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Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis

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Abstract

Objective: To investigate the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in treating osteoarthritis (OA).

Methods: Relevant studies were identified by searching the database of PubMed, Embase, the Cochrane Library and Web of Science. Randomized controlled trials (RCTs) comparing PEMF with sham-control were included.

Results: Twelve trials (n=770) comparing PEMF with sham-control were included, among which ten trials involved knee OA, two involved cervical OA and one involved hand OA. The PEMF group showed more significant pain alleviation than the sham group in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, P = 0.03) and hand OA (SMD = -2.85, 95% CI: -3.65, -2.04, P < 0.00001), but not in cervical OA. Similarly, comparing with the sham-control treatment, significant function improvement was observed in the PEMF group in both knee and hand OA patients (SMD = -0.34, 95%CI: -0.53, -0.14, P = 0.0006, and SMD = -1.49, 95%CI: -2.12, -0.86, P < 0.00001, respectively), but not in cervical OA patients. Sensitivity analyses suggested that the exposure duration <= 30 minutes per session exhibited better effects compared with the exposure duration > 30 minutes per session. Three trials reported adverse events, and the combined results showed that there was no significant difference between PEMF and the sham group.

Conclusions: The present study revealed that PEMF could alleviate pain and improve physical function for knee and hand OA patients, but not for cervical OA patients. Meanwhile, a short PEMF treatment duration (within 30 minutes) may achieve more favorable efficacy.

Level of Evidence: Level I, meta-analysis

Key words: osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

Strengths and limitations of this study

1. This study provided a comprehensive assessment on the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in patients with knee, hand and cervical osteoarthritis (OA).
2. All included studies in this meta-analysis were randomised controlled trials.
3. There was a high level of heterogeneity among various studies, because different treatment protocols of PEMF were used in the included studies.
4. There were sparse eligible trials available for the efficacy analysis of hand OA and cervical OA, and the reliability of the conclusions on these two joints were limited.

INTRODUCTION

Osteoarthritis (OA) is a widespread degenerative disease, which can lead to pain, physical dysfunction and even disability. The joints most commonly affected by OA include knees, hips, hands, neck, and feet.[1 2] A variety of medications and physical therapies have been used in the treatment of OA. However, some widely-applied drugs (e.g., chondroitin, glucosamine, intraarticular hyaluronic acid, etc.) or physical treatments (e.g., transcutaneous electrical nerve stimulation, and ultrasound) are actually not advocated by the recent Osteoarthritis Research Society International (OARSI) guidelines.[3] To date, few effective treatments for knee OA are available.

Since the early 1980s, researchers have found that pulsed electromagnetic field (PEMF) therapy could be applied to accelerate wound healing, repair fracture, reduce hematoma, and treat soft tissue injury and inflammation.[4] In addition, some studies have demonstrated that PEMF could activate the signal transduction pathway[5-7] and induce the human articular chondrocyte proliferation.[8] Being a simple, noninvasive and safe physical therapy, PEMF was considered to be an alternative treatment regimen for OA. During the past two decades, more than ten randomized controlled trials (RCTs) were conducted to explore the efficacy of PEMF in the treatment of OA, but no consensus was reached yet.[9-22] Several previous meta-analyses have evaluated the combined effects of PEMF and pulsed electrical stimulation on OA.[23 24] However, the mechanisms of PEMF and pulsed electrical stimulation are totally different. For example, PES is delivered through capacitive coupling using transcutaneous electrodes and coupling agents[25] relying on the direct application of an electrical field; whereas PEMF creates induced current through magnetic impulse.[24] To the best of our knowledge, few meta-analyses have evaluated the efficacy and safety of single PEMF for OA.

To fill in this knowledge gap, the purpose of the present study was to provide a comprehensive assessment on the efficacy and safety of single PEMF in patients with OA at different joints. It was hypothesized that PEMF could relieve pain and improve the physical function of OA patients without producing side effects.

METHODS

Search strategies and studies selection

The study records were identified in four electronic databases of PubMed, Embase, the Cochrane

Library and Web of Science through using the combination of a series of keywords and text terms describing OA and PEMF (Appendix 1). The latest literature search was conducted at October 13, 2017. Studies were included if: (1) subjects with symptomatic or radiographic OA, (2) the intervention containing PEMF versus sham-control, (3) the study was designed as a RCT, (4) the primary outcome including pain and/or function. Studies were excluded if: (1) in vitro or animal or cadaveric studies, (2) PEMF therapy used for post-operation rehabilitation, (3) other non-medicine therapy (e.g., short wave or PES), (4) cannot get full-text, (5) no data available, (6) unbalanced additional non-pharmacological treatments (e.g., exercise or hot-pack) between groups.

Quality assessment

The methodological quality of each included trial was evaluated by two independent authors based on the Cochrane handbook,[26 27] which consists of seven domains: generation of randomization sequences, allocation concealment, blinding of participants and implementers, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias. Furthermore, any of divergence was to be discussed and a third consultant was needed if necessary.[28 29] Trials involving three or more high risks of bias were considered as poor methodological quality.[30]

Data extraction and outcome measure

All the data extracted by two independent authors. The extracted information included the characteristics of participants (age, gender, body mass index, and duration of OA), balance intervention between groups, number of participants about each trial, treatment protocol of PEMF, and the type of outcome measures, baseline data, post-treatment data and change means, and standard deviations (SD) or the information from which SD could be derived, such as standard error (SE) or confidence interval (CI). The primary goal of this study was to assess the efficacy of pain alleviation and function improvement by applying the PEMF therapy for OA patients. Adverse events were considered as the secondary outcome. The efficacy of pain alleviation was measured by change of pain intensity from baseline.[31] Data from the last follow-up time point after treatment was extracted to calculate the change degree. According to Jüni *et al.,*[32 33] the higher score one on hierarchy of continuous pain-related outcomes was used if multiple pain scale measured in one study. The number of participants reported

adverse events were also extracted in order to evaluate the safety of interventions.

Statistical analysis

The Review Manager Version 5.2 was used to perform all the statistical analyses. For the reason that outcome of pain and function reported by continuous data and various scales were used for outcome assessment, the standardized mean differences (SMDs) were calculated to compare the effect of pain alleviation and function improvement between different intervention groups. For the safety outcome, the relative risk (RR) was calculated to compare the safety between two groups. Trials reported zero adverse event in both the PEMF and the sham groups were not included in the adverse events analysis.[26] 95% CI was calculated for pooled estimates for each outcome. Statistical significance was considered at $P < 0.05$. A random model was applied to pool the data. Q and I^2 statistics were calculated to assess the heterogeneity among the included studies, with a p value > 0.05 of the Q statistics and I^2 value < 50% indicating statistical homogeneity. Different exposure duration of PEMF, disease location was hypothesized to influence treatment effect. Therefore, subgroup analyses were performed according to the exposure duration of PEMF therapy (no more than 30 minutes per session or more than 30 minutes per session)[5-7] and location of OA. Funnel plots were inspected to assess publication bias.

Patient and public involvement

No patients or members of public were involved in the present study. No patients were asked to advise on interpretation or writing up of results. The results of present research will be communicated to the relevant patient community.

RESULTS

Study screening and characteristics of included studies

Figure 1 showed the flow diagram for studies screening. 192 records were identified initially and twelve studies[9-20] met the eligibility criteria and were included in this meta-analysis. The characteristics of included studies were summarized in Table 1. The risk of bias assessment (Figure 2) showed that one study[9] was regarded as low quality.

Pain relief

Twelve RCTs were included for meta-analysis of pain management.[9-20] As shown in Figure 3, PEMF group achieved a significant difference in pain improvement compared with sham group (SMD = -0.94, 95% CI: -1.49, -0.39, P =0.0008), while significant heterogeneity was observed (I^2 = 92%; P < 0.00001). Subgroup analysis showed that significant differences were observed between the PEMF and sham group on pain improvement in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, P = 0.03) and hand OA patients (SMD = -2.85, 95% CI: -3.65, -2.04, P < 0.00001), whereas no significant difference was achieved between groups in cervical OA patients (SMD = -2.33, 95% CI: -6.26, 1.61, P = 0.25). As for subgroup analysis of different exposure duration, significant difference was observed when exposure duration within 30 minutes (SMD = -1.01, 95%CI: -1.64, -0.39, P = 0.001), and no significant difference was achieved between intervention groups when exposure duration more than 30 minutes (SMD = -0.61, 95%CI: -2.25, 1.02, P = 0.46) (see Table 2). Besides, substantial asymmetry was not identified in the funnel plot.

Function improvement

Eight RCTs were included for meta-analysis of physical function improvement.[9 10 12 13 15 16 19 20] Figure 4 illustrated the beneficial effect of PEMF on physical function improvement (SMD = -0.45, 95% CI: -0.71, -0.19, P = 0.0005), and substantial heterogeneity was observed (I^2 = 54%; P = 0.03). However, the subgroup analysis of different OA locations suggested significant differences both in knee OA and hand OA (SMD = -0.34, 95%CI: -0.53, -0.14, P = 0.0006, and SMD = -1.49, 95%CI: -2.12, -0.86, P < 0.00001, respectively, see in Table 2), whereas there was no significant difference between groups in cervical OA patients (SMD = -0.27, 95% CI: -0.71, 0.16, P = 0.22). In addition, there was a significant difference on effect of function improvement when exposure duration within 30 minutes (SMD = -0.50, 95%CI: -0.81, -0.18, P = 0.002), and no significant difference was observed in more than 30 minutes group (SMD = -0.33, 95%CI: -0.82, 0.17, P = 0.20). Funnel plot also did not identify substantial asymmetry.

Adverse events

There were ten RCTs that reported adverse events.[9-11 13 14 16-20] Seven of them claimed that no adverse events were observed both in PEMF and sham group.[9 10 13 14 17 18 20] Three trials reported the adverse events of each treatment group, such as hip pain, spine pain, increased knee pain, vomiting, warming sensation, increased blood pressure, numbness of feet, paraesthesia of foot and et al, and there was no AE related drop outs in each trial.[11 16 19] There was no significant difference between the PEMF and the sham group regarding adverse events (RR = 0.83, 95%CI: 0.26, 2.64, P = 0.75) (Figure 5). Substantial asymmetry was not identified in the funnel plot.

DISCUSSION

This study provided a comprehensive assessment on the efficacy and safety of the PEMF therapy in patients with knee, hand and cervical OA. The results showed that, in comparison with the sham-control group, PEMF was more effective in both pain relief and function improvement for patients with knee OA and hand OA, but not for patients with cervical OA. In addition, PEMF did not lead to specific adverse events compared with the sham control group. Interestingly, a short duration of PEMF treatment for <= 30 minutes per session seems to achieve more favorable results. This finding may have significant implications for the clinical application of PEMF in the OA field.

Some previous systematic reviews have combined PEMF and other physical therapies together to examine their efficacy in OA patients, which might bias the results. McCarthy *et al.*[34] demonstrated that PEMF and short-wave together had limited effect in treating knee OA. In contrast, We *et al.*[35] reported different results. Based on the follow-up data extracted from different time points for subgroup analysis, they concluded that the combination of PEMF and short-wave was more effective in functional improvement, but not in pain relief, at 8 weeks after the first treatment.[35] It should be noted that[36] short-wave therapy was considered to be another type of physical therapy which was different from PEMF.[36] Similarly, another study conducted by Li *et al.*[24] reported that PEMF and PES might provide moderate benefit for OA sufferers in terms of pain relief. However, considering that PES relies on the direct application of an electrical field and PEMF creates induced current through magnetic impulse, the combined analysis of these two physical therapies may also bias the results.

The results of the present study showed that PEMF had significant effects in pain alleviation and function improvement comparing with the sham-control group in knee and hand OA patients, but not in

cervical OA patients. The poor efficacy of the treatment for cervical OA may due to the anatomical factors of cervical spine. The neurovascular structures contained in the cervical spinal canal may be compressed due to cervical OA, which will then induce a series of symptoms, such as the upper limb nerve root pain induced by nerve root compression; the chronic vertebral and basilar arterial insufficiency due to compression of vertebral arteries; the numbness of limbs and easiness to falling caused by spinal cord compression.[37 38] Although some studies showed that PEMF could enhance articular cartilage regeneration,[39 40] no evidence yet demonstrated that PEMF can reduce osteophytes formation, which may induce nerve root compression then lead to deterioration of pain and function.

The present study further examined the association between the exposure duration of PEMF and efficacy for patients with OA. The results suggested that the exposure duration <=30 minutes per session could achieved better efficacy both in pain relief and function improvement. The reason could be explained by several previous laboratory studies. A recent study exploring the effects of different PEMF treatment durations (ranged from 5 to 60 minutes) over the mesenchymal stem cells (MSC) chondrogenic differentiation reported that the expression of MSC chondrogenic markers showed the greatest increase in response to 5-20 minutes PEMF treatment.[41] Similarly, another two studies which have shown that PEMF could activate cellular signaling transduction rapidly within 5-10 minutes, whereas the signaling might be largely benumbed after 30 minutes.[5-7]

Nevertheless, limitations of the present study should be acknowledged. Firstly, since different treatment protocols of PEMF were used in the included studies, there was a high level of heterogeneity among various studies. Secondly, there were sparse eligible trials available for the efficacy analysis of hand OA and cervical OA, and the reliability of the conclusions on these two joints were limited. Finally, morphological change is a meaningful outcome for exploring the treatment efficacy of PEMF further;[19] however, the morphological changes were not reported in the present study due to the lack of relevant data. More trials are needed to evaluate the morphological changes after PEMF therapy.

CONCLUSION

The present study revealed that PEMF could alleviate pain and improve physical function for knee and hand OA patients, but not for cervical OA. Meanwhile, a short PEMF treatment duration (within 30 minutes) may achieve more favorable efficacy.

Author contributions

ZYW, DXX, XD and YLW were responsible for conception and design of the study. ZYW, XD, DXX, and YLW contributed to study retrieval. YC and YLX contributed to quality assessment. HL, TY and JTL contributed to data collection. JW and CZ contributed to statistical analysis. ZYW, XD, DXX and YLW drafted the manuscript. CZ and GHL contributed to revision of the manuscript. All authors read and approved the final manuscript.

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Declaration of financial/other relationships

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work and its conclusions.

Competing Interests statement: All authors declare that they have no conflict of interest.

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Table 1. Characteristics of included studies

Studies		Balance	N	Location of OA	Age, years (mean ± SD)	Female %	Mean BMI, kg/m^2 (mean ± SD)	Duration of OA, years (mean ± SD)	Exposure of intervention		Time point for outcome measure
									Daily time	Exposure duration	
Ay 2009	PEMF	Hot pack, TENS	55	Knee	58.9 ± 8.8	70.0	NA	3.6 ± 4.6	30 minutes	3 weeks (15 sessions)	After treatment
	Placebo				57.7 ± 6.5	76.0	NA	3.5 ± 4.1			
Bagnato 2016	PEMF	None	60	Knee	67.7 ± 10.9	70.0	27.4 ± 4.3	12.1 ± 8.2	A minimum of 12 hours	1 month (30 sessions)	1 month
	Placebo				68.6 ± 11.9	73.3	27.7 ± 4.6	12.4 ± 9.1			
Fischer 2006	PEMF	None	71	Knee	52.1 ± 1.9	71.4	29.2 ± 1.0	6.8 ± 0.7	16 minutes	6 weeks (42 sessions)	Therapy-End, 4weeks after therapy-End
	Placebo				62.1 ± 1.5	72.2	29.4 ± 0.7	6.2 ± 0.6			
Lee 2004	PEMF	None	51	Knee	63.5 ± 8.9	8.0	26.1 ± 3.1	12.7 ± 7.5	30 minutes	6weeks (18 sessions)	3, 6 weeks during treatment, 4 weeks after finishing
	Placebo				66.2 ± 8.8	11.5	27.1 ± 3.7	12.8 ± 7.6			
Nelson 2013	PEMF	Current standard of care	34	Knee	55.5 ± 2.5	73.7	33.5 ± 1.9	NA	15 minutes	6 weeks (84 sessions)	14, 29, 42 days
	Placebo				58.4 ± 2.5	66.7	34.7 ± 1.7	NA			
Nicolakis 2002	PEMF	None	36	Knee	69.0 ± 5.0	73.3	NA	NA	30 minutes	6 weeks (84 sessions)	After treatment
	Placebo				67.0 ± 7.0	47.1	NA	NA			
Pipitone (2001)	PEMF	None	75	Knee	62.0 (40–84) *	35.3	NA	4.0 (1.0–18.0) *	10 minutes and 3 times a day	6 weeks	2, 4, 6 weeks after study entry
	Placebo				64.0 (48–84) *	20.0	NA	8.0 (0.5–31.0) *			

Tejero Sánchez 2003	PEMF	None	83	Knee	67.4 ± 8.7	87.9	NA	NA	30 minutes	20 sessions	The end of therapy, one month after therapy
	Placebo				68.0 ± 8.3	88.2	NA	NA			
Thamsborg 2005	PEMF	None	83	Knee	60.4 ± 8.7	46.5	27.0 ± 4.0	7.5 ± 5.2	2 hours	6 weeks (30 sessions)	2 weeks, end of treatment, 6 weeks after end of treatment
	Placebo				59.6 ± 8.6	61.0	27.5 ± 5.7	7.9 ± 7.7			
Trock 1994 §	PEMF	Do not change basic therapeutic	86	Knee	69.2 ± 11.5	69.0	NA	9.1 ± 8.9	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
	Placebo				65.8 ± 11.7	70.5	NA	7.4 ± 7.2			
Sutbeyaz 2006	PEMF	None	34	Cervical	43.2 ± 10.3	64.7	NA	NA	30 minutes	3 weeks (42 sessions)	After treatment
	Placebo				42.1 ± 10.1	66.7	NA	NA			
Trock 1994 §	PEMF	Do not change basic therapeutic	81	Cervical	61.2 ± 13.4	28.6	NA	7.4 ± 6.7	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
	Placebo				67.4 ± 8.0	30.8	NA	8.1 ± 8.0			
Kanat 2013	PEMF	Active range of motion and resistive	50	Hand	64.0 ± 2.60	NA	NA	5.01 ± 2.3	20 minutes	10 days	After treatment
	Placebo				62.0 ± 2.40	NA	NA	4.31 ± 4.7			

N, number of participates; BMI, body mass index; OA, osteoarthritis; PEMF, pulsed electromagnetic field; NA, not available; TENS, transcutaneous electrical nerve stimulation.

* Age and duration of OA in this trial were expressed by median (range).

§ This trial provided data of knee OA and cervical OA patients respectively.

Table 2. Results of subgroup analyses.

Reason for subgroup analyses		Pooled Results of Subgroups		Heterogeneity of Subgroups	
		SMD/RR	95% CI	I^2 (%)	p Value
Pain					
Location	Knee OA	-0.54	[-1.04, 0.04]	88	0.03
	Cervical OA	-2.33	[-6.26, 1.61]	97	0.25
	Hand OA	-2.85	[-3.65, -2.04]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-1.01	[-1.64, -0.39]	91	0.001
	More than 0.5hr/session	-0.61	[-2.25, 1.02]	95	0.46
Function					
Location	Knee OA	-0.34	[-0.53, -0.14]	0	0.0006
	Cervical OA	-0.27	[-0.71, 0.16]	NA	0.22
	Hand OA	-1.49	[-2.12, -0.86]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-0.50	[-0.81, -0.18]	59	0.002
	More than 0.5hr/session	-0.33	[-0.82, 0.17]	54	0.20
Adverse event					
Exposure duration	No more than 0.5hr/session	0.42	[0.14, 1.29]	0	0.13
	More than 0.5hr/session	1.95	[0.81, 4.71]	NA	0.14

OA, osteoarthritis; SMD, standard mean difference; RR, relative risk; CI, confidence interval; NA, not available.

Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
OA: osteoarthritis, PEMF: pulsed electromagnetic field

Figure 2. Risk of bias summary of twelve included studies.

Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field

Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field

Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
PEMF: pulsed electromagnetic field

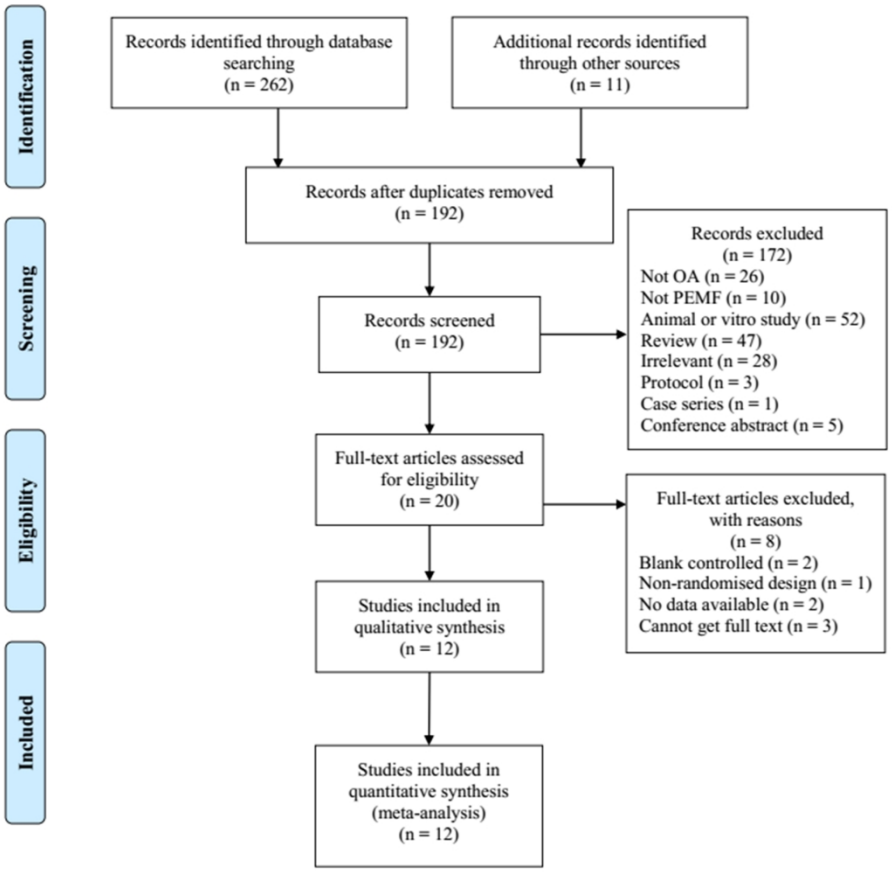

Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
OA: osteoarthritis; PEMF: pulsed electromagnetic field

173x155mm (300 x 300 DPI)

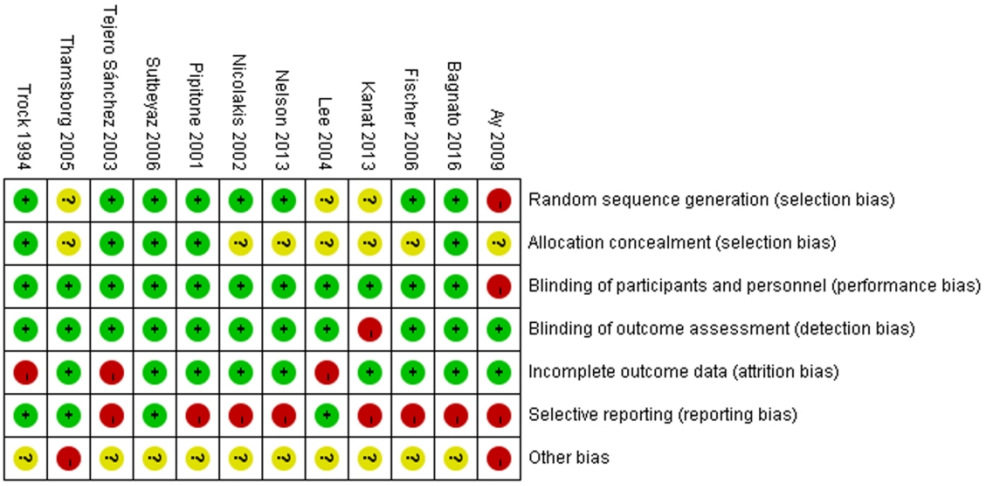

Figure 2. Risk of bias summary of twelve included studies.

173x87mm (300 x 300 DPI)

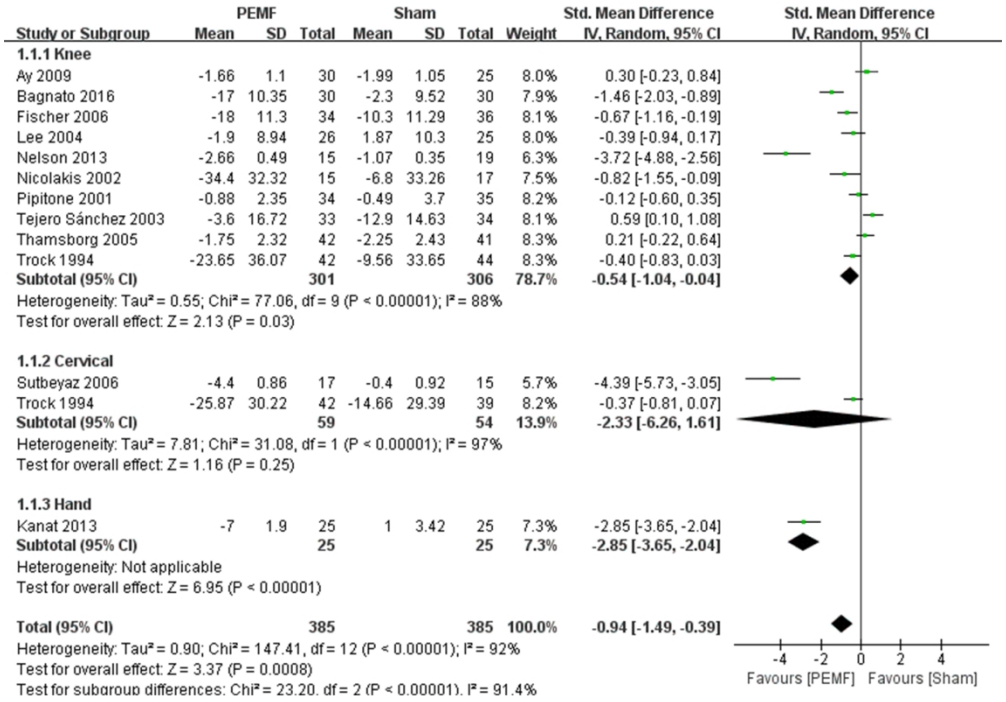

Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field

173x123mm (300 x 300 DPI)

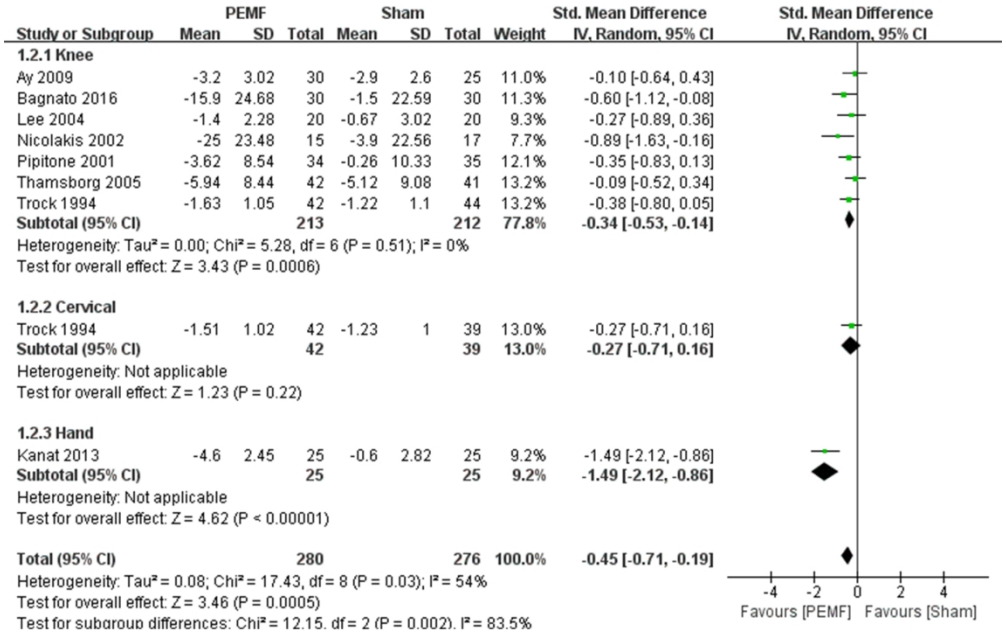

Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field

173x109mm (300 x 300 DPI)

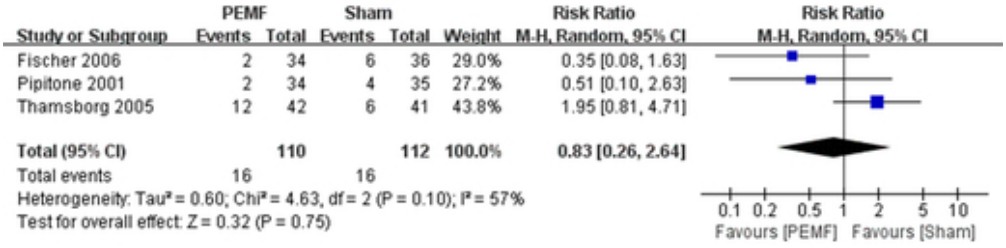

Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
PEMF: pulsed electromagnetic field

43x11mm (300 x 300 DPI)

Search Strategies

PubMed search strategy

#1 Pulsed electromagnetic field[Title/Abstract]

#2 Pulsed electromagnetic fields[Title/Abstract]

#3 Pulsed electromagnetic field[mesh]

#4 #1 or #2 or #3

#5 Osteoarthritis[Mesh]

#6 (osteoarthro*[tiab] or gonarthriti*[tiab] or gonarthro*[tiab] or coxarthriti*[tiab] or coxarthro*[tiab] or osteo?arthritis[tiab])

#7 #5 or #6

#8 randomized[tiab]

#9 placebo[tiab]

#10 controlled[tiab]

#11 random*[tiab]

#12 trial*[tiab]

#13 groups[tiab]

#14 ((singl*[tiab] or doubl*[tiab] or tripl*[tiab]) and (mask*[tiab] or blind*[tiab]))

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #4 and #7 and #15

Embase search strategy

#1 'Pulsed electromagnetic field'/exp

#2 Pulsed electromagnetic fields:ti,ab

#3 Pulsed electromagnetic field：ti,ab

#4 #1 or #2 or #3

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteoarthritis:ti,ab

#6 'Osteoarthritis'/exp

#7 #5 or #6

#8 random* or control* or trial* or placebo:ti,ab

#9 groups:ti,ab

#10 (singl* or doubl*or tripl*) and (mask* or blind*):ti,ab

#11 #8 or #9 or #10

#12 #4 and #7 and #11

Cochrane Library search strategy

#1 MeSH descriptor Pulsed electromagnetic field explode all trees

#2 Pulsed electromagnetic field:ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor osteoarthritis explode all trees

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis:ti,ab,kw

#6 #4 or #5

#7 random* or control* or trial* or placebo:ti,ab,kw

#8 Groups:ti,ab,kw

#9 (singl* or doubl*or tripl*) and (mask* or blind*):ti,ab,kw

#10 #7 or #8 or #9

#11 #3 and #6 and #10

Web of Science search strategy

#1 Topic:(Pulsed electromagnetic field)

#2 Topic:(Pulsed electromagnetic fields)

#3 #1 or #2

#4 Topic:(Osteoarthritis)

#5 Topic:(osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis)

#6 #4 or #5

#7 Topic:(randomized or placebo or controlled or random* or trial* or groups)

#8 Topic:((singl* or doubl* or tripl*) and (mask* or blind*))

#9 #7 or #8

#10 #3 and #6 and #9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4, 5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Details in Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	-
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, details in figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, details in table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6, details in figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6-7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis

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Secondary Subject Heading:	Sports and exercise medicine
Keywords:	osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

Efficacy and Safety of the Pulsed Electromagnetic Field in Osteoarthritis: A Meta-analysis

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[2] Dongxing Xie and Yilun Wang contributed equally to this article.

Abstract

Objective To investigate the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in treating osteoarthritis (OA).

Design meta-analysis.

Data sources PubMed, Embase, the Cochrane Library and Web of Science were searched through October 13, 2017.

Eligibility criteria for selecting studies Randomized controlled trials compared the efficacy of PEMF therapy with sham control in OA patients.

Data extraction and synthesis Pain, function, adverse effects and characteristics of participants were extracted. RevMan 5.2 was used to perform statistical analyses.

Results Twelve trials were included, among which ten trials involved knee OA, two involved cervical OA and one involved hand OA. The PEMF group showed more significant pain alleviation than the sham group in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, P = 0.03) and hand OA (SMD = -2.85, 95% CI: -3.65, -2.04, P < 0.00001), but not in cervical OA. Similarly, comparing with the sham-control treatment, significant function improvement was observed in the PEMF group in both knee and hand OA patients (SMD = -0.34, 95%CI: -0.53, -0.14, P = 0.0006, and SMD = -1.49, 95%CI: -2.12, -0.86, P < 0.00001, respectively), but not in cervical OA patients. Sensitivity analyses suggested that the exposure duration <= 30 minutes per session exhibited better effects compared with the exposure duration > 30 minutes per session. Three trials reported adverse events, and the combined results showed that there was no significant difference between PEMF and the sham group.

Conclusions PEMF could alleviate pain and improve physical function for knee and hand OA patients, but not for cervical OA patients. Meanwhile, a short PEMF treatment duration (within 30 minutes) may achieve more favorable efficacy. However, given the limited number of study available in hand and cervical OA, the implication of this conclusion should be cautious for hand and cervical OA.

Key words: osteoarthritis, pulsed electromagnetic field, meta-analysis, randomized controlled trial

Strengths and limitations of this study

1. This study provided a comprehensive assessment on the efficacy and safety of the pulsed electromagnetic field (PEMF) therapy in patients with knee, hand and cervical osteoarthritis (OA).
2. All included studies in this meta-analysis were randomized controlled trials.
3. There was a high level of heterogeneity among various studies, because different treatment protocols of PEMF were used in the included studies.
4. There were sparse eligible trials available for the efficacy analysis of hand OA and cervical OA, and the reliability of the conclusions on these two joints were limited.

INTRODUCTION

Osteoarthritis (OA) is a widespread degenerative disease, which can lead to pain, physical dysfunction and even disability. The joints most commonly affected by OA include knees, hips, hands, neck, and feet.[1 2] A variety of medications and physical therapies have been used in the treatment of OA. However, some widely-applied drugs (e.g., chondroitin, glucosamine, intraarticular hyaluronic acid, etc.) or physical treatments (e.g., transcutaneous electrical nerve stimulation, and ultrasound) are actually not advocated by the recent Osteoarthritis Research Society International (OARSI) guidelines.[3] To date, few effective treatments for knee OA are available.

Since the early 1980s, researchers have found that pulsed electromagnetic field (PEMF) therapy could be applied to accelerate wound healing, repair fracture, reduce hematoma, and treat soft tissue injury and inflammation.[4] In addition, some studies have demonstrated that PEMF could activate the signal transduction pathway[5-7] and induce the human articular chondrocyte proliferation.[8] Being a simple, noninvasive and safe physical therapy, PEMF was considered to be an alternative treatment regimen for OA. During the past two decades, more than ten randomized controlled trials (RCTs) were conducted to explore the efficacy of PEMF in the treatment of OA, but no consensus was reached yet.[9-22] Several previous meta-analyses have evaluated the combined effects of PEMF and pulsed electrical stimulation on OA.[23 24] However, the mechanisms of PEMF and pulsed electrical stimulation (PES) was totally different. For example, PES is delivered through capacitive coupling using transcutaneous electrodes and coupling agents[25] relying on the direct application of an electrical field; whereas PEMF creates induced current through magnetic impulse.[24] To the best of our knowledge, few meta-analyses have evaluated the efficacy and safety of single PEMF for OA.

To fill in this knowledge gap, the purpose of the present study was to provide a comprehensive assessment on the efficacy and safety of single PEMF in patients with OA at different joints. It was hypothesized that PEMF could relieve pain and improve the physical function of OA patients without producing side effects.

METHODS

Search strategies and studies selection

The study records were identified in four electronic databases of PubMed, Embase, the Cochrane

Library and Web of Science through using the combination of a series of keywords and text terms describing OA and PEMF (Appendix 1). The latest literature search was conducted at October 13, 2017. Studies were included if: (1) subjects with symptomatic or radiographic OA, (2) the intervention containing PEMF versus sham-control, (3) the study designed as a RCT, (4) the primary outcome including pain and/or function. Studies were excluded if: (1) in vitro or animal or cadaveric studies, (2) PEMF therapy used for post-operation rehabilitation, (3) other non-medicine therapy (e.g., short wave or PES), (4) cannot get full-text, (5) no data available, (6) unbalanced additional non-pharmacological treatments (e.g., exercise or hot-pack) between groups.

Quality assessment

The methodological quality of each included trial was evaluated by two independent authors based on the Cochrane handbook,[26 27] which consists of seven domains: generation of randomization sequences, allocation concealment, blinding of participants and implementers, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential bias. Furthermore, any of divergence was to be discussed and a third consultant was needed if necessary.[28 29] Trials involving three or more high risks of bias were considered as poor methodological quality.[30]

Data extraction and outcome measure

All the data extracted by two independent authors. The extracted information included the characteristics of participants (age, gender, body mass index, and duration of OA), balance intervention between groups, number of participants about each trial, treatment protocol of PEMF, and the type of outcome measures, baseline data, post-treatment data and change means, and standard deviations (SD) or the information from which SD could be derived, such as standard error (SE) or confidence interval (CI). The primary goal of this study was to assess the efficacy of pain alleviation and function improvement by applying the PEMF therapy for OA patients. Adverse events were considered as the safety outcome. The efficacy of pain alleviation was measured by change of pain intensity from baseline.[31] Data at the last follow-up time point after treatment was extracted to calculate the change degree from baseline to the last follow-up. According to the recommended hierarchy of continuous pain-related outcomes used in the meta-analyses,[32 33] the outcome data that expressed in higher ranking

scale was extracted if multiple pain scale measured simultaneously. WOMAC function was preferred measure for function outcome. If a study did not measure or report the WOMAC function, WOMAC total, SF-36 social function score or total score and physician global assessment scores were used in the analysis instead.[34] The number of participants reported adverse events were also extracted in order to evaluate the safety of interventions.

Statistical analysis

The Review Manager Version 5.2 was used to perform all the statistical analyses. For the reason that outcome of pain and function reported by continuous data and various scales were used for outcome assessment, the standardized mean differences (SMDs) were calculated to compare the effect of pain alleviation and function improvement between different intervention groups. For the safety outcome, the relative risk (RR) was calculated to compare the safety between two groups. Trials reported zero adverse event in both the PEMF and the sham groups were not included in the adverse events analysis.[26] 95% CI was calculated for pooled estimates for each outcome. Statistical significance was considered at $P < 0.05$. A random model was applied to pool the data. Q and I^2 statistics were calculated to assess the heterogeneity among the included studies, with a p value > 0.05 of the Q statistics and I^2 value < 50% indicating statistical homogeneity. Different exposure duration of PEMF, disease location was hypothesized to influence treatment effect. Therefore, subgroup analyses were performed according to the exposure duration of PEMF therapy (no more than 30 minutes per session or more than 30 minutes per session)[5-7] and location of OA. Funnel plots were inspected to assess publication bias.

Patient and public involvement

No patients or members of public were involved in the present study. No patients were asked to advise on interpretation or writing up of results. The results of present research will be communicated to the relevant patient community.

RESULTS

Study screening and characteristics of included studies

Figure 1 showed the flow diagram for studies screening. 192 records were identified initially and twelve studies[9-20] met the eligibility criteria and were included in this meta-analysis. The characteristics of included studies were summarized in Table 1. The risk of bias assessment (Figure 2) showed that one study[9] was regarded as low quality.

Pain relief

Twelve RCTs were included for meta-analysis of pain management.[9-20] As shown in Figure 3, PEMF group achieved a significant difference in pain improvement compared with sham group (SMD = -0.94, 95% CI: -1.49, -0.39, P =0.0008), while significant heterogeneity was observed (I^2 = 92%; P < 0.00001). Subgroup analysis showed that significant differences were observed between the PEMF and sham group on pain improvement in knee OA (SMD = -0.54, 95% CI: -1.04, -0.04, P = 0.03) and hand OA patients (SMD = -2.85, 95% CI: -3.65, -2.04, P < 0.00001), whereas no significant difference was achieved between groups in cervical OA patients (SMD = -2.33, 95% CI: -6.26, 1.61, P = 0.25). As for subgroup analysis of different exposure duration, significant difference was observed with exposure duration within 30 minutes (SMD = -1.01, 95%CI: -1.64, -0.39, P = 0.001), and no significant difference was achieved between intervention groups with exposure duration more than 30 minutes (SMD = -0.61, 95%CI: -2.25, 1.02, P = 0.46) (see Table 2). Besides, substantial asymmetry was not identified in the funnel plot.

Function improvement

Eight RCTs were included for meta-analysis of physical function improvement.[9 10 12 13 15 16 19 20] Figure 4 illustrated the beneficial effect of PEMF on physical function improvement (SMD = -0.45, 95% CI: -0.71, -0.19, P = 0.0005), and substantial heterogeneity was observed (I^2 = 54%; P = 0.03). However, the subgroup analysis of different OA locations suggested significant differences both in knee OA and hand OA (SMD = -0.34, 95%CI: -0.53, -0.14, P = 0.0006, and SMD = -1.49, 95%CI: -2.12, -0.86, P < 0.00001, respectively, see in Table 2), whereas there was no significant difference between groups in cervical OA patients (SMD = -0.27, 95% CI: -0.71, 0.16, P = 0.22). In addition, there was a significant difference on effect of function improvement with exposure duration within 30 minutes (SMD = -0.50, 95%CI: -0.81, -0.18, P = 0.002), and no significant difference was observed in more than 30 minutes

group (SMD = -0.33, 95%CI: -0.82, 0.17, *P* = 0.20). Funnel plot also did not identify substantial asymmetry.

Adverse events

There were ten RCTs that reported adverse events.[9-11 13 14 16-20] Seven of them claimed that no adverse events were observed both in PEMF and sham group.[9 10 13 14 17 18 20] Three trials reported the adverse events of each treatment group, which mainly included increased knee pain, hip pain, spine pain, vomiting, warming sensation, increased blood pressure, numbness of feet, paraesthesia of foot and cardiomyopathy, and there were no AE related drop outs in each trial.[11 16 19] There was no significant difference between the PEMF and the sham group regarding adverse events (RR = 0.83, 95%CI: 0.26, 2.64, *P* = 0.75) (Figure 5). Substantial asymmetry was not identified in the funnel plot.

DISCUSSION

This study provided a comprehensive assessment of the scientific literature on the efficacy and safety of the PEMF therapy in patients with knee, hand and cervical OA. The results showed that, in comparison with the sham-control group, PEMF was more effective in both pain relief and function improvement for patients with knee OA and hand OA, but not for patients with cervical OA. In addition, PEMF did not lead to specific adverse events compared with the sham control group. Interestingly, a short duration of PEMF treatment for <= 30 minutes per session seems to achieve more favorable results. This finding may have significant implications for the clinical application of PEMF in the OA field.

As a noninvasive, safe and simple therapy, the PEMF therapy is widely used to treat soft injury and bone fracture, relieve pain and inflammation, as well as many other types of diseases and pathologies.[35] In the past two decades, researchers have turned their attention to the efficacy of treating OA. Some previous systematic reviews have combined PEMF and other physical therapies together to examine their efficacy in OA patients, which might bias the results. McCarthy *et al.*[36] demonstrated that PEMF and short-wave together had limited effect in treating knee OA. In contrast, We *et al.*[37] reported different results. Based on the follow-up data extracted from different time points for subgroup analysis, they concluded that the combination of PEMF and short-wave was more effective in functional

improvement, but not in pain relief, at 8 weeks after the first treatment.[37] It should be noted that short-wave therapy was considered to be another type of physical therapy which was different from PEMF.[38] Similarly, another study conducted by Li *et al.*[24] reported that PEMF and PES might provide moderate benefit for OA sufferers in terms of pain relief. However, considering that PES relies on the direct application of an electrical field and PEMF creates induced current through magnetic impulse, the combined analysis of these two physical therapies may also bias the results.

The results of the present study showed that PEMF had significant effects in pain alleviation and function improvement comparing with the sham-control group in knee and hand OA patients, but not in cervical OA patients. The poor efficacy of the treatment for cervical OA may be due to the anatomical factors of cervical spine. The neurovascular structures contained in the cervical spinal canal may be compressed due to cervical OA, which will then induce a series of symptoms, such as the upper limb nerve root pain induced by nerve root compression; the chronic vertebral and basilar arterial insufficiency due to compression of vertebral arteries; the numbness of limbs and easiness to falling caused by spinal cord compression.[39 40] Although some studies showed that PEMF could enhance articular cartilage regeneration,[41 42] no evidence yet demonstrated that PEMF can reduce osteophytes formation, which may induce nerve root compression that can lead to deterioration of pain and function. In addition, the limited number of studies available is another reason should not be ignored.

The present study further examined the association between the exposure duration of PEMF and efficacy for patients with OA. The results suggested that the exposure duration <=30 minutes per session could achieved better efficacy both in pain relief and function improvement. The reason could be explained by several previous laboratory studies. A recent study exploring the effects of different PEMF treatment durations (ranged from 5 to 60 minutes) over the mesenchymal stem cells (MSC) chondrogenic differentiation reported that the expression of MSC chondrogenic markers showed the greatest increase in response to 5-20 minutes PEMF treatment.[43] Similarly, another two studies which have shown that PEMF could activate cellular signaling transduction rapidly within 5-10 minutes, whereas the signaling might be largely benumbed after 30 minutes.[5-7]

Nevertheless, limitations of the present study should be acknowledged. Firstly, since different treatment protocols of PEMF were used in the included studies, there was a high level of heterogeneity among various studies. Secondly, there were sparse eligible trials available for the efficacy analysis of

hand OA and cervical OA, and the accuracy of the conclusions on these two joints were limited. In addition, because the number of studies reporting the pulse frequency of application, pulse intensity, pulsed rate and other parameters of PEMF was very limited, subgroup analyses were restricted according to these parameters of PEMF. Finally, morphological change is a meaningful outcome for exploring the treatment efficacy of PEMF further;[19] however, the morphological changes were not reported in the present study due to the lack of relevant data. More trials are needed to evaluate the morphological changes after PEMF therapy.

CONCLUSION

The present study revealed that PEMF could alleviate pain and improve physical function for knee and hand OA patients, but not for cervical OA. Meanwhile, a short PEMF treatment duration (within 30 minutes) may achieve more favorable efficacy. However, given the limited number of study available in hand and cervical OA, the implication of this conclusion should be cautious for hand and cervical OA.

Author contributions

ZYW, DXX, XD and YLW were responsible for conception and design of the study. ZYW, XD, DXX, and YLW contributed to study retrieval. YC and YLX contributed to quality assessment. HL, TY and JTL contributed to data collection. JW and CZ contributed to statistical analysis. ZYW, XD, DXX and YLW drafted the manuscript. CZ and GHL contributed to revision of the manuscript. All authors read and approved the final manuscript.

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Declaration of financial/other relationships

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work and its conclusions.

Competing Interests statement: All authors declare that they have no conflict of interest.

Data sharing statement: No additional data available.

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Table 1. Characteristics of included studies

Studies		Balance	N	Location of OA	Age, years (mean ± SD)	Female %	Mean BMI, kg/m^2 (mean ± SD)	Duration of OA, years (mean ± SD)	Exposure of intervention		Time point for outcome measure
									Daily time	Exposure duration	
Ay 2009	PEMF	Hot pack, TENS	55	Knee	58.9 ± 8.8	70.0	NA	3.6 ± 4.6	30 minutes	3 weeks (15 sessions)	After treatment
	Placebo				57.7 ± 6.5	76.0	NA	3.5 ± 4.1			
Bagnato 2016	PEMF	None	60	Knee	67.7 ± 10.9	70.0	27.4 ± 4.3	12.1 ± 8.2	A minimum of 12 hours	1 month (30 sessions)	1 month
	Placebo				68.6 ± 11.9	73.3	27.7 ± 4.6	12.4 ± 9.1			
Fischer 2006	PEMF	None	71	Knee	52.1 ± 1.9	71.4	29.2 ± 1.0	6.8 ± 0.7	16 minutes	6 weeks (42 sessions)	Therapy-End, 4weeks after therapy-End
	Placebo				62.1 ± 1.5	72.2	29.4 ± 0.7	6.2 ± 0.6			
Lee 2004	PEMF	None	51	Knee	63.5 ± 8.9	8.0	26.1 ± 3.1	12.7 ± 7.5	30 minutes	6weeks (18 sessions)	3, 6 weeks during treatment, 4 weeks after finishing
	Placebo				66.2 ± 8.8	11.5	27.1 ± 3.7	12.8 ± 7.6			
Nelson 2013	PEMF	Current standard of care	34	Knee	55.5 ± 2.5	73.7	33.5 ± 1.9	NA	15 minutes	6 weeks (84 sessions)	14, 29, 42 days
	Placebo				58.4 ± 2.5	66.7	34.7 ± 1.7	NA			
Nicolakis 2002	PEMF	None	36	Knee	69.0 ± 5.0	73.3	NA	NA	30 minutes	6 weeks (84 sessions)	After treatment
	Placebo				67.0 ± 7.0	47.1	NA	NA			
Pipitone 2001	PEMF	None	75	Knee	62.0 (40–84) *	35.3	NA	4.0 (1.0–18.0) *	10 minutes and 3 times a day	6 weeks	2, 4, 6 weeks after study entry
	Placebo				64.0 (48–84) *	20.0	NA	8.0 (0.5–31.0) *			

Tejero Sánchez 2003	PEMF	None	83	Knee	67.4 ± 8.7	87.9	NA	NA	30 minutes	20 sessions	The end of therapy, one month after therapy
	Placebo				68.0 ± 8.3	88.2	NA	NA			
Thamsborg 2005	PEMF	None	83	Knee	60.4 ± 8.7	46.5	27.0 ± 4.0	7.5 ± 5.2	2 hours	6 weeks (30 sessions)	2 weeks, end of treatment, 6 weeks after end of treatment
	Placebo				59.6 ± 8.6	61.0	27.5 ± 5.7	7.9 ± 7.7			
Trock 1994 §	PEMF	Do not change basic therapeutic	86	Knee	69.2 ± 11.5	69.0	NA	9.1 ± 8.9	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
	Placebo				65.8 ± 11.7	70.5	NA	7.4 ± 7.2			
Sutbeyaz 2006	PEMF	None	34	Cervical	43.2 ± 10.3	64.7	NA	NA	30 minutes	3 weeks (42 sessions)	After treatment
	Placebo				42.1 ± 10.1	66.7	NA	NA			
Trock 1994 §	PEMF	Do not change basic therapeutic	81	Cervical	61.2 ± 13.4	28.6	NA	7.4 ± 6.7	30 minutes	4-5 weeks (18 sessions)	Midway of therapy, the last treatment, and one month later
	Placebo				67.4 ± 8.0	30.8	NA	8.1 ± 8.0			
Kanat 2013	PEMF	Active range of motion and resistive	50	Hand	64.0 ± 2.60	NA	NA	5.01 ± 2.3	20 minutes	10 days	After treatment
	Placebo				62.0 ± 2.40	NA	NA	4.31 ± 4.7			

N, number of participates; BMI, body mass index; OA, osteoarthritis; PEMF, pulsed electromagnetic field; NA, not available; TENS, transcutaneous electrical nerve stimulation.

* Age and duration of OA in this trial were expressed by median (range).

§ This trial provided data of knee OA and cervical OA patients respectively.

Table 2. Results of subgroup analyses.

Reason for subgroup analyses		Pooled Results of Subgroups		Heterogeneity of Subgroups	
		SMD/RR	95% CI	I^2 (%)	p Value
Pain					
Location	Knee OA	-0.54	[-1.04, 0.04]	88	0.03
	Cervical OA	-2.33	[-6.26, 1.61]	97	0.25
	Hand OA	-2.85	[-3.65, -2.04]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-1.01	[-1.64, -0.39]	91	0.001
	More than 0.5hr/session	-0.61	[-2.25, 1.02]	95	0.46
Function					
Location	Knee OA	-0.34	[-0.53, -0.14]	0	0.0006
	Cervical OA	-0.27	[-0.71, 0.16]	NA	0.22
	Hand OA	-1.49	[-2.12, -0.86]	NA	< 0.00001
Exposure duration	No more than 0.5hr/session	-0.50	[-0.81, -0.18]	59	0.002
	More than 0.5hr/session	-0.33	[-0.82, 0.17]	54	0.20
Adverse event					
Exposure duration	No more than 0.5hr/session	0.42	[0.14, 1.29]	0	0.13
	More than 0.5hr/session	1.95	[0.81, 4.71]	NA	0.14

OA, osteoarthritis; SMD, standard mean difference; RR, relative risk; CI, confidence interval; NA, not available.

Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
OA: osteoarthritis, PEMF: pulsed electromagnetic field

Figure 2. Risk of bias summary of twelve included studies.
The green background with "+" means low risk of bias; the red background with "-" means high risk of bias; the yellow background with "?" means unknown risk of bias. Trials involving three or more high risks of bias were considered as poor methodological quality.

Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field
Significant differences were observed between the PEMF and sham group on pain improvement in knee OA ($P = 0.03$) and hand OA patients ($P < 0.00001$), whereas no significant difference was achieved between groups in cervical OA patients ($P = 0.25$) .

Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field
Significant differences both in knee OA ($P = 0.0006$) and hand OA ($P < 0.00001$), whereas there was no significant difference between groups in cervical OA patients ($P = 0.22$).

Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
PEMF: pulsed electromagnetic field
There was no significant difference between the PEMF and the sham group regarding adverse events ($P = 0.75$).

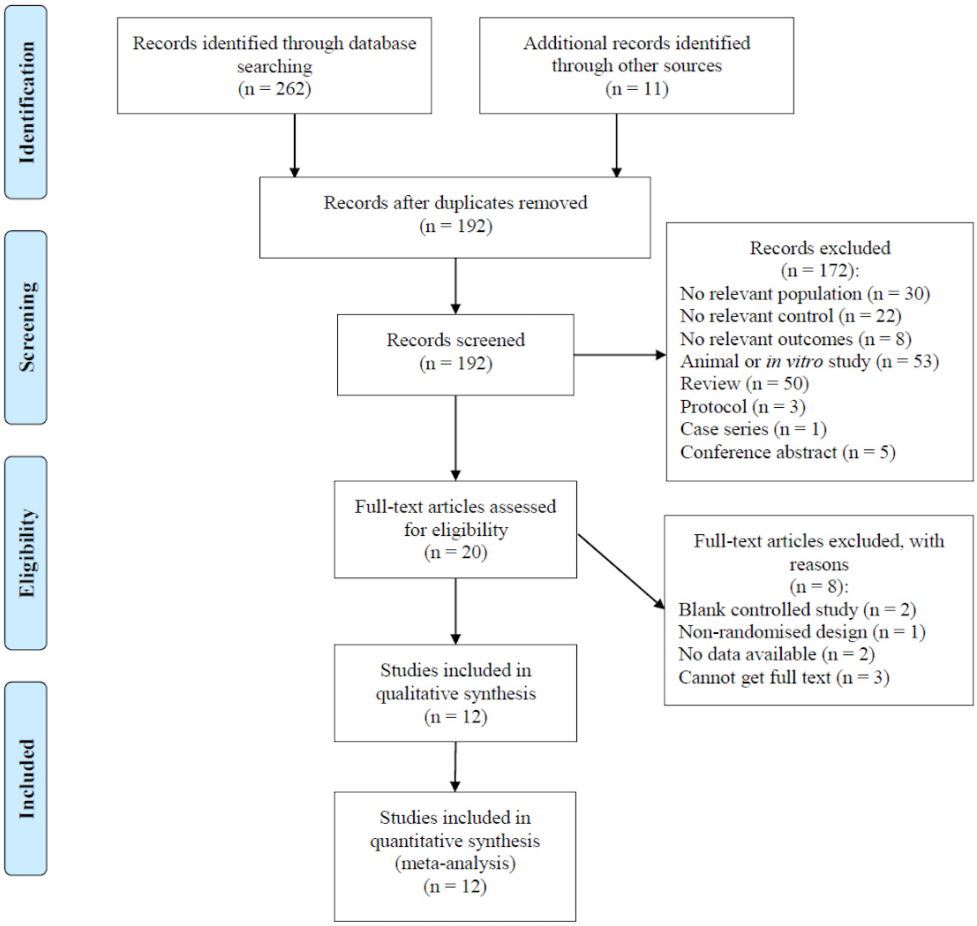

Figure 1. Flowchart of studies screening process based on the PRISMA guideline.
OA: osteoarthritis, PEMF: pulsed electromagnetic field

95x90mm (300 x 300 DPI)

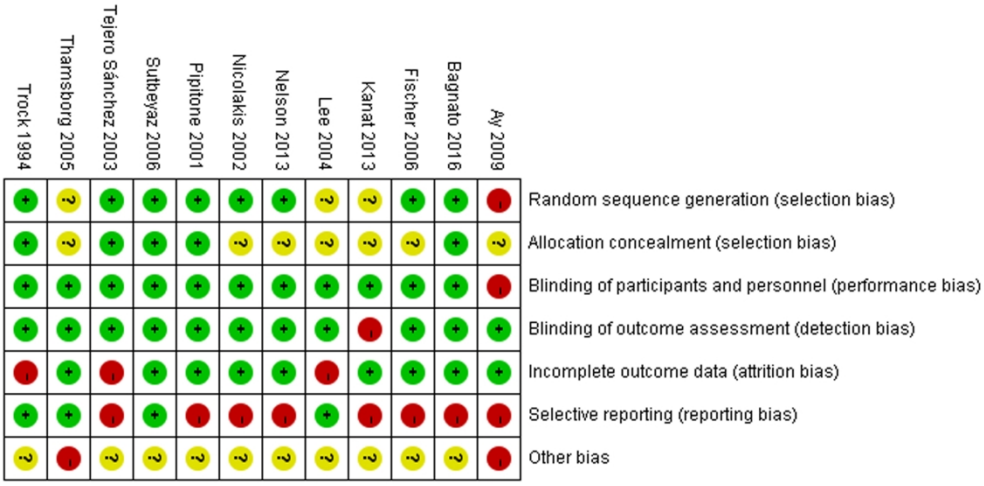

Figure 2. Risk of bias summary of twelve included studies.

173x87mm (300 x 300 DPI)

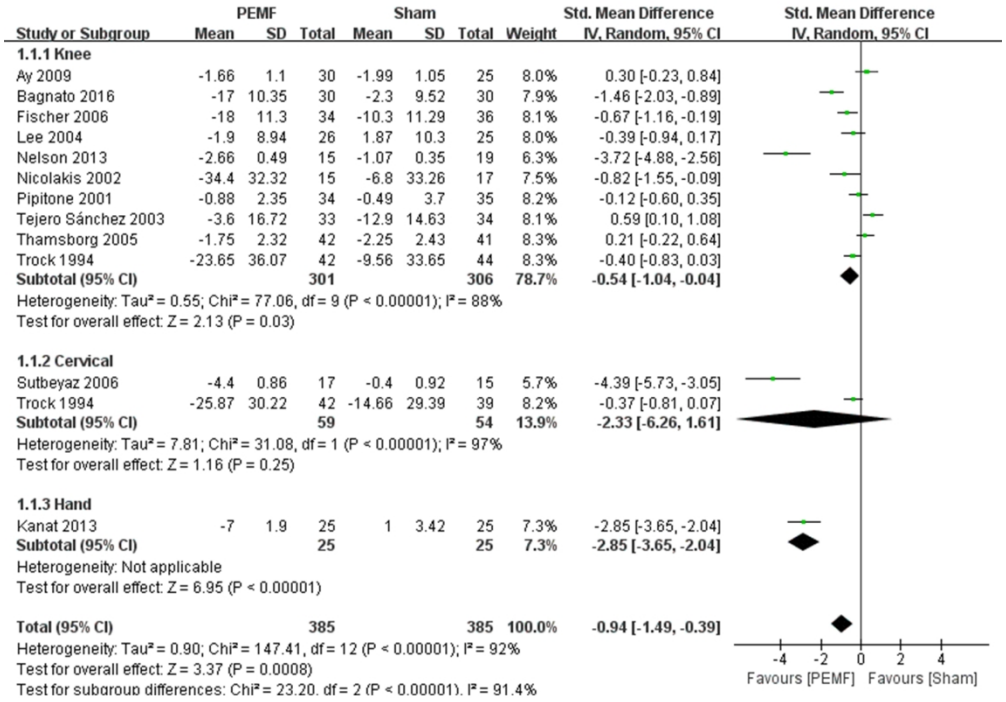

Figure 3. Forest plot of PEMF compared to sham-control on pain.
PEMF: pulsed electromagnetic field

173x123mm (300 x 300 DPI)

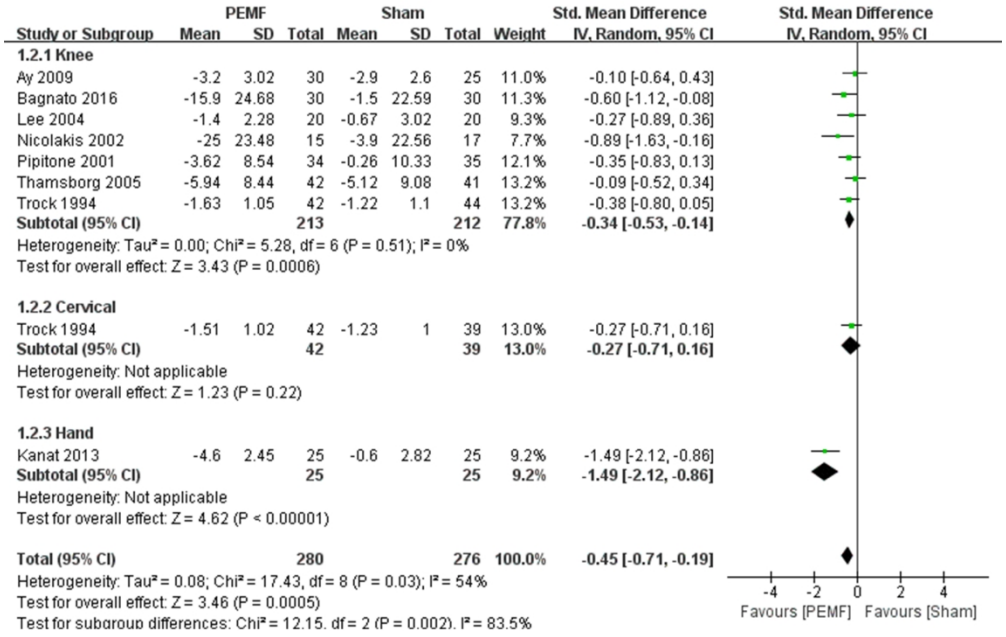

Figure 4. Forest plot of PEMF compared to sham-control on function.
PEMF: pulsed electromagnetic field

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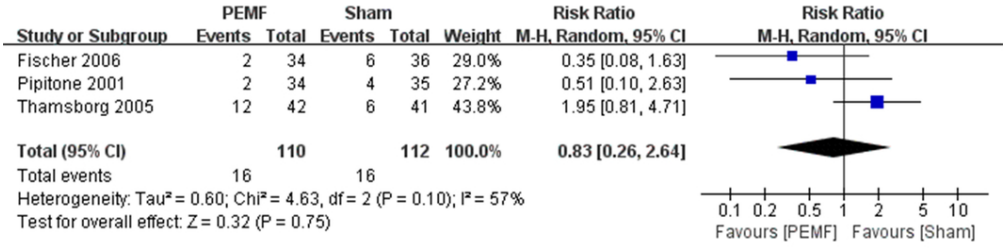

Figure 5. Forest plot of PEMF compared to sham-control on adverse events.
PEMF: pulsed electromagnetic field

89x22mm (300 x 300 DPI)

Search Strategies

PubMed search strategy

#1 Pulsed electromagnetic field[Title/Abstract]

#2 Pulsed electromagnetic fields[Title/Abstract]

#3 Pulsed electromagnetic field[mesh]

#4 #1 or #2 or #3

#5 Osteoarthritis[Mesh]

#6 (osteoarthro*[tiab] or gonarthriti*[tiab] or gonarthro*[tiab] or coxarthriti*[tiab] or coxarthro*[tiab] or osteo?arthritis[tiab])

#7 #5 or #6

#8 randomized[tiab]

#9 placebo[tiab]

#10 controlled[tiab]

#11 random*[tiab]

#12 trial*[tiab]

#13 groups[tiab]

#14 ((singl*[tiab] or doubl*[tiab] or tripl*[tiab]) and (mask*[tiab] or blind*[tiab]))

#15 #8 or #9 or #10 or #11 or #12 or #13 or #14

#16 #4 and #7 and #15

Embase search strategy

#1 'Pulsed electromagnetic field'/exp

#2 Pulsed electromagnetic fields:ti,ab

#3 Pulsed electromagnetic field：ti,ab

#4 #1 or #2 or #3

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteoarthritis:ti,ab

#6 'Osteoarthritis'/exp

#7 #5 or #6

#8 random* or control* or trial* or placebo:ti,ab

#9 groups:ti,ab

#10 (singl* or doubl*or tripl*) and (mask* or blind*):ti,ab

#11 #8 or #9 or #10

#12 #4 and #7 and #11

Cochrane Library search strategy

#1 MeSH descriptor Pulsed electromagnetic field explode all trees

#2 Pulsed electromagnetic field:ti,ab,kw

#3 #1 or #2

#4 MeSH descriptor osteoarthritis explode all trees

#5 osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis:ti,ab,kw

#6 #4 or #5

#7 random* or control* or trial* or placebo:ti,ab,kw

#8 Groups:ti,ab,kw

#9 (singl* or doubl*or tripl*) and (mask* or blind*):ti,ab,kw

#10 #7 or #8 or #9

#11 #3 and #6 and #10

Web of Science search strategy

#1 Topic:(Pulsed electromagnetic field)

#2 Topic:(Pulsed electromagnetic fields)

#3 #1 or #2

#4 Topic:(Osteoarthritis)

#5 Topic:(osteoarthro* or gonarthriti* or gonarthro* or coxarthriti* or coxarthro* or osteo?arthritis)

#6 #4 or #5

#7 Topic:(randomized or placebo or controlled or random* or trial* or groups)

#8 Topic:((singl* or doubl* or tripl*) and (mask* or blind*))

#9 #7 or #8

#10 #3 and #6 and #9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix 2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4, 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Details in Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, details in figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7, details in table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, details in figure 5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8-9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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