Arch Orthop Trauma Surg (2014) 134:1093–1106
DOI 10.1007/s00402-014-2014-8

TRAUMA SURGERY

The effects of low-intensity pulsed ultrasound and pulsed electromagnetic fields bone growth stimulation in acute fractures: a systematic review and meta-analysis of randomized controlled trials

P. F. W. Hannemann · E. H. H. Mommers · J. P. M. Schots · P. R. G. Brink · M. Poeze

Received: 22 November 2013 / Published online: 4 June 2014

Abstract
Introduction The aim of this systematic review and meta-analysis was to evaluate the best currently available evidence from randomized controlled trials comparing pulsed electromagnetic fields (PEMF) or low-intensity pulsed ultrasound (LIPUS) bone growth stimulation with placebo for acute fractures.
Materials and methods We performed a systematic literature search of the medical literature from 1980 to 2013 for randomized clinical trials concerning acute fractures in adults treated with PEMF or LIPUS. Two reviewers independently determined the strength of the included studies by assessing the risk of bias according to the criteria in the Cochrane Handbook for Systematic Reviews of Interventions.
Results Seven hundred and thirty-seven patients from 13 trials were included. Pooled results from 13 trials reporting proportion of nonunion showed no significant difference between PEMF or LIPUS and control. With regard to time to radiological union, we found heterogeneous results that significantly favoured PEMF or LIPUS bone growth stimulation only in non-operatively treated fractures or fractures of the upper limb. Furthermore, we found significant results that suggest that the use of PEMF or LIPUS in acute diaphyseal fractures may accelerate the time to clinical union.
Conclusions Current evidence from randomized trials is insufficient to conclude a benefit of PEMF or LIPUS bone growth stimulation in reducing the incidence of nonunions when used for treatment in acute fractures. However, our systematic review and meta-analysis suggest that PEMF or LIPUS can be beneficial in the treatment of acute fractures regarding time to radiological and clinical union. PEMF and LIPUS significantly shorten time to radiological union for acute fractures undergoing non-operative treatment and acute fractures of the upper limb. Furthermore, PEMF or LIPUS bone growth stimulation accelerates the time to clinical union for acute diaphyseal fractures.

Keywords Low-intensity pulsed ultrasound · Pulsed electromagnetic fields · Fractures · Healing · Nonunion

P. F. W. Hannemann (✉) · E. H. H. Mommers · J. P. M. Schots · P. R. G. Brink · M. Poeze
Department of Surgery and Traumasurgery, Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands
e-mail: pfwhannemann@gmail.com

E. H. H. Mommers
e-mail: elwin.mommers@gmail.com

J. P. M. Schots
e-mail: judith.schots@gmail.com

P. R. G. Brink
e-mail: p.brink@mumc.nl

M. Poeze
e-mail: m.poeze@mumc.nl

Introduction

Although many patient-related and surgeon-related factors can influence time to resumption of activities after an upper or lower extremity fracture, prolonged healing time may have severe socio-economic consequences, especially in the working age population [1, 2].

The two most common forms of electrophysical bone growth stimulation, pulsed electromagnetic fields (PEMF) and low-intensity pulsed ultrasound (LIPUS) bone growth stimulation, have been proposed to accelerate bone healing and reduce the incidence of disabling complications such as delayed union or nonunion and therefore lowering

financial costs by minimizing time off work and reducing the time of immobility [3, 4].

Since 1980 several trials have been conducted to test whether LIPUS and PEMF can be used to promote healing in acute fractures [3, 4]. Clinical outcomes, however, were mixed [3, 4]. We therefore conducted this systematic review and performed meta-analyses when sufficient dichotomous or continuous data were available to evaluate the best currently available evidence from randomized controlled trials comparing PEMF or LIPUS bone growth stimulation with placebo for healing of acute fractures.

Materials and methods

This systematic review and meta-analysis is reported following the guidelines of the PRISMA statement [5].

Study selection criteria

Types of studies, participants and interventions included

All clinical trials with a random allocation of participants over at least one treatment group and one control group, concerning acute fractures in adult patients treated with PEMF or LIPUS bone growth stimulation were considered in the present review. Trials including children, patients with congenital deformities and degenerative conditions and trials that focused on the treatment of delayed union (4 weeks to 6 months after a fracture) or nonunion (more than 6 months after a fracture) were excluded from the analysis.

Types of outcome measures

The primary outcome measure of this review was time to complete radiological fracture healing (union), which had to be clearly defined. The secondary outcome measures of this review were time to full clinical healing, based on validated function scoring systems or derivates of this (e.g. time until full resumption of work or time until full weight bearing in lower extremity fractures) and number of nonunions. Nonunion was defined as failure of the fracture to unite more than 6 months after injury.

Search methods for identification of studies

We performed a systematic search of three major databases: EMBASE (OvidSP 1980 through October 30 2013), MEDLINE (PubMed 1966 through October 30 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library issue 9 of 12 September 2013). Search terms were "pulsed electromagnetic fields", "PEMF", "low-intensity pulsed ultrasound", "LIPUS" and "fracture". No language restrictions were applied. Additionally, we screened the reference lists of all selected articles from the database search and additional relevant reviews and meta-analyses in order to find suitable studies for this review. Researchers in the field were contacted to inquire about any additional unpublished trials or trials in progress.

Data collection and analysis

Selection of studies

Full-text analysis of all eligible articles was performed by two reviewers separately (PFWH and JPMS) in order to independently assess whether all inclusion criteria were met. Disagreement between the reviewers was resolved by means of discussion. If necessary, a third reviewer with a degree in study methodology and clinical epidemiology was consulted for arbitration if no consensus could be reached (MP).

Strength of the evidence

Two reviewers (PFWH and JPMS) independently assessed the risk of bias in the included studies according to the methods in the Cochrane Handbook for Systematic Reviews of Interventions [6]. The following components of the risk of bias tool were assessed: sequence generation (selection bias), allocation concealment (selection bias); blinding (performance bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other biases (including description of the study protocol with sample size calculation, source of funding and other problems not covered elsewhere in the table). All items were judged as having a low, unclear or high risk of bias. We used Cohen's Kappa to estimate agreement between the two reviewers concerning assessment of risk of bias. We interpreted kappa values using the Landis and Koch criteria: values of 0.01–0.20 indicate slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement and >0.80 indicates almost perfect agreement [7]. Finally, any disagreement between the two reviewers was resolved through discussion.

Data collection

Two reviewers (PFWH and JPMS) independently extracted data from all eligible studies. Disagreement was resolved as mentioned above. For dichotomous outcomes, events from totals were extracted. For continuous outcomes, means and standard deviations were calculated. If means

and confidence intervals (CIs) were reported instead, standard deviations were calculated from these values. Incomplete data (e.g. means without standard deviations) were excluded from analysis, after contacting the authors for eventually previously unreported data.

Data pooling and analysis

A statistical meta-analysis was performed with Review Manager 5.2.

For both treatment arms in all studies, mean differences and 95 % confidence intervals (CI) were calculated for comparable continuous outcomes using a random effects model. For our primary outcome measure, time to complete radiological fracture healing and our secondary outcome measure, time until full clinical healing, values from all studies were expressed in days. For our dichotomous outcome, number of nonunions, risk ratios (RRs) and 95 % CIs using a fixed effects model were calculated. Heterogeneity between studies was tested using both the χ^2 test (significance defined as $p < 0.10$) and the I^2 tests (substantial heterogeneity defined as values >50 %) [8].

Subgroup-analysis

The included trials are characterized by extensive clinical diversity. Fractures of the upper limb or metaphyseal fractures may be expected to heal more quickly than lower limb fractures or diaphyseal fractures. To minimize this heterogeneity, the following post hoc subgroup-analyses were performed: type of treatment (operatively or non-operatively treated fractures); the site of fractures (upper or lower limb); the type of fractures (metaphyseal or diaphyseal fractures).

Results

Literature search

The search resulted in 655 potentially eligible studies (LIPUS 508, PEMF 147). After screening the titles and abstracts to see whether the inclusion criteria were met, 37 studies remained (LIPUS 29, PEMF 8). Removal of all duplicate articles resulted in 16 studies (LIPUS 13, PEMF 3) which were identified for full-text assessment of eligibility. After excluding one trial that applied high-intensity ultrasound, one study that used the dataset from an already included study and one retrospective cohort study, 737 patients from 13 trials were included [9–21] (Fig. 1). 355 participants were treated with LIPUS ($n = 209$) or PEMF ($n = 146$) bone growth stimulation, 382 participants were treated with a placebo device.

Description of included studies

The study characteristics are summarized in Table 1.

Outcome measure reporting

Reported outcomes of included studies are summarized in Table 2. Eleven of the 13 studies evaluated fracture healing, assessed by radiological examination [9–16, 19–21]. Ten studies assessed fracture healing on standard anterior posterior (AP) and lateral radiographs [9–11, 13–16, 19–21]. One study used CT scans for assessment of fracture healing [12]. In four studies, union was defined as trabecular bridging of 3 out of 4 cortices [9, 11, 13, 20]. In two studies, union was defined as bridging of 4 out of 4 cortices [10, 21]. The study using CT for assessment of fracture healing defined union as trabecular bridging of more than 50 % of the surface of the fracture and healing of 1 cortex [12]. Three studies investigating lateral malleolar fractures defined union as fading of the fracture line on AP and lateral radiographs [14–16]. In one study investigating femoral neck fractures, union was defined as trabecular bridging of 70 % of the fracture surface [19]. Primary outcome parameter time to complete radiological union could be established in eight studies [9–13, 15, 16, 21].

Two studies evaluated the number of necessary surgical revisions to establish fracture union after initial non-operative [17] or operative [20] fracture treatment.

Six studies evaluated time to clinical fracture healing [9, 11, 13, 17, 18, 21]. Healing in these studies was defined as presence of a stable fracture with no pain on manual stress or full weight bearing. Three of the 13 studies evaluated functional outcome [14, 20, 21]. One study evaluated health status [20] and two evaluated pain [17, 19]. Resumption of previous activities was outcome parameter of one study [17]. Two studies evaluated related adverse events [11, 17] and three studies evaluated bone mineral density measured with dual-energy X-ray absorptiometry (DEXA) scan [13, 14, 16]. One study evaluated plasma bone-specific alkaline phosphatase [13].

Risk of bias and methodological quality in included studies

The risk of bias assessment is summarized in Fig. 2.

Inter-rater agreement for risk of bias assessments

The overall inter-rater agreement was high (0.803). The agreement was substantial for the domains allocation of concealment (0.713), blinding of outcome assessment (0.714) and incomplete outcome data (0.717). For the domains random sequence generation (0.855) and other

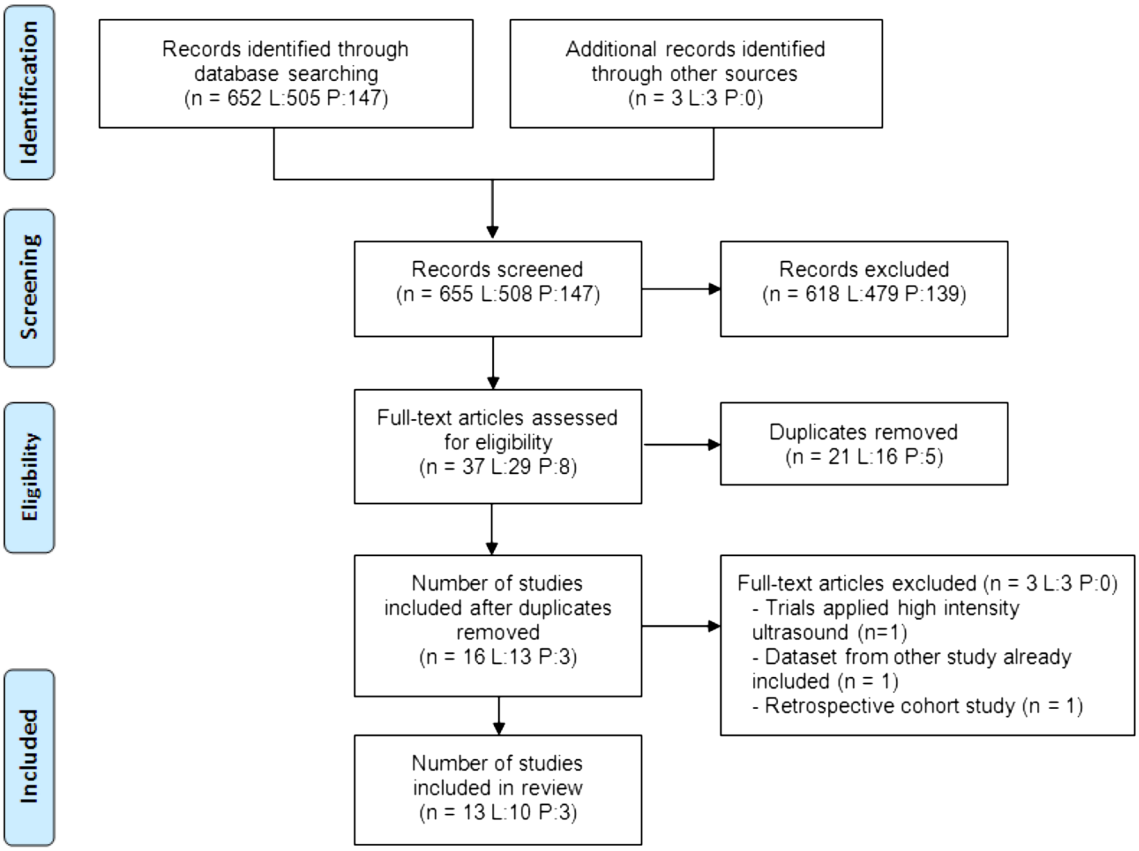


Fig. 1 Flow of trials through review

Table 1 Characteristics of included randomized controlled trials

References	Year	Intervention	Fracture location	Total number of patients (n)	Active treatment (n)	Placebo treatment (n)	Operatively treated fractures	Follow-up (months)	Follow-up completed (%)
Adie et al. [20]	2011	PEMF	Tibia	259	129	130	Yes	12	84
Emami et al. [11]	1999	LIPUS	Tibia	32	15	17	Yes	12	100
Faldini et al. [19]	2010	PEMF	Femoral neck	77	37	40	Yes	24	84
Handolin et al. [16]	2005	LIPUS	Lat malleolus	30	15	15	Yes	3	100
Handolin et al. [15]	2005	LIPUS	Lat malleolus	22	11	11	Yes	3	100
Handolin et al. [14]	2005	LIPUS	Lat malleolus	16	8	8	Yes	18	100
Hannemann et al. [21]	2012	PEMF	Scaphoid	53	24	29	No	12	77
Heckman et al. [9]	1994	LIPUS	Tibia	97	48	49	No	12	87
Kristiansen et al. [10]	1997	LIPUS	Radius	85	40	45	No	4	72
Leung et al. [13]	2004	LIPUS	Tibia	30	16	14	Yes	12	100
Lubbert et al. [17]	2008	LIPUS	Clavicle	120	61	59	No	2	84
Mayr et al. [12]	2000	LIPUS	Scaphoid	30	15	15	No	3	100
Rue et al. [18]	2004	LIPUS	Tibia	26	14	12	Yes	Unclear	100

Table 2 Reported outcomes of selected studies

Outcome	1	2	3	4	5	6	7	8	9	10	11	12	13
Number of surgical revisions[a]	x										x		
Radiographic fracture healing[b]	x	x	x	x	x	x	x	x	x	x		x	
Clinical fracture healing		x					x	x		x	x		x
Functional outcome	x					x	x						
Health status	x												
VAS scores			x								x		
Painkiller use											x		
Resumption of previous activities											x		
Adverse events		x									x		
Bone mineral density[c]				x		x				x			
Plasma BALP[d]										x			

(1) Adie et al. [20], (2) Emami et al. [11], (3) Faldini et al. [19], (4) Handolin et al. [16], (5) Handolin et al. [15], (6) Handolin et al. [14], (7) Hannemann et al. [21], (8) Heckman et al. [9], (9) Kristiansen et al. [10], (10) Leung et al. [13], (11) Lubbert et al. [17], (12) Mayr et al. [12], (13) Rue et al. [18]

[a] Refers to procedures to promote union

[b] Determined with plain X-ray or (multidetector) CT scan

[c] Measured with dual-energy X-ray absorptiometry (DEXA) scan

[d] Bone-specific alkaline phosphatase

bias (0.877), the agreement was almost perfect. There was no disagreement for selective reporting. Only the agreement for blinding of participants and personnel was moderate (0.469) (Table 3).

Primary outcome

Time to radiological union

Eight studies compared PEMF or LIPUS with regard to time to radiological union [9–13, 15, 16, 21]. The data were pooled with substantial heterogeneity between treatment groups ($I^2 = 98$ %). There were no significant differences in time to radiological union between PEMF or LIPUS and placebo [mean difference (MD) = −13.32, 95 % CI = −32.71 to 6.06, $p = 0.18$] (Fig. 3a). Four studies comparing PEMF or LIPUS to placebo with regard to time to radiological union included only non-operatively treated fractures [9, 10, 12, 21]. After pooling the data, we found heterogeneous results that significantly favoured PEMF or LIPUS treatment in non-operatively treated fractures (MD = −26.65, 95 % CI = −50.38 to −2.91, $p = 0.03$, $I^2 = 98$ %) (Fig. 3b).

Time to radiological union upper and lower limb

Three studies compared PEMF or LIPUS with placebo in fractures of the upper limb with regard to time to radiological union [10, 12, 21]. Heterogeneous results ($I^2 = 69$ %) showed a significant difference in time to radiological union in favour of PEMF or LIPUS compared to placebo (MD = −20.23, 95 % CI −32.68 to −7.77, $p = 0.001$) (Fig. 4a).

Five studies compared LIPUS and placebo in fractures of the lower limb with regard to time to radiological union [9, 11, 13, 15, 16]. The heterogeneous result ($I^2 = 99$ %) did not significantly differ between LIPUS or placebo. (MD = −14.49, 95 % CI −55.96 to 26.97, $p = 0.49$) (Fig. 4b).

Time to radiological union diaphyseal and metaphyseal fractures

After dividing the studies into two groups, diaphyseal fractures [9, 11, 13] and metaphyseal fractures [10, 12, 15, 16, 21], we found no significant differences in time to radiological union between PEMF or LIPUS and placebo regarding diaphyseal (MD = −29.43, 95 % CI −88.99 to 31.14, $p = 0.34$, $I^2 = 99$ %) or metaphyseal fractures (MD = −4.66, 95 % CI −22.78 to 13.45, $p = 0.61$, $I^2 = 93$ %) (Fig. 5a, b).

Secondary outcomes

Time to clinical union

Six studies compared PEMF or LIPUS to placebo with regard to time to clinical union [9, 11, 13, 17, 18, 21]. After pooling the data, no significant differences were found between groups (MD = −13.01, 95 % CI = −26.92

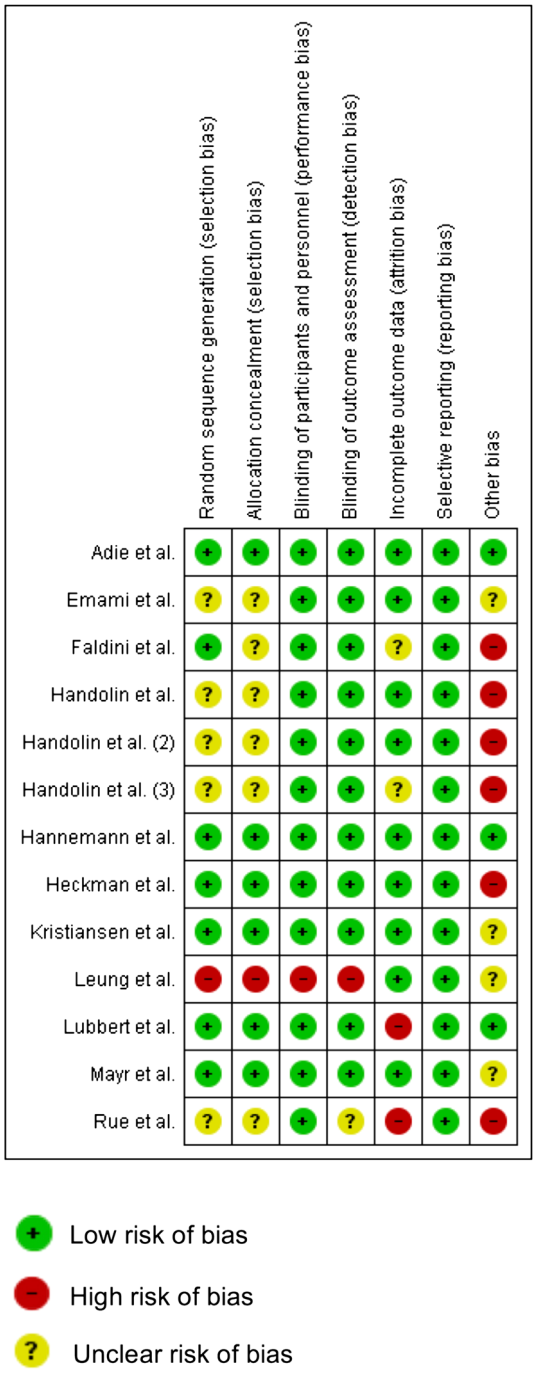


Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

to 0.89, $p = 0.07$, $I^2 = 96$ %) (Fig. 6a). When analysing non-operatively and operatively treated fractures separately we found no significant differences in non-operatively treated fractures (MD = −9.65, 95 % CI = −33.85 to 14.55, $p = 0.43$, $I^2 = 97$ %) or in operatively treated fractures (MD = −15.50, 95 % CI −39.25 to 8.25, $p = 0.20$, $I^2 = 94$ %) (Fig. 6b, c).

Table 3 Inter-rater agreement for risk of bias assessments

Assessment	κ	p	Interpretation
Overall risk of bias	0.803	$p < 0.001$	Almost perfect agreement
Random sequence	0.855	$p = 0.001$	Almost perfect agreement
Allocation of concealment	0.713	$p = 0.005$	Substantial agreement
Blinding participants	0.469	$p = 0.485$	Moderate agreement
Blinding outcome	0.714	$p = 0.118$	Substantial agreement
Incomplete outcome data	0.717	$p = 0.004$	Substantial agreement
Selective reporting	0.99		Perfect agreement
Other bias	0.877	$p < 0.001$	Almost perfect agreement

Time to clinical union upper and lower limb

Two studies compared PEMF or LIPUS with placebo in fractures of the upper limb with regard to time to clinical union [17, 21]. No significant differences were found between the groups (MD = −0.14, 95 % CI = −5.61 to 5.34, $p = 0.96$, $I^2 = 0$ %) (Fig. 7a). When analysing four studies comparing PEMF or LIPUS with placebo in fractures of the lower limb with regard to time to clinical union, heterogeneous results that significantly favoured PEMF or LIPUS were found (MD = −18.73, 95 % CI −36.25 to −1.21, $p = 0.04$, $I^2 = 97$ %) (Fig. 7b) [9, 11, 13, 18].

Time to clinical union diaphyseal and metaphyseal fractures

Four studies compared PEMF or LIPUS with placebo in diaphyseal fractures with regard to time to clinical union; heterogeneous results that significantly favoured PEMF or LIPUS were found (MD = −18.27, 95 % CI −34.59 to −1.95, $p = 0.03$, $I^2 = 97$ %) (Fig. 8a) [9, 11, 13, 18]. No significant differences were found regarding metaphyseal fractures (MD = 1.31, 95 % CI −11.45 to 14.08, $p = 0.84$, $I^2 = 0$ %) (Fig. 8b).

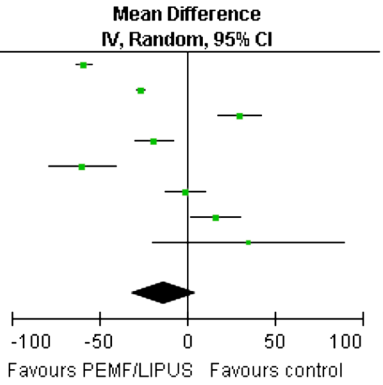
Number of nonunions

With regard to the number of nonunions, data from all 13 studies could be pooled [9–21]. Analysis revealed no significant differences between LIPUS or PEMF (28 events of nonunion in 355 patients) and placebo (35 events of nonunion in 382 patients) with regard to the number of nonunions in each group (risk ratio = 0.95, 95 % CI = 0.59 to 1.54, $p = 0.84$, $I^2 = 19$ %) (Fig. 9a). When analysing non-operatively and operatively treated fractures separately, we found no significant differences in both groups

A

Study or Subgroup	PEMF/LIPUS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Heckman et al.	89	3.7	33	148	13.2	34	13.9%	-59.00 [-63.61, -54.39]	1994
Kristiansen et al.	51	4	30	77	5	31	14.0%	-26.00 [-28.27, -23.73]	1997
Emami et al.	155	22	15	125	11	17	13.3%	30.00 [17.70, 42.30]	1999
Mayr et al.	43.2	10.9	15	62	19.2	15	13.4%	-18.80 [-29.97, -7.63]	2000
Leung et al.	80.5	21	16	140	30.8	14	12.3%	-59.50 [-78.64, -40.36]	2004
Handolin et al. (2)	62.16	16.2	15	63	15.5	15	13.4%	-0.84 [-12.19, 10.51]	2005
Handolin et al.	67.9	18.6	11	51.3	15.3	11	13.0%	16.60 [2.37, 30.83]	2005
Hannemann et al.	130	111	24	95	85	29	6.7%	35.00 [-19.12, 89.12]	2012
Total (95% CI)			**159**			**166**	**100.0%**	**-13.32 [-32.71, 6.06]**	

Heterogeneity: Tau² = 697.68; Chi² = 338.99, df = 7 (P < 0.00001); I² = 98%
Test for overall effect: Z = 1.35 (P = 0.18)



B

Study or Subgroup	Favours PEMF/LIPUS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Heckman et al.	89	3.7	33	148	13.2	34	29.8%	-59.00 [-63.61, -54.39]	1994
Kristiansen et al.	51	4	30	77	5	31	30.1%	-26.00 [-28.27, -23.73]	1997
Mayr et al.	43.2	10.9	15	62	19.2	15	28.3%	-18.80 [-29.97, -7.63]	2000
Hannemann et al.	130	111	24	95	85	29	11.7%	35.00 [-19.12, 89.12]	2012
Total (95% CI)			**102**			**109**	**100.0%**	**-26.65 [-50.38, -2.91]**	

Heterogeneity: Tau² = 485.88; Chi² = 169.71, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.20 (P = 0.03)

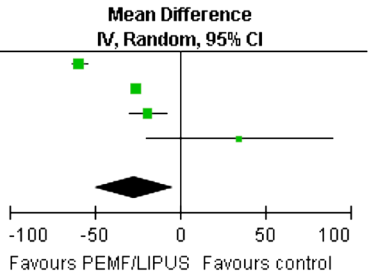
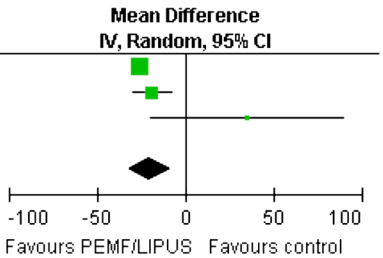


Fig. 3 **a** Time until radiological union (PEMF/LIPUS vs. placebo); **b** time until radiological union non-operatively treated fractures (PEMF/LIPUS vs. placebo)

A

Study or Subgroup	PEMF/LIPUS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kristiansen et al.	51	4	30	77	5	31	56.0%	-26.00 [-28.27, -23.73]	1997
Mayr et al.	43.2	10.9	15	62	19.2	15	39.1%	-18.80 [-29.97, -7.63]	2000
Hannemann et al.	130	111	24	95	85	29	4.8%	35.00 [-19.12, 89.12]	2012
Total (95% CI)			**69**			**75**	**100.0%**	**-20.23 [-32.68, -7.77]**	

Heterogeneity: Tau² = 70.72; Chi² = 6.36, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 3.18 (P = 0.001)



B

Study or Subgroup	PEMF/LIPUS Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Heckman et al.	89	3.7	33	148	13.2	34	20.4%	-59.00 [-63.61, -54.39]	1994
Emami et al.	155	22	15	125	11	17	20.0%	30.00 [17.70, 42.30]	1999
Leung et al.	80.5	21	16	140	30.8	14	19.6%	-59.50 [-78.64, -40.36]	2004
Handolin et al. (2)	62.16	16.2	15	63	15.5	15	20.1%	-0.84 [-12.19, 10.51]	2005
Handolin et al.	67.9	18.6	11	51.3	15.3	11	19.9%	16.60 [2.37, 30.83]	2005
Total (95% CI)			**90**			**91**	**100.0%**	**-14.49 [-55.96, 26.97]**	

Heterogeneity: Tau² = 2192.82; Chi² = 299.52, df = 4 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.69 (P = 0.49)

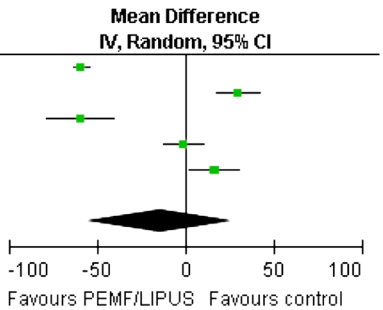


Fig. 4 **a** Time until radiological union upper limb (PEMF/LIPUS vs. placebo); **b** time until radiological union lower limb (PEMF/LIPUS vs. placebo)

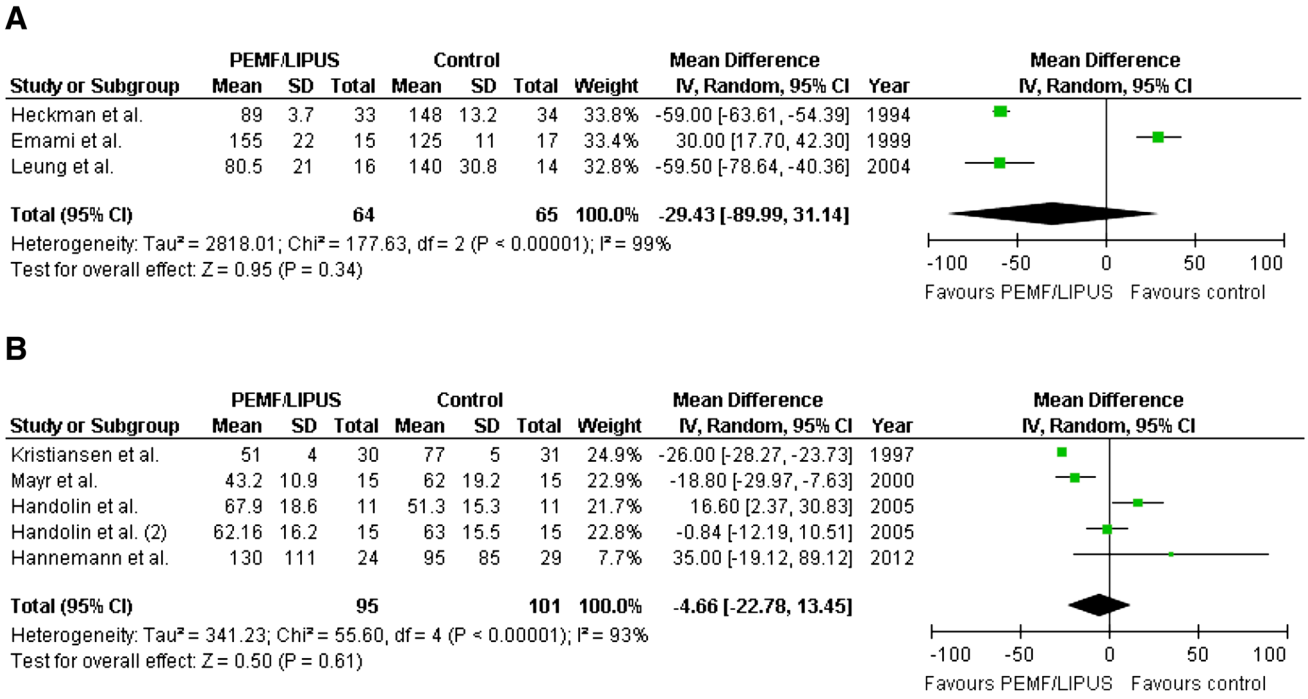


Fig. 5 **a** Time until radiological union diaphyseal fracture (PEMF/LIPUS vs. placebo); **b** time until radiological union metaphyseal fracture (PEMF/LIPUS vs. placebo)

(non-operatively treated fractures: MD = 1.18, 95 % CI = 0.38 to 3.70, $p = 0.77$, $I^2 = 0$ %; operatively treated fractures: MD = 0.91, 95 % CI = 0.53 to 1.54, $p = 0.72$, $I^2 = 51$ %) (Fig. 9b, c).

Number of nonunions upper and lower limb

Data from all 13 studies could be divided into fractures of the upper limb [10, 12, 17, 21] or lower limb [9, 11, 13–16, 18–20]. Comparing PEMF or LIPUS with placebo with regard to the number of nonunions, no significant differences in the upper limb (risk ratio = 1.18, 95 % CI = 0.38 to 3.70, $p = 0.77$, $I^2 = 0$ %) or in the lower limb (risk ratio = 0.91, 95 % CI 0.53 to 1.54, $p = 0.72$, $I^2 = 51$ %) were found (Fig. 10a, b).

Number of nonunions in diaphyseal and metaphyseal fractures

When subdividing studies comparing PEMF or LIPUS with placebo in acute diaphyseal fractures [9, 11, 13, 17, 20] (risk ratio = 1.17, 95 % CI = 0.70 to 1.95, $p = 0.56$, $I^2 = 0$ %) and acute metaphyseal fractures, respectively [10, 12, 14–16, 19, 21] (risk ratio = 0.32, 95 % CI = 0.07 to 1.43, $p = 0.13$, $I^2 = 13$ %), no significant differences were found with regard to number of nonunions (Fig. 11a, b).

Discussion

Key findings

This systematic review suggests that current evidence from randomized trials is insufficient to conclude a benefit of LIPUS or PEMF bone growth stimulation in reducing the incidence of nonunions when used for treatment in acute fractures. With regard to time to radiological union, we found heterogeneous but significant results that suggest that the use of PEMF or LIPUS in acute fractures may be beneficial, however, only in non-operatively treated fractures. The use of bone growth stimulation can accelerate the time to radiological union by approximately 27 days. Furthermore, treatment with PEMF or LIPUS may be effective in the upper limb, to shorten the time to radiological union with 20 days. Concerning time to clinical union, current evidence suggest that the use of LIPUS can be beneficial, especially in acute diaphyseal fractures, by reducing the time to clinical union by approximately 18 days.

Strengths and limitations

The findings of our study are strengthened by the broad literature search and valid methodological assessment of all included trials. Furthermore, we contacted several authors to provide previously unreported data, necessary for

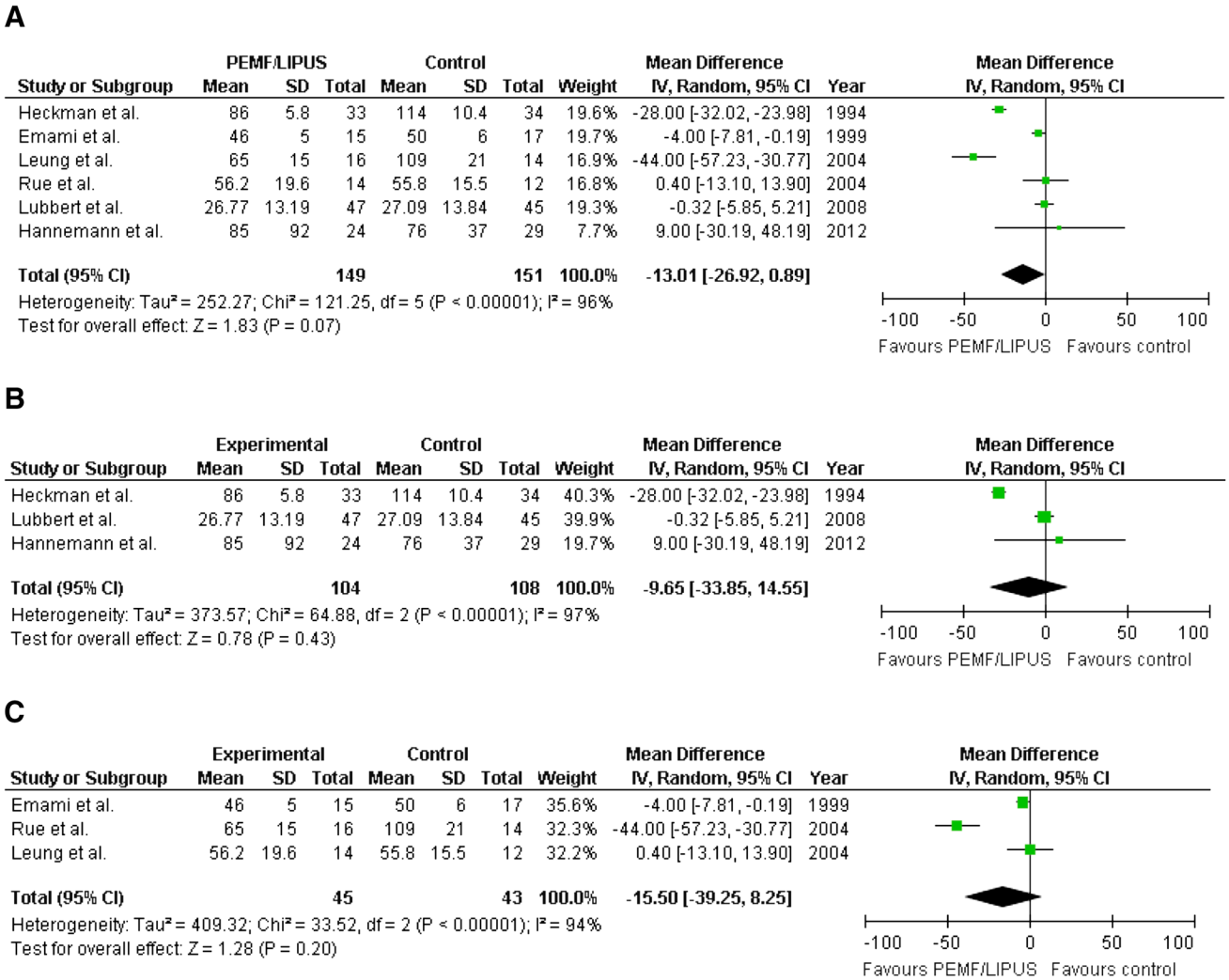


Fig. 6 **a** Time until clinical union (PEMF/LIPUS vs. placebo); **b** time until clinical union non-operatively treated fractures (PEMF/LIPUS vs. placebo); **c** time until clinical union operatively treated fractures (PEMF/LIPUS vs. placebo)

pooling of comparable outcome measurements [13, 17, 21]. Still, some of the included trials had methodological limitations such as small population samples, per protocol analysis and inadequate concealment of treatment allocation.

Pooled data for outcome parameter time to radiological union showed substantial heterogeneity ($I^2 = 97$ %). We consider the variability in criteria for radiological union to be the main factor for variation in outcome generating substantial heterogeneity. In four studies, union was defined as trabecular bridging of 3 out of 4 cortices [9, 11, 13, 20]. In two studies, union was defined as bridging of 4 out of 4 cortices [10, 21]. Three studies defined union as fading of the fracture line on the radiographs [14–16] and in one study union was defined as trabecular bridging of 70 % of the fracture surface [19]. Therefore, conclusions drawn from this heterogeneous outcome must be interpreted with caution. For outcome parameter time to clinical union, serious heterogeneity ($I^2 = 94$ %) is also considered to be caused by variability in criteria for clinical union. The studies investigating lower extremity fractures mainly used the criterion full weight bearing as indicator for clinical healing [9, 11, 13, 18], while the study by Hannemann et al. [21] investigating upper extremity fractures used pain at manipulation of the fracture site, range of motion and grip strength as criteria for determining clinical union.

Only three trials reported on the effects of PEMF in acute fractures [19–21]. This raises the question of publication bias. One study reported significantly faster healing in the active group treated with PEMF [19]. However, because of the low amount of publications, significant heterogeneity according to the outcome parameters and the lack of detailed description of the electromagnetic intervention in one study [20], the potential effects of PEMF cannot be clarified significantly.

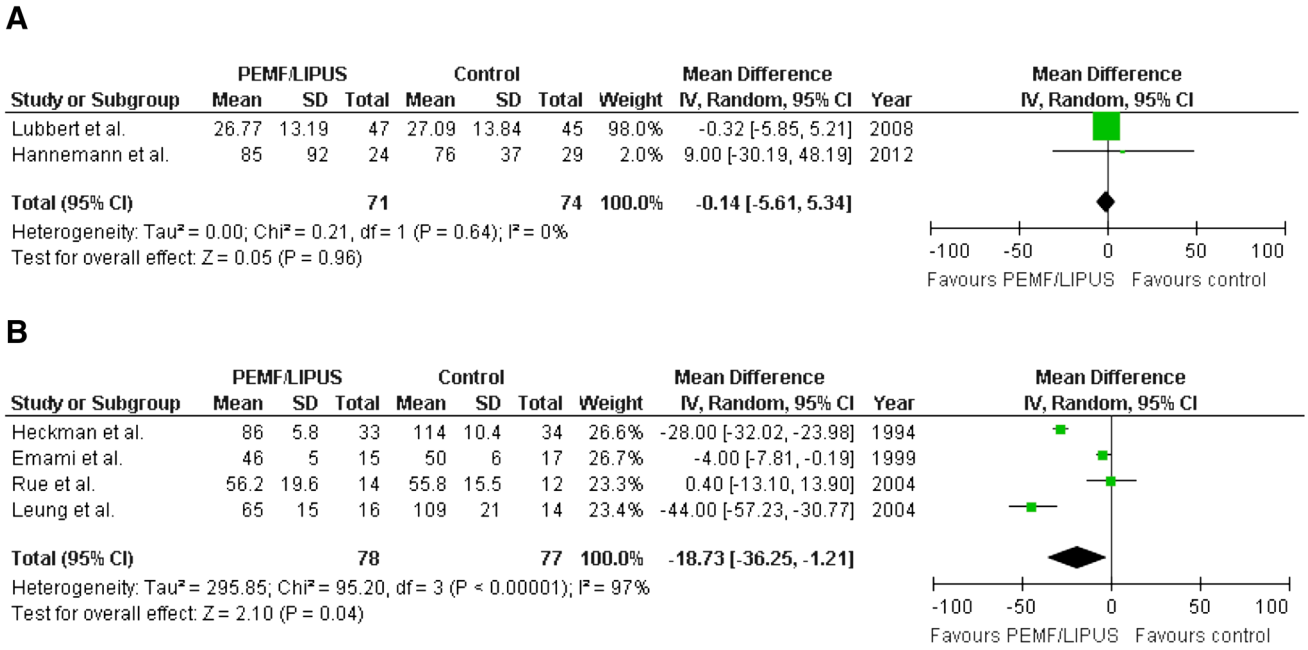


Fig. 7 **a** Time until clinical union upper limb (PEMF/LIPUS vs. placebo); **b** time until clinical union lower limb fractures (PEMF/LIPUS vs. placebo)

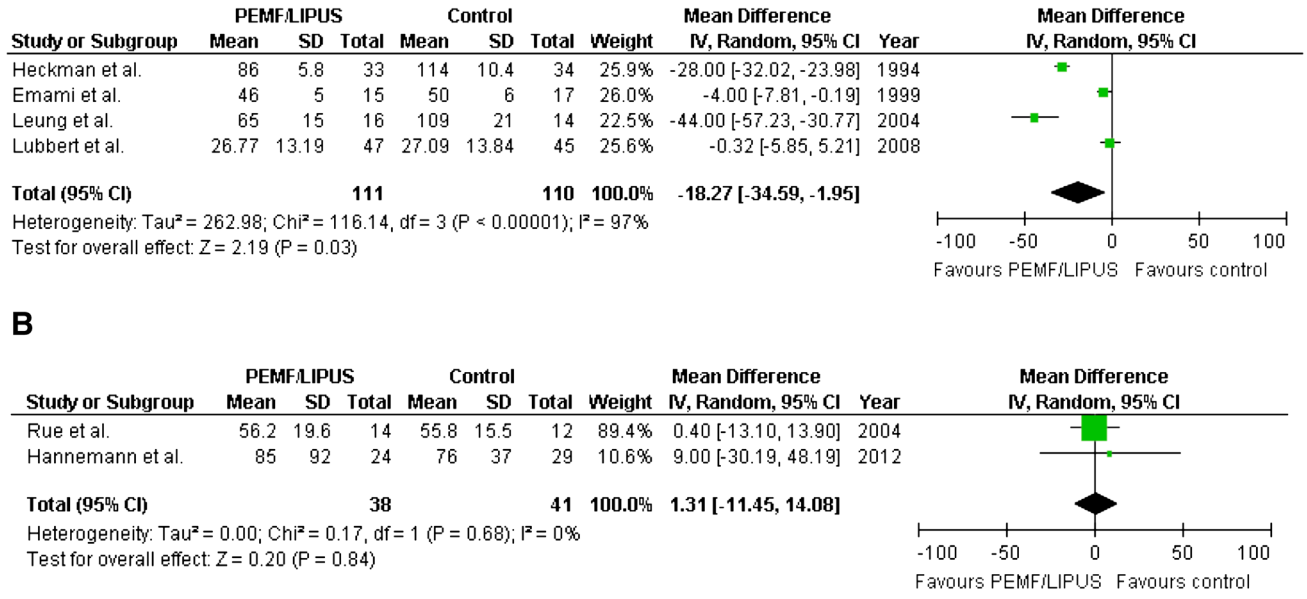


Fig. 8 **a** Time until clinical union diaphyseal fractures (PEMF/LIPUS vs. placebo); **b** time until clinical union metaphyseal fractures (PEMF/LIPUS vs. placebo)

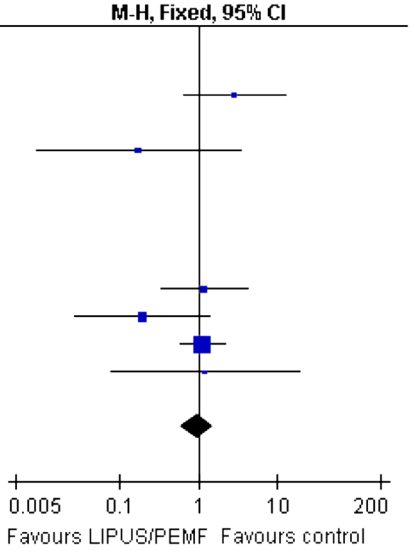
Previous research

The interest in applying physical forces for accelerated bone healing dates back to the 1950s when several animal studies investigated the effect of high-intensity ultrasound on callus formation and reported adverse effects [22]. After adjustment of the signal intensity, results from several trials reporting faster callus formation in fractures caused international interest in the use of low-intensity pulsed ultrasound (LIPUS) as a potential method to accelerate bone healing [23, 24].

A

Study or Subgroup	PEMF/LIPUS Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Heckman et al.	0	33	0	34		Not estimable	1994
Kristiansen et al.	0	30	0	31		Not estimable	1997
Emami et al.	5	15	2	17	6.0%	2.83 [0.64, 12.52]	1999
Mayr et al.	0	15	0	15		Not estimable	2000
Leung et al.	0	16	2	14	8.6%	0.18 [0.01, 3.39]	2004
Rue et al.	0	14	0	12		Not estimable	2004
Handolin et al. (3)	0	8	0	8		Not estimable	2005
Handolin et al.	0	11	0	11		Not estimable	2005
Handolin et al. (2)	0	15	0	15		Not estimable	2005
Lubbert et al.	5	52	4	49	13.3%	1.18 [0.34, 4.13]	2008
Faldini et al.	1	16	11	35	22.2%	0.20 [0.03, 1.41]	2010
Adie et al.	16	106	15	112	47.0%	1.13 [0.59, 2.16]	2011
Hannemann et al.	1	24	1	29	2.9%	1.21 [0.08, 18.32]	2012
Total (95% CI)		**355**		**382**	**100.0%**	**0.95 [0.59, 1.54]**	
Total events	28		35				

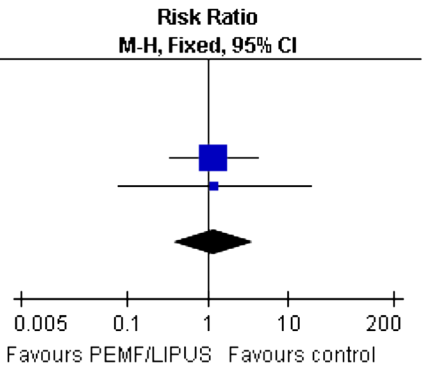
Heterogeneity: Chi² = 6.17, df = 5 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.20 (P = 0.84)



B

Study or Subgroup	PEMF/LIPUS Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Heckman et al.	0	33	0	34		Not estimable	1994
Kristiansen et al.	0	30	0	31		Not estimable	1997
Mayr et al.	0	15	0	15		Not estimable	2000
Lubbert et al.	5	52	4	49	82.0%	1.18 [0.34, 4.13]	2008
Hannemann et al.	1	24	1	29	18.0%	1.21 [0.08, 18.32]	2012
Total (95% CI)		**154**		**158**	**100.0%**	**1.18 [0.38, 3.70]**	
Total events	6		5				

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)



C

Study or Subgroup	PEMF/LIPUS Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Heckman et al.	0	33	0	34		Not estimable	1994
Kristiansen et al.	0	30	0	31		Not estimable	1997
Mayr et al.	0	15	0	15		Not estimable	2000
Lubbert et al.	5	52	4	49	82.0%	1.18 [0.34, 4.13]	2008
Hannemann et al.	1	24	1	29	18.0%	1.21 [0.08, 18.32]	2012
Total (95% CI)		**154**		**158**	**100.0%**	**1.18 [0.38, 3.70]**	
Total events	6		5				

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)

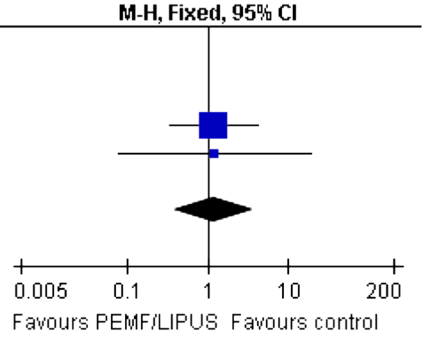


Fig. 9 **a** Number of nonunions at 6 months (PEMF/LIPUS vs. placebo); **b** number of nonunions at 6 months non-operatively treated fractures (PEMF/LIPUS vs. placebo); **c** number of nonunions at 6 months operatively treated fractures (PEMF/LIPUS vs. placebo)

The first double-blind study concerning PEMF in tibia delayed unions showed a significantly increased healing rate in the intervention group compared to the control group [25]. Several randomized clinical trials have investigated the effectiveness of LIPUS and PEMF therapy to treat delayed unions and nonunions and concluded that

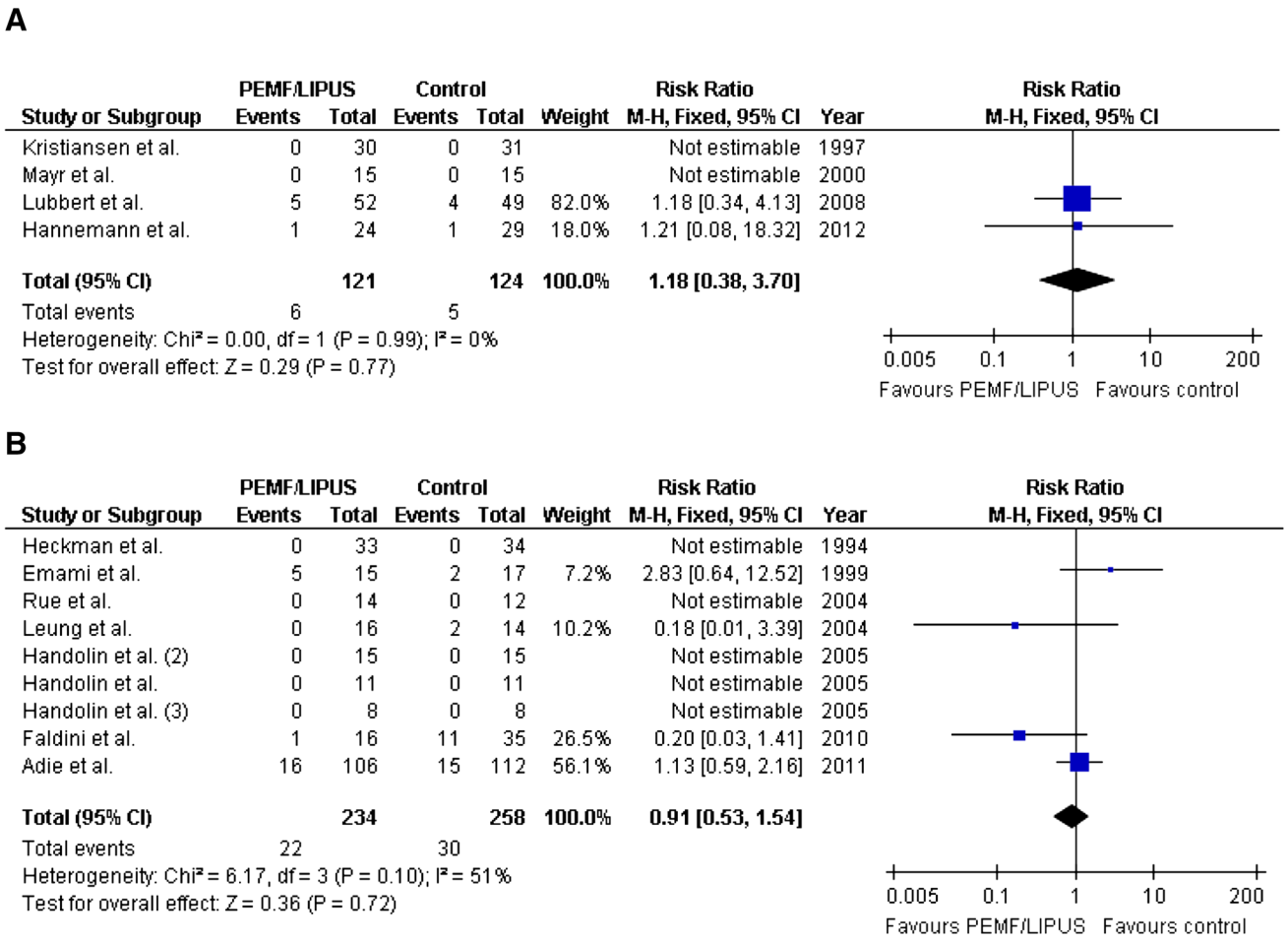


Fig. 10 **a** Number of nonunions at 6 months upper limb (PEMF/LIPUS vs. placebo); **b** number of nonunions at 6 months lower limb (PEMF/LIPUS vs. placebo)

long-bone healing up to 87 % could be achieved when using LIPUS or PEMF for delayed unions or nonunions [26–28].

Since 1980 several trials have been conducted to test whether LIPUS and PEMF can be used to promote healing in acute fractures [3, 4].

Two previous systematic reviews investigating the use of LIPUS or PEMF in acute fractures were inconclusive about the clinical relevance of LIPUS and PEMF [3, 4]. A possible explanation may be the limited number of studies included and the large heterogeneity in outcome measures. Since then a substantial number of new studies have been published including a systematic review and meta-analysis in 2012 [17, 19–21, 29]. The authors of this review selected 23 studies that used LIPUS on a variety of bone injuries, including fresh fractures, malunions or nonunions in all types of bones. They were able to pool the fresh fractures and concluded that LIPUS stimulates the radiographic bone healing in fresh fractures. However, they did not consider the type of fracture (metaphyseal or diaphyseal fractures) or the site of fractures (upper or lower limb) for the meta-analysis. Therefore, we believe that our review and meta-analysis currently provides the best available evidence to support clinical decision-making by adding methodological quality, performing a subgroup-analysis and incorporating recently published data [30].

Recommendations for future research

Further studies on the acceleration of fracture healing using PEMF and LIPUS should take into account the need for large clinical trials using an intention-to-treat analysis, proper blinding and adequate concealment of treatment allocation. Although union is a continuous process of bone reconstruction and there is no commonly accepted cut-off point for union of fractures, a valid and uniform measuring method to define radiological union for various fractures should be considered in future trials [31, 32]. This may help in reducing substantial heterogeneity in outcome parameters as stated above. Since the widespread use of PEMF

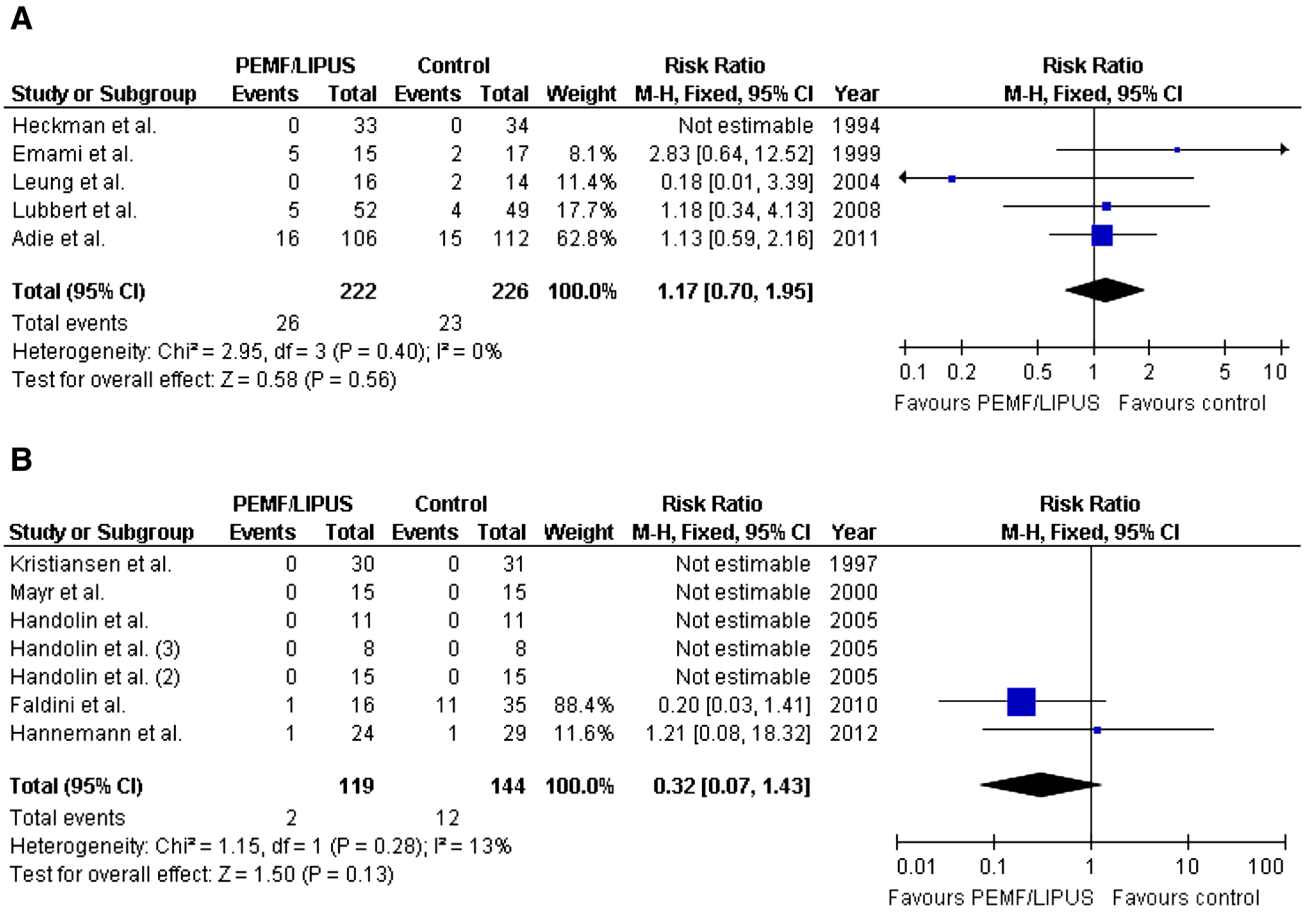


Fig. 11 **a** Number of nonunions at 6 months diaphyseal fractures (PEMF/LIPUS vs. placebo); **b** number of nonunions at 6 months metaphyseal fractures (PEMF/LIPUS vs. placebo)

and LIPUS bone growth stimulation in orthopaedics has its impact on total healthcare costs, cost-effectiveness and cost-utility analyses should also be part of future trials [33].

Conclusions

Based on trials with substantial methodological quality, this study suggests that bone growth stimulation with PEMF or LIPUS decreases healing time to radiological union for acute fractures undergoing non-operative treatment and fractures of the upper limb. LIPUS bone growth stimulation can be beneficial in the treatment of acute diaphyseal fractures to accelerate the time to clinical union. Concerning the overall rate of nonunions in acute fractures, current evidence from randomized trials has not demonstrated sufficient advantage to warrant routine use of PEMF or LIPUS.

Acknowledgments Financial support for this study was received from the Netherlands Organisation for Health Research and Development (ZonMw, reference 171001004).

Conflict of interest All named authors declare that they have no conflicts of interest to disclose. All named authors declare that they have no financial relationship with any organization that contributed to this study.

References

1. van der Molen AB, Groothoff JW, Visser GJ, Robinson PH, Eisma WH (1999) Time off work due to scaphoid fractures and other carpal injuries in The Netherlands in the period 1990 to 1993. J Hand Surg 24(2):193–198
2. Bonafede M, Espindle D, Bower AG (2013) The direct and indirect costs of long bone fractures in a working age US population. J Med Econ 16(1):169–178
3. Griffin XL, Costello I, Costa ML (2008) The role of low intensity pulsed ultrasound therapy in the management of acute fractures: a systematic review. J Trauma 65(6):1446–1452
4. Walker NA, Denegar CR, Preische J (2007) Low-intensity pulsed ultrasound and pulsed electromagnetic field in the treatment of tibial fractures: a systematic review. J Athl Train 42(4):530–535
5. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535

6. Higgins J, Altman DG (2008) Assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series. Wiley, pp 187–241
7. Landis JR, Koch GG (1977) The measurement of observer agreement for categorical data. Biometrics 33:159–174
8. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stat Med 21(11):1539–1558
9. Heckman JD, Ryaby JP, McCabe J, Frey JJ, Kilcoyne RF (1994) Acceleration of tibial fracture-healing by non-invasive, low-intensity pulsed ultrasound. J Bone Joint Surg Am Vol 76(1):26–34
10. Kristiansen TK, Ryaby JP, McCabe J, Frey JJ, Roe LR (1997) Accelerated healing of distal radial fractures with the use of specific, low-intensity ultrasound. A multicenter, prospective, randomized, double-blind, placebo-controlled study. J Bone Joint Surg Am Vol 79(7):961–973
11. Emami A, Petren-Mallmin M, Larsson S (1999) No effect of low-intensity ultrasound on healing time of intramedullary fixed tibial fractures. J Orthop Trauma 13(4):252–257
12. Mayr E, Rudzki MM, Rudzki M, Borchardt B, Hausser H, Ruter A (2000) Does low intensity, pulsed ultrasound speed healing of scaphoid fractures? Handchir Mikrochir Plast Chir 32(2):115–122
13. Leung KS, Lee WS, Tsui HF, Liu PP, Cheung WH (2004) Complex tibial fracture outcomes following treatment with low-intensity pulsed ultrasound. Ultrasound Med Biol 30(3):389–395
14. Handolin L, Kiljunen V, Arnala I, Kiuru MJ, Pajarinen J, Partio EK et al (2005) No long-term effects of ultrasound therapy on bioabsorbable screw-fixed lateral malleolar fracture. Scand J Surg 94(3):239–242
15. Handolin L, Kiljunen V, Arnala I, Kiuru MJ, Pajarinen J, Partio EK et al (2005) Effect of ultrasound therapy on bone healing of lateral malleolar fractures of the ankle joint fixed with bioabsorbable screws. J Orthop Sci 10(4):391–395
16. Handolin L, Kiljunen V, Arnala I, Pajarinen J, Partio EK, Rokkanen P (2005) The effect of low intensity ultrasound and bioabsorbable self-reinforced poly-L-lactide screw fixation on bone in lateral malleolar fractures. Arch Orthop Trauma Surg 125(5):317–321
17. Lubbert PH, van der Rijt RH, Hoorntje LE, van der Werken C (2008) Low-intensity pulsed ultrasound (LIPUS) in fresh clavicle fractures: a multi-centre double blind randomised controlled trial. Injury 39(12):1444–1452
18. Rue JP, Armstrong DW 3rd, Frassica FJ, Deafenbaugh M, Wilckens JH (2004) The effect of pulsed ultrasound in the treatment of tibial stress fractures. Orthopedics 27(11):1192–1195
19. Faldini C, Cadossi M, Deianira L, Betti E, Chiarello E, Giannini S (2010) Electromagnetic bone growth stimulation in patients with femoral neck fractures treated with screws: prospective randomized double-blind study. Curr Orthop Pract 21(3):282–287
20. Adie S, Harris IA, Naylor JM, Rae H, Dao A, Yong S et al (2011) Pulsed electromagnetic field stimulation for acute tibial shaft fractures: a multicenter, double-blind, randomized trial. J Bone Joint Surg Am Vol 93(17):1569–1576
21. Hannemann PF, Gottgens KW, van Wely BJ, Kolkman KA, Werre AJ, Poeze M et al (2012) The clinical and radiological outcome of pulsed electromagnetic field treatment for acute scaphoid fractures: a randomised double-blind placebo-controlled multicentre trial. J Bone Joint Surg Br Vol 94(10):1403–1408
22. Ardan NI Jr, Janes JM, Herrick JF (1954) Changes in bone after exposure to ultrasonic energy. Minn Med 37(6):415–420
23. Borsalino G, Bagnacani M, Bettati E, Fornaciari F, Rocchi R, Uluhogian S et al (1988) Electrical stimulation of human femoral intertrochanteric osteotomies. Double-blind study. Clin Orthop Relat Res 237:256–263
24. Azuma Y, Ito M, Harada Y, Takagi H, Ohta T, Jingushi S (2001) Low-intensity pulsed ultrasound accelerates rat femoral fracture healing by acting on the various cellular reactions in the fracture callus. J Bone Miner Res 16(4):671–680
25. Sharrard WJ (1990) A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures. J Bone Joint Surg Br Vol 72(3):347–355
26. Bassett CA, Mitchell SN, Gaston SR (1981) Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields. J Bone Joint Surg Br Vol 63(4):511–523
27. Nolte PA, van der Krans A, Patka P, Janssen IM, Ryaby JP, Albers GH (2001) Low-intensity pulsed ultrasound in the treatment of nonunions. J Trauma 51(4):693–702 discussion-3
28. Schofer MD, Block JE, Aigner J, Schmelz A (2010) Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. BMC Musculoskelet Disord 11:229
29. Bashardoust Tajali S, Houghton P, MacDermid JC, Grewal R (2012) Effects of low-intensity pulsed ultrasound therapy on fracture healing: a systematic review and meta-analysis. Am J Phys Med Rehabilitation Assoc Acad Physiatr 91(4):349–367
30. Poolman RW, Abouali JA, Conter HJ, Bhandari M (2007) Overlapping systematic reviews of anterior cruciate ligament reconstruction comparing hamstring autograft with bone-patellar tendon-bone autograft: why are they different? J Bone Joint Surg Am Vol 89(7):1542–1552
31. Bhandari M, Fong K, Sprague S, Williams D, Petrisor B (2012) Variability in the definition and perceived causes of delayed unions and nonunions: a cross-sectional, multinational survey of orthopaedic surgeons. J Bone Joint Surg Am Vol 94(15):e1091–e1096
32. Corrales LA, Morshed S, Bhandari M, Miclau T 3rd (2008) Variability in the assessment of fracture-healing in orthopaedic trauma studies. J Bone Joint Surg Am Vol 90(9):1862–1868
33. Button ML, Sprague S, Gharsaa O, Latouche S, Bhandari M (2009) Economic evaluation of bone stimulation modalities: a systematic review of the literature. Indian J Orthop 43(2):168–174