAMP) was measured by radioimmunoassay after stimulation by parathyroid hormone (PTH), prostacycline, and prostaglandin E2. Production of glycosaminoglycan (GAG) was also recorded. There was a significant difference in cAMP stimulation by PTH in the presence of a PEMF, and increased GAG production. In a similar study, Sakai et al[52] evaluated the effect of PEMF pulse bursts, as above, on cultured rabbit costal cartilage cells and human articular cartilage cells. DNA synthesis and GAG production was indirectly measured by ^{3}H-thymidine and ^{35}S-sulphuric acid incorporation. Although growth conditions were important, there was a significant increase in ^{3}H-thymidine reported. However, one must cautiously examine the presented data, as standard deviations in some cases are almost as large as the presented result.

Pezzetti et al[53] produced the best of the recent articles. Cultured human nasal and articular chondrocytes were exposed to a PEMF with single pulses at 75 Hz, producing an electric field measured at 2 mV, for up to 30 hours. Cell growth was estimated by ^{3}H-thymidine uptake. There was higher growth with nasal chondrocytes, but both cell types showed an increased growth rate with the PEMF.

A direct stimulant effect on cell growth may also be important. Nagai and Ota[54] examined the effects of 15-Hz pulse bursts, producing 15 mV/cm in air, on fertilized chick embryos. Bone morphogenic protein 2 and 4 mRNA, in individual chick calvaria, was significantly elevated with PEMFs at 15 and 17 days, but interestingly not at 19 days.

Yen-Patton et al[55] developed an artificial model for vascular endothelial injury. They observed a small but significant increase in endothelial growth rate following injury, determined by ^{3}H-thymidine incorporation, with exposure to a PEMF. They used the standard pulse burst lasting 5 milliseconds repeated at 15 Hz. Subjectively, there was altered morphology of the endothelial cells exposed to the PEMF.

Shankar et al[56] examined the effect of PEMFs on the responsiveness of neonatal rat osteoclasts to cellular, hormonal, and ionic signals. Cultured cells were added to slices of demineralized cortical bone before being stimulated. PEMF stimulation of co-cultures of osteoblast and osteoclasts showed a 2-fold stimulation of bone resorption.

It would be fair to say that some very interesting effects have been identified in these well-designed laboratory studies. As with any laboratory research, it is often difficult to extrapolate the significance to a biological system such as a fracture nonunion. Increased chondrocyte activity and calcification may underlie some of the fracture-healing effects observed clinically. Blood supply is also critical for fracture healing, being implicated as a leading factor in the development of fracture nonunion. Therefore, stimulation of angiogenesis may be a particularly important mechanism of action at a microscopic level. However, there are no documented reports of a general increase in blood supply to a treated limb due to local application of PEMFs. Finally, stimulation of bone morphogenic protein release may also be very important. However, none of the research has been taken far enough for these hypothetical mechanisms of action of PEMFs to be considered proven.

CLINICAL USE

The use of implantation electrodes will not be discussed. The electromagnetic bone stimulators can be used on a variety of fractures. The stimulators have been refined to be easily applied close to the skin or over clothes, or incorporated into plaster or thermoplastic splints. In essence, the active unit is a single floppy coil that contours to the curvature of a cylinder (ie, wrist or shin). This has the effect of producing a slightly distorted magnetic field with maximum intensity at the fracture such that the induced electric field is maximized. The power pack is rechargeable and easily portable, with built-in monitoring to record usage and therefore help achieve patient compliance.

Present indications for treatment include any fibrous or atrophic nonunion that has failed with standard management. This treatment is inherently safe, and therefore there are no real contraindications to its use. However, concern has been expressed over usage in pregnancy because of possible mutagenic effects, and in patients with pacemakers because of possible interference.

There is no standard treatment protocol for PEMF usage. However, Pethica and Brownell[57] retrospectively reviewed results of nonunion treatment with PEMF therapy. As the average daily dose increases, the shorter is the time to healing. PEMF therapy more than 9 hours a day was reported to give the best results. In a study on rabbit tibial osteotomies, Nepola et al[58] also found better results with longer PEMF exposure. Garland et al[59] performed a retrospective review of 139 fracture nonunions treated with PEMF. Patients using the device for less than 3 hours a day had a significantly worse outcome.

Finally, accurate placement of coils at the intended site of action is critical to the success of this method. Coil placement may be checked by x-ray. Patient follow-up must monitor patient compliance and device positioning. Patient follow-up should be at regular intervals for sufficiently long periods.

REFERENCES

1. Downing ND, Griffin DR, Davis TR. A comparison of the relative costs of cast treatment and intramedullary nailing for tibial diaphyseal fractures in the UK. Injury 1997;28:373-5.
2. Heckman JD, Sarasohn-Kahn J. The economics of treating tibia fractures: the cost of delayed unions. Bull Hosp Joint Dis 1997;56:63-72.
3. Basford JR. A historical perspective of the popular use of electric and magnetic therapy. Arch Phys Med Rehabil 2001;82:1261-9.
4. Noguchi K. Study on dynamic callus and electric callus. J Jpn Orthop Surg Soc 1957;31:1957.
5. Bassett C, Pawluk R, Becker R. Effects of electric currents on bone in vivo. Nature 1964;204:652-4.
6. Friedenberg ZB, Brighton CT. Bioelectric potentials in bone. J Bone Joint Surg Am 1966;48:915-23.
7. Friedenberg ZB, Kohanim M. The effect of direct current on bone. Surg Gynecol Obstet 1968;127:97-102.
8. Cochran GVB. Experimental methods for stimulation of bone healing by means of electrical energy. Bull N Y Acad Med 1972;48: 899-911.
9. Barker AT. The design of a clinical electromagnetic bone stimulator. Clin Phys Physiol Meas 1981;2:9-16.
10. Friedenberg ZB, Roberts PG, Didizian NH, et al. Stimulation of fracture healing by direct current in the rabbit fibula. J Bone Joint Surg Am 1971;53:1400-8.
11. Friedenberg ZB, Harlow MC, Brighton CT. Healing of nonunion of the medial malleolus by means of direct current: a case report. J Trauma-Injury Infect Crit Care 1971;11:883-5.
12. Brighton CT, Friedenberg ZB, Mitchell EI, et al. Treatment of nonunion with constant direct current. Clin Orthop Related Res 1977;124:106-23.
13. Becker RO, Spadaro JA, Marino AA. Clinical experiences with low intensity direct current stimulation of bone growth. Clin Orthop Related Res 1977;124:75-83.
14. Brighton CT, Adler S, Black J, et al. Cathodic oxygen consumption and electrically induced osteogenesis. Clin Orthop Related Res 1975;107:277-82.
15. Brighton CT, Hozack WJ, Brager MD, et al. Fracture healing in the rabbit fibula when subjected to various capacitively coupled electrical fields. J Orthop Res 1985;3:331-40.
16. Brighton CT, Okereke E, Pollack SR, et al. In vitro bone-cell response to a capacitively coupled electrical field: the role of field strength, pulse pattern, and duty cycle. Clin Orthop Related Res 1992;285:255-62.
17. Hartig M, Joos U, Wiesmann HP. Capacitively coupled electric fields accelerate proliferation of osteoblast-like primary cells and increase bone extracellular matrix formation in vitro. Eur Biophys J 2000;29:499-506.
18. Aaron RK, Brighton CT, Magee FP, et al. Recent advances in electrical stimulation. Contemp Orthop 1993;26:609-36.
19. Bassett CA, Pawluk RJ, Pilla AA. Acceleration of fracture repair by electromagnetic fields: a surgically non-invasive method. Ann N Y Acad Sci 1974;238:242-62.
20. De Haas WG, Lazarovici MA, Morrison DM. The effect of low frequency magnetic fields on the healing of the osteotomized rabbit radius. Clin Orthop Related Res 1979;145:245-51.
21. Bassett CA, Pilla AA, Pawluk RJ. A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing electromagnetic fields. Clin Orthop Related Res 1977;124:128-43.
22. De Haas WG, Watson J, Morrison DM. Non-invasive treatment of ununited fractures of the tibia using electrical stimulation. J Bone Joint Surgery Br 1980;62:465-70.
23. Electromagnetism and bone [editorial]. Lancet 1981;1:815-6.
24. Bassett CA, Mitchell SN, Gaston SR. Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields. J Bone Joint Surg Am 1981;63:511-23.
25. Bassett CA, Mitchell SN, Schink MM. Treatment of therapeutically resistant non-unions with bone grafts and pulsing electromagnetic fields. J Bone Joint Surg Am 1982;64:1214-20.
26. Heckman JD, Ingram AJ, Loyd RD, et al. Non-union treatment with pulsed electromagnetic fields. Clin Orthop Related Res 1981;161:58-66.
27. Bassett CA, Valdes MG, Hernandez E. Modification of fracture repair with selected pulsing electromagnetic fields. J Bone Joint Surg Am 1982;64:888-95.
28. Sharrard WJ, Sutcliffe ML, Robson MJ, et al. The treatment of fibrous non-union of fractures by pulsing electromagnetic stimulation. J Bone Joint Surg Br 1982;64:189-93.
29. Ito H, Shirai Y. The efficacy of ununited tibial fracture treatment using pulsing electromagnetic fields: relation to biological activity on nonunion bone ends. Nippon Ika Daigaku Zasshi 2001;68:149-53.
30. Abeed RI, Naseer M, Abel EW. Capacitively coupled electrical stimulation treatment: results from patients with failed long bone fracture unions. J Orthop Trauma 1998;12:510-3.
31. Sharrard WJ. Treatment of congenital and infantile pseudarthrosis of the tibia with pulsing electromagnetic fields. Orthop Clin North Am 1984;15:143-62.
32. Sutcliffe ML, Goldberg AA. The treatment of congenital pseudarthrosis of the tibia with pulsing electromagnetic fields: a survey of 52 cases. Clin Orthop Related Res 1982;166:45-57.

33. Kort JS, Schink MM, Mitchell SN, et al. Congenital pseudoarthrosis of the tibia: treatment with pulsing electromagnetic fields. Clin Orthop Related Res 1982;165:124-37.
34. Marcer M, Musatti G, Bassett CA. Results of pulsed electromagnetic fields (PEMFs) in ununited fractures after external skeletal fixation. Clin Orthop Related Res 1984;190:260-5.
35. Frykman GK, Taleisnik J, Peters G, et al. Treatment of nonunited scaphoid fractures by pulsed electromagnetic field and cast. J Hand Surg Am 1986;11:344-9.
36. Holmes GB. Treatment of delayed unions and nonunions of the proximal fifth metatarsal with pulsed electromagnetic fields. Foot Ankle Int 1994;15:552-6.
37. Bose B. Outcomes after posterolateral lumbar fusion with instrumentation in patients treated with adjunctive pulsed electromagnetic field stimulation. Adv Therapy 2001;18:12-20.
38. Bigliani LU, Rosenwasser MP, Caulo N, et al. The use of pulsing electromagnetic fields to achieve arthrodesis of the knee following failed total knee arthroplasty: a preliminary report. J Bone Joint Surg Am 1983;65:480-5.
39. Pienkowski D, Pollack SR, Brighton CT, et al. Low-power electromagnetic stimulation of osteotomized rabbit fibulae: a randomized, blinded study. J Bone Joint Surg Am 1994;76:489-501.
40. Fredericks DC, Nepola JV, Baker JT, et al. Effects of pulsed electromagnetic fields on bone healing in a rabbit tibial osteotomy model. J Orthop Trauma 2000;14:93-100.
41. Glazer PA, Heilmann MR, Lotz JC, et al. Use of electromagnetic fields in a spinal fusion: a rabbit model. Spine 1997;22:2351-6.
42. Kahanovitz N, Arnoczky SP, Nemzek J, et al. The effect of electromagnetic pulsing on posterior lumbar spinal fusions in dogs. Spine 1994;19:705-9.
43. Grace KL, Revell WJ, Brookes M. The effects of pulsed electromagnetism on fresh fracture healing: osteochondral repair in the rat femoral groove. Orthopedics 1998;21:297-302.
44. Collier MA, Kallfelz FA, Rendano VT, et al. Capacitively coupled electrical stimulation of bone healing in the horse: in vivo study with a Salter type IV osteotomy model with stainless steel surface electrodes. Am J Veterinary Res 1985;46:622-31.
45. Sharrard WJW. A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures. J Bone Joint Surg Br 1990;72:347-55.
46. Borsalino G, Bagnacani M, Bettati E, et al. Electrical stimulation of human femoral intertrochanteric osteotomies: double-blind study. Clin Orthop Related Res 1988;237:256-63.
47. Jenis LG, An HS, Stein R, et al. Prospective comparison of the effect of direct current electrical stimulation and pulsed electromagnetic fields on instrumented posterolateral lumbar arthrodesis. J Spinal Disorders 2000;13:290-6.
48. Boden SD, Schimandle JH. Biologic enhancement of spinal fusion. Spine 1995;20(24 suppl).
49. Kahanovitz N. The use of adjunctive electrical stimulation to enhance the healing of spine fusions. Spine 1996;21:2523-5.
50. Goodwin CB, Brighton CT, Guyer RD, et al. A double-blind study of capacitively coupled electrical stimulation as an adjunct to lumbar spinal fusions. Spine 1999;24:1349-57.
51. Hiraki Y, Endo N, Takigawa M, et al. Enhanced responsiveness to parathyroid hormone and induction of functional differentiation of cultured rabbit costal chondrocytes by a pulsed electromagnetic field. Biochimica et Biophysica Acta 1987;931:94-100.
52. Sakai A, Suzuki K, Nakamura T, et al. Effects of pulsing electromagnetic fields on cultured cartilage cells. Int Orthop 1991;15:341-6.
53. Pezzetti F, De Mattei M, Caruso A, et al. Effects of pulsed electromagnetic fields on human chondrocytes: an in vitro study. Calcified Tissue Int 1999;65:396-401.
54. Nagai M, Ota M. Pulsating electromagnetic field stimulates mRNA expression of bone morphogenetic protein-2 and -4. J Dental Res 1994;73:1601-5.
55. Yen-Patton GP, Patton WF, Beer DM, et al. Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis in vitro. J Cell Physiol 1988;134:37-46.
56. Shankar VS, Simon BJ, Bax CM, et al. Effects of electromagnetic stimulation on the functional responsiveness of isolated rat osteoclasts. J Cell Physiol 1998;176:537-44.
57. Pethica BA, Brownell J. The dose response relationship in PEMF therapy of ununited fractures. Washington, DC: Bioelectrical Repair and Growth Society; 1988.
58. Nepola JV, et al. Effect of exposure time on stimulation of healing in the rabbit tibial osteotomy model by a time varying pulsed electromagnetic field and by combined magnetic fields. Paper presented at the 30th Annual Meeting of the Canadian Orthopaedic Research Society; 1996; Quebec City, Canada.
59. Garland DE, Moses B, Salyer W. Long-term follow-up of fracture non-unions treated with PEMFs. Contemp Orthop 1991;22:295-302.