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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.[1] 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]

Table 1. *A table illustrating some of the clinical electrical stimulation devices used today which have been FDA approved.**

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]

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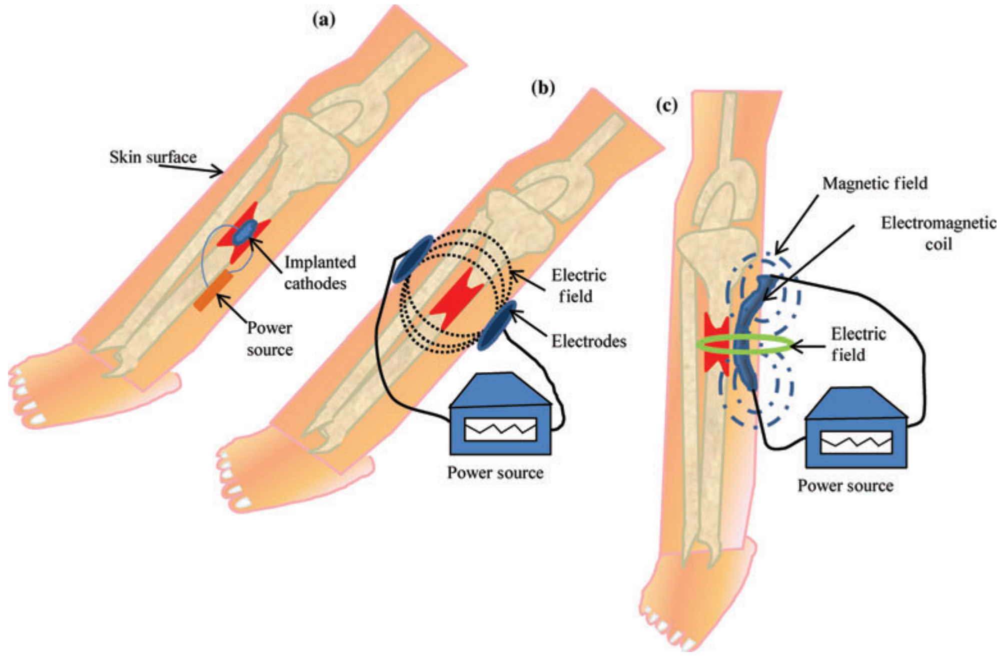

Figure 1. The three methods of administering electric stimulation are shown in this diagram. (*a*) Direct current (DC): A cathode is implanted at the fracture site which is attached to either a subcutaneous power source or an external power source to generate an electric field at the fracture site. (*b*) 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.[4] As current flows through the coils, an electromagnetic field radiates at right angles to the coil base but within the fractures site.[4] 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.[5] 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.[6] Inductive coupling and CC are beneficial treatment options for patients as they are noninvasive, painless, and surgery free.[4] Furthermore, they can be easily and conveniently used by patients at home and in most cases patients are allowed to bear weight.[4]

Electrical stimulation has shown to be effective in aiding bone healing in a variety of orthopedic conditions such as aiding internal and external fixation,[7] enhancing delayed or nonunion fractures[8] and osteotomies,[9] improving the efficacy of bone grafts,[10] treating fresh fractures,[11] and aiding femoral osteonecrosis.[12] However, the mechanism by which ES has its stimulatory effect in enhancing bone healing remains unclear.[3]

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 identity 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.*

	Level of Recommendation
Direct current	
Spinal fusion	B
Ankle/foot union	C
Osteonecrosis of the femoral head	B
Nonunion	C
Capacitive coupling	
Spinal fusion	A
Nonunion	C
Pulsed electromagnetic field	
Spinal fusion	A
Ankle/foot union	C
Osteonecrosis of the femoral head	C
Nonunion	C
Osteotomy	B
Fresh fracture	B
Congenital pseudoarthrosis	C

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

Figure 2 shows an overview of the selection of the studies used and the final articles selected for each type of ES for both clinical and in vitro studies.

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.[13-22] The production of hydroxyl ions (OH) at the cathode are shown to lower the oxygen concentration and increase the pH.[15] This environment prevents bone resorption and increase bone formation by increasing osteoblast and decreasing osteoclast action.[15] A second faradic product hydrogen peroxide (H_2O_2) is also formed at the cathode,[15] which enhances osteoclast differentiation.[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.[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.[19] Figure 3a shows a summary of DC-proposed mechanism of action.

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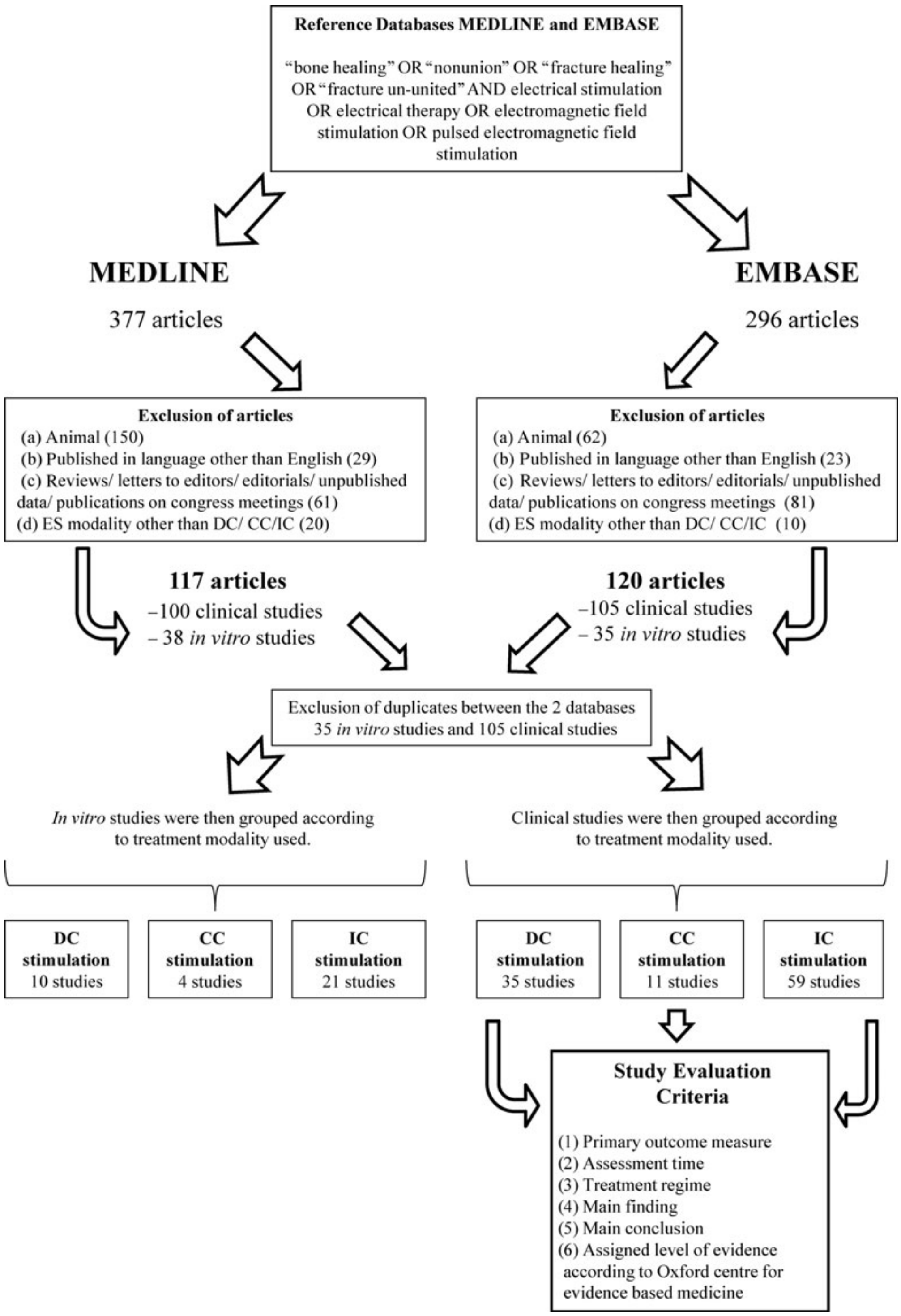

Figure 2. Flow chart demonstrates the selection criteria and process employed in the study. CC indicates capacitive coupling; DC, direct current; ES, electrical stimulation; IC, inductive coupling.

The vitro studies reviewed[23–26] that use CC describe the main mechanism by which CC stimulates bone formation is by calcium translocation via voltage-gated calcium channels.[23,24] This mechanism was proved when verapamil was administered to block the Ca^{2+} channels in osteoblasts treated with CC, as the cell proliferation consequently decreased.[24] However, once the calcium voltage-gated channels are activated, this triggers an augmenting pathway. First, there is an increase in phospholipase A_2, which raises prostaglandin E_2 synthesis.[23] This then amplifies cystolic Ca^{2+}, which increases intracellular calcium stores to activate the last step in the pathway, of enhancing the activated calmodulin levels.[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.[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[25] and transforming growth factor-beta 1 (TGF-β1) is increased by osteoblasts stimulated by CC.[26] Figure 3b shows a summary of CC-proposed mechanism of action.

Two mechanisms are described by which IC has its stimulatory effect.[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)[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.[32] Second, a key metabolic pathway for IC stimulation is the activation of intracellular calcium stores.[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.[23] Thirteen studies[35–47] reported that IC stimulates healing by upregulation of growth factor production including BMP-2,4,6,7, TGF-β1, 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)[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.[51] However, one study found no difference in fusion success after DC[49] and another LOE-1 study showed no increase in lumbar fusion rates in patients older than 60 years after DC.[48] Further LOE-2[52] proved DC to be effectively employed in lumbar interbody fusion. Direct current has been effectively used as an adjunct in hindfoot fusion[62] and revision ankle arthrosis nevertheless providing only a LOE-4[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.[12,53]

Capacitive coupling has been used to enhance bone healing in nonunions, delayed unions, and spinal fusion (Table 4)[82–92]. Two LOE-1 studies utilized CC for the treatment of nonunions. The first study[84] showed CC to be highly effective for treating long bone nonunion, but the second study used it for tibial stress fractures,[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.[86] Furthermore, LOE-4 showed that CC was effective in healing nonunions,[87,89,90] whereas LOE-1 has shown CC to enhance lumbar spinal fusion.[83]

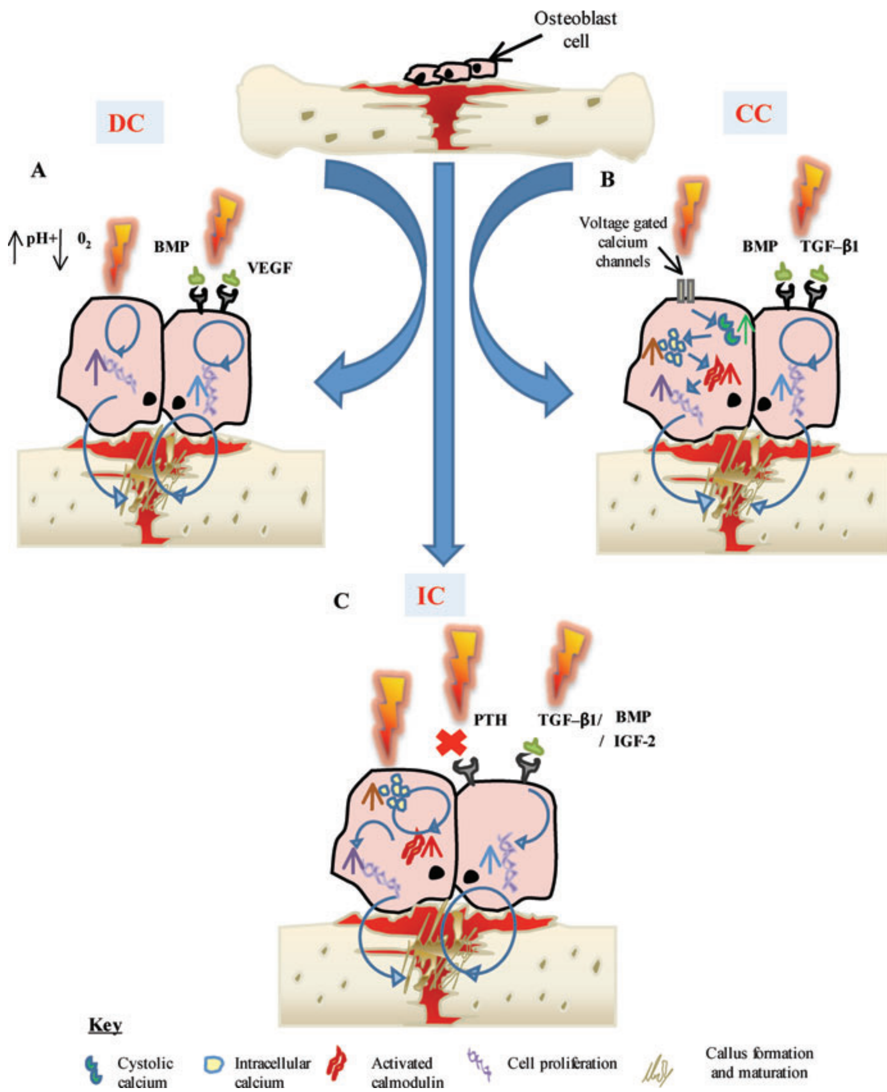

Figure 3. The proposed mechanism of action of the different types of electrical stimulation methods. (*a*) Proposed mechanism for direct current (DC). Direct current lowers the oxygen level and increases the pH, which causes an increase in osteoblast cell proliferation. This in turn enhances callus formation 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 cystolic 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.

Table 3. *Clinical studies reviewed for DC.**

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 al[48]	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 and undergoing spinal fusion	107	CT + Dallas Pain Questionnaire and Low Back Pain Rating Index	40 μA or 100 μA 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 al[49]	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
Kane[50]	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 μA, cathode $\times$4, 24 hr a day for 18 mo	18 mo	15/28 control patients compared with 25/31 active patients healed	DC increases healing rate for spinal fusion. This result is statistically significant ($P = .026$, one-tailed Fisher's exact test).

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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
Rogozinski and Rogozinski[51]	1	Randomized control trial	Test the efficacy of DC in instru-mented 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 instru-mented lumbosacral fusion as has been demon-strated in in-situ fusions
Meril[52]	2	Comparative study	Efficacy of DC in treating interbody fusion rates, ret-rospective 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%).

Steinberg et al[12]	2	Randomized control trial but compared to retrospective study	Effectiveness of core decompression and bone grafting with and without electrical stimulation was compared to nonoperative treatment avascular necrosis of the femoral head	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	Harris Hip scores and radiographic progression	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[53]	2	Non randomized control study	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).	22 decompression and DC; 11 decompression no DC; 48 nonoperatively	Radiographic and modified Hams rating sheet	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

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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
Torben[65]	2	Case control study	Treatment of tibial nonunion with either osteo-stixis with the Hoffmann apparatus with or without DC	Tibial fracture treated with Hoffman 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 al[54]	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
Brighton[55]	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 al[56]	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 al[57]	4	Case series	DC efficacy in long bone nonunion and pseu-doarthrosis	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 pseu-doarthrosis healed	Further laboratory and clinical experiments are required to define the true role of electrical stimulation in clinical practice

Connolly, 1981[58]	4	Case series	DC efficacy in nonunions	Long bone nonunion	85	Radiographic and clinical union	6 mo	6 mo	4/12 healed	DC not effective. Critical evaluation and clarification of indications are essential if DC is to be effective
Cundy and Paterson, 1990[59]	4	Case series	Retrospective long-term follow-up of patients who had DC treatment	NA	38	Radiographic union	Original treatment 3 mo	After 10 y	Still united at 10 y	This 10-y review supports the long-term safety and effectiveness of DC in treating nonuniting fractures
Day[60]	4	Case series	Efficacy of DC in long bone nonunions	Fractures without signs of healing over 3 mo by x-ray	16	Clinical and radiographic union	20 μA for 12 wk	12 wk to 2 y	11/16 healed	The technique is simple/effective. Contraindication: excessive motion at the fracture site or active infection
Dwyer and Wickham[61]	4	Case series	Efficacy of DC in spinal fusion	Patients undergoing spinal fusion	12	Radiographic union	20 μA for 12 weeks	Until union	11/12 fusion	First report of DC effectiveness in spinal fusion

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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 Ward[62]	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 al[63]	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
Heppenstall[64]	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

Kucharzyk[66]	4	Low level case control-prospective study	In 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	65	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]	4	Case series	DC efficacy as an adjunct to revision ankle arthrodesis aseptic nonunion and bone graft	Ankle arthrosis in the patients was posttraumatic in 8 and rheumatologic in 2.	10	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]	4	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	84	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

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
Paterson et al[69]	4	Case series	Treatment of congenital pseudoarthrosis with DC	Congenital pseudoarthrosis of the tibia	25 (27 sites)	Radiographic and clinical and 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 al[70]	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

Welch et al[71]	4	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[72]	4	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	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[73]	5	Expert opinion	NA	NA	NA	NA	NA	NA	NA	DC successful, healing rate 60%-80% after 3-6 mo, 20 μA for 12 wk effective

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
Cohen et al[74]	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 al[75]	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 al[76]	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 and clinical fusion	14 wk	14 wk and 1-y follow up	Fusion of talus	DC created an osteogenic environ-ment one of the factors that decrease the chance of a nonunion
Lavine and Grodzinsky[77]	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

Lavine et al[78]	5	Case report	Efficacy of DC in congenital pseu-doarthrosis	Congenital pseu-doarthrosis	2	Radiographic and clinical union	4 mo	4 mo	Fusion in both cases of pseu-doarthrosis	2 cases of congenital pseudoarthrosis of the tibia treated by DC are presented. A bone graft may be added to enhance bony union in conjunction with DC
Paterson and Simonis[79]	5	Case reports	Treatment of congenital pseu-doarthrosis with DC	Congenital pseu-doarthrosis of tibia	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	Encouraging preliminary results for DC treatment of congenital pseudoarthrosis of the tibia
Phieffer and Goulet[80]	5	Expert review	NA	NA	NA	NA	NA	NA	NA	DC has an effective role in bone healing
Steinberg et al[81]	5	Review expert opinion	NA	NA	NA	NA	NA	NA	NA	More precise evaluation methods are needed before electrical stimulation can be properly evaluated

* 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)[93-146]. Three LOE-1 studies utilized IC for tibial nonunions. The earliest study[93] showed no statistical difference in healing after stimulation, while later studies supported IC.[8,108] Furthermore, LOE-4 demonstrated IC to be effective in enhancement of long bone nonunions.[123,114,110] LOE-1 studies showed IC to be effective in enhancing healing of femoral[9] and tibial osteotomies.[104,109] LOE-1 proved IC ineffective for disuse of osteoporosis and bone formation during limb lengthening.[97] Inductive coupling has been shown to aid healing of fresh fractures by LOE-1.[11,94] Inductive coupling was supported by LOE-1 to be effective for patients undergoing interbody fusion,[106] enhancing posterolateral lumbar fusion[105] and increasing fusion rates in anterior cervical disectomy.[98] LOE-1 and LOE-4 verified that IC is successful in congenital pseudoarthrosis.[107] In contrast, LOE-1 proved IC ineffective for Perthes disease.[99] Inductive coupling has shown to effectively enhance fusion success of hindfoot arthrodesis with one LOE-1 study[96]; nonetheless, there is conflicting inconsistent LOE-4 supporting IC for aiding fusion after ankle arthrodesis.[137,139,140] 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.[13-22] For CC, molecular pathways and growth factors have been shown to enhance proliferation and differentiation of the osteoblast.[23-26] Inductive coupling was shown to enhance osteoblast differentiation and proliferation by mechanisms involving alteration of growth factors[27], gene expression,[28] and transmembrane signaling.[29] 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.[33,34] 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[46] 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.[36,37] 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 al[82]	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 al[83]	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

Table 4. *Continued*

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 King[84]	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 al[85]	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 al[86]	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

Brighton and Pollack[87]	4	Case series	Does CC aid help recalcitrant fractures	Nonunion was diagnosed from roentgenograms were no progressive signs of healing of the nonunion callus over a 3-mo period	22	Radiographic assessment	Until union: 60 kHz 5 V peak-to-peak for an average of 24.8 wk	After 12 wk and then at union if not healed at 12 wk	17/22 healed on average 22.5 wk of treatment	CC is noninvasive, involves portable equipment, allows full weight-bearing 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[88]	4	Case series	Logistic regression analysis was used to compare healing rates among the 3 treatment methods and to identify risk factors adversely affecting the heal rate	Nonunion of more than 9 mo without any healing in last 3 mo on x-ray	271 DC (167 patients), CC (56 patients), or bone graft surgery (48 patients).	Radiographic union	DC 20 μA 12 wk, CC 60 kHz 5V peak-to-peak 24 h a day for 12-24 wk	Observed at end of treatment and then if not healed for 3 monthly follow up	When no risk factors no differences among the 3 methods	As progressively more risk factors were present, the predicted heal rates decreased significantly regardless of the treatment method

Table 4. *Continued*

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 5V 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[51,50] 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.[48,49] 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.[147] 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.[54] Furthermore, rate of unions were not significantly different compared to rates after bone graft surgery.[54] 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.[59] 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[84] consisted of a small sample size and had a large variety in fracture sites between control and stimulated groups. Despite Beck et al[82] 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,[85,87,90] 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[83]; therefore, further studies are required though as to date giving a level of recommendation as A.

Table 5. *Clinical studies reviewed for Inductive coupling (IC) which is also referred to as pulsed electromagnetic field.**

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 (data set reported by Sharrard)[93]	1	Randomized control trial, interim report	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 radio-logical 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 conser-vative manage-ment of nonunion is effective and this may explain much of the success attributed to PEMF
Betti et al[94]	1	Randomized control trial	Effect of PEMF on fracture of femoral neck by 3 screws fixation	Fracture of the femoral neck	30 active 35 control	Clinical and healing rate	30, 90 d + 6, 12, 24 mo	3 mo	Decreased pain + increased consolida-tion	PEMF effective
Borsalino et al[9]	1	Randomized control trial	PEMF treatment in osteotomy of the hip in patients >70 y	Osteoarthritis of the hip	16 control and 16 treated group	Radiographic and bone density score	3 mo 8 h a day	3 mo	Significant difference between controls and active patients ($P < .01$).	In this extremely homoge-neous patient population, PEMF stimulation favored osteotomy healing

Capanna et al[95]	1	Randomized control trial	Efficacy of PEMF in healing of the junction between the allograft and the host bone after tumor resection	Host graft junctions	24 treated group and 23 control group	Healing rate	Every 2 mo till 12 mo	12 mo	13/24 active + control 13/23 healed	Host graft junction 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[96]	1	Randomized control trail	PEMF for hindfoot arthrodesis	Elective triple/subtalar arthrodesis	144	Radiographic union	12 h a day	Until union	Talonavicular joint control group healed in 17.6 wk/PEMF healed in 12.2 wk Calcaneocuboid 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

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
Eyres et al[97]	1	Randomized control trial	PEMF effect in limb lengthening	Limb lengthening was performed by the Villarubbias technique using either a unilateral or circular frame system	13 cases 18 sites	Bone density and compared to 3 radio-graphic 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 al[98]	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 Bassett[99]	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

Hanft et al[100]	1	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	31		Time to consolidation	1/2 h each day until union	Until consolidation	23.8 wk for the control versus 11.1 wk for the active group	Thus the results of this expanded pilot study demonstrate the efficacy of PEMF in accelerating the consolidation process of acute, phase 1, Charcot joint, and decreasing the amount of residual deformity
Kennedy et al[101]	1	Randomized control trial	PEMF stimulation for loosened cemented hip prostheses	Clinical symptoms severe enough to warrant revision hip surgery	37		Harris hip score and Roentgenogram were performed	6 mo at least 8 h a day	6, 12, 18, 24, and 36 mo	10/19 active healed and 2/18 control	This data suggest that for loosened cemented hip prostheses use of PEMF is a treatment option only to delay revision hip surgery
Linovitz et al[102]	1	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	201		Fusion at 9 mo, based on radiographic union	30-min treatment per day for 9 mo	3, 6, and 9 mo after surgery and 3 mo after the end of treatment	Active group, 64% healed at 9 mo compared with 43% control group	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[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 $<45^0$	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[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 5/19 control healed	PEMF positive effect on healing of osteotomies
Mammi et al 1993[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 and 7/20 control healed	PEMF positive effect on posterolat-eral arthrodesis
Mooney[106]	1	Randomized control trial	Effect of PEMF on pos-terolumbar 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 healed	PEMF positive effect on posterolat-eral lumbar fusion arthrodesis

Poli et al[107]	1	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]	1	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]	1	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]	1	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]	1	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

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
Bassett et al[110]	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[111]	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[112]	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

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	18 hips thought to have benefited by the treatment	Further exploration of PEMF is warranted in the treatment of osteonecrosis of the femoral head
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	Every 4-6 intervals	114/127 of fractures healed	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	Monthly	Group A: 33/38 healed Group B: 42/45 healing rate	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

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
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

Biglini et al[118]	4	Case series	Treatment of PEMF for adjunct to noninvasive adjunct when performing arthrodesis of the knee after failed total joint arthroplasty	Patients with a failed arthrodesis	20		Clinical and radiological union	10-14 h daily for average 5.9 mo, range from 3-12 mo	4-6 assessments 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	33		Clinical and radio-graphic union	50 kHz. 12-15 daily until united or up to 1 y	9 and 12 mo	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	56		Clinical and radio-graphic outcome	18-20 h a day for 3-10 wk	10 wk	All 10 patients with delayed union and 84% of nonunions healed	PEMF effective. Nonunions with a gap between the tibial fragments and pseudoarthroses 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

Fontanesi et al[125]	4	Case series	PEMF treatment of congenital and acquired pseudoarthrosis and of delayed unions	Congenital and acquired pseudoarthrosis and of delayed unions	153	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[126]	4	Case series	PEMF use in treating delayed and nonunion of fractures	Fractures and osteotomies with average nonunion for 8 mo	12	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[127]	4	Case series	PEMF treatment in scaphoid	Scaphoid fractures that were at least 6 mo old	44	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

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
Garland et al[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 assess-ment 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[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[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[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

Massari et al[132]	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	8 h per day for average 5 mo	At time of union	PEMF preserved 94% of Ficat stage-I or -II hips	Long-term effect of PEMF may be to promote osteogenic activity at the necrotic area and prevent trabecular fracture and subchondral bone collapse
Madronero et al[133]	4	Case series	PEMF in promoting healing of delayed union and nonunion of bone	Radius nonunion	10	Absence of callus formation	Until union average 104 d	At union	Consolidation in 6 cases	PEMF failure is associated with implanted metallic plates
Marcer et al[134]	4	Case series	Treatment of PEMF in tibia, femur, and humeri nonunions	Ununited fractures treated with external fixation	147	Clinical and radiological union	10 h a day for average 7 mo	Monthly	107/147 fractures healed	Failure to achieve union with PEMFs was most closely associated with very wide fracture gaps
Meskens et al[135]	4	Case series	Efficacy of PEMF in treatment of externally fixed ununited fractures	Nonunion of least 24 mo since injury	34	Radiographic and clinical union	At least 6 mo	At union	Success rate was 75%,	PEMF effective for nonunions

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
Meskens et al[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[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 immoblization and limited weight bearing low success rate
Satter Syed et al[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 wave form shown to be effective need further investiga-tion	
Saxena et al[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[140]	4	Case series	Electrical bone stimulation for arthrodeses of the foot and ankle in high-risk patients	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	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[141]	4	Case series	Efficacy of PEMF in united fractures	Nonunion for at least 1 y and no healing over 3 mo on x-ray	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[142]	5	Expert Opinion	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[143]	5	Expert opinion	NA	NA	NA	NA	NA	NA	NA	PEMF is successful nonunion and delayed unions
Das Sarker and Bassett[144]	5	Case report	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	

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
Gossling et al[145]	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 al[146]	5	Case report	Long-term follow-up of a patient with congenital pseudoarthrosis 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 Grodzinsky[77]	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.[8,108] However, in the study by Sharrard,[8] 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[108] 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.[9,104,109] Inductive coupling is effective in fresh fractures although supported by only 2 RCTs.[11,94] In one such study, scintimetric analysis was a primary outcome measure.[11] This did not reliably examine the effect of ES on patient's clinical outcomes and also failed to show any benefit in redisplacement 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.[94] Hence, overall, the recommendation remains as level B. Inductive coupling had no effect on regenerate bone during limb lengthening,[94] 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.[106,107] However, in one study, the radiographic criteria for fusion required only 50% incorporation of the graft[106] 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,[107] 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.[145] However, bone grafting with ES has shown to yield good results only failing to enhance bone healing in 10% to 15% of cases.[145] Bone grafting with DC[79] and IC[145] 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.[8,9,11,93,97,107] 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%,[9,11,84,93,97,108] although few studies described the statistical power of their studies.[8,84,93] 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

status. 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	1

*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 cathodes[53,54,55,56] though there was heterogeneity, as 2 studies reported

40 μA[48,65] and 3 studies used 10 μA.[51,57,75] Capacitive coupling in approximately half of the studies reported at 60 kHz at 5 V.[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,[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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