Electrical Stimulation in Bone Healing: Critical Analysis by Evaluating Levels of Evidence

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Objectives: Direct current, capacitive coupling, and inductive coupling are modes of electrical stimulation (ES) used to enhance bone healing. It is important to assess the effectiveness of ES for bone healing to ensure optimization for clinical practice. This review aims to examine the level of evidence (LOE) for the application of ES to enhance bone healing and investigate the proposed mechanism for its stimulatory effect.

Methods: MEDLINE and EMBASE searches were conducted to identify clinical and in vitro studies utilizing ES for bone healing since 1959. A total of 105 clinical studies and 35 in vitro studies were evaluated. Clinical studies were assigned LOE according to Oxford Centre for Evidence Based Medicine (LOE-1, highest; LOE-5, lowest).

Results: Direct current was found to be effective in enhancing bone healing in spinal fusion but only LOE-4 supported its use for nonunions. Eleven studies were retrieved for capacitive coupling with LOE-1 demonstrating its effectiveness for treating nonunions. The majority of studies utilized inductive coupling with LOE-1 supporting its application for healing osteotomies and nonunions. In vitro studies demonstrate that ES enhances bone healing by changes in growth factors and transmembrane signaling although no clear mechanism has been defined.

Conclusion: Overall, the studies, although in favor of ES application in bone repair, displayed variability in treatment regime, primary outcome measures, follow-up times, and study design, making critical evaluation and assessment difficult. Electrical stimulation shows promise in enhancement of bone healing; however, better-designed clinical studies will enable the optimization for clinical practice.

When bone encounters injury, it undergoes a unique process of self-regeneration to form new bone to heal itself. However, in 5% to 10% of patients this process is disrupted which leads to delayed bony healing or nonunions. This is of great consequence to the clinician as nonunions pose a huge burden on the individual in terms of continuing pain and disruption to their daily activities and increases the expenditure of medical resources.
Therefore, finding effective methods to enhance bone healing has been of great research interest, one of which is the use of electrical stimulation (ES).

In the early 1950s, Fukada and Yasuda\(^2\) demonstrated that when stress is applied to bone in such a way to cause deformity electrical potentials are generated, in areas of compression the bone was electronegative and caused bone resorption, whereas areas under tension were electropositive and produced bone. Therefore, subsequent developments were based on the idea that stimulating these endogenous electric fields using an ES device would enhance bone healing.\(^3\)

There are 3 methods of administering electrical current to bone (Fig 1), which have been used in clinical practice (Table 1) including direct current (DC), capacitive coupling (CC), and inductive coupling (IC). In several models, DC involves invasive surgical placement of electrodes.\(^1\) A cathode is placed at the site of the bone defect with an anode in the soft tissue nearby.\(^3\) Osteogenesis has been shown to be stimulated at the cathode using currents between 5 and 100 μA and varying the number of electrodes between 2 and 4.\(^3\) Since the stimulator is implanted, the therapeutic treatment is continuous but is removed once healing has occurred. Direct current is advantageous as patient compliance is minimal; however, the technique is invasive with risk of infection, tissue reaction, and soft tissue discomfort.\(^4\)

| Company | Device Name | Electrical Type | Description of Product |
|----------|-------------|----------------|------------------------|
| Orthofix | Physio-Stim Lite | PEMF | Noninvasive device for nonunions for both short and long bones |
| Orthofix | Cervical and Spinal-Stim Lite | PEMF | Noninvasive device for spinal fusion |
| Biomet  | EBI bone healing system | PEMF | Noninvasive device for nonunion fractures, failed fusions and congenital pseudarthrosis |
| Biomet  | OrthoPak 2 bone growth stimulator | CC | Noninvasive device for nonunion fractures |
| Biomet  | SpinalPak bone growth stimulator | CC | Noninvasive device for spinal fusion for one to two levels |
| Biomet  | OsteoGen and OsteoGen-D | DC | Surgically implanted device for nonunions and may also be used as an adjunct to internal/external fixation and autograft |
| Biomet  | SpF implantable spine fusion stimulator | DC | The SpF-2T and SpF-4T are indicated for spinal fusion of one or two levels, while the SpF-XL and SpF-XL IIb are indicated for fusion of three or more levels |

\( ^{*}\)DC indicates direct current; CC, capacitive coupling; FDA, Food and Drug Administration; PEMF, pulsed electromagnetic field.

Capacitive coupling involves noninvasive placement of 2 cutaneous electrodes on opposite sides of the bone to be stimulated.\(^3\) A power source, usually attached to the patients cast is then connected to the electrodes forming an electrical field within the fracture site. Using potentials of 1 to 10 V at frequencies between 20 and 200 kHz creates electric fields of 1 to 100 mV/cm, which has shown to be efficient for bone stimulation.\(^5\)
Figure 1. The three methods of administering electric stimulation are shown in this diagram. (a) Direct current (DC): A cathode is implanted at the fracture site which is attached to either a subcutaneous power source or an external power source to generate an electric field at the fracture site. (b) Capacitive coupling (CC): Two capacitive coupled electrodes are situated on the skin on either sides of the fracture site. An external power source is then attached to the electrodes, which induces an electric field at the fracture site. (c) Inductive coupling (IC): An electromagnetic current carrying coil is placed on the skin overlying the fracture site, which is attached to an external power source. The coil generates a magnetic field, which induces an electrical field at the fracture site.

Inductive coupling enhances bone healing by using pulsed electromagnetic field (PEMF) stimulation. Inductive coupling is formed by placing 1 or 2 current-carrying coils on the skin over the fracture site. As current flows through the coils, an electromagnetic field radiates at right angles to the coil base but within the fractures site. The electrical field that is formed varies in size because of the type of tissues at the fracture site and the properties of the applied magnetic field. Electromagnetic fields varying from 0.1 to 20 G have been used to create an electrical field at the fracture site of 1 to 100 mV/cm. Inductive coupling and CC are beneficial treatment options for patients as they are noninvasive, painless, and surgery free. Furthermore, they can be easily and conveniently used by patients at home and in most cases patients are allowed to bear weight.

Electrical stimulation has shown to be effective in aiding bone healing in a variety of orthopedic conditions such as aiding internal and external fixation, enhancing delayed or nonunion fractures and osteotomies, improving the efficacy of bone grafts, treating fresh fractures, and aiding femoral osteonecrosis. However, the mechanism by which ES has its stimulatory effect in enhancing bone healing remains unclear.

Therefore, we performed a systematic review to address (1) what is the proposed mechanism of action for DC, IC, and CC (2) what is the level of evidence (LOE) supporting the use of DC, CC, and IC in enhancing bone healing for orthopedic conditions.
MATERIALS AND METHODS

An electronic search of the MEDLINE through PubMed and EMBASE databases was performed to identify all relevant clinical studies that utilized ES for the treatment of bone healing from 1959 to 2009 by 2 independent reviewers (M.G., A.B.). Over the same time period, all in vitro studies that assessed the mechanism behind ES were identified. Keywords with Boolean operators used in the search included the following: “bone healing” or “nonunion” or “fracture healing” or “fracture ununited” and ES or electrical therapy or electromagnetic field stimulation or pulsed electromagnetic field stimulation. Articles were considered eligible if included the following inclusion criteria: (1) inclusion of a treatment arm receiving ES of DC, CC, or PEMF to impact bone healing; (2) evaluated the use of ES treatment for long bone and non–long bone healing (spine, scaphoid, and clavicle); (3) evaluated the use of ES to impact bone healing including the effect of ES on enhancing nonunion or malunion or delayed union, spinal fusion, pseudoarthrosis, osteotomies, fresh fractures, and femoral osteonecrosis; and (4) in vitro studies that evaluated the mechanism behind DC, CC, or PEMF. Case reports and expert opinions were included to that all related studies were identified and reviewed. Articles were excluded if they were (1) not published in English, as the reviewers would not fully understand the manuscript; (2) animal studies as these reports only show the end result whether there has been an increase or decrease in bone development and do not give details for the mechanism of ES; (3) mode of ES other than DC, CC, or IC; and (4) review papers, editorials, publications on congress meetings, unpublished data, or letters to the editor. Review articles were only used to identify any other relevant articles.

Clinical studies were then grouped by the primary method of ES used (DC, CC, or IC) and then assessed and assigned an LOE adapted from the Oxford Centre for Evidence Based Medicine (http://www.cebm.net/index.aspx?o=1025) to establish whether valid and reliable evidence supports the use of ES for bone healing. These levels, ranging from LOE-1 to LOE-5, are based on methodology and study design. In brief, these were how LOEs were assigned as follows: LOE 1 = randomized control trial; LOE-2 = cohort study; LOE-3 = case-control study; LOE-4 = Case series study; LOE-5 = expert opinion or case report.

The clinical studies were further evaluated for their study design and assessed for the direction of the main conclusion regarding the efficacy of the ES method used. To aid to this process, the following data were extracted from the clinical studies: (1) primary outcome measure, (2) assessment time—time over which ES was monitored, (3) ES treatment regime, (4) main findings, and (5) main conclusion drawn by the authors. A grade of recommendation was then assigned according to Oxford Centre for Evidence Based Medicine guidelines based on the findings for each mode of ES for different clinical situations (Table 2). In brief, the criteria used was as follows:

A = consistent level 1 studies
B = consistent level 2 or 3 studies or extrapolations* from level 1 studies
C = level 4 studies or extrapolations from level 2 or 3 studies
D = level 5 evidence or troublingly inconsistent or inconclusive studies of any level

*“Extrapolations” are where data is used in a situation that has potentially clinically important differences than the original study situation.
Table 2. Grade of recommendation for each mode of electrical stimulation for each type of bone healing diagnosis based on Oxford Centre Level of Evidence Recommendation.

| Mode of Electrical Stimulation | Direct Current | Capacitive Coupling | Pulsed Electromagnetic Field |
|-------------------------------|----------------|---------------------|-------------------------------|
| Spinal fusion                 | B              | A                   | A                            |
| Ankle/foot union              | C              |                     | C                            |
| Osteonecrosis of the femoral head | B       |                     | C                            |
| Nonunion                      | C              |                     | C                            |
| Osteotomy                     | B              |                     | C                            |
| Fresh fracture                | B              |                     | C                            |
| Congenital pseudoarthrosis    | C              |                     | C                            |

DC indicates direct current; CC, capacitive coupling; PEMF, pulsed electromagnetic field.

RESULTS

Mechanism of action of ES

The in vitro studies evaluated report that DC stimulates osteogenesis by an electrochemical reaction at the cathode ($O_2 + 2H_2O + 4e^- \rightarrow 4OH$) creating end products referred to as faradic products.\textsuperscript{13-22} The production of hydroxyl ions (OH) at the cathode are shown to lower the oxygen concentration and increase the pH.\textsuperscript{15} This environment prevents bone resorption and increase bone formation by increasing osteoblast and decreasing osteoclast action.\textsuperscript{15} A second faradic product hydrogen peroxide ($H_2O_2$) is also formed at the cathode,\textsuperscript{15} which enhances osteoclast differentiation.\textsuperscript{20} The resorption by the osteoclasts in turn triggers bone formation by the osteoblasts. The effect of $H_2O_2$ could also be due to its stimulatory action on vascular endothelial growth factor secretion by macrophages, which is important for angiogenesis in fracture healing.\textsuperscript{18} Evidence also shows that DCs’ stimulatory effect may be due to an increase in growth factor synthesis by osteoblasts, in particular bone morphogenetic protein (BMP)-2,6,7.\textsuperscript{19} Figure 3a shows a summary of DC-proposed mechanism of action.
Figure 2. Flow chart demonstrates the selection criteria and process employed in the study. CC indicates capacitive coupling; DC, direct current; ES, electrical stimulation; IC, inductive coupling.
The in vitro studies reviewed\textsuperscript{23-26} that use CC describe the main mechanism by which CC stimulates bone formation is by calcium translocation via voltage-gated calcium channels.\textsuperscript{23,24} This mechanism was proved when verapamil was administered to block the Ca\textsuperscript{2+} channels in osteoblasts treated with CC, as the cell proliferation consequently decreased.\textsuperscript{24} However, once the calcium voltage-gated channels are activated, this triggers an augmenting pathway. First, there is an increase in phospholipase A\textsubscript{2}, which raises prostaglandin E\textsubscript{2} synthesis.\textsuperscript{23} This then amplifies cytosolic Ca\textsuperscript{2+}, which increases intracellular calcium stores to activate the last step in the pathway, of enhancing the activated calmodulin levels.\textsuperscript{23} Activated calmodulin has been shown to promote cellular proliferation in bone by upregulating nucleotide synthesis and a wide array of enzymatic proteins, which enhances callus formation and maturation.\textsuperscript{23} Studies also report that CC enhances bone healing by the activation of growth factors, for example, mRNA expression of BMP-2,4,5,6,7\textsuperscript{25} and transforming growth factor-beta 1 (TGF-\textbeta\textsubscript{1}) is increased by osteoblasts stimulated by CC.\textsuperscript{26} Figure 3b shows a summary of CC-proposed mechanism of action.

Two mechanisms are described by which IC has its stimulatory effect.\textsuperscript{23,27-47} First, IC exhibits its effect on bone healing by increasing the calcium uptake of bone. This is achieved by inactivating its signal to parathyroid hormone (PTH)\textsuperscript{30,31} by preventing the store of cyclic adenosine monophosphate to build up, which is naturally associated with PTH stimulation and the expression of PTH on the cell surface membrane.\textsuperscript{32} Second, a key metabolic pathway for IC stimulation is the activation of intracellular calcium stores.\textsuperscript{23} These stores then increase activated calmodulin levels, which enhance osteoblast cell proliferation. This is the key difference to CC, where the activation of intracellular calcium is from an extracellular pathway.\textsuperscript{23} Thirteen studies\textsuperscript{35-47} reported that IC stimulates healing by upregulation of growth factor production including BMP-2,4,6,7, TGF-\textbeta\textsubscript{1}, and insulin growth factor-2 by osteoblasts. Figure 3c shows a summary of IC-proposed mechanism of action.

**LOE and efficacy of ES to enhance bone healing**

Direct current has been utilized to aid bone healing in spinal fusion, nonunions, delayed unions, and as an adjunct for promotion of bone healing in ankle surgery (Table 3)\textsuperscript{48-81}. Four studies supplied LOE-1 for utilizing DC in the treatment of spinal fusion. Direct current was found to be highly effective in the enhancement of failed spinal fusion and as an adjunct to spinal instrumentation.\textsuperscript{51} However, one study found no difference in fusion success after DC\textsuperscript{49} and another LOE-1 study showed no increase in lumbar fusion rates in patients older than 60 years after DC.\textsuperscript{48} Further LOE-2\textsuperscript{52} proved DC to be effectively employed in lumbar interbody fusion. Direct current has been effectively used as an adjunct in hindfoot fusion\textsuperscript{62} and revision ankle arthrosis nevertheless providing only a LOE-4\textsuperscript{67}. The use of DC for nonunion and delayed union is limited again by just LOE-4. LOE-2 supported the use of DC in osteonecrosis of the femoral head.\textsuperscript{12,53}

Capacitive coupling has been used to enhance bone healing in nonunions, delayed unions, and spinal fusion (Table 4)\textsuperscript{82-92}. Two LOE-1 studies utilized CC for the treatment of nonunions. The first study\textsuperscript{84} showed CC to be highly effective for treating long bone nonunion, but the second study used it for tibial stress fractures,\textsuperscript{82} finding no improvement in healing time. These findings were enhanced by an LOE-4 study where athletes with lower limb stress fractures were successfully treated with CC.\textsuperscript{86} Furthermore, LOE-4 showed that CC was effective in healing nonunions,\textsuperscript{87,89,90} whereas LOE-1 has shown CC to enhance lumbar spinal fusion.\textsuperscript{83}
Figure 3. The proposed mechanism of action of the different types of electrical stimulation methods. (a) Proposed mechanism for direct current (DC). Direct current lowers the oxygen level and increases the pH, which causes an increase in osteoblast cell proliferation. This in turn enhances callus formation and maturation, leading to bone healing. All 3 types of ES enhance growth factors. This in turn increase cell proliferation, which enhances callus formation and maturation, leading to bone healing and improved clinical outcome. (b) Proposed mechanism for capacitive coupling (CC). Capacitive coupling causes an increase in cytosolic calcium through voltage gated calcium channels. This then increases intracellular calcium, which in turn enhances activated calmodulin stores. Cell proliferation then increases, which enhances callus formation and maturation, leading to bone healing. (c) Proposed mechanism for inductive coupling (IC). Inductive coupling causes a direct increase in intracellular calcium, which in turn enhances activated calmodulin stores. Cell proliferation is increased, which enhances callus formation and maturation, leading to bone healing. BMP indicates bone morphogenetic protein; IGF-2, insulin growth factor 2; PTH, parathyroid hormone; TGF-β1, transforming growth factor beta 1; VEGF, vascular endothelial growth factor.
| DC study          | Level of Evidence | Study Design                              | Objective of Study                                                                 | Entry Requirements | Sample Size | Primary Outcome Measure                                      | Regime Treatment Regime | Assessment | Result                                     | Conclusion                                                                 |
|-------------------|-------------------|-------------------------------------------|-----------------------------------------------------------------------------------|--------------------|-------------|-------------------------------------------------------------|--------------------------|------------|-------------------------------------------|---------------------------------------------------------------------------|
| Andersen et al48   | 1                 | Multicenter randomized control trial      | Effect of DC on fusion rates after lumbar spinal fusion in patients older than 60 y | Older than 60 y    | 107         | CT + Dallas Pain Questionnaire and Low Back Pain Rating Index | 40 \( \mu \) A or 100 \( \mu \) A for 2 y | 2-y follow-up fusion rate by CT | 35% healing rate for active versus 36% in controls | DC stimulation was not effective in increasing fusion rates in this patient population |
| Jenis et al49      | 1                 | Randomized control trial                 | DC and PEMF in augmentation of lumbar fusion                                       | Undergoing lumbar spine fusion | 44 (22 PEMF/22 DC) | Bone mineral density/radiographic union                                      | Until union 1 y         | 35% excellent PEMF and 43% control and 32% DC | DC or PEMF does not significantly enhance fusion rate in instrumented lumbar arthrodesis |
| Kane50             | 1                 | Randomized control trial                 | Efficacy of DC in spinal fusion                                                   | Difficult patients: one or more previous failed fusions; a grade II or worse spondylolisthesis, a multiple-level fusion or the presence of another high-risk factor, eg, obesity | 28 control and 31 active | Radiographic union 5 \( \mu \) A, cathode \( \times 4 \) 24 hr a day for 18 mo | 18 mo 15/28 control patients compared with 25/31 active patients healed | 15/28 control patients compared with 25/31 active patients healed | DC increases healing rate for spinal fusion. This result is statistically significant \( (P = .026, \) one-tailed Fisher's exact test). |
| DC study | Level of Evidence | Study Design | Objective of Study | Entry Requirements | Sample Size | Primary Outcome Measure | Regime Treatment | Assessment | Result | Conclusion |
|----------|------------------|--------------|-------------------|--------------------|-------------|-------------------------|-----------------|------------|--------|------------|
| Rogozinski and Rogozinski\(^{51}\) | 1 | Randomized control trial | Test the efficacy of DC in instrumented fusion, especially regarding high-risk patient groups | Patients undergoing instrumented fusion, especially high-risk: smokers, previous back surgery, and multiple fusion levels | 94 active 94 control | Radiographic union | 24 daily 10 μA, cathode x2 | 20.5 mo average follow-up | 51/53 active groups and 35/41 control group had fusion | DC can improve fusion results for instrumented lumbosacral fusion as has been demonstrated in in-situ fusions |
| Meri\(^{52}\) | 2 | Comparative study | Efficacy of DC in treating interbody fusion rates, retrospective study | Undergone a posterior or anterior lumbar fusion and been followed up for 6 mo | 122 active and 103 retrospective control | CT and radiographic union | 5 μA, minimum of 24 wk | 3, 6, 12 and 24 mo | Significantly higher in active group (93% vs 75%) | Fusion rates increased by DC. Particularly striking were high-risk groups such as smokers (92% vs 71%), no internal fixation (91% vs 65%) and L4-L5 fusions (91% vs 59%). |
| Authors          | Study Design          | Study Objective                                                                 | Patient Details                                                                 | Follow-up Details                                                                 | Results and Conclusions                                                                 |
|------------------|-----------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Steinberg et al  | Randomized control    | Effectiveness of core decompression and bone grafting with and without electrical stimulation was compared to nonoperative treatment. | Avascular necrosis (AVN) of the femoral head; 116 hips with AVN; 42 decompression and grafting; 74 decompression, grafting and with DC; 55 hips with treated non-operatively. | Until union: Every 3 mo for the first year, each 6 mo for the second and third years, and yearly thereafter. DC showed less x-ray progression and achieved a better clinical score than hips with decompression and grafting alone. Decompression and grafting are safe and reasonably effective in retarding the progression of AVN but DC improves the results even further. |
| Steinberg et al  | Non randomized control| DC effect in aiding AVN decompression treatment.                                  | A number of hips were included with subchondral collapse (stage III), determined by the presence of a crescent sign with some flattening of the articular surface (stage IV). | Radiographic and modified Harris rating sheet; 22 decompression and DC; 11 decompression no DC; 48 nonoperatively. | 20 μA to 4 cathodes for 3 to 6 wk; 3,6,12 mo and then yearly onwards. DC did not change the results obtained with decompression and grafting alone. More data and longer follow-up will be required before definitive conclusions can be drawn, and we must continue our efforts to improve the management of avascular necrosis. |
| DC study | Level of Evidence | Study Design | Objective of Study | Entry Requirements | Sample Size | Primary Outcome Measure | Regime Treatment Regime | Assessment | Result | Conclusion |
|----------|------------------|--------------|-------------------|-------------------|-------------|------------------------|------------------------|------------|--------|------------|
| Torben65 | 2                | Case control study | Treatment of tibial nonunion with either osteostixis with the Hoffmann apparatus with or without DC | Tibial fracture treated with Hoffmann apparatus | 43 control and 24 active | Union—when achieve clinical stiffness | 40 μA—until achieved clinical stiffness | Monthly | 2.4 mo to union for control + 3.6 mo for control | The patients that received DC treatment experienced 30% acceleration in healing |
| Brighton et al44 | 4 | Case series | Efficacy of DC for long bone nonunions | Ununited fractures with no signs of healing signs on x-ray films for 3 mo | 80 | Radiographic union | 20 μA for 12 wk | 12 wk | 58/80 healed | DC effective in nonunion |
| Brighton55 | 4 | Case series | Efficacy of DC for tibia nonunion | Fractures open or closed | 130 | Radiographic union | 20 μA for 12 wks | 12 wk | 107/123 healed | DC successful in nonunion |
| Brighton et al56 | 4 | Case series | Efficacy of DC for long bone nonunion | Established nonunion, no evidence of healing on x-ray over last 3 mo | 57 | Radiographic union | 20 μA for 12 wk | 12 wk | 39/54 healed | DC effective treatment for nonunion |
| Brighton et al57 | 4 | Case series | DC efficacy in long bone nonunion and pseudoarthrosis | Pseudoarthrosis and nonunion average of 2.4 y | 29 | Radiographic union | 10 μA for 9 wk then increased to 20 μA for 12 wk | 12 wk | 15/24 union and 1/5 congenital pseudoarthrosis healed | Further laboratory and clinical experiments are required to define the true role of electrical stimulation in clinical practice |
| Study (Year) | Type | Condition | Treatment Duration | Healing Time | Notes |
|-------------|------|-----------|--------------------|-------------|-------|
| Connolly, 1981 | Case series | Long bone nonunion | DC efficacy in nonunions | 6 mo | 11/16 healed |
| Cundy and Paterson, 1990 | Case series | Long bone nonunion | Radiographic and clinical union | 6 mo | 38 Radiographic union, 20 µA for 12 wk |
| Day, 1988 | Case series | Long bone nonunion | Radiographic union | 6 mo | 3/12 healed, critical evaluation needed |
| Dwyer and Wickham, 1981 | Case series | Spinal fusion | Efficacy of DC in spinal fusion | 6 mo | 11/12 fusion, 20 µA for 12 weeks |

DC not effective in nonunions if indications are not fulfilled. Critical evaluation and clarification of indications are required if DC is to be effective. This 10-year review supports the long-term safety and effectiveness of DC in treating long bone nonunions.

The technique is simple and effective. Contraindication: excessive motion at the fracture site or active infection.

First report of DC effectiveness in spinal fusion.
Table 3. Continued

| DC study          | Level of Evidence | Study Design | Objective of Study                                      | Entry Requirements                                                                 | Sample Size | Primary Outcome Measure | Regime Treatment Regime | Assessment | Result       | Conclusion                                           |
|-------------------|-------------------|--------------|--------------------------------------------------------|-----------------------------------------------------------------------------------|-------------|-------------------------|-------------------------|------------|--------------|------------------------------------------------------|
| Donley and Ward62 | 4                 | Case series  | Efficacy of DC treatment for nonunion of the ankle and subtalar joints | High risk patient: Smoker, previous nonunion, osteonecrosis, history of infection, fracture type, and major medical problems | 13          | Radiographic and clinical union | Until union           | 1 y        | 11/13 healed | DC useful adjunct to rigid internal fixation and bone grafting for ankle and hindfoot fusions in high-risk patients |
| Esterhai et al63  | 4                 | Case series  | DC efficacy for humerus nonunion                       | Fractures without signs of healing over 3 mo by x-ray                              | 39          | Radiographic union      | 12 wk                   | Monthly after 12 wk treatment | 17/39 healed | Senile/disuse osteoporosis, synovial pseudoarthrosis, obesity, and osteomyelitis made treatment difficult; patient selection is critical |
| Heppenstall64     | 4                 | Case series  | DC in the treatment of tibia nonunions                 | Nonunion: no evidence of progressive healing on monthly serial roentgenograms obtained during a period of 3 mo | 40          | Clinical and radiographic union | 3 mo of 20 μA          | After 3 mo treatment | 34/40 healed | The results are equal to or better than those obtained by bone grafting; the method eliminates the complications of open bone operations |
| Reference | Type        | Design          | Participants | Methods                                                                 | Outcomes                                                                 | Findings                                                                 |
|-----------|-------------|-----------------|--------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Kucharzyk 66 | Low level case control prospective study | Instrumented high-risk lumbar fusions. 65 instrumented patients without stimulation were compared with 65 patients with instrumentation and DC | All patients underwent the same surgical procedure using spinal instrumentation (Rogozinski System) and posterolateral bone graft arthrodesis | Radiographs were clinical success Modified Smiley-Webster Scale   | Until fusion 10 d, 6 wk, 12 wk, 6 mo, 1 y, 2 y, and 3 y | Fusion success was 95.6% in the active and 87% in the control group. The results from using both instrumentation and DC in a high-risk pool of patients show higher rates of fusion and clinical success than in a similar pool that did not receive DC. |
| Midis and Conti 67 | Case series | DC efficacy as an adjunct to revision ankle arthrodesis aseptic nonunion and bone graft | Ankle arthrothesis in the patients was posttraumatic in 8 and rheumatologic in 2. | Radiographic and clinical union Minimal for 12.8 wk | 15 mo (range, 6-36 mo) 100% fusion at average 12.8 wk | All but one of these patients were satisfied with the outcome of this procedure. |
| Paterson et al 68 | Case series | Multicentered program on DC for stimulation of bone healing was by 30 Australian orthopedic surgeons | Ununited long bones fracture of at least 3 mo | Radiographic and clinical union 20 μA 3 mo but then increased to 6 mo | 3 and 6 mo 72 of 84 healed | The procedure is safe and simple, with a short hospital stay and low rate of complications. |
| DC study          | Level of Evidence | Study Design | Objective of Study                                                                 | Entry Requirements                                           | Sample Size | Primary Outcome Measure          | Regime Treatment Regime | Assessment       | Result         | Conclusion                                                                 |
|-------------------|-------------------|--------------|------------------------------------------------------------------------------------|--------------------------------------------------------------|--------------|---------------------------------|------------------------|-------------------|-----------------|---------------------------------------------------------------------------|
| Paterson et al69   | 4                 | Case series  | Treatment of congenital pseudoarthrosis with DC                                    | Congenital pseudoarthrosis of the tibia                      | 25 (27 sites)| Radiographic and clinical union  | 20 μA for at least 6 mo | Every 2 mo       | 20/27 healed    | DC shown to be effective in treating difficult problem of pseudoarthrosis |
| Tejano et al70     | 4                 | Case series  | To assess the effects of DC on fusion success, clinical outcome, and return to work in multilevel lumbar spinal fusion procedures | Multilevel procedures, pseudoarthrosis, revision, and Grade II or worse spondylolisthesis | 143          | Radiographic union              | 20 μA to 4 cathodes for minimum of 24 wk | Patients were assessed 3, 6, 12, 18, and 24 mo after surgery | Fusion success in the 118 patients was 91.5% | DC patients without instrumentation showed clinical and radiographic success higher than in recent studies without instrumentation and comparable with recent studies using instrumentation |
| Reference | Study Type | Study Design | Effect of DC | DC Dosage | Union Rate | Duration of Union | Fusion in | Comments |
|-----------|------------|--------------|--------------|-----------|------------|------------------|-----------|----------|
| Welch et al<sup>71</sup> | Case series | Examine the efficacy and safety of DC as adjunct to cervical arthrodesis | Para-axial cervical arthrodesis involving posterior spine fusion and instrumentation for instability | 20 | Radiographic and clinical fusion | Until union | Mean, 19 mo | Fusion in 15/16 at average time of 4.6 mo | The possible role and clinical utility of the DC in selected patients requiring cervical fusion, particularly at high risk for nonunion should be investigated. |
| Zichner<sup>72</sup> | Case series | Effect of DC in treatment of congenital and acquired nonunion of bone | Established nonunion, average duration of nonunion was 3.7 y (range, 10 mo-14 y) | 57 | Radiographic union | 20-25 μA for 6 mo for scaphoid, 1 y for long bone | 3 monthly intervals | Fusion in 53/57 fractures united, average duration at 5.3 mo | DC effective as an adjuvant treatment to fragment stabilization in hyporeactive and hypovascular or congenital pseudoarthrosis. |
| Brighton<sup>73</sup> | Expert opinion | NA | NA | NA | NA | NA | NA | DC successful, healing rate 60%-80% after 3-6 mo, 20 μA for 12 wk effective |
| DC study             | Level of Evidence | Study Design | Objective of Study                                                                 | Entry Requirements                                                                 | Sample Size | Primary Outcome Measure              | Regime Treatment Regime | Assessment | Result            | Conclusion                                                                 |
|---------------------|-------------------|--------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-------------|---------------------------------------|--------------------------|-------------|------------------|---------------------------------------------------------------------------|
| Cohen et al74        | 5                 | Case report  | Totally implanted DC stimulator for treatment of a nonunion in the foot            | 8 mo after attempted Lisfranc's joint fusion for Charcot arthropathy of the midfoot | 1           | Radiographic union                    | Until union              | At union    | Fracture healed | First report of DC treatment of a nonunion in the foot                   |
| Friedenberg et al75  | 5                 | Case report  | Efficacy of DC in medial malleolus nonunion                                        | Medial malleolus fracture non-weight bearing for 1 y + failed closed reduction     | 1           | Radiographic union                    | 10 μA for 9 wk          | 9 wk        | Fracture healed | Effective in medial malleolus fracture                                    |
| Janis et al76        | 5                 | Case report  | Treatment of DC in avascular necrosis of the talus                                 | Avascular necrosis of the talus and degenerative joint disease of ankle            | 1           | Radiographic union and clinical fusion| 14 wk                    | 14 wk and 1-y follow up | Fusion of talus DC created an osteogenic environment one of the factors that decrease the chance of a nonunion |
| Lavine and Grodzinsky77 | 5          | Expert opinion | NA                                                                                   | NA                                                                                 | NA          | NA                                    | NA                       | NA                      | NA                                            | The body of clinical evidence that has been produced to date suggests that electrical stimulation is valuable |
| Study                        | Study Type            | Efficacy of DC                                      | Congenital Pseudoarthrosis | Radiographic and Clinical Union | Time to Heal | Fusion in Both Cases of Congenital Pseudoarthrosis |
|------------------------------|-----------------------|-----------------------------------------------------|---------------------------|--------------------------------|--------------|-----------------------------------------------|
| Lavine et al\(^78\)          | 5 Case Report         | Efficacy of DC in congenital pseudoarthrosis        | 2                         | Radiographic and clinical union | 4 mo         | Fusion in both cases of congenital pseudoarthrosis |
| Paterson and Simonis\(^79\) | 5 Case Reports        | Treatment of congenital pseudoarthrosis with DC     | 6 (7 sites)                | Radiographic and clinical union | 20 μA for 3, 4, 6, and 8 mo | When DC removed 6/7 sites healed, mean time to heal 6 mo |
| Phieffer and Goulet\(^80\)  | 5 Expert Review       | NA                                                  | NA                        | NA                             | NA           | NA                                            |
| Steinberg et al\(^81\)      | 5 Review Expert Opinion | NA                                                  | NA                        | NA                             | NA           | NA                                            |

* DC indicates direct current; CC, capacitive coupling; FDA, Food and Drug Administration; NA, not applicable; PEMF, pulsed electromagnetic field.
Inductive coupling is extensively utilized for bone healing with 18 LOE-1 studies (Table 5). Three LOE-1 studies utilized IC for tibial nonunions. The earliest study showed no statistical difference in healing after stimulation, while later studies supported IC. Furthermore, LOE-4 demonstrated IC to be effective in enhancement of long bone nonunions. LOE-1 studies showed IC to be effective in enhancing healing of femoral and tibial osteotomies. LOE-1 proved IC ineffective for disuse of osteoporosis and bone formation during limb lengthening. Inductive coupling has been shown to aid healing of fresh fractures by LOE-1. Inductive coupling was supported by LOE-1 to be effective for patients undergoing interbody fusion, enhancing posterolateral lumbar fusion and increasing fusion rates in anterior cervical disectomy. LOE-1 and LOE-4 verified that IC is successful in congenital pseudoarthrosis. In contrast, LOE-1 proved IC ineffective for Perthes disease. Inductive coupling has shown to effectively enhance fusion success of hindfoot arthrodesis with one LOE-1 study; nonetheless, there is conflicting inconsistent LOE-4 supporting IC for aiding fusion after ankle arthrodesis. The results of this study were used to assign grades of recommendations (Table 2). There was, however, wide study heterogeneity (Table 6).

**DISCUSSION**

**Mechanisms of action of ES**

The exact mechanism by which ES enhances bone repair remains underexplored. Direct current was shown to work by an electrochemical reaction at the cathode. For CC, molecular pathways and growth factors have been shown to enhance proliferation and differentiation of the osteoblast. Inductive coupling was shown to enhance osteoblast differentiation and proliferation by mechanisms involving alteration of growth factors, gene expression, and transmembrane signaling. Calcium is upregulated by IC and CC, which is important in bone healing, as it has a role in the mineralization of bone and conducts the communication between cell surface receptors, antibodies, and hormones for DNA synthesis needed for bone healing. The upregulation of growth factor synthesis by all modes of ES acts similarly to enhance bone healing. They work in an autocrine and paracrine action to increase the cellular matrix synthesis and gene expression, which in turn increases bone cellular proliferation and differentiation, leading to enhanced callus formation and maturation. An overview of the mechanisms for ES is shown in Figure 3. With better understanding of the effect of ES at a molecular level, the effectiveness of ES for enhancement of bone healing in the clinical setting will be improved.
Table 4. Clinical studies reviewed for capacitive coupling (CC).*

| CC study            | Level of Evidence | Study Design          | Objective of study                                      | Entry Criteria                                                                 | Sample Size | Primary outcome measure | Treatment regime | Assessment time | Result                  | Conclusions                                                                 |
|---------------------|-------------------|-----------------------|--------------------------------------------------------|--------------------------------------------------------------------------------|-------------|------------------------|------------------|----------------|-------------------------|---------------------------------------------------------------------------|
| Beck et al82        | 1                 | Randomized control study | Effect of CC on stress healing fractures               | Acute tibial stress fracture for which no significant treatment aside from rest had been prescribed | 54          | Healing was confirmed when hoping for 10 cm for 30 s without pain | 15 h a day until healed 3-6 V at 60 kHz | Contacted every second day to record symptoms, when pain free magnetic resonance imaging | No difference in time to healing between active and control groups | No effect of CC on tibial stress fracture healing. CC may be indicated for more severely injured or elite athlete/recruit whose incentive to return to activity may motivate superior compliance |
| Goodwin et al83     | 1                 | Randomized control trial | To evaluate the effect of CC on the success rate of lumbar spine fusion surgery | Patients with a primary diagnosis of degenerative disc disease with or without other degenerative changes | 179         | Radiographic and clinical union | 24 h per day until healing or for 9 mo if healing delayed | 12 mo | Success 84.7% for active 64.9% for control group | CC effective in spinal fusion                                               |
| CC study | Level of Evidence | Study Design | Objective of study | Entry Criteria | Sample Size | Primary outcome measure | Treatment regime | Assessment time | Result | Conclusions |
|----------|-------------------|--------------|--------------------|----------------|-------------|------------------------|-----------------|----------------|--------|-------------|
| Scott and King⁸⁴ | 1 | Randomized control trial | Efficacy of CC and plaster in established nonunion of long bone fractures | Adult established nonunion at least 9 mo with no fracture gap | 10 active and 11 control | Radiographic and Clinical union | 6 and 9 mo | 6 mo | 6/10 active + 0/11 control group healed | CC effective for nonunion of long bones |
| Abeed et al⁸⁵ | 4 | Case series | To determine the extent to which CC can promote healing of nonunited fractures | Long bone fracture for at least 9 mo | 16 | Radiological union | A 63 kHz, 6 V peak-to-peak sine wave for 30 wk | 30 wk | 11/16 achieved union at average 15 wk | These findings confirm that CC promotes bone healing of fracture nonunion |
| Benazzo et al⁸⁶ | 4 | Case series | Treatment of stress fracture in athletes by CC | Stress fracture in athletes training at least 3 times per week detected by x-ray, scintigraphy and computed tomography | 25 fractures in 21 athletes | Radiographic and clinical union | Treatment till the fracture healed or improved | Monitored until no progress noted at 3 assessments | 22 healed, 1 not healed, 2 improved | This preliminary report shows that CC can be used safely in the treatment of these stress fractures |
| Study                        | Study Design | Primary Outcome                  | Methodology                                                                 |
|------------------------------|--------------|----------------------------------|-----------------------------------------------------------------------------|
| Brighton and Pollack\(^7\)   | Case series  | Does CC aid help recalcitrant    | Radiographic assessment was used to compare healing rates among the 3        |
|                              |              | fractures                        | treatment methods and to identify risk factors adversely affecting the heal rate |
|                              |              | Nonunion was diagnosed from      | Until union: 60 kHz 5 V peak-to-peak for an average of 24.8 wk               |
|                              |              | roentgenograms were no           | After 12 wk and then at union if not healed at 12 wk                         |
|                              |              | progressive signs of healing of  | 17/22 healed on average 22.5 wk of treatment                                 |
|                              |              | the nonunion callus over a       | CC is noninvasive, involves portable equipment, allows full weight-bearing  |
|                              |              | 3-mo period                      | on the lower extremity in a cast, is easy to apply, and does not require    |
|                              |              |                                  | precise localization of the capacitor plates, it has distinct advantages     |
|                              |              |                                  | over other methods of treating nonunion with electricity                     |
| Brighton et al\(^8\)         | Case series  | Logistic regression analysis was | DC 20 μA 12 wk, CC 60 kHz 5 V peak-to-peak 24 h a day for 12-24 wk            |
|                              |              | used to compare healing rates    | Observed at end of treatment and then if not healed for 3 monthly follow up  |
|                              |              | among the 3 treatment methods    | When no risk factors no differences among the 3 methods                      |
|                              |              | and to identify risk factors    | As progressively more risk factors were present, the predicted heal rates    |
|                              |              | adversely affecting the heal     | decreased significantly regardless of the treatment method                     |
| CC study          | Level of Evidence | Study Design | Objective of study                                                                 | Entry Criteria                                                                 | Sample Size | Primary outcome measure          | Treatment regime          | Assessment time          | Result            | Conclusions                                                                 |
|-------------------|-------------------|--------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------|----------------------------------|--------------------------|--------------------------|---------------------|-----------------------------------------------------------------------------|
| Impagliazzo et al 89 | 4                 | Case series  | Evaluate the effects of CC to stimulate osteogenesis, in patients suffering from nonunited fractures | No radiological evidence of callus formation, infection fractures included | 30          | Radiographic union               | Average 10 wk for 10 h daily until healing or at least 3 mo | Every 45-60 d until healing for at least 12 mo | Success healing rate was 84%, CC is an effective treatment, well accepted by patients and compliance is definitely high; 8 h of daily use is effective |
| Zamora-Navas et al 90 | 4                 | Case series  | Efficacy of CC in nonunion                                                        | Remained nonunited for at least 9 mo from time of injury and no radiological changes for last 3 mo | 22          | Radiographic union               | Until union average 26 wk, 60 kHz 5 V peak-to-peak | At union 16/22 achieved union at an average of 26 wk | The results were better when the fracture site was metaphyseal. The results were not affected by the presence of infection |
| Brighton and Pollack 91 | 5                 | Case report  | Treatment of CC in a recalcitrant nonunion of tibia                                | Tibial nonunion                                                               | 1           | Radiographic and clinical union  | 60 kHz 5 V peak-to-peak sine wave for 6 mo | 6 mo | 6 mo healed  | DC effective in this tibial nonunion                                      |
| Makela 92 | 5                 | Case report  | Use of CC in a nonunion related to knee prosthesis                                 | Tibia fracture after total knee replacement                                   | 1           | Radiographic union               | 12 wk                  | 12 wk | Achieved union | CC good for fracture treatment in a patient with a total joint prosthesis when surgery cannot be done |
Direct current

Using DC for spinal fusion has shown to be inconsistent with 2 LOE-1 studies, supporting its efficacy particularly in high risk patients (smokers, those with multiple back surgeries, and multilevel fusions) and 2 LOE-1 studies showing no difference in the older patient population leaving DC only level B recommendation. However, one meta-analysis supports continuous 24-hour delivery of 5 to 10 μA using 2 to 4 cathodes to be effective for spinal fusion. Therefore, more studies should be carried out to support DC for spinal fusion. Moreover, DC is effective as an adjunct to foot and ankle surgery with only a level C recommendation. Because of LOE-4 being solely reported, more evidence is required because of a wide range in follow-up (9-20 weeks), small patient population, and large differences in number of surgical inventions before DC was used (range, 1-5). No studies for DC fulfill the criteria for randomized prospective double-blind clinical trial because it would involve implantation of a placebo stimulator, which is against the regulation of human research; therefore, its effect on bone healing remains questionable leaving DC only as a recommendation C for nonunion. LOE-4 supports using DC for the application of enhancing nonunions, and bone healing rates were not affected by the presence of previous osteomyelitis or the presence of previously inserted metallic fixation devices. Furthermore, rate of unions were not significantly different compared to rates after bone graft surgery. A LOE-4 study showed 10 years after DC stimulation that all fractures had remained united with normal bone remodeling, illustrating that DC is safe and effective in the long term. However, despite its effectiveness and availability, DC has fallen out of favor compared to IC and CC. Furthermore, IC and CC are noninvasive techniques affected by patient compliance unlike DC.

Capacitive coupling

Using CC for bone healing is limited with only 2 LOE-1 studies. These studies are unreliable, as the success of CC for healing long bone nonunions by Scott and King consisted of a small sample size and had a large variety in fracture sites between control and stimulated groups. Despite Beck et al reporting good use of randomization, and blinding the outcome assessors, 86% of the patients being followed up showed no difference in the time for healing between the control and CC group. Encouragingly, LOE-4 has demonstrated CC to be effective in treating nonunions, though this unreliable evidence suggests that this application warrants further investigation leaving CC as level of recommendation as C. Using CC for spinal fusion is relatively new, with limited evidence supporting its effectiveness; therefore, further studies are required though as to date giving a level of recommendation as A.
| PEMF Study                      | Level of Evidence | Study Design                      | Objective of study                                      | Entry Criteria                                                                 | Sample Size | Primary outcome measure          | Treatment Regime                      | Assessment time | Results                      | Conclusions                                                                 |
|--------------------------------|------------------|----------------------------------|--------------------------------------------------------|-------------------------------------------------------------------------------|-------------|----------------------------------|--------------------------------------|----------------|-------------------------------|-----------------------------------------------------------------------------|
| Barker et al                   | 1                | Randomized control trial         | Efficacy of PEMF in tibial nonunions                   | United tibial diaphysis fracture for 52 wk, no sign of healing on x-ray for last 3 mo and fracture gap <0.5 cm | 17          | Clinical and radiological union   | 12-16 h a day for 24 wk or 48 wk | Every 6 wk for 48 wk | 5/9 active group and 5/7 control group healed | The high proportion of fractures uniting in the control group suggests that conservative management of nonunion is effective and this may explain much of the success attributed to PEMF |
| Betti et al                    | 1                | Randomized control trial         | Effect of PEMF on fracture of femoral neck by 3 screws fixation | Fracture of the femoral neck                                                  | 30          | Clinical and healing rate         | 30, 90 d + 6, 12, 24 mo              | 3 mo            | Decreased pain + increased consolidation | PEMF effective                                                                |
| Borsalino et al                | 1                | Randomized control trial         | PEMF treatment in osteotomy of the hip in patients >70 y | Osteoarthritis of the hip in patients <70 y                                   | 16 control and 16 treated group | Radiographi8 mo 8 h a day and bone density score | 3 mo                     |                                                                    | Significant difference between controls and active patients (P < .01).        |

Table 5. Clinical studies reviewed for Inductive coupling (IC) which is also referred to as pulsed electromagnetic field.*
| Study | Study Type | Treatment Description | Healing Time | Healing Rate | Adjuvant Use |
|-------|------------|------------------------|--------------|--------------|-------------|
| Capanna et al\(^5\) | Randomized control trial | Efficacy of PEMF in healing of the junction between the allograft and the host bone after tumor resection | Every 2 mo till 12 mo | 24 treated group and 23 control group | Healing rate was the same (67%) in both control and active patients. When adjuvant postoperative chemotherapy not used, PEMF decreased the healing time. |
| Dhawan et al\(^6\) | Randomized control trial | PEMF for elective triple/subtalar arthrodesis | 12 h a day Until union | 144 Radiographic union | Talonavicular joint control group healed in 17.6 wk; PEMF healed in 12.2 wk Calcanecuboid arthrodesis: control group 17.7 wk; 13.1 wk PEMF |

Adjunctive use of a pulsed electromagnetic field in elective hindfoot arthrodesis may increase the rate and speed of radiographic union of these joints.
| PEMF Study | Level of Evidence | Study Design | Objective of Study | Entry Criteria | Sample Size | Primary Outcome Measure | Treatment Regime | Assessment Time | Results | Conclusions |
|------------|------------------|--------------|--------------------|----------------|-------------|-------------------------|----------------|----------------|---------|-------------|
| Eyres et al97 | 1                | Randomized control trial | PEMF effect in limb lengthening | Limb lengthening was performed by the Villarubbia technique using either a unilateral or circular frame system | 13 cases 18 sites | Bone density and compared to 3 radiographic sites | 4 h daily during distraction of the limbs for 3 mo | 2-4 weekly till 12 mo | No difference in the rate or amount of new bone formed at site of distraction | Stimulation with pulsed electromagnetic fields has no effect on the regenerate bone, but does prevent bone loss adjacent to the distraction gap |
| Foley et al98 | 1                | Randomized control trial | Efficacy of PEMF to aid fusions after anterior cervical discectomy and fusion | Failed to response to nonoperative management. Smokers and multilevel fusions | 123 (160 control 163 active) | VAS score for pain, neurologic assessment, radiograph, neck disability score | 4 h a day for 3 mo | 1, 2, 3, 6, and 12 mo | At 6 mo fusion rate significantly greater for PEMF group but no difference at 12 mo | PEMF safe in the clinical setting |
| Harrison and Bassen99 | 1    | Randomized control trial | Use of pulsed electromagnetic frequency (PEMF) in the treatment of Perthes’ disease | Early Perthes disease: radiographic changes in capital femoral epiphysis were sclerosis/ sequestrum; | 11 active and 11 control | Time to weight bear | Brace worn 24 h daily + PEMF 10 h each night | 12 mo | No difference between groups in time to weight bear | PEMF does not enhance treatment for Perthes disease |
| Study              | Design       | Intervention                              | Population                                                                 | Time to consolidation | Results                                                                 |
|--------------------|--------------|-------------------------------------------|---------------------------------------------------------------------------|-----------------------|-------------------------------------------------------------------------|
| Hanft et al \(^{100}\)   | Randomized control trial | PEMF in the treatment of peripheral neuropathy | Peripheral neuropathy secondary to diabetes mellitus and with clinical, thermographic, and radiographic evidence acute (stage 1) Charcot joint | 1.2 h each day until union | 23.8 wk for the control versus 11.1 wk for the active group |
| Kennedy et al \(^{101}\)   | Randomized control trial | PEMF stimulation for loosened cemented hip prostheses | Clinical symptoms severe enough to warrant revision hip surgery | 6 mo at least 8 h a day | 10/19 active healed and 2/18 control |
| Linovitz et al \(^{102}\)   | Randomized control trial | Evaluate the effect of combined magnetic fields on the healing of primary non-instrumented posterolateral lumbar spine fusion | One-level or 2-level fusions without instrumentation, either with autograft alone or in combination with allograft | Fusion at 9 mo, based on radiographic union | Active group, 64% healed at 9 mo compared with 43% control group |

Thus the results of this expanded pilot study demonstrate the efficacy of PEMF in facilitating the consolidation process of acute, phase 1, Charcot joint, and decreasing the amount of residual deformity. This data suggest that for loosened cemented hip prostheses use of PEMF is a treatment option only to delay revision hip surgery. Adjunctive use of the combined magnetic field device was statistically beneficial in the overall patient population, as has been shown in previous studies of adjunctive bone growth stimulation for spine fusion.
Table 5. Continued

| PEMF Study | Level of Evidence | Study Design | Objective of study | Entry Criteria | Sample Size | Primary outcome measure | Treatment Regime | Assessment time | Results | Conclusions |
|------------|-------------------|--------------|--------------------|----------------|-------------|-------------------------|-----------------|-----------------|---------|-------------|
| Livesley et al\textsuperscript{103} | 1 | Randomized control trial | Efficacy of PEMF in fractures of the humerus | Minimally displaced fracture of the humerus separation of fragments less than 1 cm and angulation $< 45^\circ$ | 67 | Assessments of pain. Muscle wasting and strength tests | 30 min a day for 10 d | Assessments were carried out at 1, 2, and 6 mo, | No difference in efficacy of PEMF and control groups | PEMF not effective |
| Mammi et al\textsuperscript{104} | 1 | Randomized control trial | PEMF effect in the treatment in valgus tibial osteotomy | Tibial osteotomy | 40 | Radiographic union | 8 h a day for 2 mo | 30 and 60 d | 13/18 active | PEMF positive effect on healing of osteotomies |
| Mammi et al\textsuperscript{105} | 1 | Randomized control trial | Treatment of PEMF in spinal fusion | Posterolateral spinal fusion | 35 | Healing success rate | 2, 4, 6, and 8 mo | 4 mo | 12/15 active | PEMF positive effect on posterolateral arthrodesis |
| Mooney\textsuperscript{106} | 1 | Randomized control trial | Effect of PEMF on posterolumbal spinal fusion | Undergoing interbody spinal fusion from and anterior or posterior approach | 195 | Healing success rate | 12 mo | Minimum 12 mo | 63/97 control, 81/98 active | PEMF positive effect on posterolateral lumbar fusion arthrodesis |
| Study                  | Design          | Intervention                              | Condition            | Timing                          | Outcome                                                                 | Notes                                                                 |
|-----------------------|-----------------|-------------------------------------------|----------------------|--------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------|
| Poli et al. 107       | Randomized control trial | Congenital pseudoarthrosis with pulsing electromagnetic fields | Congenital pseudoarthrosis | 12 (6 active 6 control) | Radiographic union 10 h daily for 12 mo, Monthly first 3 mo, then 6-mo interval | No difference in limb-length imbalance or need for reoperation PEMF effective although small population, more studies needed to define PEMF role in congenital pseudoarthrosis |
| Sharrard 8            | Randomized control trial | Efficacy of PEMF and plaster in delayed union of tibia fractures | Tibial fracture with delayed union of between 16 and 32 wk | 45 | Radiological union and clinical union 12 wk 3 mo | 10/20 active and 4/21 control healed PEMF significantly influence healing in tibial fractures with delayed union |
| Simonis et al. 108    | Randomized control trial | Efficacy of PEMF and external fixator in nonunion of tibia | Tibia shaft fracture, ununited fracture at a minimum of 1 y | 34 | Clinical and radiological union 6 mo 6 mo | 16/18 active and 8/16 control healed Positive association between tibial union and PEMF |
| Traina et al. 109     | Randomized control trial | Effect of PEMF in tibia nonunions | Tibia nonunion | 18 active 19 control | Radiological union 60 d 60 d | 13/18 active and 5/19 control healed Positive effect on healing of osteotomies |
| Wahlström 11          | Randomized control trial | PEMF effect on distal end fracture of forearm | Colles fracture | 15 active and 15 control | Scintimetry (q-ratio) 2 mo 1, 2, 4, and 8 wk | The activity ratio higher at 1 + 2 wk in active than control group PEMF accelerate the early phase of healing the data need further investigation especially regarding the clinical relevance |
| PEMF Study | Level of Evidence | Study Design | Objective of Study | Entry Criteria | Sample Size | Primary Outcome Measure | Treatment Regime | Assessment Time | Results | Conclusions |
|------------|------------------|--------------|--------------------|----------------|-------------|-------------------------|------------------|----------------|---------|-------------|
| Bassett *et al* | 3 | Case series (level of evidence-3 as cross sectional international study) | International study investigating the PEMF effect in fracture healing | Disability time before entering the trials was divided into 3: <9 mo, 9-24 mo, and more than 24 mo | 1007 ununited fractures and 71 failed arthrodesis worldwide | Radiographic and clinical union | n-r | n-r | 1078 patients, 834 successfully healed, overall healing rate 77%. PEMF successful in nonunion of failed arthrodesis |
| Aaron *et al* | 4 | Case series comparative study | Compare success of healing femoral osteonecrosis by PEMF and core decompression | Only patients with AVN Ficat stage II and III | 39 PEMF group, 38 core decompression group | Clinical and radiographic outcome combined for outcome criteria | 72 kHz for 12-18 mo, 24 mo minimum average 3 y | Decompression + PEMF decreased progression | Need longer follow up time for conclusive results but PEMF shown to increase the likelihood of clinical improvement and stabilization on roentgenograms compared to core decompression for Ficat II and III lesions |
| Adams *et al* | 4 | Case series continued | Continuation of a study of the treatment of scaphoid nonunion with PEMF and cast immobilization | Scaphoid nonunion at least 6 mo old | 54 Radiographic union | Original treatment until union | NA | Healing success rate decreased from last review, 80% to 69%. | Until additional clinical studies have further defined the indications, treatment protocol, and efficacy of this method PEMF treatment should be a secondary alternative to bone-grafting procedures |
| Study Authors | Study Type | Treatment Description | Sample Size | Follow-up Details | Efficacy Details | Notes |
|---------------|------------|-----------------------|-------------|------------------|-----------------|-------|
| Bassett et al 113 | 4 Case series | Treatment of PEMF in femoral osteonecrosis | Osteonecrosis of the femoral head | 24 (28 hips) | Clinical and radiographic union | Until union 6-36 mo average 17.8 mo | Further exploration of PEMF is warranted in the treatment of osteonecrosis of the femoral head | 18 hips thought to have benefited by the treatment |
| Bassett et al 114 | 4 Case series | Efficacy of PEMF in treatment of tibial ununited diaphyseal fractures | Delayed union: no clinical or radiographic evidence of union at 4-9 mo after fracture. Nonunion: Not united by 9 mo and no radiographic evidence of callus | 127 | Radiographic union | 10 h daily until healing average of 5.2 mo | The success rate was not materially affected by the age or sex of the patient, the length of prior disability, the number of previous failed operations, or the presence of infection or metal fixation |
| Bassett et al 10 | 4 Case series | Efficacy of PEMF and autologous bone grafts (ABG) in treatment of recalcitrant nonunion | Group A: ABG and PEMF Group B: failed PEMF followed by PEMF and ABG | 83 | Radiographic and clinical union | 10 h a day until union. Group A range 2-10 mo and group B range 2-12 mo | PEMF should be considered as adjunct to bone graft of the extremities whether in a primary or a salvage situation. Even if PEMF used to decrease the disability time after the initial surgical procedure the use of this method is justified | Group A: 33/38 healed Group B: 42/45 healing rate |
| PEMF Study | Level of Evidence | Study Design | Objective of study | Entry Criteria | Sample Size | Primary outcome measure | Treatment Regime | Assessment time | Results | Conclusions |
|------------|------------------|--------------|--------------------|----------------|-------------|------------------------|-----------------|----------------|---------|-------------|
| Bassett et al.\(^{115}\) | 4 | Case series | PEMF to treat congenital and acquired pseudoarthrosis + nonunion | Iatrogenic and acquired pseudoarthrosis that had one previous unsuccessful surgery | 29 | Radiographic union | 12-16 h a day for 3-6 mo | Monthly and final at 6 mo | Overall success rate was in excess of 70% | PEMF is a simple clinical treatment, which is conducted on an outpatient basis and appears to be both safe and effective. It can be applied with or without surgery |
| Bassett and Schink-Ascani\(^{116}\) | 4 | Case series | Long term follow up of PEMF treated congenital pseudoarthrosis | Congenital pseudoarthrosis of the tibia treated with PEMF. Type I and type II had gaps less than 5 mm in width. Type III were atrophic, spindled, and had gaps in >5 mm | 91 | Radiographic progression | 10-12 h a day until union: average treatment 1.4 y (range, 4 mo-4.1 y) | Until puberty exact timing n-r | 7/ 8 type I lesions healed, 16/20 type II lesions healed with PEMF + immobilization | PEMF which is not associated with any known risk, appears to be an effective, conservative adjunct in the management of this therapeutically challenging, congenital lesion |
| Bassett\(^{117}\) | 4 | Case series | Femoral head osteonecrosis with PEMF | Osteonecrosis of the femoral head | 95 (118 hips) | Steinberg quantitative staging radiographic analysis | 10 h a day for average 49 mo | Every 2/3 mo during the 1st y + 3-6 mo thereafter | Rate of quantified progression was 16%. | PEMF treatment showed long-term improvements in symptoms and signs and a reduction in the need for early joint arthroplasty |
| Author(s) | Study Type | Treatment Modalities | Patient Population | Follow-up | Outcome Measures |
|-----------|-------------|----------------------|--------------------|-----------|------------------|
| Biglini et al \(^{118}\) | 4 Case series | PEMF for adjunct to noninvasive adjunct when performing arthrodesis of the knee after failed total joint arthroplasty | Patients with a failed arthrodesis | 10-14 h daily for average 5.9 mo, range from 3-12 mo | Clinical and radiological union within 19.3 mo and range 9-31 mo | 17/20 healed average 5.8 mo, range of 3-12 mo | The use of pulsing electromagnetic fields appears to be a valuable noninvasive adjunct when performing arthrodesis of the knee after failed total joint arthroplasty. |
| Colson et al \(^{119}\) | 4 Case series | Delayed or nonunion were treated by PEMF or by PEMF with surgery to examine healing rate | Ununited fractures of at least 5 mo duration | 50 kHz, 12-15 daily until united or up to 1 y | Clinical and radiographic union | 19/19 surgery and PEMF + 12/14 PEMF only healed | PEMF successful in nonunion. |
| De haas et al \(^{120}\) | 4 Case series | PEMF effect on ununited fractures of the tibia | Ununited fractures at least 9 mo old without any radiologic changes during last 2 mo | 18-20 h a day for 3-10 wk | Clinical and radiographic outcome | 10 wk All 10 patients with delayed union and 84% of nonunions healed | PEMF effective. Nonunions with a gap between the tibial fragments and pseudoarthrosis are better treated with bone grafting and internal fixation prior to electrical stimulation. |
Table 5. Continued

| PEMF Study          | Level of Evidence | Study Design | Objective of study                                                                 | Entry Criteria                                                                 | Sample Size | Primary outcome measure                  | Treatment Regime | Assessment time | Results                                   | Conclusions                                                                                     |
|---------------------|-------------------|--------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------|------------------------------------------|-----------------|----------------|-------------------------------------------|-----------------------------------------------------------------------------------------------|
| De haas et al 121   | 4                 | Case series  | Healing in ununited tibial fractures of the tibia by PEMF                           | Open and closed ununited fractures at a minimum of 9 mo                       | 17          | Clinical and radiographic outcome        | 20 h daily, 4-6 wk immobile + 4-6 mo mobile | Monthly until union | 15/17 fractures healed                   | The method is sufficiently promising to merit further clinical investigation                  |
| Delima and Tanna 122| 4                 | Case series  | Treatment of PEMF in nonunion                                                      | Nonunion of long bones                                                        | 29          | Radiographic union                       | 12 V upper extremity and 30 V lower extremity for 16-18 h daily for 5 mo | 8 wk, 3 mo, 5 mo and up to 1-2 y | 24/30 fractures healed                     | The result was not dependent on the age, sex, time of nonunion or the presence of infection but uniformly poor when infection and fracture instability were coexistent in the same patient |
| Dunn and Rush 123   | 4                 | Case series  | PEMF effect in ununited fractures                                                  | Delayed nonunion; no radiographic or clinical progression from 4-9 mo. Nonunion: not united 9 mo and osteotomies | 52          | Clinical and radiographic outcome       | 2-12 mo: average 6.1 mo                  | 12 mo            | 14 had bone grafting + DC with healing of 82% | Overall 42/52 fractures healed DC and PEMF                                                  |
| Fontanesi et al 124 | 4                 | Case series  | PEMF effect on treatment of congenital and acquired pseudoarthrosis and delayed unions | Established nonunion or pseudoarthrosis                                      | 35          | Clinical and radiographic outcome       | 12 h a day for between 3-12 mo            | 2 monthly and at union | 88.5% of cases healing at average 6 mo | The method was particularly useful and effective in infected fractures, failed bone grafts, revascularization of fragments showing signs of necrosis, and fractures with associated skin lesions |
| Study | Study Type | PEMF Treatment | Fracture Type | Radiographic Union | Treatment Details | Healing Rate | Notes |
|-------|------------|----------------|---------------|-------------------|------------------|-------------|-------|
| Fontanesi et al<sup>125</sup> | Case series | PEMF treatment of congenital and acquired pseudoarthrosis and of delayed unions | Congenital and acquired pseudoarthrosis and of delayed unions | Radiographic union | 10 h a day till union or up to 12 mo, Every 30-45 d till union | 126/146 (83%) healed in average of 4.5 mo | PEMF treatment seems to be capable of triggering the repair process rather than shortening the treatment time. |
| Freedman<sup>126</sup> | Case series | PEMF use in treating delayed and nonunion of fractures | Fractures and osteotomies with average nonunion for 8 mo | Radiographic Minimum of 12 h daily for 3 mo. If no healing then further 6-12 wk | 6 wk and then at 3 mo and 6 mo | 2/13 union achieved | PEMF should be reserved for cases that have exhausted conventional treatments and still have ununited fractures. |
| Frykman et al<sup>127</sup> | Case series | PEMF treatment in scaphoid | Scaphoid fractures that were at least 6 mo old | Radiographic union Until union: average 4.3 mo Monthly for average 8.4 mo | | 35/44 healed | PEMF reliable alternative method of treating nonunited scaphoid fractures: low risk, simplicity of use, and reliable healing. |
| PEMF Study | Level of Evidence | Study Design | Objective of study | Entry Criteria | Sample Size | Primary outcome measure | Treatment Regime | Assessment time | Results | Conclusions |
|------------|-------------------|--------------|-------------------|----------------|-------------|------------------------|----------------|----------------|---------|-------------|
| Garland et al\textsuperscript{128} | 4 | Case series | Long term follow up of nonunion treated with PEMF | Clinical and radiographic nonunion of at least 9 mo | 90 | Clinical and radiographic union | 3 h a day | Final assessment 4 y | 92% maintained a solid union | The success rate of PEMF treatment for nonunion repair demonstrated no statistically significant change over long-term follow-up |
| Heckman et al\textsuperscript{129} | 4 | Case series | PEMF in united fractures | United fracture at least 6-mo duration. Exclude fracture gap < 1 cm and pseudoarthrosis | 149 | Clinical and radiographic union | 12 h for at least 3 mo if no healing then further 3-6 mo | Monthly up to 1 y | 96/149 healed at an average of 11.1 mo | PEMF reasonable choice of treatment in the management of ununited fractures |
| Holmes\textsuperscript{130} | 4 | Case series | PEMF in proximal fifth metatarsal fracture | Delayed union of proximal fifth metatarsal | 9 | Radiographic union | Average 3 mo (range, 2-4 mo), Average follow-up 39 mo (range, 24-60 mo) | All healed mean time of 4 mo (range, 2-8 mo) | PEMF provides an effective alternative for the treatment of delayed unions and nonunion of the proximal fifth metatarsal |
| Ito and Shirai\textsuperscript{131} | 4 | Case series | Efficacy of PEMF in treatment of ununited tibia fractures | Ununited fracture between 6 and 27 mo old | 30 | Clinical and radiographic union | 8 h a day until union | Every 6 wk until union | 25/30 fractures healed in median interval of 8.6 ± 3.2 mo | Patient age and gender, the presence of surgical hardware, length of disability, and the number of surgical procedures did not affect the outcome. Treatment failures occurred only among lesions with a poor blood supply |
| Study | Study Type | Description | Patients | Clinical and Radiographic Progression | Treatment | Long-term Effect |
|-------|------------|-------------|----------|--------------------------------------|-----------|-----------------|
| Massari et al | 4 Case series | To investigate if PEMF can prevent or delay the progression of osteonecrosis | Patients with Ficat stage I, II, or III osteonecrosis of the femoral head | 76 hips in 66 patients | Clinical and radiographic progression | At time of union | PEMF preserved 94% of Ficat stage-I or -II hips |
| Madronero et al | 4 Case series | PEMF in promoting healing of delayed union and nonunion of bone | Radius nonunion | Absence of callus formation | Until union average 104 d | At union | Consolidation in 6 cases |
| Marcer et al | 4 Case series | Treatment of PEMF in tibia, femur, and humeral nonunions | Ununited fractures treated with external fixation | Clinical and radiological union | 10 h a day for average 7 mo | Monthly | 107/147 fractures healed |
| Meskens et al | 4 Case series | Efficacy of PEMF in treatment of externally fixed ununited fractures | Nonunion of least 24 mo since injury | Radiographic and clinical union | At least 6 mo | At union | Success rate was 75%, PEMF effective for nonunions |
| PEMF Study | Level of Evidence | Study Design | Objective of study | Entry Criteria | Sample Size | Primary outcome measure | Treatment Regime | Assessment time | Results | Conclusions |
|------------|-------------------|--------------|--------------------|----------------|-------------|------------------------|-----------------|----------------|---------|-------------|
| Meskens et al\textsuperscript{136} | 4 | Case series | Efficacy of PEMF in treatment of externally fixed tibia fractures | Fracture occurring at least 6 mo after trauma | 57 | Radiographic union | At least 6 mo | At union | 43/57 fracture healed | PEMF valuable treatment option |
| Saltzman et al\textsuperscript{137} | 4 | Case series | PEMF for delayed healing of foot and ankle arthrodesis | Nonunion after arthrodesis | 19 | Clinical and radiographic union | 10-14 h a day until union | Until union | 5/19 healed | Protocol of PEMF immobilization and limited weight bearing low success rate |
| Satter Syed et al\textsuperscript{138} | 4 | Case series | Effect of PEMF on nonunited fractures | United fractures occurring at least 2 mo after injury | 13 | 80 Hz for 14 wk | 14 wk | 11/13 healing | Narrow window for shape and amplitude of waveform shown to be effective need further investigation |
| Saxena et al\textsuperscript{139} | 4 | Case series | Efficacy of PEMF for navicular stress fractures | Navicular stress fracture during athletic activity | 11 | Time to return to activity | 10 h a day until union | Until union | Average RTA 4.2 ± 3.4 mo | 26% also had surgery. Need more evidence for this treatment |
### Saxena et al. [40]
**Type**: 4 Case series  
**Title**: Electrical bone stimulation for arthrodeses of the foot and ankle in high-risk patients  
**Details**: Diabetes, a BMI > 28, a history of previous failed arthrodeses, a history of smoking or alcohol abuse, or a history of immunosuppressive medications such as steroid.  
**Results**: 26 (28 fractures), Radiographic union, Until union, 1 mo, and every 2 wk till union, 24/28 healed. Arthrodesis of the foot and ankle may be enhanced by the use of implantable electrical bone stimulation.

### Sharrard et al. [41]
**Type**: 4 Case series  
**Title**: Efficacy of PEMF in united fractures  
**Details**: Nonunion for at least 1 y and no healing over 3 mo on x-ray.  
**Results**: 53, Clinical and radiographic union, 12-16 h daily for at least 3 mo or till union, 3 mo and then until union, Union in 38 cases, median time 6 mo. Previous or active sepsis, presence of plates or nails, the age of patient or time since the injury did not affect the results.

### Bassett et al. [42]
**Type**: 5 Expert Opinion  
**Details**: NA, NA, NA, NA, NA, NA, NA. Findings of PEMF action, have begun to place PEMF on a therapeutic par with surgically invasive methods.

### Bassett et al. [43]
**Type**: 5 Expert opinion  
**Details**: NA, NA, NA, NA, NA, NA, NA. PEMF is successful nonunion and delayed unions.

### Das Sarker and Bassett [44]
**Type**: 5 Case report  
**Details**: PEMF child humerus nonunion, Resistant lateral condyle of humerus, 1, 3 mo, 10 h daily, At union, Solid union was achieved, Effective for this nonunion, should be investigated more.
| Study                  | Level of Evidence | Study Design | Objective of study                                                                 | Entry Criteria | Sample Size | Primary outcome measure | Treatment Regime | Assessment time | Results | Conclusions                                                                 |
|-----------------------|-------------------|--------------|------------------------------------------------------------------------------------|----------------|--------------|-------------------------|------------------|----------------|---------|----------------------------------------------------------------------------|
| Gossling et al145      | 5                 | Expert opinion | Assess the effectiveness of PEMF vs surgical therapy                               | NA             | NA           | NA                      | NA               | NA             | NA      | Given the costs and potential dangers of surgery, PEMF should be considered an effective alternative |
| Ito et al146           | 5                 | Case report  | Long-term follow-up of a patient with congenital pseudarthrosis of the tibia treated with PEMF and bone grafting | Bassett type III and Boyd type II | 1            | Radiographic union      | 10 h a day for 2 y, then 1 y then further 8 mo | 7 y after treatment | At 7 y union achieved | With PEMF skeletal maturity was complete and an unacceptable degree of leg shortening had been avoided |
| Lavine and Grodzinsky77 | 5                 | Expert opinion | NA                                                                                  | NA             | NA           | NA                      | NA               | NA             | NA      | PEMF if effective and requires least patient cooperation and healing rate in the region of 70% |
Inductive coupling

The use of ICs for treating nonunion and delayed union has been successful. However, in the study by Sharrard, the age of the active group was 34.7 and in the control group, it was 45.4. Furthermore, when the results of the study of Simonis et al were adjusted for smoking, no enhancing effects were seen for IC. These limitations suggest that further clinical evidence is needed to support this application, as shown by the level of recommendation being C. Inductive coupling has been shown to be beneficial for osteotomies, but the endpoint assessment was shown to vary in 3 randomized controlled trials (RCTs) making true comparisons difficult giving an overall recommendation of B.

Inductive coupling is effective in fresh fractures although supported by only 2 RCTs. In one such study, scintimetric analysis was a primary outcome measure. This did not reliably examine the effect of ES on patient’s clinical outcomes and also failed to show any benefit in displacement rates between the groups. The subsequent study was limited, as the findings were based on a subgroup of patients using the device for more than 6 hours daily; therefore, the compliance of the patients was influential. Hence, overall, the recommendation remains as level B. Inductive coupling had no effect on regenerate bone during limb lengthening, even though bone loss in the segments of bone distal to the lengthening sites was significantly more marked using inactive coils, illustrating that IC can prevent bone loss adjacent to the distraction gap. However, multiple limbs were analyzed for the same patient, and the small population decreased the reliability of the results. Two RCTs agreed in supporting IC for enhancing spinal fusion, showing a recommendation of level A. However, in one study, the radiographic criteria for fusion required only 50% incorporation of the graft and follow-up in both studies was less than a year making definite judgment difficult. Only one LOE-1 study verified IC for congenital pseudoarthrosis, which was limited by not blinding the assessor or patients, introducing detection and performance bias, and hence better designed studies are needed giving overall assessment of recommendation of C.

Bone grafting procedures for nonunions is shown to be less successful with multiple graft procedures. However, bone grafting with ES has shown to yield good results only failing to enhance bone healing in 10% to 15% of cases. Bone grafting with DC and IC has also been shown to be effective in enhancing bone healing. Nonetheless, only 2 studies were found to use this technique.

There were certain limitations found in the studies during evaluation including the following:

1. Randomization of the RCTs was generally maintained but the allocation methods was not well-defined for the RCTs. The dropout rates were adequate being less than 26% on average with follow-up of the patient in the RCTs being nearly all greater than 86%. Although few studies described the statistical power of their studies. Therefore, more prospective, appropriately powered, well-designed, randomized clinical control trials are needed demonstrating the efficacy of ES in enhancing bone healing in nonunions, delayed unions, fresh fractures, osteotomies, and spinal fusion.

2. Outcome measures for the studies varied, including clinical or radiological union or combinations of both, bone density, scintimetric values, healing success rates, and time to weight bear or consolidation (Table 6). Very few studies looked at patient outcomes, including pain, need for revision surgery, and improvement in functional
The few studies that addressed the effect of ES on patient outcome showed no benefit in terms of pain.8,56,61

Table 6. Analysis of heterogeneity of clinical studies, including evaluation of treatment time, outcome measure, and assessment time follow-up for all 3 types of electrical stimulation.∗

|              | Number of studies for DC (n) | Number of studies for CC (n) | Number of studies for PEMF (n) |
|--------------|-------------------------------|-------------------------------|-------------------------------|
| **A**        |                               |                               |                               |
| Treatment time |                               |                               |                               |
| ≥3 mo duration | 11                            | 1                             | 15                            |
| 3- to ≥6-mo duration | 4                             | 4                             | 9                             |
| 6-mo to ≥1-y duration | 5                             | 1                             | 10                            |
| >1 y duration | 3                             | 0                             | 2                             |
| Until union duration | 7                             | 5                             | 14                            |
| Not state duration of treatment | 1                             | 0                             | 5                             |
| 24 h per day | NA                            | 2                             | 1                             |
| 10-16 h per day | NA                            | 2                             | 25                            |
| 0.5-8 h | NA                            | 0                             | 10                            |
| Not state time per day | NA                            | 7                             | 19                            |
| **B**        |                               |                               |                               |
| Outcome measure |                               |                               |                               |
| Radiographic | 19                            | 5                             | 22                            |
| Clinical | 1                             | 0                             | 7                             |
| Radiographic and Clinical | 11                            | 5                             | 21                            |
| Hoping for 30 s | 0                             | 1                             | 0                             |
| Bone density | 0                             | 0                             | 2                             |
| Time to weight bear | 0                             | 0                             | 1                             |
| Scintimetric analysis | 0                             | 0                             | 1                             |
| Time to consolidation | 0                             | 0                             | 1                             |
| **C**        |                               |                               |                               |
| Assessment time follow-up |                               |                               |                               |
| ≥3 mo | 8                             | 2                             | 7                             |
| 3 to ≥6 mo | 3                             | 3                             | 5                             |
| 6 mo to ≥1 y | 7                             | 2                             | 11                            |
| >1 y | 7                             | 0                             | 6                             |
| Until union | 6                             | 4                             | 25                            |
| Not state | 00                            | 0                             | 0                             |

∗DC indicates direct current; CC, capacitive coupling; PEMF, pulsed electromagnetic field.

3. Furthermore, there is lack of agreement of a definition for a nonunion varying from 3 months to 9 months and the entry criteria amongst studies (see Tables 3-5).84,85,88,91 Some studies define nonunion clinically, whereas some additionally incorporate radiological criteria.84,85,91 Therefore, a consensus is needed for the definition of nonunion, and thus ES studies can be reliably compared.

4. The length of assessment to assess the effectiveness of ES also varied from 2 to 18 months (Table 6). The treatment time also varied as shown in Table 6. Capacitive coupling treatment ranged from 10 weeks to 6 months for between 10 and 24 hours a day and IC ranged from 3 to 18 hours daily over a period of 3 weeks to 9 months with DC being more uniform at 12 weeks.

5. There was a degree of variety in frequency and amplitude within the type of ES subgroups (Tables 3-5). Most IC devices reported a similar frequency between 15 and 75 kHz.9,10,11,93,94,110,114,115,119 Direct current was generally reported using 20 μA across 4 cathodes53,54,55,56 though there was heterogeneity, as 2 studies reported
40 μA\textsuperscript{48,65} and 3 studies used 10 μA.\textsuperscript{51,57,75} Capacitive coupling in approximately half of the studies reported at 60 kHz at 5 V.\textsuperscript{82,87,88,90,91}

6. Few trials had more than 80 patients; for example, there were only 10 patients in DC and IC and 1 patient in CC, which was for spinal fusion (see patient number in Tables 3-5).

7. Only 3 studies compared the clinical efficacy of different methods of ES,\textsuperscript{49,63,86} which may be due to small number of patients used in ES studies. These studies are required, as they offer the potential to illustrate the most beneficial mode of ES for each orthopedic clinical problem.

In conclusion, the exact mechanism by which ES enhances bone repair is still not fully understood and needs more investigation. However, to date, DC has been documented to work by an electrochemical reaction at the cathode, and CC and IC have shown to work by alteration of growth factors and transmembrane signaling. In an era of evidence-based medicine, fracture-healing management should be based on the best available evidence to ensure high-quality, safe, and cost-effective treatment. Therefore, considering the widespread usage of ES to aid bone healing in clinical practice, our analysis shows that there have been few good quality clinical studies to support their use. This is demonstrated by the low recommendation assigned to ES for different orthopedic conditions requiring bone healing except spinal fusion (Table 2). Therefore, the optimal regime for ES treatment for bone healing needs to be further defined and standardized. Moreover, clinical studies need to have uniform outcomes and defined criteria on the effect of ES on clinical outcomes including improvement in pain, activities of daily living, and need for revision surgery. Overall, the evidence to date implies that further studies are needed to support and optimize the clinical application of ES for bone healing.

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