STIMULATION OF BONE FORMATION AND FRACTURE HEALING WITH PULSED ELECTROMAGNETIC FIELDS: BIOLOGIC RESPONSES AND CLINICAL IMPLICATIONS

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Pulsed electromagnetic fields (PEMF) have been used for several years to supplement bone healing. However, the mode of action of this non-invasive method is still debated and quantification of its effect on fracture healing is widely varied. At cellular and molecular level, PEMF has been advocated to promote the synthesis of extracellular matrix proteins and exert a direct effect on the production of proteins that regulate gene transcription. Electromagnetic fields may also affect several membrane receptors and stimulate osteoblasts to secrete several growth factors such as bone morphogenic proteins 2 and 4 and TGF-beta. They could also accelerate intramedullary angiogenesis and improve the load to failure and stiffness of the bone. Although healing rates have been reported in up to 87% of delayed unions and non-unions, the efficacy of the method is significantly varied while patient or fracture related variables could not be clearly associated with a successful outcome.

Pulsed electromagnetic fields (PEMF) have been used for the management of fracture delayed unions and non-unions for more than half a century already (1). Despite numerous studies and clinical trials, the mode of action of this non-invasive method is still debated and quantification of its effect on fracture healing is widely varied in the literature. This article mainly focuses on the cellular and molecular effect of PEMF and the overall efficacy of the method in enhancing fracture healing and promoting new bone formation.

HISTORY-DESIGN-BASIC PRINCIPLES

The use of electrical stimulation in fracture healing is not a novel concept. There have been relevant reports from as early as 1841 but the use of this method did not become widespread until the early 1950s, when Yasuda (2) demonstrated new bone formation in rabbit femora, adjacent to a cathode. He also demonstrated that there were electric potentials in bones, that were categorized into steady-state and stress-induced potentials (2). The latter develops when a bone is subjected to a bending force that causes the compressed side to become negatively charged when compared to the tensed side of the bone. This potential is known as strain gradient (3). On the other hand, steady-state potentials are potentials that arise in areas of bone activity and are independent to stress.

Until the late 1970s there was an abundance in the literature of reports describing the effects of electricity on bone growth and fracture repair. Since then, a variety of devices have been developed in order to produce electromagnetic fields to the fracture site. Recent and more widespread PEMF devices utilize non-invasive inductive coupling and can be used along with every method of fracture fixation (4). Interestingly, the electrical stimulation market is approximately worth 500 million dollars in the United States (5).

The principle underlying the application of current PEMF devices is that of inductive coupling (3). Electric current is produced by a coil, driven by an external field. This external field acts on the bone elements and it results in a secondary electrical field being produced in the bone. The secondary field is dependent on the characteristics of the applied magnetic field and tissue properties. Magnetic fields of 0.1 to 20G are usually applied in order to produce electrical fields in bone, ranging from 1 to 100 mV/cm (6)

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(Figure 1). Contra-indications to the use of PEMF include segmental bone loss, infected non-unions, synovial pseudoarthrosis and poor stability of fracture site (6).

MOLECULAR – CELLULAR - BIOMECHANICAL MECHANISMS

It seems that the overall effect of electromagnetic fields on the fracture site is to stimulate the bone in a way similar to mechanical loading (7). However, there is still ongoing debate regarding the mechanism of action of PEMF at cellular and molecular level. PEMF has been advocated to stimulate the synthesis of extracellular matrix proteins and exert a direct effect on the production of proteins that regulate gene transcription (8). Electromagnetic fields may also affect several membrane receptors including PTH, insulin, IGF-2, LDL and calcitonin receptors (9). When osteoblasts are stimulated by PEMF, they secrete several growth factors such as bone morphogenic proteins 2 and 4 and TGF-beta (3). Studies regarding the impact of PEMF on bone marrow stromal cells have demonstrated that PEMF could enhance mineralization and favour differentiation on the expense of proliferation, as shown by the upregulation of various osteogenic markers in the PEMF exposed group (10). Electromagnetic fields also enhance mRNA production of bone morphogenetic protein 2, TGF-beta1(11), osteoprotegerin(12), osteocalcin, Runx2/Cbfa1, ALP(13), matrix metalloproteinase-1 and -3, NF-κB ligand (14) and bone sialoprotein. Such findings suggest that PEMF may have a direct stimulatory

action on osteoprogenitor cells by promoting osteogenic differentiation in vivo. Similarly, PEMF has been shown to increase bone mass density and TGF-beta1 concentration in rat models. Conversely, it may significantly reduce IL-6 concentration (15). These results indicate that PEMF stimulation may efficiently suppress bone mass loss. Other signalling molecules that are induced by PEMF include the insulin receptor substrate-1 (IRS-1) protein, the S6 ribosomal subunit protein and the endothelial nitric oxide synthase, which could be also activated by PTH and insulin to the same degree as PEMF (16). In addition, PEMF has been shown to activate the m TOR pathway in pre-osteoblasts and fibrolasts (17).

It is known that mesenchymal cells express an osteogenic phenotype when treated with BMP-2, albeit in high doses (18). Besides, PEMF could enhance the osteogenic effects of BMP-2 on mesenchymal cells that exist in a calcium phosphate-rich environment. As PEMF and BMP-2 act on different pathways, they have an additive beneficial effect in promoting fracture healing (19). Therefore, PEMF could be used in vivo as an adjunct to the administration of BMP-2, in order to induce bone formation (18).

PEMF has been also found to stimulate osteogenic activity in osteoblasts-like cells by upregulating genes related to bone formation such as the HOXA10 and AKT1, genes leading to production of transduction-related factorst such as the CALM1and P2RX7, genes for cytoskeletal components such as the FN1 and VCL and genes that lead to production of extra-cellular organic matrix components such as the COL1A2 and SPARC (20). On the other hand, PEMF may down-regulate genes that are related to the degradation of matrix, such as the MMP-11 and DUSP4. Therefore, PEMF do not only induce extra-cellular matrix synthesis and mineralization but it can inhibit matrix absorption. It has been also noticed

Fig. 1. *Contemporary pulsed electromagnetic field (PEMF) device.*
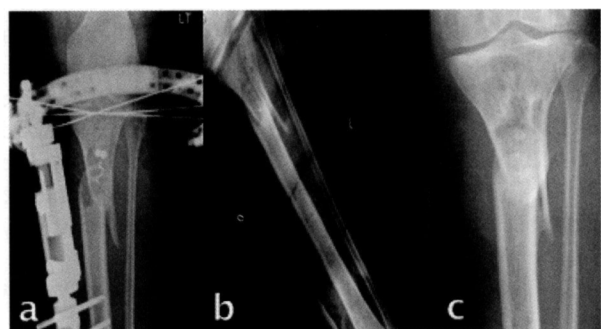
Fig. 2. *a) Open tibia fracture treated initially with external fixation, b) Introduction of pulsed electromagnetic field device (PEMF) 7 months after injury due to delayed union, c) successful result achieved 4 months afterwards.*

in osteoblast-like cultures that PEMF application could affect the expression of genes c-myc and c-fos, which are responsible for cellular proliferation and differentiation (21). Culture of animal bone marrow cells was further revealed that low frequency PEMF might both enhance (approximately 50%) and suppress (approximately 27%) the formation of osteoclast-like cells, depending on the induced electric field intensity (22). This observation casts some light into the exact wavelength and intensity that should be delivered at the bone area for achieving optimal results.

Another possible mechanism through which PEMF can enhance fracture healing is the acceleration of intramedullary angiogenesis, as indicated by a significant increase in the expression levels of angiopoietin-2 and fibroblast growth factor-2 in mice models (23). Recent data has shown that the application of PEMF may also induce angiogenesis through a paracrine angiogenic mediator other than VEGF-alpha (24). Furthermore and according to animal model studies, PEMF has vasomotor effects as it could cause significant arteriolar vasodilatation in a few minutes after its application (25).

PEMF could also have a biomechanical impact on bone structure. Three-point bending tests suggest that PEMF improves the mechanical properties of diabetic bone and specifically the load to failure and stiffness(26). Computised tomographic analysis has demonstrated as well that diabetes-induced bone architecture deterioration is partially reversed by PEMF.

CLINICAL IMPLICATIONS

As opposed to other methods of non-invasive augmentation of fracture healing, such as low-intensity pulsed ultrasound (LIPUS), PEMF has not been assessed thoroughly in robust studies of high methodological quality (7). Despite the relative scarcity of well-organized randomized controlled trials, many in vivo and in vitro studies highlight the method's potential usefulness (6). Particularly in terms of clinical practice, the efficacy quoted in treating long bone non-unions has been reported to range between 64% and 87% (Figure 2). The method seems to be also effective in undisplaced scaphoid fracture non-unions and mandibular fractures. Infection, a screw in the fracture gap, a gap of more than 5 mm and inadequate immobilization can be responsible for treatment failure (27). On the other hand, weight-bearing status, gender, whether the fracture is open or closed and whether the fractured bone is long or short, don't seem to have a statistically significant effect to treatment success. However and according to latest meta-analysis, the available clinical evidence is inefficient to conclusively suggest a clinical benefit of the method on the management

of bone non-unions (5).

Recent reports have recently also emerged indicating the potential effect of PEMF in the treatment of osteochondral traumatic defects (28). Although relevant studies are still performed in vitro, it seems that PEMF along with the application of calcium phosphate grafts could promote hyaline cartilage formation and may be considered an adjuvant therapy for the management of the these lesions.

A meta-analysis, which pooled the data from eleven studies, showed that PEMF resulted in a non-significant increase of healing rate of long bone non-unions or delayed unions (5). A potential problem with the meta-analysis was that the included studies used different settings of PEMF and they set different endpoints.

SUMMARY

PEMF can be considered an adjuvant, safe and non-invasive method for the treatment of long bone delayed unions or non-unions. Its efficacy seems to vary significantly amongst different reports while patient or fracture related variables could not be clearly associated with the success of the method. What is however clearly evident from the existing literature, is that PEMF exerts its beneficial effect on fracture biology through an impressive wealth of mechanisms and pathways, some of them depending on the characteristics of the applied wavelength and on the duration of treatment. More randomized controlled trials with a high number of patients are required to clarify the cost-effectiveness of the method for the treatment of delayed unions and non-unions.

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