The use of pulsed electromagnetic fields to induce osteogenesis

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The use of electricity to promote bone healing is a practice dating back to the early 1800's. The use of Pulsed Electromagnetic Fields (PEMF) for inducing healing of non-united fractures is becoming an increasingly popular practice. This paper discusses the theory of electrically induced osteogenesis, molecular basis of action and reasons for using PEMF. Data for non-united tibial fractures repeatedly show results of equal efficacy for PEMF treatments as compared with surgical techniques and greater efficacy than other non-invasive techniques, with substantially less patient risk. PEMF treatment is a safe procedure that may prove helpful in attaining union in delayed or non-unions.

The first successfully documented attempts to use electricity to induce bone healing in non-union and other fractures can be dated back to the early 1800's. A Japanese scientist named Yasuda performed the first scientific studies in 1953 to show that during stressing, the concave side of a bone became negatively charged when compared with the convex side(1). This is generally termed piezoelectricity, which refers to the electric fields generated in ionically symmetrical crystals like quartz, when a deformation displaces charges and polarizes the crystal(2). Yasuda found an inverse linear relationship between deformation and the resulting polarization. In this instance, an electric field was shown to induce a deformation(3).

A substance can produce a piezoelectric effect only if it lacks a center of inversion symmetry. For this reason, no substance with a cubic crystal lattice structure can exhibit piezoelectric effects(2). The calcium hydroxyapatite phase of bone (mineral phase), one of the two solid phases of bone, does not have the prerequisite asymmetry to have piezoelectric properties. Black suggests that the collagen phase (the organic phase) is not sufficiently crystalline to be piezoelectric(3). Much research remains to be done in order to clarify the origin of the observed electric fields and the associated effects (3).

It has been shown *in vivo* that a callous forms on the concave side of a stressed bone, even with the absence of a fracture(4). Later studies involving direct electrical stimulation showed that calcification occurred in the region of the negative electrode - moreso than at the positive electrode. The degree of calcification was also shown to be voltage-dependent. This led to the speculation that the negativity of the concave side of the bone promoted callous formation (1). Further study revealed that bone, after acute fracture, becomes negatively charged during the natural healing process(1).

The idea of inducing charges into the fracture site from the external surface was examined by Bassett in the 1960's (reviewed in 5). Bassett's experiment involved high voltage electrostatic and electrodynamic fields induced by metal plates exterior to the tissue. After exposure to the electrostatic fields, a 15- 20% increase in DNA synthesis and a 50% increase in collagen synthesis was found. The electrodynamic fields showed a 20% increase in DNA synthesis and up to a 300% increase in collagen synthesis (1). The cells showed differences in their rate of calcium uptake when pulses were varied. These

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important studies showed that electricity could alter the fracture healing process but the voltages used (1000 volts) were much too high for human use. Bassett then began inducing voltages with an electromagnetic coil. Bassett was the first to use pulsed electromagnetic fields (PEMF) in human subjects. The first use was for the treatment of pseudoarthrosis of the tibia. After having some success, achieving a healing rate of approximately 73%, Bassett began using PEMF on patients with delayed unions and non-unions and achieved a healing rate of approximately 77%. Patients who did not achieve healing with the PEMF treatment were treated with bone grafting in combination with PEMF; this yielded a healing rate of 93% (1,6). In November of 1979, the use of pulsed electromagnetic fields was approved as safe and effective for a limited number of clinical applications by the Food and Drug Administration of the United States (7). These applications included fracture non-union, failed joint fusion, spine fusion, and congenital pseudoarthrosis (5).

The non-union of a fracture leaves two choices for the orthopedic surgeon: waiting longer (hoping the fracture will heal on its own), or active intervention (surgery or the use of PEMF). Surgery has significant risk factors while the application of PEMF carries essentially no risk. Surgical procedures, such as grafting, internal fixation and external fixation, have been commonly used to repair fracture non-unions but all carry the risks of infection or surgical complication. Treatment with PEMF is a non-invasive procedure that induces weak electric currents in tissues by placing coils externally to the tissues and inducing changes in the behaviour of the cells in the fracture gap. The fibrocartilage of the fracture gap undergoes calcification and angiogenesis and eventually undergoes endochondral osteogenesis. One of the best features of this treatment is that it can be applied on an outpatient basis (7).

The use of PEMF is a form of inductive stimulation. The primary magnetic field induces a secondary electric field which results in currents in the tissues. Coils, when wound in the same direction, connected in series and separated by a distance which is equal to their diameter will produce a magnetic field in a region between them. These coils, when placed on either side of the limb treatment area and given a time-varying voltage of 5-15 volts, result in production of a secondary electric field with potential gradients of 1-1.5mV/cm which can be induced in bone. A pulse burst signal which repeats at 15 Hz is given by an external power supply (battery or house current) (11).

CELLULAR MECHANISM OF ACTION

Evidence from experiments on the process of endochondral ossification indicate that both extracellular matrix synthesis and calcification can be elevated when tissues are exposed to the appropriate electric fields. Different stages of endochondral ossification vary in their sensitivity to electrical stimulation, with the stem cell stage being the most sensitive (8). The electrical stimulation triggers calcification of the fibrocartilage that is in the fracture gap. This calcification then leads to neovascularization of the cartilage. It is currently believed that this is the crucial step in healing, although the full mechanism remains unknown (1).

PEMF induce currents which are not of a constant nature. Thus, through specific pulse design one can selectively exert an influence on ionic species around the cells. One can control pulse rise time, shape, duration and rate. Research has shown that with careful pulse current design one can selectively influence behavior in bone, cartilage, nerve and skin cells (5). The selective control of different cell types, including mesenchymal cells, can also be elucidated with careful manipulation of the pulsed electrical current. When treating non-union fractures, the PEMF is programmed to induce a signal to trigger calcification of the fibrocartilage in the fracture gap. This fibrocartilage is an obstacle to vascularization and osteogenesis. Once calcification of the fibrocartilage takes place, vascularization, chondroclasis and replacement by bone can occur. This is the same process involved in normal healing of fractures. The PEMF do not actually induce osteogenesis but rather induce calcification which permits the normal sequence of events in osteogenesis to occur (5).

When examining the lack of vascularization in cartilage from an electrical point of view, a hypothesis as to the reason for the avascularity may become apparent. Cartilage contains a lot of proteoglycans and is thus largely polyanionic and has a net negative charge (this is especially the case when the tissue is deformed). The endothelial tissue of vessels is negatively charged as it has a sialic acid-containing surface coat. As vessels grow towards cartilage, the two negatively-charged entities repel each other. It is quite likely that in the epiphysis, two processes act to overcome this repulsion. The cartilage is prepared for vascularization by enzymatic degradation of the proteoglycans and by calcification. These processes will reduce or even reverse the net negative charge of the region. Collagenous tissues which are mostly free of glycosaminoglycans are positively-charged and thus are optimal substrates for cells, as the positive charge will interact with the negative charge of the cells surface. It seems likely that the PEMF permit the vascular tissue invasion by triggering calcification of fibrocartilage in the non-union gap, thus neutralizing the repulsive net negative charge in the tissue (5). The increase of calcium incorporation and the increase in cartilage matrix calcification has been repeatedly demonstrated. The extent of calcification has been shown to be related to the frequency and exposure time of the PEMF treatment. After stimulation, increased levels of cAMP (cyclic adenosine monophosphate) were observed in calcifying cartilage. The studies thus show a dose-dependent relationship and are interpreted to indicate that the electromagnetic fields triggered calcification of the cartilage matrix rather than increasing the protein synthesis of the matrix (8).

THE EFFECTIVENESS OF PEMF IN NON-UNION FRACTURE HEALING

The effects of PEMF on healing horse bones was studied in a series of experiments by Cane et al.(9). Each horse was used as its own control by putting a series of holes in both front legs and applying PEMF to only one leg. Eight holes were bored into each metacarpal with equal depth reaching from the mid-diaphysis to the distal metaphysis. At the diaphyseal level, the amount of bone laid down in the 60 day trial period was significantly greater ($p<0.01$) in PEMF-treated holes than in the holes allowed to heal without intervention. The percentage difference between PEMF treated holes and control holes ranged between 40-120%. The results in the metaphyseal bone level were less conclusive (9).

This study demonstrates that low frequency PEMF may indeed enhance the process of bone deposition in areas normally having a lower level of osteogenic activity, such as the diaphysis, and are less effective at stimulating cells that are already actively laying down new bone(9). No alteration of the symmetry of bone deposition was seen, in both the PEMF-treated bone and control bone; they closed in a concentric direction from the endosteum to the periosteum. This study is limited in its demonstration because it only quantitatively examines the 60 day stage of the long and complicated bone healing process. Therefore, exactly which stage of bone healing is being affected is not clear (9). A recent study evaluated roentographic results of 40 patients who had been treated for degenerative arthrosis of the knee with valgus tibial osteotomy (10). Patients were randomly assigned to a control group (with simulated treatment) or to a treatment group receiving PEMF stimulation, and evaluated by sixty-day post-operation roentgenogram. Four orthopedic surgeons, who were unaware of the experimental conditions, then rated the osteotomy healing into four categories, with the fourth category having the most healing. The majority of the patients receiving PEMF (72.2%) were categorized into the third and fourth groups, while only a minority of the control group patients (26.3%) were placed in these categories. A clear positive effect of PEMF stimulation was seen. The results of the study also suggested that five hours of daily PEMF stimulation is a minimum effective limit. This, and other double-blind studies, have shown that electrical stimulation promotes osteogenesis in human subjects. This effect has been shown to promote the union of femoral intertrochanteric osteometies, healing of delayed unions and spinal fusions (10).

The number of hours per day of PEMF stimulation will affect the healing time. A randomized study of 283 patients showed that there was a linear decrease in healing time as the hours per day of PEMF stimulation increased (1). A study by Sharrad and colleagues (11) supported the use of PEMF stimulation for healing non-union fractures. They treated fifty-three ununited fractures that remained ununited by radiographic appearance after at least 12 months of healing (median 28 months), before starting PEMF on an outpatient basis. No patient involved in the study had surgery in the last six months before starting PEMF treatment. Thirty-eight of the fifty-three fractures (71.7% overall, 86.7% for tibial subclass) united with a median time of six months. Higher success rates of tibial unions may be explained by the increased stability of the fracture site because of the presence of an intact fibula. It was shown that the presence of infection or previous infection, the presence of plates or nails, the time since injury and the patient's age, did not significantly affect the results of the PEMF treatment. However, it was shown that poor immobilization, a fracture gap of more than 5mm, and the presence of a screw in the fracture gap are likely causes of PEMF treatment failure and if a fracture gap of over 2 mm existed, then the percentage of unions achieved was significantly reduced (11). No adverse effects of PEMF treatment were noted.

A COMPARISON OF PEMF TREATMENT AND SURGICAL INTERVENTION

A review paper by Gossling and colleagues (12) summariszes all the relevant English literature from 1977 to 1987 to compare the efficacy of PEMF treatment and surgical intervention for tibial non-union. When data from all the studies was pooled, the overall success rate for tibial ununited fractures was 82% (range 77%-100%) or 482 of a total of 569 surgical procedures; and 81% , or 1402 of 1718 tibial ununited fractures treated with PEMF. It is important to note that most patients had at least one failed surgical treatment prior to PEMF treatment. Success rates for the surgical procedure are high but the efficacy of successive surgical procedures is reduced dramatically (12). A study by Boyd and colleagues (13) reviewed 842 nonunions of long bones and showed that the rates of surgical success dropped from 88% to 66%, 64% and 50%, respectively for the first four surgical treatments. In sharp contrast to these results, many studies have demonstrated that the number of previous surgical interventions does not significantly affect the results of PEMF treatment (12).

Many controlled studies have attempted to provide control groups for the PEMF treatments to accurately compare the effects of PEMF to those of other treatment protocols. A study by DeHaas and colleagues (14) showed that the rates of healing with PEMF treatment (88%) are equal if not superior to those of bone graft treatment (83%).

The effects of infection on the healing rates of PEMF treatments is dramatically different then the effects on surgical treatments. Ten studies of ununited tibial fractures reviewed by Gossling et al. (12) showed that with surgical interventions, the healing rate was 21% lower in the infected population than in the non-infected. However, the healing rate for PEMF treatment was only 6% lower in the infected population than in the non-infected. Ten studies were reviewed to compare the healing rates of open and closed fractures by PEMF and surgical intervention. The review showed that the healing rate for open fractures was 89% for surgery and 78% for PEMF. In closed fractures, the healing rate was 85% for PEMF and only 79% in the surgical intervention category. Once again, it is important to note that the PEMF treatment group includes a large number of patients who have already had multiple failed surgical procedures. Several studies in which a large proportion of the patients (75-80%) had already undergone attempted surgical intervention showed an overall healing rate of 70-80% with PEMF (12).

When a union fails to occur with four months of PEMF treatment alone, one can almost ensure healing (failure rates of 1-1.5%) when PEMF is applied in conjunction with fresh bone grafts (15).

PULSED ELECTROMAGNETIC FIELD PROTOCOL FOR TREATMENT

A seven-step protocol has been recommended (7) for the proper use of PEMF for the healing of ununited fractures and failed arthrodesis. The protocol involves:

1) application of a snug plaster cast to control motion;
2) measurement of the cast diameter at the level of the non-union to establish intercoil distance and an appropriate "driving" voltage for each patient's pulse generator;
3) placement of the parallel coils under roentgenographic control;
4) treatment at home for 10-12 hours daily;
5) strict non-weight bearing initially;
6) monthly roentgenograms;
7) graded, protected rehabilitation, once roentgenographic and clinical evidence of early union is established.

OTHER BENEFICIAL USES OF ELECTROMAGNETIC FIELDS

It is becoming increasingly apparent that weak non-ionizing electromagnetic fields, when properly programmed for their specific "biotargets", can exert a wide range of effects. The PEMFs have been shown to not only help heal ununited broken bones but also to have other wide ranging effects such as affecting calcium efflux and influx in various brain tissues (6). The cellular effects of PEMF are numerous. Some of the effects include changes in: cellular calcium levels, receptor and second messenger function, synthesis and degradation of proteins, and transcription and translation activity. The latter has been shown to be specifically altered by different pulse characteristics (6).

Table 1: Common medical uses of PEMF.(6)

PATHOLOGY	PEMF EFFECTS
Fracture non-union absence of adequate calcification, bone formation and vascularization	increased mineralization, angiogenesis and chondral ossification
Joint fusion failure absence of adequate calcification, bone formation and vascularization	increased mineralization, angiogenesis and chondral ossification
Osteonecrosis bone death	increased angiogenesis, osteoclasis and osteoblast activity
Osteoporosis increased bony destruction with reduced bony deposition	increased angiogenesis, osteoclasis and osteoblast activity
Skin ulcers reduced vascular supply	increased angiogenesis

CONCLUSION

PEMF is a non-invasive technique and therefore eliminates the significant risks of anaesthesia, wound hematoma, infection, bone length loss and skin breakdown that the patient may encounter during a surgical procedure (12). Electrical stimulation has been shown to be successful in causing new bone formation, accelerating fracture healing, inducing healing in delayed and non-union fractures, and in healing infected non-union fractures (1). It has been shown that when deformities are corrected, the fracture is properly immobilised and when the proper duration of PEMF treatment stimulus is given, PEMF is an effective method for treating delayed union and non-union fractures (1,15).

Finally, it is important to note that many of the publications on electrical stimulation fail to give important practical details. These include: a) patient selection/follow-up criteria, b) currents applied, c) concomitant treatments, and d) patient compliance/concerns (16).

REFERENCES

1. Uhl RL. The Use of Electricity in Bone Healing. *Orthopedic Review* 1989;18:1045-1050.
2. Omar AM. Elementary Solid State Physics: Principles and Applications. Addison-Wesley Publishing Company:Don Mills, Ontario, 1975.
3. Black J. Electrical Stimulation-Its Role in Growth, Repair and Remodelling of the Musculoskeletal System. New York:Preager, 1987.
4. Brighton CT, Okereke E, Pollack SR and Clark CC. In Vitro Bone-Cell Response to a Capacitively Coupled Electrical Field. *Clinical Orthopedics and Related Research* 1992;285:255-262.

5. Bassett AL. Pulsing Electromagnetic Fields: A New Method to Modify Cell Behavior in Calcified and Noncalcified Tissues. *Calcified Tissue International* 1982;34:1-8.
6. Bassett AL. Beneficial Effects of Electromagnetic Fields. *Journal of Cellular Biochemistry* 1993;51:387-393.
7. Bassett AL, Mitchell SN and Gaston SR. Pulsing Electromagnetic Field Treatment in Ununited Fractures and Failed Arthrodesis. *JAMA* 1982;247:623-628.
8. Ciombor DMcK and Aaron RK. Influence of Electromagnetic Fields of Endochondral Bone Formation. *Journal of Cellular Biochemistry* 1993;52:37-41.16. Spadaro JA, Electrically Stimulated Bone Growth in Animals and Man. *Clinical Orthopaedics and Related Research* 1977;122:325-332.
9. Cane V, Botti P, Farneti D and Soana S. Electromagnetic Stimulation of Bone Repair: A Histomorphic Study. *Journal of Orthopaedic Research* 1991;9:908-917.
10. Mammi GI, Rocchi R, Cadossi R, Massari L and Triana GC. The Electrical Stimulation of Tibial Osteotomies. *Clinical Orthopaedics and Related Research* 1993;288:246-253.
11. Sharrard WJW, Sutcliffe ML, Robson MJ and Maceachern AG. The Treatment of Fibrous Non-union of Fractures by Pulsing Electromagnetic Stimulation. *The Journal of Bone and Joint Surgery* 1982;64:189-193.
12. Gossling HR, Bernstein RA, et al. Treatment of ununited tibial fractures: A comparison of surgery and pulsed electromagnetic fields (PEMFs). *Orthopaedics*, 1992;15:711-719.
13. Boyd HB, Lipinski SW and Wiley JH. Observations of nonunion of the shafts of the long bones, with a statistical analysis of 842 patients. *Journal of Bone and Joint Surgery* 1961;43:159-168.
14. DeHaas WG, Watson J, Morrison DM. Noninvasive treatment of united fractures of the tibia using electrical stimulation. *Journal of Bone and Joint Surgery* 1980;62:465-470.
15. Brighton CT. Symposium on Electrically Induced Osteogenesis. The Orthopaedic Clinics of North America. 1984;15: