Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults (Review)

Griffin XL, Costa ML, Parsons N, Smith N

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2011, Issue 4

http://www.thecochranelibrary.com

Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults (Review)
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
TABLE OF CONTENTS

HEADER ................................................................. 1
ABSTRACT .............................................................. 1
PLAIN LANGUAGE SUMMARY ........................................... 2
BACKGROUND .......................................................... 2
OBJECTIVES ........................................................... 3
METHODS ............................................................... 3
RESULTS ................................................................. 5
  Figure 1. ............................................................. 7
  Figure 2. ............................................................. 9
DISCUSSION ............................................................ 9
AUTHORS’ CONCLUSIONS ............................................. 11
ACKNOWLEDGEMENTS ................................................ 12
REFERENCES .......................................................... 12
CHARACTERISTICS OF STUDIES .................................... 13
DATA AND ANALYSES ................................................ 22
  Analysis 1.1. Comparison 1 Electromagnetic stimulation versus sham, Outcome 1 Proportion of fractures united. 22
  Analysis 1.2. Comparison 1 Electromagnetic stimulation versus sham, Outcome 2 Proportion of non-unions united at 24 weeks. 23
  Analysis 1.3. Comparison 1 Electromagnetic stimulation versus sham, Outcome 3 Proportion of fractures united at 12 weeks. 23
  Analysis 1.4. Comparison 1 Electromagnetic stimulation versus sham, Outcome 4 Proportion of non-unions healed at 24 weeks subgrouped by electrostimulation type. 24
ADDITIONAL TABLES .................................................. 24
APPENDICES ........................................................... 25
HISTORY ................................................................. 27
CONTRIBUTIONS OF AUTHORS ..................................... 27
DECLARATIONS OF INTEREST ....................................... 27
SOURCES OF SUPPORT ............................................... 27
DIFFERENCES BETWEEN PROTOCOL AND REVIEW .................... 28
INDEX TERMS ........................................................ 28
**ABSTRACT**

**Background**

Delayed union and non-union of fractures are a considerable cause of morbidity to patients. Laboratory studies have shown that electromagnetic fields can stimulate the formation of new bone, indicating a potential role for electromagnetic stimulation in the treatment of fractures that have failed to heal.

**Objectives**

To assess the effects of electromagnetic stimulation for treating delayed union or non-union of long bone fractures in adults.

**Search strategy**

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (May 2010), the Cochrane Central Register of Controlled Trials (in *The Cochrane Library* 2010, Issue 2), MEDLINE (1966 to May 2010) and EMBASE (1980 to 2010 Week 20), trial registers and reference lists of articles.

**Selection criteria**

Randomised controlled trials evaluating electromagnetic field stimulation for the treatment of delayed union or non-union of long bones in adults.

**Data collection and analysis**

Two authors independently selected studies and performed data extraction and risk of bias assessment. Treatment effects were assessed using risk ratios and, where appropriate, data were pooled using a random-effects model.

**Main results**

Four studies, involving 125 participants, were included. Three studies evaluated the effects of pulsed electromagnetic fields and one study, capacitive coupled electric fields. Participants with delayed union and non-union of the long bones were included, but most data related to non-union of the tibia. Although all studies were blinded randomised placebo-controlled trials, each study had limitations. The primary measure of the clinical effectiveness of electromagnetic field stimulation was the proportion of participants whose fractures had united at a fixed time point. The overall pooled effect size was small and not statistically significant (risk ratio 1.96; 95% confidence interval 0.95 to 3.99). Further trials are needed to confirm these findings.
interval 0.86 to 4.48; 4 trials). There was substantial clinical and statistical heterogeneity in this pooled analysis (I² = 58%). A sensitivity analysis conducted to determine the effect of multiple follow-up time-points on the heterogeneity amongst the studies showed that the effect size remained non-significant at 24 weeks (risk ratio 1.61; 95% confidence interval 0.74 to 3.54; 3 trials), with similar heterogeneity (I² = 57%).

There was no reduction in pain found in two trials. No study reported functional outcome measures. One trial reported two minor complications resulting from treatment.

Authors’ conclusions

Though the available evidence suggests that electromagnetic field stimulation may offer some benefit in the treatment of delayed union and non-union of long bone fractures, it is inconclusive and insufficient to inform current practice. More definitive conclusions on treatment effect await further well-conducted randomised controlled trials.

Plain Language Summary

Does electromagnetic field stimulation help heal fractures that are failing or have failed to heal?

Broken bones (fractures) that do not heal (thus do not achieve “union”) in the normal time period can lead to a loss of function and pain. This problem leads to a reduction in a person’s quality of life and may prevent their return to work with consequent costs to society. This review determines whether treatment with electromagnetic fields is effective in healing fractures that have not united based upon the best available evidence. The review only looks at fractures of the long bones. These are the upper arm bone, the two forearm bones, the thigh bone, and the two lower leg bones.

Four studies, which involved 125 participants, were included in this review. The majority of participants had suffered a broken tibia that had not healed as quickly as expected or at all. The results of this review suggest that there may be a benefit on bone healing from electromagnetic field stimulation. However, the available evidence was not good enough to be certain of this and it may not apply to current practice. Electromagnetic field stimulation appears to be safe. The two complications reported were minor involving irritation of the skin.

Background

Description of the condition

Delayed union or non-union of fractures occur in 5% to 10% of long-bone fractures. Both outcomes result in considerable morbidity, loss of independence and loss of productivity (Aaron 2004). Early recognition of delayed or non-union improves outcomes and prevents further anxiety and disability for the patient. Delayed union can be defined as when a fracture, while showing clinical or radiological signs of ongoing healing, fails to unite within the anticipated time for that fracture. Non-union can be defined as when the normal biological healing process of bone has ceased, without union occurring. Both these definitions are pragmatic and aim to represent the clinical reality of these outcomes in the context of a ‘continuous’ rather than a categorical (healed or not) process. Non-unions may be classified according to their radiographic appearance as either hypertrophic or atrophic. Hypertrophic non-unions develop abundant callus (healing tissue at fracture sites) without union, whereas atrophic non-unions show little or no callus and resorption of bone. These different types of non-union are generally thought to be caused by an adverse mechanical environment for fracture healing and a failure of fracture biology respectively.

Many factors contribute to the pathogenesis of delayed union and non-union. Important characteristics of the fracture include fracture displacement, the severity of the injury to the soft tissue envelope, energy transfer at the time of injury, infection at the fracture site and the speed and success of initial management. Iatrogenic factors include medications such as anticoagulants, steroids, some anti-inflammatory drugs and radiotherapy. There are also important patient factors such as age, mineral and vitamin deficiencies (particularly calcium and vitamins C and D) and it has been shown that smoking has a detrimental effect upon bone healing in several ways (Phieffer 2006).
Description of the intervention
In 1953, Yasuda published work on the piezoelectric forces within bone (Yasuda 1953). Since then there has been considerable interest in the manipulation of electromagnetism in bone healing. Research has concentrated on stimulating the healing of bone in established non-union. Bassett and Friedenberg were the first investigators to show that there is bone formation following electrical stimulation (Bassett 1964; Friedenberg 1970). Initially electrodes were implanted directly into the bone (Friedenberg 1971). In 1978, Bassett et al began to use externally applied electromagnetic fields in clinical cases of non-union (Bassett 1978). In all, five methods have been developed for the application of electromagnetic fields to the fracture site in order to promote healing:
- Direct current (DC) delivered via a percutaneous cathode and an anode in contact with the skin
- Direct current (DC) delivered by a completely implanted system
- Capacitive coupled electric field (CCEF) through conductive plates attached to the skin
- Pulsed electromagnetic fields (PEMF) through externally applied coils which induce low level current
- Combined electromagnetic fields (CMFs) which use both dynamic and static magnetic fields

All of these methods use low-level electrical currents (Cakirgil 1989; Karamitros 2006). Pulsed electromagnetic fields contain a broad band of frequencies, but the majority of their energy lies at the lower end of the spectrum (< 1kHz) (Bassett 1989). Both direct current methods are invasive techniques that carry the risk of infection. However, the other applications are non-invasive (Karamitros 2006) and can be used in cases of infected non-union (de Haas 1980).

How the intervention might work
The exact mechanism of action of electromagnetic stimulation is still under investigation, but research suggests that pulsed electromagnetic fields affect several aspects of fracture healing: encouraging mineralisation and angiogenesis (formation of new blood vessels), increasing DNA synthesis and altering the cellular calcium content in osteoblasts (bone producing cells) (Bassett 1989).

Why it is important to do this review
As yet there is no current consensus regarding the application of this treatment in clinical practice. An earlier systematic review conducted by some of the review authors identified a substantial evidence base of randomised and non-randomised trials evaluating the use of electromagnetic field stimulation in the management of delayed union and non-union (Griffin 2008). We considered that a comprehensive review of the literature and, where possible, meta-analysis of the data using up-to-date methods would provide the best evidence to inform current clinical practice and future research efforts.

OBJECTIVES
To assess the effects of electromagnetic stimulation for treating delayed union or non-union of long bone fractures in adults.

METHODS
Criteria for considering studies for this review
Types of studies
Randomised and quasi-randomised (method of allocating participants to a treatment which is not strictly random e.g. by date of birth, hospital record number, alternation) controlled clinical studies evaluating electromagnetic field stimulation for the treatment of delayed union or non-union of long bones.

Types of participants
Any skeletally mature adults over the age of 18 years with clinical or radiological confirmation of the diagnosis of the failure of a long bone fracture to unite. Bone healing is influenced by many varied factors including the type of bone fractures (spongy versus tubular bones). We only considered long bone fractures in order to reduce heterogeneity. Studies involving the femur, tibia, fibula, humerus, radius and ulna were eligible. The definitions of delayed union and non-union are contentious. For the purposes of this review we took a pragmatic approach and included any study in which participants are included for the management of a fracture that had failed to unite as defined by the treating clinician.

Types of interventions
Trials of all types of electromagnetic field stimulation, as described in the Background, were included, provided this was compared with either no additional treatment or a placebo. Electromagnetic field stimulation could be the only treatment or be an adjunct to treatment applied to all trial participants. Trials comparing electromagnetic field stimulation with other interventions, such as therapeutic ultrasound, were excluded.
Types of outcome measures

Just as the definition of the failure of a fracture to heal within normal physiological time frames is contentious, so is the definition of a healed fracture. For the purpose of this review we adopted the widely accepted definitions in the literature. A fracture is healed when callus is present bridging three of four cortices (hard outer margins of the bone) on orthogonal (at right angles) radiographs and there is a reduction in pain and elimination of movement at the fracture site. As expected, studies reported the proportion of participants with healed fractures at one or more fixed time points after treatment. This was thus used as the primary outcome measure for this review. As stipulated in the protocol, the primary outcome for union may have been changed if studies had exclusively presented time-to-union data.

Primary outcomes

The primary measure was the proportion of participants whose fractures had healed at a fixed time point.

Secondary outcomes

The secondary outcomes assessed were:

- the overall quantitative functional improvement of the participant using recognised patient-reported outcome measures and the return to normal limb activity
- adverse effects
- measures of pain

Timing of outcome assessment

In the protocol we anticipated that studies may report proportional incidence of union at several time points. We planned to group these assessments into three categories: short (up to 3 months), medium (between 3 and 12 months) and long-term follow-up (greater than one year). These time points are, by necessity, a compromise given the differences in typical healing times of different bones.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (May 2010), the Cochrane Central Register of Controlled Trials (in The Cochrane Library 2010, Issue 2), MEDLINE (1966 to May 2010) and EMBASE (1980 to 2010 Week 20).

In MEDLINE (PubMed) the subject specific search strategy was combined with a modified version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (Lefebvre 2009). The EMBASE subject specific search strategy was combined with the Scottish Intercollegiate Guidelines Network RCT search filter. Details of the search strategies for the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE are shown in Appendix 1. No language restrictions were applied.

Current Controlled Trials and the WHO International Clinical Trials registries were searched in order to identify studies that had not yet been reported at the time of the review.

Searching other resources

We searched reference lists of articles retrieved from the electronic search. We contacted experts in the field for any additional or unpublished articles.

Data collection and analysis

Selection of studies

Two authors (XG and NS) independently selected the studies for inclusion in the review based upon the criteria defined above. Where there was disagreement between the authors this was settled by consensus between all authors of the review.

Data extraction and management

Two authors (XG and NS) extracted data from the included studies independently using the Cochrane Bone, Joint and Muscle Trauma Group's data extraction form. Extracted data from the studies were managed and collated by the review statistician (NP), who was independent from the study selection.

Assessment of risk of bias in included studies

Each included study was assessed for the risk of bias using the recommended Cochrane Collaboration 'Risk of bias' tool (Higgins 2008). This tool incorporates assessment of randomisation (sequence generation and allocation concealment), blinding (participants, personnel and outcome assessors), completeness of outcome data, selection of outcomes reported and other sources of bias. Other sources of bias included selection bias, where we assessed the risk of bias from imbalances in key baseline characteristics (age, sex and smoking behaviour). We assessed the risk of bias associated with a) blinding and b) completeness of outcomes for patient-reported outcomes and objective outcomes separately.
Measures of treatment effect
The effect of the treatments on each participant was either union or non-union of the long bone at the chosen time point after treatment. The effects of the test treatment (electromagnetic stimulation) versus the control (sham) treatment on union was assessed using a risk ratio. Hazard ratios were not used given that time-to-event analysis was not carried out. When data for continuous outcomes, such as patient reported quality of life measures, become available in the future, we will calculate mean differences or, where studies have used different measurement tools, standardised mean differences. Ninety-five per cent confidence intervals were applied throughout.

Unit of analysis issues
Most studies reported results at a single, primary follow-up time. All studies reported simple parallel group designs involving randomisation of individual patients. Should other designs (e.g. cluster randomised designs) be reported in future, then generic inverse variance methods may be used to combine data. This, however, will only be possible for studies where appropriate estimates of variance have been reported; for instance, for cluster randomised trials where clustering has been properly accounted for in the analysis.

Dealing with missing data
We sought additional information from the authors of the included studies where the published information or data were incomplete. When the missing data could not be reliably determined for dichotomous outcomes, these were initially classed as treatment failures. In future, should continuous outcome data become available, we will not assume values of missing standard deviations in order to present these in the analyses.

Assessment of heterogeneity
We assessed for statistical heterogeneity between studies by visual inspection of the forest plot and more formally using the Chi² test and the P statistic (Higgins 2003). Where there was clearly significant heterogeneity and one or more studies appeared to be clear outliers, data for these studies were checked carefully for errors or other methodological reasons as to why they might differ from the other studies. We planned that if good reason was found why the studies differed from the majority then this it would be noted and reported and the studies removed from the main meta-analyses; however, all analyses would be performed with and without outlier studies (sensitivity analysis).

Assessment of reporting biases
The search strategy described attempts to reduce the risk of reporting bias in the inclusion of studies in this review. There were too few trials to assess the likelihood of publication bias via a funnel plot.

Data synthesis
Results of comparable groups of trials were pooled. We used a random-effects model and 95% confidence intervals.

Subgroup analysis and investigation of heterogeneity
Subgroup analysis was intended to explore possible sources of heterogeneity when significant heterogeneity was present. Three possible subgroup analyses were identified a priori:
1. Upper versus lower limb non-union. This was a pragmatic proxy for weight bearing versus non-weight bearing bones.
2. Smokers versus non-smokers.
3. Different methods of electromagnetic field stimulation: CMF versus PEMF versus CCEF versus DC methods.

Sensitivity analysis
Only the first of our three planned sensitivity analyses described below was done.
1. Examination of the intervention effects at a number of time points (pre-stipulated example was 3 months and 12 months; actual analyses based on 12 and 24 weeks). This was to provide some sensitivity to the selection of an appropriate follow-up time for assessment of the treatment effect.
2. Exploration of the results of excluding studies because they appeared to differ markedly from the majority of studies, and reporting the main analyses with and without these studies.
3. Exploration of the results of excluding studies comparing electromagnetic field stimulation with no treatment (i.e. non-placebo control).

R E S U L T S

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search
Electronic searches retrieved 52 different references to potentially relevant studies. After review of the abstracts, 10 references were thought to be relevant and the full text of each was retrieved. Some of these references were reports of the same study. In all, four studies were included and two studies were excluded. There was
no disagreement between authors (XG and NS) regarding study selection.

Included studies
Four studies, which recruited a total of 125 participants, were included in the review. Details of the individual studies are shown in the Characteristics of included studies.

Design
All four studies were randomised clinical trials comparing electromagnetic stimulation with a sham control.

Sample sizes
Each of the studies was small. The numbers of participants recruited into the individual trials were as follows:
- Barker 1984: 17
- Scott 1994: 23
- Sharrard 1990: 51
- Simonis 2003: 34

Setting
All of the studies were conducted in the UK in an NHS hospital setting. Only Sharrard 1990 was a multi-centre study; this involved 16 hospitals.

Participants
Three of the trials only included people with tibial fractures. In Barker 1984 and Simonis 2003, participants had tibial non-union, whereas Sharrard 1990 only included people with delayed union of the tibia. Scott 1994 included people with a non-union of any long bone, 15 of whom had tibial non-union. Scott 1994, Sharrard 1990 and Simonis 2003 reported the sex of the participants, two thirds of whom were male. The mean age of the participants was 39 years (range 18 to 87 years).

Interventions
Scott 1994 tested capacitive coupled electric fields, while the other three studies (Barker 1984; Sharrard 1990; Simonis 2003) tested pulsed electromagnetic fields created by externally applied coils. All four trials used sham controls. All four studies used concurrent bony stabilisation. In three studies (Barker 1984; Scott 1994; Sharrard 1990), stabilisation was achieved with either a plaster or a brace, and in Simonis 2003, with an unilateral external fixator.

Outcomes
Sharrard 1990 reported union at 12 weeks, whereas the other studies reported union at 24 weeks. Only Barker 1984 reported union at multiple time points (12, 24, 36 and 48 weeks). Barker 1984 reported clinical union, Scott 1994 reported union based on combined clinical and radiographic criteria; Sharrard 1990 reported radiographic union based on a radiologist’s and an orthopaedic surgeon’s assessments; and Simonis 2003 reported radiographic union. None of the included studies used a panel of independent radiologists to assess radiographic union.

Excluded studies
Two studies, for which full text reports were obtained, were excluded from the review (see Characteristics of excluded studies for reasons). Itoh 2008 included participants with acute fractures and Madronero 1988 reported risk factors associated with failure of electromagnetic stimulation based upon a case series.

Risk of bias in included studies
The overall quality of reporting of the studies was poor. However, each study was a randomised, sham-controlled trial and as such was likely to have reasonable internal validity. A summary of the assessment of the risk of bias in each study can be found in Figure 1.
Figure 1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 1984</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Scott 1994</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sharrard 1990</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Simonis 2003</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
Allocation
Each study stated that participants were allocated to interventions randomly. It is likely that the sequences were adequately generated and concealed.

Blinding
Each study was reported to be double-blind. In each study this was achieved by the application of a sham stimulation unit which was identical in external appearances to the active units. It is likely therefore that the blinding was effective. Of note is that Sharrard 1990 reported that one participant tampered with his device and broke the code.

Incomplete outcome data
None of the included studies explicitly reported, or justified where absent, all of the outcome data. We were unsuccessful in our attempts to contact authors for missing data.

Patient-reported outcomes
Simonis 2003 did not report any patient-reported measures. Barker 1984, Scott 1994 and Sharrard 1990 failed to report patient-reported measures for a total of nine participants. The reasons for these losses were varied and included protocol violations, incorrect recruitment and withdrawal by participants.

Objective outcomes
Three studies (Barker 1984; Scott 1994; Simonis 2003) reported sufficient data about the participants to allow an intention-to-treat analysis for the primary outcome measure. Sharrard 1990 failed to report the outcomes of four participants who had either been incorrectly recruited or had failed to comply with the trial protocol. It was not possible to include these participants in the analysis as their treatment allocations were not reported.

Selective reporting
The overall quality of the reporting of the included studies was poor. No protocols were available with which to compare the reports. The reporting of the methods and results was frequently mixed so that determining the risk of bias from selective reporting of outcomes was difficult. Only Scott 1994 reported specified, important, outcome measures that, we anticipate, would have been measured together. However, there was no clear evidence of selective reporting.

Other potential sources of bias
Three studies (Barker 1984; Scott 1994; Sharrard 1990) had an imbalance in the baseline characteristics between the treatment and control groups. The distribution of baseline characteristics in Scott 1994 and Sharrard 1990 (control group: greater average age in both) might be expected to favour electromagnetic stimulation and the sham treatment in Barker 1984 (test group: greater average age). This reflects the direction of effect in each of these studies. Two studies used sham electromagnetic stimulation units which may have produced a therapeutic effect despite being part of the placebo intervention (Barker 1984; Scott 1994). The other studies used similar deactivated units and may have been similarly biased.

Effects of interventions
There was considerable clinical heterogeneity between the studies; nonetheless pooling was considered appropriate.

Primary outcome measures
Proportion of participants achieving union
All four included studies reported data for the proportion of participants achieving union, albeit using different criteria and approaches. Details for each study are reported in the Characteristics of included studies. Given the four studies reported the incidence of union at similar time points, grouping into short, medium and long-term follow-up times was not considered necessary. The primary estimate of the treatment effect from an intention-to-treat analysis where participants whose outcome was not reported, but whose treatment allocation was known, were classed as treatment failures. The overall pooled estimate of the effect of electromagnetic stimulation on union, while favouring electromagnetic stimulation, was not statistically significant (risk ratio (RR) 1.96; 95% confidence interval (CI) 0.86 to 4.48; see Analysis 1.1 or Figure 2). There was substantial statistical heterogeneity amongst the studies (I² = 58%). We therefore conducted a sensitivity analysis to determine the treatment effect based upon pooling data by follow-up time-point. The most reasonable follow-up time-point for the pooled assessment of the treatment effect was at 24 weeks. The decision to pool outcome data from this time-point was largely pragmatic as three of the four of studies reported this (Barker 1984; Scott 1994; Simonis 2003). The estimate of the effect of electromagnetic stimulation on union at 24 weeks was not significant (RR 1.61, 95%CI 0.74 to 3.54; see Analysis 1.2). The analysis of this subset of studies did not explain the observed heterogeneity (I² = 57%). Similarly, pooling of early follow-up data at 12 weeks from Sharrard 1990 with similar data.
from Barker 1984 also produced no statistically significant treatment effect (RR 2.26, 95%CI 0.29 to 17.28; see Analysis 1.3).

Again, this analysis did not explain the observed heterogeneity ($I^2 = 57\%$). All of the studies included a sham (placebo) control in the comparator group and therefore a sensitivity analysis based upon the type of control was unnecessary.

**Figure 2. Forest plot of comparison: Electromagnetic stimulation versus sham, outcome: Proportion of fractures united.**

None of the studies appeared to differ markedly in design or clinical aspects from the others and therefore we did not conduct analyses excluding outlier studies.

Sharrard 1990, which reported the proportion of union at 12 weeks in participants with delayed union, found no statistically significant treatment effect (RR 6.75, 95% CI 0.85 to 53.37).

Each specified *a priori* subgroup analysis was considered. The analysis by the types of electromagnetic stimulation demonstrated no substantial difference between the subgroups (Analysis 1.4). There were inadequate data available to merit conducting the other subgroup analyses.

### Secondary outcome measures

**Functional patient-reported outcome measures**

None of the included studies reported any patient-reported measures of functional outcome.

**Adverse effects**

Only Scott 1994 reported on adverse events. Two participants in the electromagnetic stimulation group of this trial developed an allergic reaction on the skin underlying the applied stimulator plates which resolved with topical hydrocortisone treatment.

**Pain**

Barker 1984 and Sharrard 1990 reported pain using a visual analogue scale (Table 1). There was no report of a significant treatment effect in either study.

While favouring electromagnetic field stimulation, the overall pooled estimate of the effect size of electromagnetic stimulation on healing in the treatment of both delayed union and non-union was not statistically significant (RR 1.96; 95%CI 0.86 to 4.48). Subsequent sensitivity analyses, addressing clinical heterogeneity in time-points for outcome assessment and inclusion criteria for delayed union and non-union also did not reveal a significant treatment effect.

However, it is important to note that the estimates of effect were

---

**DISCUSSION**

**Summary of main results**

Four studies were found which fulfilled the eligibility criteria of this review. The review included data from 121 participants only.
similar in all analyses, with an approximate risk ratio of two, in favour of electromagnetic stimulation. This trend may indicate a real treatment effect, but one that has not been demonstrated in this meta-analysis of studies.

Treatment with electromagnetic fields seems to be safe. Only two adverse events were reported, both of which involved minor skin irritation.

**Overall completeness and applicability of evidence**

**Completeness of the evidence**

We have only been able to find four reports of randomised controlled trials in this field. A recent literature review by Mollon 2008 found no additional studies that fulfilled our inclusion criteria. We assess that it is likely that we have reported all the available published data from randomised controlled trials concerning electromagnetic stimulation in the treatment of delayed union and non-union of fractures of long bones in adults.

The majority of data concerned the treatment of non-union; only Sharrard 1990 included participants with delayed union. Little evidence was available concerning the treatment of bones other than the tibia.

None of the studies reported any patient-reported functional outcome measures (PROMs). There was little evidence regarding pain or adverse events. We did not specify in the protocol that we would report participant adherence to the treatment as an outcome. The treatment periods per day and the duration of total treatment of the interventions described in the studies are considerable. Reporting participant adherence in future updates of this review will be important for assessing the external validity of the studies. Although adherence was mentioned, it was not reported formally as an outcome measure in any of the included studies.

The included studies only report the use of PEMF and CCEF. We did not find reports of any RCTs of other types of electromagnetic field stimulation. Subgroup analysis by stimulation type revealed no significant effect.

Inadequate data were reported to feasibly conduct a subgroup analysis by smoking behaviour or affected limb.

**Application of the evidence to current practice**

There are several factors that may affect the application of the evidence to current practice. The management of acute fractures, delayed union and non-union of long bones has evolved over the period of time during which these studies were conducted, particularly regarding the management of fractures of the tibia. This reflects changes in the management of acute fractures; e.g. the introduction of “fixed-angle” plates and screws (Miller 2008) and the adoption of more robust guidelines regarding the treatment of open fractures (BOA/BAPS Guideline 2009) as well as changes in the management of non-union itself. These changes may affect the incidence of delayed union and non-union and hence the need for treatment of these two conditions.

Apart from Simonis 2003, the other three trials tested the effectiveness of electromagnetic stimulation as an adjunct to plaster or brace immobilisation; thus non-operative treatment of the fracture. There is a trend towards early operative intervention in fractures of long bones, which should also be borne in mind when interpreting this review.

The sample size of each study was small, and recruitment was stopped early. It is possible that such samples poorly reflect the population of patients with delayed or non-union. Scott 1994 generated his sample from a national postal survey. Although this has advantages of increasing the geographic spread of the sample, such purposeful sampling may affect the representativeness of the sample to the overall population of patients with non-union. All studies included in this review were conducted in the UK by a small number of surgeons with a special interest in non-union. Thus, caution should be taken in generalising the results of this review internationally.

Considerable patient adherence is required in order to persevere with the interventions described in this review. Various electromagnetic stimulators are currently available on the market. Recommended daily treatment times range from 20 minutes to 12 hours. We were unable to explain the considerable statistical heterogeneity between studies in this review, which potentially may be related, amongst other items, to the exact treatment interventions employed. Moreover, this review is unable to conclude that modern devices with shorter treatment periods, and potentially better patient adherence, are clinically effective. Whilst data from formal evaluation of adherence are unavailable, the impact of the clinical application of interventions of the type described in this review remains uncertain.

The included studies reported no patient related outcome measures or quality-of-life or health economics measurements. Such tools are increasingly accepted as the principal means of determining the clinical and cost effectiveness of treatments and would therefore influence the availability of electromagnetic field stimulation in some healthcare systems.

Finally, the limitations of each of the included studies mean that firm conclusions about the effectiveness of electromagnetic field stimulation cannot be made for the particular circumstances of individual trials nor collectively. The considerable worldwide variation in the use of this technology mitigates against the generalisability of the review findings should these have been conclusive.

**Quality of the evidence**

**Sources of systematic error**
Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults (Review)

A U T H O R S’ C O N C L U S I O N S

Implications for practice
This review highlights the limitations of the available evidence concerning electromagnetic field stimulation in the current management of delayed union and non-union of long bone fractures. The limited evidence suggests that electromagnetic field stimulation is likely to be safe and may offer some benefit, but this remains inconclusive and insufficient to inform current practice.

Implications for research
Without further well conducted, adequately powered randomised controlled trials it is not possible to determine the effectiveness of electromagnetic field stimulation.

It seems reasonable based upon the findings of this review that a future trial might be appropriate. We recommend a multi-centre study including patients with non-union of the tibia. This population is relatively large, even accepting a falling incidence of non-union. It might be reasonable to power this study based on the assumption that recruitment was more difficult and slower than expected. Barker 1984 explicitly stated that his report was an unexpected interim analysis due to poor recruitment. Scott 1994 reported that he anticipated criticism for stopping early. It is logical to expect therefore that these studies were under-recruited and not adequately powered. The possibility of a type II error in these studies is considerable. The potential advantages of meta-analysis to address this type of error were limited in this review as only 121 participants were included in total and the heterogeneity between the studies was significant.

The funding source of the studies and any conflicts of interests of the authors were not reported. Sharrard 1990 expressed some concern over commercial access to the study data and randomisation sequence in published correspondence after his report was published (Sharrard 1992). Such influences are difficult to establish in the included studies, partly due to the less rigorous standards of reporting existing at their times of publication.

The primary outcome of fracture healing is variably defined in the literature and likewise in the four included trials. As anticipated, we found that studies defined healing clinically and/or radiographically. This reflects the difficulty that is inherent in the assessment of union. The choice of measurement tool and the timing of assessments of union varied between studies. Radiographic union commonly follows behind clinical union and can be difficult to determine from plain radiographs. None of the included studies used a panel of independent radiologists to assess radiographic union.

Potential biases in the review process
None of the authors of this report have been involved in any of the included trials and none have any commercial or other conflict of interest.

Other sources of error
None of the studies reported a sample size calculation, but each stopped without completing recruitment. Each of the studies report that recruitment was more difficult and slower than expected. Barker 1984 explicitly stated that his report was an unexpected interim analysis due to poor recruitment. Scott 1994 reported that he anticipated criticism for stopping early. It is logical to expect therefore that these studies were under-recruited and not adequately powered. The possibility of a type II error in these studies is considerable. The potential advantages of meta-analysis to address this type of error were limited in this review as only 121 participants were included in total and the heterogeneity between the studies was significant.

The funding source of the studies and any conflicts of interests of the authors were not reported. Sharrard 1990 expressed some concern over commercial access to the study data and randomisation sequence in published correspondence after his report was published (Sharrard 1992). Such influences are difficult to establish in the included studies, partly due to the less rigorous standards of reporting existing at their times of publication.

The primary outcome of fracture healing is variably defined in the literature and likewise in the four included trials. As anticipated, we found that studies defined healing clinically and/or radiographically. This reflects the difficulty that is inherent in the assessment of union. The choice of measurement tool and the timing of assessments of union varied between studies. Radiographic union commonly follows behind clinical union and can be difficult to determine from plain radiographs. None of the included studies used a panel of independent radiologists to assess radiographic union.

We have predominantly searched the published literature. Despite efforts to contact experts we have not found any unpublished studies. Given that the period over which most of these studies were conducted trial registration was limited, it is possible that some, perhaps commercially sponsored and negative, trials were not published. We have also not searched conference abstracts. It is, therefore, possible that data exist which we have not included in this review.

There was significant heterogeneity in the meta-analyses. Due to a lack of data we were unable to conduct all of our a priori subgroup analyses to investigate the causes of this heterogeneity. We chose to pool data subgrouped by follow-up time point and type of non-union (delayed union versus non-union). We made these decisions through consensus with a view to dealing with the available data in a pragmatic manner. However, the decisions regarding the pooling of data were necessarily subjective and may be a cause of bias.

Agreements and disagreements with other studies or reviews
The findings of this review are in keeping with a similar recent meta-analysis (Mollon 2008). Mollon 2008 pooled the data from the same four studies using a random effects model based upon an analysis of the reported source data. The analysis concluded a similarly sized, non-significant treatment effect in favour of electromagnetic stimulation (RR 1.76; 95%CI 0.81 to 3.80). Various different sensitivity analyses were reported with no change to the conclusion of the primary analysis.

Potential biases in the review process
None of the authors of this report have been involved in any of the included trials and none have any commercial or other conflict of interest.
upon a estimated risk ratio of approximately two in favour of electromagnetic field stimulation. Union continues to be a difficult outcome to measure. Advanced imaging techniques such as volumetric commuted tomography may reduce the measurement error in the assessment of union. We also recommend that such a future trial report quality-of-life and disease/region specific patient-reported functional outcome measures to support the inference that improved proportions of union correlate with improved patient health. Furthermore, cost-effectiveness measures are key to enabling widespread uptake of a clinically effective technology.

**ACKNOWLEDGEMENTS**

The authors would like to thank Professor William Gillespie, Dr Helen Handoll, Dr Vicki Livingstone and Dr James Heckman for valuable comments in the development of this review, as well as the editorial staff of the Cochrane Bone, Joint and Muscle Trauma Group. We would also like to thank Elsevier for kind permission to reproduce text from another publication (Griffin 2008) used in the Background.

**REFERENCES**

**References to studies included in this review**

Barker 1984 {published data only}

Scott 1994 {published data only}


Sharrard 1990 {published data only}


Simonis 2003 {published data only}


**References to studies excluded from this review**

Itoh 2008 {published data only}

Madronero 1988 {published data only}

Additional references

Aaron 2004

Bassett 1964

Bassett 1978

Bassett 1989

BOA/BAPS Guideline 2009

Cakirgil 1989
de Haas 1980

Friedenberg 1970

Friedenberg 1971

Griffin 2008

Higgins 2003

Higgins 2008

Karamitros 2006

Lefebvre 2009

Miller 2008

Mollon 2008

Phieffer 2006

Sharrard 1992

Yasuda 1953

* Indicates the major publication for the study
## Characteristics of included studies  (ordered by study ID)

### Barker 1984

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised sham controlled trial.</th>
</tr>
</thead>
</table>
| Participants                  | Setting: NHS hospital, Sheffield, UK.  
                                    | Sample: 17 participants with tibial non-union.  
                                    | Baseline characteristics (16 participants): Mean (range) age 34 (19 to 72) years; Male: Female ratio not reported  
                                    | Inclusion criteria: Adults with a mobile fracture of the tibia which had failed to heal after one year with no improvement in the last three months  
                                    | Exclusion criteria: Operative treatment within six months, fracture line not visible across entire diaphysis, fracture within 5 cm of the knee or ankle joint line, fracture gap greater than 0.5 cm, presence of metalwork within the fracture gap, local bone disease or severe bone sepsis, patient receiving steroid treatment, external fixator in place  
| Interventions                 | All participants had a full leg plaster cast with strict non-weight bearing for at least 24 weeks  
                                    | Test treatment: Pulsed electromagnetic fields administered (1.5 mT peak, 5 ms burst waveform at 15 Hz) for periods not less than one hour with a cumulative exposure of between 12 and 16 hours per day. Treatment was given for 24 weeks or until union whichever was longer  
                                    | Comparator treatment: Sham stimulator device which underwent an internal electronic modification of the original test unit. Treatment was given until 24 weeks, if union had not been achieved at that time then participants were given an active machine  
                                    | Assigned: 9/8 (treatment / control)  
| Outcomes                      | Primary: Clinical union at 24 weeks.  
                                    | Secondary: Clinical union at 12, 36 and 48 weeks, pain and tenderness at 12, 24, 36 and 48 weeks  
| Notes                         | Participants in the control group crossed over if they had not achieved union by 24 weeks  
                                    | Reports of possible low strength electromagnetic fields being generated by the sham units  
                                    | “Interim results of a Double-blind Trial”  
                                    | Comment: This is an interim report, no further published reports of the study have been found. The possibility of a type II error is high as recruitment was incomplete  
| Risk of bias                  | Adequate sequence generation?  
                                    | Authors’ judgement: Unclear  
                                    | Description: Quote: “Patients were randomly allocated to either an active or dummy stimulator.”; “We used a minimisation procedure”  
                                    | Comment: No description of method of sequence generation or minimisation parameters  

---

*Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults (Review)*  
Copyright © 2011 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
<table>
<thead>
<tr>
<th>Allocation concealment?</th>
<th>Unclear</th>
<th>Quote: “Patients were randomly allocated to either an active or dummy stimulator.” Comment: No description of means of concealment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding? Patient reported measures</td>
<td>Yes</td>
<td>Quote: “Dummy machines differed from active ones only by a single internal connection.”; “The orthopaedic staff, the technical staff in the clinic, and the patient were unaware of the machine type supplied.” Comment: Participants and personnel were equally and effectively blind to the allocation</td>
</tr>
<tr>
<td>Blinding? Objective measures</td>
<td>Yes</td>
<td>Quote: “Dummy machines differed from active ones only by a single internal connection.”; “The orthopaedic staff, the technical staff in the clinic, and the patient were unaware of the machine type supplied.” Comment: Participants, personnel and outcome assessors were equally and effectively blind to the allocation</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? Patient reported outcomes</td>
<td>No</td>
<td>Quote: “1 of the 17 patients was allocated to the control group, but left the trial at week 18 for personal reasons...” Comment: No account for lost participant is made in the analysis</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? Objective measures</td>
<td>Yes</td>
<td>Quote: “1 of the 17 patients was allocated to the control group, but left the trial at week 18 for personal reasons...”; “He was reported to have an ununited fracture at 48 weeks.” Comment: Sufficient information to conduct intention-to-treat analysis</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Unclear</td>
<td>Radiographs were taken but the findings from these were only used for another concurrent study about inter-observer reliability of this measure. We would have expected this to have been reported here though to support the clinical definition of union All other stated measures were reported.</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Reports of possible low strength electromagnetic fields being generated by the sham units</td>
</tr>
<tr>
<td>No major imbalances in baseline characteristics?</td>
<td>No</td>
<td>There is no report of smoking status in the baseline sample characteristics. There is no account made in the analysis for the imbalance in the ages of the</td>
</tr>
</tbody>
</table>
### Participants

Setting: NHS hospital, London, UK  
Sample: 23 participants, recruited nationally by postal appeal to members of the BOA, with non-union of tibia (15), femur (4) and ulna (2) [2 excluded participants not reported]  
Baseline characteristics (21 participants): Mean (range) age 43 (23 to 87) years, Male: Female ratio 16:5  
Inclusion criteria: fracture for 9 months or longer, with no clinical or radiographic progression towards healing for at least 3 months before entering the trial. If the fracture had been present for 9 months, continuous immobilisation since injury; if the fracture had been present for more than 9 months, continuous immobilisation for at least the last 3 months before entering the trial  
Exclusion criteria: Any additional form of therapy, operative or non-operative performed in the 3 months prior to the trial (other than immobilisation), established pseudarthrosis, gap or bone defect of more than half the width of the bone at the fracture site, generalised disorders of bone metabolism, skeletally immature bone

### Interventions

Each participant’s affected limb was immobilised with either a brace or plaster, with holes cut in the plaster to allow for applying and cleaning surface electrodes. Treatment was planned for 6 months. Treatment was stopped for participants achieving union prior to this time although they were followed up to the conclusion of the study (6 months after conclusion of treatment)  
Test treatment: Orthopak bone-growth CCEF stimulators, continuously delivering 5 to 10 volt peak-to-peak sine wave at 60 kHz  
Comparator treatment: Externally identical unit to test treatment group delivering no signal other than during the brief daily check of the battery and equipment when a sub-therapeutic signal was generated (to maintain blinding)  
At 6 months, participants that had failed to achieve union were withdrawn from the study and offered an alternative treatment. If the participant wanted to receive electromagnetic stimulation then the code was broken and active treatment offered. If a participant had a healing non-union then the code was not broken and treatment was continued for a maximum of 9 months  
Assigned: 11/12 (treatment / control)

### Outcomes

Primary: Clinical and radiographic union at 6 months.  
Secondary: Adverse events.

### Notes

Radiographic union determined by single surgeon.  
Sham units delivered low strength current for up to 30 seconds in the daily battery check and when monitored by investigators during clinical visits  
Low numbers of participants (23), therefore the possibility of type II error is high  
Quote: “..a postal appeal for suitable patients was made to members of the British...”
Scott 1994 (Continued)

Orthopaedic Association...
Comments: Purposeful sampling.
Quote: "It will be questioned why this study was ended after only twenty-three patients ...
more difficult to find patients ..."
Comment: The possibility of a type II error is high as recruitment was incomplete

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
</table>
| Adequate sequence generation? | Unclear           | “...the junior one of us G.S (author) allocated the stimulator units randomly...”
|                           |                    | Comments: No method of randomisation stated.                                 |
| Allocation concealment?   | Yes                | “...the junior one of us G.S (author) allocated the stimulator units randomly...”, “The key to the code (for the Orthopak units) was concealed from investigators...” |
| Blinding? Patient reported measures | Yes              | “Double blind trial”, “Externally, all units appeared identical...”
| Blinding? Objective measures | Yes              | “...the junior one of us G.S (author) allocated the stimulator units randomly...”, “Both the clinical assessment by the junior one of us (G.S) and the radiographic assessment by the senior one of us were performed before the assignment of the units was decoded”. Comments: Junior author (G.S) performed allocation and undertook clinical assessment |
| Incomplete outcome data addressed? Patient reported outcomes | No                | “...2 patients (one from each group) were excluded from the study for a persistent failure to comply with the use of the device...”
| Incomplete outcome data addressed? Objective measures | Yes              | “...2 patients (one from each group) were excluded from the study for a persistent failure to comply with the use of the device...” “...the fracture in the patient in the placebo group united while that fracture in the placebo group did not...”
| Free of selective reporting? | Yes              | All specified outcomes reported. Relevant radiographic and clinical outcomes reported |
**Scott 1994 (Continued)**

<table>
<thead>
<tr>
<th>Free of other bias?</th>
<th>No</th>
<th>Sham units delivered low strength current for up to 30 seconds in the daily battery check and when monitored by investigators during clinical visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>No major imbalances in baseline characteristics?</td>
<td>No</td>
<td>The patients in the placebo group are older and the smoking status is not reported. Four femoral fractures assigned to the test group, none to the comparator group</td>
</tr>
</tbody>
</table>

**Sharrard 1990**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised sham controlled trial.</th>
</tr>
</thead>
</table>
| Participants | Setting: 16 NHS hospitals, UK.  
Sample: 51 participants with delayed union of the tibia.  
Baseline characteristics (45 participants): Mean (range) age 41 (18-84) years; Male: Female ratio 32:13  
Inclusion criteria: Age over 18, with a fracture of the tibial shaft that had not united after at least 16 weeks and not more than 32 weeks, treated in long leg plaster immobilisation, with 2 or more markers of fracture severity (moderate or severe) from fracture displacement or angulation, comminution and skin wound  
Exclusion criteria: Fracture within 5 cm of the knee or ankle joints, surgical procedures other than those required for initial wound management and open reduction (including internal and external fixation), after reduction the fracture ends are not apposed over at least 50% of their surface or distracted, a gap of more than half a centimetre between the bone ends at the time of selection, any severe generalised disease, systemic steroid treatment, bone disease, severely atrophic bone with spindle shaped bone ends and fractures with marked hypertrophy |
| Interventions | Each participant’s affected limb was immobilised with a full leg plaster with the knee in 20 to 30 degrees of flexion and were kept strictly non-weight bearing. Treatment was continued for 12 weeks  
Test treatment: Application of an active device delivering pulsed electromagnetic bursts of 20 individual pulses of quasi-rectangular form followed by a sharper reverse form. The bursts were repeated at 15 Hz, for a total of 12 hours per day, with minimum periods of 1 hour  
Comparator treatment: Treatment was given with a dummy device identical in appearance to the active device but short circuited  
Subsequent treatment after 12 weeks not reported.  
Assigned: ??; information for 20/27 (treatment / control) (allocation not known for 4 patients) |
| Outcomes | Primary: Radiographic union at 12 weeks  
Secondary: Mobility, pain on stressing and local tenderness at 12 weeks |
Sharrard 1990  (Continued)

Notes
Quote: "...hoped to include 100 cases..."
Comment: The possibility of a type II error is high as recruitment was incomplete
Quote: "treatment by internal or external fixation, even if temporary, led to exclusion except in 2 patients..."
Comment: Sample does not reflect population.
UK multi-centre trial was to inform the USA Food and Drug Agency
Radiographic union was assessed by single surgeon and radiologist

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Item</td>
<td>Authors' judgement</td>
<td>Description</td>
</tr>
</tbody>
</table>
| Adequate sequence generation? | Yes | “Patients were randomly allocated to either an active or dummy stimulator.”
Comments: Code was generated by an independent statistician. |
| Allocation concealment? | Yes | Code was generated by an independent statistician. |
| Blinding? Patient reported measures | Yes | “Double blind trial...” “...they were indistinguishable in external appearance and in use.”
Comments: Probably adequate. |
| Blinding? Objective measures | Yes | “Double blind trial...” “...they were indistinguishable in external appearance and in use.”
Comments: Probably adequate. |
| Incomplete outcome data addressed? Patient reported outcomes | No | Comments: Outcomes not reported for 6 participants. |
| Incomplete outcome data addressed? Objective measures | No | “...two were transferred from dummy devices to active devices at their request...”
Comments: Not included in analysis but adequate data reported
“Three patients were enrolled in error, since they were found to have had internal or external fixation”. “One patient tampered his device and broke the code”
Comments: Outcomes of participants not reported. |
| Free of selective reporting? | Unclear | The definition of union was not made clear (radiographic, clinical or both). Also the outcome of union was stratified in a manner that was not described in the methods. |
| Free of other bias? | Yes | |
Sharrard 1990  
(Continued)

| No major imbalances in baseline characteristics? | No | Quote: “There was thus a significant difference in the age distribution.”  
Comment: Treatment group median age 28 (range 18 to 84); control group median age 45 (range 18 to 76) |

Simonis 2003

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomised sham controlled trial.</th>
</tr>
</thead>
</table>
| Participants | Setting: NHS hospital, Surrey, UK.  
Study duration: 5 years, report accepted for publication in 2002  
Sample: 34 participants with non-union of the tibia.  
Baseline characteristics: Mean (range) age 34 (not reported) years; Male:Female ratio 15:2  
Inclusion criteria: Tibial shaft fracture un-united at least 1 year after the initial fracture  
Exclusion criteria: Presence of a metal implant bridging the non-union gap, radiological progression of fracture union in the 3 months prior to enrolment in the study |
| Interventions | All participants initially underwent application of a unilateral external fixator under compression and oblique fibular osteotomy. Participants were kept strictly non-weight bearing. Treatment was continued for a period of 6 months  
Test treatment: Nightly application of external coils to the fracture site producing a pulsed electromagnetic field (3 ms pulse, 40 ms pulse interval, peak current 6 A at 150 V) for a minimum of 14 hours per day  
Comparator treatment: Nightly application of a sham, deactivated device that was externally similar to the test unit for a minimum of 14 hours per day  
If after 6 months union was not achieved, treatment was considered to have failed and was discontinued  
Assigned: 18/16 (treatment / control) |
| Outcomes | Radiographic union at 6 months (follow-up interval was one month) |
| Notes | Quote: “...hoping to obtain 50 such patients...”  
Comment: The possibility of a type II error is high as recruitment was incomplete  
Quote: “...radiographs were reviewed by one of the authors...”  
Comment: Single surgeon assessment of radiographic outcome. |

Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>Quote: “The patients were then randomised into two groups.” “The statistician produced a randomised list...”</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------------------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Simonis 2003</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

**Quote:** “An independent member...delegated the electrical machine to the patients, according to a predetermined randomised list.”
Comment: Probably adequate.

**Quote:** “…dummy implants were externally indistinguishable…”, “Both produced some interference with adjacent electrical devices…”, “…the codes were only broken on completion of the trial.”
Comment: Probably adequate.

**Quote:** Not applicable as these outcomes were not measured.

**Quote:** All 34 participants completed the protocol and complete data are reported for each.

**The stated outcomes of interest were reported. However, likely concurrently measured outcomes such as adverse effects and clinical union are not reported**

**Age was evenly distributed. Though smoking was unevenly distributed, it was adjusted for in the analysis**

**Characteristics of excluded studies [ordered by study ID]**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itoh 2008</td>
<td>This study was not included because the participants had acute fractures</td>
</tr>
<tr>
<td>Madronero 1988</td>
<td>This study was not included because it was a case series. Moreover, outcomes reported were not directly relevant to this review (study of risk factors associated with failure of electrostimulation)</td>
</tr>
</tbody>
</table>
### Comparison 1. Electromagnetic stimulation versus sham

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Proportion of fractures united</td>
<td>4</td>
<td>121</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.96 [0.86, 4.48]</td>
</tr>
<tr>
<td>2 Proportion of non-unions united at 24 weeks</td>
<td>3</td>
<td>74</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.61 [0.74, 3.54]</td>
</tr>
<tr>
<td>3 Proportion of fractures united at 12 weeks</td>
<td>2</td>
<td>64</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>2.26 [0.29, 17.28]</td>
</tr>
<tr>
<td>4 Proportion of non-unions healed at 24 weeks subgrouped by</td>
<td>3</td>
<td></td>
<td>Risk Ratio (M-H, Random, 95% CI) Subtotals only</td>
<td></td>
</tr>
<tr>
<td>electrostimulation type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 CCEF</td>
<td>1</td>
<td>23</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>6.55 [0.93, 46.12]</td>
</tr>
<tr>
<td>4.2 PEMF</td>
<td>2</td>
<td>51</td>
<td>Risk Ratio (M-H, Random, 95% CI)</td>
<td>1.35 [0.69, 2.62]</td>
</tr>
</tbody>
</table>

#### Analysis 1.1. Comparison 1 Electromagnetic stimulation versus sham, Outcome 1 Proportion of fractures united.

**Review:** Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults

**Comparison:** 1 Electromagnetic stimulation versus sham

**Outcome:** 1 Proportion of fractures united

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Stimulation</th>
<th>Sham</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 1984</td>
<td>5/9</td>
<td>5/8</td>
<td>33.7 % 0.89 [0.40, 1.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott 1994</td>
<td>6/11</td>
<td>1/12</td>
<td>13.1 % 6.55 [0.93, 46.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharrard 1990</td>
<td>5/20</td>
<td>1/27</td>
<td>12.0 % 6.75 [0.85, 53.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simonis 2003</td>
<td>16/18</td>
<td>8/16</td>
<td>41.1 % 1.78 [1.06, 2.98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>58</strong></td>
<td><strong>63</strong></td>
<td>100.0 % 1.96 [0.86, 4.48]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 32 (Stimulation), 15 (Sham)

Heterogeneity: $\tau^2 = 0.36; \chi^2 = 7.14, df = 3 (P = 0.07); I^2 = 58%$

Test for overall effect: $Z = 1.60$ (P = 0.11)
**Analysis 1.2. Comparison 1 Electromagnetic stimulation versus sham, Outcome 2 Proportion of non-unions united at 24 weeks.**

Review: Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults

Comparison: 1 Electromagnetic stimulation versus sham

Outcome: 2 Proportion of non-unions united at 24 weeks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Electrostimulation</th>
<th>Sham</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 1984</td>
<td>5/9</td>
<td>5/8</td>
<td>38.1 % 0.89 [0.40, 1.97]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott 1994</td>
<td>6/11</td>
<td>1/12</td>
<td>12.9 % 6.55 [0.93, 46.12]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simonis 2003</td>
<td>16/18</td>
<td>8/16</td>
<td>49.0 % 1.78 [1.06, 2.98]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>38</td>
<td>36</td>
<td>100.0 % 1.61 [0.74, 3.54]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.26$; $\chi^2 = 4.61$, df = 2 ($P = 0.10$); $I^2 = 57\%$

Test for overall effect: $Z = 1.19$ ($P = 0.23$)

Test for subgroup differences: Not applicable

---

**Analysis 1.3. Comparison 1 Electromagnetic stimulation versus sham, Outcome 3 Proportion of fractures united at 12 weeks.**

Review: Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults

Comparison: 1 Electromagnetic stimulation versus sham

Outcome: 3 Proportion of fractures united at 12 weeks

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Electrostimulation</th>
<th>Sham</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 1984</td>
<td>2/9</td>
<td>2/8</td>
<td>54.0 % 0.89 [0.16, 4.93]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharrard 1990</td>
<td>5/20</td>
<td>1/27</td>
<td>46.0 % 6.75 [0.85, 53.37]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>29</td>
<td>35</td>
<td>100.0 % 2.26 [0.29, 17.28]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.23$; $\chi^2 = 2.31$, df = 1 ($P = 0.13$); $I^2 = 57\%$

Test for overall effect: $Z = 0.78$ ($P = 0.43$)

Test for subgroup differences: Not applicable
Analysis 1.4. Comparison 1 Electromagnetic stimulation versus sham, Outcome 4 Proportion of non-unions healed at 24 weeks subgrouped by electrostimulation type.

Review: Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults

Comparison: 1 Electromagnetic stimulation versus sham

Outcome: 4 Proportion of non-unions healed at 24 weeks subgrouped by electrostimulation type

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Electrostimulation</th>
<th>Sham</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>1 CCEF</td>
<td>6/11</td>
<td>1/12</td>
<td>100.0 %</td>
<td>6.55 [ 0.93, 46.12 ]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 11 12 100.0 % 6.55 [ 0.93, 46.12 ]

Total events: 6 (Electrostimulation), 1 (Sham)

Heterogeneity: not applicable

Test for overall effect: Z = 1.89 (P = 0.059)

2 PEMF

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Electrostimulation</th>
<th>Sham</th>
<th>Risk Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Random,95% CI</td>
<td>M-H,Random,95% CI</td>
</tr>
<tr>
<td>Scott 1994</td>
<td>5/9</td>
<td>5/8</td>
<td>40.2 %</td>
<td>0.89 [ 0.40, 1.97 ]</td>
</tr>
<tr>
<td>Simonis 2003</td>
<td>16/18</td>
<td>8/16</td>
<td>59.8 %</td>
<td>1.78 [ 1.06, 2.98 ]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 27 24 100.0 % 1.35 [ 0.69, 2.62 ]

Total events: 21 (Electrostimulation), 13 (Sham)

Heterogeneity: Tau^2 = 0.12; Chi^2 = 2.06, df = 1 (P = 0.15); I^2 = 51%

Test for overall effect: Z = 0.87 (P = 0.38)

**ADDITIONAL TABLES**

Table 1. Pain scores

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>Pain score VAS at weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Non-union median (range) [scored 0 to 4, nil to severe pain]

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>Pain score VAS at weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker 1984</td>
<td>Electrostimulation</td>
<td>0 (0 to 3)</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>1 (0 to 4)</td>
</tr>
</tbody>
</table>

Delayed union mean (SD) [range n/r, nil to severe]

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>Pain score VAS at weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharrard 1990</td>
<td>Electrostimulation</td>
<td>3.6 (2.4)</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>2.7 (2.2)</td>
</tr>
</tbody>
</table>

* t-test, P = 0.29
APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Wiley InterScience)

1. MeSH descriptor Electromagnetic Fields, this term only
2. MeSH descriptor Magnetics, this term only
3. MeSH descriptor Electric Stimulation Therapy, this term only
4. MeSH descriptor Electrodes, Implanted, this term only
5. MeSH descriptor Magnetic Field Therapy, this term only
6. (electric* and (capacitive or coupling or stimulat* or current or treatment)):ti,ab,kw
7. (electromagnetic* or EMF or PEMF or electrotherap*):ti,ab,kw
8. (current and (direct or puls* or alternating or stimulation)):ti,ab,kw
9. (interferential and (therap* or current)):ti,ab,kw
10. (coupling and (inductive or capacitive)):ti,ab,kw
11. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10)
12. MeSH descriptor Femoral Fractures, this term only
13. MeSH descriptor Humeral Fractures, this term only
14. MeSH descriptor Radius Fractures, this term only
15. MeSH descriptor Tibial Fractures, this term only
16. MeSH descriptor Ulna Fractures, this term only
17. (#12 OR #13 OR #14 OR #15 OR #16)
18. MeSH descriptor Fractures, Bone, this term only
19. MeSH descriptor Fracture Healing, this term only
20. MeSH descriptor Fracture Fixation, this term only
21. MeSH descriptor Bone Regeneration, this term only
22. (fractur*):ti,ab,kw
23. (#18 OR #19 OR #20 OR #21 OR #22)
24. (femor* or femur* or humer* or radius or radial or ulna* or tibia* or fibul* or long bone or long-bone):ti,ab,kw
25. (#23 AND #24)
26. (#17 OR #25)
27. MeSH descriptor Fractures, Ununited explode all trees
28. (non union or non-union or non-united or ununited or delayed union or union or (fractur* NEAR/2 healing)) :ti,ab,kw
29. (#27 OR #28)
30. (#11 AND #26 AND #29)

MEDLINE (PubMed)

1

Electromagnetic Fields [Mh] or Magnetics [Mh] or Electric Stimulation Therapy [Mh] or Electrodes, implanted [Mh] or Magnetic Field Therapy [Mh] or (electric* [Tw] and (capacitive [Tw] or coupling [Tw] or stimulat* [Tw] or current [Tw] or treatment [Tw])) or electromagnetic* [Tw] or EMF [Tw] or PEMF [Tw] or (current [Tw] and (direct [Tw] or puls* [Tw] or alternating [Tw] or stimulation
Electrostimulation Therapy/ or Pulsed Electric Field/ or Electromagnetic Radiation/ or exp Magnetism/ or exp Magnetotherapy/ or Electrode/
2 (electric* and (capacitive or coupling or stimulat* or current or treatment)).tw.
3 (electromagnetic* or EMF or PEMF or electrotherap*).tw.
4 (current and (direct or puls* or alternating or stimulation)).tw.
5 (interferential and (therap* or current)).tw.
6 (coupling and (inductive or capacitive)).tw.
7 or/1-6
8 Radius Fracture/ or exp Femur Fracture/ or Humerus Fracture/ or Ulna Fracture/ or Tibia Fracture/ or Tibia Shaft Fracture/ or Fibula Fracture/
9 Fracture/ or exp Fracture Healing/ or Fracture Fixation/ or Bone Regeneration/ or Fracture Treatment/ (43275)
10 fractur*.tw.
11 or/9-10
12 exp Long Bone/
13 (femor* or femur* or humer* or radius or radial or ulna* or tibia* or fibul* or long bone or long-bone).tw. (176792)
14 or/12-13
15 and/11,14
16 or/8,15
17 Fracture Nonunion/
18 (non union or non-union or nonunion or un-united or ununited or delayed union or union or (fractur* adj2 healing)).tw.
19 or/17-18
20 and/7,16,19
21 Clinical Trial/
22 Randomized Controlled Trial/
23 Randomization/
24 Single Blind Procedure/
25 Double Blind Procedure/
26 Crossover Procedure/
27 Placebo/
28 randomi?ed controlled trial$.tw.
29 rct.tw.
30 random allocation.tw.
31 randomly allocated.tw.
32 allocated randomly.tw.
33 (allocated adj2 random).tw.

EMBASE (OVID SP)
1 Electrostimulation Therapy/ or Pulsed Electric Field/ or Electromagnetic Radiation/ or exp Magnetism/ or exp Magnetotherapy/ or Electrode/
2 (electri* and (capacitive or coupling or stimulat* or current or treatment)).tw.
3 (electromagnetic* or EMF or PEMF or electrotherap*).tw.
4 (current and (direct or puls* or alternating or stimulation)).tw.
5 (interferential and (therap* or current)).tw.
6 (coupling and (inductive or capacitive)).tw.
7 or/1-6
8 Radius Fracture/ or exp Femur Fracture/ or Humerus Fracture/ or Ulna Fracture/ or Tibia Fracture/ or Tibia Shaft Fracture/ or Fibula Fracture/
9 Fracture/ or exp Fracture Healing/ or Fracture Fixation/ or Bone Regeneration/ or Fracture Treatment/ (43275)
10 fractur*.tw.
11 or/9-10
12 exp Long Bone/
13 (femor* or femur* or humer* or radius or radial or ulna* or tibia* or fibul* or long bone or long-bone).tw. (176792)
14 or/12-13
15 and/11,14
16 or/8,15
17 Fracture Nonunion/
18 (non union or non-union or nonunion or un-united or ununited or delayed union or union or (fractur* adj2 healing)).tw.
19 or/17-18
20 and/7,16,19
21 Clinical Trial/
22 Randomized Controlled Trial/
23 Randomization/
24 Single Blind Procedure/
25 Double Blind Procedure/
26 Crossover Procedure/
27 Placebo/
28 randomi?ed controlled trial$.tw.
29 rct.tw.
30 random allocation.tw.
31 randomly allocated.tw.
32 allocated randomly.tw.
33 (allocated adj2 random).tw.
HISTORY

Protocol first published: Issue 4, 2010
Review first published: Issue 4, 2011

CONTRIBUTIONS OF AUTHORS

XL Griffin was responsible for the conception, design and writing of the review. He was the co-guarantor of the review.

ML Costa was involved in the conception and design of the review. He was the co-guarantor of the review.

N Parsons was the review statistician. He was responsible for the data management and analysis plan.

N Smith was responsible for the study retrieval strategy and writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Warwick, UK.
Salaries for three authors to support the development of the protocol
External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We initially planned to present measurement error in the assessment of union as a risk of bias. On reflection we felt this was more properly considered in the Quality of the evidence as a source of error.

INDEX TERMS

Medical Subject Headings (MeSH)

*Fracture Healing; Arm Injuries [*therapy]; Fractures, Ununited [*therapy]; Leg Injuries [*therapy]; Magnetic Field Therapy [*methods]; Randomized Controlled Trials as Topic; Tibial Fractures [therapy]

MeSH check words

Adult; Humans