REVIEW ARTICLE

The Effect of Electromagnetic Stimulation on Nonunions: Myth or Reality?

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Introduction. Nonunion is a frequent complication in fracture treatment, especially in some areas of the body like the tibia. Although the process of fracture healing is complex and ill known, three kinds of systems to stimulate it have been described, which can be used either jointly or separately. These systems are biological, mechanical and biophysical. Among the latter, pulsed electromagnetic fields have been used for quite a number of years and there is already a significant amount of literature both on their mechanism of action and their clinical results.
Review of the literature. Electricity can be applied to bone pathology in three ways: directly, with capacitive devices or with inductive systems. In this paper, we review the latest developments on the effects and results of pulsed magnetic fields that induce electrical current at the fracture site; we focus only on late unions of limb fractures. We provide an analysis of the intimate action mechanisms and of their relationship with growth factors. An overview of the latest reviews published in the literature is also included.
Conclusions. Electromagnetic fields and inductive coupling have a beneficial effect on non-unions and there is enough experimental and clinical evidence to recommend their use. However, in order to obtain good results it is essential to be familiar with their indications and to follow the basic guidelines laid down for the treatment of fractures.

Key words: nonunion, stimulation, electromagnetic fields.

Acción de la estimulación electromagnética sobre los fracasos de la consolidación. ¿Falacia o realidad?

Introducción. El fracaso de la consolidación es una frecuente complicación en el tratamiento de las fracturas, sobre todo en algunas localizaciones como la tibia. Aunque el proceso de consolidación de una fractura es complejo e insuficientemente conocido, se han descrito tres sistemas de estimulación que pueden utilizarse aisladamente o de manera asociada: biológicos, mecánicos y biofísicos. Entre estos últimos los campos electromagnéticos pulsátiles se están utilizando desde hace bastantes años y existe una amplia bibliografía tanto sobre su mecanismo de acción como sobre sus resultados clínicos.
Revisión de la bibliografía. La electricidad puede aplicarse en la patología ósea de tres maneras: de manera directa, con sistemas capacitativos y con sistemas inductivos. En esta actualización se revisan las últimas aportaciones sobre los efectos y los resultados de los campos magnéticos pulsátiles que inducen una corriente eléctrica en el foco de fractura, estudiando exclusivamente este sistema en los retardos de consolidación de las fracturas de extremidades. Se analizan los mecanismos íntimos de acción y su relación con los factores de crecimiento, así como las últimas revisiones bibliográficas que han aparecido en la literatura.
Conclusiones. Los campos electromagnéticos mediante acoplamiento inductivo tienen un efecto beneficioso sobre los retrasos de la consolidación y existe suficiente soporte tanto experimental como clínico para recomendar su utilización. No obstante, es esencial conocer sus indicaciones y seguir las normas básicas en el tratamiento de las fracturas para obtener buenos resultados.

Palabras clave: pseudoartrosis, estimulación, campos electromagnéticos.

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In the USA trauma is considered to be the first cause of death in under-45 year olds and also the most costly «disease». In the USA there are 5 million fractures per year, 5-10% of which (250,000-500,000) result in failed healing and require additional treatment[2]. Specifically in tibia, delays in consolidation are seen in 5-61% and non-unions are as high as 21% in some series. To these numbers we must add those of patients who undergo new interventions to treat secondary deformities, lost work-days during recovery and, the most difficult factors to assess: psychological, social and family problems generated by incomplete or inappropriate treatment.

The basic principle in the general treatment of fractures is to stimulate physiological development of consolidation. But fracture healing is a complex biological process that requires spatial and temporal conjunction of numerous cells, hundreds of genes and the extracellular matrix in such a way that it is possible for multiple situations to alter this process[3]. Many techniques are currently in use for the treatment of delays in consolidation or non-unions, including internal fixation of different types, bone grafts, bone substitutes such as demineralized bone matrix, protein fractions such as platelet extract or morphogenetic protein and biophysical systems, including mechanical stimulation, ultrasound and electric and electromagnetic stimulation. In this update we will exclusively refer to treatment by means of electromagnetic stimulation of limb fractures that suffer delays in consolidation or non-union.

Electromagnetic stimulation, especially by means of pulsed electromagnetic field (PEMF) devices, has been used for more than 20 years in clinical practice and there is abundant literature on the mechanism of action and results of this treatment. However, there is certain skepticism amongst orthopedic surgeons as to the real value of this technique, which can be due to errors in the indications or the application of the technique. On the other hand, PEMF is used as a last therapeutic resort in cases of complex and chronic failures in consolidation, with the corresponding difficulties. Another reason for the lack of confidence in this type of treatment is the confusion surrounding paramedical treatments (such as magnetism) and the delay in determining the outcome in some cases. The aim of this study of ours is to review the latest advances and updates on stimulation of fracture calluses using PEMF.

PATHOPHYSIOLOGICAL STAGES OF FRACTURE HEALING

When a fracture takes place a complicated cascade of events is initiated, both at cellular and at biochemical and biophysical level. These come to an end when the structure and function of the damaged bone are completely restored[4].

This process has characteristics that make it different from other post-trauma healing processes. In the first place, there is no equivalence between consolidation of a fracture and healing of damaged soft tissue, since bone heals without residual scarring. On the other hand, bone repair is an authentic regenerative process that is more similar to extremity regeneration processes in amphibians than to other healing processes: the damaged bone is replaced by true bone and not by scar tissue. Although there are three types of osteogenesis (by compression, by distraction and by transformations, such a bone transport), our main interest is in fractures that carry out osteogenesis by compression and to these we will refer below.

It has been known for some time that to obtain consolidation of a fracture several phases are necessary. These begin with the formation of a hematoma and continue with cell proliferation and differentiation, all of which take place 48 hours after the initial impact. There is necrosis of the bone ends, cell death and release of intracellular contents. The decrease in pH and the oxygen pressure on one hand, and the release of chemical factors on the other, cause chemotaxis of inflammatory cells.

Similarly to what occurs when there is damage to soft tissues, the first stage in fracture healing is the activation of inflammatory reactions. Macrophages (derived from monocytes) and other inflammatory cells release different cytokines and growth factors, such as interleukin (IL)-1, IL-6, platelet derived growth factor (PDGF), transforming growth factor β (TGF-β) and fibroblast growth factor (FGF). The combined action of the growth factors released by the platelets and inflammatory cells produce chemotaxis of additional macrophages, and angiogenesis, and chemotaxis and proliferation of mesenchymal cells. Any type of treatment that prevents or annuls the initial formation of a hematoma or secondary inflammatory reactions is an obstacle to consolidation. On the contrary, the presence of growth factors, as also their therapeutic administration, stimulates the development of this stage. In the same way, an alteration caused by trauma of the bone's internal blood supply or of that of neighboring soft tissues has a negative effect on the formation of the callus. This is of basic importance in shaft fractures due to high energy trauma and/or open fractures.

As a result of the release of growth factors by platelets and inflammatory cells there is proliferation of mesenchymal cells, accompanied by proliferation of extracellular matrix, and angiogenesis increases to an even greater extent, the result is a highly vascularized fibrous callus. The fracture may still become angular, although it has already achieved a certain stability to prevent shortening. Currently the importance of mesenchymal stem cells and their differentiation is recognized and, in fact, certain therapies, still under development, for the treatment of consolidation difficulties, base their mode of action on the stimulation of mesenchymal stem cells.

Mesenchymal cells differentiate into chondrocytes and osteoblasts, initiating the formation of cartilage and reticular bone. During the second week membranous ossification begins at the periosteum, with the formation of new bone and a minimum stabilization of the fragments. There is chondrocyte hypertrophy and mineralization of the matrix.

The formation of endochondral bone is stimulated by some growth factors such as TGF-β, and FGF and especially bone morphogenetic protein (BMP).

The new bone that develops at the site of the fracture is remodeled by the activity of osteoblasts and osteoclasts. The osteoclasts cause bone resorption and the resulting cavities are filled by osteoblasts. Reticular bone with a trabecular structure is replaced by mature lamellar bone with a structure and diameter similar to undamaged bone and is associated with recanalization of the medullary cavity. This remodeling is under the direction of mechanical forces following Wolf's law and may take several years.

Fracture consolidation, therefore, is initiated by a succession of cellular events: Inflammation, followed by the formation of fibrous tissue and differentiation into cartilage ending with the formation of bone by endochondral ossification. These events are influenced by the presence of non-differentiated cells regulated by growth factors that are released locally. The term osteoinduction is used to define this phase, which is a key phase in fracture repair: a process that stimulates mitogenesis of mesenchymal non-differentiated cells forming osteoprogenitor cells capable of forming new bone.

At the same time, the differentiation of existent tissue amongst the bone fragments of the fracture is directed by mechanical forces that act on different cell populations and by vascularization of surrounding soft tissues. Load stimulates revascularization if it takes place after the initial phases of tissue differentiation in the interior of the fracture. Therefore, consolidation benefits from a first stage of initial stability that favors revascularization. After the first month, load and inter-fragment movement stimulate the formation of the callus. A prolonged rigid stabilization will cause consolidation by direct Haversian remodeling, controlled movements with fragment separation achieve consolidation with formation of intermembranous bone.

Bone architecture is permanently optimized in response to the mechanical environment, and more closely related to dynamic forces than static forces. When movements of small amplitude occur, with non-rigid stabilizations, endochondral and intramembranous ossification achieve healing. It is currently known that cyclic inter-fragment movements increase the degree of consolidation, the size of the callus and blood supply. Due to this movement, some areas of the callus are unstable and there is a rupture of new capillaries. This leads to a new release of growth factors and other active substances by platelets, and a new inflammatory reaction is initiated with the presence of macrophages. These macrophages release new growth factors and cytokines that cause new angiogenesis and granulation tissue.

As a consequence of all this the size of the callus increases and the cascade of events is repeated. Therefore, fragment movement induces a larger-sized callus, on the other hand, if stability is perfect, consolidation is achieved by direct bone repair. To summarize, we could say that to achieve consolidation it is necessary to have an adequate blood supply, viable cells must be available, appropriate signals must be generated so that the cells produce the appropriate matrix for each repair phase and the mechanical environment must be appropriate for bone deposit (Table 1).

Table 1. Necessary factors for fracture healing

1. Cells
Proliferation, differentiation and maturation. Synthesis of extracellular matrix.
Types:
– Pluripotent embryonic cells.
– Non-differentiated or stem cells.
2. Matrixes
Cell adhesion and growth, macroporosity, resistance, resorption, deposit.
Types:
– Natural: collagen, hyaluronic acid...
– Synthetic: lactic acid, bioactive ceramic components (HAP, phosphates, sulphates), bioglass…
3. Bioactive Factors
Growth factors (proteins released by cells).
Cell behavior is modulated by physical or biochemical signals through the extracellular matrix.
Types:
– Signalling peptides: transforming growth factor β (TGF- β), fibroblast growth factor (FGF), platelet derived growth factor (PDGF),(they stimulate the activity of stem cells but do not act on non-differentiated cells).
– Osteoinductive factors: BMP2,4,6,7 (acts on non-differentiated cells and stimulates the formation of extracellular matrix)

BMP: bone morphogenetic protein; HAP: hydroxyapatite.

STIMULATION METHODS

Multiple circumstances and factors that increase the formation of calluses and that therefore contribute to the healing of fractures have been described. However, in spite of many attempts, it has not been possible to produce a callus in humans using artificial means. When the consolidation process has begun it is possible to accelerate it, but when it has not begun, no technique or method is able to produce consolidation. Only the application of autografts can initiate bone healing, and only if all the other requirements mentioned are complied with: a sufficient blood supply and appropriate physical conditions.

In a search for reinitiating, stimulating or accelerating the events that lead to consolidation, many methods have been described and classically divided into: mechanical, biological and physical. This classification is only fictitious, since biological methods are not exclusively biological nor do the other methods only respond to the laws of physics. It would be better to say that the three methods operate at dif-

Table 2. Types of bone healing stimulation

1. *Biological Methods*
   - Bone grafts
     - Auto-grafts
     - Cancellous
     - Cortical
     - Cortical-Spongy
     - Vascularized
   - Allografts
     - Cryopreserved
     - Fresh
     - Liophylized
     - Demineralized
   - Xenografts
     - Kielhl Bone
   - Bone marrow
     - Fresh
     - Predifferentiated osteoblasts
     - Non-differentiated stem cells
   - Bone substitutes
     - Calcium phosphate ceramics
     - Reabsorbable calcium phosphate
     - Bioglass
   - Growth factors
     - Members of the TGF-beta familyTGF-betaBMP
       - Activin
     - Others
       - FGF 1 and 2
       - PDGF
   - Composite biosynthetic grafts
   - Gene therapy
     - BMP producing cells
   - Systemic methods
     - Prostaglandins
     - Parathyroid hormone
     - Osteogenic growth peptides
2. *Mechanical Methods*
   - Fracture fixation
   - Controlled support
   - Axial micromotion
3. *Biophysical Methods*
   - Electricity
     - Direct
     - Inductive (PEMF)
     - Capacitative
   - Ultrasound

BMP: bone morphogenetic protein; PEMF: Pulsed electromagnetic fields; FGF: fibroblast growth factor; PDGF, platelet derived growth factor; TGF-β: transforming growth factor β.

ferent levels of fracture healing and mutually stimulate each other. The so-called biological methods are not included in this up-date and will therefore not be detailed here.

Mechanical Methods

The major factor in stimulating consolidation of a fracture is sufficient stability of the focus. And this is not only valid in the treatment of recent fractures. In cases of consolidation delay, the replacement of a thin intramedullary nail by a thicker one is the treatment of choice in certain situations. It has been shown in experimental and clinical studies that axially controlled micro-movements, obtained simply by external immobilization or with intramedullary osteosynthesis systems, accelerate consolidation in shaft fractures and produce an increase in the size of the external callus. It must not be forgotten that simple ambulation with support of the limb may cause this beneficial effect on fracture healing.

Biophysical Methods

Two types of electrical phenomena have been described in bones: piezoelectricity and electric currents. When a bone becomes deformed an electric potential is generated, this phenomenon is known as piezoelectricity, and it induces changes in the pressure of interstitial fluid. This fluid travels through the small channels from the high pressure regions to the low pressure regions, causing osteocyte membranes to undergo changes similar to those caused by an electric current. To imitate this process the application of an exogenous electric field at the site of the fracture has been recommended.

A biolectric potential is another type of electric potential that appears when a fracture takes place and that becomes modified during the consolidation period. First there is a negative potential, which becomes positive over the next few hours. Subsequently, if the fracture follows its normal repair process, the potential becomes markedly negative[5]. It is currently known, as we shall see, that *in vitro* exposure of the osteoblasts to certain electrical stimulation systems increases the secretion of many growth factors, including BMP 2 and 4, TGF , and β IGF-II.

There are many clinical studies on the results of the application of electric and/or magnetic fields for healing fractured bone. Basically, these have been used when there have been consolidation failures, and in these cases following precise indications they may achieve a success rate of 75%. Some studies also recommend the application of PEMF during early stages of consolidation, to accelerate normal physiological stages; it is accepted that in a certain group of fractures, those known to be at risk, it is possible to indicate the use of electrical fields during the first stages of healing: in these cases a delay in consolidation is foreseeable and the application of electricity during the early stages seems to stimulate healing.

HISTORICAL EVOLUTION OF ELECTRIC STIMULATION IN BONE PATHOLOGY

For more than 400 years the relationship between electromagnetism and life has been a source of fascination and controversy. Both natural and artificial electromagnetic fields have been studied in a process lasting several centuries. Currently electromagnetic fields are used in many areas in which their use was previously unthinkable. We will concentrate on their use in the healing of fractures.

William Gilbert's curiosity about compasses and magnets led this XVI century English physician to study physics, a field in which his careful observation and reasoning led him to determine the basis of modern experimental science and he demonstrated that the Earth is magnetic.

Gilbert believed magnetism to be the soul of the Earth. In 1600 he published a large treatise on this subject that changed the way of presenting, discussing and proving scientific theories. This book, *De Magnete* (The Magnet, in Latin) was used as a basis for scientific Renaissance in the XVII century by Johannes Kepler, Galileo Galilei and Isaac Newton. Gilbert also introduced scientific experimental observation carried out systematically and he defined a method and a philosophy in experimental science 20 years before the famous declarations of Francis Bacon (in favor of a deductive system of empirical observation and investigation to discover Nature's secretes). Since Greek times experiments were performed, but Gilbert was the first person that methodically related experiments with theories and detailed them so that they could be duplicated by others. He called materials that attracted each other *electricks* and the force that attracted them *elecktrica*. The experts point out that, by doing this, he created the vocabulary currently used to describe electricity, including terms such as «electron». It can be considered that Gilbert made magnetism part of science.

Faraday was one of the most illustrious experimental scientists of the XIX century. This humble bookbinder began a series of experiments in 1825 with the aim of determining if he could obtain electricity from magnetism. In 1831 he was able to present his first studies with positive answers. Faraday discovered that electric current was only produced when the magnetic effect varied over time, if magnetism is constant it does not produce electricity. The history of electricity and magnetism constitute the first example of a series of purely scientific theories and experiments that later became the basis for a large-scale industry. This is an example of how scientific research became practical engineering. Electromagnetism is a very important example of the relationship between science and technology, given that the division between these is not clear. In fact it is difficult to speak of a division, since both are so interrelated that one cannot advance without the help of the other.

The case of electromagnetism is remarkable because, once discovered scientifically, it was immediately applied in practice, and this, in its turn, stimulated scientific research, opening up new scientific and technological horizons. The use of electricity in failures of consolidation goes back to the XIX century, although these cases can be considered anecdotal and are attributed to the discovery of electricity and the search for a type of energy that would revolutionize the lifestyle of those times.

In 1812 Birch, who worked in St. Thomas' Hospital, London, applied galvanic current during 6 weeks to a malunion of the tibia with 13 months' evolution: this may be considered the first reference to the use of electricity in a fracture. Over the next 50 years another 6 cases of treatment by means of electricity in cases of consolidation failure are known. In 1841 Hartshorne used electricity on a tibia fracture, in 1850 Lente published the results seen with 3 patients in whom galvanic current was applied for 10 minutes 3 times a week[6].

Over the next 100 years experiences of this type are almost completely lacking in medical literature, maybe due to a better knowledge of the pathophysiology of the fracture callus and the improvement of surgery. Better results were starting to be obtained using surgical techniques in cases of non-union.

Iwao Yasuda, born in 1909, published the first studies on piezoelectricity in bone in the fifties and it can be considered that, based on his research, electricity is first applied to pathological bone conditions with a scientific basis. Yasuda was the first researcher who measured the electrical fields generated in bone as a response to mechanical stimulation. Pressure applied to one end of a bone causes its deformity: the concave side, under compression, becomes electronegative, and the convex side, under tension, becomes electropositive. Yasuda together with Fukada demonstrated that there was new bone formation near the cathode when a microampere electric current was continuously applied to the femur in rabbits for 5 weeks. These electric phenomena produce signals which lead to osteoblastic or osteoclastic activities.

In 1971 a case was published of a non-union of the tibial malleolus in which consolidation was achieved with electric current applied directly; and in 1972 another case was published of healing of a congenital non-union of the tibia. Therefore, certain direct electrical stimulation techniques were developed that had a certain degree of success in those years.

Simultaneously another line of research developed: Invasive or semi-invasive techniques involved new aggression to the site of non-union, required a surgical procedures to implant electrodes and another surgical procedure to remove them, there was danger of infection, the possibility that a non-septic non-union become septic, and a careful follow-up was required. Basset et al[7] in 1974 introduced the use of non-invasive methods: by means of external application of alternate current using an electric coil placed at 180º, with this method magnetic fields are created that give rise to electric current in the bone, in such a way that the induced voltage helps to generate intermittent currents similar to those caused by mechanical stress. This is, therefore, electric current induced by inductive coupling.

In 1981 it had been used in 1,800 patients, in 1984 in 11,000, in 1986 in 20,000 and in 1989 in over 100,000; currently it is the most indicated system with most bibliographical support. These pulsed or inductive coupling electromagnetic fields, were seen to achieve consolidation in 75-80% of cases in the first studies published, these figures are maintained in new reviews. The FDA approved the clinical use of electromagnetic fields in 1979, after a study of 260 cases of consolidation failures, some of very long evolution that had undergone multiple previous interventions. Healing was achieved in 64% of cases, a figure that compares favorably with other types of treatment with bone grafts and other surgical techniques. Both direct stimulation methods and inductive coupling methods require: to be applied exactly on the focus of the fracture, not to violate the usual rules for the treatment of fractures and that the separation between fragments should not be greater to half the diameter of the affected bone. No electric stimulation method is of use in synovial non-union, as we shall see.

Brighton and Pollack in 1984[8] report the consolidation of a tibia non-union treated by means of another electrical stimulation system, capacitative coupling, which is portable, and therefore more comfortable for the patient. This consists in the creation of an electric field using an external source. In 1985 the same authors reported the results seen in 20 patients using this technique, in which they achieved a rate of bone union of 77% after 22 weeks of treatment[9]. Capacitative coupling requires that the electrodes be placed directly on the skin.

TYPES OF ELECTRICAL STIMULATION

We know that an electrical field in movement creates, in its turn, a magnetic field and viceversa. Electromagnetism deals with these 2 fields, since their relationship is evident. Furthermore, on bone, 2 different potentials are seen, as we have said, on one hand a piezoelectric potential (generated by mechanical deformity of the bone), and on the other hand a bioelectric potential (generated at rest).

It is also well known the area of repair and growth in live bone is electronegative. Therefore, the influence of electricity on bone is accepted and we can conclude that it is possible to interact with bone (for example, in a fracture) by means of the creation of a magnetic or electric field. However, there are several parameters that require management: Can any electromagnetic field be applied on any fracture? Evidently not, it is necessary to choose the appropriate frequency of the electromagnetic induction field. Many experiments have been carried out with all types of animals to see the different effects that different electromagnetic fields may have on them. Some of the responses to different frequencies of electromagnetic fields[10,11] are behavior alterations, sleep alterations, accelerated learning, etc.

The practical application of electrical stimulation in pathological bone conditions is carried out in different ways. On one hand the introduction of a cathode surrounding the bone graft associated to an active implantable system for 24 hours is used, for example, in hip bone necrosis. In this case, a direct or invasive system, stimulation generates osteogenesis in the neighboring tissues with a current of approximately 20 μA. The capacitative system is different, since electrodes are placed on the skin on opposite sides and connected to an external generator of electric current. In this case the frequency is between 20 and 200 kHz, generating electrical fields on the skin of $7 \mu A/cm^2$. Lastly, PEMF, with coils placed in the focus of the fracture and connected to an external generator, have been used in different configurations. The systems we use personally have a frequency of 75 Hz, with a pulsed period of 1,3 milliseconds, an intensity of 10 to 20 A/cm and a voltage of 2,5 to 4,5 mV[12].

MECHANISMS OF ACTION

It has been known for some time that PEMF regulate proteoglycans and the synthesis of collagen, increasing bone formation. We have already pointed out that a bone that undergoes deformation generates an electric potential known as piezoelectric. Well, PEMF try to cause the same effect causing intermittent polarization and depolarization.

Stimulation by means of PEMF accelerates the early phase of consolidation and some studies show[13] that there is an increase of activity at the focus of the fracture during the first phases of healing in recent fractures. There is also published evidence of the acceleration of union in osteotomies (which are really recent fractures) and in the treatment of bone necrosis (if we only mention pathological bone conditions).

Electromagnetic fields cause alterations at a tissue, cell and subcellular level. They favor cell proliferation and the synthesis of glycosaminoglycans (GAGs) in growth cartilage cells, thus accelerating endochondral ossification; intermittent stimulation is more effective in causing both effects. The differentiation and calcification of the cartilage of the fracture callus is similar to these processes in growth cartilage. One stage of the consolidation process is the invasion of fibrocartilage by new vessels, giving rise to endochondral ossification, similarly to what occurs in growth cartilage. There is consolidation failure in 5% of fractures of long bones due to persistence of fibrocartilage that does not become calcified. This can be due to several factors: decrease of vascularization of the bone ends, infection, inadequate fracture reduction, exaggerated movement of the focus. PEMF act on fibrocartilage accelerating mineralization, and not only by means of the rapid formation of vessels by endothelial cells, but by mechanisms of cell action. Therefore, fibrocartilage is necessary for electromagnetic currents to be indicated.

In synovial non-union, meaning that there is fluid between the bone ends and that these are surrounded by a neocapsule with uncontrolled movement, PEMF are not of any use. Undoubtedly their incorrect use in such cases has increased the skepticism as to the benefits of this technique. PEMF should not be used either in cases of fibrous non-unions based on the definition itself of these failures. But if, by means of immobilization and unloading, it is possible to convert the fibrous tissue into fibrocartilage, PEMF may have a beneficial effect, as some reviews indicate[14].

We are beginning to know, in greater detail, how electromagnetic fields affect bone consolidation. Currently it is known that cells of osteoblastic strains respond to PEMF by means of changes in the production of local factors[15]; these give rise to a cascade of regulatory events that end with the synthesis of growth factors[16]. The exposure of osteoblasts to PEMF stimulates the secretion of a number of growth factors (BMP 2,4 TGF-,, IGF II)[17]. A recent study[18] summarizes the already experimentally demonstrated effects of induced magnetic fields, we advise those who are interested to read this work. In general; PEMF stimulate endochondral ossification by increasing the mass of cartilage and the production of TGF-β,and other factors, without disorganizing bone formation.

CLINICAL EXPERIENCE

In spite of the abundant clinical and experimental evidence of the possibility of achieving healing of non-unions using PEMF, there is still a certain skepticism as to their clinical usefulness, as we have mentioned. However, the literature is overwhelming. In 1982 Goldberg et al[19], in a review of 11,000 cases of consolidation failures treated with PEMF found a rate of total healing of about 75%. A recently published review showed, in longitudinal cohort studies, satisfactory results in cases of non-unions and consolidation delays of 75-85%[20]. In another recent study, supported by the American Academy of Orthopedic Surgeons (AAOS)[21], the European experience with PEMF in consolidation failures is analyzed. In this review publications of 9 authors have been included, amongst them two Spaniards. The success rate with PEMF varies from 72 to 88%.

One of the reasons given for skepticism related to the use of PEMF has been the inadequate number of randomized controlled studies, this, however, is not true. Sharrard in 1990[22] published a randomized, double blind study that should overcome all lack of confidence in this method: He studied all the results of treatment with inductive coupling and immobilization in a group of 20 tibial shaft fractures, comparing them with 25 cases treated with a simulator and simple immobilization. These cases were independently assessed by a radiologist and an orthopedic surgeon and statistically significant better results were seen in the group treated with PEMF. To find uniform and comparable cases it was necessary to study 2,000 cases from 16 centers, which gives an idea of the difficulties in carrying out these types of studies in orthopedics.

More recently, Simonis et al[23] have presented the results seen in 34 patients treated with PEMF in delays of consolidation of fractures of the tibia. This was a randomized study and results of both groups were compared: external fixators were used in all patients and in the study group or group 1 treatment with PEMF was carried out, whereas in group 2 an inactive system was used. In the group treated with PEMF, 89% of cases achieved consolidation, whereas in group 2, only 50% did; this difference was statistically significant.

We published our own experience with PEMF[24] a few years ago. Our series, at that time, had 171 cases of healing failure or delay treated with inductive coupling. For the series to be homogeneous results were assessed in only 137 patients that had limb fractures. In 102 cases (74.5%) clinical and radiographical consolidation was achieved, and the technique was considered a success. As regards successful healing, there were no statistically significant differences depending on the patients' gender, or on fracture line, or fracture location, although the tibia was the bone with the highest percentage of consolidation (85%). The mean age of the successful cases was 43.6 years old (with a standard deviation [SD]: 19.6) and that of the failures 37.4 (SD: 14.7), the difference in these figures was statistically significant ($p = 0.048$). Statistically significant differences were found ($p < 0.001$) according to the separation of the fragments, achieving 78.7% consolidation when the fragments were separated by less than 5 mm (96 patients out of 122). There were also statistically significant differences related to the radiological type of non-union (83.8% of successes in hypertrophies); previous treatment (81.7% healing in previous orthopedically treated cases) ($p=0.02$); infection (77.3% of consolidation in non-septic cases) ($p=0.01$) and in relation to type of problems (98 successes in 126 cases of delays of consolidation and 4 successes in 11 non-unions) ($p=0.007$). Our study, which investigated prognostic factors related to the use of PEMF, advises the use of a scoring table to provide orientation on the effectiveness of this treatment before applying it.

During recent years the literature on clinical uses of electrical fields in pathological bone conditions has decreased. This may be due to the discontinuation of the scientific activity of two of the most important researchers: Basset and Brighton. However, the publications on its detailed mechanism of action[25] are more and more frequent and show the growing interest in this technique in fracture consolidation research. We have purposefully not referred to the indications for PEMF in other orthopedic conditions in this update. Nor have we studied the effects of other types of electrical current on pathological bone conditions.

CONCLUSIONS

Electrical field have the potential of modulating certain biological processes. If it is experimentally known, and the literature mentions it repeatedly, that PEMF stimulates consolidation in a similar manner to intermittent mechanical stress, it does not seem reasonable that at this moment in time, when progressive support to favor consolidation is universally supported, this technique should not be appropriately valued. It must be recognized, at least, that in certain types of consolidation delay and at some stage of the healing process, electrical stimulation is useful. When PEMF is used as a support for other techniques it is sometimes difficult to determine if healing was due to simple immobilization, the time elapsed, the surgical treatment carried out, or the effects of PEMF. However, the stimulating effect of PEMF on the bone callus has been experimentally proved in animals, and the literature on its usefulness in humans in cases of consolidation failure is abundant. Its advantages are many: it has a local effect that can be regulated, there is no risk of an overdose, it does not alter physiological mechanisms (it only modulates and activates), it imitates the changes triggered by mechanical stimuli and no complications or secondary effects are known. Based on the new knowledge we have gained as to the mechanism of action of biophysical stimulation, we can say it has theoretical advantages, with relation to pharmacological therapy, in that it produces sustained increases of local growth factors at the site of bone repair, without the need of large doses that may be toxic locally or systemically.

However, it is good to remember that currently, the essential factors to achieve success in the treatment of consolidation are: axial alignment, adequate stabilization and the preservation of the blood supply. Until the mechanical aspect of a fracture is not resolved (usually by means of an increase in stabilization), manipulating the biological factors related to a fracture (with electricity, grafts, etc.) has limited possibilities of success.

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Conflict of interests

The authors have declared that they have no competing interests.