The Role Of Electrical Stimulation In Fracture Healing

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Abstract

Introduction: Current methods of fracture care use various adjuncts to decrease time of fracture union, improve fracture healing, and enhance functional recovery. Electrical stimulation (ES), one of such modalities, has shown positive results in management of both fracture and soft tissue injuries. Material & MethodsA search of PubMed, Medline, CINAHL, and Embase databases was performed using the following keywords 'Electrical stimulation' and 'fracture healing'. 30 studies detailing the use of ES in fracture and soft tissue healing were identified, and their bibliographies thoroughly reviewed to identify further related articles. This review identified and summarized 30 studies which demonstrated the use of ES in fracture healing.In this review, preclinical, animal and human studies were separately reviewed to thoroughly understand the evolving role of ES in fracture healing process. This review also examines studies on signal transduction at the membrane level and on stimulation of growth factor synthesis.Exclusion Criteria: Studies not in English language, review articles, case reports, letter to editors and results published as abstracts only were excluded from this study. Conclusions: Currently most fractures affected by delayed union and non-union are treated with surgical fixation with or without bone graft. ES is an alternative, less invasive form of treatment which has shown great potential in management of these complicated fractures. Various human randomised clinical and animal studies have shown ES to improve fracture healing time. The complexity of the mechanisms by which ES produces its effect has also been studied by in-vitro studies. In the future, ES will play a significant role in the management of large scale bone defects/fractures.

INTRODUCTION

Based on the fact that bone tissue manifests electric potentials both in normal and pathological states [1], electrical stimulation has been employed to induce osteogenesis in clinical studies since 1812, when a successful treatment of the tibial nonunion with direct current was documented.[2] Especially after the discovery of electromechanical properties of bone in the 1950s [3] the development of this treatment method as an adjunct to osseous healing was accelerated both in theoretical and experimental ways. Since then, three major forms of electrical stimulation techniques have been devised for clinical use: (a) direct current (DC) using electrodes implanted in defect site; (b) capacitively coupled (CC)electric field using skin electrodes placed about the bone site to be stimulated; and (c) inductively coupled electromagnetic field (IEMF)using time-varying magnetic field.[4]

Since its inception in the early 80's, electrical stimulation has gone a long way in fracture care, however its global usage is still limited to few centers.

This review, explores the historical development of ES, the understanding of the electrical properties of bone, mode of action of ES, available evidence and studies on the role of ES in fracture healing.

MATERIAL &METHODS

A search of PubMed, Medline, CINAHL, and Embase databases was performed using the following keywords 'Electrical stimulation' and 'fracture healing'. Studies detailing the use of ES in fracture and soft tissue healing were identified, and their bibliographies thoroughly reviewed to identify further related articles. This review identified and summarized 30 studies which demonstrated the use of ES in fracture healing.

In this review, preclinical, animal and human studies were separately reviewed to thoroughly understand the evolving role of ES in fracture healing process. This review also examines studies on signal transduction at the membrane level and on stimulation of growth factor synthesis.

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HISTORY OF ELECTRICAL STIMULATION ON BONE

Nonunions and delayed unions can be the most frustrating and unforeseen complications of foot surgery and fracture management. Understanding the principles of bone healing and the use of proper internal fixation techniques can considerably assist in managing this difficult complication. The role of electricity as an aid in bone healing has been realized since 1812, when a shock of electrical fluid was used to treat a tibial non-union[7]. Later Boyer[8], Duchene, [9] Garratt, [10] Lente, [11] and Mott[12] all used various forms of electrical stimulation as augmentation in bony repair. An understanding of the concept was not fully developed and illustrated until 1953, when Yasuada, [1314] described piezoelectric properties of bone in detail. Piezoelectricity, simply stated, is a charge that is generated whenever stress is applied to a material (living or dead), in this case, bone.[1415] The positive effects of electricity on collagen and bone healing have been studied in detail by Fukada and Yasuda.[1617] This research on electrical potentials show that bone under compression is negatively charged and produces bone. Bone under tension produces a positive charge and causes bone resorption. Becker and Basset [18] stated that electrical potentials could not be piezoelectric alone because the electrically charged bone is not seen as an immediate response but is delayed. This indicated that the potential must be relying on cellular or ionic response to produce a charge. It was determined that a charge generated by living bone is different than that produced by dead bone. In 1964, Basset et al[19] reported that bone is most electronegative in areas of growth, such as fractures and epiphyseal plates. In these bioelectric properties he found that bone is most electronegative at the cathode end of an electrical current. Jahn[20] concluded in 1968 that live tissues have a secondary source of electricity from the migration of inorganic materials within bone. He further stated that calcium and phosphate attract to the cathode and sodium and chloride ions migrate to the anode side. In 1971, Friedenberg,[21] capitalized on this concept by applying a direct current to a non-union of a medical malleolar fracture. In 1981, Brighton[22] undertook the first multicenter study on the use of direct current in the treatment of nonunions. In his study of 178 nonunions, 149 (83%) achieved bony union with use of direct electrical stimulation.[22] since that time, numerous modifications of electrical stimulation have been used to assist in bone healing. Direct current, indirect current, and pulsing magnetic fields are the three most studied modalities in electrical stimulation.[23242526]

ELECTRICAL STIMULATION OF BONE

Electrical stimulators have evolved with indications for use in a variety of pathological bone states. To date, bone stimulators have been used to augment open reduction with internal and external fixation.[13] Osteogenicity of bone grafts have been assisted by the use of electrical stimulation.[27] Additionally, electrical stimulation has shown to be effective in treating infected nonunions.[28] Bone stimulators also assist in healing failed arthrodeses.[29] More recently, the use of bone stimulators have shown promise in the treatment of disuse osteoporosis.[30] Bone stimulation has come of age in the treatment of neuropathic arthropathy when conventional therapy has failed. Bone stimulation has also been shown to be effective in the treatment of osteonecrosis.[313233]

Bone stimulators have been classified into three basic categories: (1) invasive, (2) semi-invasive, and (3) noninvasive.[34] Bone stimulators function by electromagnetic stimulation, continuous and pulsed direct current, and capacitative coupling of electrical fields.[35]

INVASIVE BONE DEVICES

Invasive bone stimulators are implantable devices that provide direct current by using a generator that is implanted into the fasia of the lower leg. The cathode, which delivers energy to the bone, is placed directly into the nonunion defect. A micro connector attaches the cathode to the generator through a subcutaneous tunnel. This type of stimulator requires cast immobilization and management with nonweightbearing or weight bearing as the clinician deems necessary. Invasive devices can be used concurrently with bone grafts and can provide a synergistic effect of bone growth.[353613] These devices can also be used in the presence of active infection, although this is generally discouraged. Complications include infection, tissue reaction, and superficial soft tissue discomfort caused by protrusion of the device. Implantable devices pose other threats, such as lead breakage, limited battery life, potential battery leakage, and battery malfunction. Therefore, because of the effectiveness and availability of other noninvasive modalities, the use of invasive bone stimulation has fallen out of favour.

SEMI-INVASIVE DEVICES

The semi-invasive bone stimulation technique involves a direct current applied to a non-union through a Teflon coated stainless cathode that is inserted percutaneously into the site of the non-union. The cathode must be anchored to bone or it may dislodge. Up to four electrodes can be placed at the site, depending on the pertinent anatomy and the size of the bone

defect.[34] The self-adherent anode is placed anywhere on the surface of the skin and is attached to a power pack that is embedded in an applied cast. A nonweightbearing cast must be worn at all times to prevent motion, which can cause the cathode to break or dislodge from the non-union site.

Certain benefits and disadvantages exist to this technique of bone stimulation. Its benefits is that it requires minimal surgical dissection because the cathode is placed percutaneously and it uses a direct current, which can average 20 microamperes per cathode.[34] Disadvantages include skin irritation caused by the self-adherent anode pad which must be changed every other day by the patient.

NON-INVASIVE DEVICES

Non-invasive bone stimulators are of two general types: (1) capacitative and (2) inductive coupling. Capacitative stimulators consist of a unit with a power source (usually a 9-volt battery) and two electrode disks. The disks are attached directly to the skin on each of the non-union and a bivalved cast is applied in order to allow access to the electrodes.[34] The stimulator with its power source can be incorporated into the cast or attached to the cast with either a removable Velcro strap or a clip. The unit is then connected to the electrodes. Capacitative stimulators function to produce an internal electrical field at a frequency of 60 kilohertz (KHz). In this way, they do not require a high-voltage power source.[37] The ideal operating current level is between 5 and 10 milliamperes. Most units require between 12 and 20 weeks of use, 24 hours a day, to achieve healing. The advantages to the capacitative variety of bone stimulator are numerous. There is no pain or surgery involved with their application. Many have alarms incorporated into them that sound if there is inadequate electrode-to-skin contact or if the battery is not providing an acceptable current level. Also, a number of insurance companies reimburse for their use with nonunions because several studies point out their efficacy in this situation.[3839] In addition, they may be used conveniently by patient at home. Finally, in most cases the patient is allowed to bear weight on the casted extremity, unless excessive motion is present. There are a few disadvantages to the use of capacitative stimulators. This includes skin irritation from the electrode disc, constant monitoring to ensure an adequate battery level, and the requirement that the patient remain complaint throughout the relatively long regimen of treatment.

The second type of non-invasive bone stimulation is inductive coupling. It uses pulsed electromagnetic fields (PEMFs) to produce an inductive coupled electromagnetic field at the site of non-union. Bone induction is stimulated through the PEMF influencing fibro cartilage to initiate calcification.[37] This system consists of two external coils that are placed parallel to each over the non-union site. As the current begins to flow through the coils, electromagnetic fields are produced. These fields expand outward at right angle from the coil bases and bone is thereby penetrated.[24]

The advantage of inductive coupling mirrors those of capacitive coupling. In addition, many inductive coupling devices include an internal memory that records the frequency and duration of patient use, thereby monitoring patient compliance.[37] A disadvantage to inductive coupling is that the use of internal plate fixation could shield the fracture gap from the PEMF-generated field. In addition, it may also be a disadvantage because the patient may remove the unit at their discretion and interrupt the treatment.

The future of non invasive bone stimulators appears promising. Advantages, such as ease of use, lack of complications, and high healing rates, far outweigh potential disadvantages and make these devices valuable tools for the treatment of non-union.

MODE OF ACTION OF ELECTRICAL STIMULATION

ES has been shown to affect bone healing both by increasing growth factors and modulating cell membrane.

A) Increased expression of growth factors: ES enhances several growth factor release at fracture site. (Table 1) Various growth factors have been implicated in the positive effect of ES

Figure 1

Table 1: Regulation of growth factors by ES.

Study	Year	Technique	Model	Result
Zhuang et al(38)	1997	CC	MC3T3 osteoblast	↑ proliferation ↑ TGF-β_1 Mrna
Bodamyali et al(39)	1998	IC	Osteoblasts	↑proliferation,↑BMP-2,-4 mRNA
Nagai and Ota(40)	1994	IC	Osteoblasts	↑ BMP-2,-4Mrna
Yajima et al(41)	1996	IC	Osteoblasts	↑ BMP-4,-5,-7 MRNA
Aaron et al(42)	1999	IC	E.G. vivo (Endochondrial osteoblast)	↑ differentiation,↑TGF-β_1 Mrna +protein
Lohmann et al(43)	2000	IC	MG63 osteoblasts	↑ differentiation, ↑ TGF-β_1
Guerkov et al(44)	2001	IC	Human nonunion cells	↑ TGF-β_1
Aaron at al(45)	2002	IC	E.O.in vivo	↑ differentiation,↑ TGF-β_1
Lohmann et al(46)	2003	IC	MLO-Y4 osteocytelike cells	↑ TGF-β_1,PGE_2

Electrical stimulation has been shown to up regulate transforming growth factor beta (TGF-) mRNA, BMP, PGE2,

ES upregulated TGF-1 protein synthesis and mRNA expression coincident with increases in extra-cellular matrix protein synthesis and gene expression in an in vivo model of endochondral bone formation.[4245] Regulation of protein synthesis occurred in a dose-dependent manner in terms of both amplitude and duration of exposure. In response to ES, TGF-1 mRNA levels increased 68%, the active protein 25% and number of immunopositive cells 119% compared with control tissues.[42] ES treatment enhances chondrogenesis, endochondral calcification, and the normal physiologic expression pattern of TGF-1[45]

Enhancement of growth factor synthesis in response to Electrical stimulation demonstrated an increase in insulin-like growth factor II (IGF-II) mRNA and protein and suggested that IGF-II may in part mediate proliferation of osteoblast-like cells.[47] These results are similar to those observed in response to mechanical strain, and the stability of the signaling pathways suggests that growth factor synthesis serves to amplify electrical stimulation.[48]

B) Interaction at the cell membrane: With electric current, the induced electric fields are considerably weaker than the levels required to depolarize cell membranes and, therefore, the biological activity of these fields most likely depends on amplification mechanisms that occur during transmembrane coupling. Probable sites of amplification are transmembrane receptors (Table 2). In fact, it was demonstrated that the effects of electrical stimulation was mediated at the cell membrane either by interference with hormone receptor interactions or by blocking of receptor-adenyl cyclase coupling.[49]

The first demonstration of receptor-mediated signal transduction described the interactions of ES and parathyroid hormone (PTH) receptors.[49] Normally, PTH increases in cyclic adenosine monophosphate activity in bone cells. However, in the presence of ES, this effect was abolished. The field blocked the inhibitory effects on collagen synthesis by PTH but not by 1, 25 dihydroxy vitamin D_3, supporting the hypothesis that ES acts through membrane receptors. Further studies suggested that the effects of ES on PTH signaling were mediated through conformational changes in the transmembrane portion of the PTH receptor .[50]

Figure 2

Table 2: Receptor modulation

Study	Year	Technique	Model	Receptor
Luben et al(49)	1982	IC	Osteoblasts	PTH
Cain et al(50)	1987	IC	Osteoblasts	PTH
Hiraki et al(51)	1987	IC	Chondrocytes	PTH
Brighton and McCluskey(52)	1988	CC	Osteoblasts	PTH
Bourguignon et al(53)	1989	DC	Fibroblasts	Insulin
Cossarizza et al(54)	1989	IC	lymphocytes	IL-2
Cho et al(55)	1994	AC	fibrosarcoma	Transferrin,LDL
Fitzsimmons et al(56)	1995	IC	TE-85 osteoblasts	IGF-2
Shankar et al(57)	1998	IC	osteoblasts	Calcitonin
Varani et al (58)	2002	IC	neutrophils	Adenosine A_{2A}

In chondrocytes, by contrast, ES enhanced the cAMP response to PTH.[51] In an osteoblast culture model, a CC field decreased the cAMP response to PTH and desensitized osteoblasts to PTH.[52] Studies with human fibroblasts have demonstrated an increase in calcium translocation and the number of insulin receptors in response to an electric field.[53] These studies suggest that electric fields trigger the opening of voltage-sensitive calcium channels followed by an increase in intracellular calcium. Inductively coupled fields stimulate lymphocyte proliferation by enhancing the use of IL-2 and the expression of IL-2 receptor.[54]

These studies demonstrated that electric and electromagnetic fields can affect ligand binding and alterations in the distribution and activity of receptor populations, thereby modulating transmembrane signalling.[596061]

The evidence so far

This review will explore the preclinical, animal and human studies.

PRECLINICAL STUDIES

Numerous in vitro and in vivo studies have shown that appropriately configured electric energy stimulates the synthesis of extra-cellular matrix proteins. This increased synthesis is reflected in healing fractures and nonunion as enhanced bone repair.

STUDIES

Studies have demonstrated that cells involved in bone formation, particularly endochondral bone formation can be stimulated by appropriately configured electric fields at several phases in their cell cycle. Cell responses depend upon the predominant activity of the cell population (e.g., proliferation in pre-confluent cultures or matrix synthesis in post-confluent cultures). Osteoprogenitor cells of bone marrow or fracture callus origin respond to electrical stimulation by increasing their synthesis of extra-cellular matrix molecules. Bone marrow cells in diffusion chambers have been stimulated to synthesize cartilage and undergo endochondral calcification by demineralized bone matrix or DC stimulation[62] A significantly greater number of electrically stimulated cultures exhibited chondrogenesis and calcification than did controls. Fracture callus cells harvested from healing closed rat tibial fractures significantly increased thymidine incorporation during proliferation in response to DC electric stimulation.[63]

ANIMAL STUDIES

The effects of electrical stimulation have been studied in several animal models. Studies have examined repair of bone defects, fresh fractures and osteotomies, and fractures nonunion (Table 3). Experimental models of bone repair exhibited enhanced cell proliferation calcification, and gain of mechanical strength when stimulated with DC fields.[6465] CC stimulation has been reported to improve mechanical strength of experimental fracture repair and healing osteotomies.[6667] Several studies using ES stimulation have demonstrated increased calcification and enhanced radiographic and mechanical strength in healing bone.[6869] Exposure to ES has shown to enhance callus formation and mechanical parameters of healing in osteotomies.[70]

Figure 3

Table 3: Stimulation of osteogenesis in animal long bone models

Study	Year	Model	Technique	Stimulation
Peterson et al(65)	1982	Rabbit fibula delayed union	DC	Accelerated union
Brighton et al(66)	1985	Rabbit fibula osteotomy	CC	Accelerated union
Bassett et al(68)	1982	Dog radius osteotomy	IC	Accelerated union
Fredericks et al(71)	2000	Rabbit tibia osteotomy	IC	Accelerated union
Fredericks et al(72)	2003	Rabbit tibia osteotomy	IC	Accelerated union
Inoue et al(70)	2002	Dog tibia osteotomy	IC	Accelerated union

The volume of periosteal callus, new bone formation, and the normalized maximum torque and torional stiffness were significantly greater at 6 weeks in ES-treated osteotomies compared with untreated control osteotomies. In a study focusing on the dosimetry of ES stimulation in experimental osteotomies, dose was expressed as daily exposure duration.[71] Osteotomies treated with ES for 60 minutes/d achieved intact torsional strength by 14days after osteotomy, compared with 21 days for osteotomies treated for 30 minutes/d, and 28days in the untreated control group. Other dosimetry studies, examining daily exposure over 0.5, 3, or 6 hours per day, with a 6-hour stimulation being most effective.[72]

HUMAN STUDIES

The electrical enhancement of human fracture healing started in 1968 and was inspired by animal experiments in Japan and America.[7677787980] A study done by Torben et al[81] showed twenty-eight patients with tibial fractures treated with osteotaxis with the Hoffmann apparatus were electrically stimulated through bone screws. Forty-three other patients with tibial fractures treated with osteotaxis with the Hoffmann apparatus and no electricity constituted the control material. X-ray examination was performed every month. The electrical treatment was terminated when the fracture had attained a certain degree of stiffness. The stiffness of the fracture was determined by a mechanical measuring bridge mounted on the Hoffmann apparatus by which the fracture was loaded in bending by a spring balance. The desired degree of stiffness at which the electrical stimulation was discontinued was equivalent to clinical stability for each fracture.[828384]

Statistical analysis revealed 30% acceleration in healing in the electrically treated group. The stimulated group required an average of 2.4 months to achieve clinical stability or the

desired degree of stiffness the tibia via the Hoffmann apparatus. The control group required 3.6 months to achieve the same degree of stiffness. This difference between the experimental and control groups was highly significant ($p<0.001$). Other studies using electrical stimulation with DC or CC techniques have shown encouraging results in fresh fractures and osteotomies. (Table 4).

Figure 4

Table 4: Clinical stimulation of osteogenesis

Study	Year	Model	Technique	Result
Borsalino et al(73)	1988	Femoral osteotomy	IC	Accelerated union
Mammi et al(74)	1993	Tibial osteotomy	IC	Accelerated union
Triana et al(75)	1999	Tibial osteotomy	IC	Accelerated union

CONCLUSION

Electrical stimulation signal connective tissue cells about the biophysical demands of their physical environment and the adequacy of the extracellular matrix to meet these demands. Muscle, ligament, bone and cartilage all respond to electrical stimulation and these biophysical agents have been applied in therapeutic contexts. Many studies have observed that ES up regulates growth factor mRNA levels and protein synthesis, enhancing the synthesis of extra-cellular matrix proteins and accelerating tissue repair. ES produce sustained increases in growth factor concentrations at local sites of repair, making them useful for multiple applications in clinical repair and tissue engineering.

Over the past 15 years, investigations have begun to clarify how cells respond to biophysical stimuli by means of transmembrane signaling and gene expression for structural and signaling proteins. Different cell types and cell cycle positions, as well as the configuration and dose of electrical input, may determine which transmembrane signaling mechanisms are activated.

Several studies have implicated factitious receptor activation or blockade as key mechanisms. Subsequent studies will need to address the relationship of receptor interactions to changes in phenotypic expression of relevant cells, especially as regards extracellular matrix synthesis, in repair.

Electric and electromagnetic fields regulate extra-cellular matrix synthesis and stimulate repair of fractures and nonunions. Studies of electric and electromagnetic fields suggest they (1) regulate proteoglycan and collagen synthesis and increase bone formation in models of endochondral ossification, (2) accelerate bone formation and repair, (3) increase union rates in fractures previously refractory to healing, and (4) produce results equivalent to bone grafts. Electric and electromagnetic fields regulate the expression of genes in connective tissue cells for extra-cellular matrix proteins, which results in an increase in cartilage and bone. They also increase gene expression for and synthesis of growth factors, which may be an intermediary mechanism of activity and may amplify field effects through autocrine and paracrine signaling.

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